

Outcomes of patients with Nelson's syndrome after primary treatment

Fountas, Athanasios; Lim, Eugenie S. ; Drake, William M; Powlson, Andrew S; Gurnell, Mark; Martin, Niamh M; Seejore, Khyatisha ; Murray, Robert D; MacFarlane, James ; Ahluwalia, Rupa ; Swords, Francesca ; Ashraf, Muhammad ; Pal, Aparna ; Chong, Zhuomin ; Freel, Marie ; Balafshan, Tala ; Purewal, Tejpal S; Speak, Rowena G. ; Newell-Price, John; Higham, Claire E

DOI:

[10.1210/clinem/dgz200](https://doi.org/10.1210/clinem/dgz200)

License:

Other (please specify with Rights Statement)

Document Version

Peer reviewed version

Citation for published version (Harvard):

Fountas, A, Lim, ES, Drake, WM, Powlson, AS, Gurnell, M, Martin, NM, Seejore, K, Murray, RD, MacFarlane, J, Ahluwalia, R, Swords, F, Ashraf, M, Pal, A, Chong, Z, Freel, M, Balafshan, T, Purewal, TS, Speak, RG, Newell-Price, J, Higham, CE, Hussein, Z, Baldeweg, SE, Dales, J, Reddy, N, Levy, MJ & Karavitaki, N 2020, 'Outcomes of patients with Nelson's syndrome after primary treatment: a multicenter study from 13 UK Pituitary centers', *Journal of Clinical Endocrinology and Metabolism*, vol. 105, no. 5, pp. 1527–1537. <https://doi.org/10.1210/clinem/dgz200>

[Link to publication on Research at Birmingham portal](#)

Publisher Rights Statement:

This is a pre-copyedited, author-produced version of an article accepted for publication in *Sleep* following peer review. The version of record Athanasios Fountas, Eugenie S Lim, William M Drake, Andrew S Powlson, Mark Gurnell, Niamh M Martin, Khyatisha Seejore, Robert D Murray, James MacFarlane, Rupa Ahluwalia, Francesca Swords, Muhammad Ashraf, Aparna Pal, Zhuomin Chong, Marie Freel, Tala Balafshan, Tejpal S Purewal, Rowena G Speak, John Newell-Price, Claire E Higham, Ziad Hussein, Stephanie E Baldeweg, Jolyon Dales, Narendra Reddy, Miles J Levy, Niki Karavitaki, Outcomes of patients with Nelson's syndrome after primary treatment: a multicenter study from 13 UK Pituitary centers, *The Journal of Clinical Endocrinology & Metabolism*, , dgz200, <https://doi.org/10.1210/clinem/dgz200> is available online at: <https://academic.oup.com/jcem/advance-article/doi/10.1210/clinem/dgz200/5628028>

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

1 **Title**

2 Outcomes of patients with Nelson’s syndrome after primary treatment: a multicenter study from 13
3 UK Pituitary centers

4
5 **Authors**

6 A. Fountas^{1,2,3}, E.S. Lim⁴, W.M. Drake⁴, A.S. Powlson^{5,6}, M. Gurnell^{5,6}, N.M. Martin⁷, K. Seejore⁸,
7 R.D. Murray⁸, J. MacFarlane⁹, R. Ahluwalia⁹, F. Swords⁹, M. Ashraf¹⁰, A. Pal¹⁰, Z. Chong¹¹, M.
8 Freel¹¹, T. Balafshan¹², T.S. Purewal¹², R.G. Speak^{13,14}, J. Newell-Price^{13,14}, C.E. Higham^{15,16}, Z.
9 Hussein¹⁷, S.E. Baldeweg¹⁷, J. Dales¹⁸, N. Reddy¹⁸, M.J. Levy¹⁸, N. Karavitaki^{1,2,3}

10

11 **Affiliations**

12 ¹Institute of Metabolism and Systems Research, College of Medical and Dental Sciences, University
13 of Birmingham, Birmingham, UK; ²Centre for Endocrinology, Diabetes and Metabolism,
14 Birmingham Health Partners, Birmingham, UK; ³Department of Endocrinology, Queen Elizabeth
15 Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK; ⁴Department of
16 Endocrinology, St Bartholomew's Hospital, Barts Health NHS Trust, London, UK; ⁵Metabolic
17 Research Laboratories, Wellcome Trust-MRC Institute of Metabolic Science, University of
18 Cambridge, Cambridge, UK; ⁶NIHR Cambridge Biomedical Research Centre, Addenbrooke's
19 Hospital, Cambridge, UK; ⁷Section of Endocrinology and Investigative Medicine, Imperial College
20 London, Imperial College Healthcare NHS Trust, London, UK; ⁸Department of Endocrinology, St
21 James's University Hospital, Leeds Teaching Hospitals NHS Trust, Leeds, UK; ⁹Department of
22 Endocrinology, Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, UK;
23 ¹⁰Department of Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism, Oxford
24 University Hospitals NHS Foundation Trust, Oxford, UK; ¹¹Department of Endocrinology, Queen
25 Elizabeth University Hospital Glasgow, Glasgow, UK; ¹²Department of Diabetes and Endocrinology,
26 Royal Liverpool University Hospital, Royal Liverpool and Broadgreen University Hospitals NHS
27 Trust, Liverpool, UK; ¹³Department of Oncology and Metabolism, University of Sheffield, Sheffield,
28 UK; ¹⁴Department of Endocrinology, Royal Hallamshire Hospital, Sheffield Teaching Hospitals NHS

29 Foundation Trust, Sheffield, UK; ¹⁵Department of Endocrinology, Christie Hospital NHS Foundation
30 Trust, Manchester, UK; ¹⁶University of Manchester, Manchester Academic Health Science Centre,
31 Manchester, UK; ¹⁷Department of Endocrinology, University College London Hospitals NHS
32 Foundation Trust, London, UK; ¹⁸Department of Endocrinology, Leicester Royal Infirmary,
33 University Hospitals of Leicester NHS Trust, Leicester, UK.

34

35 **Corresponding author:**

36 Dr. Niki Karavitaki, MSc, PhD, FRCP

37 Institute of Metabolism and Systems Research, College of Medical and Dental Sciences, University of

38 Birmingham, IBR Tower, Level 2, Birmingham, B15 2TT, UK

39 Tel.: 0121 414 3826

40 Fax: 0121 415 8712 17

41 E-mail: n.karavitaki@bham.ac.uk

42

43 **Short title**

44 Outcomes of Nelson's after primary treatment

45

46 **Keywords**

47 Nelson's syndrome, Cushing's, bilateral adrenalectomy, tumor progression

48

49 **Funding**

50 This study was supported by the Clinical Endocrinology Trust, UK

51

52 **Disclosure statement**

53 RDM has research grants from Pfizer, Ipsen, and Sandoz. JNP has research and consultancy income

54 to the University of Sheffield from Novartis, Ipsen, HRA Pharma, Diurnal and Ono Pharma. SEB has

55 research grants and speaker's fees to UCLH from Novo Nordisk, Pfizer and Ipsen. NK declares

56 educational and research grants from Novartis and Pfizer. All other authors have nothing to declare.

57 **Abstract**

58 **Context:** Long-term outcomes of patients with Nelson's syndrome (NS) have been poorly explored,
59 especially in the modern era.

60 **Objective:** To elucidate tumor control rates, effectiveness of various treatments and markers of
61 prognostic relevance in patients with NS.

