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

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CHAPTER 2

How to Define Success in Prolactinoma Treatment – A Systematic Review and Theoretical Framework

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ABSTRACT

Purpose

As consensus regarding outcome sets for prolactinoma treatment evaluation is lacking, outcome parameters reported in literature were evaluated, and objective, clinically relevant outcome sets were proposed.

Methods

A systematic review of studies up to February 2, 2024. Reported biochemical and radiological parameters, clinician-reported findings, patient-reported outcomes (PROs), and definitions of disease remission, control and recurrence were extracted and placed into clinical context. Subsequently, objective and clinically relevant definitions of clinical outcomes were proposed based on the findings, with comprehensive outcome sets to evaluate treatment success.

Results

One hundred thirty-seven articles were included. Albeit ill-defined or subjective, 23 unique prolactin parameters, and 73 unique radiological parameters were reported. Seventy articles included clinician-reported findings, and none reported PROs. Ultimately, 27 unique definitions of remission, 3 unique definitions of disease control, and 20 unique definitions of recurrence were reported. We propose two separate definitions for biochemical and clinical remission/recurrence - either evaluating prolactin levels only, or including symptomology, gonadal function, and radiology. Integrated outcome quadrants were illustrated to objectively categorize treatment success by combining achievement of treatment goals with occurrence of adverse effects. A three-tier outcome set based on the Value-Based Healthcare principles was provided.

Conclusions

Heterogeneity in reported outcome parameters using varying definitions hamper comparison of prolactinoma treatment outcomes. This study proposes objective, easily applicable, and clinically relevant definitions of clinical outcomes, and offers a comprehensive outcome set. These parameters enable comparison of outcomes across treatment modalities and medical centers to gain insight into this rare disease and improve prolactinoma care.

INTRODUCTION

Prolactinomas are generally treated with dopamine agonists (DAs), resulting in biochemical normalization in approximately 90% of patients, and persistent normoprolactinemia in 16-21% of patients after DA withdrawal [1]. An alternative first-line treatment is surgery, which results in normoprolactinemia in 80-92% of patients [1-3], and recurrence of hyperprolactinemia in 10 and 25% of micro- and macroprolactinomas, respectively [4].

Assessment of treatment success is more complex than solely evaluating prolactin levels, and preferably includes appraisal of side effects, complications, health-related quality of life (HR-QoL), and personal treatment goals (e.g., fertility). Disease heterogeneity necessitates a nuanced understanding of pathophysiology and clinical features to set patient-centered goals and interpret outcomes, especially when comparing results between treatment modalities.

Scientific interest in prolactinomas and treatment outcomes has steadily increased over the past decades. In research, a range of parameters are being used, including biochemical, radiological, and clinician-reported outcomes. Although patient-reported outcomes (PROs) are important, their role in outcome evaluations remains to be elucidated. The Value Based Health Care (VBHC) framework by Porter et al. provides guidance on organizing outcomes in three tiers [4]. However, this framework of standardized outcome sets has not been established for prolactinomas, leading to limited comparability between studies.

Clearly defined outcome parameters are a prerequisite for prospective registries and trials, care evaluation in pituitary centers of excellence (PTCOEs) and dedicated shared decision making. Therefore, this study discusses clinical considerations regarding outcome parameters for prolactinomas, systematically reviews outcome measures reported in literature, and provides suggestions for well-defined, clinically relevant outcome sets to use in clinical practice and research.

METHODS

Study design

This study is composed of three parts:

I. Clinical considerations regarding interpretation of relevant outcome parameters for prolactinomas (i.e., prolactin levels, hypopituitarism and secondary hypogonadism, radiology, clinician-reported findings, and PROs), and a systematic review of their use in literature.
II. Systematic review of reported definitions of *remission*, *disease control* and *recurrence*, and suggestions for objective, clinically relevant definitions based on considerations described in (I).
III. Recommendations for comprehensive outcome sets to evaluate prolactinoma treatment.

Systematic review

Data sources and search

The studies included in this systematic review were partly derived from a previous systematic review and meta-analysis performed by our group, which included studies up to April 13, 2017 [2]. On February 2, 2024, an update of this search strategy was performed. As shown in Suppl. Table 1 [5], the strategy included three terms: (1) patient population (2) treatment, and (3) outcomes [2]. Seven digital libraries were searched (Academic Search Premier, Cochrane Library, Embase, Emcare, PsycInfo, PubMed and Web of Science).

Study selection

Studies were selected by two independent researchers (KAH and VRvT) following title, abstract, and full-text screening. Disagreements were resolved by discussion and consensus, and, in case of persistent disagreement, the majority vote was chosen by consultation of a third researcher (ICMP). Randomized controlled trials, cohort-studies and cross-sectional studies reporting on outcomes of medical treatment and transsphenoidal surgery of radiologically confirmed prolactinoma were included if they reported one of the following outcomes: disease remission after DA or transsphenoidal surgery, disease control on DA, disease recurrence, or HR-QoL. The following studies were excluded: reporting primarily on patients <16 years-old, fewer than 10 patients, or without original data. When cohorts overlapped, the largest cohort was included.

Data extraction

The following data was extracted independently by KAH and VRvT: publication year, study design, duration of follow-up, DA withdrawal criteria, definitions of disease control, recurrence, and remission. Moreover, all reported definitions describing prolactinoma outcomes, including biochemical, radiological, and clinical (clinician-reported findings, and PROs) outcomes were collected. In this systematic

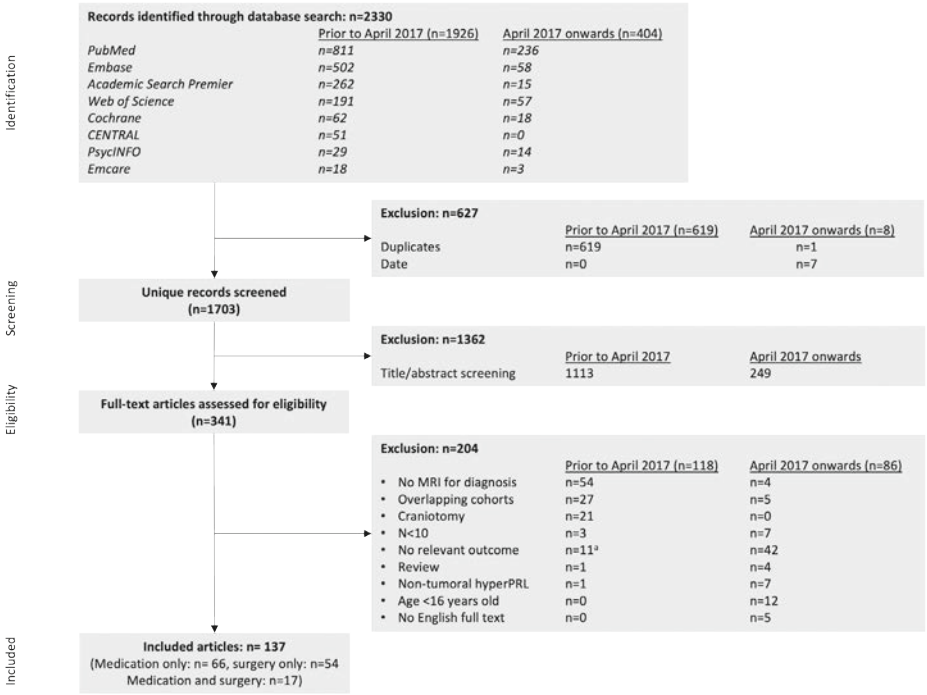
review, the physician's interpretation of medical history, physical examination, and (ophthalmological) function tests were considered clinician-reported findings. Normoprolactinemia was defined as prolactin within the laboratory-specific reference range standardized for sex and menopausal status. Details concerning the extracted variables are summarized in Suppl. Table 2 [5].

RESULTS

Included studies (Figure 1)

A total of 1703 unique studies were identified, of which 1362 were excluded based on title and abstract. Full-text screening of 341 articles was performed, after which 137 studies were included in this review. In total, 66 studies reported on medical outcomes, 54 studies reported on surgical outcomes, and 17 studies reported on both. All extracted data are shown in Suppl. Table 3 [5].

Figure 1 Flow chart of screening and inclusion



HyperPRL, hyperprolactinemia.

[a] Four studies that were included in the previous systematic review were excluded from the current study, as they only reported on side effects or costs without evaluating treatment success.

I. EVALUATION OF OUTCOME PARAMETERS DESCRIBED IN LITERATURE

1. Prolactin levels

a. Clinical considerations and interpretation

Serum prolactin is determined using automated immunometric immunoassays, in which the prolactin protein reacts with immobilized capture antibodies and labeled antibodies for detection. The signal generated after washing is proportional to the sample's prolactin concentration [6]. Manufacturers provide assay-specific reference ranges for men, pre- and postmenopausal women, and sometimes for pregnant women. The expected reference ranges supplied by the manufacturer are established by testing samples from approximately 100-200 healthy individuals and determination of the central 95% of values. These are to be verified by laboratories for their own population [6]. Although reference ranges vary between laboratories [7, 8], reporting the upper limit of normal (ULN) facilitates interpretation across centers. Serum prolactin is a sensitive and objective measure of disease activity without necessitating dynamical testing. However, physiological variations of individual prolactin setpoints not corresponding with established reference ranges may occur.

When evaluating prolactinoma treatment outcomes, it is important to consider that various other conditions may induce (additional) hyperprolactinemia (generally <5xULN), potentially interfering with outcome interpretations (e.g., liver cirrhosis, renal insufficiency, primary hypothyroidism, or stalk compression). Moreover, antipsychotics, antidepressants, anti-emetics, protease inhibitors, and opiates may induce hyperprolactinemia [9]. Furthermore, physiological alterations, caused by the ovulatory and luteal phase of the menstrual cycle, pregnancy, stress, exercise, and high-protein meals cause hyperprolactinemia of varying severity [10]. Repeated cannulated prolactin sampling may rule out some of these causes of hyperprolactinemia at initial diagnosis, but also during evaluation of treatment success. This particularly important in cases with recovery of the gonadal axis in absence of complete prolactin normalization.

To correctly interpret prolactin levels, clinical manifestations and radiology should be taken into account. For instance, macroprolactinemia, caused by anti-prolactin antibodies (mostly IgG) bound to prolactin, can lead to biologically inactive hyperprolactinemia detected by the assay [10]. Prolactin recovery <40% after polyethylene glycol precipitation confirms macroprolactinemia [10]. Macroprolactinemia should be ruled out in patients with asymptomatic hyperprolactinemia (<200ng/mL) during the diagnostic phase [11], and if a combination of macroprolactinemia and monomeric prolactinoma-related hyperprolactinemia is present, this should be considered during evaluation of disease activity. Furthermore, although rare in modern assays, high-dose hook effects falsely normalize or slightly elevate prolactin levels in extreme hyperprolactinemia by saturating assay antibodies [12]. As prolactin usually

positively correlates with tumor size, samples in patients with giant adenomas and typical prolactinoma symptoms should be diluted [11]. Thus, prolactin is an essential parameter in evaluating treatment success that should be interpreted considering clinical findings and radiology.

b. Reported prolactin parameters (Suppl. Table 4 [5])

Prolactin levels were reported in 136 out of 137 studies. Twenty-three unique prolactin parameters were used: prolactin normalization (96 studies), absolute (nadir) post-treatment prolactin (78 studies), categorical parameters (e.g., prolactin decrease yes/no) (3 studies), percentages of change (4 studies), and undefined outcomes such as '*prolactin near ULN*' (1 study), and '*prolactin <10ng/mL*' without providing the ULN (1 study).

Two studies reported using cannulated, un-stressed prolactin levels [13, 14], whereas the other studies did not report on the method of prolactin measurements. Two studies reported average prolactin levels of multiple measurements [15, 16]. No study reported on interpretation of prolactin levels in case of concomitant use of prolactin-elevating medication or pregnancy during follow-up.

c. Prolactin levels in the reported definitions of disease remission (Figure 2, Suppl. Table 5 [5])

Prolactin levels were included in all but one definition of remission [17]. Remission entailed normalization of prolactin below the ULN in most studies, with two studies aiming for other cut-off values [18, 19]. Five studies mentioned a cut-off value without stating the ULN [20-24], and one study stated the unspecified aim of achieving '*healthy prolactin levels*' [25]. One definition of remission allowed either normalization of prolactin, or reduction of >95% of baseline prolactin [26], and another allowed asymptomatic prolactin values up to 1.5xULN [27]. One study reported separate definitions for biochemical and clinical remission, allowing asymptomatic prolactin levels above the ULN for *clinical remissio*n if gonadal function was restored [28].

2. Gonadal status

a. Clinical considerations

Prolactin suppresses the gonadal axis by direct suppression of gonadotropin-releasing hormone (GnRH) and indirectly through Kisspeptin [29, 30]. Therefore, restoration of the gonadal axis is an indicator of treatment success. In females, secondary hypogonadism is characterized by low estradiol levels combined with inadequately low to normal luteinizing hormone (LH) and follicle-stimulating hormone (FSH) leading to anovulatory menstrual cycles [31]. Gonadotrophins should be measured in the morning and be interpreted considering the patient's age and phase of the menstrual cycle [31, 32]. In males, low serum testosterone levels and/or reduced spermatogenesis with inadequately low to normal gonadotrophins are indicative of secondary hypogonadism [33]. Serum testosterone is a marker for androgen status and should be measured in absence of acute

illness, before 10 AM after an overnight fast to account for its diurnal rhythm, and food- and illness-induced suppression [34-36]. Approximately 2-4% of testosterone circulates in unbound bioactive form, whereas approximately 44% is tightly bound to sex hormone binding protein (SHBG) and 50-54% is loosely bound to albumin [34, 36, 37]. Therefore, measurement of free testosterone is advised in patients with total testosterone levels near the lower limit of normal or with suspected albumin or SHBG abnormalities. Taking these factors into account, the clinical diagnosis of female and male secondary hypogonadism can be made. However, in clinical practice, interpretation of female gonadotropins might be complicated, as the phase of the cycle is not always known. Moreover, other causes of acquired secondary hypogonadism, including mass effect- or trauma-related pituitary or hypothalamic damage, ischemic, inflammatory, or infectious diseases, metabolic disturbances, drug-induced hypogonadism, and hypothalamic dysfunction should be considered [31, 32, 38]. Thus, restoration of gonadal function (i.e., restoration of the menstrual cycle with estradiol levels >200 pmol/L depending on the cycle phase, or normalization of morning fasting free testosterone levels [31, 33]) is a good indicator for prolactinoma disease control, with pregnancy being proof of eugonadism. However, persistent hypogonadism should not always be interpreted as treatment failure because other factors may contribute.

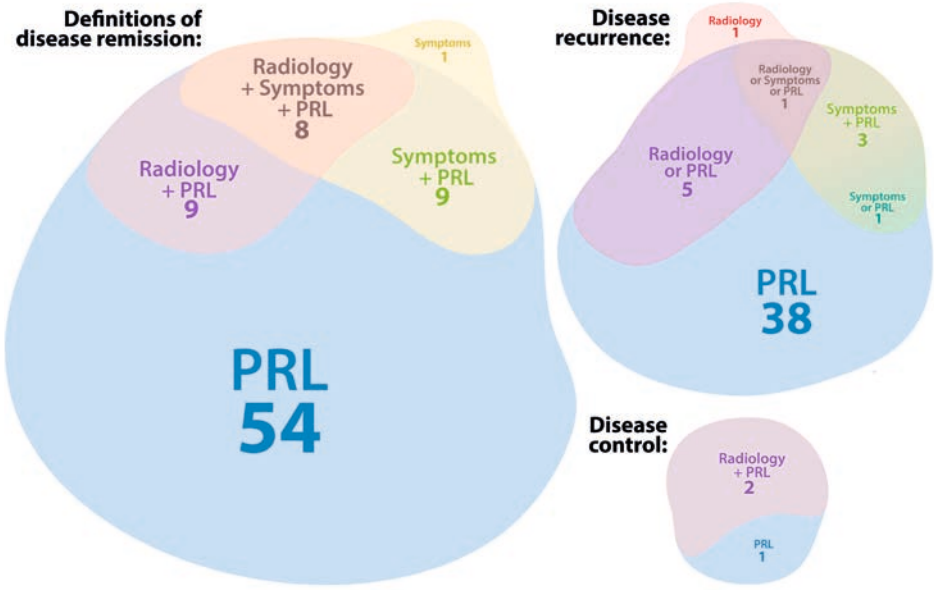
b. Reported parameters concerning hypogonadism (Suppl. Table 4 [5])

Twenty-six studies reported on improvement of hypopituitarism (including hypogonadism) after treatment. Nineteen studies reported specifically on improvement of hypogonadism, of which only two stated a definition. Andereggen et al. defined hypogonadism as *'normal-low levels of gonadotropins in parallel with low estradiol levels'*, and Kabootari et al. defined central hypogonadism as *'amenorrhea for >3 months in women and sexual dysfunction in men with low levels of gonadal hormones and normal to low levels of LH and FSH'* [39].

c. Gonadal status in the reported definitions of disease remission (Figure 2, Suppl. Table 5 [5])

Two studies included the gonadal status or the menstrual cycle in their definition of remission, with one defining remission as *'reoccurrence of normal menstrual cycle and PRL<10 ng/mL that could be normally stimulated ≥2.5xULN by thyrotropin-releasing hormone and metoclopramide' [21].* The other study defined clinical remission as *'restoration of the gonadal function and resolution of complaints without prolactin normalization'* [28].

Figure 2 Visual representation of parameters used in the definitions of disease remission, disease recurrence and disease control as reported in literature. The number of studies using the specific parameters in their definition are provided. Sixty-three studies reported a total of 81 definitions of remission, among which 27 unique definitions. Fourty-six studies reported 49 definitions of disease recurrence, among which 20 unique definitions, and three studies reported four unique definitions of disease control



PRL, serum prolactin; *symptoms*, clinician-reported symptoms; *Radiology*, MRI of the pituitary.

3. Radiological parameters

a. Clinical considerations

Magnetic resonance imaging (MRI) is the gold standard for radiological prolactinoma diagnosis, and it provides information about the prolactinoma's relationship with critical structures. Tumor shrinkage is an objective measure of response to medical treatment and knowing there is no clear remnant on MRI may relieve patients' stress. Moreover, the absence of residual tumor mass after DA withdrawal is positively correlated with the probability of persistent normoprolactinemia [11, 40, 41], and consecutive post-treatment imaging can identify subtle growth of a remnant and determine feasibility of (re)resection. However, prolactin levels are superior to evaluate total resection, as interpretation of imaging after surgery is hampered by post-operative hemorrhage, and fluid collections early after surgery, and difficulty to discriminate between resection cavity and scar tissue at later timepoints [42]. Moreover, MRIs are not suitable for repeated screening for recurrent disease, due to insufficient sensitivity for small remnants and excessive costs. Thus, imaging offers prognostic information about durability of remission and enables evaluation of decompression yet has limited value in evaluation of disease remission.

b. Reported radiological parameters (Suppl. Table 6 [5])

Ninety-six studies reported on radiological outcomes. In total, 73 unique parameters were used. (Gross) total resection (27 studies), and complete tumor disappearance after DA treatment (27 studies) were reported most frequently. Five unique parameters concerning volume or tumor mass were reported (23 studies), and seven concerned tumor diameter (24 studies).

Fifteen different percentages of tumor volume/diameter reduction were reported. Eleven subjective undefined measures were reported, such as '*subtotal resection*' (7 studies), '*significant debulking/tumor shrinkage*' or "*partial removal*" (1 study each).

One study reported on the lesion's intensity on MRI and the time to appearance of low signal intensity (months) [43] and one reported on cystic degeneration [44].

c. Radiological parameters in the reported definitions of remission (Figure 2, Suppl. Table 5 [5])

Thirteen studies included radiological parameters in their definition of remission (medical n=5 [45-49], surgical n=10 [17, 22, 27, 48-54]). Most studies aimed for the absence of a remnant on MRI. However, one study aimed for stable tumor size after DA withdrawal [46], and another study on surgical remission aimed for >50% tumor reduction on MRI three months post-surgery [22].

4. Clinician-reported findings

a. Clinical considerations

Being derived from interpretation of clinical signs and symptoms clinician-reported findings offer indirect insight into the patients' wellbeing and HR-QoL. Physicians who know their patient well can identify overlooked symptoms and assess their severity objectively due to their clinical experience. Contrary to patient reported outcome measures (PROMs), clinical history taking offers the flexibility to rephrase questions to ensure the patients' understanding and to focus on personalized topics. Moreover, clinician-reported findings are particularly relevant in patients unable to complete PROMs. Unfortunately, clinician-reported findings have been shown to correlate poorly with PROMs [48-50]. Moreover, use of clinician-reported findings in research is hampered by incomplete and unstandardized reporting in (electronic) health records. Hence, clinician-reported outcomes complement PROMs, without replacing them.

b. Reported clinician-reported findings and visual measurements (suppl. Table 7 [5])

Seventy studies reported clinician-reported findings. Visual symptoms were most frequently reported, with 28 studies reporting on visual field defects, 3 studies on visual acuity, and 16 studies on unspecified '*visual symptoms*'. Galactorrhea, headaches, and

subfertility were reported by 13, 11 and 4 studies, respectively. Only 2 studies reported mood disturbances. Eleven studies reported '*symptoms*' without further specification.

c. Clinician-reported findings in the reported definitions of remission (Figure 2, Suppl. Table 5 [5])

Sixteen studies included clinician-reported findings concerning symptomatology in their definition of remission [17, 21, 25, 27, 28, 49, 51-60]. Fifteen studies aimed for complete resolution of symptoms, without specifying which symptoms, and 1 study aimed for '*evidence of clinical remission*' without stating its definition [60].

5. Patient-reported outcomes

a. Clinical considerations

PROMs can be either generic, such as the Short Form 36 (SF-36) and EuroQoL 5D (EQ-5D), or pituitary-specific, such as the Leiden Bothers and Needs – pituitary (LBNQ-Pituitary). The LBNQ-Pituitary is the only validated questionnaire for pituitary adenomas, measuring disease burden (Bothers) and Needs for attention of the treating physician [46]. Generic PROMs, widely used in literature, enable comparison between studies and diseases. However, they may lack the sensitivity to detect prolactinoma-specific changes in HR-QoL [47]. Therefore, using a combination of both is advised [7].

PROMs aim to assess the patients' perspective on disease, treatment and HR-QoL, without subjective interpretation by healthcare providers. Moreover, the patient might feel freer to report sensitive topics that are difficult to discuss in person. However, one must realize that PROMs can merely approximate true HR-QoL. It remains unclear to what extent a single PROM accurately reflects the multifaceted and dynamic nature of HR-QoL. PROMs have a few inherent limitations that should be considered. Firstly, PROMs are subject to varying interpretation, based on age, gender, cultural background, reading ability, understanding of the language and phrasing of questions – with most not being validated in prolactinomas. Secondly, PROMs are composed of a fixed set of questions not tailored to the individual, potentially causing confusion when questions do not align with the patient's situation. Thirdly, responses may be influenced by comorbidity, mood, life events, and recall bias. Although it is valuable to gain insight into the patient's overall wellbeing, this complicates the use of PROMS in treatment evaluations. Fourthly, the time-burden of completing PROMs may decrease response rate, hampering validity of outcomes due to selective non-response. Lastly, implementation in clinical practice may be challenging and time consuming. Thus, PROMs are essential to gain insight in HR-QoL, yet interpretation of the results and implementation in clinical practice are complex.

b. Reported patient-reported outcomes

No studies reported on PROMS.

Table 1 proposed definitions of clinical outcomes

Clinical outcome		Definition
Disease remission	Biochemical	Normoprolactinemia[a,b] >3 months after DA withdrawal or >6 weeks post-surgery while off DA for >3 months
	Clinical	Prolactin >1xULN or with uninterpretable prolactin levels[c] with resolution of typical prolactinoma-related symptoms (i.e., galactorrhea, loss of libido, subfertility, menstrual cycle disturbances or erectile dysfunction)[d], and recovery of gonadal function without a certain remnant on conventional MRI and without treatment indication
	Radiological	No adenoma remnant on conventional MRI
Disease control	Prolactinoma without mass effects	Normoprolactinemia[a] during DA treatment without typical prolactinoma-related symptoms (see above) and with stable or decreased tumor size[e] in all dimensions on conventional MRI
	Prolactinoma causing mass effects	Normoprolactinemia[a] during DA treatment without typical prolactinoma-related symptoms (see above) and with radiologically and clinically[f] confirmed resolution of compression and without size increase in any dimension on conventional MRI
	Radiological	Stable or decreasing adenoma size on conventional MRI
Disease recurrence	Biochemical	Hyperprolactinemia (>1.0xULN) measured at least twice[g] after initial biochemical remission
	Clinical	Recurrence of prolactinoma-related[h] symptoms that had receded after initial biochemical or clinical disease remission
	Radiological	Reappearance of an adenoma on conventional MRI after radiological remission
Hypogonadism	Female	Oligomenorrhea or amenorrhea with persisting levels of serum estradiol below 200 pmol/L
	Male	Morning fasting serum testosterone levels below the lower limit of normal after correction for albumin and sex hormone-binding protein

DA dopamine agonist; *xULN* times upper limit of normal.

[a] Normoprolactinemia is defined as prolactin within the laboratory-specific upper limit of normal for sex and menopausal status.

[b] In case of mild hyperprolactinemia (<5xULN) a second unstressed, fasting cannulated measurement during the early follicular phase of the menstrual cycle should be performed if physiological prolactin elevation is suspected.

