General Introduction
GENERAL INTRODUCTION

External beam radiation therapy (RT) in pituitary adenoma results in excellent local tumor control rates and improvements in excessive hormonal secretion. Furthermore, RT is a well-tolerated (and non-invasive) treatment modality and offers a valuable curative treatment option to patients. However, the safety of RT has been questioned in particular because of concerns related to possible long-term radiation-induced side effects, although serious late complications of RT are uncommon. However, these concerns are often used to delay or reject RT in pituitary adenoma patients. The perception is that RT is damaging and the efficacy is questioned. However, many of these perceptions and concerns are based on selected studies and observations from an era in time where old RT techniques were used with larger treatment volumes and RT schedules with higher total dose. In addition, in many studies regarding long-term side effects, comparisons were made between irradiated pituitary adenoma patients and the general population instead of between irradiated and non-irradiated patients. As a consequence, potential other disease characteristics and treatment related factors were not taken into account.

The general objectives of the studies presented in this thesis was to assess the long-term side effects of conventional RT in comparison to the outcomes of patients treated with surgery-alone and the reference population in order to improve an evidence-based approach in clinical decision making in pituitary adenoma patients, more specifically, in patients with non-functioning adenomas (NFA), acromegaly, or Cushing’s disease.

PITUITARY ADENOMAS

Pituitary adenomas comprise 8-19% of all intracranial tumors [1-3]. Pituitary adenomas are considered a diverse group of benign tumors arising from the anterior pituitary gland (i.e. adenohypophysis) and are the most commonly encountered type of pituitary tumors [4]. In the general population, the overall estimated prevalence of pituitary adenomas, based upon autopsy and radiologic studies, is 16.7 % [5].

Pituitary adenomas are classified according to tumor size and extension and divided into micro-adenomas (dimension < 10 mm) and macro-adenomas (dimension ≥ 10 mm). Based on hormonal activity, they can be clinic-pathologically divided into non-functioning or functioning adenomas. A non-functioning adenoma has no clinical or biochemical features of excessive hormonal secretion and refers to hormonally inactive pituitary adenoma. Functional adenomas are characterized by excessive pituitary hormonal secretion. Growth hormone (GH)-secreting (i.e. somatotroph) adenomas present with the clinical syndrome of acromegaly in adults and gigantism in adolescents. Furthermore, Cushing’s disease and Nelson’s syndrome are caused by a hypersecretion of adrenocorticotropic hormone (ACTH) (i.e. corticotroph), while
(excessive) prolactin-secreting adenomas result in prolactinomas and represent clinically the most prevalent type of all pituitary adenomas [6]. Finally, other functioning adenoma subtypes are gonadotrophinomas (i.e. follicle-stimulating hormone or luteinizing hormone-secreting adenomas) and thyrotrophinomas (i.e. thyrotropin-secreting adenomas), but these types are very rare.

Pituitary adenoma patients may present with a variety of clinical signs and symptoms relating to local tumor mass effects, hormonal insufficiency due to loss of normal pituitary function (i.e. hypopituitarism), and/or effects of excessive pituitary hormonal activity. Although pituitary adenomas are classified as benign tumors, pituitary adenoma disease can be locally invasive and the afore mentioned signs and symptoms may cause serious morbidity and mortality.

The scope of this thesis is on long-term side effects of conventional RT in pituitary adenoma patients, more specifically, in patients with a NFA, GH- or ACTH secreting adenoma diagnosis, and therefore, other pituitary adenoma subtypes will not be further highlighted in this general introduction.

NON-FUNCTIONING PITUITARY ADENOMA

Incidence and prevalence
Several studies reported about NFA incidence and prevalence rates. A Standardized Incidence Ratio (SIR) of 17.9 NFAs per million per year was reported in a recently published population based study of pituitary adenoma patients diagnosed in Malta during the period 2000-2011 [7]. The majority of the NFAs were macro-adenomas with a reported SIR of 9.2 per million per year. An incidence estimation of 5.6 per million per year was based upon operated NFA patients during the period 1985-1996 in Denmark [8]. An increase in the incidence of NFAs was reported in the time period 1958-1991 in Sweden [9]. The average reported incidence per year was 7.13 per million inhabitants during 1958-1979, and after 1980, it was 9.76 per million per year. A prevalence between 138 and 259 per million was reported in populations from Belgium, United Kingdom and Malta [7,10,11]. More specifically, the prevalence of NFA macro-adenomas was estimated at 168 per million [7]. The reported differences in incidence and prevalence may de due to differences in NFA data registration (e.g. clinical versus pathological diagnosis). The incidence and prevalence rates of NFAs for the Netherlands are unknown.