62 **Patients, design, and setting:** Retrospective cohort study of 68 patients from 13 UK pituitary centers
63 with median imaging follow-up of 13 years (range 1-45) since NS diagnosis.

64 **Results:** Management of Cushing's disease (CD) prior to NS diagnosis included
65 surgery+adrenalectomy (n=30, eight patients had two and one had three pituitary operations),
66 surgery+radiotherapy+adrenalectomy (n=17, two received >1 courses of irradiation, two had ≥ 2
67 pituitary surgeries), radiotherapy+adrenalectomy (n=2) and adrenalectomy (n=19). Primary
68 management of NS mainly included surgery, radiotherapy, surgery+radiotherapy and observation; 10-
69 year tumor progression-free survival was 62% (surgery 80%, radiotherapy 52%, surgery+radiotherapy
70 81%, observation 51%). Sex, age at CD or NS diagnosis, size of adenoma (micro-/macroadenoma) at
71 CD diagnosis, presence of pituitary tumor on imaging prior adrenalectomy, mode of NS primary
72 management were not predictors of tumor progression. Mode of management of CD before NS
73 diagnosis was a significant factor predicting progression, with the group treated by
74 surgery+radiotherapy+adrenalectomy for their CD showing the highest risk (HR 4.6; 95% CI, 1.6-
75 13.5). During follow-up, 3% of patients had malignant transformation with spinal metastases and 4%
76 died of aggressively enlarging tumor.

77 **Conclusions:** At 10 years follow-up, 38% of the patients diagnosed with NS showed progression of
78 their corticotroph tumor. Complexity of treatments for the CD prior to NS diagnosis, possibly
79 reflecting corticotroph adenoma aggressiveness, predicts long-term tumor prognosis.

80

81 **Précis**

82 In this multicentre study of patients with Nelson's syndrome, 10-year tumor progression-free survival
83 was 62%. Complexity of treatments for the Cushing's before Nelson's diagnosis predicts prognosis.

84

85 **Introduction**

86

87 Cushing's disease (CD) has a prevalence of 4-6 cases per 100,000 population and an annual incidence
88 of 1-2 per million (1-3). Its first line treatment is trans-sphenoidal adenectomy with remission rates
89 reported between 31% and 100% (4). **Recurrence rates after initial successful surgery range between**
90 **10.6% and 20% during variable follow-up periods (5-8).** Refractory hypercortisolemia from persistent
91 or recurrent CD remains a therapeutic challenge and bilateral adrenalectomy (BLA) is one of the
92 available management options. Despite its effectiveness in achieving immediate biochemical control,
93 the risk for development of Nelson's syndrome (NS) **or, as it has also been proposed as an alternative**
94 **name in the last years, corticotroph tumor progression (9)** is a potential drawback of this approach.

95 Consensus on what defines NS is lacking. The most widely accepted definition includes corticotroph
96 adenoma progression associated with increasing plasma ACTH levels (with or without the presence of
97 pigmentation). It should be noted, however, that in some published series, demonstration of enlarging
98 pituitary adenoma has not been considered as a necessary diagnostic criterion (10-17). The prevalence
99 of NS shows high variation amongst studies influenced by the diagnostic criteria used, the length of
100 follow-up after BLA and possible referral bias of the reporting centers; Ritzel *et al.* in a systematic
101 review of 24 studies including 768 patients found a median prevalence of 21% (range 0-47%) during
102 median follow-up of 61 months (range 29-294) after BLA (18). Management options for NS include
103 observation, surgery, radiation therapy and pharmacotherapy (alone or in combination) (19,20) but in
104 a number of cases, aggressive tumor is associated with a poor prognosis and increased mortality
105 (15,16,21-28).

106 Long-term outcomes of patients with NS, especially in the modern era, have been poorly explored.
107 This is due to the limited number of published series, often from single centres, each with very small
108 number of patients (given the rarity of NS), and commonly with short follow-up (14,23,26,28-38).
109 The interpretation of their results is further complicated by the inclusion in the final analyses of
110 tumors already showing recurrence after the primary management of NS (14,15,21,24,32,39-41), by
111 the lack of information about other previous therapies (21,24,26,30,39,40,42) and by the
112 heterogeneity in the criteria defining successful treatment of NS (14,15,21,23,27,30,34,35).

113 To elucidate the clinical behavior of corticotroph tumors after the diagnosis of NS, we performed a
114 multicenter, retrospective, cohort study in a large series of patients who have undergone long-term
115 follow-up from 13 UK pituitary centers, and assessed, systematically, the effectiveness of various
116 management approaches, rates of tumor control and markers of prognostic relevance.

117

118

119

120

121

122

123

124

125

126

127

128

129

130

131

132

133

134

135

136

137

138

139

140

141 **Patients and Methods**

142

143 *Study design and patients*

144 This was a retrospective cohort study from 13 UK pituitary centers. The records of the patients
145 diagnosed with NS and followed-up in each participating center were reviewed and clinical,
146 laboratory and imaging data, as well as treatment outcomes were recorded. The patients were
147 identified from the databases of each center. The study was retrospective in nature and involved no
148 intervention beyond routine patient care, and data were collected on a dedicated proforma. It was
149 registered with and approved as a clinical audit by the respective Hospitals [Audit reference number
150 in coordinating center (Queen Elizabeth Hospital Birmingham): 14011].

151 For the diagnosis of NS, imaging (evidence of corticotroph adenoma growth or, if previous pituitary
152 imaging negative for tumor, new identification of tumor), biochemical [lack of suppressibility of
153 plasma ACTH (<200 pg/ml) two hours after morning glucocorticoid dose (11,43) and/or gradually
154 increasing morning ACTH levels usually checked at least 20 hours after the last glucocorticoid dose]
155 and clinical criteria (development of skin pigmentation) were used. Given the variability of ACTH
156 assays between centers, the long period covered by the study **and the impact of timing of ACTH**
157 **measurements in relationship with the dose and type of glucocorticoid**, specific plasma ACTH cut-off
158 values were not established and each center used its own protocol for this criterion.

159 Imaging analysis, follow-up and the management of the patients were based on the decisions of the
160 local endocrine, neurosurgical and oncology teams. Progression of underlying corticotroph tumor was
161 diagnosed on the basis of radiological appearances. Follow-up period was defined from the time of
162 NS diagnosis until last pituitary imaging or, for survival estimation, until last clinical review or death.

163

164 *Statistical analyses*

165 Percentages were calculated for categorical data and medians with ranges for continuous variables.
166 Tumor progression-free curves and overall survival curves were generated by the Kaplan-Meier
167 method and the differences between outcomes in the various subgroups by the log-rank test. Cox
168 regression analysis was used to assess the effect of various factors on tumor progression and Hazard

169 Ratios (HR) with 95% confidence intervals (CI) were estimated. There was no significant departure
170 from proportional hazards assumptions for any of the variables. The level of significance was set at
171 $p<0.05$. Statistical analyses were performed by IBM SPSS Statistics for Windows, Version 22.0.
172 Armonk, NY: IBM Corp.

