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# Outcome of non-functioning pituitary adenomas that regrow after primary treatment

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#### 43 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.

47 Objective: To assess the probability of further regrowth(s), predictive factors and outcomes of
48 management approaches in patients with CNFA who have been diagnosed with adenoma regrowth after
49 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 2<sup>nd</sup> regrowth rate was 35.3% (n=90 52 53 patients) (36.2% after surgery;12.5% after radiotherapy;12.7% after surgery combined with 54 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  $2^{nd}$  CNFA regrowth. Amongst those with 55 2<sup>nd</sup> adenoma regrowth, the 5-year 3<sup>rd</sup> regrowth rate was 26.4% (24.4% after surgery;0.0% after 56 57 radiotherapy;0.0% after surgery combined with radiotherapy;48.3% with monitoring). Overall, patients with a CNFA regrowth had probability of a 3<sup>rd</sup> regrowth 4.4% at 5 years, and 10.0% at 10 years, and the 58 type of management of the 1<sup>st</sup> regrowth was the only risk factor. Malignant transformation was diagnosed 59 60 in two of 237 patients.

61 Conclusions: Patients with regrown CNFA after primary treatment continue to carry considerable risk of 62 tumor progression necessitating long-term follow-up. Management approach of the regrowth is the major 63 factor determining this risk; monitoring has >60% risk of progression at 5 years and a substantial number 64 of patients will ultimately require intervention.

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68	Es	sential points:
69	•	In this retrospective cohort study, we found that clinically non-functioning pituitary adenomas
70		diagnosed with regrowth after primary treatment continue to carry a considerable risk of further
71		progression.
72	•	Management approach of the regrowth is the major factor determining the risk of further growth.
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#### 93 Introduction

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

97 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 98 99 exert pressure effects to surrounding structures. Epidemiological studies suggest that at the time of 100 detection, 67-90% are macroadenomas representing the clinically relevant tumors in the group of CNFAs 101 (1,2,5). Surgery with or without adjuvant radiotherapy is the mainstay of treatment for the 102 macroadenomas, particularly if they are associated with visual compromise or are in close proximity to 103 the optic pathways. The treatment aims to improve/reverse the consequences of the pressure effects and to 104 prevent further tumor growth. Despite advances in the surgical and radiotherapy techniques, tumor 105 control is not always achieved; thus, data from our centres, as well as from other departments, suggest 5-106 year regrowth rates 15-66% after surgery alone (6-9), and 2-28% after surgery followed by adjuvant 107 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. 108

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.

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

#### 137 *Study design and patients*

138 This was a retrospective cohort study in two large UK specialist referral centers (Birmingham and 139 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 140 141 adjuvant radiotherapy), were reviewed. These were identified from the databases of the centers in which 142 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 143 144 "primary CNFA" was used to describe the CNFA at the time of original diagnosis (before any regrowth). 145 The study was retrospective in nature and involved no intervention beyond routine patient care. It was 146 registered with and approved as an audit by the respective Hospitals.

147 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 3 148 months post-operatively. In our series of 237 regrown CNFAs, 94% had tumor residual visible on scan 149 150 postoperatively and 6% did not. Subsequent management was based on the decision of the endocrine, 151 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 152 153 further enlargement in cases managed by monitoring). Follow-up period was defined from the time of 154 detection of a regrowth until last imaging. Demographic characteristics, treatments, immunohistochemical 155 and imaging findings, further tumor progression(s), their management and subsequent outcomes were 156 recorded.

