General Discussion
Concerns related to possible long-term side-effects of radiation therapy (RT), such as second tumors, stroke and increased mortality, are often used to delay or reject RT in pituitary adenoma patients. Many of these concerns are based on selected studies and observations from an era in time where old RT techniques were used and RT schedules with higher total dose. Furthermore, in previous studies on second tumors, stroke and mortality, comparisons were made between irradiated pituitary adenoma patients and the general population instead of irradiated and non-irradiated patients with the same disease. Consequently, potential other pituitary adenoma disease and treatment related risk factors were not taken into account. The magnitude of the potential excess risks of RT is thus a widely debated issue, and should be balanced with the probably already increased risk without RT. Therefore, large cohort studies of patients treated with and without RT are crucial to provide a more direct assessment of the true excess risk of RT on second tumors, stroke and mortality.

Previously, our group demonstrated that immediate postoperative RT in residual NFA has no additional negative impact on pituitary function and life expectancy compared to patients with residual disease and followed by an active surveillance policy [1]. Furthermore, we showed that postoperative RT in NFA patients was not associated with reduced quality of life or cognition when compared with surgery alone [2].

The cohort studies presented in this thesis were therefore focused on assessing and comparing the incidence of (second) tumors, stroke and the possible associated negative impact on mortality, aspects relating to quality of life (QoL) and other long-term side effects of conventional RT in pituitary adenoma patients treated with surgery and postoperative RT versus surgery alone and with a population without pituitary adenoma disease (i.e. the reference population).

Second tumors, mortality and stroke in pituitary adenoma patients

Several studies evaluated the risk of RT on developing second tumors and the impact on mortality in pituitary adenoma patients. Some reported on an increased risk for second intracranial [3-5] or extracranial [6] tumors and an increase in mortality [7,8] in patients treated with surgery and RT. However, no firm support for an increased incidence of second intracranial [6,9] or extracranial [3,5] tumors and mortality [1,10] was found by others. In all these studies, the incidence of second tumors and mortality in patients treated with surgery and RT was compared with the incidence observed in a normal reference population. The aim of our study described in chapter 2 was to assess and compare the incidence of intra- and extracranial tumors and mortality in pituitary adenoma patients treated with postoperative RT and surgery alone. The results of this study shows no significant increase of second (intra- and extracranial) tumors and mortality after RT compared with that observed after treatment with surgery alone. In the previous studies that reported on an increased incidence of second intracranial tumors compared to a normal reference population, the absolute observed
numbers are small and based on a few incident cases with a reported risk of 1.9% at 20 years [3,4]. Although these findings are of potential concern, it should be noted that, as a consequence of this low incidence, the reported confidence intervals are wide. Furthermore, the irradiated patients who developed intracranial tumors were treated with outdated RT techniques consisting of 2 fields [4], 3 fields [5] and telecobalt [4] resulting in large RT treatment volumes with high RT dose and were irradiated at a relatively young age [4,5]. Furthermore, our findings in chapter 2 shows an increased mortality incidence in all pituitary adenoma patients (i.e. non-functioning adenomas (NFA), acromegaly, and Cushing’s disease) in comparison with the reference population. This finding can be explained by uncontrolled disease itself in some patients, like in acromegaly [11,12] and in Cushing’s disease [13], and the presence of hypopituitarism [14-17] in both treatment groups.