Clinical signs and symptoms
NFA accounts for approximately one-third of all pituitary adenomas types [4]. The median age at diagnosis is approximately 47-52 years [7,8,10]. The reported duration of symptoms until diagnosis is about 0.8 years [10]. NFAs are almost always macro-adenomas and, therefore,
usually present with symptoms relating to local tumor mass effects on the surrounding tissues. The most commonly reported complaints are frequent headache, visual impairments (classically bitemporal hemianopsia) and symptoms relating to the effects of hypopituitarism [12-14]. Clinical features of a pituitary adenoma (i.e. non-functional and functional) include decreased libido and/or erectile dysfunction in men, irregular menses or amenorrhea in pre-menopausal women, and fatigue (single or combined deficiencies of thyroid hormone, cortisol, GH and gonadotrophins) [15].

**Mortality**

It is a matter of debate whether NFA patients have an increased mortality risk. In a Danish cohort study of operated NFA patients in the time period between 1985 and 1996, death from cardio-vascular, cerebro-vascular and malignant diseases in patients was similar to that in the general population [8]. In this study, female sex was a risk factor, while type of surgery (i.e. craniotomy or trans-sphenoidal) and RT were not identified as risk factors. In addition, in a Dutch series of NFA patients operated between 1979 and 1998 with residual tumor after surgery, immediate postoperative RT did not result in an additional need for conventional hormonal substitution therapy in comparison to a wait and see strategy [16]. Furthermore, life expectancy was similar in both treatment groups and did not differ from the general population.

**ACROMEGALY**

*Incidence and prevalence*

The average incidence of GH-secreting pituitary adenomas is estimated at around 3.3 per million persons per year [17]. A prevalence was reported between 86 and 124.5 cases per million in three population-based, cross-sectional studies [7,10,11]. The incidence and prevalence numbers of acromegaly in the Netherlands are not available.

*Clinical signs and symptoms*

Acromegaly is a clinical syndrome in adults that results from excessive GH-secretion and is characterized by an acquired somatic disfigurement and associated with systemic manifestations. The most common cause of acromegaly is a GH-secreting pituitary adenoma. GH-secreting adenomas represent approximately 20% of all pituitary adenomas [6]. The median age at diagnosis is approximately 44-47 years [7,10]. Clinical symptoms of acromegaly present in a variety of ways and develop insidiously with a mean duration of 8 years [17] leading to a considerable delay in diagnosis. Most patients at diagnosis have macro-adenomas, and therefore, presenting symptoms are commonly due to local tumor mass effects and to somatic and metabolic effects resulting from prolonged exposure of excessive GH secretion. Clinical symptoms due to local tumor mass effects and effects of hypopituitarism are previously
described in this introduction (see NFA clinical signs and symptoms). Clinical features of acromegaly due to excessive GH secretion include coarse facial features (e.g. large lips and widened nose, hypertrophy of frontal bones and prognathism), enlargement of the acra, including soft tissue thickness of hands and feet, and pigmented skin tags and hypertrichosis. Other features are fatigue, headaches, hyperhidrosis, arthropathy, paresthesia, colon polyps and visceromegaly (e.g. tongue, liver, thyroid gland). Long-term manifestations of acromegaly includes cardiovascular (e.g. cardio-myopathy and hypertension) and respiratory (e.g. sleep apnea) diseases. Lastly, other complications are related to the endocrine (e.g. reproduction, sexual dysfunction or other pituitary deficiencies) and metabolic (e.g. diabetes mellitus and hypertriglyceridemia) systems.

