

3

Radiotherapy is not associated with reduced quality of life and cognitive function in patients treated for nonfunctioning pituitary adenoma

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Abstract

Purpose To assess the influence of different treatment modalities on long-term health-related quality of life (HR-QoL) and cognitive problems among patients who had been treated for nonfunctioning pituitary adenoma (NFA).

Methods and Materials Eighty-one patients (49 men and 32 women, aged 55 ±10 years) with a minimal follow up period of 1 year after treatment for NFA participated in this cross-sectional study. Sixty two patients were initially treated by transsphenoidal surgery and 19 by craniotomy. Subsequently, 45 out of these 81 subjects (56%) received additional radiotherapy (RT) after surgery because of a tumor remnant or regrowth. All subjects filled in standardized questionnaires measuring HR-QoL, depression, fatigue and cognitive problems.

Results Patients who underwent additional RT more frequently underwent a craniotomy and were younger at surgery, but not at entering this study. They also used more hormonal substitution. Most HR-QoL domains showed a similar score in patients who underwent RT, when compared with patients who did not receive RT. However, vitality and physical functioning proved to be better in RT subjects, and RT subjects also had better scores for depression, and physical and mental fatigue (all $p < 0.05$). Some aspects of HR-QoL of patients who have been successfully treated for NFA are reduced compared with the normal population, but this was much more pronounced in the group that did not receive RT. In multivariate analysis, RT remained significantly associated with improved HR-QoL. No differences in cognitive function scores were observed.

Conclusion Postoperative RT in patients with NFA is not associated with reduced quality of life or cognition when compared with surgery alone.

Introduction

Nonfunctioning pituitary adenomas (NFAs) are the most common tumors of the anterior pituitary. Transsphenoidal surgery is the treatment of choice, but complete surgical removal is frequently not achieved. Radiotherapy (RT) is often given as adjuvant treatment in the postoperative period to patients with a tumor remnant or regrowth. Retrospective studies show that RT can effectively reduce the chance of tumor regrowth, as reviewed by several investigators¹⁻³. Current medical practice involves RT for large postoperative tumor remnants and sequential MRI surveillance for smaller tumors followed by RT in the presence of tumor expansion in many centers^{1,4}. The restrictive use of postoperative RT for NFAs is a consequence of absence of regrowth in a number of cases, the excellent local control with radiation therapy when applied at time of recurrence, and concerns related to possible long-term side effects⁵. The most important of these complications is radiation-induced hypopituitarism and its associated excess mortality⁶, although the role of RT per se on pituitary function remains disputed⁷. Radiation-induced tumor formation and damage to the optic chiasm are also reported but are considered rare under modern RT dosing schedules⁸⁻¹⁰. In addition, neuropsychological changes after pituitary RT have been reported¹¹⁻¹⁷. However, many studies on this subject are undersized, and results are potentially confounded by inhomogeneous group composition and incomplete hormonal substitution. Further, type and date of surgery, age, and duration of follow-up have usually not been taken properly into account to assess the impact of modern RT.

With these considerations in mind, we sought to determine whether the use of RT in the postoperative period has a significant effect on health-related quality of life (HR-QoL) and cognitive function. We report data from a large and homogeneous cohort of patients with NFAs.

Methods and Materials

Patients

Patients with histologically proven NFA were eligible for participation in this study if they were between 20 and 70 years of age and if the interval between their last treatment (RT or surgery) and the quality-of-life assessment was at least 12 months. Both surgery and RT were performed in the University Medical Center Groningen, which is a large tertiary referral centre for patients with pituitary pathology. To assure accuracy and completeness of our data collection, patients were only recruited for participation if they were still actively followed at our endocrine outpatient clinic. All patients included in this study received surgery as primary treatment, in some cases followed by a second surgical procedure if a large remnant accessible for surgery persisted. Radiotherapy was

given postoperatively to patients with a remnant or after evidence of regrowth. Patients with NFA were retrospectively identified by reviewing several different hospital databases on surgery, radiotherapy, and diagnoses at the endocrine clinic. Thus, a total of 90 eligible patients could be identified who received primary surgical treatment for NFA in our hospital between January 1963 and January 2005.