RT might act as a risk factor for stroke in pituitary adenoma patients, but available epidemiological studies discussed in the review by Erfurth et al. do not provide evidence to consider RT as a stronger risk factor compared to other risk factors related to the pituitary adenoma disease and/or other treatments [18]. Therefore, the aim of our study in chapter 3 was to assess and compare the incidence of stroke and stroke subtype in pituitary adenoma patients treated with postoperative RT and surgery alone. This study shows no significant increases in neither the incidence of stroke nor differences in the causative mechanisms or anatomic localizations of stroke compared with that observed among surgery alone patients. Furthermore, our study shows an increased incidence of stroke in all pituitary adenoma patients in comparison with the reference population (chapter 3). These results suggest that risk factors other than RT may have contributed to the development of stroke. Indeed, in our study the primary risk factor for stroke in pituitary adenoma patients (i.e. NFA, acromegaly and Cushing’s disease) is pre-existent coronary or peripheral artery disease. Some investigators suggested that surgical trauma to the vasculature or extent of surgery [18,19] may have played a role in the risk of stroke. In addition, hormone excess (i.e. acromegaly or Cushing’s disease) or hormone deficiency (i.e. hypopituitarism due to the disease, surgery, and/or RT) may act as risk factors for stroke [18] indirectly by inducing secondary hypertension, insulin resistance, or dyslipidemia, and directly by interactions with cellular pathways that are important in the process of atherosclerotic plaque formation, plaque instability, and thrombosis [20].

The strength of our observational studies described in chapter 2 and 3 is that the concerns related to RT in irradiated patients were evaluated by making a direct comparison with similar patients treated with surgery alone and with the reference population. In previous other cohort studies, comparisons were made between irradiated patients and the general population. As a consequence, potential other pituitary adenoma disease characteristics and treatment related risk factors were not taken into account. Furthermore, the studies on second tumors (chapter 2) and stroke (chapter 3) describes a large cohort of 462 pituitary adenoma patients with longer follow-up duration (i.e. 14 years) compared with other investigators. Finally, in the
stroke study (chapter 3), several other well established stroke risk factors were assessed besides RT, additional Computed Tomography (CT)-imaging was used to confirm stroke diagnosis and stroke type, and causative mechanism and anatomic localization of ischemic stroke was assessed, illustrating our detailed data collection.

There are several limitations that should be taken into account. The studies described in chapter 2 and 3 are retrospective cohort studies and non-randomized, and therefore, difficult to control for possible confounding factors and bias between the two treatment groups. Furthermore, the reported lack of significance does not mean that there are no differences in the incidence of second tumors, mortality and stroke between patients treated with RT and surgery alone, but, if present, that the differences and absolute risk between the two treatment groups are relatively small. Therefore, from the results of our studies we cannot exclude that RT does not cause second tumors or stroke in pituitary adenoma patients. Furthermore, the second tumors and strokes diagnosed in patients treated with RT may still represent a long-term side effect of RT. Finally, although our study did not show that RT was associated with an increased incidence of second tumors (chapter 2), in clinical decision making, the age of the patient - especially in younger patients with long life expectancies - should certainly be taken into consideration in the decision regarding treatment benefit versus risk ratio of RT.

Radiological brain abnormalities and cognitive performance in NFA patients

White-matter lesions (WMLs) and cerebral atrophy are well known radiological detectable abnormalities of the brain in primary brain tumor patients treated with RT [21-23] and there appears to be a correlation with diminished cognitive function [23]. In NFA patients, the radiological brain effects of RT (i.e. WMLs and cerebral atrophy) are unknown and have not yet been investigated. In addition, NFA patients compared with primary brain tumor patients, are treated with a lower total RT dose and in general a smaller RT treatment volume, a fixed intracranial tumor position, and have no exposure to disease- and treatment related factors relating to malignant disease. The aim of the study described in chapter 4 was to assess and compare several brain abnormalities (i.e. WMLs, cerebral atrophy, brain infarctions, abnormalities of the temporal lobes and hippocampi) on Magnetic Resonance Imaging (MRI) in NFA patients treated with or without RT. Our study shows that brain abnormalities on MRI are not observed more frequently in NFA patients treated with RT compared with patients treated with surgery alone. Furthermore, there is no significant increase in severity of WMLs and cerebral atrophy in RT patients compared with surgery alone patients.