#### 157 *Statistical analyses*

158 Percentages were calculated for categorical data and medians with ranges for continuous variables. The 159 regrowth-free curves were generated by the Kaplan-Meier method. Cox regression analysis was used to

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

182 Second regrowth

We identified 237 patients with CNFA showing 1<sup>st</sup> 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  $2^{nd}$  regrowth (median age 64.9 years, range 32.3-88.9 – males/females 42/48). The 5-year rate for  $2^{nd}$  CNFA regrowth was 35.3% (Table 2, Figure 1A). When analyzed based on the type of management for the 1<sup>st</sup> regrowth, this was 36.2% after  $2^{nd}$  surgery alone (n=33), 12.5% after radiotherapy alone (n=58), 12.7% after  $2^{nd}$  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 1<sup>st</sup> 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 2<sup>nd</sup> regrowth were type of management offered 197 198 for the 1<sup>st</sup> regrowth (type of treatment with reference category "Monitoring": HR surgery 0.393, 95% CI 199 0.205-0.754, p=0.005; HR radiotherapy 0.098, 95% CI 0.046-0.210, p<0.001; HR surgery and 200 radiotherapy 0.174, 95% CI 0.092-0.330, p<0.001), sex (with reference category "Female": HR in males 201 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 0.675-202 203 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 2<sup>nd</sup> 204

regrowth (type of treatment with reference category "Monitoring": HR surgery 0.463, 95% CI 0.2380.901, *p*=0.023; HR radiotherapy 0.098, 95% CI 0.045-0.212, *p*<0.001; HR surgery and radiotherapy</li>
0.182, 95% CI 0.093-0.353, p<0.001 - sex with reference category "Female": HR in males 0.565; 95% CI</li>
0.370-0.863, *p*<0.008).</li>

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In one of the patients with a 2<sup>nd</sup> 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 1<sup>st</sup> 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.

217 *Further regrowth(s)* 

Of the 90 patients presenting with a  $2^{nd}$  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  $2^{nd}$  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 3<sup>rd</sup> regrowth (median age 66.3 years, range 44.5-73.3 - males/females 10/12). The 3<sup>rd</sup> regrowth rate at 5 years was 26.4% (Table 2, Figure 2A).
When analyzed based on the modality of treatment offered for the 2<sup>nd</sup> 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 1<sup>st</sup> 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 3<sup>rd</sup> 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).

237 In the whole group of patients with a 1<sup>st</sup> regrowth (and after excluding seven with no follow-up after the 2<sup>nd</sup> one), the 3<sup>rd</sup> regrowth rate was 4.4% at 5 years, 10.0% at 10 years and 15.1% at 15 years. On univariate 238 Cox regression analysis, the only risk factor for this was the type of management of the 1<sup>st</sup> regrowth (type 239 240 of treatment with reference category "Monitoring": HR surgery 0.046, 95% CI 0.005-0.429, p=0.007; HR 241 radiotherapy 0.058, 95% CI 0.011-0.313, p=0.001; HR surgery and radiotherapy 0.062, 95% CI 0.012-242 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) 243 244 were not.

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### 253 Discussion

254 This is the first large series of non-selected consecutive patients with regrown CNFA assessing 255 systematically further tumor progression and management outcomes during a long follow-up period. We have found 5- and 10-year 2<sup>nd</sup> regrowth rates of 35.3% and 46.7%, respectively, indicating the 256 257 requirement for regular, long-term monitoring. Therapeutic intervention with surgery and/or radiotherapy 258 provided optimal outcomes, whereas with monitoring alone, there is substantial probability for further 259 enlargement (63.4% and 81.9% at 5 and 10 years, respectively). Management approach of the regrowth 260 (active treatment or monitoring) is the major factor determining the risk of further growth(s). The 261 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, 262 263 0.84% had malignant transformation.

