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Outcome of non-functioning pituitary adenomas that regrow after primary treatment: a study from two large UK centers

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Abstract

Context: Despite the significant risk of regrowth of clinically non-functioning pituitary adenomas (CNFAs) after primary treatment, systematic data on the probability of further tumor progression and the effectiveness of management approaches are lacking.

Objective: To assess the probability of further regrowth(s), predictive factors and outcomes of management approaches in patients with CNFA who have been diagnosed with adenoma regrowth after primary treatment.

Patients, Design,Setting: Retrospective cohort study on 237 patients with regrown CNFA managed in two UK referral centers.

Results: Median follow-up was 5.9 years (range 0.4-37.7). The 5-year 2nd regrowth rate was 35.3% (n=90 patients) (36.2% after surgery;12.5% after radiotherapy;12.7% after surgery combined with radiotherapy;63.4% with monitoring). Of those managed by monitoring, 34.8% eventually were offered intervention. Type of management and sex were risk factors for 2nd CNFA regrowth. Amongst those with 2nd adenoma regrowth, the 5-year 3rd regrowth rate was 26.4% (24.4% after surgery;0.0% after radiotherapy;0.0% after surgery combined with radiotherapy;48.3% with monitoring). Overall, patients with a CNFA regrowth had probability of a 3rd regrowth 4.4% at 5 years, and 10.0% at 10 years, and the type of management of the 1st regrowth was the only risk factor. Malignant transformation was diagnosed in two of 237 patients.

Conclusions: Patients with regrown CNFA after primary treatment continue to carry considerable risk of tumor progression necessitating long-term follow-up. Management approach of the regrowth is the major factor determining this risk; monitoring has >60% risk of progression at 5 years and a substantial number of patients will ultimately require intervention.

Essential points:

- In this retrospective cohort study, we found that clinically non-functioning pituitary adenomas diagnosed with regrowth after primary treatment continue to carry a considerable risk of further progression.
- Management approach of the regrowth is the major factor determining the risk of further growth.

Introduction

Clinically non-functioning pituitary adenomas (CNFAs) are pituitary tumors not associated with clinical evidence of hormonal hypersecretion. They have a prevalence of 7-41.34/100000 people (1-4) and a standardized incidence rate of 1.02-2.34/100000 (3-5).

Unless incidentally detected, CNFAs usually escape early diagnosis due to the lack of clinical manifestations of hormonal hypersecretion, and are mostly discovered when they are large enough to exert pressure effects to surrounding structures. Epidemiological studies suggest that at the time of detection, 67-90% are macroadenomas representing the clinically relevant tumors in the group of CNFAs (1,2,5). Surgery with or without adjuvant radiotherapy is the mainstay of treatment for the macroadenomas, particularly if they are associated with visual compromise or are in close proximity to the optic pathways. The treatment aims to improve/reverse the consequences of the pressure effects and to prevent further tumor growth. Despite advances in the surgical and radiotherapy techniques, tumor control is not always achieved; thus, data from our centres, as well as from other departments, suggest 5-year regrowth rates 15-66% after surgery alone (6-9), and 2-28% after surgery followed by adjuvant radiotherapy (6,7,10,11). These observations dictate close monitoring, usually with annual imaging in the early post-operative years, aiming to avoid the consequences of late diagnosis of regrowth.

Management options for regrown CNFAs include further surgery, radiotherapy, a combination of these, or close monitoring: the decision is influenced by factors including adenoma size/location, patient's age, co-morbidities, pituitary reserve, and available surgical and radiotherapy expertise. Despite the significant risk of CNFA regrowth after primary treatment, series systematically analyzing the outcome of regrown CNFAs in terms of further tumor progression are lacking. As a result of this, we have no reliable data on the risk of further regrowth(s) and on the effectiveness of various approaches, and current decisions on the optimal management of this group of patients lack an evidence base.

In an attempt to provide this important information, we have performed a collaborative retrospective cohort study of two large specialist UK referral centers, allowing us to systematically assess the probability of further CNFA growth, predictive factors and the outcomes of management approaches in a large series of patients diagnosed with CNFA regrowth and followed-up for a prolonged period. Furthermore, we have estimated the probability of multiple episodes of adenoma progression after the first regrowth, providing novel data on the poorly explored area of clinically aggressive CNFA behavior and resistance to treatments.