[c] Due to pregnancy, lactation or prolactin-elevating medication.

[d] Symptoms should preferably be patient-reported. Clinician-reported symptoms may be used if patient-reported data are not available.

[e] Either tumor volume or the largest tumor diameter.

[f] Excluding permanent visual deficits due to previous compression, as evaluated by the multidisciplinary team of a pituitary center of excellence.

[g] The second measurement should be an unstressed, fasting, cannulated measurement during the early follicular phase of the menstrual cycle if physiological prolactin elevation is suspected.

[h] Symptoms that the patient recognizes from the initial prolactinoma diagnosis.

II. PROPOSED DEFINITIONS (TABLE 1)

Definitions of remission, disease control and recurrence as reported in literature are evaluated below and propositions for clinically relevant definitions are made.

Disease remission (Figure 2, Suppl. Table 5 [5])

As reported above, published definitions of remission were heterogeneous, consisting of varying combinations of parameters. Sixty-three studies reported 81 definitions of remission, among which 27 unique definitions. The most commonly reported definition was prolactin normalization (n=42), of which 17 definitions required the patients to be withdrawn from DA treatment, 2 definitions allowed patients to be on DA treatment, and 23 definitions did not specify DA treatment status. Timing of measurements varied greatly, with most studies reporting remission at last follow-up.

Biochemical remission

According to Merriam-Webster Dictionary, the medical term remission is defined as "*a state or period during which the symptoms of a disease are abated*" [61]. As illustrated by many variations throughout literature, this definition is difficult to apply to prolactinoma, with symptoms being non-specific (e.g., headaches, and psychological and cognitive complaints), potentially being caused by unrelated pathology. Moreover, cognitive and psychological complaints may persist for years after biochemical normalization [62]. Requiring resolution of all potentially prolactinoma-related symptoms may cause overtreatment and underestimation of true remission rates.

Prolactin normalization is a more reliable marker for remission, as used in most studies. Complete normalization (<1.0xULN) is desirable, as recurrence rates are lowest in patients in whom normoprolactinemia has been achieved [3]. Although radiological tumor disappearance was a common criterion for remission, we propose excluding radiological parameters from the definition of biochemical remission (due to insufficient sensitivity - see paragraph 3*a*). Thus, we propose to define *biochemical remission* as prolactin levels within the laboratory-specific reference range (<1.0xULN) >6 weeks post-surgery and >3 months after DA withdrawal, due to the long half-life of cabergoline.

Clinical remission

Biochemical remission does not imply the absence of symptoms or restoration of HR-QoL, as recovery is a process and symptoms may (partly) persist. By contrast, symptoms may reside, and the gonadal axis may recover despite mild persisting hyperprolactinemia due issues described in paragraph *1a*. The absence of biochemical remission should, therefore, not always be interpreted as treatment failure.

The term clinical remission is suitable in the following specific clinical scenario: prolactin levels >1xULN, or uninterpretable prolactin levels (due to pregnancy, lactation

or co-medication), without typical prolactinoma-related symptoms (i.e., galactorrhea, loss of libido, subfertility, menstrual cycle disturbances or erectile dysfunction [11]), with recovery of gonadal function, and without a certain remnant on MRI, or treatment indication. The prolactinoma-related symptoms should preferably be patient-reported but may also be clinician-reported if not available.

Although optimizing HR-QoL is the most important treatment goal for patients with prolactinoma, including HR-QoL as a factor in the definition of clinical remission is not appropriate due to several reasons. Firstly, remission status is merely one of the many factors that affect HR-QoL [63]. Due to its multifactorial determinants, HR-QoL is highly variable and quantifying HR-QoL is inherently complex. Secondly, it remains uncertain to what extent HR-QoL can be accurately captured by PROMS, and thirdly, there are no reference ranges, especially no age- and sex-dependent ones. Therefore, including HR-QoL or using PROMS as a proxy for HR-QoL in the definition of clinical remission is not feasible. Alternatively, by incorporating objective measures such as symptomatology, gonadal status, and radiological outcomes, we believe that achieving clinical remission may contribute to improved HR-QoL.

Differentiating between biochemical and clinical remission is relevant for two reasons: (1) to classify patients with a clinically satisfactory result not adhering to the strict biochemical criteria; (2) to enable a more holistic treatment evaluation. While biochemical remission is the preferred outcome in research, clinical remission is the most relevant outcome in clinical practice. Both are meaningful and have their merits.

Radiological remission

As mentioned above, radiological remission, i.e., the absence of an adenoma remnant on conventional MRI, is less informative regarding persistence of active disease than biochemical or clinical remission status, as MRI has limited sensitivity to small (postoperative) remnants. On the other hand, the presence of an adenoma remnant on conventional MRI does carry prognostic information about the persistence of active disease and should be reported in combination with biochemical/clinical remission status.

Evaluating remission in pregnant patients

Patients becoming pregnant during follow-up pose a challenge in research, due to the physiological rise of prolactin levels [10]. Ultimately, conception is an excellent outcome for patients wishing to conceive, demonstrating restoration of gonadal function. Patients who are pregnant at the time of outcome assessment can, therefore, be classified as being in *clinical remission* if they conceived without use of DAs or medical assistance. Biochemical remission should be assessed six weeks after cessation of breast feeding.

Disease control (Suppl. Table 8 [5])

Three studies reported four unique definitions of disease control. One study differentiated between complete (i.e., prolactin normalization), and partial disease control (i.e., prolactin reduction to <3xULN without normalization while using DAs) [69]. The other studies required prolactin normalization with '*stable neuroimaging*' during DA treatment [49], or with >50% tumor reduction without specifying DA treatment status [48]. Two studies reported disease control at last follow-up [49, 69], and one study did not report the timing of measurement [48].

Disease control implies the disease sequalae are suppressed by medical treatment, without full resolution of the disease itself. In accordance with most studies, we propose to define *disease control* as follows: prolactin normalization while using DAs without typical prolactinoma-related symptoms (i.e., galactorrhea, loss of libido, subfertility, menstrual cycle disturbances or erectile dysfunction [11]). For non-compressive prolactinomas, adenoma diameter/volume on MRI should be stable or reduced. In patients with compressive prolactinomas, tumor diameter/volume should be reduced until compression is alleviated (radiologically and clinically). Prolactin levels should not be medically lowered below the laboratory-specific lower limit of normal, because hypoprolactinemia is associated with impaired metabolic health [70, 71], sexual dysfunction and depressive symptoms [72, 73]. Conversely, temporary hypoprolactinemia directly postoperative is desirable, as lower postoperative prolactin levels are predictive of long-term cure [74] and typically return to normoprolactinemic levels in the following weeks to months.

Radiological control

Radiological control is defined as the presence of a stable or decreasing adenoma size in all dimensions on conventional MRI irrespective of prolactin levels.

Discordant responses to treatment

DAs effectively induce normoprolactinemia and tumor shrinkage in most cases [1]. Prolactin levels and tumor size decrease most rapidly during the first six months of treatment [64] and decline of prolactin levels typically precedes tumor shrinkage [65]. More rarely, treatment responses are discordant, with volume increase despite a marked drop in prolactin levels, or tumor shrinkage without declining prolactin levels. Interestingly, none of the studies included in this systematic review described discordant responses. Our proposed definitions may aid to correctly classify these patients.

Case reports describing tumor enlargement despite declining prolactin levels concern macro- and giant prolactinomas treated with either bromocriptine or cabergoline [75-77]. Potential explanations include noncompliance with treatment, or a different etiology, i.e. non-functioning adenomas with stalk compression, asymptomatic apoplexies or cystic degeneration [66, 75, 76, 78]. In some cases, perceived adenoma enlargement may

be explained by improving sensitivity of CT-scans rather than adenoma enlargement – as most reports describing discordant adenoma growth concern early cases in which CT scans were used instead of MRI [66, 76]. Alternatively, tumor shrinkage with worsening hyperprolactinemia has been described [67]. This phenomenon may be caused by physiological or drug-induced hyperprolactinemia (as described above) or, more rarely, by distant metastases as seen in pituitary carcinoma [11].

Thus, discordant treatment responses should prompt further investigation to confirm or exclude alternative etiologies, even though the underlying mechanisms may not always be identifiable. When categorizing patients with discordant responses, those who are normoprolactinemic with stable-sized, non-compressive adenoma may be considered to have controlled disease. Conversely, tumor growth is an indicator of inadequate disease control. Patients with persisting hyperprolactinemia should be classified as uncontrolled irrespective of tumor shrinkage.

Disease recurrence (Suppl. Table 9 [5])

Forty-six studies reported 20 unique definitions of disease recurrence. Most definitions required elevation of prolactin above ULN irrespective of radiological findings or symptoms, without the need for repeat measurements (n=38). Two studies applied alternative prolactin cut-offs: >2xULN [79], and >30ng/mL without reporting reference values [13]. Three studies required recurrence of hyperprolactinemia and clinician-reported symptoms [27, 54, 80], and five studies defined recurrence as either hyperprolactinemia or tumor regrowth on MRI [17, 22, 48, 81, 82]. One study required either radiological tumor regrowth or symptoms [51] and one study required either hyperprolactinemia, adenoma regrowth, or recurrence of symptoms [83]. One study differentiated between early and late recurrence (being either ≤3 months or > 3 months post-surgery) [57], and two studies differentiated between '*biologic' or 'general recurrence*' (i.e., hyperprolactinemia) and '*radiological recurrence*' (i.e., tumor regrowth) [56, 84]. Most studies evaluated recurrence throughout follow-up, without predefined timing of evaluation.

We propose to differentiate between *biochemical* and *clinical recurrence*, as not all biochemical recurrences necessitate treatment, whereas clinical recurrences do. We propose to define *biochemical recurrence* as confirmed serum prolactin elevation (>1xULN) in two separate measurements after initial biochemical remission with exclusion of physiological and drug-induced hyperprolactinemia. The second measurement should be an unstressed, cannulated measurement during the early follicular phase of the menstrual cycle if physiological hyperprolactinemia is suspected (see paragraph *1a*). We propose to define *clinical recurrence* as recurrence of prolactinoma-related symptoms that had receded after initial biochemical or clinical disease remission. Routine radiological surveillance is not advised after achievement of remission. In cases with increasing prolactin levels (not yet reaching the upper limit of normal), *radiological recurrence*, i.e.,

reappearance of an adenoma on conventional MRI after initial radiological remission, may provide an additional argument for the presence of active disease. In the absence of increasing prolactin levels, one should consider alternative etiologies such as a non-functioning adenoma or postoperative changes.

III. CLINICALLY RELEVANT OUTCOME SETS

An objective, easily applicable, and clinically relevant outcome set incorporating personalized treatment goals is discussed below.

Treatment goals

Establishing treatment goals prior to treatment initiation is essential to determine relevant outcome parameters, as these may vary throughout the heterogeneous patient population. Patients can grossly be categorized into two main groups according to treatment goals.

The first group concerns patients with non-invasive micro- and macroprolactinoma who generally have been diagnosed due to galactorrhea, or hypogonadal symptoms. Optic chiasm compression may be present in some compressive yet non-invasive macroadenomas. Achieving sustained normoprolactinemia *(i.e., biochemical remission)* is the primary treatment goal, with decompression of the optic chiasm potentially being a second goal. In specific cases in which normoprolactinemia cannot be achieved, for instance due to DA resistance or intolerance and a preference to withhold from surgery, one may opt for hormonal replacement therapy without normoprolactinemia.

The second group consists of patients with larger, invasive, and compressive macro- and giant prolactinomas. Besides hyperprolactinemia-related symptoms, wellbeing is impaired due to mass effects, and DA-free normoprolactinemia is usually not feasible. The primary treatment goal is alleviation of mass-related symptoms through mass reduction, and the second goal is lowering or normalizing prolactin levels, with either natural restoration of gonadal function or gonadal replacement therapy.

Additionally, there is a subgroup of patients treated for subfertility. Although these patients may experience hyperprolactinemic and mass-induced symptoms, an important goal of treatment is conception of a healthy child. This personal goal should be combined with the goals described above.

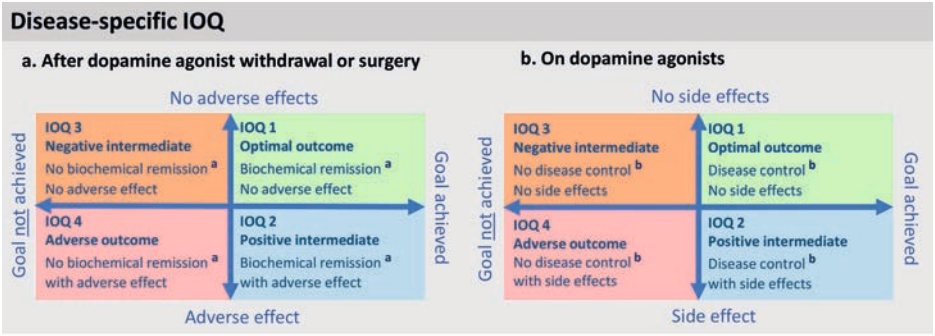
Categorizing treatment outcomes: integrated outcome quadrants (Figure 3)

Integrated outcome quadrants (IOQs) can objectively categorize treatment outcomes into four groups based on achievement of treatment goals and adverse effects. This concept was introduced to evaluate surgical treatment in pituitary adenomas [85] and is also

applicable to medical treatment. IOQs incorporate individualized treatment goals, enabling objective comparison of results between PTCOEs and treatment modalities. The IOQ for biochemical remission is useful after DA withdrawal or surgery aiming for total resection, whereas the IOQ for disease control can be used for patients using DAs. The IOQs evaluating mass effects and fertility are useful for patients with compressive prolactinomas, and patients treated for subfertility, respectively (Suppl. Figure 1 [5]).

To enable holistic outcome evaluations in clinical practice, a patient-centered IOQ may be used next to the disease/symptom-specific IOQs when applicable. This IOQ uses a combination of outcome parameters consistent with the term *clinical remission*: recovery of hypogonadism, resolution of typical prolactinoma symptoms (galactorrhea, loss of libido, subfertility, menstrual cycle abnormality and erectile dysfunction [11]), and no certain lesion on MRI or treatment indication (Suppl. Figure 1 [5]).

Figure 3 Integrated outcome quadrants for evaluating treatment success a) after dopamine agonist withdrawal or surgery, and b) while using dopamine agonists



IOQ integrated outcome quadrant.

[a] Biochemical remission is defined as normalization of serum prolactin (within the upper limit of normal) without use of dopamine agonists.

[b] Disease control is defined as normalization of serum prolactin and resolution of typical prolactinoma-related symptoms (i.e., galactorrhea, loss of libido, subfertility, menstrual cycle disturbances or erectile dysfunction - Pituitary Society consensus statement, 2023) with resolution of compression and without size increase in any dimension for patients with compressive prolactinoma, or with stable or decreased size in patients with non-compressive prolactinoma.

Outcome sets for evaluation of prolactinoma treatment (Figure 4)

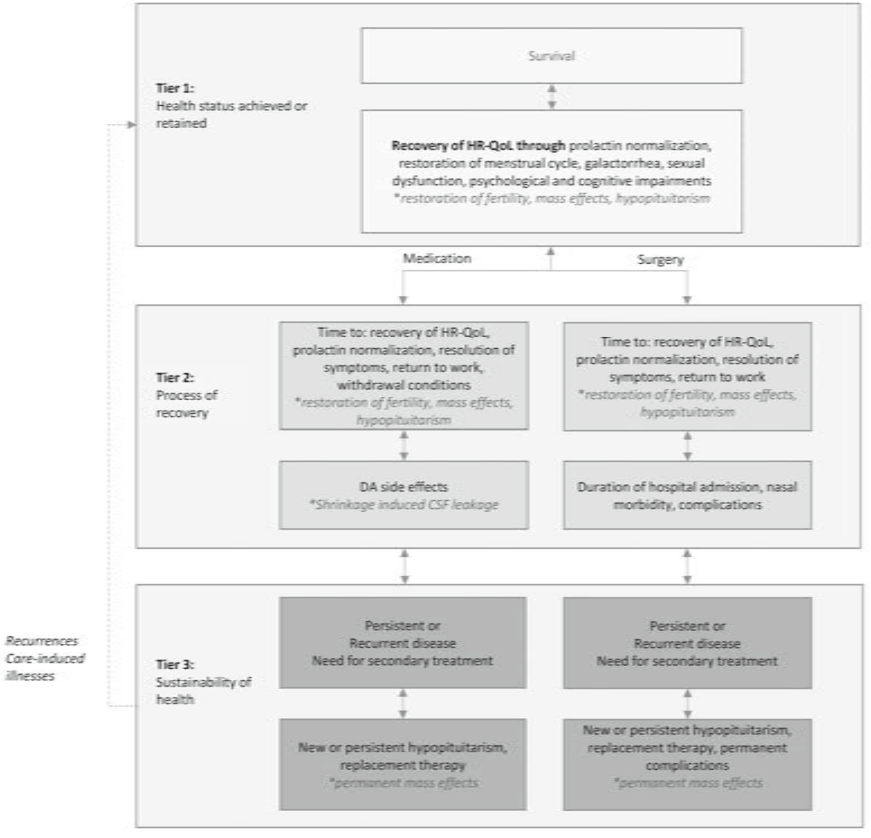
The three-tier hierarchy by Porter et al. offers a comprehensive framework based on the VBHC principles, to report outcomes during three phases of the care cycle, aiming to improve quality of care, enhancing cost-efficacy by focusing on patient-relevant outcomes [4].

The ***first tier*** focusses on the health status achieved or retained, i.e., core outcomes at the endpoint of treatment: HR-QoL (measured using a generic and a disease-specific PROM), the applicable IOQ to evaluate treatment success (Figure 3, Suppl. Figure 1 [5]), and normalization of prolactin levels with restoration of hyperprolactinemia- and hypogonadism-associated symptoms. Optional goals include restoration of mass-related symptoms and fertility. We advise evaluating treatment success after approximately two years for medically treated patients (after potential withdrawal attempts), or one year after surgery to allow restoration to endocrine equilibrium.

The ***second tier*** describes the recovery process, i.e., health changes from baseline to the endpoint of treatment, including the time to: recovery of HR-QoL, prolactin normalization, resolution of symptoms, and sometimes time to return to work. Time to achieve withdrawal conditions and DA side effects should be reported for medically treated patients, and the duration of hospitalization and complications should be reported for surgically treated patients. The second tier starts at initiation of treatment and ends approximately two years after medication initiation, or one-year post-surgery (as described above).

The ***third tier*** describes the sustainability of health, including persistent or recurrent disease and the need for secondary treatment. Relevant factors include an IOQ (long-term disease success), long-term complications, persisting or new hypopituitarism, and need for hormonal replacement. Permanent mass-induced symptoms should be evaluated after treatment of compressive prolactinomas. A suitable time to measure the third tier is approximately 5 years after treatment initiation.

Figure 4 Three tier Value Based Healthcare model for prolactinomas



Outcome set

Tier 1:

Patient-reported: hyperprolactinemia- and hypogonadism related-symptoms, HR-QoL (SF-36, LBNQ-Pituitary)

Clinician-reported: hyperprolactinemia- and hypogonadism related-symptoms

**Pregnancy (outcomes)*

Biochemical: prolactin (xULN), evaluation of hypopituitarism/ hypogonadism

Treatment success: IOQ (outcome depending on treatment goal)

Radiological: adenoma remnant on conventional MRI (size, location)

**Mass-related: visual field, visual acuity, neurological symptoms, headaches*

Tier 2:

Patient-reported: hyperprolactinemia- and hypogonadism related-symptoms, HR-QoL (SF-36, LBNQ-Pituitary)

Clinician-reported: time to resolution of hyperprolactinemia- and hypogonadism-related symptoms, DA side effects, surgical complications

**Pregnancy (outcomes)*

Biochemical: time to normalization of prolactin (xULN), evaluation of hypopituitarism/hypogonadism

Radiological: adenoma remnant on conventional MRI (size, location)

**Mass-related: visual field, visual acuity, neurological symptoms, headaches*

Tier 3:

Patient-reported: hyperprolactinemia- and hypogonadism related-symptoms, HR-QoL (SF-36, LBNQ-Pituitary), DA side effects

Clinician-reported: hyperprolactinemia- and hypogonadism-related symptoms, long-term/permanent complications, replacement therapy, need for secondary treatment

**Pregnancy (outcomes)*

Biochemical: prolactin (xULN), evaluation of hypopituitarism/ hypogonadism

Treatment success: IOQ (outcome depending on treatment goal)

Radiological: adenoma remnant on conventional MRI (size, location)

**Mass-related: visual field, visual acuity, neurological symptoms, headaches*

* when applicable. *CSF* cerebrospinal fluid; *DA* dopamine agonist; *HR-QoL* health-related quality of life; *IOQ*, integrated outcome quadrants; *LBNQ-Pituitary*, Leiden Bothers and Needs Pituitary; *SF-36*, short form-36; *xULN*, times upper limit of normal.

DISCUSSION

Many, mostly subjective, prolactinoma outcome parameters were reported in literature and definitions of clinical outcomes varied across studies. This study evaluates outcome parameters and provides suggestions for clinically relevant objective definitions. Ultimately, a standardized outcome set depending on individual treatment goals is proposed.

Standardization of outcome sets is important to compare outcomes across PTCOEs. Ideal outcome parameters should be objective, easily applicable and clinically relevant. The definitions of *biochemical remission*, *disease control* and *recurrence* as shown in Table 1 adhere to these criteria. Because mild hyperprolactinemia may persist due to physiological processes, co-medication or because prolactin levels may be uninterpretable (e.g., during pregnancy), the authors emphasized the need for a patient-centered definition to describe this group. Although the term *clinical remission* is less objective, and the possibility of a small remnant cannot be excluded, it enables a more realistic categorization of patients with a clinically satisfactory result, albeit not adhering to the strict criteria for biochemical remission. Use of these definitions in research can improve comparability of studies, thereby enhancing knowledge about prolactinoma treatment.

IOQs - integrating treatment goals and adverse effects - categorize treatment outcomes, enabling comparison of outcomes between treatments and PTCOEs irrespective of treatment goals [85]. Setting individualized goals prior to treatment initiation is a prerequisite for use of IOQs. The definitions of remission and disease control as described above can be used within this framework (Figure 3, Suppl. Figure 1 [5]). The holistic, patient-centered IOQ allows a more personalized approach and may support treatment choices.

PROMs were not included in evaluations of treatment success in literature, although optimizing HR-QoL is an important goal of treatment. Intuitively, HR-QoL improves after prolactin normalization and adenoma shrinkage, because hyperprolactinemia-, hypogonadism- and mass-related symptoms should recede, however, little is known about HR-QoL after prolactinoma treatment [86]. A few aspects may prevent researchers from using PROMs. Firstly, interpretation of PROMs is complex, as outcomes are affected by many factors other than the prolactinoma itself (e.g., life events and comorbidity). Secondly, setting general PROM-related goals is difficult because treatment may aim to improve HR-QoL in case of impaired wellbeing caused by prolactinoma symptoms or DA side effects, whereas the aim may be stabilization of HR-QoL in case of a preventive debulking. Moreover, lacking reference values prevent meaningful interpretation of results. Thus, further research is required to determine how to incorporate PROMs in prolactinoma outcome sets.

Comparison of treatment outcomes and sharing experiences and data across PTCOEs is essential to improve prolactinoma care, considering it is a rare disease. The concepts postulated in this study may be used to determine suitable outcome parameters for the creation of an international database. Pituitary specialists should evaluate these outcome parameters to achieve expert consensus on the most important variables for such a database. Future studies should focus on the patient's perspective on treatment success, for instance using interviews. Moreover, the costs of outcome evaluations should be assessed (e.g., by analysis using quality-adjusted life years).