264 Non-functioning pituitary macroadenomas comprise the most common pituitary tumor requiring surgical 265 intervention. However, a number of patients will experience tumor regrowth after primary treatment; 266 thus, previously published literature analyzing the outcomes of patients from Oxford and Birmingham, as well as data from other large centers, have shown that 1<sup>st</sup> adenoma regrowth relates to the extent of CNFA 267 268 removal (10-year regrowth rate if no residual adenoma 0-6% and significantly increased to 42-53% if 269 intrasellar remnant, and to 77-80% if extrasellar remnant) (8,9,12) and to the administration of adjuvant 270 radiotherapy, which significantly reduces adenoma progression (5-year regrowth rate 2-28%) (6.7,10,11). 271 Furthermore, based on an Oxford cohort, the risk of enlargement increases with the length of follow-up, 272 with 20% of the events detected at least 10 years after surgery (9). Tumor behavior after the detection of the 1<sup>st</sup> CNFA regrowth has not been previously systematically determined; the relative rarity and the 273 274 generally considered slow growth rate of CNFAs possibly explain the lack of relevant data, in addition to 275 the necessity for prolonged follow-up. In this retrospective cohort study of 237 patients with regrown 276 CNFAs and a median follow-up of 5.9 years after the detection of the 1<sup>st</sup> regrowth, we have confirmed that tumor progression remains a significant possibility with a 10-year 2<sup>nd</sup> regrowth rate of 46.7% and 3<sup>nd</sup> 277

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 1<sup>st</sup> 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.

287 The decision to intervene and the modality of treatment after detection of adenoma progression depends 288 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 2<sup>nd</sup> 289 290 regrowth, imaging surveillance was the management approach; repeat surgery was offered in 14%, 291 radiotherapy in 24.6% and surgery combined with radiotherapy in 21.2%. We found that radiotherapy 292 (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, 293 294 rendering irradiation an attractive option. It should be noted, however, that the advances in imaging and 295 surgical techniques have reduced the challenges and risks related with re-operation (14), making this 296 approach an alternative option that could provide a stop/gap during the period when the patient wishes to 297 avoid radiotherapy. Invasion of the cavernous sinus is not a reason for favoring surgery, but repeat 298 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 299 analysis of the outcomes of the 2<sup>nd</sup> regrowths, although the small sample size in each management group 300 remains a challenge. Studies specifically looking at the impact of radiotherapy on regrown CNFAs are 301 302 lacking. The published literature includes series of patients with residual or regrown adenoma managed

303 by various radiation modalities in tertiary radiotherapy centers which have been analyzed all together, 304 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 305 306 (19), there is controversy on its indications and timing, and in many centers, this is deferred until 307 detection of adenoma regrowth. Within the constraints of comparing with historical data from previous 308 literature in which radiotherapy was offered immediately after surgery (6,7,10), our outcomes after 309 irradiation for regrowth suggest that this approach achieves similar local control rates, allowing for 310 deferral of its use until detection of regrowth, and reducing the number of patients offered unnecessarily 311 irradiation. This approach requires close imaging monitoring aiming to detect the regrown mass at an 312 early stage, before its size dictates debulking surgery, and poses difficulties for the safe and effective 313 administration of the radiotherapy.

Radiographic evidence of CNFA progression does not necessarily require therapeutic intervention and 314 315 imaging surveillance is a rational approach in asymptomatic regrowths or when intervention is 316 contraindicated. The outcome of monitoring for regrown CNFAs has not been previously assessed. We found that after detection of the 1<sup>st</sup> episode of enlargement, the 5-year rate of further enlargement was 317 63.4% (48.3% after the detection of  $2^{nd}$  regrowth) pointing out the importance of close monitoring and of 318 319 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 1<sup>st</sup> regrowth, 34.8% required 320 321 intervention. Factors predicting further progression have not been identified, and data on the natural 322 history of non-operated presumed CNFAs would not apply to this specific group of tumors which have 323 already demonstrated progressive behavior despite treatment. Notably, the growth of CNFAs is 324 characterized by different models of unknown pathophysiology (exponential, logistic with initial growth 325 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, 326 327 found considerable variability in tumor volume doubling-time (between 1 and 27.2 years), confirming the

328 significant variation in tumor progression; interestingly, no significant correlation between initial volume329 and doubling time was confirmed.