**Mortality**

In several studies acromegaly is associated with increased mortality compared to age and sex matched reference populations [18-20], mostly due to cardiovascular [18-21], cerebrovascular [18-20] and respiratory disease [19,20]. A meta-analysis of 16 studies (covering a study period between 1937-2003) on mortality in acromegaly reported a weighted mean SMR of 1.72 (95% CI 1.62-1.83). In the studies with trans-sphenoidal surgery as the primary treatment, the weighted mean of the SMR was 1.32 (95% CI 1.12-1.56) [22]. Various independent predictors of acromegaly associated mortality are reported, such as GH levels of > 2.5 μg/l, elevated insulin-like growth factor 1 (IGF-1) level, hypertension, old age, time of delay from diagnosis, male gender, malignancy, cardiovascular disease at diagnosis, prior pituitary RT, ACTH-dependent adrenal insufficiency, and treatment with hydrocortisone of > 25 mg per day [18,20,21,23-25]. A meta-analysis of the effect of lowering the serum levels of GH and IGF-1 showed that patients with random serum GH < 2.5 μg/l following treatment, had mortality close to expected levels (SMR 1.1 95% CI 0.9-1.4) compared with a SMR of 1.9 (95% CI 1.5-2.4) for those with final GH > 2.5 μg/l. Similarly, a normal serum IGF-1 for age and sex at last follow-up after treatment was associated with a SMR of 1.1 (95% CI 0.9-1.4) compared with a SMR of 2.5 (95% CI 1.6-4.0) for those with continued IGF-1 elevation [26]. Some studies demonstrated an increased mortality in patients with persistent acromegaly disease compared to patients with controlled disease [24,25] and compared to a reference population [25,27]. However, results from other and more recent studies in patients diagnosed or operated between 1970 and 2009 demonstrated no significant increase in mortality compared to age and sex matched reference populations [25,27-31].
CUSHING’S DISEASE

Incidence and prevalence
The reported incidence of Cushing’s disease ranges between 1.2 and 2.4 per million persons per year [32,33]. The estimated prevalence of ACTH-secreting adenomas is reported between 12 and 55 per million inhabitants [7,10,11,33]. The incidence and prevalence rates for Cushing’s disease are unknown in the Netherlands.

Clinical signs and symptoms
Cushing’s disease is a clinical syndrome caused by an excessive ACTH-secreting pituitary adenoma and represents one variant of Cushing’s syndrome (i.e. any cause of glucocorticoid excess). ACTH-secreting adenomas represent approximately 10 to 15% of all pituitary adenomas [4,6] and are more invasive than most other pituitary adenomas. The median age at diagnosis is approximately 36-46 years [7,32,34] and more frequently diagnosed in women [32,34-36]. The mean duration of symptoms until diagnosis is approximately 2-3 years [34,37,38]. ACTH-secreting adenomas are frequently micro-adenomas [35], and therefore, the clinical manifestations of Cushing’s disease include predominantly signs and symptoms caused by excess ACTH-secretion without local tumor mass effects. The clinical features of Cushing’s disease are variable, and no single pattern of symptoms is seen in all patients. Patients may present with central obesity with “buffalo hump” phenomenon (i.e. increased supraclavicular and dorso-cervical fat pads), rounded “moon-like” facies, proximal muscle weakness, thin skin with purple striae and ecchymoses, and hirsutism. Other clinical features are fatigue, menstrual irregularity, decreased libido, impotence, mood changes and irritability, cognitive impairment, poor wound healing, easy bruising, bone fractures and osteoporosis, hypertension and diabetes mellitus.

Mortality
Several series reported on increased mortality in Cushing’s disease [39-42], primarily due to cardiovascular disease [40]. A meta-analysis on mortality in Cushing’s disease of 7 studies with a study period between 1960 and 2009 demonstrated excess mortality with an overall reported SMR 2.2 (95% CI 1.45-3.41) and a pooled SMR of 5.5 (95% CI 2.7-11.3) for patients with persistent disease [40]. Furthermore, a Dutch study reported an increased mortality in patients previously treated for Cushing’s disease compared with patients treated for non-functioning macro-adenomas. RT and hypopituitarism were not associated with increased mortality risk in the patients with Cushing’s disease compared to the patients with non-functioning macro-adenomas. This study implies that previous, transient overexposure to cortisol is associated with increased mortality [42]. Various independent predictors of mortality are reported, such as older age at diagnosis [39,41,43], persistence of hypertension [39],
and abnormalities of glucose metabolism after treatment [39], preoperative plasma ACTH concentration [43] and exposure time to excess glucocorticoids [43]. Nevertheless, other groups with study periods ranging from 1965 to 2010 demonstrated similar survival in patients with Cushing’s disease compared to age- and sex matched reference populations [44-46]. In addition, the meta-analysis results showed that mortality of the Cushing’s disease patients in remission did not differ significantly from the general population [40].