CONCLUSION

Heterogeneity in reported outcome parameters with varying definitions hamper comparison of treatment outcomes in prolactinomas. Using a standardized, objective, easily applicable and clinically relevant outcome set enables comparison of outcomes across treatments and centers**.** This study provides an outcome set based on the VBHC principles, adaptable to various treatment goals. PROMs should be included as one of the core outcomes, yet more research is required to elucidate appropriate strategies to include them in objective treatment goals.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1 Search strategies per electronic database

PubMed
(((“Prolactinoma”[majr] OR “Prolactinoma”[ti] OR “Prolactinomas”[ti] OR “prolactinom*”[ti] OR “Lactotroph*”[ti] OR “PRL-secreting”[ti] OR “PRL secreting”[ti] OR “microprolactinoma”[ti] OR “micro-prolactinoma”[ti] OR “micro prolactinoma”[ti] OR “microprolactin*”[ti] OR “micro-prolactin*”[ti] OR “micro-prolactin*”[ti] OR “Hyperprolactinemia”[Majr] OR “Hyperprolactinemia”[ti] OR “Hyperprolactinaemia”[ti]) AND (“endoscop*”[ti] OR “Endoscopy”[majr:noexp] OR “Neuroendoscopy”[majr] OR “neuroendoscop*”[ti] OR “adenectom*”[ti] OR “transsphenoid*”[ti] OR “trans sphenoid*”[ti] OR “Sphenoid Bone/surgery”[majr] OR “Endonasal*”[ti] OR “Endo-nasal*”[ti] OR “Transnasal Endoscop*”[ti] OR “Surg*”[ti] OR “resect*”[ti] OR “operation*”[ti] OR “operativ*”[ti] OR “microsurg*”[ti] OR “microscop*”[ti] OR “Surgical Procedures, Operative”[majr] OR “Neurosurgical Procedures”[majr:noexp] OR “Neurosurgery”[majr] OR “Brain/surgery”[majr] OR “neurosurg*”[ti] OR “surgery”[subheading] OR “dopamine agonists”[majr] OR “dopamine agonist”[ti] OR “dopamine agonists”[ti] OR “Dopaminergic*”[ti] OR “Cabergoline”[Substance Name] OR “Cabergoline”[ti] OR “Dostinex”[ti] OR “Parlodel”[ti] OR “bromocriptine”[majr] OR “Bromocriptine”[ti] OR “Quinagolide”[ti] OR “quinagolide”[Substance Name] OR “Norprolac”[ti] OR “medical treatment”[ti] OR “medical therapy”[ti] OR “pharmacological treatment”[ti] OR “pharmacological therapy”[ti] OR “Drug Therapy”[majr] OR “drug therapy”[ti] OR “drug treatment”[ti] OR “pharmacother*”[ti]) AND (“Quality of Life”[mesh] OR “Health Surveys”[mesh] OR “Surveys and Questionnaires”[mesh] OR “Self Report”[mesh] OR “Patient Outcome Assessment”[mesh] OR “Health Status Indicators”[mesh] OR “Quality of Life”[tw] OR “QoL”[tw] OR “HRQL”[tw] OR “HRQOL”[tw] OR “PQoL”[tw] OR “AQoL”[tw] OR “subjective wellbeing”[tw] OR “subjective well-being”[tw] OR “Patient Reported Outcome”[tw] OR “Patient Reported Outcomes”[tw] OR “patient reported”[tw] OR “PRO”[tw] OR “PROs”[tw] OR “PROM”[tw] OR “PROMs”[tw] OR “health survey”[tw] OR “health surveys”[tw] OR “Questionnaires”[tw] OR “questionnaire”[tw] OR “Self reports”[tw] OR “Self report”[tw] OR “Self-reported”[tw] OR “Patient Outcome Assessments”[tw] OR “Patient Outcome Assessment”[tw] OR “health status indicator”[tw] OR “health status indicators”[tw] OR “health status indicat*”[tw] OR “outcome instrument”[tw] OR “outcome instruments”[tw] OR “health score”[tw] OR “health scores”[tw] OR “health scor*”[tw] OR “remission induction”[mesh] OR “remission”[tw] OR “cure”[tw] OR “recurrence”[mesh] OR “recurrence”[tw] OR “relapse”[tw] OR “normal prolactin”[tw] OR “normalized prolactin”[tw] OR “normalized prolactin”[tw] OR “Pregnancy”[mesh] OR “pregnancy”[tw] OR “pregnancies”[tw] OR “Galactorrhea”[mesh] OR “galactorrhoea”[tw] OR “menstrual cycle”[mesh] OR “Menstruation Disturbances”[mesh] OR “amenorrhea”[tw] OR “oligomenorrhea”[tw] OR “menstrual”[tw] OR “ovarian”[tw] OR “menstruation”[tw] OR “control”[tw] OR “Erectile dysfunction”[mesh] OR “erectile”[tw] OR “impotence”[tw] OR “Drug-Related Side Effects and Adverse Reactions”[mesh] OR “drug event”[tw] OR “drug events”[tw] OR “side effect”[tw] OR “side-effect”[tw] OR “side effects”[tw] OR “side-effects”[tw] OR “drug reaction”[tw] OR “toxicity”[tw] OR “toxicities”[tw] OR “Costs and Cost Analysis”[mesh] OR “cost”[tw] OR “costs”[tw] OR “pricing”[tw] OR “Quality-Adjusted Life Years”[mesh] OR “Quality-Adjusted Life Years”[tw] OR “QALY”[tw] OR “complications”[Subheading] OR “Postoperative Complications”[mesh] OR “Intraoperative Complications”[mesh] OR “complication”[tw] OR “complications”[tw] OR “Diabetes Insipidus”[mesh] OR “diabetes insipidus”[tw] OR “Meningitis”[mesh] OR “meningitis”[tw] OR “Hypopituitarism”[mesh] OR “hypopituitarism”[tw] OR “hyponatremia”[mesh] OR “hyponatremia”[tw] OR “hyponatraemia”[tw] OR “Visual acuity”[mesh] OR “decreased visual acuity”[tw] OR “Vision, Low”[mesh] OR “loss of vision”[tw] OR “Hemianopsia”[mesh] OR “hemianopsia”[tw] OR “Hemorrhage”[mesh] OR “haemorrhag*”[tw] OR “hemorrhag*”[tw] OR “hematoma*”[tw] OR “haematoma*”[tw] OR “Sinusitis”[mesh] OR “sinusitis”[tw] OR “Hyponatremia”[mesh] OR “hyponatremia”[tw] OR “hyponatraemia”[tw] OR “Cerebrospinal Fluid Leak”[mesh] OR “cerebrospinal fluid leak”[tw] OR “CSF leak”[tw] OR “rhinorrhea*”[tw] OR “Carotid Artery Injuries”[mesh] OR “Carotid Artery Injuries”[tw] OR “Carotid Artery Injury”[tw] OR “carotid injury”[tw] OR “carotid injuries”[tw] OR “Epistaxis”[mesh] OR “epistaxis”[tw] OR “Pneumocephalus”[mesh] OR “pneumocephalus”[tw] OR “Thrombosis”[mesh] OR “thrombosis”[tw] OR “DVT”[tw] OR “Pulmonary Embolism”[mesh] OR “pulmonary embolism”[tw] OR “Blood Transfusion”[mesh] OR “transfusion”[tw] OR “Pneumonia”[mesh] OR “pneumonia”[tw] OR “Respiratory Insufficiency”[mesh] OR “Respiratory Insufficiency”[tw] OR “respiratory failure”[tw] OR “Infections”[mesh] OR “infection*”[tw] OR “Heart Arrest”[mesh] OR “Heart Arrest”[tw] OR “cardiac arrest”[tw] OR “Myocardial Infarction”[mesh] OR “myocardial infarction”[tw] OR “Stroke”[mesh] OR “stroke”[tw] OR “Death”[mesh] OR “death”[tw] OR “outcome”[tw] OR “outcomes”[tw] OR “Pathologic Complete Response”[Mesh] OR “Pathologic Complete Response”[tw] OR “In Full Remission”[tw] OR “In Complete Remission”[tw] OR “Remission Induction”[Mesh] OR “Induction of Remission”[tw] OR “Remission Induction”[tw] OR “Remission, Spontaneous”[Mesh] OR “Spontaneous Remission”[tw] OR “Spontaneous Healing”[tw] OR “remission”[tw] OR “disease remission”[tw] OR “disease control”[tw] OR “control of disease”[tw] OR “effective treatment”[tw] OR “effective treatments”[tw] OR “effective therapy”[tw] OR “effective therapies”[tw] OR “effective

therapeutic"[tw] OR "effective intervention"[tw] OR "effective interventions"[tw] OR "treatment efficacy"[tw] OR "treatments efficacy"[tw] OR "therapy efficacy"[tw] OR "therapies efficacy"[tw] OR "therapeutic efficacy"[tw] OR "intervention efficacy"[tw] OR "interventions efficacy"[tw] OR "normoprolactinemia"[tw] OR "normoprolactinem*"[tw] OR "normoprolactinaemia"[tw] OR "normoprolactinaem*"[tw] OR "disease cure"[tw] OR "cure"[tw] OR "curability"[tw] OR "cures"[tw] OR "cured"[tw])) NOT ("Animals"[mesh] NOT "Humans"[mesh]) NOT (("case reports"[ptyp] OR "case report"[ti]) NOT ("Review"[ptyp] OR "clinical study"[ptyp] OR "case series"[tw])) AND (english[la] OR dutch[la] OR german[la] OR french[la]) AND ("2017/01/01"[PDAT] : "3000/12/31"[PDAT]))

Embase

(((exp *"Prolactinoma"/ OR "Prolactinoma".ti OR "Prolactinomas".ti OR "prolactinom*".ti OR "Lactotroph*".ti OR "PRL-secreting".ti OR "PRL secreting".ti OR "microprolactinoma".ti OR "micro-prolactinoma".ti OR "micro prolactinoma".ti OR "microprolactin*".ti OR "micro-prolactin*".ti OR "micro-prolactin*".ti OR exp *"Hyperprolactinemia"/ OR "Hyperprolactinemia".ti OR "Hyperprolactinaemia".ti) AND ("endoscop*".ti OR *"Endoscopy"/ OR exp *"Neuroendoscopy"/ OR "neuroendoscop*".ti OR "adenectom*".ti OR "trans-sphenoid*".ti OR "transsphenoid*".ti OR "Sphenoid"/su OR "Endonasal*".ti OR "Endo-nasal*".ti OR "Transnasal Endoscop*".ti OR "Surg*".ti OR "resect*".ti OR "operation*".ti OR "operativ*".ti OR "microsurg*".ti OR "microscop*".ti OR exp *"surgery"/ OR exp *"Neurosurgery"/ OR exp *"Brain"/su OR "neurosurg*".ti OR exp *"dopamine receptor stimulating agent"/ OR "dopamine agonist".ti OR "dopamine agonists".ti OR "Dopaminergic*".ti OR exp *"Cabergoline"/ OR "Cabergoline".ti OR "Dostinex".ti OR "Parlodel".ti OR exp *"bromocriptine"/ OR "Bromocriptine".ti OR "Quinagolide".ti OR exp *"quinagolide"/ OR "Norprolac".ti OR "medical treatment".ti OR "medical therapy".ti OR "pharmacological treatment".ti OR "pharmacological therapy".ti OR exp *"Drug Therapy"/ OR "drug therapy".ti OR "drug treatment".ti OR "pharmacother*".ti) AND (exp *"Quality of Life"/ OR exp *"Health Survey"/ OR exp *"Questionnaire"/ OR exp *"Self Report"/ OR exp *"Outcome Assessment"/ OR exp *"Health Status Indicator"/ OR "Quality of Life".ti,ab OR "QoL".ti,ab OR "HRQL".ti,ab OR "HRQOL".ti,ab OR "PQoL".ti,ab OR "AQoL".ti,ab OR "subjective wellbeing".ti,ab OR "subjective well-being".ti,ab OR "Patient Reported Outcome".ti,ab OR "Patient Reported Outcomes".ti,ab OR "patient reported".ti,ab OR "PRO".ti,ab OR "PROs".ti,ab OR "PROM".ti,ab OR "PROMs".ti,ab OR "health survey".ti,ab OR "health surveys".ti,ab OR "Questionnaires".ti,ab OR "questionnaire".ti,ab OR "Self reports".ti,ab OR "Self report".ti,ab OR "Self-reported".ti,ab OR "Patient Outcome Assessments".ti,ab OR "Patient Outcome Assessment".ti,ab OR "health status indicator".ti,ab OR "health status indicators".ti,ab OR "health status indicat*".ti,ab OR "outcome instrument".ti,ab OR "outcome instruments".ti,ab OR "health score".ti,ab OR "health scores".ti,ab OR "health scor*".ti,ab OR exp *"remission"/ OR "remission".ti,ab OR "cure".ti,ab OR exp *"recurrent disease"/ OR "recurrence".ti,ab OR "relapse".ti,ab OR "normal prolactin".ti,ab OR "normalized prolactin".ti,ab OR "normalized prolactin".ti,ab OR exp *"Pregnancy"/ OR "pregnancy".ti,ab OR "pregnancies".ti,ab OR exp *"Galactorrhea"/ OR "galactorrhoea".ti,ab OR exp *"menstrual cycle"/ OR exp *"Menstruation Disorder"/ OR "amenorrhea".ti,ab OR "oligomenorrhea".ti,ab OR "menstrual".ti,ab OR "ovarian".ti,ab OR exp *"menstruation"/ OR "menstruation".ti,ab OR "control".ti,ab OR exp *"Erectile dysfunction"/ OR "erectile".ti,ab OR exp *"impotence"/ OR "impotence".ti,ab OR exp *"adverse outcome"/ OR exp *"adverse event"/ OR exp *"adverse drug reaction"/ OR "drug event".ti,ab OR "drug events".ti,ab OR "side effect".ti,ab OR "side-effect".ti,ab OR "side effects".ti,ab OR "side-effects".ti,ab OR "drug reaction".ti,ab OR "toxicity".ti,ab OR "toxicities".ti,ab OR exp *"health care cost"/ OR "cost".ti,ab OR "costs".ti,ab OR "pricing".ti,ab OR exp *"Quality Adjusted Life Year"/ OR "Quality-Adjusted Life Years".ti,ab OR "QALY".ti,ab OR exp *"complication"/ OR "complication".ti,ab OR "complications".ti,ab OR exp *"Diabetes Insipidus"/ OR "diabetes insipidus".ti,ab OR exp *"Meningitis"/ OR "meningitis".ti,ab OR exp *"Hypopituitarism"/ OR "hypopituitarism".ti,ab OR exp *"hyponatremia"/ OR "hyponatremia".ti,ab OR "hyponatraemia".ti,ab OR exp *"Visual acuity"/ OR "decreased visual acuity".ti,ab OR exp *"Low Vision"/ OR "loss of vision".ti,ab OR exp *"Hemianopia"/ OR "hemianopsia".ti,ab OR exp *"Bleeding"/ OR "haemorrhag*".ti,ab OR "hemorrhag*".ti,ab OR "hematoma*".ti,ab OR "haematoma*".ti,ab OR exp *"Sinusitis"/ OR "sinusitis".ti,ab OR exp *"Hyponatremia"/ OR "hyponatremia".ti,ab OR "hyponatraemia".ti,ab OR exp *"liquorrhea"/ OR "cerebrospinal fluid leak".ti,ab OR "CSF leak".ti,ab OR "rhinorrhea*".ti,ab OR exp *"Carotid Artery Injury"/ OR "Carotid Artery Injuries".ti,ab OR "Carotid Artery Injury".ti,ab OR "carotid injury".ti,ab OR "carotid injuries".ti,ab OR exp *"Epistaxis"/ OR "epistaxis".ti,ab OR exp *"Pneumocephalus"/ OR "pneumocephalus".ti,ab OR exp *"Thrombosis"/ OR "thrombosis".ti,ab OR "DVT".ti,ab OR exp *"Lung Embolism"/ OR "pulmonary embolism".ti,ab OR exp *"Blood Transfusion"/ OR "transfusion".ti,ab OR exp *"Pneumonia"/ OR "pneumonia".ti,ab OR exp *"Respiratory Failure"/ OR "Respiratory Insufficiency".ti,ab OR "respiratory failure".ti,ab OR exp *"Infection"/ OR "infection*".ti,ab OR exp *"Heart Arrest"/ OR "Heart Arrest".ti,ab OR "cardiac arrest".ti,ab OR exp *"Heart Infarction"/ OR "myocardial infarction".ti,ab OR exp *"cerebrovascular accident"/ OR "stroke".ti,ab OR exp *"Death"/ OR "death".ti,ab OR "outcome".ti,ab OR "outcomes".ti,ab OR "Pathologic Complete Response".ti,ab OR "In Full Remission".ti,ab OR "In Complete Remission".ti,ab OR "Induction of Remission".ti,ab OR "Remission Induction".ti,ab OR "Spontaneous Healing".ti,ab OR "disease remission".ti,ab OR exp *"disease control"/ OR "disease control".ti,ab OR "control of disease".ti,ab OR "effective treatment".ti,ab OR "effective treatments".ti,ab OR "effective therapy".ti,ab OR "effective therapies".ti,ab OR "effective therapeutic".ti,ab OR "effective intervention".ti,ab OR "effective interventions".ti,ab OR "treatment efficacy".

ti,ab OR "treatments efficacy".ti,ab OR "therapy efficacy".ti,ab OR "therapies efficacy".ti,ab OR "therapeutic efficacy".ti,ab OR "intervention efficacy".ti,ab OR "interventions efficacy".ti,ab OR "normoprolactinemia".ti,ab OR "normoprolactinem*".ti,ab OR "normoprolactinaemia".ti,ab OR "normoprolactinaem*".ti,ab OR "disease cure".ti,ab OR "cure".ti,ab OR "curability".ti,ab OR "cures".ti,ab OR "cured".ti,ab)) NOT (exp "Animals"/ NOT exp "Humans"/) NOT (("case reports"/ OR "case report".ti OR (case AND (report OR reports)).jw) NOT (exp "Review"/ OR "clinical study"/ OR exp "Clinical Trial"/ OR "case series".ti,ab)) AND (english.la OR dutch.la OR german.la OR french.la) AND 2017:2024.(sa_year))

o NOT (conference review or conference abstract).pt

Web of Science

(((TI=("Prolactinoma" OR "Prolactinoma" OR "Prolactinomas" OR "prolactinom*" OR "Lactotroph*" OR "PRL-secreting" OR "PRL secreting" OR "microprolactinoma" OR "micro-prolactinoma" OR "micro prolactinoma" OR "microprolactin*" OR "micro-prolactin*" OR "micro-prolactin*" OR "Hyperprolactinemia" OR "Hyperprolactinemia" OR "Hyperprolactinaemia") AND (TI=("endoscop*" OR "Endoscopy" OR "Neuroendoscopy" OR "neuroendoscop*" OR "adenectom*" OR "trans-sphenoid*" OR "transsphenoid*" OR "Endonasal*" OR "Endo-nasal*" OR "Transnasal Endoscop*" OR "Surg*" OR "resect*" OR "operation*" OR "operativ*" OR "microsurg*" OR "microscop*" OR "surgery" OR "Neurosurgery" OR "neurosurg*" OR "dopamine receptor stimulating agent" OR "dopamine agonist" OR "dopamine agonists" OR "Dopaminergic*" OR "Cabergoline" OR "Cabergoline" OR "Dostinex" OR "Parlodel" OR "bromocriptine" OR "Bromocriptine" OR "Quinagolide" OR "quinagolide" OR "Norprolac" OR "medical treatment" OR "medical therapy" OR "pharmacological treatment" OR "pharmacological therapy" OR "Drug Therapy" OR "drug therapy" OR "drug treatment" OR "pharmacother*") OR AK=("endoscop*" OR "Endoscopy" OR "Neuroendoscopy" OR "neuroendoscop*" OR "adenectom*" OR "trans-sphenoid*" OR "transsphenoid*" OR "Endonasal*" OR "Endo-nasal*" OR "Transnasal Endoscop*" OR "Surg*" OR "resect*" OR "operation*" OR "operativ*" OR "microsurg*" OR "microscop*" OR "surgery" OR "Neurosurgery" OR "neurosurg*" OR "dopamine receptor stimulating agent" OR "dopamine agonist" OR "dopamine agonists" OR "Dopaminergic*" OR "Cabergoline" OR "Cabergoline" OR "Dostinex" OR "Parlodel" OR "bromocriptine" OR "Bromocriptine" OR "Quinagolide" OR "quinagolide" OR "Norprolac" OR "medical treatment" OR "medical therapy" OR "pharmacological treatment" OR "pharmacological therapy" OR "Drug Therapy" OR "drug therapy" OR "drug treatment" OR "pharmacother*")) AND (TI=("Quality of Life" OR "Health Survey" OR "Questionnaire" OR "Self Report" OR "Outcome Assessment" OR "Health Status Indicator" OR "Quality of Life" OR "QoL" OR "HRQL" OR "HRQOL" OR "PQoL" OR "AQoL" OR "subjective wellbeing" OR "subjective well-being" OR "Patient Reported Outcome" OR "Patient Reported Outcomes" OR "patient reported" OR "PRO" OR "PROs" OR "PROM" OR "PROMs" OR "health survey" OR "health surveys" OR "Questionnaires" OR "questionnaire" OR "Self reports" OR "Self report" OR "Self-reported" OR "Patient Outcome Assessments" OR "Patient Outcome Assessment" OR "health status indicator" OR "health status indicators" OR "health status indicat*" OR "outcome instrument" OR "outcome instruments" OR "health score" OR "health scores" OR "health scor*" OR "remission" OR "remission" OR "cure" OR "recurrent disease" OR "recurrence" OR "relapse" OR "normal prolactin" OR "normalized prolactin" OR "normalized prolactin" OR "Pregnancy" OR "pregnancy" OR "pregnancies" OR "Galactorrhea" OR "galactorrhoea" OR "menstrual cycle" OR "Menstruation Disorder" OR "amenorrhea" OR "oligomenorrhea" OR "menstrual" OR "ovarian" OR "menstruation" OR "menstruation" OR "control" OR "Erectile dysfunction" OR "erectile" OR "impotence" OR "impotence" OR "adverse outcome" OR "adverse event" OR "adverse drug reaction" OR "drug event" OR "drug events" OR "side effect" OR "side-effect" OR "side effects" OR "side-effects" OR "drug reaction" OR "toxicity" OR "toxicities" OR "health care cost" OR "cost" OR "costs" OR "pricing" OR "Quality Adjusted Life Year" OR "Quality-Adjusted Life Years" OR "QALY" OR "complication" OR "complication" OR "complications" OR "Diabetes Insipidus" OR "diabetes insipidus" OR "Meningitis" OR "meningitis" OR "Hypopituitarism" OR "hypopituitarism" OR "hyponatremia" OR "hyponatremia" OR "hyponatraemia" OR "Visual acuity" OR "decreased visual acuity" OR "Low Vision" OR "loss of vision" OR "Hemianopia" OR "hemianopsia" OR "Bleeding" OR "haemorrhag*" OR "hemorrhag*" OR "hematoma*" OR "haematoma*" OR "Sinusitis" OR "sinusitis" OR "Hyponatremia" OR "hyponatremia" OR "hyponatraemia" OR "liquorrhea" OR "cerebrospinal fluid leak" OR "CSF leak" OR "rhinorrhea*" OR "Carotid Artery Injury" OR "Carotid Artery Injuries" OR "Carotid Artery Injury" OR "carotid injury" OR "carotid injuries" OR "Epistaxis" OR "epistaxis" OR "Pneumocephalus" OR "pneumocephalus" OR "Thrombosis" OR "thrombosis" OR "DVT" OR "Lung Embolism" OR "pulmonary embolism" OR "Blood Transfusion" OR "transfusion" OR "Pneumonia" OR "pneumonia" OR "Respiratory Failure" OR "Respiratory Insufficiency" OR "respiratory failure" OR "Infection" OR "infection*" OR "Heart Arrest" OR "Heart Arrest" OR "cardiac arrest" OR "Heart Infarction" OR "myocardial infarction" OR "cerebrovascular accident" OR "stroke" OR "Death" OR "death" OR "outcome" OR "outcomes" OR "Pathologic Complete Response" OR "In Full Remission" OR "In Complete Remission" OR "Induction of Remission" OR "Remission Induction" OR "Spontaneous Healing" OR "disease remission" OR "disease control" OR "disease control" OR "control of disease" OR "effective treatment" OR "effective treatments" OR "effective therapy" OR "effective therapies" OR "effective therapeutic" OR "effective intervention" OR "effective interventions" OR "treatment efficacy" OR "treatments efficacy" OR

