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Introduction to Radiation therapy in pituitary adenomas

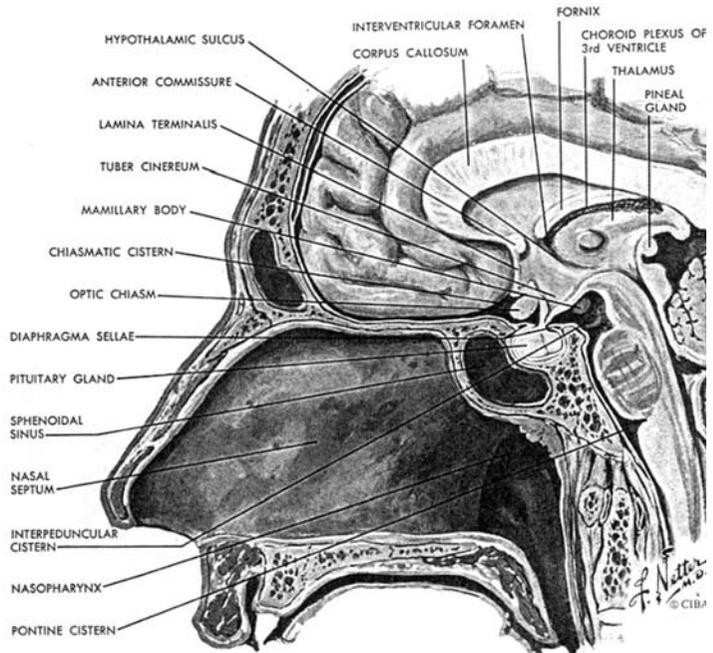


Figure 1
Midsagittal view of the pituitary gland in relation to the bony structures and the brain (adapted from Netter)

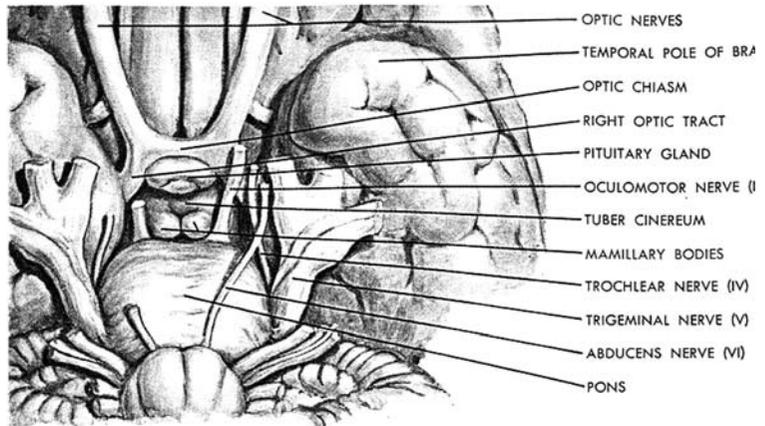


Figure 2
View on the caudal side of the brain, showing the pituitary gland in relation to the optic structures and other cranial nerves (adapted from Netter).

Introduction

A multidisciplinary approach is currently preferred in diagnosis and treatment decision-making in pituitary adenoma patients. In the multidisciplinary neuro-endocrine meetings of the University Medical Center Groningen, the clinical benefits as opposed to potential side effects of radiation therapy, as reported by other centres, were frequently debated, resulting in suboptimal consistency in our approach to this patient category. In order to increase our understanding of the clinical consequences of (post-operative) radiation therapy as compared to no radiation therapy, it was decided to evaluate the outcome of this treatment among pituitary adenoma patients treated in our institution during the past decades. The single-centre cohort studies described in this thesis are aimed to improve evidence-based decision-making in pituitary adenoma patients.

Pituitary Anatomy

The pituitary gland is a bean-shaped small organ, located in the sellar fossa, in the centre of the skull base at the base of the brain. The word “pituitaria” is derived from the Greek word “ptuo”, which means “spew” and the Latin word “ptuita” (mucus). The normal size of the gland is approximately 10 mm in length, 5 to 10 mm in height and 10 to 15 mm in width (Figure 1 and Figure 2). The normal weight is 500-600 mg. This organ plays a central role in hormone regulation; it integrates hormonal signals that control adrenal, thyroid, reproductive, growth, and metabolic functions.

