Radiological Assessment of Non-Functional Pituitary Adenomas

Christopher Wood

[1]Intensive Care Registrar, James Cook Hospital, Marton Road, Middlesbrough, United Kingdom

Abstract: *Background: Non-functional pituitary adenomas (NFPAs) are the most common form of pituitary neoplasia. A lack of clinical guidance relating to the frequency of radiological follow-up of NFPAs remains problematic both in tumours presenting clinically and incidentally. Post-operative disease recurrence is achieved by annual assessment by magnetic resonance imaging for at least ten years to identify late disease recurrence. Objectives: Study the frequency and interval duration of MRI scans in patients with NFPAs to implement guidance for a cost effective scanning regime. Methods: Retrospective study was carried out in James Cook University Hospital, between 1993-2013, investigating all patients with NFPAs who were managed by a single surgeon. Eighty nine patients were identified from endocrine databases and theatre logbooks. Results: Seventy two NFPA patients were managed surgically and 17 were managed conservatively. Of the surgically managed subgroup, fifty nine patients had clear compression of the optic compression. The majority of NPFA's were diagnosed with a CT or MRI scan, 34 and 29, respectively. The overall mean time to achieve 'no change' and tumour re-growth was significantly shorter in the conservatively managed patients, in comparison to the surgical group 1.2 vs 3.9 years and 0.9 vs 3.4 years, respectively. Seven hundred and fifteen scans were investigated. Conclusion: Late recurrence can occur in some patients, however it is uneconomical to carry out further scanning following steady state. Goldmann perimetry and serial hormone analysis may reduce health care costs once steady state has been achieved.*

Keywords: Non-functional pituitary adenomas (NFPAs), Radiology, follow-up

1. Introduction

Pituitary adenomas (PA) are benign tumour, characteristically lacking a capsule and are composed of adenohypophyseal cell (1). PA account for around 15% of brain tumours and 30% of pituitary tumours (2). PA can be classified in a radiological and endocrinological manner in relation to size or function, respectively. Most PA are functional (75%) resulting in the hyper secretion of key hormones, which include prolactin, growth hormone and cortisol. However, twenty five percent of tumours are non-function "silent" and do not secrete detectable levels of plasma active polypeptides, however, immunohistochemistry staining identifies that most non-functional tumours still positive for pituitary hormones (3).

Presentation, NFPAs can usually present in one of three ways, development of new neurological symptoms relating to mass effect leading to visual disturbance, an incidental pituitary mass following cerebral imaging for another indication and finally pituitary hypofunction secondary compression of normal pituitary tissue (4,5).

Neurological manifestations are diverse (6,7). Visual impairment is caused by extension and direct compression of the adenoma onto the optic chiasm most commonly presenting with superior temporal quadrantanopia. The onset of such symptoms is often insidious and leads to impaired visual acuity. Headache remains the second most common neurological symptom affecting up to forty percent of patients. Other less common presentations include cerebrospinal fluid rhinorrhea and pituitary apoplexy.

The increasing widespread use of magnetic resonance imaging (MRI) of head and neck pathology has led to the increasing identification of intracerebral pathologies (8). Hall *et al* reported up to ten percent of the adult population have detected pituitary pathologies on MR imaging which are suggested of a diagnosis of pituitary adenomas (9).

Pituitary adenomas are the most common tumour class which undergoes surgical resection (90%), the remaining intracellular tumours include: Rathke's cleft cyst (30%), crangiopharyngiomas (15%) and metastatic carcinomas (10%). The treatment goals are three fold; firstly to reduced neurological symptoms improving visual acuity, secondly, remove neoplastic tissue to prevent further recurrence and finally replacement of hormones due to compression of pituitary cells. Incidentalomas are usually management conservatively in the absence of hormonal hyper secretion, visual-field defects and hypopituitarism (10). Serial screening by magnetic resonance imaging is effective (11). Tumours which increase in size and require debulking surgery would under gotranssphenoidal surgery (12).

Transsphenoidal surgery aims to reduces the size of the pituitary adenoma allowing post-operative radiation to remove residual disease. A systematic review and meta-analysis by Murhad and colleagues reported that complete resection as defined by the surgeon was only achieved in twenty percent of cases. However, transsphenoidal surgery remains relatively safe with a low mortality (<1%) and complication rates (<5%) (13).

Common complications include; new visual field defects, infections (meningitis) and cerebrospinal fluid leakage (14). Postoperative improvements in visual field acuity have been reported in up to eighty percent of cases, however hormonal deficits are persistent and require ongoing oral replacement (15).

Post-operative management is usually a two stage process. Firstly, adjuvant radiotherapy should be offered to reduce any residual tissue which can be performed via conventional radiation therapy or more accurate stereotactic radiation. Follow-up studies assessing stereotactic radiation have been positive. Results suggest stable adenoma size, few neurological complications, however one third of patients

experience hormonal deficiencies (16,17). Follow-up serial imaging preferably by magnetic resonance imaging scans is advised on annual basis, however their duration and frequency is not clearly stated (15).