In a previous study by Brummelman et al. memory and executive functioning was assessed and compared in a large (n = 84) homogenous group of NFA patients treated with and without RT [24]. NFA patients displayed a worse cognitive performance compared to the reference population, but no major influence of pituitary RT on cognition was found. However, relatively small effects of RT on cognition could not be excluded (e.g. due to different RT techniques
and dose distributions). Therefore, we refined the strategy and related radiation dose to the hippocampus and the prefrontal cortex (PFC) to cognitive performance typically associated with these brain areas of interest (chapter 5). In this study, we show that there were no significant differences on memory and executive functioning between the conventional three-, four-, and five-field RT techniques groups. Furthermore, a dose-response relationship, by relating detailed radiation dosimetry to the temporal lobes, hippocampi and the PFC, with cognition could not be established. Our results may suggest that the multiple field RT techniques and RT dose prescriptions used in our center appear to operate within safe limits and do not have a major effect on memory and executive functioning.

The strength of our study in chapter 4 was the quantitative and qualitative assessments of several brain abnormalities with pre- and post-treatment MRI scans available for all patients. Furthermore, the incidence of brain abnormalities in irradiated patients was compared with patients treated with surgery alone as a reference group. In our cognition study (chapter 5), we tested a homogenous patient group of NFA patients, and thereby, we were able to exclude confounding results like hormone excess or other treatment related factors. Furthermore, the fixed intracranial tumor position in NFA patients excludes potential confounding influences of the localization of both the brain tumor and subsequent targeted focal RT on cognitive performance.

Some limitations need to be addressed. The studies of chapter 4 and 5 consisted of 86 and 75 NFA patients. Lack of significance in radiological brain abnormalities and cognitive test performance in groups with small patient numbers yields low statistical power, and therefore, does not mean that there are no differences between the treatment groups, but that small effects may not have been detected. Furthermore, the study designs were non-randomized, and therefore limited to infer causality, and have potential confounding and selection bias. The disease characteristics (e.g. larger and more invasive adenomas) of RT patients are somewhat different compared to NFA patients treated with surgery alone. Finally, cognition was only assessed with a relatively limited test battery (chapter 5) and focused only on memory and executive functioning. Several tests to assess the cognitive domains of memory and executive functioning would be a more sensitive approach and other cognitive domains should be examined as well.

Sexual function in pituitary adenoma patients

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. Sexual function is still a poorly studied aspect of quality of life in pituitary adenoma patients. The aim of the study in chapter 6 was to assess and compare sexual function in pituitary adenoma patients treated with or without
General Discussion

postoperative RT and with or without testosterone substitution therapy. The results of our study shows no significant differences in sexual function between pituitary adenoma patients treated with RT and surgery alone. These results may suggest that patients with hormonal substitution therapy are adequately substituted and that subtle physiological derangements do not negatively affect the sexual function.

The strength of our study is that the sexual function of patients were compared with patients of the same age.

A limitation of the study is its cross-sectional study design. The study was non-randomized, and therefore, there were several significant differences between RT and surgery alone patients regarding the clinical characteristics, which potentially could have influenced sexual function outcomes. Furthermore, a heterogeneous group of pituitary adenoma patients was studied (i.e. NFA, acromegaly and Cushing’s disease). Finally, a reference population was not included, and the sexual function outcomes of patients could not be compared to an age-matched reference population. Therefore, it is not yet clear to what extent the sexual function of patients is impaired, and whether sexual dysfunction is more prevalent in pituitary adenoma patients.

Implications for future follow-up programs and patient care
In chapter 3 we show that the primary risk factor for stroke in pituitary adenoma patients is pre-existent coronary or peripheral artery disease. Therefore, the question arises as to whether future follow-up programs should pay more attention to early detection of patients at risk for stroke (i.e. patients with evidence of pre-existent coronary or peripheral artery disease), and preventive management of modifiable cardiovascular risk factors that may reduce stroke risk. So far, there are no studies that assessed the impact of conventional medical treatment options for stroke prevention in this patient group. However, our findings suggest that it may be reasonable to aim for early antihypertensive and lipid-lowering medical treatment for primary prevention in pituitary adenoma patients with an additional atherosclerotic risk factor [25].