The pituitary gland is divided in the anterior and the posterior lobe, the so-called adeno- and neurohypophysis. The anterior lobe contains 75 percent of the pituitary gland, in which different hormones are produced. The most important are: growth hormone (GH), prolactin (Pr), adrenocorticotrophic hormone (ACTH), thyrotropin (TSH), luteinising hormone (LH) and follicle-stimulating hormone (FSH), produced by at least 5 different cell-types. These different cell types are clustered and have their own position in the pituitary gland; ACTH and TSH in the centre of the anterior pituitary lobe and PR and GH at both lateral sides. The posterior lobe is a storage for anti-diuretic hormone (ADH) and oxytocin, produced in the hypothalamus. The pituitary gland has a connection with the hypothalamus via the pituitary stalk and portal system. Neighbouring structures are the optic chiasm and optic nerves antero-superior, the sphenoid sinus antero-inferior, the cavernous sinus and the cranial nerves III, IV, V and VI at both lateral sides and dorsal the clivus.

Pituitary adenomas

Pituitary adenomas originate only in the anterior lobe. In the vast majority of cases, they are monoclonal and are characterised by complete disruption of the reticulin fi-

bre network in contrast to pituitary hyperplasia¹. These adenomas are benign lesions, comprising 10-15% of all intracranial tumours^{2,3}. Pituitary adenomas can be divided in secreting and non-secreting tumours. Secreting tumours produce an excess of pituitary hormones with each its own syndrome: Pr (Prolactinoma), GH (Acromegaly, gigantism), ACTH (Cushing's disease), TSH (Thyrotrophinoma), and LH/FSH (Gonadotrophinoma). Although almost all pituitary adenomas are classified as benign, many of these lesions are locally invasive and cause major morbidity and mortality. The pathogenetic mechanism in pituitary tumour genesis is complex and enigmatic⁴.

Incidence en prevalence

The incidence for all pituitary adenomas is estimated at 80 million persons per year. An increase in the incidence is reported in the time period 1958-1991 in Sweden³. The peak incidence occurs in the fourth to the sixth decade of life⁵. Incidence and prevalence numbers for the Netherlands are not available.

In a systematic review, the prevalence of pituitary adenomas in the general population has been estimated at 16.7% (14.4% in autopsy studies and 22.5% in radiologic studies). The prevalence of macroadenomas (>1 cm) has been estimated at 0.16-0.2%⁶. These figures contradict the conventional view of pituitary tumours as rare; pituitary adenomas are in fact common in the general population.

Approximately 25% of all pituitary adenomas are clinically non-functioning/non-secreting (NFA). The incidence is estimated at 10 per million persons per year. In Belgium, the prevalence of clinically significant non-secreting pituitary adenomas was 138/1.000.000. The male to female ratio is estimated at: 3 : 2⁸.

The incidence of prolactin producing pituitary adenomas (PR) is estimated at 6-10 per million persons per year and the prevalence at 60-100 per million⁹. A female preponderance is observed of 20 to 1 in microadenomas; in macroadenomas female to male ratio is equal.

The incidence of growth-hormone producing pituitary adenomas (GH) is estimated at 4-6 per million persons per year and the prevalence at 40-60 per million^{9,10}. The incidence of ACTH producing pituitary adenomas (ACTH) is estimated at 2-3 per million persons per year and the prevalence at 20-30 per million⁹.

TSH (Thyrotrophinoma) and LH/FSH (Gonadotrophinoma) are rare pituitary adenomas⁹. Because of their rarity these tumours are not discussed in detail.

