

Non-functioning pituitary tumours

- mortality, morbidity and tumour progression

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“Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning.”

Sir Winston Churchill (1874-1965), *Speech in November 1942*

NON-FUNCTIONING PITUITARY TUMOURS - MORTALITY, MORBIDITY AND TUMOUR PROGRESSION

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ABSTRACT

Non-functioning pituitary tumours, i.e. non-functioning pituitary adenomas (NFPA) and craniopharyngiomas (CP), are histologically benign tumours. They are, however, associated with hypopituitarism, diabetes insipidus and other local symptoms caused by the tumour itself or its treatment. Previous studies have shown an excess mortality in patient populations with hypopituitarism, caused by various aetiologies. The mortality rates and factors predicting the mortality in NFPA and CP patients are largely unknown. Modern replacement therapy for patients with hypopituitarism includes treatment with growth hormone (GH) replacement therapy (GHRT). GH has known mitogenic effects, and is considered to possibly increase the risk of tumour progression in patients with a history of pituitary tumours.

This thesis is based on four studies aimed to investigate whether GHRT influences the risk of tumour progression and to study mortality and morbidity in patients with NFPA or CP.

In two case-control studies the frequency of tumour progression was investigated in patients with NFPA or CP treated with and without GHRT. The 10-year tumour progression free survival rate in NFPA patients with and without GHRT was 74% and 70%, respectively. The corresponding figures for CP patients were 88% and 57%. In a population-based registry-study of 2795 NFPA patients an excess mortality was demonstrated in women and in patients diagnosed at or before 40 years of age. In another population-based registry-study of 307 CP patients, mortality and morbidity were highly increased, especially in patients with a childhood-onset of the disease. The incidences of type 2 diabetes mellitus, cerebral infarction and severe infection were 5-fold elevated compared to the general population.

In conclusion, GHRT does not affect the frequency of tumour progression in patients with NFPA or CP. Furthermore, there is an increased mortality in women and young patients with NFPA and an excess mortality in CP patients, especially in patients with childhood-onset of CP.

Key words: Non-functioning pituitary adenoma, Craniopharyngioma, Mortality, Morbidity, Growth hormone replacement therapy, Residual tumour, Radiation therapy, Tumour progression

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LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

- Paper I. **Comparing progression of non-functioning pituitary adenomas in hypopituitarism patients with and without long-term GH replacement therapy.**
Olsson DS, Buchfelder M, Schlaffer S, Bengtsson B-Å, Jakobsson K-E, Johannsson G, Nilsson AG.
European Journal of Endocrinology, 2009 161 (5):663-669.
- Paper II. **Tumour recurrence and enlargement in patients with craniopharyngioma with and without GH replacement therapy during more than 10 years of follow-up.**
Olsson DS, Buchfelder M, Wiendieck K, Kremenevskaja N, Bengtsson B-Å, Jakobsson K-E, Jarfelt M, Johannsson G, Nilsson AG.
European Journal of Endocrinology, 2012 166 (6):1061-1068.
- Paper III. **Mortality in patients with non-functioning pituitary adenoma – a population-based study.**
Olsson DS, Johannsson G, Bryngelsson I-L, Trimpou P, Nilsson AG, Andersson E.
Manuscript.
- Paper IV. **Mortality and morbidity in patients with craniopharyngioma – a population-based study.**
Olsson DS, Andersson E, Bryngelsson I-L, Nilsson AG, Johannsson G.
Manuscript.

All papers have been accepted for oral presentation at The Endocrine Society's Annual Meeting (*Paper I*, 2009, Washington, USA; *Paper II*, 2011, Boston, USA; *Paper III* and *Paper IV*, 2014, Chicago, USA).

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ABBREVIATIONS

Cancer Registry	The Swedish Cancer Registry
Cause of Death Registry	The Swedish National Cause of Death Registry
CI	Confidence interval
CP	Craniopharyngioma
DI	Diabetes insipidus
GH	Growth hormone
GHD	Growth hormone deficiency
GHRT	Growth hormone replacement therapy
HR	Hazard ratio
IGF-I	Insulin-like growth factor - I
IGFBP-3	Insulin-like growth factor-binding protein - 3
MRI	Magnetic resonance imaging
NFPA	Non-functioning pituitary adenoma
RT	Radiation therapy
SD	Standard deviation
SIR	Standardised incidence ratio
SMR	Standardised mortality ratio
PFSR	Progression free survival rate
Patient Registry	The Swedish National Patient Registry
T2DM	Type 2 diabetes mellitus

1 GENERAL INTRODUCTION

1.1 History

It is unclear when the first pituitary tumour was described, but the Austrian physician A. de Haen (1704-1776) is believed to be the first to link a pituitary mass to symptoms in a female patient with amenorrhoea [1]. More than one hundred years later, O. Minkowski proposed that abnormalities in the pituitary gland could be associated with a disease - acromegaly [2]. A few years later, in 1909, H. Cushing suggested that tumours in the pituitary gland could lead to hypo- or hyper-secretion of hormones [3]. One of the first to describe the entity of what later would be known as craniopharyngioma (CP) was J. Erdheim, when he in 1904 presented a series of ten patients with nests of squamous epithelium at the junction between the infundibulum and the pituitary [4]. Almost thirty years later, in 1932, H. Cushing was the first to use the designation craniopharyngioma [5]. Since then, the knowledge about the pituitary and its associated tumours has grown enormously and has today expanded into an independent area of research.

1.2 Pathogenesis and epidemiology

Today we know that pituitary adenomas originate from cells in the pituitary gland and consist of secreting pituitary adenomas and non-functioning pituitary adenomas (NFPA). Pituitary adenomas are a tumour group with different aetiologies consisting of prolactinomas (26-51%), NFPAs (27-36%), GH-producing adenomas (9-16%), ACTH-producing adenomas (3-15%) and TSHomas (1%) [6-8]. CP is an epithelial tumour, whose origin is uncertain [9]. Several theories on the aetiology of CP have been suggested, but one hypothesis is that CP tumours arise from metaplasia of adenohypophyseal cells in the pituitary stalk or gland [10,11]. CP tumours have been demonstrated to have two different primary histological appearances, the adamantinomatous and the papillary subtype, but there are also cases with a mixture of these subtypes [12]. NFPAs and CPs have only rarely been described to transform into malignant tumours [13,14].

The annual incidence of NFPA has been reported to be 1.0-1.1 cases per 100 000 inhabitants in two studies from the Nordic countries [6,15]. Mean age at diagnosis is 50-54 years [15-17], with no difference between men and women [16]. CP, which is a less common tumour, has an annual incidence of 0.13-0.17 cases per 100 000 inhabitants [18,19] but constitute 5-15% of intracranial tumours in children [20,21]. In patients with CP, the age at diagnosis has been reported to have a bimodal shape, with one peak during childhood and another during adulthood [18,22,23].

1.3 Symptoms and signs

The manifestations of a non-functioning pituitary tumour are determined by tumour size, the velocity of tumour growth and the direction of the tumour expansion. The presenting symptoms are often visual field defects or symptoms related to hormonal deficiencies but can also be headache, symptoms from pressure on cranial nerves, rhinorrhoea or nausea [16,17,24-29]. In some cases the presenting symptom can be a haemorrhage or an infarction of the adenoma, i.e. tumour apoplexy, which can lead to sudden expansion of the tumour resulting in acute headache, visual impairment and hypopituitarism [30]. It is not unusual that a pituitary mass causes a bitemporal hemianopsia due to pressure on the central optic chiasm of the tumour mass. Depending on the duration of the pressure an optic atrophy can develop leading to irreversible visual field defects and reduced acuity. For patients with childhood-onset of a pituitary tumour (mainly CP) failure of growth due to hypopituitarism can be an early symptom leading to further medical evaluation [27-29]. Early symptoms in women with pituitary masses are amenorrhoea, anovulation and infertility [16,25] that can lead the investigation into examining the function of the pituitary gland.

1.4 Tumour treatment

After the introduction of magnetic resonance imaging (MRI) the number of incidentally found pituitary tumours, especially NFPA, has increased. This has increased the number of patients with NFPA that can be followed with a wait and see strategy. The natural history of NFPA is to some degree unclear. The existing studies have been small and investigated incidentally found tumours or tumours leading to symptoms for which surgery was postponed for various reasons [31-34].

The therapeutic options for patients with a non-functioning pituitary tumour are surgery, radiation therapy (RT), medical therapy and conservative treatment. Individual factors, such as severity of symptoms (especially optic nerve compression) as well as tumour type and location, influence the choice of treatment. If a pituitary tumour threatens the optic chiasm, the primary choice of tumour treatment is surgery [31,33]. When surgical treatment is performed, the first-hand choice is a transsphenoidal approach, whereas the transcranial approach is used in complicated cases and when the tumour cannot be resected from inside the sella. In addition to the nature of the tumour, the outcome of surgery is highly dependent on the experience of the surgeon [35].

For CP tumours the primary treatment is surgery. In CP tumours that are predominantly cystic the resection can be facilitated by preoperative fluid aspiration. The question of whether gross total remove should be attempted has been debated. Today many centres try to perform a gross total removal as long as hazardous manipulations of critical brain areas can be avoided [36]. Several factors, including firm attachment of the tumour capsule to blood vessels or hypothalamic tissue, may inhibit the surgeon from executing a total gross removal and instead aim for a partial removal and preservation of the vessels and the hypothalamus [36,37].

In most cases when total tumour removal is not possible or when is not attempted, the second line of treatment is RT. RT treatment is also used in recurrent NFPA and CP tumours when surgical treatment is no longer an option. Although treatment with RT has shown a high rate of tumour control [38-41], it is also associated with an increased risk of developing additional pituitary hormone deficiencies, an increased risk of optic neuropathy as well as secondary brain tumours [42-46]. In addition, RT for pituitary tumours has been associated with an increased morbidity and mortality due to cerebrovascular diseases [47-49]. The combination of these side effects and a suggested increased cerebrovascular mortality has resulted in some centres using RT more conservatively in the general treatment of NFPA and CP patients during the last decade.