173

174

175

176

177

178

179

180

181

182

183

184

185

186

187

188

189

190

191

192

193

194

195

196

197 **Results**

198

199 *Characteristics of patients with NS*

200 Sixty-eight patients were included. Their characteristics are shown in Table 1. Treatment of CD
201 included a) pituitary surgery and BLA (n=30; eight patients had two and one patient had three
202 pituitary surgeries prior to BLA), b) pituitary surgery and radiotherapy and BLA [n=17; one patient
203 received three courses of radiotherapy (conventional fractionated x1 and stereotactic radiosurgery x2),
204 one patient two courses of radiotherapy (conventional fractionated x1 and gamma knife x1), one
205 patient had two pituitary surgeries before the radiotherapy, one patient had two pituitary surgeries
206 followed by radiotherapy and then two further pituitary surgeries; in two patients radiotherapy was
207 offered shortly after the adrenalectomy], c) radiotherapy and BLA (n=2; in one patient radiotherapy
208 was offered shortly after the adrenalectomy) and d) BLA only (n=19, in 12 of them after 1981, and of
209 these, seven after 1992) [pituitary surgery was not attempted due to lack of adenoma on imaging].

210 **Medical treatment (ketoconazole) had been offered for a short period in one patient.** The median time
211 between first pituitary surgery for CD and BLA was one year (range 3 months-21 years).

212 Steroid replacement after the BLA was mainly with hydrocortisone in total daily dose ranging
213 between 15 and 40 mg [two patients were prescribed prednisolone (total daily dose 5-7.5 mg) and four
214 were prescribed cortisone acetate (total daily dose 37.5 mg)].

215 NS was diagnosed between 1969 and 2018 [after 1990 in 87% (59/68) of the patients]. In 53 patients,
216 the diagnosis was established by imaging combined with biochemical/clinical criteria. In 14 patients,
217 the diagnosis was established by biochemical/clinical criteria [in this group, 12 cases were diagnosed
218 after 1980 and on imaging, presence of pituitary tumor (which had not grown compared with previous
219 scans) was documented in nine]. Specific diagnostic details were not available for one patient. The
220 median time between BLA and NS diagnosis was 3 years (range 3 months-32 years, range between 1st
221 and 3rd quartile 2-11 years).

222 The management of patients after the diagnosis of NS is shown in Table 2 and overall, it included a)
223 pituitary surgery (n=10), b) radiotherapy (n=22; conventional fractionated in 19, Cyber knife in one
224 and gamma knife in two), c) pituitary surgery and radiotherapy (n=18; conventional fractionated in

225 16, gamma knife in two – one of these patients also had a carmustin implant inserted), d) observation
226 (n=16) and e) pasireotide (n=2, under a trial). In five of the cases offered radiotherapy for the NS, a
227 previous course of conventional fractionated irradiation had also been administered for the
228 management of CD prior to NS diagnosis.

229

230 *Outcomes of patients after NS diagnosis*

231 Median follow-up from diagnosis of NS until last imaging was 13 years (range 1-45) (imaging
232 monitoring data were available for 65 patients).

233 Steroid replacement at last assessment was mainly with hydrocortisone in total daily dose ranging
234 between 10 and 30 mg [four patients were on prednisolone (total daily dose 5-7.5 mg)].

235

236 *i) Tumor progression in the whole group of patients with NS*

237 During the follow-up period, 18 patients had further tumor progression associated with increase in
238 their ACTH levels. The 10-year tumor progression-free survival was 62% for the whole group. There
239 was a significant difference in these rates according to type of primary treatment for the NS: 80% for
240 surgery, 52% for radiotherapy alone, 81% for surgery and radiotherapy and 51% for observation
241 ($p=0.029$); in pairwise comparisons, there were significant differences between surgery vs
242 observation, surgery and radiotherapy vs observation, and surgery and radiotherapy vs radiotherapy
243 ($p<0.05$), whereas for surgery vs radiotherapy alone, significance was borderline ($p=0.054$). Details
244 on tumor progression-free survival are shown in Figure 1 and Table 3. **Analysis of the group of**
245 **patients diagnosed with NS after 1990 showed 10-year progression-free survival 57% (71% for**
246 **surgery, 46% for radiotherapy alone, 76% for surgery and radiotherapy and 46% for observation;**
247 **$p=0.057$).**

248

249 *ii) Tumor progression in the group with NS diagnosis based on imaging combined with* 250 *biochemical/clinical criteria*

251 In this group, the 10-year tumor progression-free survival was 65%, but there was no significant
252 difference in rates according to type of primary treatment for the NS: 78% for those treated with

253 surgery, 38% for radiotherapy, 85% for surgery and radiotherapy and 72% for observation ($p=0.079$).

254 Details on tumor progression-free survival are shown in Figure 2 and Table 3.

255 The patient offered pasireotide as primary treatment, received this for 12 months and during this
256 period, tumor stability was reported. Two years later, a 6 months course of temozolomide was given
257 due to increasing ACTH levels (not associated with tumor enlargement). This led to reduction in
258 ACTH concentrations and tumor size, with no evidence of tumor progression after two years further
259 follow-up.

260

261 *iii) Tumor progression in the group with NS diagnosis based on biochemical/clinical criteria*

262 In this group, the 10-year progression-free survival was 50% (Table 3). The small number of cases in
263 each management subgroup did not allow further analyses.

264 The patient on pasireotide had a short course of this treatment, which was stopped due to development
265 of diabetes mellitus; five years later, the tumor remained stable.

266

267 *iv) Predictors of tumor progression after the primary management of NS*

268 Cox regression analysis showed that sex, age at CD or NS diagnosis, size of adenoma (micro-
269 /macroadenoma) at CD diagnosis, presence of pituitary tumor on imaging prior to adrenalectomy,
270 interval between adrenalectomy and diagnosis of NS (<3 or ≥ 3 years, based on our median interval for
271 NS diagnosis), mode of primary management for NS and the diagnostic criteria for NS (imaging
272 combined with biochemical/clinical or only biochemical/clinical criteria) were not predictors of tumor
273 progression. Mode of management of CD before the diagnosis of NS was a significant factor
274 predicting tumor progression with the group treated by surgery and radiotherapy and BLA showing
275 the highest risk (HR 4.6; 95% CI, 1.6-13.5) (Table 4). This finding remained even after adjusting for
276 mode of primary management for the NS. These results did not change after analyzing the data of the
277 group diagnosed by imaging combined with biochemical/clinical criteria (Table 4) **or of the group**
278 **diagnosed with NS after 1990.**

279

280 *v) Outcomes of patients with tumor progression after primary management of NS*

281 The 18 patients with further tumor growth were offered various therapies which are shown along with
282 outcomes until last follow-up in Table 5. Amongst them, at last assessment, only one had ACTH
283 levels within the reference range. Three patients showed further tumor growth and two had malignant
284 transformation of their tumor (with spinal metastases) (7 and 14 years after the diagnosis of NS).

285

286 *vi) Mortality*

287 Median follow-up from diagnosis of CD until last review or, if the patient died, until date of death
288 was 26 years (range 5-60) and from diagnosis of NS until last review or, if the patient died, until date
289 of death was 16 years (range 0.5-48).

290 During the follow-up period, 13 patients died; in three of them, death was due to causes directly
291 related to the NS (all had an enlarging mass extending in the brain and in one of them there were also
292 spinal metastases) at the age of 73, 45 and 60 years.