Clinical symptoms

NFAs, frequently macroadenomas, usually present with signs as a result of local mass effect and extension outside the sella turcica. Symptoms are bitemporal hemianopsia, decreased visual acuity, ophthalmoplegia and signs and symptoms as a consequence of hormonal insufficiency. Loss of vision due to NFA is caused by compression of the optic

system and results in visual field defects in 85% and in complete blindness in 2% of NFA-patients⁸. Ophthalmoplegia is caused by invasion of the tumour in the cavernous sinus, compressing the third, fourth and sixth cranial nerve.

Hypopituitarism due to pituitary adenoma is caused directly by destruction or compression of normal pituitary tissue or indirectly due to compression of the pituitary stalk or of the portal circulation with focal necrosis of normal pituitary tissue as a result¹¹. The prevalence of hypopituitarism is largely restricted to macroadenomas¹². Features of pituitary insufficiency include decreased libido and/or erectile dysfunction in men, irregular menses or amenorrhea in premenopausal women, and fatigue (thyroid hormone, cortisol, GH deficiency or deficiencies).

Secreting pituitary adenomas are in general smaller than NFA at the time of diagnosis, because their symptoms are based on excessive hormone production.

Prolactinoma with its hypersecretion of prolactin in women can result in irregular menses or amenorrhea, galactorrhea and loss of libido. In men, loss of libido and impotence is observed.

With GH excess, leading to the syndrome of acromegaly, features develop insidiously over decades, often resulting in a delay of 5 to 10 years in diagnosis after the estimated onset of symptoms. Symptoms are enlargement of the acra (facial bones, hands and feet), paresthesias, excessive sweating, arthropathy, headache, tiredness, and sleep apnoea.

Cushing's disease is caused by ACTH overproduction and characterized by weight gain, centripetal fat distribution, fatigue, memory loss, irritability, depression, muscle weakness, osteoporosis and purple striae.

Mortality

Overall mortality is reported to be higher in pituitary adenoma patients in comparison with the normal population, primarily as a result of cardiovascular and cerebrovascular disease³.

In a large cohort of mainly non-functioning pituitary adenomas of the Royal Marsden Hospital, the overall age adjusted relative risk (RR) of death was 1.76 in comparison with the normal population¹³. The few deaths from progressive pituitary adenoma and from second brain tumours accounted for only a small excess mortality. An increased mortality was reported due to cerebrovascular accidents. In the pituitary adenoma cohort of 334 patients, treated between 1962 and 1986, 128 deaths were observed versus 80.9 expected (RR of death: 1.58 (95% CI: 1.32 - 1.9). Of these 128 deaths, 33 (26%) were due to cerebrovascular deaths compared with 8.04 expected (RR 4.11: 95%CI: 2.84 - 5.75). Three of the 33 cerebrovascular deaths were due to subarachnoidal haemorrhage, compared to 0.54 expected deaths (RR 5.51: 95%CI: 1.14 - 16.09). Any relationship with hypopituitarism, extent of surgery or radiation therapy could not be found.

The Danish registry however reported no increased mortality due to cardiovascular and cerebrovascular disease. In this study, type of surgery and radiation therapy were not identified as risk factors, while female sex was a risk factor⁸. Moreover, no increased mortality due to malignant disease was reported in all kinds of pituitary adenoma⁸.

Other groups however, report an increased mortality in incompletely controlled acromegaly patients in comparison with the general population due to cardiovascular and malignant disease^{14,15}.

Patients with untreated Cushing's syndrome have excess mortality¹⁶.

Treatment modalities

Active surveillance

An incidentaloma, most frequently a microadenoma (<1 cm), is diagnosed in about 10 percent of healthy persons on MRI, made for other reasons^{17,18}.

Patients with an incidentaloma have a slightly increased risk of morbidity and mortality, which implies a benefit of early diagnosis¹⁹. Therefore a conservative approach with repeat scanning done at yearly intervals is suggested¹⁷.

Medication

Non-functioning pituitary adenomas in general do not respond to medical treatment²⁰. Patients with a prolactinoma have a treatment response of 95% on dopamine-agonists and therefore medical treatment is the first choice.