1.5 Hypopituitarism and growth hormone deficiency

Hypopituitarism is defined as a non-adequate secretion of one or several of the hormones produced by the anterior lobe of the pituitary gland. Many patients with a non-functioning pituitary tumour develop hypopituitarism, due to the volume effect of the tumour or as a consequence of tumour treatment. Somatotropin deficiency, i.e. growth hormone (GH) deficiency (GHD), is often the first hormone deficiency to occur and is present in almost all patients with a pituitary tumour who have received RT and in 60-80% of patients treated with surgery alone as tumour treatment [42,50,51]. These patients also often develop additional hormone deficiencies, i.e. gonadotropin, thyrotropin and/or cortotropin deficiency. Diabetes insipidus (DI) is less common (0-10%) in patients with NFPA [16,17,52,53] but frequent in patients with CP, especially after surgical treatment when approximately 60% of CP patients suffer from DI [51,54]. Historically all hormone deficiencies excluding GHD have been treated with replacement therapy. The clinical picture of non-replaced GHD in hypopituitary adults was recognised in the beginning of the 1990s and it has been associated with increased vascular mortality, premature atherosclerosis, abnormal body composition, reduced bone mass, an unfavourable lipid profile, reduced muscle strength and fatigue and reduced quality of life [55-62]. The paediatric use of GH therapy started already in the 1950s, when physicians first treated children with short stature and severe GHD [63]. Since then, many children have been able to reach normal or near normal final height with the help of GH therapy. In addition to enabling short statured children to reach full height, GH replacement therapy (GHRT) has been shown to improve most of the abnormalities in adult GHD [64-67]. Long-term GHRT has therefore become common practice in many countries. The efficacy and safety profile of GHRT has led to a continuation of long-term GHRT in adults and continued therapy of GHD children into adulthood if GHD is still present.

1.6 Mitogenic effects of GH and IGF-I

Already in the 1950s, it was suggested that GH had a role in the development of malignant tumours, since hypophysectomy was seen to induce remission in patients with metastatic mammary carcinoma [68]. Today, after more than half a century, circulating and extra pituitary expression of GH and insulin-like growth factor-I (IGF-I) has been proposed to have a roll in the development and progression of tumours. The

evidence is based on animal models where different types of transgenic mice with reduced levels of GH and IGF-I are resistant to carcinogenesis induced by chemicals [69-71]. In contrast, transgenic mice with excess human-GH or IGF-I have shown an increased rate of mammary tumours or epidermal tumours [72-74]. Since GH and IGF-I are mitogenic factors and studies have found GH receptors in both NFPA and CP cells [75-77], there is a theoretical risk of an increased frequency of tumour progression in patients treated with long-term GHRT [78,79].

Due to the clinical benefits in patients with GHD, long-term GHRT has become common practice in many countries. There are, for reason mentioned above, some concerns regarding the possibility that GH and IGF-I may be associated with cancer and an elevated risk of tumour progression. Patients with acromegaly who, often for many years, have supraphysiological levels of GH and IGF-I have been studied with conflicting results. Some studies have shown an increased risk of cancer in acromegalic patients [80-83] whereas other studies have not been able to demonstrate this [84,85]. These conflicting data cannot rule out that the elevated GH and IGF-I concentrations may play a role in the risk of cancer. Popovic et al. showed an increased incidence of neoplasia in acromegalic patients, although the incidence was not higher than in patients with NFPA [86]. Another study described an increased incidence of colorectal cancer in patients with hypopituitarism without GHRT [87]. These results suggest that there may be another explanation for the increased incidence of malignancies in acromegaly, such as an inherently higher risk in hypopituitarism, or that patients with pituitary adenomas are prone to develop neoplasia in general, or the use of RT in this patient population [45,87]. It is important to remember when comparing GHRT to acromegaly that the aim of GHRT is to obtain physiological levels of GH and not supra-physiological levels as in acromegaly.

Several studies have investigated the association between serum IGF-I concentrations and malignancies in the normal population. For instance, Chan et al. have shown a positive association between prostate cancer risk and serum IGF-I concentrations in the highest quartile of the normal range [88]. In a meta-analysis of the association between concentrations of IGF-I and insulin-like growth factor-binding protein-3 (IGFBP-3) with prostate cancer, colorectal cancer, breast cancer and lung cancer, high circulating concentrations of IGF-I or IGFBP-3 were associated with an increased risk of prostate cancer, colorectal cancer and premenopausal breast cancer [89]. These associations were modest and vary between tumour sites. In addition, the frequency of secondary neoplasms was not elevated in a large population of adult GHD patients treated with long-term GHRT [90].

Since GH and IGF-I are known mitogenic factors, there is a theoretical risk that GHRT could potentially increase the rate of tumour progression in patients with pituitary tumours. This is an important safety issue for the majority of hypopituitary patients who have an underlying pituitary tumour. Occasionally case reports appear regarding patients with rapid growth of a pituitary tumour after initiation of GHRT [91,92]. In addition it has been shown that patients who develop progression of a pituitary tumour have an excess mortality [93]. Thus, the question of whether GHRT increases the

tumour progression rate is important not only for achieving local tumour control but also for the overall outcome in these patients.

1.7 Tumour progression

Tumour progression in non-functioning pituitary tumours is often reported as tumour progression free survival rate (PFSR). Most studies define tumour progression as any increase in the tumour size depicted at imaging regardless of clinical symptoms or need of additional tumour treatment. The PFSR varies between NFPA and CPs and is therefore described separately.

1.7.1 Tumour progression in patients with NFPA

Tumour progression rate may be underestimated in older studies when computerised tomography was used instead of MRI, which is routinely used in the management of pituitary tumours today. The 10-year PFSR in NFPA patients whose tumour treatment involved RT has been reported to be 89%-98% [25,38,39,94] (Table 1). In patients treated with surgery alone, the 10-year PFSR for patients with and without a residual tumour after the primary tumour treatment was 23%-58% and 91%-100%, respectively [25,95]. Thus, the risk of tumour progression is strongly dependent on the outcome of the primary surgical treatment as well as on whether RT was part of the primary tumour treatment [16,24,25].

Three early studies on patients with pituitary tumours, including those with NFPA, who received GHRT, did not report an increase in the tumour progression rate. They indeed had low progression rates compared to historical series [58,96,97] (Table 1). These studies had severe limitations as the tumours had mixed aetiologies, there was also a short follow-up, no comparison with a control group and, in some a high percentage of initial RT. These factors may confound detection of any negative effect of GHRT, in particular on a slowly growing tumour such as NFPA.

In the first comparative study of 55 NFPA patients with GHRT, Buchfelder et al. showed a similar frequency of tumour progression in patients with and without GHRT [98] (Table 1). The optimal setting for investigating any stimulating effect of GHRT on tumour cells is to study RT naive NFPA, since RT has a well-known anti-proliferative effect. Arnold and colleagues studied the effect of GHRT on 23 RT naive NFPA patients receiving GHRT for a mean duration of 4.6 years and did not find that GHRT was an independent predictor of tumour progression [99]. In summary, larger comparative studies of NFPA patients with longer follow-up are still needed to unravel whether GHRT is associated with an increased risk of tumour progression.

Table 1. Tumour progression free survival in NFPA patients sub-grouped depending on GHRT.

Study – First author [ref]	No. of patients	Aetiology	Mean follow-up (yrs)	RT	Progression free survival rate: 10 years
All patients treated with GHRT §					
Frajese [96]	100	Mixed	2.8 [^]	91%	(NED) 1 patient had tumour progression
Abs [58]	1034	Mixed	0.8	No data	(NED) 6 patients had tumour progression
Chung [97]	48	Mixed	3.2 [□]	0%	(NED) 3 patients had tumour progression
Comparison between patients with and without GHRT §					
Hatrick [100]	47 (GHRT)	Mixed	3.6	38%	(NED) 2 patients had tumour progression
	28 (No GH)	Mixed	3.4	75%	(NED) 2 patients had tumour progression
Buchfelder [98]	55 (GHRT)	All NFPA	5 (At least)	20%	(NED) 29% had tumour progression
	55 (No GH)	All NFPA	5 (At least)	24%	(NED) 22% had tumour progression
Arnold [99]	23 (GHRT)	All NFPA	4.6	0%	(NED) 35% had tumour progression
	107 (No GH)	All NFPA	6.8	0%	(NED) 36% had tumour progression
Reference series in patients without GHRT					
Gitteos [38]	63	All NFPA	8.1	0%	47%
	63	All NFPA	9.1	100%	93%
Brada [94]	252	All NFPA	10.5 [□]	100%	94%
Flickinger [101]	112	All NFPA	No data	100%	89%
Park [39]	132	All NFPA	3.8 [□]	0%	49%
	44	All NFPA	5.7 [□]	100%	98%
O’Sullivan [95]	126	All NFPA	5.7 [□]	0%	49%

GHRT, Growth hormone replacement therapy, NED, No exact data; NFPA, Non-functioning pituitary adenoma; RT, Radiation therapy; [^], Calculated number; [□], Follow-up period presented as median value; §, For patients treated with GHRT the mean follow-up time refers to the mean duration of GHRT.

1.7.2 Tumour progression in patients with CP

Craniopharyngiomas have a strong tendency to progress and infiltrate the surrounding structures, which affects the choice and aggressiveness of tumour treatment. As for NFPAAs, the progression rate for CP is strongly affected by the inclusion of RT in the primary treatment. The 10-year PFSR in CP patients with initial RT treatment has been reported to be 83%-92% [27,41,102] (Table 2). In CP patients treated with surgery alone the 10-year PFSR was 41% for patients with a residual tumour after primary tumour treatment [27]. The corresponding figure for patients treated surgically without any residual tumour was 47%-81% [27,36,102].

Table 2. Tumour progression free survival in CP patients sub-grouped depending on GHRT.

Study – First author [ref]	No. of patients	Aetiology	Mean follow-up (yrs)	RT	Progression free survival rate: 10 years
All patients treated with GHRT §					
Clayton [103]	23	All CP	3.8	48%	(NED) 7 patients had tumour progression
Cowell [104]	62	All CP	3.8	No data	(NED) 7 patients had tumour progression
Chung [105]	50	Mixed	3.0□	70%	(NED) 4 patients had tumour progression
Darendeliler [106]	1038	All CP	2.8□	32%	63%
Comparison between patients with and without GHRT §					
Karavitaki [107]	32 (GHRT)	All CP	6.3	66%	(NED) 4 patients had tumour progression
	53 (No GH)	All CP	8.3	32%	(NED) 22 patients had tumour progression
Rohrer [108]	22 (GHRT)	All CP	8.8□ ×	34%×	(NED) 11 patients had tumour progression
	7 (No GH)	All CP	8.8□ ×	34%×	(NED) 4 patients had tumour progression
Müller [109]	54 (GHRT)	All CP	2.8□	26%×	GHRT had no effect on the progression free survival
	60 (No GH)	All CP	3.0	26%×	
Reference series in patients without GHRT					
Van Effenterre [29] *	122	All CP	7.5	6%	60%
Duff [27] *	96	All CP	10×	0%	69%
	25	All CP	10×	100%	92%
Stripp [102] *	57	All CP	7.6□ ×	0%	42%
	18	All CP	7.6□ ×	100%	84%
Rajan [41] #	173	All CP	12□	100%	83%

CP, Craniopharyngioma; GHRT, Growth hormone replacement therapy; NED, No exact data; RT, Radiation therapy; ×, For the entire study; *, No information about GHRT in the paper; □, Follow-up period presented as median value; #, 26 children were treated with GHRT; §, For patients treated with GHRT the mean follow-up time refers to the mean duration of GHRT.