Our work moves forward from a previous publication by Coulter and colleagues in 2006 (18). However, this study not only expands the follow-up duration by up to six years but also the number of patients recruited.

2. Material and Methods

A retrospective study of all patients presenting with a NFPA who were managed by a single surgeon at James Cook University Hospital (JCUH) between September 1996 and June 2013. A Patient lists was Identified by endocrine record. Data was obtained from hospital records and internal radiological systems using a standard pro forma and collected on a Microsoft excel database. Diagnosis of NFPA was confirmed histologically post-operatively for symptomatic patients. All CT and MR images were reported, with changes in tumour size being noted as the central finding within the study. A standard MRI protocol of T2-weighted axial and T1-weighted coronal and sagittal high-resolution sequences were performed. The hospital audit committee ratified the study.

The following criteria was met before patients were included within the study; one, Postoperative histological analysis confirmed the diagnosis of NFPA. Two, patients who presented with an incidentaloma, whom were managed conservatively, required a radiological sellar lesion with hormonal hyposecretion. The duration of follow-up was defined by the date between the interval of transsphenoidal surgery and last scan date. The analysis for stability was defined by the time it takes for the tumour to show no further change in growth (increase or decrease) for two successive scans. Regrowth was subsequently, defined as an increase in mass size reported by a radiologist.

3. Results

3.1 Patient demographics

A total of eighty nine patients were identified between September 1996 to June 2013 who were managed by a single surgeon. Seventy two patients were managed surgically and seventeen were managed conservatively. There were forty four male and forty five female patients identified. The mean age of presentation was 65.4 $\pm$11.9 years (Range 35-91 years). The median duration of follow up was 93.6 months (Range 21.3-237.5 months). Five patients died during their follow-up with unrelated pathology. Sixty-nine patients presented with a pituitary macroadenoma, with the most common clinical presentations being bitemporal hemianopia (42.3%) and headache (35.2%), followed by temporal visual field loss (26.8%) and erectile dysfunction (12.7%).

3.2 Radiological tumour follow-up

A total of 730 scans were performed (Table -1). Of which, 614 scans (75%) were conducted postoperatively. In total 85.4% where MR and 14.6% were computerised tomography imaging studies. All scans were reported with 641 (89.7%) being reported by a neuro-radiologist, 74 (10%) by general consultant radiologists and 15 (2%) scans were unknown. Eighteen scans identified an increase in tumour size, seventeen of which were identified by Magnetic resonance imaging. Consisting of 9 pre-operative scans and 7 post-operative scans. The earliest post-operative scan which reported an increase in tumour size was 1.2 months and the latest time for an increase in size was 77 months.

Table 1: Total number of scans, breakdown by radiologist subspecialty

	Sub-class	Total values	%
Scan at presentation	CT	34	29
	MRI	29	25
	Both	25	22
	Unknown	28	24
Reporting	Neuroradiologist	641	88
	Radiologist	74	10
	Unknown	15	2
Total number of scans		730	
Mean Years follow up (years)		7.9	

Mean years follow-up
Median time to stability was defined as the time taken to achieve stability in 50% of NFPAs. Sixty post-operative patients (84.5%) achieved stability (i.e. Two consecutive stable scans) and were included in the Kaplan-Meirer survival curve (Figure-1).The time at which 50% and 90% of tumours became radiologically stable was 34 and 83 months, respectfully. The earliest time observed to obtain a stable tumour state in a patient was 11 months following surgery and the latest was 119 months.

Importantly, once stability was achieved no subsequent scans identified an increase in tumour size. The mean ($\pm$ SEM) time duration in months between follow up scans were: 1st scan = 9.50 $\pm$1.15, 2nd scan = 11.01 $\pm$0.79, 3rd scan = 25.21 $\pm$1.48, 4th scan = 16.91 $\pm$1.33, 5th scan = 17.77 $\pm$1.63, 6th scan = 20.75 $\pm$2.32, 7th scan = 16.39 $\pm$1.44, 8th scan 19.22 $\pm$2.50, 9th scan = 16.77 $\pm$5.55 and finally the 10th scan = 8 $\pm$0.

3.3 Treatment

Seventy two patients underwent surgical debulking via a transsphenoidal approach to eliminate mass effect following diagnosis. Of the patients who undertook surgery 61 received RT, those that did not receive RT were generally unfit, one patient refused and another did not require treatment due to an absence of any residual tumour.