TREATMENT OF PITUITARY ADENOMAS

Surgery
Surgery is considered the gold standard treatment in most NFA, GH-secreting and ACTH-secreting adenoma patients. The main goals of surgical treatment are resection of the adenoma, decompression of tumor mass effects, improve visual impairments, reduce excessive pituitary hormonal activity to normal levels (if possible) in secreting adenomas, improve survival and quality of life (QoL). In the past 100 years there have been major advances in pituitary imaging and the surgical techniques used in pituitary surgery. Trans-sphenoidal microscopic surgery is the preferred surgical approach for most pituitary adenomas. Trans-cranial surgery is usually only performed in case of a contraindication for trans-sphenoidal surgery (e.g. sphenoid sinusitis or ectatic midline “kissing” carotid arteries) or in case of a macro-adenoma with significant lateral suprasellar extension that cannot be adequately resected by the trans-sphenoidal approach. The use of the fiberoptic endoscope is a recent innovation in pituitary surgery and has shown improvements in the duration of surgery and visual impairments [47].

Complete surgical removal of the pituitary macro-adenoma is not always accomplished due to the close proximity of critical structures (i.e. sinus cavernosus, arachnoid membrane) and associated unacceptable surgical risks. The efficacy of surgery is determined by the size and extension of the adenoma and the surgeon’s experience. In a review including only series with NFA macro-adenoma patients mainly treated by trans-sphenoidal surgery the 10 year progression-free survival was 50-79% after surgery-alone [48]. However, in daily clinical practice, a substantial portion of the NFA patients requires bulk resection by craniotomy. A perhaps more realistic 10 year progression-free survival after surgery-alone of 47% and 22% [16,49] is reported by others. A meta-analysis showed that surgery-alone was associated with increased risk of tumor recurrence in NFA patients compared with a combined approach of surgery and RT (RR 1.97; 95% CI, 1.15-3.35) [50]. Trans-sphenoidal surgery improves visual field defects in 78% of patients with visual field defects prior to surgery [50]. In patients with GH-secreting adenomas, GH and IGF-I levels normalize in 40-70% of cases, depending on the size of the adenoma, pre-operative GH concentrations and experience of the surgeon [51]. In ACTH-secreting adenomas, trans-sphenoidal surgery results in remission rates of 60-90% in micro-adenomas and 50-70% in macro-adenomas, depending on local invasion, the
experience of the neurosurgeon, follow-up time and the definition of remission [52,53]. Repeat surgery in case of persistent disease or recurrence results into lower reported remission rates of 70% [54]. Improvements of pituitary function occurs in less of a third of patients operated by trans-sphenoidal surgery, however, most patients need hormonal replacement therapy [50]. Lastly, in most patients additional treatments (i.e. second surgery, RT or medical therapy) are often necessary.

**Radiation therapy**

External beam RT is generally used as second-line treatment to prevent tumor progression after an incomplete resection, as a salvage treatment in case of a recurrence after surgery, or in case of secreting adenomas where hormonal control cannot be achieved after surgery and medical therapy. However, in acromegaly patients with uncontrolled disease after surgery, RT and medical therapy can be considered as an effective treatment option. In that case, RT offers the potential for cure in acromegaly or reduces the maintenance dose of medical therapy. The main aims of RT are long-term local tumor control, normalization of hormone excess in secreting adenomas, improve survival and QoL. RT has been used for more than 100 years and offers a valuable curative treatment option in pituitary adenomas. The linear accelerator (LINAC) is the most common form of therapeutic RT photon delivery today. The most common method of RT planning and treatment by the LINAC is three-dimensional (3D) conformal therapy and is interchangeably termed conventional RT. External beam RT is given either as conventional/conformal fractionated or as a stereotactic RT technique. Stereotactic RT techniques are a refinement of high conformal RT and enables a more precise localization of the pituitary adenoma and organs at risk and more precise treatment delivery. Stereotactic RT is a technique in the delivery of RT that can be given as fractionated (i.e. multiple daily RT doses) stereotactic conformal radiation therapy (SCRT), or as a single treatment given in one large RT dose, i.e. stereotactic radiosurgery (SRS). The most experience with SRS delivery has been with Gamma knife (GK), but other stereotactic methods of RT delivery are with the LINAC, Cyber knife (CK) or with proton therapy. Modern RT techniques are aiming to reduce the amount of normal brain receiving significant high doses of radiation and this may translate into a reduction of the possible long-term side effects of RT. The most common RT regimen is fractionated RT using a total RT dose of 45 to 50.4 Gy in fractions of 1.8 Gy [55]. A higher RT total dose does not improve local tumor control [56].