293 The 5- and 10-year overall survival rates since NS diagnosis were 81% and 69%, respectively.

294

295

296

297

298

299

300

301

302

303

304

305

306

307

308

309 **Discussion**

310

311 This is the largest study to date reviewing outcomes of patients with NS with prolonged follow-up.
312 We found that the 10-year tumor progression-free survival was 62% and that surgery with or without
313 adjuvant radiotherapy offered as primary treatment for the Nelson's had tumor control rates 81% and
314 80%, respectively. Amongst a number of factors assessed, complexity of CD treatment prior to the
315 diagnosis of NS was the only significant predictor of tumor progression. The management of the
316 patients with tumor progression was variable and, in this group, five developed metastatic disease or
317 further tumor growth [28% (5/18) - 8% of the total series with imaging follow-up].

318 Studies assessing outcomes of patients with NS managed primarily by surgery combined or not with
319 radiotherapy are extremely limited and of small sample size (usually <5 cases) (9,22,28,33,34,37,44).
320 Xing *et al.*, in a series of 23 patients treated with surgery between 1980 and 1999 and followed for a
321 mean period of 3.6 years, found further tumor growth in 17.4% (31). Similar results were reported by
322 Zielinski *et al.*, in 10 patients offered surgery between 2000 and 2005; tumor progression was found
323 in 20% of the cases during mean follow-up of 45.3 months (23). The short monitoring interval is a
324 limitation of both reports. In another series by Kelly *et al.* of 13 patients, managed between 1978 and
325 1993 and followed-up for a median period of 17 years, tumor growth was reported in 14.3% (1/7) of
326 those managed by surgery and radiotherapy (15). Less optimal outcomes have been reported by
327 Kemink *et al.* in 15 cases diagnosed with NS between 1969 and 1998; further tumor progression was
328 found in 3 out of 6 patients (50%) who had surgery as primary treatment for the NS during median
329 follow-up of only 2.2 years (27).

330 In our study, tumor progression-free survival was only 52% when radiotherapy was administered as
331 primary treatment for the NS. Notably, 4 out of 22 patients in this group had already received a course
332 of conventional fractionated irradiation for the management of their CD, possibly reflecting a more
333 aggressive corticotroph tumor behavior. This group may also represent selected cases not amenable to
334 surgical management due to tumor location and this needs to be taken into account when interpreting
335 the results. Previous literature assessing the impact of this approach as primary treatment for the NS is
336 scarce, as most relevant studies include cases with already recurrent NS in their analyses

337 (21,26,39,42). Further tumor growth was reported in 16.7% (2/12) and in 0% (0/5) of patients with NS
338 treated primarily with stereotactic radiosurgery by Graffeo *et al.* (follow-up duration not available)
339 and Vik-Mo *et al.* (median follow-up 9.4 years), respectively (22,42). Selection bias and small sample
340 size challenge the practical significance of these studies. Interestingly, Assie *et al.* (9), in a series of
341 21 patients with corticotroph adenoma progression after BLA, showed that at least in the first years
342 after BLA, in most cases, tumor growth had no clinically detectable sequelae and was treatable (by
343 surgery and/or radiotherapy). This series included a selected group of patients, as those offered
344 pituitary irradiation prior to BLA had been excluded. Furthermore, the tumor progression was
345 detected at an early stage (81% presenting as microadenomas) due to close monitoring protocols after
346 the adrenalectomy.

347 Surveillance is an approach usually considered for patients with NS and small tumors not causing
348 mass effects to vital surrounding structures. In our series, observation was associated with a 51%
349 tumor progression-free survival at 10 years and in most of these cases, active treatment (surgery,
350 radiotherapy, medical therapy or combination of these) was subsequently offered. High rates of tumor
351 progression have been reported by Kemink *et al.*; this was 87.5% (7/8) for patients managed
352 conservatively and followed-up for a median period of 2.5 years (27). In six of these cases, surgery or
353 radiotherapy was offered, whereas in the seventh one, massive pituitary hemorrhage occurred five
354 years after diagnosis of NS.

355 Since the first description of NS, there has been heterogeneity in its diagnostic criteria and a formal
356 consensus is still not available (43). Currently, the most widely accepted strategy involves
357 demonstration of corticotroph adenoma progression. Nonetheless, rising ACTH levels, even in the
358 absence of obvious tumor enlargement, may lead to the development of adrenal rest tumors and cause
359 significant negative psychological effects due to pigmentation, and as such need to be considered as a
360 criterion in the diagnosis of NS (45-49). In 79% of our cases, diagnosis was established by imaging
361 combined with biochemical/clinical criteria. Analysis of the outcomes specifically for this group
362 showed 10-year tumor progression-free survival of 65% with no significant difference between the
363 various primary treatments for the NS ($p=0.079$), possibly due to the small sample size. In 21% of the
364 cases, biochemical/clinical criteria had been applied by the treating clinicians and notably, in 9 out of

365 12 patients, a corticotroph tumor was already present on imaging. Various management approaches
366 had been used and the 10-year corticotroph tumor progression-free probability was 50%. The limited
367 number of cases did not allow further analyses according to type of NS management in this subgroup.
368 The pathophysiological mechanisms leading to NS are not completely understood. Tumor progression
369 driven by the reduced negative glucocorticoid feedback on CRH production after the BLA or
370 reflection of the natural history of a tumor programmed to behave aggressively from the outset are
371 suggested hypotheses (20). Given that not all patients will develop NS after BLA, tumors showing
372 progression are most likely a subset with an aggressive phenotype (43). Notably, it has been suggested
373 that *USP8* mutations do not drive corticotroph adenoma progression that leads to NS (50). Data on
374 factors predicting further tumor growth after the primary management of NS have not been previously
375 published. In our study, amongst a number of parameters assessed, only mode of management of the
376 CD prior to NS diagnosis was a significant predictive factor. Interestingly, the hazard ratio for those
377 treated by pituitary surgery and radiotherapy and BLA was 4.6 ($p=0.006$); this group had received
378 multiple treatments for their CD and the possibility that the complexity in their management reflects
379 corticotroph adenoma aggressiveness from the outset cannot be excluded.

380 Recurrent NS represents a challenging clinical scenario; management remains individualised and due
381 to the scarce relevant literature it is not evidence-based. Studies focusing on long-term outcomes after
382 surgery alone are not available. Gamma knife radiosurgery halted tumor progression in four NS
383 patients with recurrent corticotroph tumor during median follow-up of 3.85 years (42). In our series, a
384 number of approaches (including surgery, radiotherapy, pasireotide, chemotherapy, temozolomide and
385 monitoring, alone or in combination) were employed with varied success. Three patients showed
386 further tumor growth, while two (3% of those with imaging follow-up data) had malignant
387 transformation (7 and 14 years after the diagnosis of NS). Notably, the overall reported rate of
388 pituitary carcinomas is only 0.1-0.2% of all pituitary tumors (51). Cases of aggressive or malignant
389 tumor behavior have been previously reported and can be associated with high mortality (15,16,21-
390 28). Overall, 4.4% (3/68) of our patients died due to NS-related causes. Our understanding of the
391 relevant pathogenetic mechanisms is still limited and, unfortunately, identification of tumors at risk
392 for progression to carcinoma remains difficult (51).