Acromegalic patients respond in 65% of the cases on somatostatin analogues and in more than 90% on Pegvisomant, a GH-receptor antagonist. Side-effects of somatostatin analogues are diarrhea in 11%, flatulence in 8%, hair loss in 8%, episodically abdominal cramps in 3%, and gallbladder abnormalities in <10% of the patients. Pegvisomant is expensive and in general does not result in tumour shrinkage²¹ and may even result in tumour growth²².

In case of Cushing's disease, medication is directed at decreasing adrenal steroid secretion (e.g. ketoconazole, metyrapone, aminoglutethimide). These drugs frequently lose effectiveness when the decrease in cortisol secretion results in enhanced ACTH secretion, leading to escape from the competitive blockade on adrenal steroid biosynthesis. Long-term ketoconazole is not recommended because of the risk of liver function impairment. Mortality due to medication has not been reported.

Surgery

Surgery was first used by Horsley in 1889 but was refined by Cushing²³. The treatment of choice is either transsphenoidal or transcranial neurosurgical adenomectomy, aiming at complete tumour removal or decompression of surrounding structures. The trans-

sphenoidal approach usually allows for potential resection of a sellar tumour without entering the subarachnoid space, thereby minimizing the risk of complications such as cerebrospinal fluid leakage or meningitis. Complete surgical removal is often impossible, because of the invasive character of microadenomas and larger pituitary adenomas, with infiltration of the neighbouring structures such as arachnoid membrane, dura, sinus cavernosus and the skull base^{24,25}.

The neurosurgeon's conclusions on complete resection during operation is different from the conclusions on MRI²⁶. This clarifies the statement of Turner et al. who demonstrated that the surgeon's assessment of complete surgical removal was unrelated to recurrence²⁷. Specialization improves the outcome of pituitary surgery with less morbidity and mortality²⁸. Differences in results among centres for pituitary surgery should be interpreted with caution even for those confined to comparable criteria of remission²⁸. Nowadays minimal invasive neurosurgery i.e. endoscope assisted trans-sphenoidal microsurgery is applied²⁹.

Non-functioning pituitary adenomas are most frequently macroadenomas at diagnosis. In 90% of the cases, only a partial resection can be performed³⁰.

Concerning prolactinoma, surgery is only rarely performed, in case of resistance or intolerance to medication.

In regard to acromegaly, 75% of the tumours are macroadenomas, which often extends laterally into the cavernous sinus or dorsally to the suprasellar region¹⁰. The cure rate with surgery alone for intrasellar lesions is 59-95%^{21,28} and for larger tumours 26-68%^{21,28}. Intraoperative GH-measurements and intraoperative MRI, can improve results^{31,32}.

For Cushing's disease, the immediate postoperative cure rate after first surgery for microadenomas varies between 78-97% and for macroadenomas between 50-60%³³. After curative resection, the recurrence percentage is 5-25%³⁴.

Although small series have shown, that neurosurgery can improve pituitary hypofunction^{11,35-38}, more often deterioration of the pituitary function will occur³⁰. Other specific side effects of surgery are leakage of cerebrospinal fluids, some degree of nasal discomfort and transient diabetes insipidus or mild SIADH (syndrome of inappropriate vasopressin secretion).

The mortality rate of neurosurgery is reported to vary between 0.26 and 3%³⁹.

Radiation therapy

External beam radiation therapy for pituitary adenomas has been applied for more than 100 years and the first results were reported by Beclere and Gramegna, two French physicians in 1909⁴⁰.

Because of a high operative mortality in the early 20th century, radiation therapy was a primary method of treatment at that time. Surgery, however, was the only method

to restore vision. Gradually, it was discovered that surgery followed by radiation therapy was more effective than surgery alone⁴¹. In the sixties, there were differences in opinion regarding the role of radiation therapy in NFA. Some investigators in the USA advocated primary radiation therapy, but others recommended surgery followed by radiation therapy, promoted also by the British and Scandinavian schools. Nowadays, because of improved neurosurgical techniques, surgery is the treatment of choice in NFA with compression. Primary radiation therapy is only applied if the patient refuses surgery or the general condition of the patient does not allow neurosurgery.