330 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 331 332 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 333 334 verified to be of prognostic significance (24). In our series of CNFAs with already one episode of 335 progression, type of management of the regrowth was a predictor of further progress and sex was a predictor only for the 2<sup>nd</sup> episode; the significance of the latter finding remains to be elucidated. Young 336 337 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 338 multiple regrowths (25.26) and our study with 28 cases (16% of the cohort) did not support this. Notably, 339 340 previous analysis of patients with CNFA in Oxford had shown that staining for ACTH was not an independent predictor of 1<sup>st</sup> regrowth (9). Nonetheless, cases of silent ACTH adenomas showing 341 aggressive behavior after the 1<sup>st</sup> regrowth have been reported (25) and one of the two CNFAs in our study 342 343 showing malignant transformation was a silent corticotroph adenoma.

344 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 345 346 been previously published. In our series, malignant transformation was diagnosed in 0.8% of CNFAs 347 diagnosed with regrowth. Although latency periods between 4 months to 18 years have been reported, in 348 our cases the interval was extensive (21 and 35 years). Overall, prognosis is poor and most of the patients 349 die within one year of diagnosis (27). However, one of our patients had an unusual clinical course with 350 survival of at least 9 years, highlighting the unpredictable behavior of this condition. The development of 351 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 remainenigmatic.

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.

361 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 362 importance of continuing follow-up after therapeutic interventions, as these do not offer definitive tumor 363 364 stability. It also proves the significance of regular, long-term monitoring of regrown CNFAs not offered 365 treatment, as continued progress is seen in a substantial number of patients who will ultimately require 366 intervention. The decision for intervention needs to be taken in a multidisciplinary setting and will rely on 367 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 368 all disciplines involved in the management of these patients (endocrinology, oncology, neurosurgery) and 369 370 highlight the necessity of gaining a better understanding of the biological behavior of these tumors.

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

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

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#### 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 <sup>1</sup>	28 (16.9%)
Plurihormonal <sup>2</sup>	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 1 <sup>st</sup> regrowth from date of surgery of primary	50 (3-485)
CNFA (months) (median, range)	
Management of 1 <sup>st</sup> regrowth <sup>3</sup> n (%)	
Surgery	33/236 (14.0%)
Radiotherapy	58/236 (24.6%)
Surgery and adjuvant radiotherapy <sup>4</sup>	50/236 (21.2%)
	95/236 (40.3%)

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

<sup>1</sup>Combined or not with other hormones. <sup>2</sup>Combination of hormones other than ACTH. <sup>3</sup>One patient, who died shortly after the diagnosis of regrowth and had no follow-up scan, has been excluded. <sup>4</sup>Two patients from this group 

had also received radiotherapy as adjuvant treatment after the original surgery of the primary CNFA. 

546	Table 2. 2 <sup>nd</sup>	<sup>1</sup> and 3 <sup>rd</sup> regrowth	rates at 5 and	l at 10 years fol	low-up
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Group of patients	2 <sup>nd</sup> regrowth rate at 5 years	2 <sup>nd</sup> regrowth rate at 10 years
	25.2%	12.50
Total group*	35.3%	46.7%
	Males 28.2%	Males 38.8%
	Females 44.7%	Females 57.0 %
Surgery for 1 <sup>st</sup> regrowth	36.2%	47.8%
Radiotherapy for 1 <sup>st</sup> regrowth	12.5%	17.7%
Surgery and Radiotherapy for 1 <sup>st</sup> regrowth	12.7%	26.1%
Monitoring for 1 <sup>st</sup> regrowth	63.4%	81.9%
Group of patients	3 <sup>rd</sup> regrowth rate at 5 years	3 <sup>rd</sup> regrowth rate at 10 years
Total group	26.4%	33.1%
Surgery for 2 <sup>nd</sup> regrowth	24.4%	35.2%
Radiotherapy for 2 <sup>nd</sup> regrowth	0.0%	0.0%
Surgery and Radiotherapy for 2 <sup>nd</sup> regrowth	0.0%	0.0%
Monitoring for 2 <sup>nd</sup> regrowth	48.3%	58.6%

\*  $2^{nd}$  regrowth rate for the total group within the follow-up period: 38%.