Patients and Methods

Study design and patients

This was a retrospective cohort study in two large UK specialist referral centers (Birmingham and Oxford). The records of the patients with histologically-confirmed CNFA who, during their follow-up were diagnosed with regrowth of the adenoma after primary treatment (this was surgery with or without adjuvant radiotherapy), were reviewed. These were identified from the databases of the centers in which patients are classified according to diagnosis. The period covered for the primary surgery of the CNFA was between January 1963 and December 2011 and the follow-up period ended in June 2016. The term "primary CNFA" was used to describe the CNFA at the time of original diagnosis (before any regrowth). The study was retrospective in nature and involved no intervention beyond routine patient care. It was registered with and approved as an audit by the respective Hospitals.

Adenoma regrowth was diagnosed on the basis of radiological appearances with or without associated clinical manifestations. The extent of adenoma resection was determined by imaging performed at least 3 months post-operatively. In our series of 237 regrown CNFAs, 94% had tumor residual visible on scan postoperatively and 6% did not. Subsequent management was based on the decision of the endocrine, neurosurgical and oncology teams. Imaging surveillance after the detection of regrowth was mostly performed every 1-2 years. The endpoints were further CNFA regrowths (enlargement after treatment or further enlargement in cases managed by monitoring). Follow-up period was defined from the time of detection of a regrowth until last imaging. Demographic characteristics, treatments, immunohistochemical and imaging findings, further tumor progression(s), their management and subsequent outcomes were recorded.

Statistical analyses

Percentages were calculated for categorical data and medians with ranges for continuous variables. The regrowth-free curves were generated by the Kaplan-Meier method. Cox regression analysis was used to

assess the effect of various factors on regrowth and Hazard Ratios (HR) with 95% confidence intervals (CI) were estimated. The number of subjects with no tumor visible on imaging after surgery was very small and this precluded any analysis based on whether there was visible tumor or not. There was no significant departure from proportional hazards assumptions for any of the variables. The level of significance was set at $p<0.05$. Statistical analyses were performed by IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.

Results

Second regrowth

We identified 237 patients with CNFA showing 1st regrowth after primary treatment, representing an overall 31% of the total of 765 who were treated (9,10,12). Of the 765 patients treated, 678 (88.6%) had some tumor visible after surgery and 32.9% of these had regrowth, whereas 87 (11.4%) had no tumor visible after surgery and 16.3% of these had regrowth. In 678 patients with residual tumor, the regrowth rates were 28.3% without adjuvant irradiation and 4.4 % with adjuvant irradiation. The characteristics of the 237 patients are shown in Table 1. Eight were diagnosed between 1977 and 1988, and the remaining ones after 1990.

During a median follow-up of 5.9 years (range 0.4-37.7), 90 patients showed a 2nd regrowth (median age 64.9 years, range 32.3-88.9 – males/females 42/48). The 5-year rate for 2nd CNFA regrowth was 35.3% (Table 2, Figure 1A). When analyzed based on the type of management for the 1st regrowth, this was 36.2% after 2nd surgery alone (n=33), 12.5% after radiotherapy alone (n=58), 12.7% after 2nd surgery combined with radiotherapy (n=50), and 63.4% with simple monitoring (n=95) (Table 2, Figure 1B). Of the CNFAs managed by monitoring after the 1st episode of tumor progression, 34.8% eventually were offered intervention (surgery or radiotherapy or combination of these) due to further enlargement.