Questionnaires on quality of life and cognition, use of medication, presence of co-morbidity, and social status were sent to all patients by mail. Use of medication and presence of comorbidity was also confirmed by investigation of the medical charts. Laboratory results from the last visit (i.e., < 1 year earlier) to the outpatient clinic were used. Written informed consent was obtained from all subjects.

Questionnaires

RAND 36. Health-related quality of life was measured with the RAND 36 (which is identical to the 36-item short form health survey [SF36]). This questionnaire contains 36 questions that record several dimensions of general well-being during the previous 4 weeks. The items are formulated as statements or questions with Likert scale response options. The 36 questions are organized into eight scales (physical functioning, physical problems, bodily pain, general health, vitality, social functioning, emotional problems, and mental health) that are linearly converted to a scale of 0 to 100. The first three parameters measure physical health, the last three parameters measure mental health, and the general health and vitality scales are sensitive to both physical and mental health outcomes. Higher scores represent better quality of life¹⁸. Normative data by age are available for the Dutch population¹⁹.

Multidimensional Fatigue Inventory-20. The Multidimensional Fatigue Inventory-20 (MFI-20) records fatigue and contains 20 statements, organized into five scales (general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue), with a maximum score of 20 on each subscale²⁰. Higher scores indicate a higher level of fatigue or impairment. Dutch normative data were derived from Smets et al.²¹.

Hospital Anxiety and Depression Scale. The Hospital Anxiety and Depression Scale (HADS) consists of 14 items pertaining to anxiety and depression²². Each item is scored as a number, with a maximal score for each subscale (anxiety or depression) of 21. Higher scores indicate more severe anxiety or depression. A score of 6 or higher on the depression scale or 7 or higher on the anxiety scale indicates clinical depression or anxiety. Dutch normative data were derived from Spinhoven et al.²³.

Cognitive Failures Questionnaire. The Cognitive failures Questionnaire is a measure of everyday cognitive problems. This 25-item questionnaire measures failures in perception, memory, and action in everyday life. The total score ranges 0-100, with higher scores reflecting more cognitive problems^{24,25}.

Laboratory assays

Plasma insulin-like growth factor-1 (IGF-1) was measured by radioimmunoassay after acid-ethanol extraction (Nichols Institute of Diagnostics, San-Juan Capistrano, CA). Age-adjusted Z scores of plasma IGF-1 were calculated using values obtained in healthy subjects. Plasma cortisol was measured by radioimmunoassay (Elecsys 2010; Roche diagnostics, Basel, Switzerland). An automatic immunoassay (Perkin Elmer Life Sciences, Groningen, The Netherlands) was used to determine free T4.

Statistical analysis

Differences were assessed with t tests (for continuous variables) or chi-square tests (for categorical variables). An α level of 0.05 was used for determining statistical significance. When differences between groups reached statistical significance, the magnitude of the effects was determined by Cohen's *d*, a commonly used measure for effect size²⁶. A value of ± 0.5 was considered the medium effect size. Multiple linear regression was used to determine associations between measures of quality of life, cognitive function, treatment modalities, and demographic characteristics. Backward linear regression modeling was applied using a *p* value < 0.04 for entry and a *p* > 0.05 for removal of the selected variables.