"therapy efficacy" OR "therapies efficacy" OR "therapeutic efficacy" OR "intervention efficacy" OR "interventions efficacy" OR "normoprolactinemia" OR "normoprolactinem*" OR "normoprolactinaemia" OR "normoprolactinaem*" OR "disease cure" OR "cure" OR "curability" OR "cures" OR "cured") OR AK=("Quality of Life" OR "Health Survey" OR "Questionnaire" OR "Self Report" OR "Outcome Assessment" OR "Health Status Indicator" OR "Quality of Life" OR "QoL" OR "HRQL" OR "HRQOL" OR "PQoL" OR "AQoL" OR "subjective wellbeing" OR "subjective well-being" OR "Patient Reported Outcome" OR "Patient Reported Outcomes" OR "patient reported" OR "PRO" OR "PROs" OR "PROM" OR "PROMs" OR "health survey" OR "health surveys" OR "Questionnaires" OR "questionnaire" OR "Self reports" OR "Self report" OR "Self-reported" OR "Patient Outcome Assessments" OR "Patient Outcome Assessment" OR "health status indicator" OR "health status indicators" OR "health status indicat*" OR "outcome instrument" OR "outcome instruments" OR "health score" OR "health scores" OR "health scor*" OR "remission" OR "remission" OR "cure" OR "recurrent disease" OR "recurrence" OR "relapse" OR "normal prolactin" OR "normalized prolactin" OR "normalized prolactin" OR "Pregnancy" OR "pregnancy" OR "pregnancies" OR "Galactorrhea" OR "galactorrhoea" OR "menstrual cycle" OR "Menstruation Disorder" OR "amenorrhea" OR "oligomenorrhea" OR "menstrual" OR "ovarian" OR "menstruation" OR "menstruation" OR "control" OR "Erectile dysfunction" OR "erectile" OR "impotence" OR "impotence" OR "adverse outcome" OR "adverse event" OR "adverse drug reaction" OR "drug event" OR "drug events" OR "side effect" OR "side-effect" OR "side effects" OR "side-effects" OR "drug reaction" OR "toxicity" OR "toxicities" OR "health care cost" OR "cost" OR "costs" OR "pricing" OR "Quality Adjusted Life Year" OR "Quality-Adjusted Life Years" OR "QALY" OR "complication" OR "complication" OR "complications" OR "Diabetes Insipidus" OR "diabetes insipidus" OR 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OR "Heart Infarction" OR "myocardial infarction" OR "cerebrovascular accident" OR "stroke" OR "Death" OR "death" OR "outcome" OR "outcomes" OR "Pathologic Complete Response" OR "In Full Remission" OR "In Complete Remission" OR "Induction of Remission" OR "Remission Induction" OR "Spontaneous Healing" OR "disease remission" OR "disease control" OR "disease control" OR "control of disease" OR "effective treatment" OR "effective treatments" OR "effective therapy" OR "effective therapies" OR "effective therapeutic" OR "effective intervention" OR "effective interventions" OR "treatment efficacy" OR "treatments efficacy" OR "therapy efficacy" OR "therapies efficacy" OR "therapeutic efficacy" OR "intervention efficacy" OR "interventions efficacy" OR "normoprolactinemia" OR "normoprolactinem*" OR "normoprolactinaemia" OR "normoprolactinaem*" OR "disease cure" OR "cure" OR "curability" OR "cures" OR "cured") OR AB=("Quality of Life" OR "Health Survey" OR "Questionnaire" OR "Self Report" OR 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OR "oligomenorrhea" OR "menstrual" OR "ovarian" OR "menstruation" OR "menstruation" OR "control" OR "Erectile dysfunction" OR "erectile" OR "impotence" OR "impotence" OR "adverse outcome" OR "adverse event" OR "adverse drug reaction" OR "drug event" OR "drug events" OR "side effect" OR "side-effect" OR "side effects" OR "side-effects" OR "drug reaction" OR "toxicity" OR "toxicities" OR "health care cost" OR "cost" OR "costs" OR "pricing" OR "Quality Adjusted Life Year" OR "Quality-Adjusted Life Years" OR "QALY" OR "complication" OR "complication" OR "complications" OR "Diabetes Insipidus" OR "diabetes insipidus" OR "Meningitis" OR "meningitis" OR "Hypopituitarism" OR "hypopituitarism" OR "hyponatremia" OR "hyponatremia" OR "hyponatraemia" OR "Visual acuity" OR "decreased visual acuity" OR "Low Vision" OR "loss of vision" OR "Hemianopia" OR "hemianopsia" OR "Bleeding" OR "haemorrhag*" OR "hemorrhag*" OR "hematoma*" OR "haematoma*" OR "Sinusitis" OR "sinusitis" OR "Hyponatremia" OR 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"Hyperprolactinemia" OR "Hyperprolactinemia" OR "Hyperprolactinaemia") OR AK=("Prolactinoma" OR "Prolactinoma" OR "Prolactinomas" OR "prolactinom*" OR "Lactotroph*" OR "PRL-secreting" OR "PRL secreting" OR "microprolactinoma" OR "micro-prolactinoma" OR "micro prolactinoma" OR "microprolactin*" OR "micro-prolactin*" OR "micro-prolactin*" OR "Hyperprolactinemia" OR "Hyperprolactinemia" OR "Hyperprolactinaemia")) AND TI=("endoscop*" OR "Endoscopy" OR "Neuroendoscopy" OR "neuroendoscop*" OR "adenectom*" OR "trans-sphenoid*" OR "transsphenoid*" OR "Endonasal*" OR "Endo-nasal*" OR "Transnasal Endoscop*" OR "Surg*" OR "resect*" OR "operation*" OR "operativ*" OR "microsurg*" OR "microscop*" OR "surgery" OR "Neurosurgery" OR "neurosurg*" OR "dopamine receptor stimulating agent" OR "dopamine agonist" OR "dopamine agonists" OR "Dopaminergic*" OR "Cabergoline" OR "Cabergoline" OR "Dostinex" OR "Parlodel" OR "bromocriptine" OR "Bromocriptine" OR "Quinagolide" OR "quinagolide" OR "Norprolac" OR 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Cochrane

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"adenectom*" OR "trans-sphenoid*" OR "transsphenoid*" OR "Endonasal*" OR "Endo-nasal*" OR "Transnasal Endoscop*" OR "Surg*" OR "resect*" OR "operation*" OR "operativ*" OR "microsurg*" OR "microscop*" OR "surgery" OR "Neurosurgery" OR "neurosurg*" OR "dopamine receptor stimulating agent" OR "dopamine agonist" OR "dopamine agonists" OR "Dopaminergic*" OR "Cabergoline" OR "Cabergoline" OR "Dostinex" OR "Parlodel" OR "bromocriptine" OR "Bromocriptine" OR "Quinagolide" OR "quinagolide" OR "Norprolac" OR "medical treatment" OR "medical therapy" OR "pharmacological treatment" OR "pharmacological therapy" OR "Drug Therapy" OR "drug therapy" OR "drug treatment" OR "pharmacother*"):ti AND ("Quality of Life" OR "Health Survey" OR "Questionnaire" OR "Self Report" OR "Outcome Assessment" OR "Health Status Indicator" OR "Quality of Life" OR "QoL" OR "HRQL" OR "HRQOL" OR "PQoL" OR "AQoL" OR "subjective wellbeing" OR "subjective well-being" OR "Patient Reported Outcome" OR "Patient Reported Outcomes" 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"drug event" OR "drug events" OR "side effect" OR "side-effect" OR "side effects" OR "side-effects" OR "drug reaction" OR "toxicity" OR "toxicities" OR "health care cost" OR "cost" OR "costs" OR "pricing" OR "Quality Adjusted Life Year" OR "Quality-Adjusted Life Years" OR "QALY" OR "complication" OR "complication" OR "complications" OR "Diabetes Insipidus" OR "diabetes insipidus" OR "Meningitis" OR "meningitis" OR "Hypopituitarism" OR "hypopituitarism" OR "hyponatremia" OR "hyponatremia" OR "hyponatraemia" OR "Visual acuity" OR "decreased visual acuity" OR "Low Vision" OR "loss of vision" OR "Hemianopia" OR "hemianopsia" OR "Bleeding" OR "haemorrhag*" OR "hemorrhag*" OR "hematoma*" OR "haematoma*" OR "Sinusitis" OR "sinusitis" OR "Hyponatremia" OR "hyponatremia" OR "hyponatraemia" OR "liquorrhea" OR "cerebrospinal fluid leak" OR "CSF leak" OR "rhinorrhea*" OR "Carotid Artery Injury" OR "Carotid Artery Injuries" OR "Carotid Artery Injury" OR "carotid injury" OR "carotid injuries" OR "Epistaxis" OR "epistaxis" OR "Pneumocephalus" OR "pneumocephalus" OR "Thrombosis" OR "thrombosis" OR "DVT" OR "Lung Embolism" OR "pulmonary embolism" OR "Blood Transfusion" OR "transfusion" OR "Pneumonia" OR "pneumonia" OR "Respiratory Failure" OR "Respiratory Insufficiency" OR "respiratory failure" OR "Infection" OR "infection*" OR "Heart Arrest" OR "Heart Arrest" OR "cardiac arrest" OR "Heart Infarction" OR "myocardial infarction" OR "cerebrovascular accident" OR "stroke" OR "Death" OR "death" OR "outcome" OR "outcomes" OR "Pathologic Complete Response" OR "In Full Remission" OR "In Complete Remission" OR "Induction of Remission" OR "Remission Induction" OR "Spontaneous Healing" OR "disease remission" OR "disease control" OR "disease control" OR "control of disease" OR "effective treatment" OR "effective treatments" OR "effective therapy" OR "effective therapies" OR "effective therapeutic" OR "effective intervention" OR "effective interventions" OR "treatment efficacy" OR 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Manusal selection:
LA=(english OR dutch OR german OR french)
PY=(2017 OR 2018 OR 2019 OR 2020 OR 2021 OR 2022 OR 2023 OR 2024))
(conference abstract OR meeting abstract OR conference proceeding OR conference proceedings):pt

Emcare

(((exp *"Prolactinoma"/ OR "Prolactinoma".ti OR "Prolactinomas".ti OR "prolactinom*".ti OR "Lactotroph*".ti OR "PRL-secreting".ti OR "PRL secreting".ti OR "microprolactinoma".ti OR "micro-prolactinoma".ti OR "micro prolactinoma".ti OR "microprolactin*".ti OR "micro-prolactin*".ti OR "micro-prolactin*".ti OR exp

"Hyperprolactinemia"/ OR "Hyperprolactinemia".ti OR "Hyperprolactinaemia".ti) AND ("endoscop".ti OR *"Endoscopy"/ OR exp *"Neuroendoscopy"/ OR "neuroendoscop*".ti OR "adenectom*".ti OR "trans-sphenoid*".ti OR "transsphenoid*".ti OR "Endonasal*".ti OR "Endo-nasal*".ti OR "Transnasal Endoscop*".ti OR "Surg*".ti OR "resect*".ti OR "operation*".ti OR "operativ*".ti OR "microsurg*".ti OR "microscop*".ti OR exp *"surgery"/ OR exp *"Neurosurgery"/ OR "neurosurg*".ti OR exp *"dopamine receptor stimulating agent"/ OR "dopamine agonist".ti OR "dopamine agonists".ti OR "Dopaminergic*".ti OR exp *"Cabergoline"/ OR "Cabergoline".ti OR "Dostinex".ti OR "Parlodel".ti OR exp *"bromocriptine"/ OR "Bromocriptine".ti OR "Quinagolide".ti OR exp *"quinagolide"/ OR "Norprolac".ti OR "medical treatment".ti OR "medical therapy".ti OR "pharmacological treatment".ti OR "pharmacological therapy".ti OR exp *"Drug Therapy"/ OR "drug therapy".ti OR "drug treatment".ti OR "pharmacother*".ti) AND (exp *"Quality of Life"/ OR exp *"Health Survey"/ OR exp *"Questionnaire"/ OR exp *"Self Report"/ OR exp *"Outcome Assessment"/ OR exp *"Health Status Indicator"/ OR "Quality of Life".ti,ab OR "QoL".ti,ab OR "HRQL".ti,ab OR "HRQOL".ti,ab OR "PQoL".ti,ab OR "AQoL".ti,ab OR "subjective wellbeing".ti,ab OR "subjective well-being".ti,ab OR "Patient Reported Outcome".ti,ab OR "Patient Reported Outcomes".ti,ab OR "patient reported".ti,ab OR "PRO".ti,ab OR "PROs".ti,ab OR "PROM".ti,ab OR "PROMs".ti,ab OR "health survey".ti,ab OR "health surveys".ti,ab OR "Questionnaires".ti,ab OR "questionnaire".ti,ab OR "Self reports".ti,ab OR "Self report".ti,ab OR "Self-reported".ti,ab OR "Patient Outcome Assessments".ti,ab OR "Patient Outcome Assessment".ti,ab OR "health status indicator".ti,ab OR "health status indicators".ti,ab OR "health status indicat*".ti,ab OR "outcome instrument".ti,ab OR "outcome instruments".ti,ab OR "health score".ti,ab OR "health scores".ti,ab OR "health scor*".ti,ab OR exp *"remission"/ OR "remission".ti,ab OR "cure".ti,ab OR exp *"recurrent disease"/ OR "recurrence".ti,ab OR "relapse".ti,ab OR "normal prolactin".ti,ab OR "normalized prolactin".ti,ab OR "normalized prolactin".ti,ab OR exp *"Pregnancy"/ OR "pregnancy".ti,ab OR "pregnancies".ti,ab OR exp *"Galactorrhea"/ OR "galactorrhoea".ti,ab OR exp *"menstrual cycle"/ OR exp *"Menstruation Disorder"/ OR "amenorrhea".ti,ab OR "oligomenorrhea".ti,ab OR "menstrual".ti,ab OR "ovarian".ti,ab OR exp *"menstruation"/ OR "menstruation".ti,ab OR "control".ti,ab OR exp *"Erectile dysfunction"/ OR "erectile".ti,ab OR exp *"impotence"/ OR "impotence".ti,ab OR exp *"adverse outcome"/ OR exp *"adverse event"/ OR exp *"adverse drug reaction"/ OR "drug event".ti,ab OR "drug events".ti,ab OR "side effect".ti,ab OR "side-effect".ti,ab OR "side effects".ti,ab OR "side-effects".ti,ab OR "drug reaction".ti,ab OR "toxicity".ti,ab OR "toxicities".ti,ab OR exp *"health care cost"/ OR "cost".ti,ab OR "costs".ti,ab OR "pricing".ti,ab OR exp *"Quality Adjusted Life Year"/ OR "Quality-Adjusted Life Years".ti,ab OR "QALY".ti,ab OR exp *"complication"/ OR "complication".ti,ab OR "complications".ti,ab OR exp *"Diabetes Insipidus"/ OR "diabetes insipidus".ti,ab OR exp *"Meningitis"/ OR "meningitis".ti,ab OR exp *"Hypopituitarism"/ OR "hypopituitarism".ti,ab OR exp *"hyponatremia"/ OR "hyponatremia".ti,ab OR "hyponatraemia".ti,ab OR exp *"Visual acuity"/ OR "decreased visual acuity".ti,ab OR exp *"Low Vision"/ OR "loss of vision".ti,ab OR exp *"Hemianopia"/ OR "hemianopsia".ti,ab OR exp *"Bleeding"/ OR "haemorrhag*".ti,ab OR "hemorrhag*".ti,ab OR "hematoma*".ti,ab OR "haematoma*".ti,ab OR exp *"Sinusitis"/ OR "sinusitis".ti,ab OR exp *"Hyponatremia"/ OR "hyponatremia".ti,ab OR "hyponatraemia".ti,ab OR exp *"liquorrhea"/ OR "cerebrospinal fluid leak".ti,ab OR "CSF leak".ti,ab OR "rhinorrhea*".ti,ab OR exp *"Carotid Artery Injury"/ OR "Carotid Artery Injuries".ti,ab OR "Carotid Artery Injury".ti,ab OR "carotid injury".ti,ab OR "carotid injuries".ti,ab OR exp *"Epistaxis"/ OR "epistaxis".ti,ab OR exp *"Pneumocephalus"/ OR "pneumocephalus".ti,ab OR exp *"Thrombosis"/ OR "thrombosis".ti,ab OR "DVT".ti,ab OR exp *"Lung Embolism"/ OR "pulmonary embolism".ti,ab OR exp *"Blood Transfusion"/ OR "transfusion".ti,ab OR exp *"Pneumonia"/ OR "pneumonia".ti,ab OR exp *"Respiratory Failure"/ OR "Respiratory Insufficiency".ti,ab OR "respiratory failure".ti,ab OR exp *"Infection"/ OR "infection*".ti,ab OR exp *"Heart Arrest"/ OR "Heart Arrest".ti,ab OR "cardiac arrest".ti,ab OR exp *"Heart Infarction"/ OR "myocardial infarction".ti,ab OR exp *"cerebrovascular accident"/ OR "stroke".ti,ab OR exp *"Death"/ OR "death".ti,ab OR "outcome".ti,ab OR "outcomes".ti,ab OR "Pathologic Complete Response".ti,ab OR "In Full Remission".ti,ab OR "In Complete Remission".ti,ab OR "Induction of Remission".ti,ab OR "Remission Induction".ti,ab OR "Spontaneous Healing".ti,ab OR "disease remission".ti,ab OR exp *"disease control"/ OR "disease control".ti,ab OR "control of disease".ti,ab OR "effective treatment".ti,ab OR "effective treatments".ti,ab OR "effective therapy".ti,ab OR "effective therapies".ti,ab OR "effective therapeutic".ti,ab OR "effective intervention".ti,ab OR "effective interventions".ti,ab OR "treatment efficacy".ti,ab OR "treatments efficacy".ti,ab OR "therapy efficacy".ti,ab OR "therapies efficacy".ti,ab OR "therapeutic efficacy".ti,ab OR "intervention efficacy".ti,ab OR "interventions efficacy".ti,ab OR "normoprolactinemia".ti,ab OR "normoprolactinem*".ti,ab OR "normoprolactinaemia".ti,ab OR "normoprolactinaem*".ti,ab OR "disease cure".ti,ab OR "cure".ti,ab OR "curability".ti,ab OR "cures".ti,ab OR "cured".ti,ab)) NOT (exp "Animals"/ NOT exp "Humans"/) NOT (("case reports"/ OR "case report".ti OR (case AND (report OR reports)).jw) NOT (exp "Review"/ OR "clinical study"/ OR exp "Clinical Trial"/ OR "case series".ti,ab)) AND (english.la OR dutch.la OR german.la OR french.la) AND 2017:2024.(sa_year))

PsychINFO

(((TI("Prolactinoma" OR "Prolactinoma" OR "Prolactinomas" OR "prolactinom*" OR "Lactotroph*" OR "PRL-secreting" OR "PRL secreting" OR "microprolactinoma" OR "micro-prolactinoma" OR "micro prolactinoma" OR "microprolactin*" OR "micro-prolactin*" OR "micro-prolactin*" OR "Hyperprolactinemia" OR

"Hyperprolactinemia" OR "Hyperprolactinaemia") OR MJ("Prolactinoma" OR "Prolactinoma" OR "Prolactinomas" OR "prolactinom*" OR "Lactotroph*" OR "PRL-secreting" OR "PRL secreting" OR "microprolactinoma" OR "micro-prolactinoma" OR "micro prolactinoma" OR "microprolactin*" OR "micro-prolactin*" OR "micro-prolactin*" OR "Hyperprolactinemia" OR "Hyperprolactinemia" OR "Hyperprolactinaemia")) AND (TI("endoscop*" OR "Endoscopy" OR "Neuroendoscopy" OR "neuroendoscop*" OR "adenectom*" OR "trans-sphenoid*" OR "trans-sphenoid*" OR "Endonasal*" OR "Endo-nasal*" OR "Transnasal Endoscop*" OR "Surg*" OR "resect*" OR "operation*" OR "operativ*" OR "microsurg*" OR "microscop*" OR "surgery" OR "Neurosurgery" OR "neurosurg*" OR "dopamine receptor stimulating agent" OR "dopamine agonist" OR "dopamine agonists" OR "Dopaminergic*" OR "Cabergoline" OR "Cabergoline" OR "Dostinex" OR "Parlodel" OR "bromocriptine" OR "Bromocriptine" OR "Quinagolide" OR "quinagolide" OR "Norprolac" OR "medical treatment" OR "medical therapy" OR "pharmacological treatment" OR "pharmacological therapy" OR "Drug Therapy" OR "drug therapy" OR "drug treatment" OR "pharmacother*") OR MJ("endoscop*" OR "Endoscopy" OR "Neuroendoscopy" OR "neuroendoscop*" OR "adenectom*" OR "trans-sphenoid*" OR "transsphenoid*" OR "Endonasal*" OR "Endo-nasal*" OR "Transnasal Endoscop*" OR "Surg*" OR "resect*" OR "operation*" OR "operativ*" OR "microsurg*" OR "microscop*" OR "surgery" OR "Neurosurgery" OR "neurosurg*" OR "dopamine receptor stimulating agent" OR "dopamine agonist" OR "dopamine agonists" OR "Dopaminergic*" OR "Cabergoline" OR "Cabergoline" OR "Dostinex" OR "Parlodel" OR "bromocriptine" OR "Bromocriptine" OR "Quinagolide" OR "quinagolide" OR "Norprolac" OR "medical treatment" OR "medical therapy" OR "pharmacological treatment" OR "pharmacological therapy" OR "Drug Therapy" OR "drug therapy" OR "drug treatment" OR "pharmacother*")) AND TX("Quality of Life" OR "Health Survey" OR "Questionnaire" OR "Self Report" OR "Outcome Assessment" OR "Health Status Indicator" OR "Quality of Life" OR "QoL" OR "HRQL" OR "HRQOL" OR "PQoL" OR "AQoL" OR "subjective wellbeing" OR "subjective well-being" OR "Patient Reported Outcome" OR "Patient Reported Outcomes" OR "patient reported" OR "PRO" OR "PROs" OR "PROM" OR "PROMs" OR "health survey" OR "health surveys" OR "Questionnaires" OR "questionnaire" OR "Self reports" OR "Self report" OR "Self-reported" OR "Patient Outcome Assessments" OR "Patient Outcome Assessment" OR "health status indicator" OR "health status indicators" OR "health status indicat*" OR "outcome instrument" OR "outcome instruments" OR "health score" OR "health scores" OR "health scor*" OR "remission" OR "remission" OR "cure" OR "recurrent disease" OR "recurrence" OR "relapse" OR "normal prolactin" OR "normalized prolactin" OR "normalized prolactin" OR "Pregnancy" OR "pregnancy" OR "pregnancies" OR "Galactorrhea" OR "galactorrhoea" OR "menstrual cycle" OR "Menstruation Disorder" OR "amenorrhea" OR "oligomenorrhea" OR "menstrual" OR "ovarian" OR "menstruation" OR "menstruation" OR "control" OR "Erectile dysfunction" OR "erectile" OR "impotence" OR "impotence" OR "adverse outcome" OR "adverse event" OR "adverse drug reaction" OR "drug event" OR "drug events" OR "side effect" OR "side-effect" OR "side effects" OR "side-effects" OR "drug reaction" OR "toxicity" OR "toxicities" OR "health care cost" OR "cost" OR "costs" OR "pricing" OR "Quality Adjusted Life Year" OR "Quality-Adjusted Life Years" OR "QALY" OR "complication" OR "complication" OR "complications" OR "Diabetes Insipidus" OR "diabetes insipidus" OR "Meningitis" OR "meningitis" OR "Hypopituitarism" OR "hypopituitarism" OR "hyponatremia" OR "hyponatremia" OR "hyponatraemia" OR "Visual acuity" OR "decreased visual acuity" OR "Low Vision" OR "loss of vision" OR "Hemianopia" OR "hemianopsia" OR "Bleeding" OR "haemorrhag*" OR "hemorrhag*" OR "hematoma*" OR "haematoma*" OR "Sinusitis" OR "sinusitis" OR "Hyponatremia" OR 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"control of disease" OR "effective treatment" OR "effective treatments" OR "effective therapy" OR "effective therapies" OR "effective therapeutic" OR "effective intervention" OR "effective interventions" OR "treatment efficacy" OR "treatments efficacy" OR "therapy efficacy" OR "therapies efficacy" OR "therapeutic efficacy" OR "intervention efficacy" OR "interventions efficacy" OR "normoprolactinemia" OR "normoprolactinem*" OR "normoprolactinaemia" OR "normoprolactinaem*" OR "disease cure" OR "cure" OR "curability" OR "cures" OR "cured")) NOT TI("veterinary" OR "rabbit" OR "rabbits" OR "animal" OR "animals" OR "mouse" OR "mice" OR "rodent" OR "rodents" OR "rat" OR "rats" OR "pig" OR "pigs" OR "porcine" OR "horse" OR "horses" OR "equine" OR "cow" OR "cows" OR "bovine" OR "goat" OR "goats" OR "sheep" OR "ovine" OR "canine" OR "dog" OR "dogs" OR "feline" OR "cat" OR "cats") NOT (TI"case report" OR MJ"case report"))

Manual selection:
LA=(english OR dutch OR german OR french)
PY=(2017 OR 2018 OR 2019 OR 2020 OR 2021 OR 2022 OR 2023 OR 2024)

Academic Search Premier

(((TI("Prolactinoma" OR "Prolactinoma" OR "Prolactinomas" OR "prolactinom*" OR "Lactotroph*" OR "PRL-secreting" OR "PRL secreting" OR "microprolactinoma" OR "micro-prolactinoma" OR "micro prolactinoma" OR "microprolactin*" OR "micro-prolactin*" OR "micro-prolactin*" OR "Hyperprolactinemia" OR "Hyperprolactinemia" OR "Hyperprolactinaemia") OR KW("Prolactinoma" OR "Prolactinoma" OR "Prolactinomas" OR "prolactinom*" OR "Lactotroph*" OR "PRL-secreting" OR "PRL secreting" OR "microprolactinoma" OR "micro-prolactinoma" OR "micro prolactinoma" OR "microprolactin*" OR "micro-prolactin*" OR "micro-prolactin*" OR "Hyperprolactinemia" OR "Hyperprolactinemia" OR "Hyperprolactinaemia")) AND (TI("endoscop*" OR "Endoscopy" OR "Neuroendoscopy" OR "neuroendoscop*" OR "adenectom*" OR "trans-sphenoid*" OR "transsphenoid*" OR "Endonasal*" OR "Endo-nasal*" OR "Transnasal Endoscop*" OR "Surg*" OR "resect*" OR "operation*" OR "operativ*" OR "microsurg*" OR "microscop*" OR "surgery" OR "Neurosurgery" OR 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"quinagolide" OR "Norprolac" OR "medical treatment" OR "medical therapy" OR "pharmacological treatment" OR "pharmacological therapy" OR "Drug Therapy" OR "drug therapy" OR "drug treatment" OR "pharmacother*")) AND (TI("Quality of Life" OR "Health Survey" OR "Questionnaire" OR "Self Report" OR "Outcome Assessment" OR "Health Status Indicator" OR "Quality of Life" OR "QoL" OR "HRQL" OR "HRQOL" OR "PQoL" OR "AQoL" OR "subjective wellbeing" OR "subjective well-being" OR "Patient Reported Outcome" OR "Patient Reported Outcomes" OR "patient reported" OR "PRO" OR "PROs" OR "PROM" OR "PROMs" OR "health survey" OR "health surveys" OR "Questionnaires" OR "questionnaire" OR "Self reports" OR "Self report" OR "Self-reported" OR "Patient Outcome Assessments" OR "Patient Outcome Assessment" OR "health status indicator" OR "health status indicators" OR "health status indicat*" OR "outcome instrument" OR "outcome instruments" OR "health score" OR "health scores" OR "health scor*" OR "remission" OR 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"QoL" OR "HRQL" OR "HRQOL" OR "PQoL" OR "AQoL" OR "subjective wellbeing" OR "subjective well-being" OR "Patient Reported Outcome" OR "Patient Reported Outcomes" OR "patient reported" OR "PRO" OR "PROs" OR "PROM" OR "PROMs" OR "health survey" OR "health surveys" OR "Questionnaires" OR "questionnaire" OR "Self reports" OR