On univariate Cox regression analysis, risk factors for a 2nd regrowth were type of management offered for the 1st regrowth (type of treatment with reference category “Monitoring”: HR surgery 0.393, 95% CI 0.205-0.754, p=0.005; HR radiotherapy 0.098, 95% CI 0.046-0.210, p<0.001; HR surgery and radiotherapy 0.174, 95% CI 0.092-0.330, p<0.001), sex (with reference category “Female”: HR in males 0.642; 95% CI 0.423-0.974, p=0.037), and age at diagnosis of the primary CNFA (HR 1.021, 95% CI 1.005-1.038, p=0.009), whereas type of adenoma immunostaining was not (HR 0.833, 95% CI 0.675-1.027, p=0.088). Multivariate regression using the factors significant on univariate analysis revealed that only the type of treatment and sex (risk lower in males) remained significant risk factors for a 2nd

regrowth (type of treatment with reference category "Monitoring": HR surgery 0.463, 95% CI 0.238-0.901, p=0.023; HR radiotherapy 0.098, 95% CI 0.045-0.212, p<0.001; HR surgery and radiotherapy 0.182, 95% CI 0.093-0.353, p<0.001 - sex with reference category "Female": HR in males 0.565; 95% CI 0.370-0.863, p<0.008).

In one of the patients with a 2nd regrowth, the CNFA progression was manifested with metastatic disease in the brain and spine (pituitary carcinoma with positive staining for gonadotrophins); this was detected 35 years after the initial operation for CNFA and 27 years after the 1st regrowth. It was managed by surgery and radiotherapy to the metastatic disease followed by temozolomide four years later due to progression. Further progress was detected three years later and three cycles of lomustine were administered, but were discontinued due to thrombocytopenia: two years later, the metastatic burden has remained unchanged.

Further regrowth(s)

Of the 90 patients presenting with a 2nd episode of CNFA enlargement, two were not included in the review of further outcomes (one with the pituitary carcinoma with positive staining for gonadotrophins and another patient with no follow-up scan who died shortly after the detection of CNFA progression). The remaining 88 were managed by surgery alone (n=31), radiotherapy alone (n=8), surgery combined with radiotherapy (n=11), or simply monitoring (n=38). Seven subjects had no follow-up imaging after the management of the 2nd regrowth and were excluded from the subsequent evaluations.

During a median follow-up of 4.3 years (range 0.2-29.3), 22 had a 3rd regrowth (median age 66.3 years, range 44.5-73.3 - males/females 10/12). The 3rd regrowth rate at 5 years was 26.4% (Table 2, Figure 2A). When analyzed based on the modality of treatment offered for the 2nd regrowth, this was 24.4% after surgery, 0.0% after radiotherapy, 0.0% after surgery combined with radiotherapy and 48.3% after monitoring (Figure 2B).

One of these patients, who initially harbored a silent corticotroph adenoma, presented with metastatic disease in the spine 20 years after the primary surgery, and 18 years after the detection of the 1st regrowth; she died one year later. During this interval, she had developed three episodes of regrowths and clinically manifest Cushing's disease requiring three surgical operations, two courses of radiotherapy, and gamma knife therapy.

Of the 22 patients with a 3rd regrowth, 14 had further follow-up and had been managed by surgery (n=4), or monitoring (n=10); at a median period of 2.1 years (range 0.8-13.8), seven had a further adenoma enlargement (all managed by monitoring).

In the whole group of patients with a 1st regrowth (and after excluding seven with no follow-up after the 2nd one), the 3rd regrowth rate was 4.4% at 5 years,10.0% at 10 years and 15.1% at 15 years. On univariate Cox regression analysis, the only risk factor for this was the type of management of the 1st regrowth (type of treatment with reference category "Monitoring": HR surgery 0.046, 95% CI 0.005-0.429, p=0.007; HR radiotherapy 0.058, 95% CI 0.011-0.313, p=0.001; HR surgery and radiotherapy 0.062, 95% CI 0.012-0.309, p=0.001), whereas sex (HR 1.371, 95% CI 0.590-3.186, p=0.454), age at primary surgery (HR 1.021, 95% CI 0.987-1.056, p=0.225), and immunostaining (HR 1.117, 95% CI 0.676-1.844, p=0.667) were not.

