

# Radiotherapy in Non-Functioning Pituitary Macroadenoma: Mansoura Experience

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**OBJECTIVE** The current retrospective study aims to evaluate the management of non-functioning pituitary macroadenoma through the assessment of experience on clinical, biochemical, radiological features, and treatment outcome of patients, and to identify prognostic factors affecting progression-free survival (PFS).

**METHODS** Data of 55 patients with non-functioning pituitary macroadenoma presented to the Clinical Oncology and Nuclear Medicine department between 1998 and 2009 were investigated.

**RESULTS** The most common symptom was visual disturbance (38.2%) followed by headache (27.3%). The presence of male predominance was observed (1.4:1). Ten patients received radiotherapy (RT) only. Extrasellar extension was the more common treatment. The overall response rate was 72.8% with completed response at 16.4%. Memory and intellectual sequelae were the most common late complications of treatment (14%). The ten-year PFS was at 84.6%. PFS was found to be significantly better with higher dose of RT (up to 54 Gy), treatment by both surgery and RT, absence of visual field defect, and tumor localized to sella, whereas it was not significantly affected by age and sex.

**CONCLUSION** The data confirmed that the prevalence of mass effect and hypopituitarism in patients with non-functioning pituitary macroadenoma is elevated. Conventional external RT up to 54 Gy is safe and effective in controlling non-functioning pituitary macroadenoma with tolerable and acceptable morbidity.

**KEY WORDS:** non-functioning pituitary macroadenoma, radiotherapy, prognostic factors, survival.

## Introduction

Pituitary adenomas are indolent tumors accounting for 10% to 15% of all diagnosed intracranial neoplasms<sup>[1]</sup>. Clinically non-functioning pituitary adenomas (NFPA), with an estimated prevalence of 70 cases/million to 90 cases/million, are the most common type of pituitary macroadenoma, comprising approximately 50% of pituitary tumors<sup>[2]</sup>. NFPAs mostly present symptoms related to invasion or compression of the surrounding structures, such as cranial nerve paralysis and visual field defects due to invasion of the adjacent cavernous sinus and impingement of the optic apparatus, respectively<sup>[3]</sup>.

The initial treatment goal aimed at relieving compressed structures is usually achieved through surgical tumor mass reduction, which improves visual field and pituitary function defects by approximately 90%<sup>[4]</sup> and 30%<sup>[5]</sup> of cases, respectively. Unfortunately, complete

surgical excision is more difficult to obtain, and “gross total removal” is only reported in roughly 35% to 40% of macroadenomas<sup>[6]</sup>. Regrowth rates following surgery are as high as 75% at ten years, leading to the introduction of post-operative adjuvant pituitary radiotherapy (RT) in some patients principally with a large tumor remnant or tumor perceived as “aggressive”<sup>[7]</sup>.

Conventional fractionated external beam RT irradiated the whole pituitary fossa and any tumor extension using megavoltage machines at a daily dose of 150 cGy to 200 cGy up to a total dose of 4500 cGy to 5400 cGy<sup>[8]</sup>. Stereotactic RT, both in the form of radiosurgery or fractionated stereotactic RT, enable high radiation dose delivery to the tumor with relatively little irradiation to surrounding tissues and sharp fall-off radiation at target margins<sup>[9]</sup>. The potential downside to this rapid fall-off in RT is the possibility of missing tumor deposits that are not identified on high-resolution imaging during radio-surgery planning<sup>[10]</sup>.

Radiosurgery can be delivered using photon techniques that include gamma-knife surgery using cobalt 60, as well as linear accelerators and proton-beam therapy using heavy charged particles<sup>[11]</sup>.

Early pituitary radiosurgery results for residual or recurrent NFPA show promising outcomes in terms of disease control, with a low rate of additional pituitary hormone deficiencies<sup>[12]</sup>. However, radiosurgery is preferably reserved to small volume tumors, lying within a defined minimal distance (3–5 mm) from the optic apparatus.

Intensity-modulated RT is a form of 3D conformal RT (3DCRT) that can achieve a higher degree of conformality via dynamic multileaf collimators, thus maximizing treatment dose to the lesion while sparing normal surrounding structures. However, its role in NFPA treatment remains to be determined<sup>[13]</sup>.

