PRolaCT - three Multicenter Prolactinoma Randomized Clinical Trials

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This study aims to investigate if endoscopic trans-sphenoidal prolactinoma resection as a first line treatment (PRolaCT-1), or as an equally valid second line treatment after a short (2-12 months) or long (>12 months) period of pretreatment with...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Hypothalamus and pituitary gland disorders
Study type	Interventional

Summary

ID

NL-OMON54709

Source
ToetsingOnline

Brief title
PRolaCT

Condition

- Hypothalamus and pituitary gland disorders
- Endocrine neoplasms benign
- Endocrine gland therapeutic procedures

Synonym
prolactin secreting pituitary adenoma, Prolactinoma

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: ZonMw

Intervention

Keyword: prolactinoma, quality of life, remission rate, treatment

Outcome measures

Primary outcome

This study has two main outcomes, including the health-related quality of life after 12 months as measured on the mental health sub scale of the Short-Form 36 questionnaire; and the percentage of patients in remission after 36 months, where remission is defined as normoprolactinaemia (a prolactin below the upper limit of normal as defined by the laboratory where it is measured) in the absence of dopamine agonist treatment or an actual pregnancy that was established in the absence of dopamine agonist treatment.

Secondary outcome

The secondary outcomes of this study are:

- Remission rate, according to the above mentioned definition, 27 and 60 months after randomization.

- Biochemical disease control, defined as normoprolactinaemia (a prolactin below the upper limit of normal as defined by the laboratory where it is measured), or an actual pregnancy, with or without dopamine agonist treatment, measured 12 months after randomisation.

- Disease recurrence, 36 and 60 months after randomisation, defined as recurrence of hyperprolactinaemia in the absence of dopamine agonist treatment in patients who achieved disease remission at T=27.

- Clinical symptom control 12, 27, 36 and 60 months after randomization, defined as:

> the absence of psychiatric symptoms measured with the Hospital Anxiety and Depression Scale; and

> the absence of physical symptoms that are associated with prolactinoma, i.e. galactorrhea, hypogonadism, loss of libido, subfertility, emotional complaints, headache and visual complaints.

- Tumor shrinkage after 12 and 36 months, defined as a reduction in maximal diameter or tumor volume of at least 20% on pituitary MRI.

- Normal(ized) pituitary functioning 12, 36 and 60 months after randomisation, defined as normal funtioning of the following pituitary axes:

> gonadal axis, assessed with measurement of FSH, LH and estrogen or testosterone

> thyroidal axis, assessed with measurement of TSH and free T4

> corticoid axis, assessed with measurement of morning cortisol and if suppressed an additional CRH- or synacthen-test

> growth hormone axis, assessed with measurement of IGF-1 and additional GH-suppression test or insulin-tolerance test, when indicated

> ADH secretion, assessed with measurement of serum sodium

- The occurrence of adverse reactions to treatment after 12 and 36 months, defined as the occurrence of side effects to dopamine agonist treatment documented with the use of the National Cancer Institute Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE*) and a modified Impulse Control Disorder Questionnaire (ICD-Q); and the occurrence of complications to surgery.

- HRQoL after 36 and 60 months, defined by the scores on all sub scales of the

SF-36.

- Disease burden after 12, 36 and 60 months, defined by the bother score on the Leiden Bother and Needs Questionnaire.

- Cost-effectiveness after 12 andd 36 months, calculated from:

> Quality-of-Life adjusted life-years (QALY's), based on the EQ-5D-5L, measured at baseline and 6, 9, 12, 18, 24, 27, 30 and 36 months after randomisation.

> Healthcare costs, calculated from inventory with the iMTA Medical Consumption Questionnaire (iMCQ), measured at baseline and every 6 months thereafter, until 36 months after randomisation.

> Productivity loss in the work field, measured with the iMTA Productivity Costs Questionnaire (iPCQ) at baseline and every 6 months thereafter until 36 months after randomisation.

From amendment 7 dated 19-11-2024 onwards, the cost-effectiveness questionnaires will no longer be filled out.

Study description

Background summary

Current guidelines describe dopamine agonists, e.g. cabergoline, as first line of treatment for prolactinoma patients. Only a selection of patients with a prolactinoma undergoes surgical resection. Although most patients are under good clinical control, the majority needs prolonged treatment with a dopamine agonist, because 2-year remission rates remain low. While up to 40% of patients experience side-effects. In contrast, endoscopic trans-sphenoidal prolactinoma

resection results in immediate remission in more than 80-90% of patients with a low rate of long term morbidity from complications (< 3%). Thus, our hypothesis is that early or upfront endoscopic trans-sphenoidal surgery in patients with a non-invasive prolactinoma of limited size, will increase the health-related quality of life and the remission rate.

Study objective

This study aims to investigate if endoscopic trans-sphenoidal prolactinoma resection as a first line treatment (PRolaCT-1), or as an equally valid second line treatment after a short (2-12 months) or long (>12 months) period of pretreatment with a dopamine agonist is superior to standard care for several outcome parameters of treatment. The main objectives are to investigate this for quality of life and remission rate. The secondary objectives are to investigate this for biochemical disease control, recurrence rates, clinical symptom control, tumor shrinkage on MRI, pituitary functioning, the occurrence of adverse reactions to treatment, disease burden, and cost-effectiveness.