A few studies have been performed to assess whether GHRT influences the risk of tumour progression in CP patients during the past 30 years (Table 2). In one of the first studies, Clayton et al., published their experiences in 1988 after having treated 23 paediatric CP patients with GHRT for a mean follow-up time of 3.8 years and found that seven patients had tumour progression [103]. Almost 20 years later, Darendeliler presented the results of the KIGS (Pfizer International Growth database) registry-study in terms of recurrence of brain tumours in paediatric patients receiving GHRT. In 1038 CP patients with a median duration of GHRT of 2.8 years the 10-year PFSR was 63% [106].

Three studies have directly compared the progression rate in CP patients with and without GHRT (Table 2). Karavitaki et al. showed a lower frequency of tumour progression in 32 patients with GHRT compared to 53 patients without [107]. The frequency of RT treatment was, however, more than doubled in the GHRT group compared to non-GHRT group. Rohrer and colleagues showed similar frequencies of tumour progression in 22 patients with GHRT compared to seven patients without GHRT [108]. In the most recent paper, Müller and colleagues assembled a multicentre study and recruited 54 childhood-onset CP patients with GHRT and 60 controls. GHRT was not found to be an individual risk factor for tumour progression, but the median duration of GHRT in this study was only 2.8 years [109].

In summary, previous non-comparative studies do not suggest that there is an increase in the tumour progression rate in CP patients receiving GHRT, nor do the few comparative studies of GHRT in CP patients, which have had a limited number of patients or short duration of therapy.

1.8 Mortality and morbidity

A long list of local tumour-related symptoms and symptoms caused by hypopituitarism have been described in patients with non-functioning pituitary tumours, but for many years the long-term effects on mortality was unknown. In 1990, Rosén and Bengtsson showed that patients with hypopituitarism, mainly caused by non-functioning pituitary tumours, had an excess mortality, particularly from vascular diseases [55]. In the years following, two out of three retrospective studies, including between 172 and 348 patients, showed an excess mortality in hypopituitary patients [110-112]. A decade after Rosén and Bengtsson published their paper, Tomlinson and colleagues presented results from the West Midlands Hypopituitary database in which 1014 hypopituitary patients (57% NFPA, 12% CPs) were studied regarding mortality [49]. This large study also showed an increase in the overall mortality ratio in hypopituitary patients compared to the general population (standardised mortality ratio (SMR) 1.9, 95% confidence interval (CI) 1.6-2.2). Subgrouping by specific aetiologies showed that NFPA and CP had SMRs of 1.7 (95% CI 1.3-2.2) and 9.3 (95% CI 5.8-15), respectively. In NFPA patients, the excess mortality was mainly explained by deaths due to respiratory and vascular diseases. For CP patients, the excess mortality was caused by respiratory and cerebrovascular deaths.

1.8.1 Mortality in patients with NFPA

In Nilsson and colleagues' registry-based study of 2279 patients with pituitary adenoma, mortality was investigated during the time period 1958 to 1991 [15]. Patients with acromegaly and Cushing's disease were excluded. Since prolactin measurements were not used in routine clinical care during more than half of the duration of that study, it is likely that a substantial number of prolactinomas was included in the study population. The study reported an excess mortality (SMR 2.0, 95% CI 1.9-2.2) in patients with a pituitary adenoma and a significantly higher mortality in women compared to men. The most common cause of death was cardiovascular disease, including cerebrovascular disease. Later, Lindholm and colleagues were unable to

confirm the excess mortality reported by Nilsson et al. in a surgical series of 160 NFPA patients (SMR 1.2, 95% CI 0.9-1.6) [113]. However, after subgrouping regarding to gender, they found an increased mortality ratio in women with NFPA compared to the general population. The mortality in NFPA patients is therefore still somewhat unclear. In addition, the impact of clinical factors such as surgery, RT, hypopituitarism, DI or age at diagnosis on mortality is largely unknown.

1.8.2 Mortality and morbidity in patients with CP

For patients with CP, Bülow et al. (1998) was the first to report an excess mortality (SMR 5.6, 95% CI 3.7-8.2) in a series of 60 patients, mainly due to cardiovascular causes, including cerebrovascular causes [114]. Since then, two retrospective series of 70 and 54 patients from referral centres have reported an increased SMR of 8.8 (95% CI 5.4-13) and 2.9 (1.4-5.0), respectively [23,115]. In addition, Pereira et al. also reported a possible increase in the incidence of cerebrovascular accidents and myocardial infarctions compared to the general population [115].

Despite the fact that CPs receive a great deal of attention from many physicians, as stated by Dr J. T. Rutka “There is perhaps no other primary brain tumour that evokes more passion, emotion, and, as a result, controversy than does the craniopharyngioma” [116], there are only three small studies from referral centres that have investigated the mortality in CP patients. As a consequence, the effect of clinical factors such as age at diagnosis, tumour treatment and hormone deficiencies on mortality and morbidity in CP patients are still largely unknown.

2 AIM

Overall aim of this thesis was to study tumour progression as well as mortality and morbidity in patients with NFPA and CP.

The specific aims of the thesis were:

Paper I: To study if growth hormone replacement therapy increases the frequency of tumour progression in patients with NFPA.

Paper II: To study if growth hormone replacement therapy increases the frequency of tumour progression in patients with CP.

Paper III: To study mortality in patients with NFPA.

Paper IV: To study mortality and morbidity in patients with CP.

3 SUBJECTS AND METHODS

3.1 Study design and subjects

3.1.1 Paper I

The study was performed as a case-control study. The cases consisted of a sub-population from an ongoing open long-term study of GHRT in consecutive adult patients with hypopituitarism, including GHD, caused by different aetiologies, at the Centre for Endocrinology and Metabolism at the Sahlgrenska University Hospital, Gothenburg, Sweden [66,67]. To be eligible for this study, patients needed to fulfil three inclusion criteria: I) hypopituitarism and GHD caused by NFPA, II) GHRT for at least two years and III) imaging performed before commencement of GHRT and after at least two years of treatment. A total of 121 patients with NFPA were included in the study. The characteristics and primary treatment of the enrolled patients are presented in Table 3. The vast majority of the patients (95%) were evaluated with MRI on the final imaging. GHD was diagnosed using conventional criteria [66,67].

Table 3. Details of enrolled NFPA patients treated with GHRT and controls.

	NFPA patients with GHRT	Controls (Non-GHRT)
Number of patients	121	114
Gender, M/F (%)	66/34	66/34
Age at diagnosis, years	49.6±12.8 (19-74)	51.6±12.0 (15-75)
Observation period, years	9.9±3.9 (2-17)	10.1±4.4 (2-21)
<i>Primary tumour treatment</i>		
Surgery alone	71%	76%
Radiation therapy alone	1%	0%
Surgery combined with radiation therapy	28%	24%

Values presented as means ± SD (range), if not stated otherwise. GHRT, Growth hormone replacement therapy; NFPA, Non-functioning pituitary adenoma.

The control group of non-GHRT treated patients was created by matching the GHRT treated patients with patients in the database at the Department of Neurosurgery at the Erlangen-Nuremberg University Hospital in Germany. Three matching criteria were mandatory (NFPA aetiology, type of initial tumour treatment and absence of GHRT) and four criteria were dispositive (gender, age, age at diagnosis and duration of follow-up). The matching process resulted in 114 control patients, whose details can be seen in Table 3. The last imaging evaluation was performed with MRI in 91% of the control group.

Both the GHRT treated patients and the controls were divided into two groups depending on whether RT had been part of the initial tumour treatment. The GHRT patients were further subdivided depending on the absence or presence of a known residual tumour after the initial tumour treatment. On the basis of comparison of the

imaging appearance of the sella turcica at the end of the observation period to baseline, the GHRT patients and the controls were categorised as either having tumour progression or not. All tumour recurrence or enlargement was classified as tumour progression at the time it first was seen on imaging, regardless of the size or clinical relevance. Tumour progression was classified to be of clinical significance if any intervention with surgery or RT was necessary. All imaging was performed as part of the routine clinical surveillance programme.

3.1.2 Paper II

The study was performed as a case-control study. The cases consisted of a sub-population from the same ongoing open long-term study of GHRT as described for Paper I. The cases in this study were selected based on three inclusion criteria: I) hypopituitarism and GHD caused by CP; II) GHRT for at least three years; and III) imaging performed before commencement of GHRT and after at least two years of treatment. Fifty-six CP patients were eligible for inclusion in the analysis and their characteristics are shown in Table 4. The last imaging in the study was performed by MRI in 77% of the patients.

Table 4. Details of enrolled CP patients treated with GHRT and controls.

	CP patients with GHRT	Controls (Non-GHRT)
Number of patients	56	70
Gender, M/F (%)	57/43	49/51
Age, years	46.6±16.1 (22-75)	45.7±16.2 (6-76)
Age at diagnosis, years	25.1±16.4 (4-62)	32.3±16.9 (2-65)
Observational period, years	13.6±5.0 (3-28)	13.4±7.8 (3-34)
<i>Primary tumour treatment</i>		
Surgery alone	45%	64%
Surgery combined with radiation therapy	50%	26%
Cyst-puncture alone	2%	3%
Cyst-puncture combined with radiation therapy	4%	6%
Radiation therapy alone	0%	1%
Residual tumour after primary treatment	29%	47%

Values presented as means ± SD (range), if not stated otherwise. CP, Craniopharyngioma; GHRT, Growth hormone replacement therapy.

The control patients, all without GHRT, were sampled from the hospital database at the Department of Neurosurgery at Erlangen-Nuremberg University Hospital in Germany. The process of sampling the control patients involved three mandatory criteria (CP aetiology, absence of GHRT and type of initial tumour treatment) and four dispositive criteria (gender, age, age at diagnosis and duration of follow-up). The characteristics of the controls and the result of the sampling process are shown in Table 4. The last imaging in the study was performed with MRI in 74% of the control patients.