Immobilisation of the head of the patient to apply more precisely the radiation therapy to the tumour has been improved, starting with no immobilisation devices, followed by tape and later on by immobilisation masks and stereotactic frames.

Outlining the tumour for target volume definition in radiation therapy has been improved due to better imaging techniques. In the beginning, plain skull films, pneumoencephalography and later on cerebral angiography were used in outlining the tumour with its suprasellar and parasellar extension. Since the availability of CT-scans in the seventies this technique has been used for tumour outlining, followed by MRI 10 years later. Nowadays, MRI is the preferred modality - if applicable and available - for primary evaluation of the pituitary gland and outlining the tumour for radiation therapy co-registered with the planning-CT scan⁴².

Radiation therapy treatment schedules

Between 1930 and 1945 the general approach was to use multiple courses of low-dose radiation, repeated at intervals of 4 to 8 weeks. In general, a total of 3 to 5 courses were applied, guided by patient's visual response. Daily doses of 200 rads were used to a total dose ranging from 2450 to 3000 rads per course.

Between 1945 and 1955, this policy changed into multiple courses of medium dose radiation (i.e. total dose of 30-40% more per course) and repeated with shorter intervals.

From 1955 the multiple course approach was abandoned because it was more deleterious for the normal tissues, due to the total accumulated dose of the different courses in a shorter overall treatment time. Since then, single-course high dose radiation therapy has generally been applied, intended to deliver a radiation dose sufficiently high to achieve permanent tumour control. The total dose increased in time from 2000 to 3000 rads in 2-3 weeks, to 3500 to 4500 rads in 4 to 5 weeks. Occasionally, the total dose exceeded 5000 rads in 5-6 weeks, based on higher success rates (i.e. improved vision) with a higher dose.

In 1953 the International Commission on Radiological Units and Measurements introduced the concept of absorbed dose and defined its unit, the rad. The rad was in use until the introduction after 1960 by Le Systeme Internationale (SI) of the SI unit for absorbed dose, called "Gray", defined as J/kg. 100 rad is 1 J/kg is 1 Gray.

In the sixties an initial slow build-up treatment with a small daily increment of 25 to 50 cGray for the first three to four days was applied in order to minimize any radiation-induced edema in the optic chiasm. Nowadays, we have abandoned the incremental dose in the first treatment week and the most frequently used schedules are 23 to 25 fractions with a total dose of 45 to 50 Gray. Higher doses do not improve local control⁴³.

Besides fractionation, the radiation source used also changed in time, based on technical improvements. In the period 1930 to 1940 200 kV photons were used, followed by 250 kV photons in the period 1940 to 1960. In 1955 the 25 MeV betatron came into use, followed in 1962 by the cobalt 60 machine. In 1966 the introduction of the linear accelerator was started, generating 6MV photons, still in use nowadays.

The irradiation techniques evolved in time as well; the older two lateral opposed field technique irradiated a large volume normal brain with an equivalent or even higher dose of what was applied to the tumour with reports of brain necrosis as a result of that. This technique was replaced by at least a three-field technique, consisting of 2 lateral fields and one vertex field, or a plan with multiple fields with wedges, following a bi-coronal 110° arc, better targeting the high dose to the tumour and reducing the high dose volume in the normal brain. Both coplanar techniques are still in use today⁴⁴.

Since the availability of 3D radiation treatment planning systems in the nineties of the previous century, non-coplanar radiation techniques became possible. It became clear that for stereotactically guided conformal radiation therapy to volumes above 13 ml, four to six non-coplanar fixed fields are clearly superior to coplanar field arrangements, whereas even techniques approaching dynamic conformal radiation therapy such as a 30-field approach reveal no further sparing of normal brain tissue⁴⁵. This technique has been introduced in the Radiation Oncology Department of the University Medical Center Groningen in 2001.