393 Data on the effectiveness of pharmacotherapy with sodium valproate, octreotide, dopamine agonists,
394 cyproheptadine and peroxisome proliferator-activated receptor γ agonists in NS are limited and
395 inconclusive or not optimal (19,20,52). More recently, pasireotide has been shown to reduce ACTH
396 levels in NS but its effects on tumor volume have not been clearly established (53,54). Furthermore,
397 biochemical and radiological improvement has been reported in some (55,56), but not all (57)
398 published cases of aggressive tumors treated with temozolomide. In our series, pasireotide and
399 temozolomide had been used on an individual basis and robust conclusions on their effectiveness in
400 NS resistant to other treatments are not possible. Nonetheless, based on the European Society of
401 Endocrinology Clinical Practice Guidelines, temozolomide is recommended in the treatment of
402 aggressive pituitary tumors and carcinomas and needs to be considered in cases of aggressive
403 Nelson's tumors (58).

404 The strengths of our study are the large number of patients (with the vast majority diagnosed in the
405 MRI era allowing earlier NS detection) and the systematic assessment of tumor behavior during a
406 long follow-up period. Limitations include its retrospective design (although prospective studies on
407 this topic may not be practically feasible) and the potential selection bias in the management
408 approaches offered, as these were tailored to the individual patient rather than based on an established
409 algorithm.

410 In conclusion, our multicenter study provides systematic data on long-term tumor behavior in the
411 context of NS. Tumor progression was diagnosed in 38% of the cases at 10 years follow-up. Surgery
412 +/- radiotherapy after the NS diagnosis show 10-year progression-free survival rates between 80 and
413 81%. Complexity of previous treatments for the CD prior to NS diagnosis, possibly reflecting
414 corticotroph adenoma aggressiveness, predicts tumor prognosis after the diagnosis of NS. Malignant
415 transformation was diagnosed in 3% of our patients, as opposed to the 0.1-0.2% reported rate of
416 carcinoma in all pituitary adenomas highlighting the potential distinct position of NS in the landscape
417 of pituitary tumors. **Based on our results, detection of corticotroph tumor progression is an important
418 element in the diagnosis of the syndrome. Nonetheless, biochemical criteria (lack of suppressibility of
419 plasma ACTH two hours after morning glucocorticoid dose and/or gradually increasing morning
420 ACTH levels usually checked at least 20 hours after the last glucocorticoid dose) without**

421 identification of tumor enlargement on imaging need to be also considered in the diagnostic approach
422 of this condition, as in this particular group, tumor progression was detected in 36% and 50% of the
423 cases at 5 and at 10 years follow-up, respectively. Furthermore, based on our series, active
424 management with surgery combined or not with radiotherapy is a suggested management approach as
425 it is associated with more optimal outcomes in terms of tumor control. This is particularly relevant for
426 cases requiring complex treatments for the CD prior to the diagnosis of NS. Small tumors not causing
427 mass effects to surrounding structures could be managed by surveillance and in a number of cases,
428 active treatment will be later necessary. Due to its rarity, predictors for malignant transformation
429 guiding therapeutic algorithms has not been possible. Further studies elucidating the pathophysiology
430 and molecular predictive factors for corticotroph tumor progression after BLA will open avenues for
431 improvements in the management and prognosis of these patients.

432

433 **Acknowledgments**

434 We are grateful to all health care professionals involved in the care of the patients.

435

436 **References**

- 437 1. Agustsson TT, Baldvinsdottir T, Jonasson JG, Olafsdottir E, Steinthorsdottir V, Sigurdsson G,
438 Thorsson AV, Carroll PV, Korbonits M, Benediktsson R. The epidemiology of pituitary
439 adenomas in Iceland, 1955-2012: a nationwide population-based study. *Eur J Endocrinol.*
440 2015;173(5):655-664.
- 441 2. Lindholm J, Juul S, Jorgensen JO, Astrup J, Bjerre P, Feldt-Rasmussen U, Hagen C,
442 Jorgensen J, Kosteljanetz M, Kristensen L, Laurberg P, Schmidt K, Weeke J. Incidence and
443 late prognosis of cushing's syndrome: a population-based study. *J Clin Endocrinol Metab.*
444 2001;86(1):117-123.
- 445 3. Etxabe J, Vazquez JA. Morbidity and mortality in Cushing's disease: an epidemiological
446 approach. *Clin Endocrinol (Oxf).* 1994;40(4):479-484.
- 447 4. Pivonello R, De Leo M, Cozzolino A, Colao A. The Treatment of Cushing's Disease. *Endocr*
448 *Rev.* 2015;36(4):385-486.

- 449 5. Hofmann BM, Hlavac M, Martinez R, Buchfelder M, Muller OA, Fahlbusch R. Long-term
450 results after microsurgery for Cushing disease: experience with 426 primary operations over
451 35 years. *J Neurosurg.* 2008;108(1):9-18.
- 452 6. Lambert JK, Goldberg L, Fayngold S, Kostadinov J, Post KD, Geer EB. Predictors of
453 mortality and long-term outcomes in treated Cushing's disease: a study of 346 patients. *J Clin*
454 *Endocrinol Metab.* 2013;98(3):1022-1030.
- 455 7. Ntali G, Asimakopoulou A, Siamatras T, Komninos J, Vassiliadi D, Tzanela M, Tsagarakis S,
456 Grossman AB, Wass JA, Karavitaki N. Mortality in Cushing's syndrome: systematic analysis
457 of a large series with prolonged follow-up. *Eur J Endocrinol.* 2013;169(5):715-723.
- 458 8. Salenave S, Gatta B, Pecheur S, San-Galli F, Visot A, Lasjaunias P, Roger P, Berge J, Young
459 J, Tabarin A, Chanson P. Pituitary magnetic resonance imaging findings do not influence
460 surgical outcome in adrenocorticotropin-secreting microadenomas. *J Clin Endocrinol Metab.*
461 2004;89(7):3371-3376.
- 462 9. Assie G, Bahurel H, Coste J, Silvera S, Kujas M, Dugue MA, Karray F, Dousset B, Bertherat
463 J, Legmann P, Bertagna X. Corticotroph tumor progression after adrenalectomy in Cushing's
464 Disease: A reappraisal of Nelson's Syndrome. *J Clin Endocrinol Metab.* 2007;92(1):172-179.
- 465 10. Ding XF, Li HZ, Yan WG, Gao Y, Li XQ. Role of adrenalectomy in recurrent Cushing's
466 disease. *Chin Med J (Engl).* 2010;123(13):1658-1662.
- 467 11. Jenkins PJ, Trainer PJ, Plowman PN, Shand WS, Grossman AB, Wass JA, Besser GM. The
468 long-term outcome after adrenalectomy and prophylactic pituitary radiotherapy in
469 adrenocorticotropin-dependent Cushing's syndrome. *J Clin Endocrinol Metab.*
470 1995;80(1):165-171.
- 471 12. Littley MD, Shalet SM, Beardwell CG, Ahmed SR, Sutton ML. Long-term follow-up of low-
472 dose external pituitary irradiation for Cushing's disease. *Clin Endocrinol (Oxf).*
473 1990;33(4):445-455.
- 474 13. Smith PW, Turza KC, Carter CO, Vance ML, Laws ER, Hanks JB. Bilateral adrenalectomy
475 for refractory Cushing disease: a safe and definitive therapy. *J Am Coll Surg.*
476 2009;208(6):1059-1064.