Discussion

This is the first large series of non-selected consecutive patients with regrown CNFA assessing systematically further tumor progression and management outcomes during a long follow-up period. We have found 5- and 10-year 2nd regrowth rates of 35.3% and 46.7%, respectively, indicating the requirement for regular, long-term monitoring. Therapeutic intervention with surgery and/or radiotherapy provided optimal outcomes, whereas with monitoring alone, there is substantial probability for further enlargement (63.4% and 81.9% at 5 and 10 years, respectively). Management approach of the regrowth (active treatment or monitoring) is the major factor determining the risk of further growth(s). The probability of multiple episodes of CNFA progression is 4.4% and 10.0% at 5 and 10 years, respectively, with the rate increasing on prolonged follow-up. Of the CNFAs with regrowth after primary treatment, 0.84% had malignant transformation.

Non-functioning pituitary macroadenomas comprise the most common pituitary tumor requiring surgical intervention. However, a number of patients will experience tumor regrowth after primary treatment; thus, previously published literature analyzing the outcomes of patients from Oxford and Birmingham, as well as data from other large centers, have shown that 1st adenoma regrowth relates to the extent of CNFA removal (10-year regrowth rate if no residual adenoma 0-6% and significantly increased to 42-53% if intrasellar remnant, and to 77-80% if extrasellar remnant) (8,9,12) and to the administration of adjuvant radiotherapy, which significantly reduces adenoma progression (5-year regrowth rate 2-28%) (6,7,10,11). Furthermore, based on an Oxford cohort, the risk of enlargement increases with the length of follow-up, with 20% of the events detected at least 10 years after surgery (9). Tumor behavior after the detection of the 1st CNFA regrowth has not been previously systematically determined; the relative rarity and the generally considered slow growth rate of CNFAs possibly explain the lack of relevant data, in addition to the necessity for prolonged follow-up. In this retrospective cohort study of 237 patients with regrown CNFAs and a median follow-up of 5.9 years after the detection of the 1st regrowth, we have confirmed that tumor progression remains a significant possibility with a 10-year 2nd regrowth rate of 46.7% and 3nd

regrowth rate of 33.1%, dictating regular, life-long monitoring. Chang *et al.* (13) in a series of 81 regrown CNFAs (median follow-up 3.62 years), managed by surgery with or without radiotherapy, analyzed the outcome of 52 patients with follow-up more than 2 years and reported a 5-year progression rate of 8.5%. However, the small sample size and the short observation period are major drawbacks of this study.

Although there is no consensus on the definition of aggressive CNFAs, it is generally considered that this group is characterized by a high risk of regrowth(s) and resistance to treatments. In our study, we have estimated the probability of multiple episodes of progression in CNFAs diagnosed with a 1st regrowth suggesting clinically aggressive behavior: this was 4.4% and 10.0% at 5 and 10 years, respectively, with the percentage increasing with further follow-up confirming the long natural history of these tumors.

The decision to intervene and the modality of treatment after detection of adenoma progression depends on many factors including proximity to the chiasm/visual deterioration, tumor location/size, age, pituitary reserve, co-morbidities, available surgical and radiotherapy expertise. In 40.3% of our cases with a 2nd regrowth, imaging surveillance was the management approach; repeat surgery was offered in 14%, radiotherapy in 24.6% and surgery combined with radiotherapy in 21.2%. We found that radiotherapy (alone or in combination with surgery) offers optimal local control with 5- and 10-year regrowth rates 12.5-12.7% and 17.7-26.1%, respectively. With surgery alone, these were 36.2% and 47.8%, respectively, rendering irradiation an attractive option. It should be noted, however, that the advances in imaging and surgical techniques have reduced the challenges and risks related with re-operation (14), making this approach an alternative option that could provide a stop/gap during the period when the patient wishes to avoid radiotherapy. Invasion of the cavernous sinus is not a reason for favoring surgery, but repeat operation may be inevitable for very large or close to the optic pathways tumors requiring close monitoring and early detection of continuing growth potential. Similar findings were reached after analysis of the outcomes of the 2nd regrowths, although the small sample size in each management group remains a challenge. Studies specifically looking at the impact of radiotherapy on regrown CNFAs are lacking. The published literature includes series of patients with residual or regrown adenoma managed