All patients, both GHRT treated patients and controls, were divided on the basis of their tumour status at baseline. Patients without a residual tumour at baseline were categorised of either having recurrence or no recurrence at the end of the observational

period. Patients with a known residual tumour at baseline were categorised at the end of the observational period as to the presence or absence of tumour enlargement. Tumour recurrence and tumour enlargement were determined by a comparison of the imaging appearance of the sella turcica at the end of the observation period to baseline. Regardless of size or clinical relevance, all tumour recurrences or enlargements were classified as tumour progression, at the time it was first detected by imaging. Tumour progression that required intervention with cyst-puncture, surgery or RT was classified as being of clinical significance. All imaging was performed as part of the routine clinical surveillance programme.

3.1.3 Paper III

The study was performed as a nationwide, registry-based study of patients with NFPA in Sweden. The Swedish National Patient Registry (Patient Registry), which reached national coverage in 1987, was used to identify patients with NFPA. Information regarding mortality was gathered from The Swedish Cause of Death Registry (Cause of Death Registry). Both registries uphold a high quality and are maintained by The National Board of Health and Welfare [117,118]. The Swedish personal identification number makes it possible to link the two registries together.

To ensure a high quality in the inclusion phase [119] the following combination of inclusion criteria were used: Patients should either 1) have been given the NFPA diagnosis (ICD-10: D35.2) from a medical/endocrine care unit at least twice or 2) have been given the NFPA diagnosis from a neurological or neurosurgical care unit at least once and also at least once from a medical/endocrine care unit. Patients that at any time had been diagnosed with secreting pituitary adenoma, craniopharyngioma, pituitary cyst or a pinealoma were excluded before the inclusion criteria were applied to the Patient Registry. An internal validation of the NFPA diagnosis was performed in all patients who originated from the Sahlgrenska University Hospital's uptake area.

Patients with a diagnosis of NFPA were identified from January 1st, 1997, when the ICD-10 classification was implemented, to the end of the study, December 31st, 2011. Identified patients were included in the study either on the date of diagnosis or at the start of the study, January 1st, 1987. Patients were followed to study mortality from the time of diagnosis to death or end of the study. Information regarding surgical treatments and RTs were obtained from the Patient Registry from initiation of ICD-10 classification (January 1st, 1997) until December 31st, 2011.

The inclusion criteria identified 2795 patients (1502 men, 1293 women) in the Patient Registry whose characteristics can be seen in Table 5. More than 20 000 patient-years were included in the analysis. The internal validation of the NFPA diagnosis was performed in 467 patients and resulted in a positive predictive value of 91%. Merely one percentage of the patients had aetiologies not affecting the sella region.

Table 5. Characteristics of included patients with non-functioning pituitary adenoma, diagnosed between Jan 1st, 1987 and Dec 31st, 2011 in Sweden.

	Number of patients
Patients with non-functioning pituitary adenoma	2795
Men (%)	1502 (54)
Women (%)	1293 (46)
Mean age at diagnosis, years (range)	58 (1-97)
Men, years (SD)	60 (15)
Women, years (SD)	56 (18)
Mean follow-up time, years (range)	7 (0-25)
Patients with hypopituitarism (%)	1500 (54)
Patients with diabetes insipidus (%)	145 (5)
Patients without hormonal deficiencies (%)	1266 (45)
Patients diagnosed at or before 40 years of age (%)	423 (15)
Patients diagnosed before 1 st Jan, 1997 (%)	322 (12)
Patients diagnosed between 1 st Jan, 1997 and 31 st Dec, 2011 (%)	2473 (88)
Treatments of patients diagnosed between 1st Jan, 1997 and 31st Dec, 2011	
No surgical treatment or radiation therapy (%)	1172 (47)
Surgical treatment (%)	1276 (52)
At least two surgical treatments (%)	265 (11)
Radiation therapy (%)	104 (4)

SD, Standard deviation.

3.1.4 Paper IV

The study was performed as a nationwide, registry-based study of patients with CP in Sweden. Patients with CP were identified in the Patient Registry and The Swedish Cancer Registry (Cancer Registry). In Sweden it is mandatory to report all malignant tumours and some benign tumours, including CP, to the Cancer Registry [120]. Mortality and morbidity were collected from the Patient Registry, the Cause of Death Registry and the Cancer Registry. All three registries are reported to uphold a high quality [117,118,121]. The Swedish personal identification number made it possible to cross-reference between the registries and follow a patient throughout the study period.

To utilise the strength of both the Patient Registry and the Cancer Registry the following inclusion criteria were used: Patients should either 1) have been diagnosed with CP in the Cancer Registry (ICD-O/3 code C75.1 and C24/histological code 881) or 2) have been given the CP diagnosis (ICD-10 code D35.3) from a neurosurgical or neurological care unit at least once and/or from an internal medicine/endocrine care unit at least twice during the identification period. Patients that at any time had been diagnosed with a secreting pituitary adenoma were excluded before the inclusion criteria were applied to the registries. An internal validation of the CP diagnosis was performed in all patients who originated from the Sahlgrenska University Hospital's uptake area.

Since the diagnosis of CP was assigned a unique diagnostic code only from the 10th version of the ICD classification, patients with a diagnosis of CP were identified from January 1st, 1997, when ICD-10 classification was implemented in Sweden, to the end of the study, December 31st, 2011. Identified patients were then included in the study either on the date of diagnosis or at the start of the study, January 1st, 1987. Patients were followed to study mortality and morbidity from the time of diagnosis to death or end of the study. Information regarding surgical treatments and RTs were obtained from the Patients Registry during the ICD-10 classification period.

The inclusion criteria identified 307 CP patients (151 men, 156 women) who were enrolled in the study. The average follow-up time was nine years, which resulted in over 2800 patient-years included in the analysis. Additional characteristics for the CP patients can be seen in Table 6. The internal validation of the CP diagnosis in 86 patients originating from the Sahlgrenska University Hospital's uptake area resulted in a positive predictive value of 97% and a sensitivity of 92%. Only three patients were incorrectly labelled with CP and had a NFPA (n=2) or an opticus glioma (n=1).

Table 6. Characteristics of included patients with craniopharyngioma, diagnosed between Jan 1st, 1987 and Dec 31st, 2011 in Sweden.

	Number of patients
Patients with craniopharyngioma	307
Men (%)	151 (49)
Women (%)	156 (51)
Mean age at diagnosis, years (range)	35 (0-81)
Mean follow-up time, years (range)	9 (0-25)
Patients with hypopituitarism (%)	250 (81)
Patients with diabetes insipidus (%)	110 (36)
Patients without hormonal deficiencies (%)	54 (18)
Patients with childhood-onset (%)	106 (35)
Mean age at diagnosis (SD)	10 (4.6)
Patients with adult-onset (%)	201 (65)
Mean age at diagnosis (SD)	49 (15)
Patients diagnosed before Jan 1 st , 1997 (%)	73 (24)
Patients diagnosed between Jan 1 st , 1997 to Dec 31 st , 2011 (%)	234 (76)
Treatments of patients diagnosed between Jan 1st, 1997 to Dec 31st, 2011	
Surgical treatment (%)	194 (83)
At least two surgical treatments (%)	72 (31)
Radiation therapy treatment (%)	70 (30)

SD, Standard deviation; Childhood-onset of craniopharyngioma was defined as receiving the diagnosis at age of 18 years or lower.

3.2 Statistical methods

3.2.1 Paper I-II

All descriptive statistical analyses are presented as mean value and SD if not stated otherwise. Comparisons between different groups of patients were performed using Student's t-test. The level of significance was set at $p < 0.05$ with a two-way test. Kaplan-Meier survival curves were obtained to describe the progression-free survival of the patients. The log-rank test was used to compare tumour progression-free times between subgroups.

In Paper II, Cox-regression analyses were used to analyse the impact of potential co-variables (gender, age at diagnosis, GHRT, residual tumour and RT) on tumour progression. A SAS macro [122] was used to calculate the adjusted survival probabilities including a 95% CI, stratified by GHRT. The level of significance was set at $p < 0.05$ with a two-way test.

3.2.2 Paper III-IV

All descriptive statistical analyses are presented as mean value and SD if not stated otherwise. Comparisons between different groups of patients were performed using Student's t-test. Person-years at risk were calculated from study inclusion to follow-up diagnosis/death or end of study and were stratified according to gender, five-year age groups, and one-year calendar periods. The expected number of cases for each stratum was calculated using the general Swedish population as reference. The observed cases of follow-up diagnoses/deaths among the included subjects were compared to the expected using SMRs and standardised incidence ratios (SIRs). SIRs for each diagnosis were calculated depending on if the patients received the specific diagnosis on a yearly basis, with the exception of the diagnoses of type 2 diabetes mellitus (T2DM) and severe visual impairment, which were analysed on the basis of the first event only. SIR calculations were only used in Paper IV. Ninety-five percent CIs were calculated assuming a Poisson distribution of the observed numbers. None of the patients in the subgroups that were internally validated were lost to follow-up. Subgroup analyses in patients depending on gender, age at diagnosis, RT, and hormonal deficiencies have been performed. SMRs and SIRs for non-overlapping subgroups were compared to each other [123]. Average years of life lost (cut off at age: 75) [124] was calculated for the entire study population and subgroups. Overall survival rates were analysed with the Kaplan-Meier method. Annual incidence rates with 95% CIs were estimated for NFPAs and CPs in Sweden between 1997 and 2011.

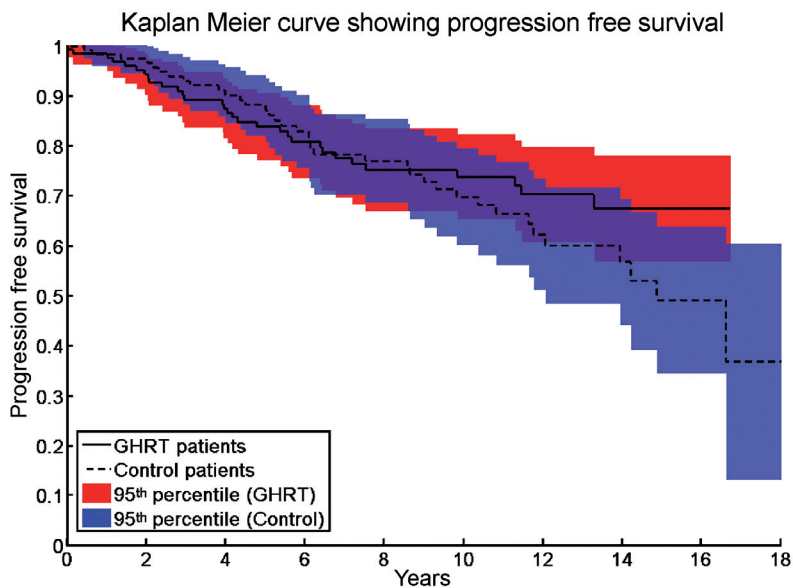
4 RESULTS

4.1 Paper I

4.1.1 Patients treated with GHRT

Tumour progression, i.e. tumour recurrence or tumour enlargement, was seen in 31 (26%) out of 121 patients treated with GHRT during the study period. In 19 patients the tumour progression was deemed to be clinically significant (Table 7). The overall 10-year PFSR for all patients with GHRT was 74% (Fig 1). Subgrouping depending on whether patients had received initial RT resulted in a 10-year PFSR of 88% and 66% for patients with and without initial RT, respectively. Progression rates for GHRT patients subgrouped depending on the presence of residual tumour after the primary tumour treatment and the use of initial RT are presented in Table 7.