Non-functioning pituitary adenoma

Most NFAs are incompletely resected, because they are inaccessible for complete resection for the neurosurgeon due to the critical structures in this area. In case of residual disease, it has been reported that immediate postoperative radiation therapy results in high local control rates of 90-95%¹³ and that an active surveillance policy results in a high local recurrence rate (50-80%) within 10 to 15 years²⁷. The reason to postpone radiation therapy in case of residual disease is that in most series ultimate local control rates with active surveillance policies, with salvage radiotherapy in case of regrowth, are similar to immediate postoperative radiation therapy. In addition, it has been assumed that delay of radiation therapy can prevent or delay hypopituitarism with its additional sequelae. One should be aware of the fact that the pituitary function is already affected in 50% of the cases immediately after first surgery⁵⁴.

Prolactinoma

For prolactinoma, reported cure rates after radiation therapy alone or in combination with surgery vary between 25% and 93% respectively^{34,44}. Radiation therapy in prolactinoma patients is currently only rarely applied.

GH-secreting pituitary adenoma

In acromegaly, radiation therapy can realize a reduction in GH excess of 30-50% in the first year, followed by 10-15% in the years thereafter. Despite the development of potent medical therapies and the improvement of neurosurgical techniques at least 10-20% of patients will need any form of radiation therapy. In addition to decreasing GH excess, radiation therapy has been shown to influence favourably the clinical consequences of the reduction in soft tissue excess, visual symptoms, headache and glucose intolerance, thereby confirming a favourable impact on the disease²¹.

ACTH-secreting pituitary adenoma

For Cushing's disease reported cure rates after radiation therapy alone or in combination with surgery vary between 50% and 80% respectively^{34,44,46}.

Mortality and radiation therapy

Increased mortality due to radiation therapy is a subject for debate. It was already mentioned that in a large cohort of mainly non-functioning pituitary adenomas the overall age adjusted relative risk (RR) of death was 1.76 in comparison with the normal population¹³. A possible risk factor, mentioned in this cohort for increased mortality, was radiation therapy, but this factor showed no statistical significance.

The Danish registry however reported no increased mortality due to cardiovascular and cerebrovascular disease. In this study surgery type and radiation therapy were not identified as risk factors, while female sex was a risk factor⁸. Moreover, no increased mortality due to malignant disease was reported in all kinds of pituitary adenoma⁸.

Side-effects of radiation therapy

Acute side-effects

Acute side-effects due to fractionated radiation therapy are mild to moderate erythema, dry desquamation^{47,48}, otitis externa^{47,49}, otitis media^{47,49}, tinnitus⁴⁹, olfactory and gustatory changes^{49,50}, temporary localized epilation at the beam entrance and exit depending on the

radiation dose^{47,50,51}, headache⁴⁹ and mild transient post radiation therapy somnolence⁵². In general, all these side-effects are minor, well tolerated and self-limiting in most patients⁵⁰.

Late side-effects

Late side-effects or toxicity of the normal tissues due to radiation therapy will - as a general radiobiological rule - be smaller in fractionated radiation therapy. The risk of radiation-induced complications is expected to be rare with modern equipment, modern techniques and current recommended doses of 45 to 50 Gray in 1.8 Gray fractions in an overall treatment time of 5 weeks⁵³.

Hypopituitarism

In the past, the normal pituitary gland has been thought to be relatively radioresistant, tolerating doses up to 190 Gray without showing pathological damage. In time it became clear that radiation therapy can induce hypopituitarism⁵⁴. It is the most prevalent late side effect as a result of direct damage to the pituitary and also secondary to hypothalamic damage⁵⁵, as is evidenced by appropriate pituitary responses to administration of exogenous hypothalamic releasing hormones⁵⁶⁻⁵⁸. There is some evidence to suggest that direct injury to hypothalamic neurones, rather than reduced cerebral blood flow, is the major cause of progressive hypothalamic-pituitary dysfunction after fractionated cranial irradiation. Direct damage to the cell nuclei in the hypothalamus may explain the delayed onset of hormone deficiency, because these cells are dividing slowly and die during mitosis years later before losing their function⁵⁹. Radiation doses in excess of 50 Gray can have a direct effect upon pituitary function. However, at doses below 50 Gray, hypopituitarism may initially be caused by hypothalamic dysfunction⁶⁰.