More frequent anterior pituitary dysfunction<sup>[14]</sup>, radiation optic neuropathy<sup>[15]</sup>, cerebrovascular disease<sup>[16]</sup>, induction of secondary tumors<sup>[17]</sup>, and change of neuro-cognitive and neuropsychological functions<sup>[18]</sup> are proposed to be adverse sequelae of RT.

To improve existing management protocols on NFP macroadenoma, the present study retrospectively evaluated Mansoura Clinical Oncology and Nuclear Medicine Department’s experience in managing non-functioning pituitary macroadenoma through the assessment of its clinical, biochemical, radiological features and treatment outcome. In addition, the current study aims to identify the prognostic factors affecting progression-free survival (PFS).

## Patients and Methods

A retrospective data of fifty-five patients with NFP macroadenomas who attended the Clinical Oncology and Nuclear Medicine Department at Mansoura University hospital between 1998 and 2009 were collected from patients’ files and then investigated. Tumors greater than or equal to 10 mm dimension were considered macroadenomas.

The patients’ demographic data and biochemical results confirming hypopituitarism, clinical presentation,

line of treatment and treatment outcomes, and PFS and its prognostic factors were investigated. X-rays, CT head scan, and/or MRI were re-evaluated and investigated to analyze the mass (size, invasion, and relationship to the optic chiasma). Visual field assessments were collected from ophthalmology reports in the files.

Hypopituitarism included deficiency of the growth hormone, gonadal hormones, thyroid, and adrenal axis. Hypogonadal symptoms included complaints of diminished libido, oligo-amenorrhea, and infertility or erectile dysfunction. Diabetes insipidus was diagnosed through vasopressin deficiency, whereas adrenal axis was evaluated through insulin tolerance test.

Ten patients were treated using RT alone because these patients refused surgery or were unfit for surgical interference due to medical problems, whereas 45 patients received RT after transcranial or transsphenoidal surgery due to residual tumor.

Patients were treated with cobalt 60 or linear accelerators 6 MV to 10 MV photons using the two-field opposed lateral technique or three-field technique. The total radiation dose ranged from 45 Gy to 54 Gy, with a daily fraction size from 1.8 Gy to 2 Gy. The median overall treatment time was 27 d, which ranged from 25 d to 30 d. Fifty patients were treated using 2D conventional RT, whereas five patients (9.1%) were treated using 3DCRT. 3DCRT means conforming the prescription dose to the target volumes while lowering dose to normal tissues through many steps. These steps include patient immobilization, CT planning, delineation of target volume and critical structure, design beam and field shaping, dose calculation, plan optimization and evaluation, treatment documentation, and plan treatment and verification. Response was assessed through radiological investigations (CT or MRI), biochemical hormonal level, and clinical symptoms.

The follow up data for treatment responses, side effects of treatment, and progression were assessed first at three months after treatment, followed by every six months thereafter for two years, and then annually. Clinical response to RT was evaluated according to the criteria set by WHO<sup>[19]</sup>.

Progression was defined as the recurrence of completely disappeared or re-growth of residual tumor on CT or MRI and/or recurrence of clinical symptoms or biochemical hormonal changes. PFS was calculated from the date of start treatment to the date of documented progression.

## Statistical analysis

The data were coded and entered into a computer using SPSS version 15.0. The results were expressed as number, percentiles, and medians because the data were non-normal distributions. Categorical variables were compared using chi-square tests. Independent prognostic variables used in the multivariate analysis were age, sex, dose of RT, line of treatment, tumor extension, and visual field defects. Survival functions (OAS and PFS) were estimated using the Kaplan–Meier test. All statistical

tests were two-sided, wherein  $P < 0.05$  was considered to indicate statistical significance.

## Results

The study group included 55 patients: 32 male and 23 female (1.4:1). The median age of the patients was 45 years. The most common clinical presentation was visual disturbance (38.2%) followed by headache (27.3%), hypopituitarism (14.5%), and incidental diagnosis (9%). Forty-five patients received post-operative RT due to residual tumor after surgical resection, and 10 patients (18.2%) received RT as the only line of treatment because the patients refused surgery or were medically unfit. Extrasellar extension (80%) was the most common feature (Table 1).