- 477 14. De Tommasi C, Vance ML, Okonkwo DO, Diallo A, Laws ER, Jr. Surgical management of
478 adrenocorticotrophic hormone-secreting macroadenomas: outcome and challenges in patients
479 with Cushing's disease or Nelson's syndrome. *J Neurosurg.* 2005;103(5):825-830.
- 480 15. Kelly PA, Samandouras G, Grossman AB, Afshar F, Besser GM, Jenkins PJ. Neurosurgical
481 treatment of Nelson's syndrome. *J Clin Endocrinol Metab.* 2002;87(12):5465-5469.
- 482 16. Howlett TA, Plowman PN, Wass JA, Rees LH, Jones AE, Besser GM. Megavoltage pituitary
483 irradiation in the management of Cushing's disease and Nelson's syndrome: long-term follow-
484 up. *Clin Endocrinol (Oxf).* 1989;31(3):309-323.
- 485 17. Lawrence JH, Linfoot JA. Treatment of acromegaly, Cushing disease and Nelson syndrome.
486 *West J Med.* 1980;133(3):197-202.
- 487 18. Ritzel K, Beuschlein F, Mickisch A, Osswald A, Schneider HJ, Schopohl J, Reincke M.
488 Clinical review: Outcome of bilateral adrenalectomy in Cushing's syndrome: a systematic
489 review. *J Clin Endocrinol Metab.* 2013;98(10):3939-3948.
- 490 19. Patel J, Eloy JA, Liu JK. Nelson's syndrome: a review of the clinical manifestations,
491 pathophysiology, and treatment strategies. *Neurosurg Focus.* 2015;38(2):E14.
- 492 20. Barber TM, Adams E, Ansorge O, Byrne JV, Karavitaki N, Wass JA. Nelson's syndrome. *Eur*
493 *J Endocrinol.* 2010;163(4):495-507.
- 494 21. Caruso JP, Patibandla MR, Xu Z, Vance ML, Sheehan JP. A Long-Term Study of the
495 Treatment of Nelson's Syndrome With Gamma Knife Radiosurgery. *Neurosurgery.*
496 2018;83(3):430-436.
- 497 22. Graffeo CS, Perry A, Carlstrom LP, Meyer FB, Atkinson JLD, Erickson D, Nippoldt TB,
498 Young WF, Pollock BE, Van Gompel JJ. Characterizing and predicting the Nelson-Salassa
499 syndrome. *J Neurosurg.* 2017;127(6):1277-1287.
- 500 23. Zielinski G, Witek P, Maksymowicz M. Outcomes in pituitary surgery in Nelson's syndrome-
501 -therapeutic pitfalls. *Endokrynol Pol.* 2015;66(6):504-513.
- 502 24. Wilson PJ, Williams JR, Smee RI. Nelson's syndrome: single centre experience using the
503 linear accelerator (LINAC) for stereotactic radiosurgery and fractionated stereotactic
504 radiotherapy. *J Clin Neurosci.* 2014;21(9):1520-1524.

- 505 25. Kasperlik-Zaluska AA, Bonicki W, Jeske W, Janik J, Zgliczynski W, Czernicki Z. Nelson's
506 syndrome -- 46 years later: clinical experience with 37 patients. *Zentralbl Neurochir.*
507 2006;67(1):14-20.
- 508 26. Pollock BE, Young WF, Jr. Stereotactic radiosurgery for patients with ACTH-producing
509 pituitary adenomas after prior adrenalectomy. *Int J Radiat Oncol Biol Phys.* 2002;54(3):839-
510 841.
- 511 27. Kemink SA, Grotenhuis JA, De Vries J, Pieters GF, Hermus AR, Smals AG. Management of
512 Nelson's syndrome: observations in fifteen patients. *Clin Endocrinol (Oxf).* 2001;54(1):45-52.
- 513 28. Jordan RM, Cook DM, Kendall JW, Kerber CW. Nelson's syndrome and spontaneous
514 pituitary tumor infarction. *Arch Intern Med.* 1979;139(3):340-342.
- 515 29. Espinosa-de-Los-Monteros AL, Sosa-Eroza E, Espinosa E, Mendoza V, Arreola R, Mercado
516 M. LONG-TERM OUTCOME OF THE DIFFERENT TREATMENT ALTERNATIVES
517 FOR RECURRENT AND PERSISTENT CUSHING DISEASE. *Endocr Pract.*
518 2017;23(7):759-767.
- 519 30. Wattson DA, Tanguturi SK, Spiegel DY, Niemierko A, Biller BM, Nachtigall LB, Bussiere
520 MR, Swearingen B, Chapman PH, Loeffler JS, Shih HA. Outcomes of proton therapy for
521 patients with functional pituitary adenomas. *Int J Radiat Oncol Biol Phys.* 2014;90(3):532-
522 539.
- 523 31. Xing B, Ren Z, Su C, Wang R, Yang Y, Hu Y. Microsurgical treatment of Nelson's
524 syndrome. *Chin Med J (Engl).* 2002;115(8):1150-1152.
- 525 32. Ganz JC, Backlund EO, Thorsen FA. The effects of Gamma Knife surgery of pituitary
526 adenomas on tumor growth and endocrinopathies. *Stereotact Funct Neurosurg.* 1993;61
527 Suppl 1:30-37.
- 528 33. Tran LM, Blount L, Horton D, Sadeghi A, Parker RG. Radiation therapy of pituitary tumors:
529 results in 95 cases. *Am J Clin Oncol.* 1991;14(1):25-29.
- 530 34. Burke CW, Adams CB, Esiri MM, Morris C, Bevan JS. Transsphenoidal surgery for
531 Cushing's disease: does what is removed determine the endocrine outcome? *Clin Endocrinol*
532 *(Oxf).* 1990;33(4):525-537.

- 533 35. Grigsby PW, Stokes S, Marks JE, Simpson JR. Prognostic factors and results of radiotherapy
534 alone in the management of pituitary adenomas. *Int J Radiat Oncol Biol Phys.*
535 1988;15(5):1103-1110.
- 536 36. Thomas CG, Jr., Smith AT, Griffith JM, Askin FB. Hyperadrenalism in childhood and
537 adolescence. *Ann Surg.* 1984;199(5):538-548.
- 538 37. Urbanic RC, George JM. Cushing's disease--18 years' experience. *Medicine (Baltimore).*
539 1981;60(1):14-24.
- 540 38. Cassar J, Doyle FH, Lewis PD, Mashiter K, Noorden S, Joplin GF. Treatment of Nelson's
541 syndrome by pituitary implantation of yttrium-90 or gold-198. *Br Med J.* 1976;2(6030):269-
542 272.
- 543 39. Marek J, Jezkova J, Hana V, Krsek M, Liscak R, Vladyka V, Pecen L. Gamma knife
544 radiosurgery for Cushing's disease and Nelson's syndrome. *Pituitary.* 2015;18(3):376-384.
- 545 40. Levy RP, Fabrikant JI, Frankel KA, Phillips MH, Lyman JT, Lawrence JH, Tobias CA.
546 Heavy-charged-particle radiosurgery of the pituitary gland: clinical results of 840 patients.
547 *Stereotact Funct Neurosurg.* 1991;57(1-2):22-35.
- 548 41. Ludecke DK, Breustedt HJ, Bramswig J, Kobberling J, Saeger W. Evaluation of surgically
549 treated Nelson's syndrome. *Acta Neurochir (Wien).* 1982;65(1-2):3-13.
- 550 42. Vik-Mo EO, Oksnes M, Pedersen PH, Wentzel-Larsen T, Rodahl E, Thorsen F, Schreiner T,
551 Aanderud S, Lund-Johansen M. Gamma knife stereotactic radiosurgery of Nelson syndrome.
552 *Eur J Endocrinol.* 2009;160(2):143-148.
- 553 43. Munir A, Newell-Price J. Nelson's Syndrome. *Arq Bras Endocrinol Metabol.*
554 2007;51(8):1392-1396.
- 555 44. Gil-Cardenas A, Herrera MF, Diaz-Polanco A, Rios JM, Pantoja JP. Nelson's syndrome after
556 bilateral adrenalectomy for Cushing's disease. *Surgery.* 2007;141(2):147-151; discussion 151-
557 142.
- 558 45. Shekarriz M, Schneider C, Sabanegh E, Kempter F, Waldherr R. Excessive testosterone
559 production in a patient with Nelson syndrome and bilateral testicular tumors. *Urol Int.*
560 1996;56(3):200-203.