Results

Ninety patients were eligible and were sent questionnaires on quality of life, mood, and cognition. Eighty-one patients (49 men and 32 women, age 55 ± 10 years) returned all questionnaires (response rate, 90%). Sixty-two had been operated by transsphenoidal route and 19 by craniotomy. Fourteen patients had needed a second surgical intervention. Subsequently, 46 of 81 subjects received additional RT after surgery because of a tumor remnant or regrowth. Average time between surgery and RT was approximately 8 months. Conventional external beam RT was administered in a daily dosage of 1.8 – 2.0 Gy, resulting in a total dose of 45 – 50 Gy, using a two-field opposed lateral technique or a three-, four- or five- field technique. All radiation treatment fields were applied daily, five times per week, with an overall duration of 35 days. In the time period 1963-1990, the radiation dose to the tumor was prescribed at the tumor encompassing isodose. From 1991 onward it was prescribed at a central point in the tumor, according to the recommendations of the International Commission on Radiation Units and Measurements.

Patient characteristics of those who received RT and those who did not are given in Table 1 (next page). Patients who underwent RT more frequently had a craniotomy, were younger at time of surgery, and their duration of follow-up was longer. They also used more hormonal substitution, although this only reached statistical significance for the use of thyroid hormone. Current age, social status, educational level, full-time/part-time employment, social security benefit, and comorbidity were all similar between both groups.

Table 1 Patient characteristics

	RT+	RT-	P-value*
Number	45	36	
Age (y) [#]	58 (32-70)	56 (34-70)	NS
Sex (male/female)	26/19	23/13	NS
Primary treatment			0.004
Transsphenoidal surgery	29	33	
Craniotomy	16	3	
Age at primary treatment (y)	43 (13-67)	50 (16-67)	0.000
Duration of follow-up (y)	12 (1-43)	4 (1-30)	0.008
2nd surgical treatment	10	4	NS
Postoperative radiotherapy			
Age at radiotherapy (y)	46 (14-68)	-	
Time between primary treatment and radiotherapy (y)	0.7 (0-31)	-	
Duration of follow-up after radiotherapy (y)	10 (1-26)	-	
Substitution of pituitary axis			
Number of anterior pituitary hormones substituted: 0/1/2/3/4	2/10/10/14/9	6/10/8/6/6	NS
Thyroid hormone	31 (69%)	17 (47%)	0.049
Cortisol	32 (71%)	21 (58%)	NS
Growth hormone	16 (36%)	9 (25%)	NS
Sex hormones	29 (64%)	21 (58%)	NS
Antidiuretic hormone	5 (11%)	3 (8%)	NS

Data are given as median (ranges), absolute numbers and percentages.
RT+: group with postoperative radiotherapy.
RT-: group without postoperative radiotherapy.
*: P-value by χ^2 -test, # the study included only patients in the age range 20 - 70.

Most HR-QoL domains showed a similar score in patients who underwent RT, when compared with patients who did not receive RT (Table 2). However, physical functioning (effect Size [ES], 0.44), vitality (ES, 0.47), mood (HADS - depression) (ES, 0.56), and physical and mental fatigue (MFI-20) (both ES, 0.54) were reported to be significantly worse in patients who did not receive RT. No differences in cognitive function scores were observed. In the group that did not receive RT, social functioning, vitality, and general health perception (three domains of RAND 36), fatigue, and depression scores were significantly worse than in the reference population. In contrast, in patients who underwent RT only general health perception was less than in the reference population, whereas physical functioning, pain (RAND 36) and anxiety (HADS) were even better.

Table 2 Health related quality of life and cognition in patients with or without radiotherapy.