Radiation-induced hypopituitarism depends, besides on the total dose, on fraction size⁶¹. It increases in time for at least 10 years⁶². The severity, as measured by the number of anterior pituitary hormone deficiencies, depends on the total dose. Higher radiation dose given to the pituitary gland will result in a more rapid onset of hypopituitarism⁶⁰. Among patients who developed multiple hormone deficiencies, the most frequent order of loss of anterior pituitary hormone function was GH, followed by LH/FSH, ACTH and then TSH.

Permanent radiation induced diabetes insipidus has not been reported^{30,61}. An explanation for the difference in radiosensitivity between the anterior and posterior pituitary lobe might be that the posterior lobe is only a storage place for hormones.

Pituitary function and pregnancy

In young adults with normal postoperative pituitary function and wish of future siblings, some advocate not to give radiation therapy in order to avoid the possibility of

radiation-induced hypopituitarism, even if there is an increased risk on tumour recurrence with all its consequences⁶³. Infertility due to hypopituitarism in men and women can be corrected with exogenous gonadotropins^{64,65}.

Cerebrovascular disease (CVD)

A relationship between radiation therapy for pituitary adenoma and (as a consequence) CVD has not been found⁶⁶. Cerebral infarctions manifested at intervals of 3.2-14.6 years after RT. Three out of seven patients with cerebral infarction had evidence of vascular disease outside the treatment field. Only age was a negative prognostic factor.

Out of 331 patients of The Royal Marsden cohort, 64 developed CVD after primary treatment of pituitary adenoma. In comparison with the normal population there was a relative risk of 4.1 (95% CI: 3.6-4.7%). The actuarial incidence of CVD after primary treatment of pituitary adenoma was 4% (95% CI: 2-7%) at 5 years, 11% (95% CI: 8-14%) at 10 years, and 21% (95% CI: 16-28%) at 20 years measured from the date of radiation therapy. In this cohort, age, radiation therapy dose and extent of surgery were independent predictors for CVD.

Erfurth et al. stated that radiation therapy might act as a risk factor for CVD, but not stronger than other risk factors for CVD in all types of pituitary patients⁶⁷. Until this moment it is not clear if applied radiation therapy is a risk factor in relation to CVD afterwards.

Tumour induction

Tumour induction inside the brain

A cumulative risk of tumour induction inside the brain after surgery and radiation therapy of 1.3% (95%CI: 0.4-3.9%) to 2% (95%CI: 0.9-4.4%) over the first 10 years, and of 1.9% (95%CI: 0.7-5%) to 2.4% (95% CI: 1.2-5%) over the first 20 years has been reported^{68,69}. The relative risk of a secondary brain tumour as compared to the incidence in the normal population is 9.4. The median time to detection is 7 years for glioma, 9.7 years for sarcoma and 13.8 years for meningioma.

However, no firm support for an increased incidence of a second brain tumour is found by others in a cohort of 279 NFA patients treated between 1931 and 1988. Two astrocytomas – 7 and 24 years after irradiation - and one meningioma – 19 years after irradiation - were found (RR 2.7; 95%CI; 0.6-7.8)⁷⁰.

A genetic trait that predisposes to both pituitary tumours and brain tumours is an alternative causal factor. To support this idea, there are reports of the co-occurrence of meningioma and pituitary adenoma in non-irradiated patients⁷¹. Radiation-induced meningiomas differ from “spontaneous meningiomas” in location, multiplicity and aggressive biological behaviour⁷².

There is no evidence that cranial irradiation per se is the causal factor. A cohort study of non-irradiated pituitary tumour patients, who have the same initial malignancy, is needed.

Tumour induction outside the brain

A relative risk for malignant tumours outside the brain of 3.91 is reported in patients with NFA in comparison with the general population⁷³. The absolute incidence in the general population is estimated at 0.45%. In acromegalic patients the risk is not increased in comparison with NFA patients⁷³. However, no significant excess for cancer outside the brain is seen by others in pituitary patients in comparison with the general population^{69,74}. The role of radiation therapy as risk factor is not yet clear and should be balanced with the probably already increased risk without radiation therapy.