- 561 46. Ntalles K, Kostoglou-Athanassiou I, Georgiou E, Ikkos D. Paratesticular tumours in a patient
562 with Nelson's syndrome. *Horm Res.* 1996;45(6):291-294.
- 563 47. Verdonk C, Guerin C, Lufkin E, Hodgson SF. Activation of virilizing adrenal rest tissues by
564 excessive ACTH production. An unusual presentation of Nelson's syndrome. *Am J Med.*
565 1982;73(3):455-459.
- 566 48. Johnson RE, Scheithauer B. Massive hyperplasia of testicular adrenal rests in a patient with
567 Nelson's syndrome. *Am J Clin Pathol.* 1982;77(4):501-507.
- 568 49. Baranetsky NG, Zipser RD, Goebelsmann U, Kurman RJ, March CM, Morimoto I, Stanczyk
569 FZ. Adrenocorticotropin-dependent virilizing paraovarian tumors in Nelson's syndrome. *J*
570 *Clin Endocrinol Metab.* 1979;49(3):381-386.
- 571 50. Perez-Rivas LG, Theodoropoulou M, Puar TH, Fazel J, Stieg MR, Ferrau F, Assie G, Gadelha
572 MR, Deutschbein T, Fragoso MC, Kusters B, Saeger W, Honegger J, Buchfelder M,
573 Korbonits M, Bertherat J, Stalla GK, Hermus AR, Beuschlein F, Reincke M. Somatic USP8
574 mutations are frequent events in corticotroph tumor progression causing Nelson's tumor. *Eur*
575 *J Endocrinol.* 2018;178(1):59-65.
- 576 51. Yoo F, Kuan EC, Heaney AP, Bergsneider M, Wang MB. Corticotrophic pituitary carcinoma
577 with cervical metastases: case series and literature review. *Pituitary.* 2018;21(3):290-301.
- 578 52. Munir A, Song F, Ince P, Walters SJ, Ross R, Newell-Price J. Ineffectiveness of rosiglitazone
579 therapy in Nelson's syndrome. *J Clin Endocrinol Metab.* 2007;92(5):1758-1763.
- 580 53. Daniel E, Debono M, Caunt S, Girio-Fragkoulakis C, Walters SJ, Akker SA, Grossman AB,
581 Trainer PJ, Newell-Price J. A prospective longitudinal study of Pasireotide in Nelson's
582 syndrome. *Pituitary.* 2018;21(3):247-255.
- 583 54. Katznelson L. Sustained improvements in plasma ACTH and clinical status in a patient with
584 Nelson's syndrome treated with pasireotide LAR, a multireceptor somatostatin analog. *J Clin*
585 *Endocrinol Metab.* 2013;98(5):1803-1807.
- 586 55. Kurowska M, Nowakowski A, Zielinski G, Malicka J, Tarach JS, Maksymowicz M, Denew
587 P. Temozolomide-Induced Shrinkage of Invasive Pituitary Adenoma in Patient with Nelson's

588 Syndrome: A Case Report and Review of the Literature. *Case Rep Endocrinol.*
589 2015;2015:623092.

590 56. Moyes VJ, Alusi G, Sabin HI, Evanson J, Berney DM, Kovacs K, Monson JP, Plowman PN,
591 Drake WM. Treatment of Nelson's syndrome with temozolomide. *Eur J Endocrinol.*
592 2009;160(1):115-119.

593 57. Bruno OD, Juarez-Allen L, Christiansen SB, Manavela M, Danilowicz K, Vigovich C,
594 Gomez RM. Temozolomide Therapy for Aggressive Pituitary Tumors: Results in a Small
595 Series of Patients from Argentina. *Int J Endocrinol.* 2015;2015:587893.

596 58. Raverot G, Burman P, McCormack A, Heaney A, Petersenn S, Popovic V, Trouillas J,
597 Dekkers OM. European Society of Endocrinology Clinical Practice Guidelines for the
598 management of aggressive pituitary tumours and carcinomas. *Eur J Endocrinol.*
599 2018;178(1):G1-g24.

600
601
602
603
604
605
606
607
608
609
610
611
612
613
614
615

616

617 **Legends for figures and tables**

618

619 **Table 1.** Characteristics of patients with Nelson’s syndrome.

620

621 **Table 2.** Primary management of Nelson’s syndrome.

622

623 **Table 3.** Tumor progression-free survival after Nelson’s syndrome diagnosis.

624

625 **Table 4.** Hazard ratios of Nelson’s tumor progression after its primary treatment estimated according
626 to mode of management of Cushing’s disease using the Cox regression model.

627

628 **Table 5.** Management and outcomes of patients with further corticotroph tumor progression after the
629 primary management of Nelson’s syndrome.

630

631 **Figure 1.** (a) Tumor progression-free survival for the total group of patients with Nelson’s syndrome,
632 (b) Tumor progression-free survival according to management approach for the Nelson’s syndrome.

633

634 **Figure 2.** Cases with Nelson’s syndrome diagnosis based on imaging combined with
635 biochemical/clinical criteria: (a) Tumor progression-free survival for the total group of patients with
636 Nelson’s syndrome, (b) Tumor progression-free survival according to management approach for the
637 Nelson’s syndrome.

638

639

640

641

642

643

644

645 **Table 1.**

Total number	68
Sex	
Males/females	10/58
Age at diagnosis of Cushing’s disease	
Median (range) (years)	30 (11-69)
Size of adenoma at diagnosis of Cushing’s disease	
Microadenoma	37
Macroadenoma	8
No information	23*
Management of Cushing’s disease	
Pituitary surgery and adrenalectomy	30
Pituitary surgery and radiotherapy and adrenalectomy	17
Radiotherapy and adrenalectomy	2
Adrenalectomy	19
Presence of pituitary tumor on imaging prior to adrenalectomy	
Yes	23 (MRI 19, CT 4)
No	20 (MRI 15, CT 5)
No information	25**
Median age at diagnosis of Nelson’s syndrome	
Median (range) (years)	42 (13-73)

646 MRI: Magnetic resonance imaging; CT: computed tomography

647 * In 17/23 patients, Cushing’s disease was diagnosed before 1990.

648 **In 20/25 patients, adrenalectomy took place before 1990.