	RT+	RT-	P-value	Population reference	RT+	RT-	P-value
	mean ± SD				mean Z-score ± SD*		
RAND-36							
Physical functioning	84±18	74±23	NS	82±23	0.31±0.80 [¶]	-0.16±1.01	0.024
Social functioning	85±19	77±23	NS	87±21	-0.06±0.88	-0.40±1.08 [¶]	NS
Role limitations due to physical problems	76±38	69±41	NS	79±36	-0.03±1.02	-0.19±1.07	NS
Role limitations due to emotional problems	88±30	78±37	NS	84±32	0.05±1.01	-0.24±1.17	NS
Mental health	79±14	72±20	NS	77±18	0.13±0.74	-0.28±1.10	NS
Vitality	66±17	56±25	0.042	67±20	-0.03±0.82	-0.51±1.18 [¶]	0.045
Pain	84±19	81±23	NS	80±26	0.27±0.76 [¶]	0.13±0.90	NS
General health perception	60±19	59±24	NS	73±23	-0.31±0.82 [¶]	-0.39±1.05 [¶]	NS
HADS							
Anxiety	3.6±2.9	5.0±4.4	NS	4.7±3.6	-0.30±0.81 [¶]	0.08±1.22	NS
Depression	3.0±2.5	5.0±4.4	0.018	3.5±3.4	-0.16±0.73	0.43±1.30 [¶]	0.018
MFI-20							
General fatigue	10.3±4.3	11.6±5.6	NS	9.9±5.2	0.08±0.82	0.33±1.08	NS
Physical fatigue	9.2±4.0	11.8±5.4	0.015	8.8±4.9	0.07±0.82	0.62±1.10 [¶]	0.015
Reduced activity	8.8±4.3	10.6±5.1	NS	8.7±4.6	0.03±0.93	0.42±1.10 [¶]	NS
Reduced motivation	8.9±3.7	10.1±5.3	NS	8.2±4.0	0.18±0.94	0.46±1.31 [¶]	NS
Mental fatigue	8.4±4.8	10.9±5.3	0.035	8.3±4.8	0.03±1.00	0.53±1.10 [¶]	0.035
CFQ							
Memory	28±18	28±22	NS	na			
Distractibility	35±18	36±19	NS	na			
Blunders	30±16	29±20	NS	na			
(memory for) Names	46±23	51±24	NS	na			

* Z-scores for the RAND-36 are based on different age-groups. ¶ mean Z-score different from 0 (P < 0.05). na: not available

Table 3 Multivariate analysis of RAND 36 Z- scores.

	Physical functioning	Social functioning	Role limitations due to physical problems	Role limitations due to emotional problems	Mental health	Vitality	Pain	General health perception
Radiotherapy	+0.56 [¶]					+0.48*		
Male patients	+0.48*							
Intact HPA axis	+0.57 [¶]					+0.53*	+0.44*	
IGF-1 Z score > -2					+0.47*			
2 nd operation						+0.61*	+0.56*	

The model includes independent continuous variables (age, age at primary (surgical) treatment, duration of follow-up after primary treatment, IGF-1 Z-score and free T4 concentration) and dichotomous independent variables (sex (male versus female), radiotherapy (yes versus no), type of primary surgical operation (transsphenoidal versus craniotomy), substitution of individual pituitary axis (yes versus no), IGF-1 Z-score < -2 (yes versus no) and substitution of total number of anterior pituitary axis (n = 0,1,2,3 or 4)) HPA axis: Hypothalamic Pituitary Adrenal axis
[¶] P < 0.01, * P < 0.05 Note that the effect size is measured in standard deviation.

No differences in quality of life or cognitive functioning were observed related to the current age, age at primary treatment, primary surgical operation route, or the second surgical intervention. Hormonal substitution for loss of anterior pituitary function also had no effect on HR-QoL.

Multivariate analysis independently identified that RT, sex, cortisol substitution therapy, IGF-1 Z score < -2, and a second pituitary operation were independent determinants of quality of life (RAND 36) (Table 3). Improved RAND scores were seen in patients who received RT, in male patients, in patients with an intact corticotrophic axis, in patients with IGF Z score > -2, and in patients who underwent a second surgical procedure. Effect sizes of these independent variables ranged from 0.4 to 0.6.

Discussion

We found no negative outcomes and even some limited positive effects in the perception of mental and physical health after RT in a large cohort of patients with NFA.