Brain necrosis

The overall incidence of brain necrosis has been estimated at 0.2%⁷⁵. This incidence will decline with modern equipment, such as stereotactic radiotherapy, and the currently recommended doses.

Radiation Optic Neuropathy (RON)

A prevalence of 0.53% for Radiation Optic Neuropathy in NFA has been reported⁷⁶. The incidence will decline with modern radiation therapy equipment and current recommended radiation therapy doses. An effective treatment for RON is not available⁷⁶.

Permanent radiation induced damage of the cranial nerves III, IV, V and VI has not been reported in series with modern radiation therapy equipment and currently recommended radiation therapy doses.

Cognitive function

Patients with pituitary tumours may have impairment of both memory and executive function. No correlation has been found with tumour size and type⁷⁷. The decrease in cognitive function seemed to be more pronounced among those treated with radiation therapy and mainly affected the executive function⁷⁸. No short-term memory loss have been observed that is clearly attributed to radiation therapy^{50,79}.

Research suggests that the pathogenesis of radiation induced neurocognitive deficit may involve radiation induced injury to proliferating neuronal progenitor cells in the subgranular zone of the hippocampus, which is a critical neurological centre for learning and memory⁸⁰.

One should be aware that others reported no cognitive impairment due to radiation therapy in GH-deficient pituitary adenoma patients, not receiving GH-replacement⁸¹.

Quality of Life

Patients with a pituitary adenoma in general have impairment in both physical and mental health measures compared with the normal population⁸². Patients with a non-functioning adenoma however, have a greater impairment in measures of mental function than in physical function compared with the normal population and patients with other pituitary adenomas⁸².

Page et al. reported impaired quality of life among patients with non-functioning pituitary adenoma who were irradiated, in comparison with those who were not irradiated. Patients were more depressed and emotionally affected. It remains unclear, whether these differences are direct effects of radiation therapy or indirect effects due to hormone abnormality or perception of disease severity⁸³. The reasons why radiation therapy was applied were not mentioned in this paper and the differences found can be due to selection bias.

Nielsen et al. used the Short Form and Major depression inventory questionnaires⁸ to assess quality of life and depression among patients with non-functioning pituitary adenomas. In transsphenoidally operated patients, mental health scores were similar to the general population, while in patients that underwent craniotomy, mental health and mental component scores were lower. Radiation therapy, pituitary status or repeat surgery did not affect these quality of life dimensions. Age at first operation was an independent risk factor for reduced physical functioning. There was no influence of radiation therapy on depression.

Based on these results, it still remains unclear whether quality of life is negatively affected by radiation therapy⁷⁸.

Aims of this thesis

The main objective of this thesis is to evaluate the results of radiation therapy among patients with pituitary adenomas with regard to treatment efficacy, side-effects and quality of life.

1

To determine the role of radiation therapy in residual non-functioning pituitary adenoma in relation to local control, side effects and overall survival, as reviewed in the literature and evaluated in our series. *Chapter 2*

2

To evaluate the influence of radiation therapy on cognitive function and quality of life in patients with non-functioning pituitary adenoma.

Chapter 3

3

To establish the incidence of RON in acromegaly and its risk factors in the literature. This side-effect has been evaluated in irradiated acromegalic patients in the University Medical Center Groningen and is presented in a complete updated review. *Chapter 4-5*

4

To establish the incidence of RON in non-functioning pituitary adenomas in the literature in addition to our own series, presented in the first available review published on this subject. *Chapter 6*

5

To investigate the diagnostic role of new-imaging techniques: how are Positron Emission Tomography (PET) imaging characteristics affected by surgery and radiation therapy for pituitary adenoma. *Chapter 7*

6

Finally, we investigated whether the position of head and neck cancer patients with conformal non-coplanar radiation techniques could be determined from portal images of oblique radiation beams. *Chapter 8*

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