"Self report" OR "Self-reported" OR "Patient Outcome Assessments" OR "Patient Assessment" OR "health status indicator" OR "health status indicators" OR "health status indicat*" OR "outcome instrument" OR "outcome instruments" OR "health score" OR "health scores" OR "health scor*" OR "remission" OR "remission" OR "cure" OR "recurrent disease" OR "recurrence" OR "relapse" OR "normal prolactin" OR "normalized prolactin" OR "normalized prolactin" OR "Pregnancy" OR "pregnancy" OR "pregnancies" OR "Galactorrhea" OR "galactorrhoea" OR "menstrual cycle" OR "Menstruation Disorder" OR "amenorrhea" OR "oligomenorrhea" OR "menstrual" OR "ovarian" OR "menstruation" OR "menstruation" OR "control" OR "Erectile dysfunction" OR "erectile" OR "impotence" OR "impotence" OR "adverse outcome" OR "adverse event" OR "adverse drug reaction" OR "drug event" OR "drug events" OR "side effect" OR "side-effect" OR "side effects" OR "side-effects" OR "drug reaction" OR "toxicity" OR "toxicities" OR "health care 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OR "intervention efficacy" OR "interventions efficacy" OR "normoprolactinemia" OR "normoprolactinem*" OR "normoprolactinaemia" OR "normoprolactinaem*" OR "disease cure" OR "cure" OR "curability" OR "cures" OR "cured") OR KW("Quality of Life" OR "Health Survey" OR "Questionnaire" OR "Self Report" OR "Outcome Assessment" OR "Health Status Indicator" OR "Quality of Life" OR "QoL" OR "HRQL" OR "HRQOL" OR "PQoL" OR "AQoL" OR "subjective wellbeing" OR "subjective well-being" OR "Patient Reported Outcome" OR "Patient Reported Outcomes" OR "patient reported" OR "PRO" OR "PROs" OR "PROM" OR "PROMs" OR "health survey" OR "health surveys" OR "Questionnaires" OR "questionnaire" OR "Self reports" OR "Self report" OR "Self-reported" OR "Patient Outcome Assessments" OR "Patient Outcome Assessment" OR "health status indicator" OR "health status indicators" OR "health status indicat*" OR "outcome instrument" OR "outcome instruments" OR "health score" OR "health scores" OR "health scor*" OR "remission" OR "remission" OR "cure" OR "recurrent disease" OR "recurrence" OR "relapse" OR "normal prolactin" OR "normalized prolactin" OR "normalized prolactin" OR "Pregnancy" OR "pregnancy" OR "pregnancies" OR "Galactorrhea" OR "galactorrhoea" OR "menstrual cycle" OR "Menstruation Disorder" OR "amenorrhea" OR "oligomenorrhea" OR "menstrual" OR "ovarian" OR "menstruation" OR "menstruation" OR "control" OR "Erectile dysfunction" OR "erectile" OR "impotence" OR "impotence" OR "adverse outcome" OR "adverse event" OR "adverse drug reaction" OR "drug event" OR "drug events" OR "side effect" OR "side-effect" OR "side effects" OR "side-effects" OR "drug reaction" OR "toxicity" OR "toxicities" OR "health care cost" OR "cost" OR "costs" OR "pricing" OR "Quality Adjusted Life Year" OR "Quality-Adjusted Life Years" OR "QALY" OR "complication" OR "complication" OR "complications" OR "Diabetes Insipidus" OR "diabetes insipidus" OR "Meningitis" OR "meningitis" OR "Hypopituitarism" OR "hypopituitarism" OR "hyponatremia" OR "hyponatremia" OR "hyponatraemia" OR "Visual acuity" OR "decreased visual acuity" OR "Low Vision" OR "loss of vision" OR "Hemianopia" OR "hemianopsia" OR "Bleeding" OR "haemorrhag*" OR "hemorrhag*" OR "hematoma*" OR "haematoma*" OR "Sinusitis" OR "sinusitis" OR "Hyponatremia" OR "hyponatremia" OR "hyponatraemia" OR "liquorrhea" OR "cerebrospinal fluid leak" OR "CSF leak" OR "rhinorrhea*" OR "Carotid Artery Injury" OR "Carotid Artery Injuries" OR "Carotid Artery Injury" OR "carotid injury" OR "carotid injuries" OR "Epistaxis" OR "epistaxis" OR "Pneumocephalus" OR "pneumocephalus" OR "Thrombosis" OR "thrombosis" OR "DVT" OR "Lung Embolism" OR "pulmonary embolism" OR "Blood Transfusion" OR "transfusion" OR "Pneumonia" OR "pneumonia" OR "Respiratory Failure" OR "Respiratory Insufficiency" OR "respiratory failure" OR "Infection" OR "infection*" OR "Heart Arrest" OR "Heart Arrest" OR "cardiac arrest" OR "Heart Infarction" OR "myocardial infarction" OR "cerebrovascular accident" OR "stroke" OR "Death" OR "death" OR "outcome" OR "outcomes" OR "Pathologic Complete Response" OR "In Full Remission" OR "In Complete Remission" OR "Induction of Remission" OR "Remission Induction" OR "Spontaneous Healing" OR "disease remission" OR "disease control" OR "disease control" OR "control of disease" OR "effective treatment" OR "effective treatments" OR "effective therapy" OR "effective therapies" OR "effective therapeutic" OR "effective intervention" OR "effective interventions" OR "treatment efficacy" OR "treatments efficacy" OR "therapy efficacy" OR "therapies efficacy" OR "therapeutic efficacy" OR "intervention efficacy" OR "interventions efficacy" OR "normoprolactinemia" OR "normoprolactinem*" OR "normoprolactinaemia" OR "normoprolactinaem*" OR "disease cure" OR "cure" OR "curability" OR "cures" OR "cured"))) NOT TI("veterinary" OR "rabbit" OR "rabbits" OR "animal" OR "animals" OR "mouse" OR "mice" OR "rodent" OR "rodents" OR "rat" OR "rats" OR "pig" OR "pigs" OR "porcine" OR "horse" OR "horses" OR "equine" OR "cow" OR "cows" OR "bovine" OR "goat" OR "goats" OR "sheep" OR "ovine" OR "canine" OR "dog" OR "dogs" OR "feline" OR "cat" OR "cats") NOT (TI"case report" OR MJ"case report"))

Manual selection:
LA=(english OR dutch OR german OR french)
PY=(2017 OR 2018 OR 2019 OR 2020 OR 2021 OR 2022 OR 2023 OR 2024)

Supplementary Table 2 Definitions of variables for which data were extracted

Variable	Explanation if necessary
Study characteristics	
First author	
Publication year	
Study design	Cohort / randomized controlled trial / cross-sectional. For cohort studies and cross-sectional studies consecutive patient inclusion was reported when performed
Prospective or retrospective	
Duration of follow-up in months (mean ± SD)	
Definitions	
Criteria for withdrawal	As reported
Disease control	As reported
Successful withdrawal	As reported
Recurrence	As reported
Remission	As reported
Outcome parameters describing treatment success	
Radiological parameters	Outcome parameters based on MRI of the pituitary
Biochemical parameters	Outcome parameters based on laboratory measurements, i.e., related to pituitary hormones
Clinician-reported symptoms and visual measurements	Outcome parameters based on the physician's interpretation of clinical findings. Visual field defects, visual acuity and anthropometric parameters were also reported here
Moment of measurement	Moment of measurement of the radiological, biochemical and clinical parameters as reported by the study (either days/months/years after initiation of the study for parameters concerning medical treatment, or since surgery for studies reporting on surgical treatment)

Supplementary Table 3a Outcome parameters per study for studies reporting on medical treatment only

Study characteristics					Outcomes describing treatment response			
					Definitions			
First author (publication year)	**Study design**	**Pro/retro**	**Duration of follow-up in months (mean ± SD)**	**Criteria for withdrawal**	**Disease control**	**Successful withdrawal**	**Recurrence**	**Remission**
Studies reporting on treatment outcomes on DA (without withdrawal)								
Kabootari [1] (2023)	Cohort	NR	6	NR	NR	NR	NR	NR
Elazime [2] (2022)	Cohort	Retro	Micro: 42 Macro: 52	NR	NR	NR	NR	NR
Irfan [3] (2022)	Cohort	Retro	Median 40 (range: 12-288)	NR	NR	NR	NR	NR
Hage [4] (2022)	Cohort	Retro	Median 7 [IQR 3-14]	NR	NR	NR	NR	NR
Sheikh [5] (2022)	Cohort	Pro	24	NR	NR	NR	NR	NR
Kim 1 [6] (2021)	Cohort	Retro	NR	NR	NR	NR	NR	NR
Akkus [7] (2020)	Cohort	Retro	127 ± 84	NR	NR	NR	NR	DA treated for ≥ 2 years, with normal PRL, no lesion on MRI
Almalki [8] (2020)	Cohort	Retro	756 (range 24-156)	NR	NR	NR	NR	PRL ≤ 25ug/L or >50% reduction from baseline at 12 months

	Outcome variables			
	Radiological parameters	**Biochemical parameters**	**Clinician-reported findings and visual measurements**	**Moment of measurement**
	NR	PRL normalization (n(%)), PRL (ng/ml), Hypogonadism (n(%)),	Anthropometric data	3, 6 months
	Tumor size stabilization (n(%)), tumor size regression (n(%)), disappearance of adenoma (n(%)), tumor aggravation (n(%))	PRL normalization (n (%)), Time to PRL normalization (months)	Symptoms[a]	During follow-up
	Radiologic response: ≥50% reduction in tumor size. Absolute tumor size	PRL (ng/mL)	**Clinical response:** improvement or resolution of clinical features / visual disturbances with DA	3, 6, 12, 18, 24 months
	Change in maximal tumor diameter (%)	PRL normalization (n(%)), PRL (ng/mL), Prolactin drop per month (%)	NR	2 months, during follow-up
	Total disappearance on MRI (n(%)), tumor volume reduction (n(%)), PRL reduction (%), >50% tumor reduction (n(%)), ≥75% tumor volume reduction (n(%))	≥75% PRL decrease (n(%))	NR	4-8-12-18-24 months
	Combined response: >50% volume reduction on MRI + PRL normalization.			
	Radiologic responder: ≥50% tumor volume reduction (%). Max. tumor diameter (mm), tumor volume (cm^3), tumor volume reduction at last follow-up.	**Biochemical responder:** PRL normalization. Time to PRL normalization (months), pituitary hormone replacement (n(%)), hypopituitarism recovery (n(%))	NR	Last follow-up
	Responder: PRL normalization + ≥50%.			
	No visible tumor (n(%)), tumor diameter (mm)	PRL (ng/mL)	NR	NR
	Radiologic response: no visible lesion or >50% reduction from baseline. Complete tumor disappearance (n(%)), tumor diameter (cm), tumor diameter change (%), tumor volume (cm^3)	PRL (ng/mL), PRL change (%), testosterone normalization (n(%)), hypopituitarism (n(%)), need for additional treatment (surgery, RT) (n(%))	Menstrual cycle, galactorrhea, sexual function, visual field	During follow-up

Supplementary Table 3a Outcome parameters per study for studies reporting on medical treatment only *(continued)*

Study characteristics					Outcomes describing treatment response			
					Definitions			
First author (publication year)	**Study design**	**Pro/retro**	**Duration of follow-up in months (mean ± SD)**	**Criteria for withdrawal**	**Disease control**	**Successful withdrawal**	**Recurrence**	**Remission**
Espinosa-Cárdenas [9] (2020)	Cohort (consecutive)	Retro	Median 20 [IQR 11–34]	PRL normalization, ≥50% tumor size reduction	NR	Normal PRL, no tumor regrowth	HyperPRL, regrowth of adenoma or reappearance of symptoms (F: galactorrhea or menstrual abnormalities, M: sexual dysfunction)	NR
Vermeulen [10] (2020)	Cohort	Retro	>12	NR	NR	NR	NR	NR
Akinduro [11] (2019)	Cohort (consecutive)	Retro	NR	NR	NR	NR	NR	NR
Burlacu [12] (2019)	Cohort	Retro	12 ± 3	NR	NR	NR	NR	NR
Watanabe [13] (2017)	Cohort (consecutive)	Retro	Median 54.3 (range 5.3-137.2)	DA treatment > 5 years	NR	NR	NR	No recurrence for >12 months after CAB withdrawal
Dogansen [14] (2016)	Cohort (consecutive)	Retro	108.8 ± 55.1	DA treatment > 2 years, normal PRL, tumor size <50%	NR	NR	PRL increase > ULN after DA withdrawal	NR
Bueno [15] (2016)	Cross-sectional	Retro	NR	NR	NR	NR	NR	NR
Almalki [16] (2015)	Cohort (consecutive)	Retro	Male: 27.3 ± 6.1 Female: 26.3 ± 9.6	NR	NR	NR	NR	NR

	Outcome variables			
	Radiological parameters	**Biochemical parameters**	**Clinician-reported findings and visual measurements**	**Moment of measurement**
	Tumor reduction (%), visible tumor remnant (%)	PRL reduction (%), time to recurrence (months), need to resume CAB (n(%))	Visual field, menstrual cycle, galactorrhea	Within follow-up
	Radiologic response: ≥50% tumor shrinkage in coronal surface under DA. Tumor volume (cm^3)	PRL decrease (%), time to PRL normalization (months)	NR	3 – 4 months, during follow-up
	Responsive: PRL normalization + ≥50% tumor shrinkage of coronal surface under DA			
	NR	PRL (ng/mL), PRL decrease rate (ng/mL/month), need for additional treatment (RT, surgery) (n(%))	NR	6, 12, 18, 24, subsequent 12 month intervals
	NR	**Early prolactin response:** PRL normalization after ≤3 months DA treatment. PRL normalization (n(%)), need for surgery (n(%))	NR	1 year
	Good response: PRL normalization and >50% reduction of largest tumor coronal surface after 1 year DA treatment.			
	Tumor disappearance (n(%)), change in tumor size (n(%))	PRL normalization (n(%)), time to PRL normalization (months), need for surgery (n(%))	Recovery of gonadal function, time to recovery of menstrual cycle (months)	During follow-up
	Residual tumor diameter (mm), tumor shrinkage (%), tumor disappearance, max. tumor shrinkage (%)	(Nadir) PRL (ng/mL), reduction in PRL (%), recurrence (n(%)), time to recurrence (months)	Galactorrhea, oligo-amenorrhea impotence, decreased libido	Before DA withdrawal, at recurrence, within follow-up
	NR	**Responder:** PRL normalization on CAB ≤ 3.0 mg/week. **Non-responder:** no PRL normalization on CAB ≤ 3.0 mg/week.	NR	NA
	Tumor size (cm^3), decrease in tumor volume (cm^3 and %)	PRL normalization (n(%)), PRL reduction (%), PRL decrease (n(%)), need for additional treatment (surgery) (n(%))	visual field defects, sexual function	6 months, last follow-up

Supplementary Table 3a Outcome parameters per study for studies reporting on medical treatment only *(continued)*

Study characteristics					Outcomes describing treatment response			
					Definitions			
First author (publication year)	**Study design**	**Pro/retro**	**Duration of follow-up in months (mean ± SD)**	**Criteria for withdrawal**	**Disease control**	**Successful withdrawal**	**Recurrence**	**Remission**
Andrysiak Mamos [17] (2015)	Cohort (consecutive)	NR	12	NR	NR	NR	NR	NR
Auriemma [18] (2015)	Cohort (consecutive)	Pro	24	NR	NR	NR	NR	NR
Kurosaki [19] (2015)	Cohort	NR	Range: 26–93	NR	NR	NR	NR	NR
Pala [20] (2015)	Cohort (consecutive)	Pro	6	NR	NR	NR	NR	NR
Vilar [21] (2015)	Cohort (consecutive)	Pro	Median 12 (range: 3-26)	NR	NR	NR	PRL > ULN for gender	NR
Bancos [22] (2014)	NA	Cross-sectional	NA	NR	NR	NR	NR	NR
Shimon [23] (2014)	Cohort (consecutive)	Retro	76.8	NR	NR	NR	NR	NR
Cho [24] (2014)	Cohort	NR	Median 30 (range: 6-99)	NR	NR	NR	NR	**Biochemical**: PRL<30ng/mL (i.e., F: 1.0xULN for, M: 1.7xULN)
Ciresi [25] (2013)	Cohort (consecutive)	Retro	12	NR	NR	PRL normalization for gender on CAB	NR	NR
Hajder [26] (2013)	Cohort	Pro	24	NR	NR	NR	NR	NR
Karavitaki [27] (2013)	Cohort (consecutive)	Pro	Minimal 36	NR	NR	NR	NR	NR
Rastogi [28] (2013)	RCT	Pro	16±6	NR	NR	NR	NR	NR

	Outcome variables			
	Radiological parameters	**Biochemical parameters**	**Clinician-reported findings and visual measurements**	**Moment of measurement**
	Max. controlled tumor size (mm)	PRL normalization (n(%)), PRL (ng/mL) time to PRL normalization (months), pituitary axes (mIU/L, ng/dL, pg/mL)	Headache, visual acuity improvement, libido, erectile disfunction	1, 3, 6, 12 months
	Decrease in tumor size (%)	PRL normalization (n(%)), PRL (ng/mL), multiple metabolic parameters	Asthenia, libido reduction, erectile disfunction, anthropometric parameters	12, 24 months
	Reduction of tumor size >80% (n(%)), signal intensity (low/iso/high) (n(%)), time to low signal intensity area appearance (months)	PRL normalization (n(%)), time to PRL normalization (months), need for additional treatment (surgery) (n(%))	NR	Within follow-up
	NR	PRL normalization (n(%)), time to PRL normalization (months), PRL decrease (ug/L), pituitary axes (IU/L, pg/mL, nmol/L), multiple metabolic parameters	Anthropometric parameters	3, 6 months
	Tumor enlargement at recurrence (n(%))	PRL (ng/mL), recurrence (n(%)), time to recurrence (months)	Amenorrhea, galactorrhea	At recurrence, at end of follow-up
	NR	Tumor size (mm), hypopituitarism (n(%))	NR	NA
	Tumor disappearance (n(%)), tumor shrinkage (n(%)), tumor size (mm)	PRL normalization (n(%)), PRL (ng/mL), time to PRL normalization (months), PRL decrease (ng/mL), hypogonadism (n(%)), need for additional treatment (surgery) (n(%))	Visual acuity, diplopia	At follow-up
	Decrease in tumor size (n(%), %), residual mass (%)	PRL normalization (%), PRL (ng/mL), time to PRL normalization (months), need for additional treatment (surgery) (n(%))	Visual symptoms, diplopia, headache	3, 6 months, end of follow-up
	Tumor volume (mm^3)	PRL (mU/L), multiple metabolic parameters	Anthropometric data	12 months
	Decrease of max. tumor diameter (%)	PRL normalization (n(%)), gonadotropins (IU/L)	NR	24 months
	Decrease in max. tumor diameter (%)	PRL normalization (n(%)), time to PRL normalization (months), hypopituitarism (n(%))	NR	Within follow-up
	Tumor shrinkage (%), tumor shrinkage ≥50% (n(%))	PRL normalization (n(%)), PRL (ug/L), time to composite endpoint (weeks)	Visual field	End of follow-up
	composite outcome: PRL normalization, tumor shrinkage ≥50% from baseline, at end of follow-up			

Supplementary Table 3a Outcome parameters per study for studies reporting on medical treatment only *(continued)*

Study characteristics					Outcomes describing treatment response			
					Definitions			
First author (publication year)	**Study design**	**Pro/retro**	**Duration of follow-up in months (mean ± SD)**	**Criteria for withdrawal**	**Disease control**	**Successful withdrawal**	**Recurrence**	**Remission**
Anagnostis [29] (2012)	Cohort	Retro	84.7 ± 9.2	Normal PRL for 1 year on lowest dose, tumor shrinkage	NR	NR	NR	PRL normalization and stable tumor size after drug cessation
Athanasoulia [30] (2012)	NA	Cross-sectional	NA	NR	NR	NR	NR	NR
Yang [31] (2011)	Cohort	NR	44.1 (range: 7-144)	NR	NR	NR	NR	NR
Bhansali [32] (2010)	Cohort (consecutive)	Pro	6	NR	NR	NR	NR	NR
Rae-Cho [33] (2009)	Cohort (consecutive)	Retro	19 (range: 9-43)	NR	NR	NR	NR	NR
Delgrange [34] (2009)	Cohort (consecutive)	Retro	NR	NR	NR	NR	NR	NR
Vallette [35] (2009)	Consecutive	Cross-sectional	NA	NR	NR	NR	NR	NR
Ono [36] (2008)	Cohort (consecutive)	Pro	12	NR	NR	NR	NR	NR
Vilar [37] (2008)	Cohort (consecutive)	Retro	NR	NR	NR	NR	NR	NR
Wu [38] (2008)	Cohort (consecutive)	Retro	60.3 ± 20.8	NR	NR	NR	NR	NR
Delgrange [39] (2006)	Cohort (consecutive)	Retro	Range: 12-156	NR	NR	NR	NR	NR
De Rosa [40] (2006)	Cohort (consecutive)	Pro	24	NR	NR	NR	NR	NR

	Outcome variables			
	Radiological parameters	**Biochemical parameters**	**Clinician-reported findings and visual measurements**	**Moment of measurement**
	Disappearance of tumor (n(%)), tumor diameter (cm), decrease in adenoma size (n(%)), tumor regrowth after DA withdrawal (n(%))	PRL normalization (n(%)), PRL (ng/mL)	Menstrual cycle	prior to DA withdrawal, within follow-up
	NR	PRL normalization (n(%))	Libido, mood, fatigue	NA
	Total volume reduction >25% (n(%)), total volume reduction <25% (n(%)), total volume reduction (%)	PRL reduction (%), need for additional treatment (RT, surgery) (n(%)),	visual symptoms, ptosis, sexual disfunction, menstrual cycle	1 week, 3 months, within follow-up
	Tumor size reduction (cm^3 and %)	PRL normalization (%), PRL (ug/L), gonadotrophins (iu/L)	Headache, visual field, visual acuity, erectile dysfunction, libido, galactorrhea gynecomastia, decreased shaving frequency, infertility, arrested puberty	1, 2, 6 months
	Tumor size decrease (%)	PRL normalization (n(%)), PRL reduction (%), PRL <20ng/mL (n(%)), PRL decrease (%), improvement of testosterone level (n(%))	Visual field	3, 9, 12 months, last follow-up
	Significant tumor shrinkage: >30% decrease in craniocaudal diameter (n(%)), residual tumor ≤5 mm (n(%))	PRL normalization (n(%)), time to PRL normalization (months), CAB dose required for PRL normalization (mg/week)	NR	1 year, within follow-up
	NR	PRL normalization (n(%)), PRL (ug/L), PRL reduction (%)	NR	NA
	NR	PRL normalization (cumulative percentage), PRL (ug/L and %), restoration of gonadotrophins (n(%))	Menstrual cycle, galactorrhea, visual function	1, 3, 6, 9, 12 months
	Significant tumor shrinkage: >50% reduction of pretreatment tumor volume (n(%)). Tumor disappearance (n(%))	PRL normalization (n(%)), restoration of hypogonadism (n(%))	Galactorrhea, menstrual cycle	During follow-up
	Tumor disappearance (n(%)), tumor residual (n(%)), empty sella (n(%))	PRL normalization (n(%)), recurrence after DA withdrawal (n(%)), panhypopituitarism (n(%)), need for additional treatment (RT) (n(%))	Visual symptoms	During follow-up, at last follow-up
	Significant tumor shrinkage: tumor shrinkage >30% craniocaudally or >50% coronally (n(%))	Long-term[a] PRL normalization (n(%))	NR	≤ 3 months, last follow-up
	NR	PRL normalization (n(%)), PRL (mU/L), testosterone (nmol/L), semen quality parameters	NR	6, 12, 24 months

Supplementary Table 3a Outcome parameters per study for studies reporting on medical treatment only *(continued)*

Study characteristics					Outcomes describing treatment response			
					Definitions			
First author (publication year)	**Study design**	**Pro/retro**	**Duration of follow-up in months (mean ± SD)**	**Criteria for withdrawal**	**Disease control**	**Successful withdrawal**	**Recurrence**	**Remission**
Chattopadhyay [41] (2005)	Cohort (consecutive)	Pro	30.7 ± 14.4	NR	NR	NR	NR	NR
De Rosa [42] (2004)	Cohort (consecutive)	NR	6	NR	NR	NR	Nr	NR
Colao [43] (2003)	Cohort (consecutive)	Pro	6	Normal PRL >1 year and tumor size <50%	NR	NR	NR	NR
Corsello [44] (2003)	Cohort (consecutive)	Pro	38.9 (range: 13-68)	NR	NR	NR	NR	NR
Di Sarno [45] (2001)	Cohort (consecutive)	Retro	24	NR	NR	NR	NR	NR
Pontikides [47] (2000)	Cohort (consecutive)	Pro	3	NR	NR	NR	NR	NR
Schultz [48] (2000)	Cohort	NR	31.6 (range: 2-72)	NR	NR	NR	NR	NR
Cannavo [49] (1999)	Cohort (consecutive)	Retro	NR	NR	NR	NR	NR	NR
Delgrange [50] (1996)	Cohort (consecutive)	NR	Range: 1-34	NR	NR	NR	NR	NR
Morange [51] (1996)	Cohort (consecutive)	NR	36	NR	NR	NR	NR	NR