Health-related quality of life was measured in this study with the RAND 36 questionnaire, which has been shown to be a reliable and valid instrument with good internal consistency. Results were compared with age-adjusted normative data for the Dutch population¹⁹. We found that social functioning, vitality, and general health perception (three domains of RAND 36) were significantly lower in the group that did not receive RT when compared with the reference population. In contrast, in patients who underwent RT only general health perception was worse than in the age-matched control population, whereas physical functioning, pain (RAND 36), and anxiety (HADS) were not adversely affected, and their score was even slightly better. The group of patients that underwent RT reported significantly higher levels of vitality and less depressive symptoms and physical and mental fatigue, with effect sizes ranging from 0.47 to 0.56, indicating a clinically relevant medium size effect. This suggests that RT may be beneficial to self-perceived health. Our results are in contrast to those found by Page *et al.*²⁷. They used the SF36 questionnaire, identical to the RAND 36, and reported that patients treated with RT for nonfunctioning pituitary tumors were more depressed and anxious than those who underwent mastoid surgery. However, this study group of patients with NFA was smaller than ours, and only 18 patients had received RT after surgery. Further, it is not clear from their report whether they properly corrected for age in each individual patient. Noad *et al.*²⁸ recently reported data on the effects of RT on cognitive function and quality of life in patients with pituitary disease. Of the 71 patients who were assessed, 33 had nonfunctioning adenomas, 15 of whom underwent RT. It was concluded from data of their entire group that patients who had received RT had no significant change in the quality of life as measured by the physical and mental health composite of the SF36. Recently, Dekkers *et al.*²⁹ reported on the diminished quality of life in patients with nonfunctioning pituitary macroadenomas. Although RT was very infrequently applied in this study, a small subanalysis by means of linear regression revealed that RT was not an independent predictor for reduced quality of life. Thus, results from smaller studies on the effects of RT on quality of life are in accordance with our findings.

We extensively looked for a selection bias but did not find one. Age at surgery and duration of follow-up are potential candidates. However, both in univariate and multivariate analysis, RT remained a strong and independent predictor for quality of life, and neither age at surgery nor duration of follow-up were of any importance. Socioeconomic status and comorbidity also did not differ between groups. Further, RT was given to patients with tumors that were larger or growing more aggressively. The RT group even needed more hormone substitution therapy and more often underwent a

craniotomy. Therefore, we believe that a selection bias toward a better quality of life for patients who underwent RT is unlikely.

We found higher scores for depression in the group that did not receive RT. Scores for anxiety were similar between both groups. Noad et al.²⁸ also used the HADS and found no treatment effect for RT. However, as mentioned earlier, their group size of NFA patients was very small. A report from Peace et al.¹⁶ is in accordance with our findings. They used the Beck Depression Inventory and the State-Trait Anxiety Inventory to assess self-reported mood and found that RT exerted a mild protective effect on depression.

Several studies suggest that patients with pituitary tumors may continue to suffer from cognitive impairment even after treatment of their disease^{11,15,17,30}. McCord et al.¹⁴ suggested that RT for pituitary tumors may be associated with cognitive impairment. However, their assessment contained no formal, objective measures of cognitive impairment and relied entirely on self-report. Grattan-Smith et al.³⁰ performed neuropsychological testing in a group of patients with pituitary adenoma and reported memory and executive function impairments in these patients when compared with a control group. In this study, no specific cause of the neuropsychological impairment was found, and patients treated with RT performed equally when compared with those who did not receive RT. Peace et al.¹⁵ found deficits primarily on test of executive function, but they found them in response to surgery and not RT. Anterograde memory deficits were found by Guinan et al.¹¹ in patients with pituitary tumors. However, there was no negative treatment effect of pituitary RT. In accordance with the lack of evidence of reduced cognitive performance associated with RT, we also found no indications of cognitive impairment as a consequence of RT.

In conclusion, no negative outcomes and even some limited positive effects in the perception of mental and physical health after RT were found in a large cohort of patients with NFA. Our results are reassuring and raise no concern that RT applied after surgery in the treatment of NFA leads to reduced quality of life or impaired cognition.

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Subjective ratings vs objective measurement of cognitive function: In Regard to van Beek et al.