In pituitary adenoma patients conventional RT results in an excellent long-term local tumor control with reported rates of 90-97% at 10 years [16,49,57,58]. Local tumor control is similar in non-secreting and secreting adenomas regardless of the size of the pituitary adenoma remnant [59]. In GH-secreting adenomas RT results in an improvement of excessive hormonal secretion in 60-70% of patients at 10 years [60,61]. More specifically, a reduction of GH to 50% by RT was reported after a mean time of 27 ± 5 months and 87% of patients had a serum
GH concentration of < 5 mU/L without GH suppressive medication after 15 years of follow-up [60]. Furthermore, IGF-1 levels were reported normal in 63% of patients treated with RT after 10 years [61]. In ACTH-secreting adenomas, RT results in normalization of cortisol levels in 80-85% of patients at 10 years [62,63]. In most Cushing’s disease patients, remission (i.e. normalization of plasma and urinary cortisol) occurs during the first two years after RT treatment [62]. The efficacy of SCRT treatment is comparable to conventional RT and there is no evidence that single fractions SRS produces a faster decline of elevated hormone levels than fractionated treatment [59].

Medical therapy
Medical therapy is generally used as second-line treatment in secreting pituitary adenomas after unsuccessful surgery and after surgery and postoperative RT due to a slow onset of RT effects. The main goal of medical therapy is to control hormone excess, improve survival and QoL. Medical therapy is by definition not a curative treatment option in pituitary adenomas.

There is no established effective medical therapy available for NFA [48]. Medical therapy in acromegaly is generally used as adjuvant treatment in patients who do not achieve biochemical control after surgery or develop recurrence of disease after surgery and results in life-long medical treatment. However, in patients who are treated with postoperative RT, medical therapy is used to bridge the therapeutic effects of RT, and is stopped after biochemical remission. Somatostatin analogues (SSAs) (e.g. octreotide or lanreotide), a GH-receptor blocker (i.e. pegvisomant) and dopamine agonists (e.g. bromocriptine or pergolide) are the three classes of drugs used to medically control disease activity. SSAs are considered as first-line medical therapy in acromegaly. Treatment with SSAs results in decrease of GH secretion in approximately 49-60% of patients, normalizes IGF-I levels in 48-66% of patients, and induces tumor shrinkage in 30-50% [64,65]. SSAs were introduced in the 1990s. The GH-receptor blocker pegvisomant is generally used in patients who are resistant to or cannot tolerate SSAs [66], although regional differences are noted. They are highly effective in normalizing IGF-I levels in more than 90% of patients [51,65]. In 2003 pegvisomant became available as medical therapy. Dopamine agonist normalizes GH and IGF-I levels in 10-44% of patients [67]. In Cushing’s disease, medical therapy is generally only used prior to surgery and awaiting the therapeutic effects of postoperative RT. For Cushing’s disease, steroidogenesis inhibitors (i.e. mitotane, ketoconazole, metopirone and hypnomidate), glucocorticoid receptor antagonist (i.e. mifepristone), and ACTH lowering agents (e.g. cabergoline, pasireotide) are examples of the classes of drugs that can be used to treat hypercortisolism. The medical therapy of first choice in Cushing’s disease is the steroidogenesis inhibitor ketoconazole [68] and is effective in about 50% of patients [52]. Long-term use of ketoconazole is not recommended due to poor long-term efficacy and side effects [66]. Other medical therapies have been proposed [69]. However, the available data on the efficacy of (other) medical
therapy used in Cushing’s disease is difficult to interpret due to varying criteria for defining a clear and effective response to treatment and disease control and lack of reference values [70].

LONG-TERM SIDE EFFECTS OF TREATMENT - THE REVERSE OF THE MEDAL

Surgery
Side-effects of surgery are mainly related to the surgical procedure or the post-operative period but can have an impact on the long-term.