Study design

This protocol covers three similar but individual, unblinded Randomized Clinical Trials (RCTs), that will run simultaneously; (1) PRolaCT-1, an RCT that compares endoscopic trans-sphenoidal surgery as a first line treatment to standard care in newly diagnosed, treatment naïve patients; (2) PRolaCT-2, an RCT that compares endoscopic trans-sphenoidal surgery as an early treatment to standard care in patients that have had short term treatment (2-12 months) with medication; and (3) PRolaCT-3, an RCT that compares endoscopic trans-sphenoidal surgery as an equal second line treatment to standard care in patients who have persisting prolactinoma and had treatment with medication for a long period of time (>12 months).

As mentioned in Amendment 6 dated 19-01-2024, all randomized arms (PRolaCT-1,2,3) will be closed because of low willingness to randomize. All eligible patients will therefore be inclded in the observational arm (PRolaCT-O).

Intervention

The intervention groups of the three RCTs are referred to a participating neurosurgical expertise center for extensive neurosurgical counseling with the intention to perform the endoscopic trans-sphenoidal adenoma resection, when the patients consents to this. The control groups receive standard care (thus primary treatment with a dopamine agonist) by their own endocrinologist or gynecologist, in the local hospital.

Study burden and risks

A risk of participation in this study is that endoscopic trans-sphenoidal prolactinoma resection is performed in patients who in standard care would not have underwent this surgery or would have at a later moment. The risk of complications from the endoscopic surgery is low, with long-term morbidity occurring in less than 3% and a mortality rate of <0.4-1%. The potential benefit is a high chance of remission, relieving the patient from the need for prolonged dopamine agonist treatment. As these treatments have not yet been compared in a randomized clinical trial, it is the aim of this study to further assess the extent of this benefit and its effect on the quality of life in a randomized clinical trial design. The only way to adequately perform such a study is with participation of the patients who suffer from the condition that is aimed to be investigated.
As study follow up is designed to reflect routine clinical follow up, in both the intervention as the control group, the burden of participation is kept to a minimum. In addition to the documentation of clinical follow up, all participants are asked to fill in a number of questionnaires on several moments during the course of this study. The time this should cost a patient varies from 30-60 minutes at the 5 time points connected to study visits (T=0, T=12, T=27, T=36 and T=60), to 10-30 minutes at 5 additional time points spread over the first three years of the study.
There is no direct therapeutic effect expected for the patients participating in the control groups of this study. However, it is thought that the burden of their participation in this study is outweighed by the potential benefit for all patients with a relatively small, non-invasive prolactinoma, if our hypothesis is thought to be right.
From amendment 6 dated 19-01-2024 onwards, participants are no longer subject to increased risk due to the closing of the randomization arms of the study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- At least 18 years of age.
- A history of signs and symptoms compatible with the diagnosis prolactinoma.
- New, recent (PRolaCT-1) or known diagnosis of hyperprolactinaemia, defined as a prolactin level 2 times the local laboratory maximum. At the time of randomization hyperprolactinaemia is still present, or was present < 12 months before inclusion (PRolaCT-2 and PRolaCT-3)
- No clear alternative explanation for hyperprolactinaemia, e.g. medication use.
- Presence of a clearly identifiable (persisting) pituitary mass on MRI with a diameter smaller than 25mm, and more importantly not invading the cavernous sinus and having an optimal chance to achieve surgical remission. A representative MRI at the time of randomization is required, this MRI should generally not be older than 12 months for all PRolaCT arms.
- Competent, or having proxy who can sign on their behalf.
- One of the following, dividing patients in to our three RCTs:
* PRolaCT-1: no prior treatment for prolactinoma;
* PRolaCT-2: treatment with a dopamine agonist for 2-12 months; or
* PRolaCT-3: treatment with a dopamine agonist for >12 months

As mentioned in Amendment 6 dated 19-01-2024, all randomized arms (PRolaCT-1,2,3) will be closed because of low willingness to randomize. All eligible patients will therefore be inclded in the observational arm (PRolaCT-O).

As mentioned in Amendment 7 dated 19-11-2024, participants of all pretreatment duration groups (PRolaCT-1,2,3) will be recruited for the observational arm, resulting in a total of 3x220 participants = 660 participants.

Exclusion criteria

- Contraindication for one of the treatment modalities, e.g. severe side effect of cabergoline, contraindications to surgery, or a clear indication for surgical resection.
- Pregnancy at the time of randomization.
- Clinical acromegaly.
- Prior radiotherapy to the pituitary gland area.
- Severe renal failure (eGFR <30 ml/min).
- Insufficient understanding of the Dutch or English language.
- Other medical conditions that to the opinion of the physician are not compatible with inclusion in a trial.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	21-06-2019
Enrollment:	660
Type:	Actual

Ethics review

Approved WMO

Date:	12-03-2019
Application type:	First submission

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	15-11-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	21-01-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	19-01-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	23-12-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	05-06-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	01-02-2024
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	04-02-2025
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL63919.058.18