Four patients required subsequent surgical intervention in the presence of tumour regrowth. Two patients underwent transsphenoidal surgery to remove residual tumour, this occurred at 2 months and 3 years following the initial intervention. Another patient, initially refused radiotherapy following their first surgery, however required a second

procedure one year later. Finally, one patient experienced rapid tumour regrowth following surgery and elected to wait until Goldman perimetry indicated chiasmal compression.re – 2 compared the number of years follow-up post-surgical intervention to mean duration (years) to achieve criterion; first post-operative scan, tumour stability and regrowth. Kaplan-Meier survival curves were implemented to assess the time required for tumours to become stable. The time required to achieve two stable scans (stability) was plotted against the number of tumours in surgically management patients.
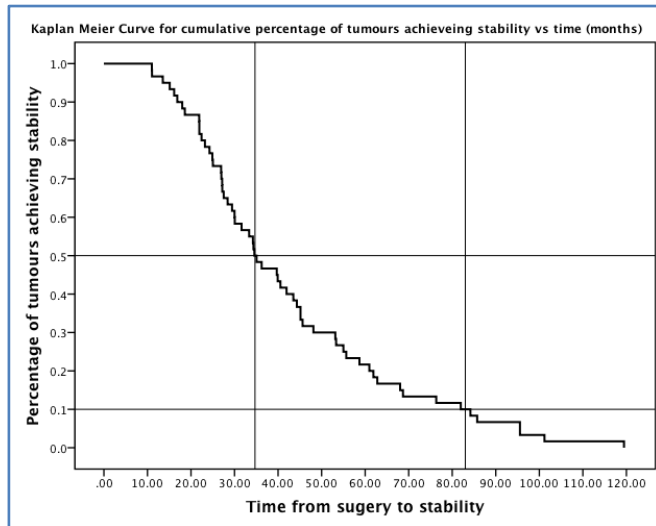

Figure 1: Kaplan-Meirer survival curve. Sixty post-operative patients (84.5%) achieved stability. Time at which 50% and 90% of tumours became radiologically stable was 34 and 83 months, respectively

3.4 Statistical Analysis

Descriptive analysis of data was achieved through SPSS for Mac, version 21. Statistical significance was defined at $p<0.05$.

4. Discussion

Our study highlights the findings from the follow-up study assessing the radiological management of eight nine patients over a ten year period with the mean follow-up duration of eight years. The mean regrowth occurred within 3 years with late adenoma regrowth occurring in one cases 15.3 years following surgical resection. The overall mean time to achieve 'no change' and tumour regrowth was significantly shorter in the conservatively managed patients, in comparison to the surgical group 1.2 vs 3.9 years and 0.9 vs 3.4 years, respectively.

Our data supports a previous study by coulter and colleagues acknowledging that further radiological follow-up after five years may not be economically sensible in light of our data suggesting tumour stability within two years and average regrowth will occur within less than four years (18). Thus clinical and biochemical assessment beyond this time will allow identification and management of the small number of patients with later regrowth recurrence. Thus, reducing the patient need for magnetic resonance imaging and costs whilst increasing resource availability without negatively

influencing patient care. Roelfsema and colleagues performed a structural review and meta-analysis confirming disease recurrences peaked between 1 and 5 years after surgery (19). However an Oxford based retrospective study of one hundred and fifty five patients over a ten year period reporting significant risk of regrowth in young patients with post-operative disease, resulting in upto twenty percent relapse rates after a ten year period (20).Moreover, O'Sullivan performed a longitude study over a twenty five year period, who identified recurrence rate of upto 33.5% (21). Dekker and colleagues followed up 102 non-functioning pituitary macroadenomas (NFMA) over a twelve year period of which only nine patients developed tumour regrowth (22). However, unlike our study the mean time to tumour regrowth was 6.9 years.

Over eight percent of patients who underwent primary surgical resection required radiotherapy mainly due to the presence of residual tumour. However, the rates of post-operative radiotherapy have been lower in other patient cohorts with positive outcomes. Bradley and colleagues studied a post-surgical population of individuals who underwent transsphenoidal surgery. Reporting the unirradiated cohort had 90% recurrence-free survival at 5 years, concluding that imaging can be delayed by upto five years for up to fifteen years in patients with adequate disease resection (23). Similarly, Soto-Ares and colleagues confirmed these findings reporting suggesting the lack of application for radiotherapy in the absence of residual disease, with subsequent MRI assessment at 3, 5 and 10 years to identify late disease recurrence (24). Postoperative radiological follow-up by MRI is superior to computed tomography, the latter being reserved where MRI is contraindicated due to patient choice, claustrophobia or body mass index (25). Excellent quality and reproducibility of pituitary images underpins effective follow-up. Our study reports diagnostic scans at presentation included both CT and MRI at relatively equal values of 25%, with a further 25% of patients requiring CT with subsequent MRI imaging. A further quarter of patients underwent imaging, however the modality of which was unclear. Of all the scans performed approximately 90% were reported by a dedicated neuro-radiologists.

Our study has multiple limitations, firstly, it is a retrospective study resulting in selection bias and limitations in data collection due to an inability to collect data from radiological systems and case note identification. Secondly, our data focuses on follow-up of NFPA and lacks holistic patient assessment based on functional assessment and co-morbidities. However it does provide an extended period of assessment for a rare disease pathology.

5. Summary

Routine regular post-operative imaging remains uneconomical for patients and hospital institutions. Our study highlights the need for serial imaging for five years with subsequent delayed imaging at seven and half and ten years for late recurrence. Moreover, serial hormone concentrations and Goldmann perimetry may be indicated in high risk groups to identify at patients requiring further debulking surgery.

6. Acknowledgments

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