	Outcome variables			
	Radiological parameters	**Biochemical parameters**	**Clinician-reported findings and visual measurements**	**Moment of measurement**
	Tumor disappearance (n(%)), max. tumor diameter (mm), tumor size (cm^3), tumor shrinkage >50%/74.8%/95% (n(%)), cystic degeneration (n(%))	PRL (ng/mL), testosterone (ug/L), improvement of pituitary- and gonadal function n(%))	Visual field	During follow-up, last follow-up
	NR	PRL normalization (n(%)), LH (IU/L), FSH (IU/L), testosterone (IU/L)	Nocturnal penile tumescence (events/ night)	6 months
	Tumor disappearance (n(%)), tumor size reduction (%), notable tumor shrinkage[a] (n(%)), tumor size increase (n(%))	PRL normalization (n(%)), PRL (ug/L), PRL decrease (%)	Menstrual cycle, libido	6 months
	Significant tumor size reduction: >25% volume reduction. Decrease in tumor size (cm^3), tumor volume (cm^3), empty sella (n(%))	PRL normalization (n(%)), PRL decrease (%, ug/L), time PRL normalization (months), hypopituitarism (n(%)), normalization of testosterone (n(%)), sperm quality improvement (n(%))	Visual field, libido, sexual potency, headache, galactorrhea	3, 6, 12 months, during follow-up
	Nadir tumor diameter (mm), max. tumor diameter decrease (%), tumor disappearance (n(%))	PRL normalization (n(%)), nadir PRL (ug/L), dose to achieve PRL normalization (mg/week), PRL decrease (%), recovery of gonadal function (n(%))	Galactorrhea, visual field, sexual function	6, 24 months
	Tumor volume (mm^3), tumor size (mm), tumor volume decrease (n(%))	PRL normalization (n(%) and uU/ mL)	Symptoms[a], visual field	3 months
	Tumor disappearance (n(%)), time to tumor shrinkage (months), tumor size increase (n(%))	PRL normalization (n(%)), persistent normal PRL (n(%)), PRL>ULN (n(%)), PRL higher/ lower/ unchanged compared to baseline (n(%))	NR	Within follow-up, 6 weeks post DA withdrawal
	Tumor disappearance (n(%)), tumor size (mm), increase/ decrease in tumor size (n(%))	PRL normalization (n(%)), persistent normoPRL (n(%)), PRL (ug/L), PRL decrease (n(%)), PRL increase in normal range (n(%)), effective CAB dose (mg/week), need for additional treatment (surgery) (n(%))	Gonadal status, menstrual cycle, pregnancy (outcome), libido, sexual function (n(%))	During follow-up, 1 year after withdrawal
	Tumor shrinkage (%)	PRL normalization (n(%)), PRL reduction (n(%))	Galactorrhea, menstrual cycle, headaches, visual field, pregnancy	Within follow-up
	partial anti-tumoral effect[a] (n(%)), significant tumor shrinkage[a] (n(%)), tumor growth (n(%))	PRL normalization (n(%)), PRL (ug/L), Hypogonadism (n(%)), testosterone level improvement (n(%))	Amenorrhea, ovulatory menstrual cycle, sexual function, headaches, pregnancy (outcome) (n(%))	3-6 months, 2, 3 years

Supplementary Table 3a Outcome parameters per study for studies reporting on medical treatment only *(continued)*

Study characteristics					Outcomes describing treatment response			
					Definitions			
First author (publication year)	**Study design**	**Pro/retro**	**Duration of follow-up in months (mean ± SD)**	**Criteria for withdrawal**	**Disease control**	**Successful withdrawal**	**Recurrence**	**Remission**
Studies reporting on treatment outcomes after DA withdrawal								
Telci Caklili [52] (2022)	Cohort	Retro	100±58	NR	NR	NR	NR	NormoPRL >1 year after DA withdrawal, without radiologic evidence of tumor
Kim 2 [53] (2021)	Cohort	Retro	After withdrawal: median 26 (range: 12-97)	PRL normalization on CAB 0.25mg-0.5mg/week	NR	Normal PRL after CAB withdrawal	PRL >ULN after CAB withdrawal	Normal PRL after CAB withdrawal
Hage [54] (2020)	Cohort	Retro	79.9 ±47.6	well controlled PRL (generally <10) on CAB 0.5mg/week or BRO 2.5mg/day, reduction in max. tumor diameter	NR	Normal PRL	hyperPRL	Normal PRL after DA withdrawal
Indirli [55] (2019)	Cohort	Retro	24 months	PRL normalization, evident[a] tumor shrinkage on DA ≥ 12 months	NR	Normal PRL	Recurrence of hypePRL confirmed on two occasions	Normal PRL after DA withdrawal
Huang [56] (2018)	Cohort	Retro	63.5 (range: 30–145)	NR	NR	No recurrence of hyperPRL or tumor growth	Recurrence of hyperPRL or tumor growth	NR
Ji [57] (2017)	Cohort	Retro	Median: 23.9 (range: 3.0–176.8)	NR	NR	NR	PRL>ULN after DA withdrawal	PRL<ULN
Teixeira [58] (2017)	Cohort	Retro	NR	NR	NR	NR	PRL>ULN and need to restart DA	NR
Sala [59] (2016)	Cohort	Retro	12	Normal PRL, restoration of gonadal function and tumor shrinkage	NR	NR	PRL >30ng/mL[b] after CAB withdrawal	NR
Mallea-Gil [60] (2016)	Cohort	Retro	Range: 108-396	Menopause or tumor shrinkage and normal PRL	NR	NR	NR	NR

	Outcome variables			
	Radiological parameters	**Biochemical parameters**	**Clinician-reported findings and visual measurements**	**Moment of measurement**
	tumor shrinkage on MRI (%)	PRL (ng/mL), maximum testosterone (ng/mL), hypopituitarism (n(%))	Fertility in those desiring fertility (n(%)), symptoms[a.] impulse control disorders (n(%))	Within follow-up
	Percentile of tumor reduction: (initial maximal diameter minus maximal diameter before CAB withdrawal) divided by initial maximal tumor diameter. Tumor size (mm)	PRL (ng/mL)	NR	At withdrawal, during follow-up
	NR	PRL (ng/mL), PRL change (%), achievement of withdrawal conditions (n(%)), time to reach withdrawal conditions (months), time to recurrence (months)	NR	2 months, at withdrawal, during follow-up
	Tumor disappearance (n(%)), tumor size decrease (%), max. tumor diameter (mm)	PRL (mIU/L), PRL decrease (%)	Regular menstrual cycle	At withdrawal, during follow-up
	Tumor disappearance (n(%)), tumor shrinkage on MRI (%), tumor shrinkage <50% (n(%)), tumor enlargement (n(%))	PRL normalization (n(%)), PRL (ng/ml), improvement of hypopituitarism (n(%))	Libido, potence, visual defects	During follow-up, last follow-up
	Tumor disappearance (n(%)), smallest tumor diameter (mm), tumor shrinkage >50% (n(%)), size reduction (%)	PRL nadir (ng/mL)	NR	Within follow-up
	NR	PRL (ng/mL), recovery of gonadal function (n(%))	NR	At withdrawal, during follow-up
	Tumor disappearance (n(%))	PRL (ng/mL)	NR	Prior to withdrawal, 3, 6, 12 months after withdrawal, during follow-up
	Tumor disappearance (n(%)), tumor size decrease (n(%)), tumor unchange (n(%))	PRL (ng/mL), need for treatment restart (n(%))	NR	Before withdrawal, 4-12 months after withdrawal, last follow-up

Supplementary Table 3a Outcome parameters per study for studies reporting on medical treatment only *(continued)*

Study characteristics					Outcomes describing treatment response			
					Definitions			
First author (publication year)	**Study design**	**Pro/retro**	**Duration of follow-up in months (mean ± SD)**	**Criteria for withdrawal**	**Disease control**	**Successful withdrawal**	**Recurrence**	**Remission**
Kwan-charoen [61] (2014)	Cohort (consecutive)	Pro	Recurrence: median 6.1 (range: 1-60) Persistent remission: median 42 (range: 24-60)	DA treatment >2 years, normal PRL, CAB dose ≤1 mg/week	NR	NR	PRL> ULN for gender and age	NR
Yarman [62] (2012)	Cohort	Retro	61 (range 12-128)	NR	NR	NR	NR	NR
Barber [63] (2011)	Cohort (consecutive)	Retro	Range: 18-36	DA treatment >3 years, normal PRL	NR	NR	Recurrence of PRL > ULN for sex	NR
Huda [64] (2010)	Cohort	Pro	All: NR Patients in remission: 58±18	DA treatment >1 year, normal PRL >1 year	NR	NR	PRL>ULN on two occasions > 1 month apart without presence of macroprolactinemia	NR
Kharlip [65] (2009)	Cohort (consecutive)	NR	All: NR Patients in remission: median 15 (range 2-48)	Tumor shrinkage (for macro <10mm)	NR	NR	2x PRL>ULN after DA withdrawal	PRL normalization within ULN
Colao [66] (2007)	Cohort (consecutive)	Pro	Micro: 47 ± 29, Macro: 44 ± 28	Normal PRL >1 year, tumor size <50%	NR	NR	PRL>ULN after DA withdrawal with or without symptoms with repeated elevated PRL measurement after 7-10 days	NR
Di Sarno [46] (2000)	Cohort (consecutive)	Retro	12	DA treatment for 1 year	NR	NR	Recurrence of hyperPRL after DA withdrawal	NR

BRO bromocriptine; *CAB* cabergoline; *DA* dopamine agonist; *F* female; *FSH* follicle stimulating hormone; *hyperPRL* hyperprolactinemia; *LH* luteinizing hormone; M male, *max.* maximum; *NR* not reported; *PRL* prolactin; *pro* prospective; *QUI* quinagolide; *RCT* randomized controlled trial; *retro* retrospective; *SD* standard deviation; *ULN* upper limit of normal.

[a] Not defined

[b] Upper limit of normal not reported

	Outcome variables			
	Radiological parameters	**Biochemical parameters**	**Clinician-reported findings and visual measurements**	**Moment of measurement**
	NR	PRL (ng/mL), time to recurrence (months)	NR	Within follow-up
	Tumor disappearance (n(%)), tumor shrinkage (%), tumor shrinkage (n(%)), enlargement of tumor after DA withdrawal (n(%))	PRL normalization (n(%)), need for replacement therapy (n(%)), recurrence after DA withdrawal (n(%)), need for restart DA (n(%)), valvulopathy (n(%))	Visual field, conceived a child (n(%))	Within follow-up
	Reduction in tumor size (substantial[a]/ modest[a]/ none) (n(%))	PRL (mIU/L), time to recurrence (months)	NR	On DA, at time of recurrence
	Abnormal[a] MRI prior to DA discontinuation (n(%))	PRL (ug/L), recurrence (n(%)), nadir PRL (ug/L),	NR	Prior to withdrawal, 3, 6, 12 months after withdrawal, at time of recurrence
	Size reduction on MRI	PRL nadir (ng/mL), time to recurrence (months), PRL at recurrence (ng/mL)	NR	Prior to DA withdrawal, within follow-up
	Nadir tumor diameter (mm), tumor regrowth after DA withdrawal (n (%))	PRL (mU/L), duration of normal PRL after withdrawal (months),	Symptoms[a] (n(%))	24-96 months after withdrawal
	Tumor disappearance (n(%)), tumor shrinkage (%), tumor volume (mm^3), tumor volume reduction 4-40%, 2-70%, >80% (n(%))	PRL normalization (n(%)), PRL (mU/L), PRL nadir (mU/L), PRL suppression (%), time to recurrence (months)	Visual field, galactorrhea, gonadal & sexual function	3, 6, 12 months
	Treatment success: PRL normalization at 6 months and tumor shrinkage at 24 months			

Supplementary Table 3b Outcome parameters per study for studies reporting on surgical treatment only

Study characteristics				Outcomes describing treatment response		
				Definitions		
First author (publication year)	**Study design**	**Pro/ retro**	**Duration of follow-up in months (mean ± SD)**	**Disease control**	**Recurrence**	**Remission**
Chen [67] (2024)	Cohort (consecutive)	Retro	NR	NR	NR	**Initial:** PRL normalization within 3 days without adjuvant therapy
Findlay [68] (2024)	Cohort	Retro	NR	NR	NR	NR
Demir [69] (2023)	Cohort	Retro	Median: 28 (range: 12-44)	NR	Increase in adenoma size or PRL>20 ug/L[b] in patients who were in remission at 3 months post-surgery	**Initial surgical remission**: PRL <20 ug/L[b] for ≥3 months post-surgery without DAs and tumor reduction >50% on MRI at 3 months post-surgery. **Long-term surgical remission**: no increase in tumor size and PRL <20 ug/L[b] at last follow-up.
Kalyvas [70] (2023)	Cohort (consecutive)	Retro	59.9 ± 35.5	NR	PRL >ULN after biochemical surgical remission	**Early**: PRL normalization within 3 months post-surgery without DA. **Last follow-up remission:** normal PRL at last follow-up irrespective of DA treatment.
Kim [71] (2023)	Cohort	Retro	51.3 (range: 12–156)	NR	NR	No visible mass on MRI 48 hours after surgery + normal PRL ≥3 months post-surgery
Ottenhausen [72] (2023)	Cohort (consecutive)	Retro	34.9 ± 60.3	NR	NR	*Reported inconsistently:* Methods section: postoperative PRL <15 ng/mL[b] Results section: morning fasting basal PRL <22.3 ng/mL[b] at last follow-up
Özaydin [73] (2023)	Cohort	Retro	NR	NR	NR	NR
Su [74] (2023)	Cohort (consecutive)	Retro	44.0 ± 2.33	NR	NR	**Early postoperative remission**: PRL normalization and no symptoms 1 week post-surgery. **Long-term remission**: PRL normalization without DA at last follow-up.
Uzuner [75] (2023)	Cohort	Retro	74.9 (range: 6–207)	NR	**Early**: recurrence of hyperPRL ≤3 months after initial PRL normalization. **Late**: recurrence of hyperPRL >3 months after initial PRL normalization.	PRL <ULN and relief of preoperative symptoms[a]

	Outcome variables			
	Radiological parameters	**Biochemical parameters**	**Clinician-reported findings and visual measurements**	**Moment of measurement**
	Total resection (n(%))	PRL (ng/mL)	NR	1, 3 days
	Local control on MRI: tumor stability, size decrease or complete eradication from immediate post-surgical imaging to imaging at 3-6 months post-surgery. GTR (n(%))	PRL normalization (n(%))	Visual symptoms	3-6 months, last follow-up
	GTR (n(%)), tumor, subtotal resection[a] (n(%)), growth (n(%))	PRL (ng/mL), persistent DA-fee follow-up (n(%)), restoration of hypopituitarism (n(%)), need for additional treatment (DA, RT, surgery)(n(%))	Visual field	1 week, last follow-up
	Total resection (n(%)) **Near-total resection**: 95% (n(%)). **Subtotal resection:** <95% (n (%)).	PRL (ng/mL), need for additional treatment (DA, RT, surgery) (n(%))	Visual acuity, visual field	Prior to discharge, 3, 6 months
	Total resection (n(%)), subtotal resection[a] (n(%))	Changes in pituitary function (n(%)), need for additional treatment (DA, RT, surgery, temozolomide) (n(%))	NR	3 months, within follow-up
	GTR (n(%)), residual tumor (n(%))	Need for additional treatment (DA, RT, surgery) (n(%))	Visual disturbances	Within follow-up
	Total resection (n(%))	PRL (ng/mL), need for additional treatment (DA/RT/surgery) (n(%))	NR	1 week, last follow-up
	Total resection (n (%))	PRL normalization (n(%)), PRL (ng/mL)	NR	1 day, 3, 6 months, last follow-up
	Total resection (n(%)), subtotal resection[a] (n(%))	PRL <10ng/mL (n (%)) (i.e., M: 0.7xULN, F: 0.4xULN), PRL normalization (n(%)), need for additional treatment (DA) (n(%))	Symptoms[a]	1 day, 3 months

Supplementary Table 3b Outcome parameters per study for studies reporting on surgical treatment only (continued)

Study characteristics				Outcomes describing treatment response		
				Definitions		
First author (publication year)	**Study design**	**Pro/ retro**	**Duration of follow-up in months (mean ± SD)**	**Disease control**	**Recurrence**	**Remission**
Van Trigt [76] (2023)	Cohort (consecutive)	Retro	Median: 43 (range: 2–71)	NR	NR	**Biochemical**: PRL normalization (< 1.0xULN). **Clinical**: restoration of gonadal function and resolution of complaints without PRL normalization.
Zandbergen [77] (2023)	Cohort (consecutive)	Retro	Median: 28.0 (range: 15.0–55.5)	NR	Recurrence of symptomatic hyperPRL after an episode of remission, regardless of tumor growth on MRI	PRL normalization (<1xULN) or asymptomatic mild hyperPRL (≤1.5xULN) with total resection without the need for DA treatment. **Short term:** ≤6 months **long-term:** at last follow-up, ≥1 year
Abou-Al-Shaar [78] (2022)	Cohort	Retro	66.4 ± 54.3	NR	NR	**Immediate remission**: 7 AM PRL <20 ng/mL in 14 days post-surgery without adjuvant therapy. **Late remission**: 7 AM PRL <20 ng/mL at 12 months without adjuvant therapy.
Force [79] (2022)	Cohort (consecutive)	Retro	Median: 3.3 (range: 0.1 - 70.9)	NR	HyperPRL after initial PRL normalization	**Early**: PRL normalization on day 1 while off DA for ≥4 weeks
Huber [80] (2022)	Cohort (consecutive)	Retro	NR	NR	NR	PRL<ULN at 3 months and last follow-up
Iuliano [81] (2022)	Cohort (consecutive)	Retro	37.3 (range: 1-126)	NR	NR	NR
Lasolle [82] (2023)	Cohort (consecutive)	Retro	Median: 22.7 (range: 1.1–126.5)	NR	Elevation of PRL after a remission with or without MRI lesion	PRL<ULN without DA
Scherer [83] (2022)	Cohort (consecutive)	Retro	Median: 8 (range: 1-97)	NR	NR	Repeated PRL <ULN at ≥6 weeks post-surgery without DA
Wan [84] (2022)	Cohort	Retro	NR	NR	NR	PRL normalization
Anderegg-gen [85] (2021)	Cohort (consecutive)	Retro	Median: 80 [IQR: 13–408]	NR	NR	**Early**: PRL < ULN 3 months postoperative. **Long-term**: PRL < ULN at last follow-up.

	Outcome variables			
	Radiological parameters	**Biochemical parameters**	**Clinician-reported findings and visual measurements**	**Moment of measurement**
	Tumor mass reduction (n(%))	PRL normalization (n(%)), recurrence (n(%)), need for additional treatment (DA, RT, surgery) (n(%))	Visual disturbances	6 months, last follow-up
	GTR (n(%)), subtotal resection[a]	PRL normalization (n(%)), need for additional treatment (DA, RT, surgery) (n(%)), resolution of hypopituitarism and hypogonadism (no/partially/complete) (n(%))	NR	1 week, 6 months, last follow-up (≥1 year)
	NR	Need for additional treatment (DA, RT, surgery) (n(%))	NR	14 days, 12 months
	NR	PRL normalization (n(%)), post-surgery DA dose decrease (n(%)), need for additional treatment (DA) (n(%)), recurrence (n(%))	Pregnancy	1 day, within follow-up
	NR	PRL (ug/L), need for additional treatment (DA) (n(%))	NR	3 months, last follow-up
	NR	PRL (ng/mL), PRL normalization (n(%)), need for additional treatment (DA, RT, surgery) (n(%))	NR	Within follow-up
	NR	5-year recurrence free survival rate (n(%)), need for additional treatment (DA, RT) (n(%))t	Pregnancy (outcome)	5 years, within follow-up
	Extent of resection on intraoperative MRI (complete resection/ residual adenoma (n(%))	Need for additional treatment (DA, RT, surgery) (n(%))	NR	6, 8, 12 weeks
	GTR: absence of residual enhancing lesions on MRI post-surgery (n %)). **Near total resection**: 90-99% tumor reduction (n(%)). **subtotal resection:** 70-89% tumor reduction (n(%)). **partial resection**: <70% tumor reduction (n(%)).	PRL (ng/mL)	NR	Postoperative[a], Within follow-up
	NR	PRL (ug/L), recurrence free interval (months)	NR	3 months, last follow-up

Supplementary Table 3b Outcome parameters per study for studies reporting on surgical treatment only (continued)

Study characteristics				Outcomes describing treatment response		
				Definitions		
First author (publication year)	**Study design**	**Pro/ retro**	**Duration of follow-up in months (mean ± SD)**	**Disease control**	**Recurrence**	**Remission**
Baussart [86] (2021)	Cohort (consecutive)	Retro	Median: 18.2 (range: 2.8-155)	NR	Increased PRL after initial normalization	**Biological remission**: PRL normalization and no symptoms
Giese [87] (2021)	Cohort	Retro	3	NR	NR	PRL normalization 3 months post-surgery without additional DA
Park 1 [88] (2021)	Cohort (consecutive)	Retro	Median 139.1 (Range: 12.2-319.6)	NR	**Biologic:** hyperPRL during follow-up. **Radiologic**: local progression observed on radiologic images during follow-up.	**Complete**: PRL normalization on morning day 1.
Penn [89] (2021)	Cohort	Retro	39.4 ± 42.1	Postoperative PRL normalization at last follow-up with or without postoperative use of DA	PRL >ULN	**Surgical cure**: postoperative PRL normalization at last follow-up without need for DA.
Wei [90] (2021)	Cohort	Retro	39.5 ± 2.17	NR	**General**: recurrence of elevated PRL levels ≥6 months after surgery. **Radiologic**: residual tumor increase ≥25% after subtotal resection or ±0.1cm^3 tumor volume after total resection	**Early postoperative remission**: PRL normalization and no symptoms 1 week after surgery
Lu [91] (2020)	Cohort	Retro	Median: 30 (Range: 12-75)	NR	Reactivation of hormonal disease, radiologic disease, or both during follow-up, in patients who have undergone tumor resection and have experienced ≥6 months of disease-free survival	No clinical or hormonal symptoms and no radiologic remnants
Nevzati [92] (2020)	Cohort (consecutive)	Retro	NR	NR	NR	**Initial**: PRL <10 ng/dL <48h post-surgery (i.e., F premenopausal: 0.4xULN, postmenopausal: 0.5xULN, M: 0.8xULN) **Follow-up**: normal PRL at a later postoperative time point[a], no DA treatment

	Outcome variables			
	Radiological parameters	**Biochemical parameters**	**Clinician-reported findings and visual measurements**	**Moment of measurement**
	NR	PRL (ng/mL)	Symptoms[a]	2 days, ≥3 months
	NR	PRL (ng/mL) recovery of hypopituitarism (n(%))	Menstrual cycle, pregnancy	5 days, 3 months
	GTR (n (%)), subtotal resection[a] (n (%)), residual tumor (n(%))	PRL normalization (n(%)), PRL (ng/mL), need for additional treatment (DA, RT) (n(%))	NR	During follow-up
	Progression: tumor growth on MRI. GTR (n (%)), subtotal resection[a] (n (%)), tumor progression (n(%))	PRL (ng/mL), need for additional treatment (DA, surgery)(n(%)), biochemical control	NR	1, 2 days, during follow-up
	Total resection (n(%))	PRL normalization (n(%)), PRL (ng/mL), DA dose reduction (n(%))	NR	1 day, 1 week, 3 months
	NR	PRL controlled[a] (n(%)), PRL (NR)	NR	Day 3, 12 months
	Surgical cure: no disease recurrence as of the latest follow-up.			
	NR	PRL (ng/dL), need for additional treatment (DA), (n(%)), DA treatment at last follow-up (n(%))	NR	48 hours, last follow-up

Supplementary Table 3b Outcome parameters per study for studies reporting on surgical treatment only (continued)

Study characteristics				Outcomes describing treatment response		
				Definitions		
First author (publication year)	**Study design**	**Pro/ retro**	**Duration of follow-up in months (mean ± SD)**	**Disease control**	**Recurrence**	**Remission**
Zielinski [93] (2020)	Cohort (consecutive)	Pro	82.2 ± 34.6	NR	NR	**Early**: PRL normalization and no symptoms at 3 months post-surgery **Long-term:** PRL normalization and no symptoms at last follow-up
Micko [94] (2019)	Cohort (consecutive)	Retro	37 (range: 4-143)	NR	Recurrence of hyperPRL >3 months post-surgery after initial PRL normalization	PRL<ULN
Han [95] (2018)	Cohort	Retro	13.5 (3-24)	NR	Recurrence of hyperPRL with or without radiologic evidence	No clinical symptoms, healthy[a] PRL
Yi [96] (2018)	Cohort (consecutive)	Retro	Median: 53 (range: 33-74)	NR	Elevated PRL during follow-up, irrespective of symptoms or neuroradiologic findings	PRL normalization without DA treatment for ≥2 months
Yoo [97] (2018)	Cohort (consecutive)	Retro	NR	NR	NR	NR
Fraioli [98] (2017)	Cohort	NR	Short pre-treatment: 88. Long pre-treatment: 50	NR	Recurrence of hyperPRL	NR
Akin [99] (2016)	Cohort (consecutive)	Retro	Median: 36 (range: 24-84)	NR	Increase in PRL with or without radiologic evidence of tumor after initial remission	PRL normalization and asymptomatic and no radiologically visible residual
Song [100] (2017)	Cohort	Retro	NR	NR	Symptom relapse or tumor reappearance confirmed by MRI after initial remission	**Initial**: PRL normalization immediately after surgery and disappearance of all symptoms after total adenoma excision. **Follow-up**: normal PRL and total resection confirmed by MRI 1 year post-surgery.
Delgrange [101] (2015)	Cohort	Retro	F: 143±5, M: 123±8	NR	PRL>ULN during follow-up after initial normalization	PRL normalization maintained to end of follow-up without DA