by various radiation modalities in tertiary radiotherapy centers which have been analyzed all together, making the estimation of clear outcomes for our group of interest not possible; nonetheless, overall optimal control rates are reported (11,15-18). In view of the suggested adverse effects of radiotherapy (19), there is controversy on its indications and timing, and in many centers, this is deferred until detection of adenoma regrowth. Within the constraints of comparing with historical data from previous literature in which radiotherapy was offered immediately after surgery (6,7,10), our outcomes after irradiation for regrowth suggest that this approach achieves similar local control rates, allowing for deferral of its use until detection of regrowth, and reducing the number of patients offered unnecessarily irradiation. This approach requires close imaging monitoring aiming to detect the regrown mass at an early stage, before its size dictates debulking surgery, and poses difficulties for the safe and effective administration of the radiotherapy.

Radiographic evidence of CNFA progression does not necessarily require therapeutic intervention and imaging surveillance is a rational approach in asymptomatic regrowths or when intervention is contraindicated. The outcome of monitoring for regrown CNFAs has not been previously assessed. We found that after detection of the 1st episode of enlargement, the 5-year rate of further enlargement was 63.4% (48.3% after the detection of 2nd regrowth) pointing out the importance of close monitoring and of a timely decision to intervene when the tumor is in proximity with the chiasm or shows continued progress. Amongst our regrown CNFAs managed by monitoring after a 1st regrowth, 34.8% required intervention. Factors predicting further progression have not been identified, and data on the natural history of non-operated presumed CNFAs would not apply to this specific group of tumors which have already demonstrated progressive behavior despite treatment. Notably, the growth of CNFAs is characterized by different models of unknown pathophysiology (exponential, logistic with initial growth followed by deceleration) (20), and predictive parameters are not available. Honegger *et al.* (20) in a selected retrospective series of 12 operated (and non-irradiated) CNFAs presenting with enlargement, found considerable variability in tumor volume doubling-time (between 1 and 27.2 years), confirming the

significant variation in tumor progression; interestingly, no significant correlation between initial volume and doubling time was confirmed.

The pathophysiological mechanisms implicated in aggressive CNFA behavior have not been elucidated and validated prognostic biomarkers are not available (21). Established clinical predictors of CNFA regrowth after primary treatment are the extent of adenoma resection and post-operative irradiation (9,22,23), whereas age, sex, initial tumor size, invasiveness and histology have not been consistently verified to be of prognostic significance (24). In our series of CNFAs with already one episode of progression, type of management of the regrowth was a predictor of further progress and sex was a predictor only for the 2^{nd} episode; the significance of the latter finding remains to be elucidated. Young age at diagnosis of the primary CNFA and type of immunostaining did not predict aggressive behavior. Notably, there is controversy as to whether CNFAs staining for ACTH demonstrate worse prognosis with multiple regrowths (25,26) and our study with 28 cases (16% of the cohort) did not support this. Notably, previous analysis of patients with CNFA in Oxford had shown that staining for ACTH was not an independent predictor of 1^{st} regrowth (9). Nonetheless, cases of silent ACTH adenomas showing aggressive behavior after the 1^{st} regrowth have been reported (25) and one of the two CNFAs in our study showing malignant transformation was a silent corticotroph adenoma.

Pituitary carcinomas account for 0.1% of pituitary tumors and require multidisciplinary treatment approach (27). Data on the rate of regrown CNFAs demonstrating malignant transformation have not been previously published. In our series, malignant transformation was diagnosed in 0.8% of CNFAs diagnosed with regrowth. Although latency periods between 4 months to 18 years have been reported, in our cases the interval was extensive (21 and 35 years). Overall, prognosis is poor and most of the patients die within one year of diagnosis (27). However, one of our patients had an unusual clinical course with survival of at least 9 years, highlighting the unpredictable behavior of this condition. The development of florid Cushing's syndrome and malignant transformation from a silent corticotroph adenoma, as in our

second case of pituitary carcinoma, is exceptionally rare and the biological mechanisms remain enigmatic.