Figure 1. Progression-free survival in NFPA patients with and without GHRT.



There was no significant difference between the groups ($p=0.36$). GHRT, Growth hormone replacement therapy.

4.1.2 Control patients

During the study period, 37 (32%) out of the 114 control patients developed tumour progression (Table 7). The tumour progression was considered to be clinically significant in 32 patients. The overall 10-year PFSR for the control patients was 70% (Fig 1). For control patients without initial RT the 10-year PFSR was 59%. None of the 27 control patients with initial RT developed tumour progression during the study.

Table 7. Tumour progression in GHRT patients and control patients and a comparison of subgroups with regard to initial radiation therapy and residual tumour after primary tumour treatment.

	Tumour progression	No tumour progression	No tumour progression or clinically insignificant tumour progression #
GHRT patients (n=121)	n=31 (26%)	n=90 (74%)	n=102 (84%)
-without RT (n=86)	n=27 (31%)	n=59 (69%)	n=70 (81%)
-with residual adenoma (n=54)	n=24 (44%)	n=30 (56%)	n=38 (70%)
-without residual adenoma (n=32)	n=3 (9%)	n=29 (91%)	n=32 (100%)
-with RT (n=35)	n=4 (11%)	n=31 (89%)	n=32 (91%)
-with residual adenoma (n=17)	n=2 (12%)	n=15 (88%)	n=16 (94%)
-without residual adenoma (n=18)	n=2 (11%)	n=16 (89%)	n=16 (89%)
Control patients (n=114)	n=37 (32%)	n=77 (68%)	n=82 (72%)
-without RT (n=87)	n=37 (43%)	n=50 (57%)	n=55 (63%)
-with RT (n=27)	n=0 (0%)	n=27 (100%)	n=27 (100%)

GHRT, Growth hormone replacement treatment; RT, Radiation therapy; #, Clinically insignificant tumour progression was defined as tumour progression not resulting in additional tumour treatment.

4.1.3 Comparison between patients with and without GHRT

The 10-year PFSR in patients with GHRT was 74%, while it was 70% in control patients. No significant difference in the PFSR between patients with GHRT and control patients was found (p-value: 0.36; Fig 1), nor were there significant differences in PFSR between GHRT patients and control patients who had received initial RT (p-value: 0.09) or not (p-value: 0.45).

4.2 Paper II

4.2.1 Long-term outcome for all patients

Tumour progression, i.e. tumour recurrence or tumour enlargement, was experienced by 39 patients (31%) out of the total study population of 126 CP patients. In 34 patients the tumour progression was judged to be clinically significant. The overall 10-year PFSR was 72% for the entire study population (Table 8). All patients were divided in groups depending on whether they had received initial RT or not and whether they had a residual tumour after their primary tumour treatment or not. The PFSRs for these four subgroups are shown in Table 8. The 10-year PFSR for all patients with initial RT was 90% compared to 58% for patients without initial RT.

The outcome regarding tumour progression was analysed using a Cox-regression, which showed that initial RT (Hazard ratio (HR) 0.13, 95% CI 0.05-0.33) and the presence of a residual tumour after primary tumour treatment (3.2, 1.6-6.2) were both associated with significant effects on tumour progression. Age at diagnosis (HR 1.0, 95% CI 1.0-1.0) and gender (0.55, 0.28-1.1) had no significant effect on tumour progression.

Table 8. Tumour progression-free survival for the entire population and subgroups divided depending on GHRT, initial RT and residual tumour after primary treatment.

	Progression-free survival at		
	5 years	10 years	15 years
All CP patients (n=126)	82%	72%	67%
- No initial RT & No residual tumour (n=56)	78%	66%	57%^
- No initial RT & Residual tumour (n=17)	47%	32%	24%
- Initial RT & No residual tumour (n=21)	100%	100%	90%
- Initial RT & Residual tumour (n=32)	91%	82%	72%
CP patients treated with GHRT (n=56)	91%	88%	79%
- Adjusted for uneven distributed factors*	88%	85%	72%
CP patients not treated with GHRT (n=70)	75%	57%	53%
- Adjusted for uneven distributed factors*	79%	65%	60%

CP, Craniopharyngioma; GHRT, Growth hormone replacement therapy; RT, Radiation therapy; *, Adjusted for initial RT, residual tumour after primary treatment and gender (Cox-regression); ^, Last event recorded at 13.1 years of follow-up.

4.2.2 Comparison between patients with and without GHRT

Out of the 56 CP patients treated with GHRT, nine patients (16%) developed tumour progression during the study period (Table 9). All nine patients had clinically significant tumour progression. Among the 70 control patients with CP, who were not treated with GHRT, 30 patients (43%) had tumour progression. The tumour progression was clinically significant in 25 control patients. The effect of initial RT on the tumour progression rate in GHRT and control patients is shown in Table 9.

Table 9. Tumour progression rates in patients with and without GHRT and a comparison of subgroups with regard to initial radiation therapy.

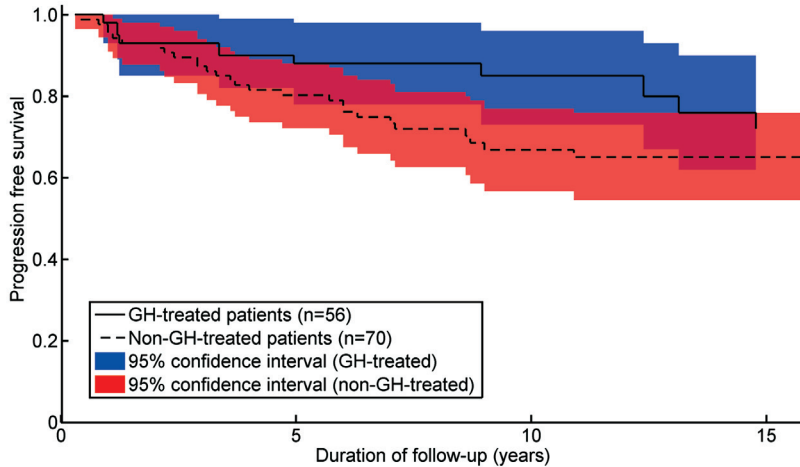
	Tumour progression	No tumour progression	No tumour progression or clinically insignificant tumour progression #
Patients treated with GHRT (n=56)	n=9 (16%)	n=47 (84%)	n=47 (84%)
- Without initial RT (n=26)	n=8 (31%)	n=18 (69%)	n=18 (69%)
- With initial RT (n=30)	n=1 (3%)	n=29 (97%)	n=29 (97%)
Patients not treated with GHRT (n=70)	n=30 (43%)	n=40 (57%)	n=45 (64%)
- Without initial RT (n=47)	n=25 (53%)	n=22 (47%)	n=25 (53%)
- With initial RT (n=23)	n=5 (22%)	n=18 (78%)	n=20 (87%)

GHRT, Growth hormone replacement therapy; RT, Radiation therapy; #, Clinically insignificant tumour progression was defined as tumour progression not resulting in additional tumour treatment

The unadjusted 10-year PRSRs for patients with and without GHRT were 88% and 57%, respectively (Table 8). An analysis using Cox-regression showed that initial RT (HR 0.16, 95% CI 0.06-0.40) and the presence of a residual tumour (2.6, 1.3-5.3) significantly affected the tumour progression whereas GHRT (0.57, 0.26-1.3) and gender (0.57, 0.29-1.1) did not. After adjusting for unevenly distributed factors between the groups (initial RT, residual tumour and gender) the PFSRs for GHRT patients and controls were 85% and 65% (Fig 2).

Figure 2. Progression-free survival in CP patients with and without GHRT.

Tumour progression free survival adjusted for initial RT, residual tumour and gender



Cox-regression of progression-free survival rates adjusted for initial RT, residual tumour and gender in patients treated with and without GHRT. No association between GHRT and tumour progression was found (HR 0.57; 95% CI 0.26-1.3; p-value: 0.17). GH, Growth hormone; GHRT, GH replacement therapy; RT, Radiation therapy.

Additionally, the patients were also analysed regarding clinically significant tumour progression, i.e. needing further tumour treatment, which resulted in a 10-year PFSR for clinically significant progression of 88% for GHRT patients and 63% for control patients. A Cox-regression analysis showed that initial RT (HR 0.12, 95% CI 0.04-0.36) and the presence of a residual tumour after primary progression (2.2, 1.1-4.7) significantly affected clinically significant tumour progression, whereas GHRT (0.65, 0.29-1.5) and gender (0.72, 0.35-1.4) did not. No associations between GHRT and tumour progression or clinically significant tumour progression were found.

4.3 Paper III

The mean annual incidence for NFPA was 20.3 (95% CI 18.8-21.9) cases per million in Sweden between 2002 and 2011. The age at diagnosis (60.2 ± 15 vs. 56.2 ± 18 ; p-value: <0.001) and the incidence rate (21.8, 95% CI 19.7-23.9 vs. 18.9, 17.8-19.9; p-value: 0.03) were higher for men compared to women. Hypopituitarism and DI were reported in 54% and 5% of the patients, respectively.

4.3.1 Overall mortality

During the study period, 473 patients died compared to the expected number of 431, resulting in an overall SMR for NFPA patients of 1.10 (95% CI 1.00-1.20) (Table 10). Patients diagnosed with NFPA at or before the age of 40 had an SMR of 2.7 (95% CI 1.2-5.1). Subgrouping depending on tumour treatment showed that patients with only one surgical treatment of the pituitary had a similar mortality rate compared to the general population, whereas patients who had received multiple surgeries or had been

treated with RT and at least one surgical treatment had excess mortality. The average years of life lost for the entire population was 2.78 years.

Table 10. Standardised mortality ratios for patients with non-functioning pituitary adenoma in Sweden.