	Outcome variables			
	Radiological parameters	**Biochemical parameters**	**Clinician-reported findings and visual measurements**	**Moment of measurement**
	NR	PRL normalization (n(%)), PRL (ng/mL)	NR	1 day, 3 months, last follow-up
	NR	PRL (ng/mL)	NR	Day 1, last follow-up
	Subtotal resection: 80-100% removal (n(%)). **Partial resection**: <80% resection (n (%)).	PRL normalization (n(%)), PRL decrease (%), <75% PRL decrease (n(%)), no PRL change (n(%)) **Intra-operative observation:** total tumor removal (n(%))	Sexual function, visual field, visual function, headache	Intra-operative, 1, 7 days, 3 months
	NR	**Partial response**: hyperPRL with clinical persisting symptoms despite significant fall in PRL during DA treatment. PRL normalization (n(%)), need for additional treatment (DA) (n(%)), hypopituitarism (n(%))	Headache, galactorrhea, menstrual cycle, pregnancy (outcomes)	1 day, 2 months, during follow-up
	Total resection (n(%))	PRL normalization (n(%)), need for additional treatment (DA, RT, surgery) (n(%))	NR	2 months, during follow-up
	Total resection (n(%))	PRL normalization (n(%)), hormonal remission (n(%))[a], need for additional treatment (DA) (n(%)), PRL reduction to <70ng/mL without need for additional treatment (n(%)), improvement of hyperPRL (n(%))[a], dose reduction after surgery (n(%)), no improvement (n(%))[a]	Improvement of hyperPRL-related symptoms (n(%))[a]	During follow-up
	NR	Need for additional treatment (DA, RT, temozolomide) (n(%))	visual acuity	1, 7 days, 3 months, during follow-up
	Total removal tumor (n(%)), partial tumor removal (n(%))	**BRO responder**: PRL decline >50%. PRL (ng/mL)	**Symptom improvement:** improvement of >1 symptom postoperative. Headache, visual field, libido,	1 year, during follow-up
	Tumor progression: regrowth on MRI despite postoperative DA	PRL normalization (n(%)), need for additional treatment (DA, RT, surgery, temozolomide) (n(%))	NR	During follow-up

Supplementary Table 3b Outcome parameters per study for studies reporting on surgical treatment only (continued)

Study characteristics				Outcomes describing treatment response		
				Definitions		
First author (publication year)	**Study design**	**Pro/ retro**	**Duration of follow-up in months (mean ± SD)**	**Disease control**	**Recurrence**	**Remission**
Smith [102] (2015)	Cohort (consecutive)	Retro	Median: 12 (range: 3-69)	NR	NR	NR
Yan [103] (2015)	Cohort	Retro	12	NR	NR	NR
Dai [104] (2014)	Cohort (consecutive)	NR	54 (range: 6-72)	NR	PRL increase with or without radiologic tumor mass after previous remission	PRL normalization and no symptoms and no radiologic tumor remnants, without need for DA
Paluzzi [105] (2014)	Cohort (consecutive)	Retro	37 (range: 3-114)	NR	NR	PRL normalization without DA at last follow-up
Ikeda [106] (2013)	Cohort	Retro	144	NR	Recurrence of hyperPRL	PRL normalization
Maric [107] (2012)	Cohort	NR	NR	NR	NR	PRL normalization day 7 post-surgery
Primeau [108] (2012)	Cohort (consecutive)	Retro	85±62	NR	PRL>ULN ≥6 months post-surgery	PRL normalization for ≥6 months
Babey [109] (2011)	Cohort (consecutive)	Retro	All: NR Micro: median: 30.2 (range: 6-77), Macro: median: 40.3 (range: 10-73)	NR	PRL>ULN irrespective of symptoms and neuroradiologic findings	Normal PRL on morning after surgery
Hofstetter [110] (2011)	Cohort (consecutive)	Pro	22.8 (range: 1-76)	NR	NR	PRL normalization
Qu [111] (2011)	Observational (consecutive)	Retro	Median: 45 (range: 13–121)	NR	PRL>ULN during follow-up, regardless of symptoms and neuroradiologic findings	**Initial**: postoperative normalization of morning basal PRL, without DA for ≥4 weeks before surgery. **Follow-up:** morning fasting PRL<ULN at last follow-up without DA treatment for ≥3 months.
Gondim [112] (2010)	Cohort (consecutive)	Retro	All: median: 61.5 (range: 8-132). Prolactinoma: NR	Hormonal control after surgery	NR	NR

	Outcome variables			
	Radiological parameters	**Biochemical parameters**	**Clinician-reported findings and visual measurements**	**Moment of measurement**
	NR	PRL normalization with / without additional DA (n(%)), need for additional treatment (DA, RT) (n(%))	NR	6 months, during follow-up
	Total resection (n(%)), subtotal resection[a] (n(%)), massive resection[a] (n(%))	PRL normalization (n(%)), need for additional treatment (DA) (n(%))	Menstrual cycle, fertility galactorrhea, pregnancy	1 day, during follow-up
	NR	Relapse-free survival period (months)	NR	During follow-up
	Total resection: complete macroscopic removal. **Near-total**: >95% tumor removal. **subtotal**: 75-95% tumor removal, partial: <75% tumor removal	Need for additional treatment (DA, RT) (n(%))	Visual field	During follow-up
	NR	PRL normalization (n(%))	Menstrual cycle	5 years, during follow-up
	NR	Restoration of hypopituitarism (n(%))	NR	7 days, 6, 18 months
	postoperative residue: any abnormal residual tissue reported by radiologist on first MRI 3 months post-surgery	Need for additional treatment (DA) (n(%)), postoperative DA dose needed for PRL normalization (mg/w), relative reduction of PRL on DA (%)	NR	During follow-up
	NR	PRL (ug/L)	Menstrual cycle, sexual function	1 day, during follow-up
	GTR (n(%))	PRL (ng/mL), need for additional treatment (RT) (n(%))	NR	During follow-up
	Visible tumor on MRI (n(%)), tumor volume (cm^3)	PRL normalization (n(%)), PRL (ng/mL), 5-year recurrence free survival rate (%), need for additional treatment (DA, RT, surgery) (n(%))	NR	3, 4 months, 5 years, during follow-up, at last follow-up
	Total removal: no residual tumor intra-operatively and on MRI. **Subtotal**: >80% removal. **Partial**: <80% removal.	Need for additional treatment (DA, RT) (n(%)), recurrence (n(%))	NR	During follow-up

Supplementary Table 3b Outcome parameters per study for studies reporting on surgical treatment only (continued)

Study characteristics				Outcomes describing treatment response		
				Definitions		
First author (publication year)	**Study design**	**Pro/ retro**	**Duration of follow-up in months (mean ± SD)**	**Disease control**	**Recurrence**	**Remission**
D'Haens [113] (2009)	Cohort (consecutive)	Retro	All: 18 (range: 1-76). Prolactinoma: NR	NR	NR	PRL normalization ≥6w post-surgery
Yano [114] (2009)	Cohort	Retro	NR	NR	NR	PRL normalization
Dehdashti [115] (2008)	Cohort (consecutive)	Retro	Median: 5 (range: 4–31)	NR	NR	**Cure**: PRL normalization 1 day post-surgery and evidence of clinical remission
Frank [116] (2006)	Observational	Retro	All: 54 (range: 15–94). Prolactinoma: NR	NR	NR	PRL normalization at last follow-up without DA for ≥2 months
Wolfsberger [117] (2003)	Cohort (consecutive)	Retro	Median: 84 (range: 24-156)	NR	NR	PRL normalization at follow-up visit
Kristof [118] (2002)	Cohort (consecutive)	Retro	All: 44 Prolactinoma: NR	NR	PRL>ULN after initial remission regardless of clinical or MRI findings	PRL<ULN early[a] and 3 months post-surgery
Losa [119] (2002)	Cohort (consecutive)	NR	50.3 ± 3	NR	Elevated PRL levels irrespective of symptoms and neuroradiologic findings after remission for ≥6 months	**Biochemical**: postoperative PRL normalization without DA ≥ 2 months
Guieu [120] (1999)	Cohort (consecutive)	NR	18 (range: 12-24)	NR	NR	Reoccurrence of normal menstrual cycle ≤6 months post-surgery and PRL<10ng/mL[b] and could be normally stimulated ≥2.5xULN by TRH and metoclopramide at 9 days and 1 year post-surgery

DA dopamine agonist; *GTR* gross total resection; *hyperPRL* hyperprolactinemia; *IQR* interquartile range; *PRL* prolactin; *pro* prospective; *retro* retrospective; *RT* radiotherapy; *SD* standard deviation; *TRH* thyrotropin-releasing hormone, *xULN* times upper limit of normal.

[a] Not specified.

[b] Upper limit of normal not reported.

	Outcome variables			
	Radiological parameters	**Biochemical parameters**	**Clinician-reported findings and visual measurements**	**Moment of measurement**
	NR	Need for additional treatment (surgery) (n(%))	NR	During follow-up
	Tumor removal >95% (n(%))	NR	Visual acuity, visual field	During follow-up
	GTR: absence of visible tumor intra-operatively and on MRI	PRL normalization (n(%)), need for additional treatment (RT) (n(%))	Visual function	1 day, during follow-up
	NR	PRL normalization (n(%))	Visual acuity, visual field, trigeminal neuralgia	During follow-up
	NR	PRL normalization (n(%)), PRL (ng/mL), resolution of hypopituitarism (n(%)), need for additional treatment (DA) (n(%))	NR	Early postoperative[a], last follow-up
	Tumor diameter (mm)	PRL (ng/mL), improvement of anterior pituitary function (n(%))	NR	During follow-up
	NR	**Partial response**: significant fall of PRL, but persistent hyperPRL and clinical symptoms. PRL normalization n(%)), PRL (ug/L), PRL near[a] upper limit of normal (n(%)), restoration gonadal function (n(%)), need for additional treatment (DA/RT/surgery) (n(%)) time to recurrence (months)	Headache, menstrual cycle, sexual function, libido, pregnancy (outcome), infertility	5, 6 days, during follow-up
	Tumor size (mm)	Initial slope of curve of PRL decrease in time after resection (%)	Menstrual cycle	9 days, 6 months, 1 year

Supplementary Table 3c Outcome parameters per study for studies reporting on both medical and surgical treatment

Study characteristics				Outcomes describing treatment response			
				Definitions			
First author (publication year)	**Study design**	**Pro/ retro**	**Duration of follow-up in months (mean ± SD)**	**Criteria for withdrawal**	**Disease control**	**Successful withdrawal**	**Recurrence**
Himonakos [121] (2023)	Cohort	Retro	Median: 108 [IQR: 48-180]	NR	NR	NR	NR
Kumar [122] (2023)	Cohort	Retro	Median: 33 [IQR: 15-50]	NR	NR	NR	NR
Osorio [123] (2023)	Cohort	Retro	109 ± 249	NR	NR	NR	HyperPRL after documented remission status
Chen [124] (2022)	Cohort	Pro	61.9 ± 32.0	NR	NR	NR	Recurrence of symptoms and hyperPRL during follow-up after surgical remission
Eshkoli [125] (2022)	Cohort	Retro	Median: 96 [IQR: 48–153]	NR	NR	NR	NR

		Outcome variables			
	Remission	**Radiological response**	**Biochemical response**	**Clinician-reported findings and visual measurements**	**Moment of measurement**
	NR	**Tumor response**: ≥30% decrease of maximum tumor diameter at last MRI. **Tumor enlargement:** ≥ 20% increase in sum of the accessible diameters. Tumor disappearance (n(%)), tumor max. diameter (mm)	PRL<2xULN (n(%)), hypopituitarism (n(%)), need for additional treatment (DA, RT, surgery) (n(%))	Visual field	During follow-up, last follow-up
		Combined response: PRL normalization + ≥30% decrease in the maximum tumor diameter at last MRI.			
	NR	**Tumoral response**: ≥50% reduction in baseline tumor volume at last follow-up. Volume reduction (%)	**Hormonal response**: PRL normalization (n(%)). Time to PRL normalization (months), hypopituitarism (n(%)), need for additional treatment (DA, RT, surgery) (n(%))	NR	During follow-up, at last follow-up
	Medical: PRL normalization while on medical therapy. **Surgical**: PRL normalization 6 weeks post-surgery.	**Subtotal resection:** residual tumor visible on post-surgery imaging. GTR (n(%))	PRL normalization (n(%))	NR	NR
	Initial: PRL normalization day 1. **Long-term**: normal PRL at last follow-up. **Partial:** significant decrease of PRL yet no normalization on day 1. **Surgical remission:** resolution of symptoms and no tumor mass on MRI and PRL normalization ≥12 weeks post-surgery.	**GTR**: no significant residual tumor at 3 months.	PRL (ng/mL) , time to recurrence (months), need for additional treatment (DA) (n(%))	NR	1 day, 12 weeks, 3 months, last follow-up
	NR	Tumor volume reduction (n(%))	PRL normalization (n(%)), PRL (xULN), need for additional treatment (DA, RT, surgery) (n(%))	Visual field	During follow-up, last follow-up
		Overall response: PRL normalization or PRL < 3 xULN			

Supplementary Table 3c Outcome parameters per study for studies reporting on both medical and surgical treatment *(continued)*

Study characteristics				Outcomes describing treatment response			
				Definitions			
First author (publication year)	**Study design**	**Pro/ retro**	**Duration of follow-up in months (mean ± SD)**	**Criteria for withdrawal**	**Disease control**	**Successful withdrawal**	**Recurrence**
Biagetti [126] (2021)	Cohort	Retro	12	NR	NR	NR	NR
Cander [127] (2021)	Cohort	Retro	Median: 44 (range: 6–180)	NR	NR	NR	NR
Mattogno [128] (2021)	Cohort (consecutive)	Retro	Mean: 102.2 (range: 12–438)	NR	PRL normalization, stable neuroimaging during DA	NR	NR
Park 2 [129] (2021)	Cohort	Retro	All: NR DA: median: 54 (range: 13–154). Surgery: median: 64 (range: 15–182)	Treatment duration ≥2 years, PRL normalization, no tumor on MRI	PRL normalization and >50% tumor reduction	NR	PRL > ULN or evidence of recurrence on MRI during follow-up after DA-free remission
Rudman [130] (2021)	Cohort	Retro	90	NR	NR	NR	NR
Hamidi [131] (2019)	Cohort (consecutive)	Retro	Median: 58 (range: 0.1-423.6)	NR	NR	NR	NR

		Outcome variables			
	Remission	**Radiological response**	**Biochemical response**	**Clinician-reported findings and visual measurements**	**Moment of measurement**
	NR	**Radiologic response**: >50% tumor shrinkage at 12 months (n(%)). Tumor shrinkage (%)	PRL normalization (n(%)), PRL (ng/L), improvement of hypogonadism (n(%)), need for additional treatment (RT) (n(%))	NR	3, 4, 12 months
		Good responder: PRL normalization and tumor shrinkage >50% at 12 months. **Poor responder**: elevated PRL or tumor shrinkage <50% at 12 months.			
	>95% reduction of baseline PRL or PRL normalization	**Significant radiologic decrease**: 30% decrease in tumor diameter or 50% decrease in volume. Tumor volume reduction (%)	Prolactin decrease (%), improvement of hypopituitarism (n(%)), need for additional treatment (DA, RT, surgery) (n(%))	Visual field	3, 6, 24 months
	Cure: no symptoms and PRL normalization and no evidence of residual/recurrent tumor ≥12 months after surgery or DA withdrawal.	NR	PRL (ng/mL)	NR	1 day, during follow-up
	Surgery only: PRL normalization and no tumor on MRI throughout follow-up. DA only: PRL normalization, no lesion on MRI after DA withdrawal.	Tumor reduction (%)	**Disease control**: PRL normalization and >50% tumor diameter reduction. Normalization PRL (%), time to recurrence (months)	NR	During follow-up
	NR	**Shrinkage following DA (without surgery):** absolute decrease of max. tumor size of ≥5mm or decrease ≥20%. Tumor diameter (mm)	**Response**: PRL< 3.0 xULN at end of follow-up. PRL (ng/mL), testosterone (ng/mL), low testosterone (n(%)), need for additional treatment (RT, surgery (n(%))	Sexual function, visual field, visual acuity	12 months, last follow-up
	NR	**Complete structural response**: no visible tumor on follow-up MRI or at completion of study. Final tumor volume (cm^3)	**Complete biochemical response**: PRL normalization (n(%)) with ≥12 months follow-up duration. PRL (ng/mL), PRL change (ng/mL), PRL decline (%), Nadir PRL on DA (ng/mL), time to nadir PRL on DA (months), need for additional treatment (surgery, RT) (n(%))	Headache, visual field	During follow-up, last follow-up

Supplementary Table 3c Outcome parameters per study for studies reporting on both medical and surgical treatment *(continued)*

Study characteristics				Outcomes describing treatment response			
				Definitions			
First author (publication year)	**Study design**	**Pro/ retro**	**Duration of follow-up in months (mean ± SD)**	**Criteria for withdrawal**	**Disease control**	**Successful withdrawal**	**Recurrence**
Lv [132] (2019)	Cohort	Retro	60.0±4.6	NR	NR	NR	NR
Iglesias [133] (2018)	Cohort	Retro	Median 58 (range 0.1-423.6)	NR	NR	NR	NR
Andereggen 1 [134] (2017)	Cohort (consecutive)	Retro	Median: 90 (range: 13–408 months)	DA treatment 24 months, tumor size <50%	NR	NR	Increase in PRL >ULN during follow-up after previous remission irrespective of radiologic findings
Andereggen 2 [135] (2017)	Cohort (consecutive)	Retro	63±62	DA treatment 24 months, tumor size <50%	NR	NR	Increase in PRL levels >ULN after previous remission, or radiologic findings
Andujar-Plata [136] (2017)	Cohort (consecutive)	Retro	108 ± 64	NR	NR	NR	NR
Shimon [137] (2016)	Cohort	Retro	94 ± 61	NR	**Complete**: PRL normalization. **Partial:** no PRL normalization but reduction to <3xULN.	NR	NR

BMI body mass index; *DA* dopamine agonist; *max.* maximum; *NR* not reported; *PRL* prolactin; *pro* prospective; IQR interquartile range; *retro* retrospective; *RT* radiotherapy; *SD* standard deviation; *xULN* times upper limit of normal.
[a] Not specified.
[b] Upper limit of normal not reported.

	Outcome variables				
	Remission	**Radiological response**	**Biochemical response**	**Clinician-reported findings and visual measurements**	**Moment of measurement**
	NR	Tumor disappearance (n(%)), tumor shrinkage (%), degree of resection (%)	**First PRL reduction:** percentage PRL decrease 1 month after DA as contrasted with basal PRL level. **Nadir PRL**: lowest value during follow-up after intervention. PRL normalization (n(%)), PRL (ng/mL), PRL reduction (%), need for additional treatment (DA, RT, surgery) (n(%)), hypopituitarism (n(%))	Visual field	1 month, during follow-up
	NR	Tumor size decrease (%), tumor present on last MRI (n(%))	**Clinical cure**: normoprolactinemia maintained for >1 year without therapy and no radiologic evidence of pituitary tumor. Hypopituitarism (n(%), need for additional treatment (RT, surgery) (n(%))	NR	During follow-up
	PRL normalization at 3 months follow-up	NR	PRL (ug/L), PRL decrease (ug/L), prolactin control[a] (n(%)), need for additional treatment (DA) (n(%), hypogonadism (n(%)), hypopituitarism (n(%))	Amenorrhea, galactorrhea, headache, BMI (kg/m^3)	3 months, last follow-up
	Surgical: PRL normalization at 3 months follow-up	NR	PRL (ug/L), PRL decrease (ug/L) low testosterone (n(%)), hypopituitarism (n(%)), pathological bone density (n(%)), pathological fractures (n(%)), osteopenia (n(%)), need additional treatment (DA) (n(%))	Erectile dysfunction, libido, BMI (kg/m^3)	3 months, last follow-up
	NR	Tumor free (n(%)), significant[a] debulking (n(%)), final tumor volume (cm^3), tumor size decrease (%), tumor remnant (n(%))	PRL normalization (n(%)), PRL <2x ULN (n(%)), PRL (ng/mL), PRL decrease (%), need for additional treatment (DA, RT, surgery) (n(%)), resolution of pituitary hematoma or apoplexy (n(%)), recovery of pituitary function (n(%))	Resolution of compressive symptoms (n(%)), visual deficits	During follow-up, last follow-up
	NR	**Clinically significant tumor shrinkage**: reduction >33% in ≥2 tumor diameters compared to baseline.	PRL normalization (n(%)), time to PRL normalization (months), testosterone normalization (n(%)), need for additional therapy (DA, RT, surgery, temozolomide) (n(%)), hormonal remission[a] (n(%))	visual acuity	During follow-up, last follow-up

Supplementary Table 4 Summary of reported biochemical parameters

Category	Variable	Frequency per study type			
		Medical treatment	Surgical treatment	Medical and surgical treatment	Total
Prolactin levels	PRL normalization (n(%))	41	41	14	96
	PRL controlled[a]			1	1
	Nadir PRL (ng/L, mu/L, u/L, ULN)	6		2	8
	PRL (ng/L, mu/L, u/L, ULN)[b]	35	25	10	70
	PRL> ULN	1			1
	PRL decrease (%)	16	1	3	20
	PRL change (%)	1			1
	PRL decrease (ng/L, mu/L, u/L, ULN)	5		3	8
	PRL decrease (y/n) (n(%))	3			3
	PRL< 2xULN			2	2
	PRL< 3.0xULN			2	2
	PRL < 10 ng/mL (not reference range)		1		1
	PRL <70ng/mL (not reference range)		1		1
	PRL < 75% decrease (n(%))		1		1
	PRL > 95% decrease (n(%))			1	1
	PRL near[a] upper limit of normal		1		1
	Improvement[a] of PRL		1		1
	PRL not changed (n(%))		1		1
	Initial slope of PRL decrease curve after resection (%)		1		1
	Time to composite outcome (weeks)	1			1
	PRL-drop per month (%)	1			1
	PRL decrease rate (ng/mL/month)	1			1
Measurements concerning DA treatment	Time to PRL normalization on DA (months)	12		2	14
	DA dose needed for PRL normalization (mg/week)	3	1		4
	Relative reduction of PRL on DA (%)		1		1
	Achievement of DA dose reduction		3		3
	Achievement of withdrawal conditions (y/n)(n(%)		1		1
	Time to achieve withdrawal conditions (months)	1			1
Measurements concerning recurrence	Recurrence (n(%))	19	24	5	48
	Time to recurrence (after withdrawal) (months)	9	1	2	12
	5-year recurrence free survival rate (n(%))		2		2
	Recurrence free survival (months)		2		2
	Persistent drug-free follow-up (n(%))		1		1
	PRL after withdrawal	2			2
	Persistent normoPRL (n(%))	4			4
	PRL compared to baseline (lower/higher/unchanged) (n(%))	1			1
	PRL increase in normal range (n(%))	1			1
	PRL at recurrence (ng/L, mu/L, u/L, ULN)	1			1
	Need for DA restart after withdrawal (n(%))	3			3
	DA treatment at last follow-up (n(%))	1	1		2
Hypopituitarism	Pituitary substitution therapy		1		1
	Pituitary deficiency including hypogonadism	12	6	8	26
	Hypogonadism only	14	2	3	19

DA dopamine agonist; *n* no; *normoPRL* normoprolactinemia; *n* number; *PRL* prolactin; *xULN* times upper limit of normal; *y/n* yes/no.

[a] Not specified.

[b] Including one study reporting on surgical treatment that did not state the unit of measurement.