Postoperative complications
Serious complications occurs in ≤ 5% of patients (i.e. cerebrospinal fluid leakage, fistula, meningitis, or new visual field defect) [50]. The complication rate is lower in experienced pituitary neurosurgeons and in high-volume hospitals [71]. Surgical complications are more likely with the trans-cranial than the trans-sphenoidal approach (mortality RR 4.89, 95% CI, 3.15-6.46, new pituitary hormone deficits RR 4.90, 95% CI, 2.94-7.82, persistent diabetes insipidus RR 2.50, 95% CI 1.05-5.35) [50]. The complication rates are higher and the success rates are rates lower in repeat surgery for recurrent or residual pituitary adenoma [72].

Hypopituitarism
Pre-operatively, the majority of pituitary macro-adenoma patients have pituitary hormone deficiencies. In patients operated for NFA macro-adenomas, hypopituitarism is still present after surgery in a considerable proportion of patients: GH deficiency in about 83%, LH/FSH deficiency in about 60%, and TSH and ACTH deficiency in about 30% of patients [48]. The reported new pituitary hormone deficiencies ranges from 7-22% of patients after surgery [47,73] and is determined by the pituitary adenoma size, extent of the resection and the surgeons experience [73]. The risk of hypopituitarism is higher after repeat (trans-sphenoidal) surgery and ranges from 41 to 50% [54]. Furthermore, a clear association was demonstrated between the extent of surgery and postoperative hypopituitarism with pituitary deficiency rates of 88%, 33% and 14% following hypophysectomy, hemihypophysectomy and selective adenonectomy, respectively [53]. Persistent diabetes insipidus occurs in ≤ 5% of patients [50].

Quality of Life
Quality of life is impaired in pituitary adenoma patients compared with the general population [74]. Furthermore, patients who underwent trans-frontal surgery have poorer outcomes in terms of psychological well-being compared to patients treated with trans-sphenoidal surgery [75].
Mortality
A meta-analysis showed that trans-sphenoidal surgery was associated with a 1% risk of mortality [50]. In addition, in-hospital mortality is lower in higher-volume hospitals and in higher volume surgeons [71].

Radiation therapy
Long-term side effects of RT are in general defined as effects occurring after 3 months or longer after the start of RT treatment.

Hypopituitarism
The most important and frequent reported long-term side-effect of pituitary RT is the development of new pituitary hormone deficiencies. Radiation-induced hypopituitarism (RIH) is insidious over months or years, progressive and non-reversible. The severity of and frequency of RIH correlates with the total RT dose and the length of follow-up. In pituitary adenoma patients with a normal pituitary function before the start of RT, hormonal replacement therapy with sex hormones, thyroid hormones or glucocorticoids is required in 15-27% of patients at 10 years after RT treatment [58,61].

Second tumors
A second intracranial tumor is the most feared long-term side effect of RT. Several studies evaluated the risk of RT on developing second tumors in pituitary adenoma patients. Some reported on an increased risk for second intracranial [76-78] or extracranial [79] tumors in patients treated with surgery and RT. However, no firm support for an increased incidence of second intracranial [79,80] or extracranial [76,78] tumors was found by others. All these previous studies compared the incidence of second tumors in patients treated with surgery and RT with the incidence observed in a normal reference population. As a consequence, potential other disease or treatment related factors that may be responsible for the increased incidence in tumors were not taken into account. In the studies that reported on a increased incidence of second intracranial tumors compared to a normal reference population, the absolute observed numbers were small and based on a few incident cases with an reported risk of 1.9% at 20 years [58,76] and characterized by wide confidence intervals. In most cases, the benefits of postoperative RT in pituitary adenoma patients, with otherwise uncontrolled disease, outweigh the absolute small risk of second tumor induction.

Stroke
In pituitary adenoma cohort studies an increased stroke risk has been reported [81] while others reported no increased stroke incidence [82]. These studies compared the stroke incidence in irradiated pituitary adenoma patients with the incidence observed in a normal
reference population. Such comparisons could be biased by imbalances in the presence of other stroke risk factors that are related to the pituitary adenoma disease and/or other treatments. RT might act as a risk factor for stroke, but available epidemiological studies discussed in the review by Erfurth et al. do not provide evidence to consider pituitary RT as a stronger risk factor compared to other risk factors in pituitary adenoma patients [83]. Therefore, to evaluate the concerns related to RT on stroke incidence a direct comparison should be made with similar patients treated with surgery-alone.