Mortality	Expected no. of deaths	No. of deaths	SMR	95% CI	p-value
Overall mortality					
Non-functioning pituitary adenoma (n=2795)	430.7	473	1.10	1.00-1.20	*
Men (n=1502)	279.3	278	1.00	0.88-1.12	NS
Women (n=1293)	151.5	195	1.29	1.11-1.48	***
Patients diagnosed ≤ 40 years old (n=423)	3.4	9	2.68	1.23-5.09	*
Cause-specific mortality					
ICD-10 Chapter 1 - Infectious diseases	7.2	15	2.08	1.17-3.44	*
Men (n=1502)	4.6	11	2.41	1.20-4.31	*
Women (n=1293)	2.6	4	1.52	0.41-3.89	NS
ICD-10 Chapter 9 - Circulatory diseases	180.9	219	1.21	1.06-1.38	**
Men (n=1502)	119.7	132	1.10	0.92-1.31	NS
Patients with HP and/or DI (n=957)	82.4	81	0.98	0.78-1.22	NS
Patients without both HP and DI (n=545)	37.3	51	1.37	1.02-1.80	*
Women (n=1293)	61.3	87	1.42	1.14-1.75	**
Patients with HP and/or DI (n=572)	30.2	50	1.66	1.23-2.18	**
Patients without both HP and DI (n=721)	31.1	37	1.19	0.84-1.64	NS
Ischaemic heart disease	86.1	94	1.09	0.88-1.34	NS
Men (n=1502)	61.3	60	0.98	0.75-1.26	NS
Women (n=1293)	24.8	34	1.37	0.95-1.92	NS
Cerebrovascular disease	38.8	67	1.73	1.34-2.19	***
Men (n=1502)	23.2	39	1.68	1.19-2.30	**
Women (n=1293)	15.6	28	1.79	1.19-2.59	**
Malignant neoplasms	114.7	87	0.76	0.61-0.94	**
Patients with HP and/or DI (n=1529)	75.5	54	0.72	0.54-0.93	*
Patients without both HP and DI (n=1266)	39.2	33	0.84	0.58-1.18	NS
Overall mortality in subgroups					
Patients with hypopituitarism (n=1500)	269.3	286	1.06	0.94-1.19	NS
Men (n=946)	193.0	181	0.94	0.81-1.08	NS
Women (n=554)	76.3	105	1.38	1.12-1.66	**
Patients with diabetes insipidus (n=145)	12.9	22	1.71	1.07-2.58	*
Men (n=60)	8.0	10	1.26	0.60-2.31	NS
Women (n=85)	4.9	12	2.43	1.26-4.25	**
Patients without both HP and DI (n=1266)	160.0	183	1.14	0.98-1.32	NS
Men (n=545)	85.4	95	1.11	0.90-1.36	NS
Women (n=721)	74.5	88	1.18	0.95-1.45	NS
Patients without both surgery and RT (n=1172) □	173.4	198	1.14	0.99-1.31	NS
Patients with 1 surgery and no RT (n=960) □	124.4	125	1.01	0.84-1.20	NS
Patients with ≥2 surgeries or with ≥1 surgery and RT (n=316) □	24.3	40	1.65	1.18-2.24	**
Patients treated with RT (n=104) □	10.9	29	2.67	1.79-3.84	***

Standardised mortality ratio (SMR) is presented with 95% confidence interval (CI) and p-value. SMR was not calculated (NC) for groups with <4 observed events. NS, Not significant; HP, Hypopituitarism; DI, Diabetes insipidus; □, Patients diagnosed between 1st Jan 1997 and 31st Dec 2011; RT, Radiation therapy; *, <0.05; **, <0.01; ***, <0.001.

Women with NFPA had excess mortality, while men with NFPA did not (Table 10). The mortality ratio was significantly higher in women compared to men (SMR 1.29, 95% CI 1.11-1.48 vs. 1.00, 0.88-1.12; p-value: <0.01). In addition, women with either hypopituitarism or DI had an increased mortality ratio compared to the general population, whereas no significant excess mortality could be shown for men with hormone deficiencies.

4.3.2 Cause specific mortality

Deaths due to infectious diseases (ICD-10 Chapter 1) and circulatory diseases (ICD-10 Chapter 9) were increased for patients with NFPA compared to the general population (Table 10). No excess mortality due to ischaemic heart disease was demonstrated, whereas the mortality ratio was increased for cerebrovascular disease. SMR for malignant diseases was decreased in all NFPA patients and was numerically even lower in patients with hypopituitarism and/or DI. Death due to circulatory diseases was increased for women compared to the general population but not so for men.

4.4 Paper IV

The mean annual incidence of CP was 0.17 (95% CI 0.15-0.20) cases per 100 000 inhabitants in Sweden between 1997 and 2011. The age at diagnosis in the 307 CP patients demonstrated a bimodal pattern with one peak during childhood (5-10 years) and another during adulthood (45-50 years) (Table 6). Hypopituitarism and DI were reported in 81% and 36% of the patients, respectively.

4.4.1 Mortality

During the study period, 54 deaths were observed in the 307 CP patients, compared to the expected number of 14.1, resulting in an overall SMR of 3.8 (95% CI 2.9-5.0) (Table 11). The SMR for patients with childhood-onset CP was significantly higher than for patients with adult-onset of their disease (SMR 17, 95% CI 6.3-37 vs. 3.5, 2.6-4.6; p-value: <0.001). Patients with reported hypopituitarism had an SMR of 4.3 (95% CI 3.1-5.8) and patients with DI had an SMR of 6.1 (3.5-9.7). In contrast, patients without hormonal deficiencies had an SMR of 2.7 (95% CI 1.4-4.6). In addition, death caused by circulatory diseases (ICD-10 Chapter 9) was increased in patients with hypopituitarism and/or DI compared to the general population. Furthermore, death caused by ischaemic heart disease (SMR 3.6, 95% CI 1.6-6.8) and cerebrovascular disease (SMR 5.1, 95% CI 1.7-12) was significantly increased in the study population. Additional subgroup analyses are shown in Table 11. The average years of life lost was 14.6 years (men 12.8 years, women 16.7 years) for the entire study population.

4.4.2 Morbidity

Morbidity was analysed in the study population. The incidence of T2DM (SIR 5.6, 95% CI 3.8-8.0), fracture (2.1, 1.4-3.0), severe infection (needing hospital admission) (5.9, 3.4-9.4), cerebral infarction (7.1, 5.0-9.9) and severe visual impairment (89, 33-193) were all significantly increased compared to the general population. No increase in the incidence of myocardial infarction (SIR 0.7, 95% CI 0.2-1.7) could be found in the

study populations compared to the general population. Patients with childhood-onset of CP had a clearly increased incidence of T2DM (SIR 34, 95% CI 9.3-88) and cerebral infarction (364, 194-623) compared to the general population. Women with CP had a significantly higher incidence of T2DM (SIR 8.7, 95% CI 5.2-14 vs. 3.7, 1.9-6.4; p-value: <0.03) and cerebral infarction (SIR 10.7, 95% CI 6.5-17 vs. 5.1, 2.9-8.3; p-value: <0.05) compared to men.

Table 11. Standardised mortality ratios for patients with craniopharyngioma in Sweden.

Mortality	Expected no. of deaths	No. of deaths	SMR	95% CI	p-value
Overall mortality					
Craniopharyngioma (n=307)	14.1	54	3.8	2.9-5.0	***
Men (n=151)	9.0	29	3.2	2.2-4.7	***
Women (n=156)	5.1	25	4.9	3.2-7.2	***
Childhood-onset of craniopharyngioma (n=106)	0.3	6	17	6.3-37	***
Adult-onset of craniopharyngioma (n=201)	13.7	48	3.5	2.6-4.6	***
Cause-specific mortality					
ICD-10 Chapter 9 - Circulatory diseases	4.8	17	3.6	2.1-5.7	***
Patients with DI and/or hypopituitarism (n=253)	3.0	13	4.3	2.3-7.4	***
Patients without DI and hypopituitarism (n=54)	1.8	4	2.3	0.6-5.8	NS
Men (n=151)	3.4	9	2.7	1.2-5.1	*
Patients with DI and/or hypopituitarism (n=127)	2.3	6	2.6	1.0-5.7	NS
Patients without DI and hypopituitarism (n=24)	1.1	3	2.8	0.6-8.1	NS
Women (n=156)	1.4	8	5.7	2.5-11	***
Patients with DI and/or hypopituitarism (n=126)	0.7	7	9.5	3.8-20	***
Patients without DI and hypopituitarism (n=30)	0.7	1	NC	NC	NC
Ischaemic heart disease	2.5	9	3.6	1.6-6.8	**
Cerebrovascular disease	1.0	5	5.1	1.7-12	**
All malignant neoplasms	4.9	8	1.6	0.7-3.2	NS
Overall mortality in subgroups					
Patients with DI (97% with hypopituitarism) (n=110)	2.8	17	6.1	3.5-9.7	***
Men (n=51)	1.9	12	6.3	3.3-11	***
Women (=59)	0.9	5	5.5	1.8-13	**
Patients with hypopituitarism (n=250)	9.5	41	4.3	3.1-5.8	***
Men (n=124)	6.5	22	3.4	2.1-6.8	***
Women (n=126)	3.0	19	6.2	3.8-12	***
Patients without both DI and hypopituitarism (n=54)	4.5	12	2.7	1.4-4.6	**
Men (n=24)	2.5	6	2.4	0.9-5.3	NS
Women (n=30)	2.1	6	2.9	1.1-6.3	*
Patients treated with radiation therapy (n=70) □	1.9	11	5.9	2.9-11	***
Patients not treated with radiation therapy (n=164) □	7.1	25	3.5	2.3-5.2	***

Standardised mortality ratio (SMR) is presented with 95% confidence interval (CI) and p-value. SMR was not calculated (NC) for groups with less than three observed events. Childhood-onset of craniopharyngioma was defined as receiving the diagnosis at age of 18 years or lower. NS, Not significant; DI, Diabetes insipidus; □, For patients diagnosed between Jan 1st, 1997 to Dec 31st, 2011; *, <0.05; **, <0.01; ***, <0.001.

5 GENERAL DISCUSSION

This thesis aims to further increase our understanding of the mortality, morbidity and tumour progression in patients with non-functioning pituitary tumours. Even though non-functioning pituitary tumours comprise at least one-third of all pituitary tumours, most of the research has been focused on the hormone secreting subtypes. Therefore, many aspects of non-functioning pituitary tumours are less fully explored. This thesis has demonstrated, in two case-control studies (Paper I and II), that the rate of tumour progression was not affected by long-term GHRT in patients with NFPA or CP. Furthermore, two population-based registry-studies (Paper III and IV) have shown an excess mortality in women and young patients with NFPA and an increased mortality and morbidity ratio in CP patients, especially in patients with childhood-onset of the disease.