The limitations of our study are its retrospective, non-randomized nature making it vulnerable to selection bias for the management approaches (however, a prospective randomized study may not be practically feasible) and the fact that a (small) number of patients lacked follow-up after detection of further enlargement (in most of them repeat imaging had not taken place by the end of the project). The advantages are the large number of well characterized and non-selected subjects with a rare condition from two large pituitary UK referral centers followed-up for a long period, who were analyzed systematically in terms of tumor progression, providing novel data for clinical practice.

Our study provides novel and systematic data on the previously unknown natural history of regrown CNFAs and on the poorly explored area of clinically aggressive CNFA behavior. It establishes the importance of continuing follow-up after therapeutic interventions, as these do not offer definitive tumor stability. It also proves the significance of regular, long-term monitoring of regrown CNFAs not offered treatment, as continued progress is seen in a substantial number of patients who will ultimately require intervention. The decision for intervention needs to be taken in a multidisciplinary setting and will rely on a risk-benefit balance with one of the major factors being the prevention of visual morbidity. Given that a prospective study of this scale and duration is unlikely to be feasible, our results aid decision making for all disciplines involved in the management of these patients (endocrinology, oncology, neurosurgery) and highlight the necessity of gaining a better understanding of the biological behavior of these tumors.

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Figure 1. Kaplan-Meier 2nd regrowth-free survival curves (A) total group of patients with a 1st regrowth, (B) stratified by type of treatment of the 1st regrowth (surgery, radiotherapy, surgery and radiotherapy, monitoring).

Figure 2. Kaplan-Meier 3rd regrowth-free survival curves (A) total group of patients with a 2nd regrowth, (B) stratified by type of treatment of the 2nd regrowth (surgery, radiotherapy, surgery and radiotherapy, monitoring).

Table 1. Characteristics of patients with regrown CNFA

Number of patients	237
Sex n (%) (males/females)	134/103 (56.5%/43.5%)
Age at time of surgery for primary CNFA (years) (median, range)	52.1 (12-86)
Immunostaining of adenoma* n (%)	
FSH/LH or their subunits	67 (40.4%)
Null cell	60 (36.1%)
ACTH[1]	28 (16.9%)
Plurihormonal[2]	9 (5.4%)
GH	1 (0.6%)
PRL	1 (0.6%)
Adjuvant radiotherapy after surgery of primary CNFA n (%)	30 (12.7%)
Interval of diagnosis of 1st regrowth from date of surgery of primary CNFA (months) (median, range)	50 (3-485)
Management of 1st regrowth[3] **n (%)**	
Surgery	33/236 (14.0%)
Radiotherapy	58/236 (24.6%)
Surgery and adjuvant radiotherapy[4]	50/236 (21.2%)
Monitoring	95/236 (40.3%)

Primary CNFA: CNFA at the time of original diagnosis (before any regrowth).

Radiotherapy: fractionated external irradiation in all cases except two in which radiosurgery was offered.

*Data are provided based on 166 cases with the relevant information available.

[1]Combined or not with other hormones. [2]Combination of hormones other than ACTH. [3]One patient, who died shortly after the diagnosis of regrowth and had no follow-up scan, has been excluded. [4]Two patients from this group had also received radiotherapy as adjuvant treatment after the original surgery of the primary CNFA.

Table 2. 2nd and 3rdregrowth rates at 5 and at 10 years follow-up

Group of patients	2nd regrowth rate at 5 years	2nd regrowth rate at 10 years
Total group*	35.3%	46.7%
	Males 28.2%	Males 38.8%
	Females 44.7%	Females 57.0 %
Surgery for 1st regrowth	36.2%	47.8%
Radiotherapy for 1st regrowth	12.5%	17.7%
Surgery and Radiotherapy for 1st regrowth	12.7%	26.1%
Monitoring for 1st regrowth	63.4%	81.9%
Group of patients	**3rd regrowth rate at 5 years**	**3rd regrowth rate at 10 years**
Total group	26.4%	33.1%
Surgery for 2nd regrowth	24.4%	35.2%
Radiotherapy for 2nd regrowth	0.0%	0.0%
Surgery and Radiotherapy for 2nd regrowth	0.0%	0.0%
Monitoring for 2nd regrowth	48.3%	58.6%

* 2nd regrowth rate for the total group within the follow-up period: 38%.