**Brain necrosis**

The overall incidence of brain necrosis is estimated at 0.2% in pituitary adenoma patients [84]. Although brain necrosis is a severe long-term complication, in pituitary adenoma it is considered as a rare side-effect of RT with a reported incidence based upon old literature where old RT techniques and higher RT doses were used. Modern RT treatment techniques and RT treatment doses of 45 to 50.4 Gy in 1.8 Gy fractions are safe in preventing brain necrosis.

**Radiation optic neuropathy**

Radiation optic neuropathy (RON) is considered a severe, but rare complication of external beam RT, and defined as a sudden and profound irreversible loss of vision affecting the optic nerve or chiasm. An estimated overall incidence of 0.5% was reported in a review of NFA patients treated with external beam photon RT [85]. Furthermore, another review showed that RON occurred in 1.36% of GH-secreting adenoma patients treated with external beam photon RT [86]. It is expected that the incidence will further decline with modern RT techniques and current recommended safe RT treatment doses of 45 to 50.4 Gy in 1.8 Gy fractions.

**Cognition and radiological brain effects**

Pituitary adenoma patients may have impairment of memory and executive function [87]. Studies about the effects of RT on cognition in pituitary adenoma patients treated with RT have shown conflicting results [87,88]. These inconsistent results on cognition may have been attributed to small sample sizes and inhomogeneous patient groups according to the pituitary adenoma diagnosis (e.g. NFA, acromegaly and Cushing’s disease), surgery (i.e. type and date), medical treatment and hormonal substitution therapy. Furthermore, in irradiated pituitary adenoma patients, the total dose, fraction dose and treated brain volume or brain region may have an impact on the incidence and severity of cognitive impairments. However, detailed dosimetric studies of the brain in relation to objective measures of cognition are not available in humans.

In pituitary adenoma patients, the radiological brain effects of RT (i.e. white-matter lesions and cerebral atrophy) are unknown and have not yet been investigated. However,
several studies have reported on long-term radiological brain effects in patients treated with RT for primary brain tumors. In irradiated primary brain tumor patients, radiological brain abnormalities are associated with larger RT treatment volumes, higher RT doses, and older age of the patient [89-91] and there appears to be a correlation with cognitive function [92]. However, adverse brain effects in these patients may also be influenced by (other) disease-related factors (e.g. degree of malignancy, tumor recurrence, neurologic co-morbidity) and treatment-related factors [91,93]. In contrast, compared to primary brain tumor patients, pituitary adenoma patients are treated with a lower total RT dose and in general smaller RT treatment volumes, have a fixed intracranial tumor position, and have no exposure to (other) disease- and treatment related factors relating to malignant brain disease. Therefore, this patient group provides an excellent opportunity for further investigations relating RT effects with radiological brain abnormalities and cognition.

**Quality of Life**
Several studies have shown that postoperative RT is not associated with reduced quality of life in pituitary adenoma patients [75,94,95].

**Sexual functioning**
In pituitary adenoma patients, sexual dysfunction may occur as a result of (sex) hormone deficiencies or hormone excess on sexual functions. The pituitary adenoma disease itself and the treatment(s) (i.e. surgery and/or postoperative RT) can result in hypopituitarism and, more specifically, in sex hormone deficiencies. However, there are no studies available about the long-term side effects of the different treatment modalities on sexual function in pituitary adenoma patients. In addition, little is known about the effects of sex hormone substitution therapy on sexual function.

**Mortality**
In several studies, RT itself was not identified as a risk factor for mortality in pituitary adenoma patients [8,42]. A number of studies showed excess mortality in patients with hypopituitarism [96-99]. However, no firm support for an increased mortality in pituitary adenoma patients was found by others [8,16,100,101].

**Medical therapy**
The long-term side effects of medical therapy in acromegaly and Cushing’s disease are less known. Medical therapy is by definition not a curative treatment. In addition, life-long treatment in persistent acromegaly disease represents a major concern because of its high costs and uncertain effects on hard-endpoints such as mortality.
Side effects