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To the Editor

We read with great interest the manuscript of van Beek et al.¹ in which the authors report on the impact of radiotherapy on long-term health-related quality of life (HRQOL) and cognitive problems among patients treated for nonfunctioning pituitary adenoma (NFA). Following treatment, HRQOL, depression, fatigue, and cognitive functioning of irradiated and unirradiated patients was assessed using self-report questionnaires. Patients with or without RT attained comparable HRQOL scores in most domains and RT was even significantly associated with improved HRQOL in a multivariate model. No differences in cognitive function scores were observed.

Although we think that studies into the cognitive effects of treatment of these patients should be strongly encouraged, we would at the same time like to caution against the use of self-report questionnaires as a means to measure cognitive functioning.

Numerous studies that focus on perceptions of cognitive functioning have consistently found these self-reports to be unrelated to objective performance in distinct patient groups, including those with cancer², coronary artery bypass surgery^{3,4}, multiple sclerosis^{5,6}, temporal lobe epilepsy surgery⁷, and HIV⁸. In cancer patients, and potentially also in those with pituitary adenomas, cognitive complaints might more likely reflect feelings of anxiety, depression and fatigue than a loss of cognitive abilities². Considering the elevated levels of depression and fatigue in the study of van Beek and colleagues, this is most likely also the case in patients with NFA. We suggest these findings strongly argue against relying on patient reports to assess cognitive function. Objective testing remains the method of choice for assessing higher cognitive functions.

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To the Editor

We agree with Klein and colleagues that objective testing is very important in assessment of cognitive functioning. They raise an important question with regard to the strategy of elucidating possible cognitive deterioration in patients receiving postoperative radiotherapy to the pituitary gland.

Klein et al. state that numerous studies found discrepancies between self-report measures of cognitive functioning and objective tests. This finding is likely subject to publication bias. In addition, several studies mentioned by Klein are flawed by comparing global measures of self-report cognitive functioning with a single global objective neurocognitive score calculated as the mean of all the (standardized) scores¹⁻³. This is far from a balanced comparison. In fact, when analyzed in a proper way, Middleton found that patients' perceptions of their performance on specific tasks correlated with their objective performance on those tasks². Podewils and colleagues reported similar results and concluded that individuals experiencing changes in cognitive function appeared to have some awareness of their condition⁴.

Further, in a cross-sectional study design, patients with non-functioning pituitary adenomas show differences in baseline characteristics, in treatment (type of surgery, radiotherapy), and in outcome (presence of residual non-functioning adenoma, hypopituitarism). In addition, this group receives multiple substitution therapy e.g. growth hormone, hydrocortisone and thyroid hormone, with all the intrinsic imperfections of hormone replacement strategies in mimicking normal hormone secretion⁵. Sometimes patients and doctors choose not to substitute sex steroid or growth hormone deficiencies. Effects of endogenous hormone deficiencies and exogenous substitution therapy may not be the same with respect to cognitive functioning. Moreover, different surgical routes may damage different parts in the brain. And putative deleterious effects of radiotherapy will differ in time. Radiotherapy used to be given several decades ago with two opposing lateral fields, potentially damaging the temporal lobes. Modern radiotherapy evolved to use a multiple-field technique in order to spare more normal surrounding tissue from the effects of ionizing radiation^{6,7}. Thus, multiple factors are present that are likely to affect multiple different parts of the brain and therefore different cognitive domains. As a result, objective testing (even screening) in this group is far from easy. Based on previous study reports, no obvious deficits in cognitive functioning were expected. It is a logical next step and common practice to ask the patient if they experience deficits in their own cognitive functioning. We chose the Cognitive Failures Questionnaire and found no differences with regard to the application of radiotherapy⁸. Further studies are warranted and should include interviewing partners for cognitive problems in their spouses. Subsequently, formal testing can be performed with special attention the reported problems in cognitive functioning. At-

tention should be paid to the choice of these tests because many show a high inter-rater variability and lack of validation.

Yours sincerely,

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