Sexual function is a poorly studied aspect of quality of life in pituitary adenoma patients. In chapter 6 on sexual function, the high response rate of 68% of our patients may reflect the importance of sexual function to our patients. Therefore, the quality of patient care may further improve by paying more attention to sexual function during consultations and follow-up in the endocrinology out-patient clinic. The sexual function questionnaires used in our study may help physicians and patients in bringing up the subject of sexual problems during out-patient follow-up clinics and may in the future be part of patient related outcome measurements.

No randomized controlled studies are available regarding the efficacy and long-term side effects between surgery, postoperative RT and/or medical therapy in pituitary adenoma patients, and all the evidence is based on observational studies. Furthermore, information on the effects of different treatment modalities on endpoints of survival and QoL is limited.
in pituitary adenoma patients [26]. Other important endpoints of treatment are tumor control
and long-term side effects. Of all the different treatment modalities (surgery, medical therapy
and RT), the RT studies excels in long reported follow-up duration compared to the other
treatments. The long-term side effects of medical therapy in acromegaly and Cushing’s
disease are less known. Furthermore, its long-term use in clinical practice is often not a
point of discussion, and in acromegaly represents a major concern because of its high costs.
Clinicians ought to be more aware of medical treatment costs.

**Technological improvements in RT**
The RT patients included in this thesis were treated with conventional external beam RT
between 1962 and 2010. In this period of almost 50 years, major technological improvements
have been made in RT, such as patient immobilization, the clinical application of modern
imaging, rigid and deformable image co-registration, use of computerized 3-dimensional
(3D) treatment planning systems, and more precise treatment delivery techniques, such as
stereotactic RT and intensity modulation [26]. The results of our observational studies on
long-term side effects of RT in pituitary adenoma patients treated with or without RT showed
no significant differences between the two treatment groups. However, these studies were
not designed to investigate cause-effect relationships of long-term RT treatment side-effects.
Therefore, improvements in target volume definition resulting in smaller RT volumes with less
exposure of high dose radiation to normal tissues, and by modern RT treatment techniques
enabling to achieve a steeper dose gradient from the planning target volume to the normal
surrounding tissues are important, and may in the future translate into a clinical benefit in
terms of a further reduction of possible long-term side effects of RT.

**Stereotactic radiosurgery and stereotactic conformal RT**
Modern and more precise RT treatment delivery techniques that have been clinically applied
in pituitary adenoma patients are stereotactic radiosurgery (SRS) and stereotactic conformal
RT (SCRT). SCRT is a treatment technique suitable for all pituitary adenoma sizes and the
efficacy in terms of local tumor control and improvement of excessive hormonal secretion
is comparable to conventional RT [27]. Single fractions SRS can only be safely delivered in
small pituitary adenomas less than 3 cm in diameter and located more than 3 mm to 5 from the
optical system [27]. SRS does not result in better local tumor control rates for small pituitary
adenomas compared to fractionated RT for all pituitary adenoma sizes [27]. Furthermore, there
is no evidence that SRS results in a faster decline of elevated hormone levels in secreting
pituitary adenomas [27,28], or that sparing of the pituitary function is superior compared with
conventionally fractionated RT [29]. However, the number of hospital visits is very limited
which is more convenient for patients, and is interesting from a cost-effective perspective.
Furthermore, the potential difference in biological effectiveness between a single SRS
treatment and a comparable dose of a fractionated treatment, in terms of the therapeutic ratio for pituitary adenomas, is not yet defined [27]. Lastly, the clinical significance of an increase in the volume of normal brain receiving lower RT doses with stereotactic treatment is not clear at present.

Until now, there are almost no data available about the potential reduction in long-term side effects by using stereotactic RT techniques because long-term follow-up studies are lacking [27]. Therefore, studies with longer reported follow-up (i.e. > 5 years) are necessary to compare the long-term RT side effects between stereotactic and conventionally fractionated RT.