In acromegaly, the most frequently reported side-effects of SSAs are gastrointestinal symptoms occurring in 30% of patients [64]. Biliary tract abnormalities are reported in up to 50% of patients [102]. Hyperglycemia is observed in about 15% of patients. Other infrequently reported side-effects include liver function disturbances, hepatitis, anaphylaxis and hair loss [64]. SSAs are administered by subcutaneous or intramuscular injections and injection side pain reaction is a common side effect. The GH-receptor blocker pegvisomant is also administered by injections. Evidence is lacking about long-term effects on improved signs and symptoms of disease, quality of life, patient compliance and safety [103]. However, lipohypertrophy and hepatocellular liver enzyme disturbances have been described in several reports [104]. Lastly, there are concerns that long-term treatment with pegvisomant may result in pituitary adenoma growth [64]. Both in acromegaly and Cushing’s disease dopamine agonists can be used. The most common side-effects of dopamine agonists are nausea, orthostatic hypotension and mental disturbances [104]. Less frequent reported side-effects are depression, constipation, Raynaud’s phenomenon, and alcohol intolerance [104]. Dopamine agonists are administered orally. In Cushing’s disease, treatment with the steroidogenesis inhibitor ketoconazole can cause transaminitis in 10% of patients and severe hepatotoxicity necessitating dose adjustments or discontinuation of treatment [104]. Furthermore, ketoconazole can cause a decrease in sex steroid levels resulting in decreased libido and impotence [104]. Experience with long-term use of medical therapy in Cushing’s disease is limited, but data from prolactinomas and Parkinson’s patients show potential valvulopathy on long-term treatment with the dopamine agonist cabergoline especially with higher doses [104].

Quality of Life

Treatment with SSAs is associated with poorer quality of life compared to patients who are cured, in spite of similar IGF-1 concentrations [105].

Costs

In acromegaly, a disadvantage of medical therapy relates to life-long treatment and therefore the associated high costs. SSAs (e.g. octreotide 10 to 30 mg per day per patient) are first-line therapy but costly, and the long-term use, especially life-long treatment, makes this a significant issue. The costs of SSAs are approximately €26,000 to €76,000 per year in the Netherlands (www.medicijnkosten.nl). Unfortunately, the GH-receptor blocker pegvisomant (i.e. 10 to 30 mg per day per patient) is also an expensive treatment. The costs of pegvisomant are approximately €28,000 to €84,000 per year per patient in the Netherlands (www.medicijnkosten.nl.) In the United Kingdom standards for determining cost-effectiveness of therapies, pegvisomant was reported not to represent good value for money [103]. Dopamine agonists (e.g. bromocriptine 10 mg to 20 mg per day per patient) are relatively inexpensive
and costs are approximately €300 to €1,200 per year in the Netherlands (www.medicijnkosten.nl) but have less efficacy compared to SSAs and the GH-receptor blocker pegvisomant.

**Mortality**

Therapies for acromegaly and the associated co-morbidities have lowered the risk of mortality almost to the level of the general population [22]. There is only one report that compared the effects of SSAs therapy alone with pituitary adenomectomy. The investigators found that survival of non-diabetic patients treated with SSAs was comparable to that of curative neurosurgery. On the contrary, in diabetic patients, SSAs therapy as primary therapy may be less effective than adenomectomy in reducing mortality rate [30].

**AIMS OF THIS THESIS**

The main objective of this thesis is to evaluate health-related outcome of postoperative RT among patients with pituitary adenomas. More specifically, the assessment of the occurrence of second tumors, stroke, brain abnormalities on Magnetic Resonance Imaging (MRI), cognition and sexual function is investigated.

**SHORT OUTLINE OF THIS THESIS**

General introduction.

**Chapter 1**

To assess and compare the incidence of intra- and extracranial tumors and mortality in pituitary adenoma patients treated with postoperative RT and surgery alone.

**Chapter 2**

To assess and compare the incidence of stroke and stroke subtype in pituitary adenoma patients treated with postoperative RT and surgery alone.

**Chapter 3**

To assess and compare brain abnormalities on MRI in non-functioning pituitary macro-adenoma patients treated with or without RT.

**Chapter 4**

To explore the effect of RT on cognition by relating the radiation dose on radiosensitive brain areas to cognitive test performance.

**Chapter 5**
To assess and compare sexual function in pituitary adenoma patients treated with postoperative RT and surgery alone.

**Chapter 6**

Letter to the Editor.
The role of radiotherapy in the treatment of non-functioning pituitary adenomas.

**Chapter 7**

General discussion.

**Chapter 8**
REFERENCES


Chapter 1


[87] Peace KA, Orme SM, Padayatty SJ, Godfrey HP, Belchetz PE. Cognitive dysfunction in patients with pituitary tumour who have been treated with transfrontal or transsphenoidal surgery or medication. Clin Endocrinol (Oxf) 1998;49:391-396.