5.1 Epidemiology

Previous studies have reported the annual incidence of NFPA to be between 1.0 and 1.1 cases per 100 000 inhabitants without any gender difference and demonstrated a peak of incidence at the age-band of 60-70 years [6,15]. Paper III, however, reported an almost doubled annual incidence of NFPA (2.0 cases per 100 000 inhabitants per year) compared to earlier studies and confirmed a peak of incidence at the age-band of 60-65 years. The high incidence of NFPA was not totally unforeseen considering that Nilsson and colleagues reported an almost doubled incidence rate of NFPA between 1958 and 1991. In addition, the incidence and age at diagnosis of NFPA was significantly higher in men compared to women. The lower age at diagnosis in the current study among women might possibly be explained by the fact that gonadotropin deficiency is easier to detect in women due to the early influence on the menstrual cycle in younger women.

CP has been reported to have an annual incidence rate of 0.13-0.17 cases per 100 000 inhabitants in two studies from the USA [18,19]. The reported incidence of CP in Paper IV corresponds well with these earlier studies, which indicate that the inclusion method with an internal validation have been effective. Our study also confirms the previously described [18,19,22] bimodal pattern of age at diagnosis, with one peak during childhood and another during adulthood.

5.2 Frequency of hormonal deficiencies

The frequencies of hypopituitarism and DI have not been described earlier in a population of NFPA patients not selected on referral to tertiary centre and on the basis of surgical treatment. However, the frequencies of hypopituitarism and DI in surgical series have been reported to be 68%-85% and 0%-10%, respectively [16,17,52,53,113]. In Paper III, which is the first to describe the frequency of hormonal deficiencies in an unselected NFPA population, the reported frequency of hypopituitarism was 54% and 5% for DI. Only 53% of the patients in Paper III had been treated with surgical treatment or RT, which may in part explain the lower frequency of hypopituitarism

compared to earlier studies were all patients had received one of these forms of tumour treatment.

In CP patients the reported frequencies of hypopituitarism and DI are higher compared to patients with NFPA. Stripp and colleagues showed that 91% of CP patients treated with surgical and/or RT treatment suffered from hypopituitarism after long-term follow-up [102]. In our population of 307 CP patients, the reported frequency of hypopituitarism was 81%. The somewhat lower frequency reported in the current thesis may be explained by the fact that not all patients had received surgical treatment or RT. Earlier studies have shown a tendency towards an increase in the frequency of hormone deficiencies after the tumour treatment [28,102]. In addition, RT, which frequently causes hypopituitarism [42], was reported to be used in only 30% of the patients in Paper IV compared to 56% in the study from Stripp and colleagues.

5.3 Tumour progression

Tumour progression in both NFPA and CP patients differs widely depending on the radicality of the surgical treatment and whether RT is used as primary tumour treatment. In earlier studies, RT has been shown to have a strong protective effect against tumour progression [27,38,39,102]. This notion was supported by Paper I and II where NFPA and CP patients with initial RT had significantly higher PFSR compared to patients without initial RT. For CP patients, initial RT and the absence of residual tumour after the primary tumour treatment were independent factors associated with a higher PFSR. When evaluating the high PFSR associated with RT, one should keep the side effects of RT in mind and that RT can in most cases only be applied once.

5.3.1 Tumour progression and GHRT

Since GH and IGF-I are known to be mitogenic hormones, there have been some concerns regarding the long-term effects of GHRT. A known mitogenic hormone, such as GH, could increase tumour progression in patients with a history of pituitary tumour, especially in patients with a residual tumour. The first studies in patients with pituitary tumours (including NFPA) to investigate this important safety issue consisted of small non-comparative series of patients and did not find an elevated frequency of tumour progression in GHRT patients [96,97,125].

Only two previous studies have investigated the tumour progression rate in small series of NFPA patients with and without GHRT [98,99]. In these studies, GHRT was not shown to affect the frequency of tumour progression. In Paper I, no increase in tumour progression rate was seen in 121 patients with GHRT compared to 114 NFPA patients without GHRT. Since RT may conceal a potential increase in the tumour progression frequency, the subgroup of patients without initial RT was independently analysed. The results showed no difference in the tumour progression rate between GHRT and control patients without initial RT. This study, with the largest population of NFPA patients and the longest duration of GHRT so far, also demonstrated that tumour progression in GHRT patients with a known residual tumour and no initial RT was comparable to earlier publications [16,24].

In CP patients where tumour progression and its treatment often cause increased morbidity, e.g. hypopituitarism, the possible stimulating effect of GHRT on tumour progression was studied by Clayton and colleagues in 1988 [103]. This study and other early studies of GHRT in CP patients, in which no direct comparison was made to non-GHRT patients, did not indicate that GHRT treated patients had a higher frequency of tumour progression [104,105].

There are few previous studies that have compared tumour progression rate in CP patients with and without GHRT [107-109]. These studies have either had a short follow-up or a large disparity in the frequency of RT between GHRT patients and controls, but they have not supported that GHRT should be associated with a higher frequency of tumour progression. Paper II in this thesis reports results from the largest study to date, on 56 CP patients treated with GHRT and 70 controls followed for over 13 years. The long follow-up and the adjusted analyses for initial RT in the current study made it possible to better investigate the frequency of tumour progression than earlier studies. After adjusting for unevenly distributed factors (gender, initial RT and residual tumour) no significant difference in the tumour progression rate was found between CP patients with and without GHRT, nor could an effect of GHRT be demonstrated when only tumour progression leading to further tumour treatment was analysed.

5.4 Mortality and morbidity

An excess mortality has been shown in patients with hypopituitarism caused by various aetiologies [55,110,111]. Still, only a few studies have investigated the mortality in NFPA patients [15,113]. In the largest previous study, Nilsson and colleagues showed an excess mortality for patients with pituitary adenoma diagnosed between 1958 and 1991 in Sweden, even though this material most likely included a large proportion of prolactinomas [15]. The excess mortality was due to cardiovascular disease and malignant neoplasm. In this thesis, excess mortality was demonstrated in the largest NFPA population studied to date. During the study period, measurements of prolactin were used and the internal validation showed that less than one percent of the patient population had prolactinomas. Subgrouping according to gender supported the results from earlier studies where there was an increase in the mortality ratio for women but not among men. Increased mortality was seen in patients diagnosed at an age less than 40 years, which stands in contrast to the study from Nilsson et al., which found the highest mortality in patients diagnosed at an age between 40 and 69 years. The current study confirmed, however, an excess mortality due to circulatory disease, but found no increased risk of death from malignant tumours. On the contrary, a reduced risk of death from malignant tumours was seen in NFPA patients, especially in patients with hypopituitarism and/or DI. Additionally, in women, hypopituitarism and DI were both associated with an excess mortality. Tumour treatment with RT or multiple surgical treatments was also associated with an increased mortality ratio, whereas no excess mortality was found in patients with only one surgical treatment.

Patients with CP are known to have an increased morbidity mainly involving endocrine, hypothalamic, neurological and psychological sequelae, resulting in an impaired quality

of life [28,37,126]. Although, little was previously known whether common diseases such as myocardial infarction, cerebrovascular disease, fracture and malignant tumours also increase their morbidity. Pereira and colleagues suggested a possibly elevated incidence of cerebrovascular accident and myocardial infarction in a study of 54 CP patients [115]. The population based study in Paper IV is the first to report a 5-fold increased incidence of T2DM, severe infection and cerebral infarction in CP patients compared to the general population. Additionally, the incidence of fracture was doubled in patients with CP. However, the previously suggested increase in myocardial infarctions could not be demonstrated in the 307 CP patients in Paper IV. Furthermore, no excess incidence was seen for malignant tumours. Interestingly, women had a higher incidence of T2DM and cerebral infarction compared to men. Contributing factors to the increased morbidity, in addition to the pituitary and hypothalamic damage, could be that CP patients often exhibit features of the metabolic syndrome [127] and that some CP patients are treated with RT.

An excess mortality in patients with CP has previously been described in three small series (54-70 patients) from referral centres [23,114,115]. In addition, Tomlinson and colleagues reported a greatly increased mortality ratio in 118 CP patients with hypopituitarism [49]. The excess mortality in these studies has mostly been attributable to cardiovascular and respiratory deaths. Paper IV in the current thesis, which consisted of 307 patients followed for a mean time of nine years, supported that there is an excess mortality for patients with CP. As indicated by earlier studies, the current study also found that circulatory diseases were responsible for the excess mortality. Mortality due to ischaemic heart disease and cerebrovascular disease was increased, whereas the previously reported excess of deaths attributed to respiratory diseases could not be confirmed. Moreover, Paper IV is the first study to report the mortality ratio in patients with childhood-onset of CP and in patients with and without hormonal deficiencies. The analyses showed a higher mortality ratio in patients with childhood-onset compared to patients with an adult-onset of their disease. In addition, hormone deficiencies, especially DI, were associated with higher mortality.

A potentially contributing factor to the excess mortality in NFPA patients and the elevated morbidity and mortality in CP patients is hypopituitarism and its treatment, which today is not completely physiological. This notion is supported by Tomlinson and colleagues who showed that patients with non-replaced gonadotropin deficiency had excess mortality [49]. In addition, studies of patients with Addison's disease have suggested that the glucocorticoid replacement regime used today may be associated with excess mortality [128]. The impaired glucocorticoid axis may be a plausible contributor to the excess mortality due to infectious disease seen in NFPA patients. The discrepancy in CP patients between the excess in death due to ischaemic heart disease and the fact that the incidence of myocardial infarction was not elevated may be attributed to a greater vulnerability in hypopituitary patients. Another possible explanation for this discrepancy could be that patients with sudden deaths were misclassified as circulatory deaths instead of death due to adrenal crisis [129]. This thesis has demonstrated a worse outcome in women compared to men, particularly in NFPA patients. These findings, with an excess mortality in women, are supported by an earlier meta-analysis of patients with hypopituitarism caused by various aetiologies,

mostly non-functioning pituitary tumours [130]. A contributing factor to the elevated mortality found in women with CP could be the higher incidence rate of T2DM compared to men. In addition, it has previously been suggested that women with hypopituitarism have more marked body compositional and metabolic abnormalities than men [131,132]. This may affect the morbidity and mortality in women considering that historically a substantial number of hypogonadal women did not receive sex steroid replacement [55].