The overall response (OAR) rate was 72.8% with complete response in 16.4% and stable disease (SD) in 20%, whereas progressive disease (PD) was observed in 7.3% (Table 2).

Memory and intellectual sequelae were the most common late complications of treatment (14%) followed by hypopituitarism (8%), and then visual complications at 6% (Table 3).

Three patients died during follow-up because of accidental causes, and progression free survival was 84.6% (Fig. 1) (95% CI: 110.360 to 119.332).

On the multivariate analysis of prognostic factors on PFS, PFS was found significantly better with higher RT doses (up to 54 Gy) ( $P = 0.046$ ), treatment using both surgery and RT ( $P = 0.039$ ), localized tumor to the sella ( $P = 0.036$ ), and absence of visual field defect ( $P = 0.033$ ).

**Table 1.** Patient characteristics ( $n = 55$ ).

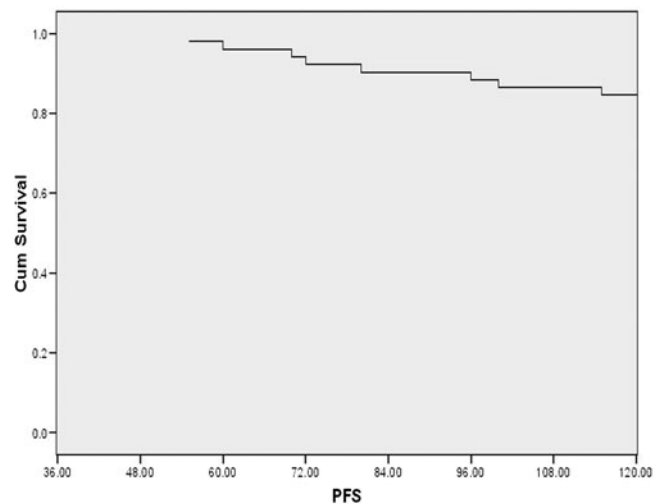
Characteristics	No. of patients (%)
Age, years	
Range: 35 to 53	
Median: 45	
Gender	
Male	32 (58.2)
Female	23 (41.8)
Symptoms	
Visual disturbance	21 (38.2)
Headache	15 (27.3)
Hypopituitarism	8 (14.5)
Nausea and vomiting	4 (7.3)
Diabetes insipidus	2 (3.6)
Incidental diagnosis	5 (9.1)
Type of treatment	
Radiotherapy alone	10 (18.2)
Radiotherapy and surgery	45 (81.8)
Tumor extension	
Localized to sella	11 (20)
Extension outside sella	
Suprasellar extension	14 (25.5)
Cavernous sinus infiltration	22 (40)
Infrasellar extension	8 (14.5)
Dose of RT, Gy	
45 to 49	27 (49.1)
50 to 54	28 (50.9)

**Table 2.** Response rate.

Response	No. of patients (%)
Complete response	9 (16.4)
Partial response	31 (56.4)
Overall response	40 (72.8)
Stable disease	11 (20)
Progressive disease	4 (7.3)

**Table 3.** Late complications of 2D conventional RT (50 patients).

Complications	No. of patients (%)
Hypopituitarism	4 (8)
Optic apparatus	3 (6)
Memory and intellectual changes	7 (14)



**Fig. 1.** Progression-free survival.

**Table 4.** Prognostic factors of progression free survival.

	95% CI	Odds ratio	P
Dose	0.01351–1.098	0.1218	0.046
Treatment	1.289–52.18	8.200	0.039
Extension	0.01419–1.053	0.1222	0.036
Visual field defect	1.158–23.39	5.205	0.033
Age	0.1528–3.392	0.7200	1.00
Gender	0.2686–5.974	1.267	1.00

By contrast, age and sex showed no statistically significant effect on PFS ( $P = 1$ ) (Table 4).

## Discussion

NFPA diagnosis is often delayed and usually presented as a macroadenoma because of the lack of hypersecretory endocrine signs and symptoms. Macroadenoma is a clinical manifestation that is usually insidious and represented by endocrinological symptoms, such as hypopituitarism and neurological symptoms due to mass effects<sup>[20]</sup>. An increasing number of patients have been incidentally diagnosed as harboring pituitary

adenoma because of the increased availability and use of MRI<sup>[21]</sup>. Although incidentally diagnosed NFPA can often be followed conservatively, more than one-third show significant growth on serial imaging, approximately 5% exhibit evidence of visual deficits, and 15% show some degree of pituitary dysfunction<sup>[22]</sup>.