Supplementary Table 5 Definitions of remission per study

Study	Type of remission	Definition of remission	Parameters included in definition			Timing of measurement
			Bio-chemical	Radio-logical	Clinician-reported symptoms	
Studies reporting on medical treatment only						
Almalki (2020) [8]		PRL≤25ug/L[a] or >50% reduction from baseline	X			12 months
Hage (2020) [53]		Normal PRL after DA withdrawal	X			Within follow-up (mean 24 months)
Indirli (2019) [54]		Normal PRL after DA withdrawal	X			Within follow-up (24 months)
Ji (2017) [56]		PRL<ULN	X			Within follow-up (range 3-177 months)
Rae-Cho (2014) [24]	Biochemical	PRL<30ng/mL (i.e., F: 1.0xULN, M: 1.7xULN)	X			Within follow-up (median 30 months)
Kharlip (2009) [64]		PRL normalization within ULN	X			Within follow-up (median time to recurrence: 3 months)
Telci Caklili (2022) [51]		Normoprolactinemia after DA withdrawal, without radiologic evidence of tumor	X	X		> 12 months
Akkus (2020) [7]		DA treated for ≥2 years, with normal PRL, no lesion on MRI	X	X		NR
Anagnostis (2012) [29]		PRL normalization and stable tumor size after drug cessation	X	X		> 12 months
Watanabe (2017) [13]		No recurrence[b] after cabergoline withdrawal				> 12 months
Studies reporting on surgical treatment only						
Chen (2024) [67]	Initial	PRL normalization without adjuvant therapy	X			Within 3 days
Lasolle (2023) [82]		PRL<ULN without DA	X			3 months, last follow-up (median 23 months)
Ottenhausen (2023) [72]		Methods section: postoperative PRL <15 ng/mL[a] Results section: morning fasting basal PRL <22.3 ng/mL[a]	X			Methods section: NR Results section: Last follow-up (mean 35 months)
Kalyvas (2023) [70]	Early	PRL normalization without DA	X			3 months
	Last follow-up	Normal PRL irrespective of DA treatment	X			Last follow-up (mean 60 months)
Abou-Al-Shaar (2022) [78]	Immediate	7 AM PRL <20 ng/mL[a] without adjuvant therapy	X			Within 14 days
	Late	7 AM PRL <20 ng/mL[a] without adjuvant therapy	X			12 months
Force (2022) [79]	Early	PRL normalization while off DA for ≥4 w	X			Day 1
Huber (2022) [80]		PRL<ULN	X			3 months and last follow-up (duration NR)
Scherer (2022) [83]		Repeated PRL <ULN without DA	X			≥6 weeks
Wan (2022) [84]		PRL normalization	X			12 months

Supplementary Table 5 Definitions of remission per study *(continued)*

Study	Type of remission	Definition of remission	Parameters included in definition			Timing of measurement
			Bio-chemical	Radio-logical	Clinician-reported symptoms	
Andereggen (2021) [85]	Early	PRL < ULN	X			3 months
	Long-term	PRL < ULN	X			Last follow-up (median 80 months)
Giese (2021) [87]		PRL normalization without additional DA	X			3 months
Park 1 (2021) [88]		PRL normalization	X			Morning day 1
Penn (2021) [89]		Postoperative PRL normalization without need for DA	X			Last follow-up (mean 33 months)
Nevzati (2020) [92]	Initial	PRL <10 ng/dL (i.e., F premenopausal: 0.4xULN, postmenopausal: 0.5xULN, M: 0.8xULN)	X			< 48 hours
	Follow-up	Normal PRL at a later postoperative time point[b], no DA treatment	X			NR
Micko [94] (2019)		PRL<ULN	X			Last follow-up (mean 37 months)
Yi [96] (2018)		PRL normalization without DA treatment	X			≥2 months
Delgrange [101] (2015)		Maintained PRL normalization without DA	X			Throughout follow-up (F: mean 143 months, M: mean 123 months)
Paluzzi (2014) [105]		PRL normalization without DA	X			Last follow-up (mean 37 months)
Ikeda [106] (2013)		PRL normalization	X			7–10 days, 6 months, and 1–5 years
Maric [107] (2012)		PRL normalization	X			Day 7
Primeau [108] (2012)		PRL normalization	X			≥6 months
Qu (2011) [111]	Initial	postoperative normalization of a morning basal PRL, without DA for ≥4 weeks before surgery	X			NR
	Follow-up	Morning fasting PRL<ULN without DA treatment for ≥3 months	X			Last follow-up (madian 45 months)
Babey [109] (2011)		PRL normalization	X			Morning day 1
Hofstetter (2011) [110]		PRL normalization	X			NR
D'Haens [113] (2009)		PRL normalization	X			≥6 weeks
Yano [114] (2009)		PRL normalization	X			NR
Frank [116] (2006)		PRL normalization without DA for ≥2 months	X			Last follow-up (mean 54 months)
Wolfsberger [117] (2003)		PRL normalization	X			Follow-up visit (median 84 months)

Supplementary Table 5 Definitions of remission per study *(continued)*

Study	Type of remission	Definition of remission	Parameters included in definition			Timing of measurement
			Bio-chemical	Radio-logical	Clinician-reported symptoms	
Kristof [118] (2002)		PRL<ULN	X			Early[a] and 3 months
Losa [119] (2002)		Postoperative PRL normalization without DA ≥ 2 months	X			≥6 months
Su [74] (2023)	Early	PRL normalization and no symptoms	X		X	1 week
	Long-term	PRL normalization without DA	X			Last follow-up (mean 44 months)
Van Trigt [76] (2023)	Biochemical	PRL normalization (< 1.0xULN)	X			6 months and last follow-up (median 43 months)
	Clinical	Restoration of gonadal function and resolution of complaints without PRL normalization			X	6 months and last follow-up (median 43 months)
Demir [69] (2023)	Initial	PRL <20 ug/L[a] without DAs and tumor reduction >50% on MRI	X	X		≥3 months
	Long-term	No increase in tumor size and PRL <20 ug/L[a]	X	X		Last follow-up (median 28 months)
Kim [71] (2023)		No visible mass on MRI after surgery and normal PRL	X	X		MRI: 48 hours PRL: ≥3 months
Uzuner [75] (2023)		PRL <ULN and relief of preoperative symptoms[b]	X		X	Day 1 and long-term[b]
Wei [90] (2021)	Early	PRL normalization and no symptoms	X		X	1 week
Baussart [86] (2021)	Biochemical	PRL normalization and no symptoms	X		X	Within follow-up (median 18 months)
Zielinski [93] (2020)	Early	PRL normalization and no symptoms	X		X	3 months
	Long-term	PRL normalization and no symptoms	X		X	Last follow-up (mean 82 months)
Han (2018) [95]		No clinical symptoms, healthy[b] PRL	X		X	Last follow-up (range 3-24 months)
Dehdashti [115] (2008)	Cure	PRL normalization and evidence of clinical remission	X		X?	Day 1
Guieu [120] (1999)		Reoccurrence of normal menstrual cycle and PRL<10ng/mL[a] and could be normally stimulated ≥2.5xULN by TRH and metoclopramide	X		X	Menstrual cycle: ≤6 months PRL stimulation: day 9 and 12 months
Lu [91] (2020)		No clinical or hormonal symptoms and no radiologic remnants	X?	X	X	NR
Zandbergen [77] (2023)	Short-term	PRL normalization (<1xULN) or asymptomatic mild hyperPRL (≤1.5xULN) with total resection without the need for DA treatment	X	X	X	≤6 months
	Long-term	PRL normalization (<1xULN) or asymptomatic mild hyperPRL (≤1.5xULN) with total resection without the need for DA treatment	X	X	X	Last follow-up (≥ 12 months)

Supplementary Table 5 Definitions of remission per study *(continued)*

Study	Type of remission	Definition of remission	Parameters included in definition			Timing of measurement
			Bio-chemical	Radio-logical	Clinician-reported symptoms	
Song [100] (2017)	Initial	PRL normalization and disappearance of all symptoms after total adenoma excision	X	X	X	Immediately[b] after surgery
	Follow-up	Normal PRL and total resection confirmed by MRI	X	X		12 months
Akin [99] (2016)		PRL normalization and asymptomatic and no radiologically visible residual	X	X	X	Last follow-up (median 36 months)
Dai [104] (2014)		PRL normalization and no symptoms and no radiologic tumor remnants, without need for DA	X	X	X	NR
Studies reporting on medical and surgical treatment						
Osorio [123] (2023)	Medical	PRL normalization while on medical therapy	X			NR
	Surgical	PRL normalization	X			6 months
Chen [124] (2022)	Initial	PRL normalization	X			Day 1
	Long-term	PRL normalization	X			Last follow-up (mean 62 months)
	Partial	Significant decrease of PRL yet no normalization	X			Day 1
	Surgical	Resolution of symptoms and no tumor mass on MRI and PRL normalization	X	X	X	≥12 weeks
Cander [127] (2021)		>95% reduction of baseline PRL or PRL normalization	X			3 months
Andereggen 1 [134] (2017)		PRL normalization	X			3 months
Andereggen 2 [135] (2017)	Surgical	PRL normalization	X			3 months
Park 2 [129] (2021)	Medical	PRL normalization, no lesion on MRI after DA withdrawal	X	X		Throughout follow-up (median 54 months)
	Surgical	PRL normalization and no tumor on MRI	X	X		Throughout follow-up (median 64 months)
Mattogno [128] (2021)		No symptoms and PRL normalization and no evidence of residual/recurrent tumor post-surgery or after DA withdrawal	X	X	X	≥12 months

None of the definitions included patient-reported outcomes. *DA* dopamine agonist; *F* female; *M* male; *NR* not reported; *PRL* prolactin; *TRH* thyrotropin-releasing hormone; *xULN* times upper limit or normal.

[a] Upper limit of normal not provided.

[b] Not defined.

Supplementary Table 6 summary of reported radiological parameters

Category	Variable	Frequency per study type			
		Medical treatment	Surgical treatment	Medical and surgical treatment	Total
Complete response	Tumor disappearance (n(%))	23		4	27
	GTR (n(%))		9	2	13
	Total resection (n(%))		14		14
Volume/mass	Tumor volume (mm^3/cm^3)	11	1	2	14
	Tumor volume decrease (cm^3)	1			1
	Tumor volume decrease (%)	3		2	5
	Tumor volume decrease (n(%))	1		1	2
	Tumor mass reduction (n(%))		1		1
Diameter	Tumor diameter/size (mm/cm)	8	2	1	11
	Max. tumor diameter (mm/cm)	3		1	4
	Max. controlled tumor size/diameter (mm)	1			1
	Nadir tumor diameter (mm)	1			1
	Tumor diameter change/decrease (%)	4			4
	Nadir/smallest tumor diameter (mm)	3			3
Percentages	≥ 20% increase in sum of the accessible diameters			1	1
	>95% tumor removal (n(%))		3		3
	>95% tumor shrinkage (n(%))	1			1
	<95% tumor removal (n(%))		1		1
	90-99% tumor reduction (n(%))		1		1
	>80% tumor size reduction (n(%))	1			1
	>80% tumor volume reduction (n(%))	1			1
	80-100% tumor removal (n(%))		2		2
	<80% tumor resection (n(%))		2		2
	75-95% tumor removal (n(%))		1		1
	≥75% tumor volume reduction (n(%))	1			1
	>74.8% tumor shrinkage (n(%))	1			1
	<75% tumor removal (n(%))		1		1
	70-89% tumor reduction (n(%))		1		1
	<70% tumor reduction (n(%))		1		1

Supplementary Table 6 summary of reported radiological parameters *(continued)*

Category	Variable	Frequency per study type			
		Medical treatment	Surgical treatment	Medical and surgical treatment	Total
	≥50% tumor shrinkage/size reduction (n(%))	2			2
	≥50% tumor volume reduction (n(%))	1		1	2
	≥50% tumor shrinkage in coronal tumor surface (n(%))	2			2
	>50% tumor shrinkage (n(%))	2		1	3
	>50% tumor volume reduction (n(%))	3			3
	<50% tumor shrinkage (n(%))	1			1
	>33% reduction in ≥ tumor diameters (n(%))			1	1
	>30% tumor shrinkage in craniocaudal diameter (n(%))	1			1
	>30% decrease of max. tumor diameter (n(%))			1	1
	4-40% tumor volume reduction (n(%))	1			1
	>25% tumor volume reduction (n(%))	2			2
	<25% tumor volume reduction (n(%))	1			1
Other measures of size	Tumor size change (n(%))	2			2
	Tumor size reduction (n(%))	4			4
	Tumor size reduction/tumor shrinkage (%)	16		4	20
	Degree of resection (%)			1	1
	Tumor size increase (n(%))	3			3
	Max. tumor shrinkage (%)	2			2
	Tumor shrinkage (yes/no)(n(%))	2			2
	Tumor size stabilization (n(%))	2			2
	Tumor unchanged (n(%))	1			1
	Percentile of tumor reduction	1			1
	Tumor enlargement/progression/(re)growth (n(%))	7	3		10
	Tumor reduction (%)			1	1
Undefined measures	'notable' tumor shrinkage (n(%))	1			1
	'significant' tumor shrinkage	1			1
	'significant' debulking			1	1
	'substantial' resection	1			1

Supplementary Table 6 summary of reported radiological parameters *(continued)*

Category	Variable	Frequency per study type			
		Medical treatment	Surgical treatment	Medical and surgical treatment	Total
	'massive' resection		1		1
	'subtotal' resection		7		7
	'modest' tumor reduction	1			1
	'partial antitumoral effect'	1			1
	'partial tumor removal'		1		1
	'abnormal' MRI	1			1
	No improvement		1		1
Remnants	Residual tumor (n(%))	2	5	3	10
	Residual mass (%)	1			1
	Residual tumor ≤5 mm (n(%))	1			1
	Empty sella (n(%))	2			2
Time	Time to tumor shrinkage (months)	1			1
	Time to low signal intensity area appearance (months)	1			1
Structural changes	Cystic degeneration (n(%))	1			1
	Signal intensity (low/iso/high)(n(%))	1			1

GTR gross total resection; max. maximal; n number; *iso* isointense.

Supplementary Table 7 Summary of clinician-reported findings

Category	Variable	Frequency per study type			
		Medical treatment	Surgical treatment	Medical and surgical treatment	Total
General interpretation	Need for secondary treatment	11	32	14	57
General symptoms	Mood	2			2
	Fatigue	2			2
	Asthenia	1			1
	Symptoms[a]	2	8	1	11
Hyperprolactinemia related symptoms	Galactorrhea	10	2	1	13
	Gynecomastia	1			1
Hypogonadism related symptoms	(sub)fertility	2	2		4
	Pregnancy (+outcomes)	4	6		10
	Sexual function	14	3	2	19
	menstrual cycle	13	7	1	21
	Time to restoration menstrual cycle (months)	1			1
	Libido	8	2	1	11
	Shaving frequency	1			1
	Arrested puberty	1			1
	Semen quality	2			2
	nocturnal penile tumescence (events/night)	1			1
Mass effects	Visual field defects	14	7	7	28
	Visual symptoms[a]	5	8	3	16
	Visual acuity	2	1		3
	Diplopia	2			2
	Ptosis	1			1
	Compressive symptoms[a]			1	1
	Trigeminal neuralgia		1		1
	Headache	5	4	2	11
Bone health	Bone density			1	1
	Osteopenia			1	1
	Pathological fractures			1	1
Metabolic health	Anthropometric data	4		2	6
	Metabolic health (biochemical)	3			3

[a] Not specified

Supplementary Table 8 Definitions of disease control per study

Study	Type of disease control	Definition of disease control	Parameters included in definition			Timing of measurement
			Biochemical	Radiological	Clinician-reported symptoms	
Studies reporting on medical and surgical treatment						
Mattogno [128] (2021)		PRL normalization, stable neuroimaging during DA treatment	X	X		Last follow-up (mean 102 months)
Park 2 [129] (2021)		PRL normalization and >50% tumor reduction	X	X		NR
Shimon [137] (2016)	Complete	PRL normalization	X			Last follow-up (mean 8 months)
	Partial	No PRL normalization but reduction to <3xULN	X			Last follow-up (mean 8 months)

None of the definitions included patient-reported outcomes. *DA* dopamine agonist; *NR* not reported; *PRL* prolactin; *xULN* times upper limit of normal.

Supplementary Table 9 Reported definitions of disease recurrence per study

Study	Type of recurrence	Definition of recurrence	Parameters included in definition			Timing of measurement
			Bio-chemical	Radio-logical	Clinician-reported symptoms	
Studies reporting on medical treatment only						
Kim 2 [52] (2021)		PRL (>ULN) after CAB withdrawal	X			During follow-up (median 26 months)
Hage [53] (2020)		hyperPRL	X			2 months, during follow-up (mean 80 months)
Indirli [54] (2019)		Recurrence of hyperPRL confirmed on two occasions	X			During follow-up (24 months)
Ji [56] (2017)		PRL>ULN after DA withdrawal	X			During follow-up (median 24 months)
Dogansen [14] (2016)		PRL increase above ULN after DA withdrawal	X			During follow-up (mean 109 months)
Sala [58] (2016)		PRL >30ng/mL[a] after CAB withdrawal	X			During follow-up (12 months)
Vilar [21] (2015)		PRL > ULN for gender	X			During follow-up (median 12 months)
Kwancharoen [60] (2014)		PRL> ULN for gender and age	X			During follow-up (median 6 months)
Barber [62] (2011)		Recurrence of PRL > ULN for sex	X			During follow-up (range: 18-36 months)
Huda [63] (2010)		PRL>ULN on two occasions > 1 month apart without presence of macroprolactinemia	X			During follow-up (mean 58 months)
Kharlip [64] (2009)		2x PRL>ULN after DA withdrawal	X			During follow-up (median 15 months)
Colao [65] (2007)		PRL>ULN after DA withdrawal with or without symptoms with repeated elevated PRL measurement after 7-10 days	X			Within 24-96 months
Di Sarno [66] (2000)		Recurrence of hyperPRL after DA withdrawal	X			3, 6, 12 months
Espinosa-Cárdenas [9] (2020)		HyperPRL, re-growth of adenoma or reappearance of symptoms (F: galactorrhea or menstrual abnormalities, M: sexual dysfunction)	X	Or X	Or X	During follow-up (median 20 months)
Huang [55] (2018)		Recurrence of hyperPRL or tumor growth	X	Or X		During follow-up (mean 64 months)
Teixeira [57] (2017)		PRL>ULN and need to restart DA	X		X	During follow-up (duration NR)
Studies reporting on surgical treatment only						
Kalyvas [70] (2023)		PRL >ULN after biochemical surgical remission	X			3, 6 months
Lasolle [82] (2023)		Elevation of PRL after a remission with or without MRI lesion	X			During follow-up (median 23 months)
Uzuner [75] (2023)	Early	Recurrence of hyperPRL after initial PRL normalization	X			≤3 months
	Late	Recurrence of hyperPRL after initial PRL normalization	X			>3 months

Supplementary Table 9 Reported definitions of disease recurrence per study *(continued)*

Study	Type of recurrence	Definition of recurrence	Parameters included in definition			Timing of measurement
			Bio-chemical	Radio-logical	Clinician-reported symptoms	
Force [79] (2022)		HyperPRL after initial PRL normalization	X			During follow-up (mean 3 months)
Baussart [86] (2021)		Increased PRL after initial normalization	X			During follow-up (median 18 months)
Penn [89] (2021)		PRL >ULN	X			During follow-up (mean 39 months)
Micko [94] (2019)		Recurrence of hyperPRL >3 months post-surgery after initial PRL normalization	X			>3 months, Last follow-up (mean 37 months)
Han [95] (2018)		Recurrence of hyperPRL with or without radiologic evidence	X			During follow-up (mean 14 months)
Yi [96] (2018)		Elevated PRL during follow-up, irrespective of symptoms or neuroradiologic findings	X			During follow-up (median 53 months)
Fraioli [98] (2017)		Recurrence of hyperPRL	X			During follow-up (short pretreatment: mean 88 months, long pretreatment: mean 50 months)
Akin [99] (2016)		Increase in PRL with or without radiologic evidence of tumor after initial remission	X			During follow-up (median 36 months)
Delgrange [101] (2015)		PRL>ULN during follow-up after initial normalization	X			During follow-up (F: mean 143 months, M: mean 123 months)
Dai [104] (2014)		PRL increase with or without radiologic tumor mass after previous remission	X			During follow-up (mean 54 months)
Ikeda [106] (2013)		Recurrence of hyperPRL	X			5 yearrs, during follow-up (mean 144 months)
Primeau [108] (2012)		PRL>ULN ≥6 months post-surgery	X			≥6 months, during follow-up (mean 85 months)
Babey [109] (2011)		PRL>ULN irrespective of symptoms and neuroradiologic findings	X			During follow-up (micro: median 30 months, macro: median 40 months)
Qu [111] (2011)		PRL>ULN during follow-up, regardless of symptoms and neuroradiologic findings	X			During follow-up (median 45 months)
Kristof [118] (2002)		PRL>ULN after initial remission regardless of clinical or MRI findings	X			During follow-up (mean 44 months)
Losa [119] (2002)		Elevated PRL levels irrespective of symptoms and neuroradiologic findings after remission for ≥6 months	X			≥6 months, during follow-up (mean 50 months)

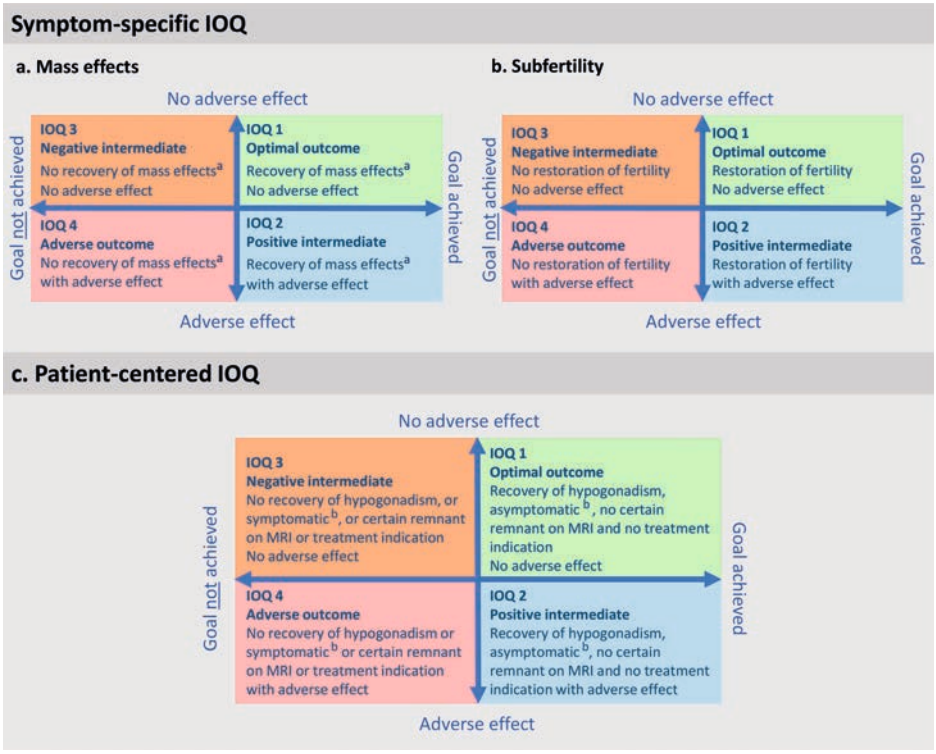
Supplementary Table 9 Reported definitions of disease recurrence per study *(continued)*

Study	Type of recurrence	Definition of recurrence	Parameters included in definition			Timing of measurement
			Bio-chemical	Radio-logical	Clinician-reported symptoms	
Park 1 [88] (2021)	Biologic	HyperPRL	X			During follow-up (median 139 months)
	Radiologic	Local progression observed on radiologic images		X		During follow-up (median 139 months)
Wei [90] (2021)	General	Recurrence of elevated PRL levels ≥6 months after surgery	X			≥6 months, during follow-up (mean 40 months)
	Radiologic	Residual tumor increase ≥25% after subtotal resection or ±0.1cm^3 tumor volume after total resection		X		During follow-up (mean 40 months)
Lu [91] (2020)		Reactivation of hormonal disease, radiologic disease, or both during follow-up, in patients who have undergone tumor resection and have experienced ≥6 months of disease-free survival	X	Or X		≥6 months, during follow-up (median 30 months)
Song [100] (2017)		Symptom relapse or tumor reappearance confirmed by MRI after initial remission		X	Or X	1 year, during follow-up (duration NR)
Zandbergen [77] (2023)		Recurrence of symptomatic hyperPRL after an episode of remission, regardless of tumor growth on MRI	X		X	1 week, 6 months, last follow-up (median 28 months)
Demir [69] (2023)		Increase in adenoma size or PRL>20 ug/L[a] in patients who were in remission at 3 months post-surgery	X	Or X		>3 months, last follow-up (median 28 months)
Studies reporting on medical and surgical treatment						
Osorio [123] (2023)		HyperPRL after documented remission status	X			NR
Andereggen 1 [134] (2017)		Increase in PRL >ULN during follow-up after previous remission irrespective of radiologic findings	X			3 months, last follow-up (median 90 months)
Chen [124] (2022)	Surgical	Recurrence of symptoms and hyperPRL during follow-up after surgical remission	X		X	Last follow-up (mean 62 months)
Park 2 [129] (2021)		PRL > ULN or evidence of recurrence on MRI during follow-up after DA-free remission	X	Or X		During follow-up (DA: median 54 months, surgery: median 64 months)
Andereggen 2 [135] (2017)		Increase in PRL levels >ULN after previous remission or radiologic findings	X	Or X		3 months, last follow-up (median 63 months)

None of the definitions included patient-reported outcomes. *DA* dopamine agonist; *F* female; hyperPRL hyperprolactinemia; *M* male; *macro* macroprolactinoma; *micro* microprolactinoma; *NR* not reported; PRL prolactin; ULN upper limit of normal.

[a] Upper limit of normal not provided.

Supplementary Figure 1 Simple and composite integrated outcome quadrants regarding common treatment goals for patients with prolactinoma



IOQ integrated outcome quadrant.

[a] Mass effects include reduced visual acuity, visual field defects, headaches, cranial nerve palsy, compression hydrocephalus and reduced consciousness.

[b] Typical prolactinoma symptoms: galactorrhea, loss of libido, subfertility, menstrual cycle abnormality and erectile dysfunction (Pituitary Society consensus statement, 2023).

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