The current thesis also demonstrated an excess mortality in NFPA patients with multiple surgery or RT as well as in CP patients treated with RT. Larger tumours or tumours that progress need more aggressive tumour treatment and are more likely to cause hormone deficiencies, both aspects that are likely to affect the outcome. This notion is supported by Erfurth et al., who demonstrated that macro-adenoma patients with tumour progression had a higher mortality rate than patients without tumour progression [93]. Interestingly, this thesis also suggested that death due to malignant tumours was reduced in NFPA patients, especially in patients with hormone deficiencies. Patients with Laron syndrome, who have very low IGF-I concentrations, have been shown to have a decreased risk of cancer [133]. In contrast, two papers have reported a normal or elevated frequency of death due to malignant tumours in hypopituitary patient without GHRT [15,87]. Both these studies most likely include patients with prolactinoma that may affect the incidence of malignant tumours, since elevated levels of prolactin in normal women have been suggested to be associated with breast cancer [134]. Further studies are needed to investigate whether hypopituitarism, most likely including GHD in many cases, affects the risk of malignant tumours.

5.5 Methodological considerations

5.5.1 Paper I-II

In Paper I and II, patients and controls originate from two different hospitals, the Sahlgrenska University Hospital, Gothenburg, Sweden and the Erlangen-Nuremberg University Hospital, Erlangen, Germany. Different study sites may introduce discrepancies, even though the management of the patients at the two centres have in all major aspects been similar. The Department of Neurosurgery at Erlangen-Nuremberg University Hospital, Erlangen, Germany is a well-known referral centre for patients with pituitary tumours and receives cases from a large part of Germany and also from other parts of Europe. This fact may influence the mixture of the cases that are treated at their centre.

The baseline for the observational period differs between the GHRT treated patients and the controls. In the GHRT treated patients, the baseline was set at commencement of GHRT because the time period before GHRT was not part of the study. In controls, the time for the primary tumour treatment was used as baseline. This circumstance led to a longer follow-up period after initial tumour treatment for GHRT treated patients compared to the controls, and may potentially overestimate tumour progression in GHRT patients.

Furthermore, the presence of a residual tumour or a tumour progression in GHD patients with NFPA or CP has not been used as a contraindication for GHRT at the Department of Endocrinology at the Sahlgrenska University Hospital. This should most likely diminish the possibility of selection bias that would have been induced had GHRT been reserved for those without tumour progression or residual tumours.

Both Paper I and II are the largest studies to date, in terms of number of patients and length of follow-up in NFPA and CP patients investigating the effects of GHRT on tumour progression. Especially, when studying NFPAs, which are slowly growing tumours, the length of the follow-up period is of utter importance. The comparison to control groups and the analyses depending on initial tumour treatment are all strengths of Paper I and II.

5.5.2 Paper III-IV

The nature of a registry-study is such that the amount of available data is predetermined and that no new contact between investigators and patients will take place. Therefore, one of the most important phases in a registry-based study is the inclusion phase. The investigators need to include patients that truly fulfil the inclusion criteria, often patients with a specific diagnosis or patients exposed to a certain factor, while managing to achieve good coverage. Many registry-based studies, such as Dekkers et al. [135], completely rely on the accuracy of the registries when including the patients, both regarding specificity and sensitivity of the inclusion phase. Nielsen and colleagues have shown that a combination of diagnostic codes and department codes can be used to achieve higher sensitivity and specificity when constructing criteria to include a specific type of patients [119]. Since all results in registry-based studies are closely dependent on inclusion of the “right” patients, an internal validation of the inclusion criteria was incorporated in Paper III and IV of the thesis. This strategy does not preclude the studies from including miss-classified patients but provides the investigators with a method to evaluate the inclusion criteria.

Limitations of the registry-based studies in paper III and IV include that detailed information regarding the surgical treatments and RT, many specifics regarding the tumours, as well as body weight were not available. In addition, all registry-based studies rely on the accuracy of the registries used for the data collection. The registries used in Paper III and IV, the Swedish Health Registries maintained by The National Board of Health and Welfare, are well known to uphold a high quality [117,118,121]. The accuracy of the treatment codes is, however, not so well studied.

Another methodological issue that needs to be considered in a nationwide study is the possibility of different local traditions when diagnosing patients with NFPA and CP. Since Sweden is a rather small country and the majority of endocrinologist are working at specialised centres at university hospitals or collaborate with these centres, the possibility for large discrepancies in the criteria for NFPA or CP diagnoses are unlikely.

The strengths of Paper III and IV are the nationwide sample, with large populations, and that the methods of inclusion were internally validated. Combinations of multiple

exclusion and inclusion criteria as well as internal validations of the NFPA and CP diagnoses were used to minimise the inherent problems with registries. The method used in Paper III and IV is a possible model for future studies.

5.5.3 Overlapping study populations

No overlap of the study populations was seen between Paper I and II as well as between Paper III and IV.

The GHRT treated patients from the Department of Endocrinology at the Sahlgrenska University Hospital in Paper I and II were included in the nationwide study populations of Paper III and IV. The outcome analyses in Paper III and IV differ completely from the analyses performed in Paper I and II.

6 CONCLUSION

This thesis has demonstrated that long-term treatment with GHRT was not associated with an increased tumour progression rate in patients with NFPA or CP. This was also true for the subgroup of patients with a residual tumour after the initial tumour treatment. In conclusion, patients with NFPA or CP with GHD can safely be treated with long-term GHRT with regard to pituitary tumour progression.

There was an excess mortality in women and young patients with NFPA. Hypopituitarism and DI were both risk factors for mortality in women with NFPA. Furthermore, treatment with RT and multiple surgical treatments were associated with an increased mortality. The excess mortality was contributed to an increase in infectious and circulatory deaths. An excess mortality was also demonstrated for patients with CP, especially for patients with childhood-onset of their disease. The increased mortality was mainly due to circulatory diseases. Furthermore, CP patients had an increased incidence of T2DM, fracture, severe infection and cerebral infarction. Hypopituitarism and DI were found to negatively affect the outcome in CP patients both regarding morbidity and mortality. In conclusion, the excess in mortality seen in women and young patients with NFPA and CP and those with hormone deficiencies suggest that these may be in the greatest need of improvements in medical care.

7 FUTURE PERSPECTIVES

When conducting research on tumour progression, it is obvious that a model for predicting tumour progression would be very beneficial. If tumour progression could be predicted accurately it would not only help physicians in selecting tumour treatment but it may also enable a decrease in the frequency of MRI imaging for tumour surveillance during follow-up. A tumour marker associated with tumours that are prone to progress would be helpful to individualise management. Another possibility could be if one could find a clinical factor linked to patients with pituitary tumours that are likely to progress. A prediction model would not only guide the choice of tumour treatment but would also in many cases reassure the patient.

Replacement therapy with GH has been shown to reduce many of the symptoms in patients with hypopituitarism and GHD. The effect of GHRT have been studied for many years, none-the-less the possible effect on mortality is still largely unknown. The mortality in GHRT treated patients has received renewed attention as Carel and colleagues have suggested that GHRT is associated with an increased risk of death in patients with isolated growth hormone deficiency or childhood short stature [136]. This could, however, not be confirmed in a study of GHRT treated patients with similar disorders from Belgium, the Netherlands and Sweden [137]. Further studies are needed to investigate the effects of GHD and GHRT on mortality in both children and adults.

In Paper III, patients with NFPA, especially patients with hormonal deficiencies, were found to have a decreased mortality due to malignant neoplasm. This finding is interesting, considering that patients with Laron syndrome, with extremely low concentrations of IGF-I, are known to have a very low risk of cancer [133]. Other studies on hypopituitary patients without GHRT have, however, shown a normal or elevated frequency of death due to malignant tumours [15,87]. The evident continuation would be to investigate the incidence of malignant tumours to see if NFPA patients, in addition to possibly decreased mortality, also have a decreased incidence of malignant tumours, or whether these patients only have an improved prognosis.

In Paper III and IV, woman as well as patients overall, diagnosed at a young age were found to have an excess mortality in NFPA and CP patients. Hypopituitarism and DI seems to be contributing factors to the increased mortality in these patients. The next step would be to investigate the underlying cause of the excess mortality and thereby gain knowledge how to improve the management of these patients.

SAMMANFATTNING PÅ SVENSKA

Icke hormonproducerande hypofystumörer, innefattande icke hormonproducerande hypofysadenom (NFPA) och kraniofaryngiom (CP), är godartade hjärntumörer som ibland kan växa aggressivt lokalt. Patienter med NFPA eller CP drabbas ofta av hormonella brister, diabetes insipidus och andra lokalt utlösta symtom på grund av tumören eller tumörbehandlingen. Tidigare studier har visat att patienter med hormonella brister orsakade av olika etiologier har en ökad dödlighet, framförallt i cerebrovasculära sjukdomar. Patienter med hormonella brister erhåller hormonell ersättningsbehandling som numera ofta även inkluderar substitution med tillväxthormon (GHRT). Det har funnits en viss rädsla för att tillväxthormon, som är tillväxtfrämjande, skulle kunna öka risken för tumörtillväxt och recidiv hos patienter med hypofystumörer. I denna avhandling studerades tumörtillväxt och recidiv samt dödlighet och sjukdomsförekomst i fyra studier av patienter med NFPA eller CP.

I två fall-kontroll studier undersöktes frekvensen av NFPA- och CP-patienter med och utan GHRT som fick tumörtillväxt eller recidiv. Andelen NFPA-patienter som klarade sig utan tumörtillväxt och recidiv efter 10 år var 74% för GHRT patienter och 70% för patienter utan GHRT. Motsvarande siffror för patienter med CP var 88% för GHRT patienter och 57% för patienter utan GHRT. En populationsbaserad registerstudie på 2795 NFPA-patienter visade på en förhöjd dödlighet hos kvinnor (SMR 1,29; 95% CI 1,11-1,48) och hos patienter diagnostiserade innan 40 års ålder (SMR 2,7; 95% CI 1,2-5,1) jämfört med den svenska befolkningen. En annan populationsbaserad registerstudie på 307 CP-patienter visade på en generellt förhöjd dödlighet hos dessa patienter (SMR 3,8; 95% CI 2,9-5,0), speciellt bland patienter där sjukdomen debuterade under barndomen (SMR 17; 95% CI 6,3-37). Dessutom var sjukdomsförekomsten förhöjd hos CP-patienterna för följande sjukdomar, diabetes mellitus typ 2, cerebrala infarkter, frakturer och svåra infektioner jämfört med den svenska befolkningen.

Sammanfattningsvis visar denna avhandling att det ej finns någon förhöjd frekvens av tumörtillväxt eller recidiv hos NFPA- eller CP-patienter som har fått GHRT. Dessutom påvisades att kvinnor och unga patienter med NFPA har en förhöjd dödlighet samt att CP-patienter, framförallt de som diagnostiserats under barndomen, har en förhöjd dödlighet och sjukdomsförekomst.

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