In the present study, patient's age ranged from 35 years to 53 years. This result is comparable with that reported by Miller<sup>[23]</sup>, wherein the peak incidence of the pituitary adenoma was found in the fourth and fifth decades. Male to female ratio in the present study was 1.4:1, showing male predominance. This result is close to the ratio observed in another regional study at Agha Khan University hospital, wherein the ratio was 1.8:1<sup>[24]</sup>.

The most common presenting symptom was visual disturbance (38.2%). This finding coincides with some studies that reported figures ranging from 37% to 96%<sup>[25]</sup>. The visual symptoms observed can be attributed to the occurrence of direct compression and ischemia because of compression to the blood vessels<sup>[26]</sup>.

The second common symptom was headache, with a prevalence of 27.3%. Headache usually occurs under the involvement of pain sensitive fibers in the sellar diaphragm<sup>[27]</sup>. This finding is different from that reported by Cury et al.<sup>[28]</sup>, wherein visual disturbance was reported equal to headache in the frequency of presentation. Thapar K et al.<sup>[29]</sup> reported asymptomatic adenomas of pituitary gland in 6% to 25% of patients as demonstrated on systematic MRI. In the present study, incidental diagnosis was reported in 9% of the patients. The upward growth of macroadenomas is more common because the tumor passes through the path of least resistance; however, downward projection is also observed in some cases<sup>[26]</sup>. In the present study, infra-sellar and suprasellar extensions were reported in 14.5% and 25.5%, respectively.

The RT for NPFA aims in controlling tumor volume with no or minimal damage to the normal pituitary gland, and to at least, inhibit cell proliferation with the stabilization of tumor size<sup>[30]</sup>.

In the present study, the OAR rate was 72.8%, with SD in 20% and PD in 7.3%. These results are lower compared with those reported by Sasaki et al.<sup>[31]</sup>, wherein the OAR rate was 86% and SD was found in 12%. However, in contrast to the present study, not all patients in their study had macroadenoma.

As regards to late complications of 2D conventional RT on 50 patients, hypopituitarism was recorded in four patients (8%), which is lower than the prevalence observed in US registry (12%)<sup>[32]</sup>. Optic complications were recorded in three patients (6%). This result is lower than that reported by Cury et al.<sup>[28]</sup> (11.2%). The risk of chiasmal damage is directly related to the total administered dose and the dose per fraction of RT, and probably occurs secondary to damage to the vasa nervorum<sup>[33]</sup>. Late neuropsychological impairments, which are mainly memory and intellectual changes, were observed in 14% of patients in this study. These sequelae have been reported to varying degrees following pituitary surgery and/or RT<sup>[34]</sup>. Several independent variables, including the effects of surgery, RT, and hypopituitarism, act in consent to cloud the relative contribution of each variable to cause these sequelae<sup>[35]</sup>.

No patients developed brain necrosis in the present study, whereas Sasaki et al.<sup>[31]</sup> reported one case of brain necrosis in their research who received a radiation dose of 60 Gy, and this result could be explained by the less maximum radiation dose received in our study (54 Gy).

3DCRT and late complications cannot be assessed in the present study because of the small number (5) and short-term follow-up of patients.

PFS was found in 84.6%. This result is in agreement with other studies showing PFS of 82% to 97%<sup>[30,36,37]</sup>. A significantly better PFS was found with higher dose of RT, and this result is similar with that reported by Grigsby et al.<sup>[38]</sup> and Zaugg et al.<sup>[39]</sup>. These studies also mentioned that PFS is significantly related to the presence of visual field defects and suprasellar extension, which are similar to our findings. Patients treated using surgery and RT showed significantly higher PFS. This result is similar with that found by van den Bergh et al.<sup>[40]</sup>.

## Conclusion

Data of the present study confirmed the elevated prevalence of mass effect and hypopituitarism in patients harboring NFP macroadenoma. Conventional external RT up to 54 Gy is safe and effective in controlling NFP macroadenoma with tolerable and acceptable morbidity.

## Conflict of Interest Statement

No potential conflicts of interest were disclosed.

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