Proton therapy
In proton therapy, accelerated proton particles are used to treat a target volume (i.e. tumor). The beam properties of proton SRS or SCRT are expected to result in better sparing of surrounding normal tissues compared to the currently used photon RT. The risk of potential long-term side effects of RT may therefore further decrease due to the effects of minimizing radiation exposure to the normal surrounding (brain) tissues. This advantage of proton therapy is therefore considered an attractive RT treatment option in pituitary adenoma patients who can benefit from RT. Pituitary adenomas are benign tumors and patients have a long life expectancy with treatment, and therefore at risk for developing long-term side effects of RT [28]. Until now, very limited data are available regarding the efficacy and long-term side effects of proton therapy in pituitary adenoma. Currently, there are no proton therapy facilities available in the Netherlands.

FUTURE PERSPECTIVES

It is recommended to refer and treat pituitary adenoma patients in high-volume hospitals to further improve the quality of outcome for patients, given the relative low incidence of pituitary adenoma disease, the required experience and expertise of all the involved medical disciplines, and the wide range of the different treatment modalities. Therefore, the optimal management of pituitary adenomas consists of a multidisciplinary approach involving neurosurgeons, endocrinologists, radiation oncologists and all other relevant medical disciplines (e.g. pathologists, radiologists, ophthalmologist and ear-, nose- and throat surgeon). The optimal treatment should be discussed in this multidisciplinary team and with the patient considering all the pros and cons on the efficacy, (long-term) side effects and costs of all the different treatment modalities. 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, and future studies are recommended.
There are no randomized controlled trials (RCTs) available on the efficacy and possible long-term side effects of postoperative RT in pituitary adenoma patients. An RCT is not the most suitable study design and is not practically feasible for evaluating efficacy and long-term side-effects of RT, given the low incidence of the pituitary adenoma disease, and the specific indications for RT. 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. Randomization to 'no RT' may not be ethically approvable in cases that are not amendable to surgery or medical therapy and RT is indicated for local or hormonal control. Future prospective observational studies consisting of larger patients cohorts with long follow-up are recommended to elucidate the long-term side effects of RT compared with surgery alone. Therefore, treatment in high volume-hospitals and future research collaborations (national/international) are desired to generate larger patient cohorts. In addition, future prospective observational studies are recommended to determine the most beneficial method in stereotactic RT delivery in terms of efficacy, long-term side effects, QoL and costs. Furthermore, with the use of modern and precise RT treatment delivery techniques, a uniform delineation guideline and recommendation for a contouring method and atlas of the organs at risk (OARs) (e.g. temporal lobes, hippocampi, PFC, whole brain, optic nerves, chiasm, pituitary) for pituitary adenoma disease is important and desired, and will in the future facilitate correlation studies between long-term brain side-effects and dosimetric research between different RT institutes.

Finally, it is recommended to perform longitudinal studies with comprehensive cognitive test batteries and a baseline measurement before the start of treatment to assess and compare the effects of RT and surgery alone treatment on cognition. In this way, the disease effects and treatment related factors on cognition can be distinguished.

**CONCLUSIONS**

None of our observational studies shows significant differences in long-term side-effects between pituitary adenoma patients treated with RT and surgery alone. However, the reported lack of significance does not mean that there is no difference in long-term side effects, but that the differences and absolute risks of RT are small. Therefore, the decision to treat with postoperative RT is based on a careful assessment of the balance of benefits and risks in the individual pituitary adenoma patient. The risk of serious radiation-induced long-term side effects is low with the RT techniques applied in the last decades and is expected to be lower with modern and more advanced RT techniques. Therefore, in most pituitary adenoma patients with otherwise uncontrolled disease, the benefits of postoperative RT outweighs the absolute small risk of serious side-effects.
REFERENCES