649

650

651

652

653

654

655

656

657 **Table 2.**

All patients	
Pituitary surgery	10
Radiotherapy*	22
Pituitary surgery and radiotherapy**	18
Observation	16
Pasireotide	2
Patients diagnosed based on positive imaging combined with biochemical/clinical criteria	
Pituitary surgery	9
Radiotherapy*	16
Pituitary surgery and radiotherapy**	16
Observation	11
Pasireotide	1
Patients diagnosed based on biochemical/clinical criteria	
Pituitary surgery	1
Radiotherapy	5
Pituitary surgery and radiotherapy	2
Observation	5
Pasireotide	1
Patient with no available diagnostic criteria	
Radiotherapy	1

658 *Four patients had a previous course of conventional fractionated radiotherapy for the management of
659 Cushing’s disease.

660 **One patient had a previous course of conventional fractionated radiotherapy for the management of
661 Cushing’s disease.

662

663

664

665

666

667

668

669 **Table 3.**

Groups of patients	<i>Tumor progression-free survival</i>			
	5 years	10 years	15 years	<i>p</i> value
All patients				
Total group (n=63)	77%	62%	49%	
Pituitary surgery (n=10)	80%	80%	80%	0.029
Radiotherapy (n=21)	80%	52%	35%	
Pituitary surgery and radiotherapy (n=17)	87%	81%	73%	
Observation (n=15)	70%	51%	31%	
Nelson's syndrome diagnosis based on positive imaging combined with biochemical/clinical criteria				
Total group (n=49)	80%	65%	53%	
Pituitary surgery (n=9)	78%	78%	78%	0.079
Radiotherapy (n=15)	71%	38%	28%	
Pituitary surgery and radiotherapy (n=15)	92%	85%	75%	
Observation (n=10)	90%	72%	36%	
Nelson's syndrome diagnosis based on biochemical/clinical criteria				
Total group (n=14)	64%	50%	43%	

670

671 **Two patients offered pasireotide for the management of Nelson's syndrome have been excluded from**
672 **the Kaplan Meier analyses.**

673

674

675

676

677
678
679

Table 4.

Mode of treatment of Cushing's disease	HR (95% CI)	<i>p</i> value
Total Group		
Pituitary surgery and adrenalectomy (reference)		
Radiotherapy and adrenalectomy	0.848 (0.098-7.319)	0.881
Pituitary surgery and radiotherapy and adrenalectomy	4.573 (1.554-13.450)	0.006
Adrenalectomy	0.251 (0.048-1.312)	0.102
Group of those diagnosed with positive imaging combined with biochemical/clinical criteria		
Pituitary surgery and adrenalectomy (reference)		
Radiotherapy and adrenalectomy	0.502 (0.058-4.344)	0.532
Pituitary surgery and radiotherapy and adrenalectomy	3.881 (1.331-11.321)	0.013
Adrenalectomy	0.264 (0.053-1.315)	0.104

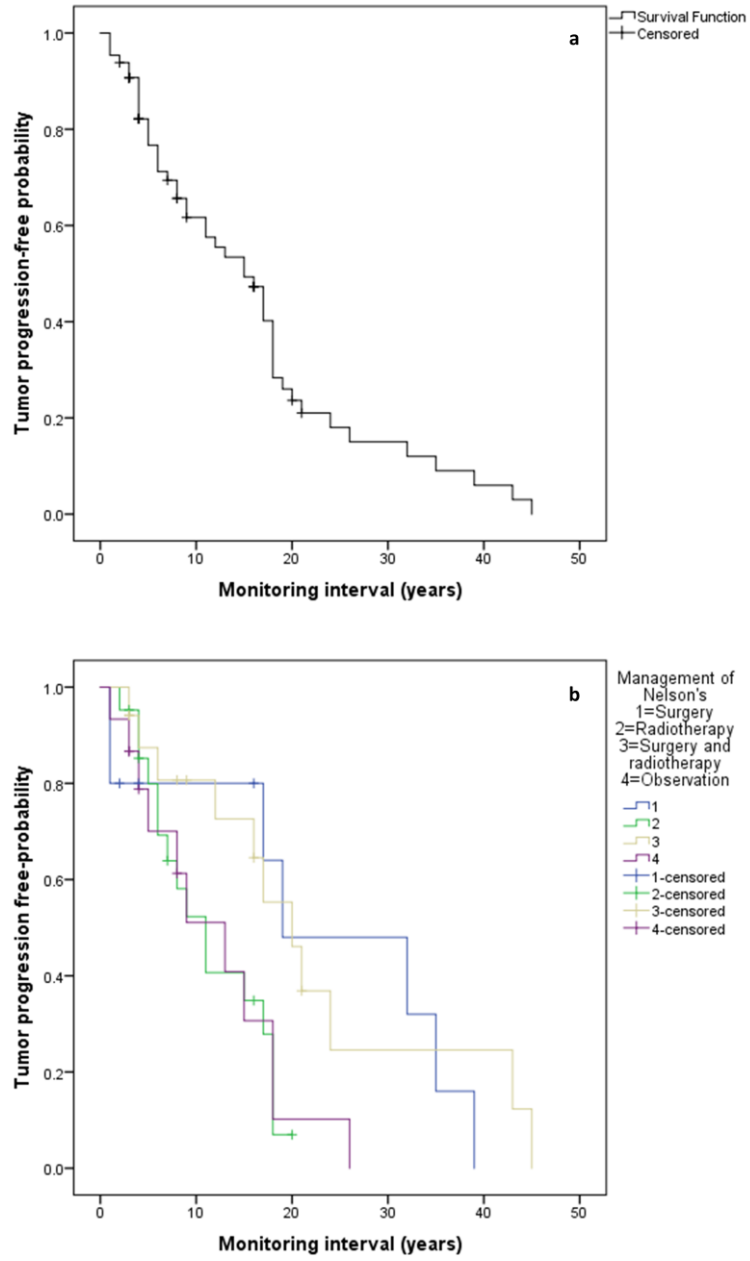
680 HR: Hazard ratio, CI: Confidence intervals

681
682
683
684
685
686
687
688
689
690
691
692
693

Patient number	Management of further corticotroph tumor progression	Outcome
1	TSS, chemotherapy, RT, unsuccessful trials of cabergoline, octreotide, rosiglitazone	Spinal metastases detected 8 years after RT treated surgically 13 years after detection of spinal metastases: empty sella, stable spinal metastases
2	Gamma knife, chemotherapy interrupted by stroke, pasireotide trial ceased due to diabetes, unsuccessful trials of cabergoline and octreotide	8 years after gamma knife: stable tumor on imaging
3	Stereotactic radiosurgery	8 years after stereotactic radiosurgery: tumor reduced in size
4	Stereotactic radiosurgery	10 years after stereotactic radiosurgery: tumor reduced in size
5	TSS and Cyber knife	3 years after Cyber knife: tumor increased in size, awaiting further management decisions
6	TSS	8 years after TSS: stable tumor on imaging
7	Awaiting further management decisions	
8	Monitoring	4 years after detection of tumor progression: stable tumor on imaging
9	TSS	Further increase in tumor size 2 years after TSS managed by gamma knife 4 years after gamma knife: stable tumor on imaging
10	Stereotactic radiosurgery	4 months after stereotactic radiosurgery: stable tumor on imaging
11	Diagnosed with spinal metastases treated by local RT and temozolomide	Gradual increase in tumor size and death due to pituitary carcinoma 3 years after detection of metastatic disease
12	TSS and Pasireotide	1 year after TSS: stable tumor on imaging
13	TSS	18 years after TSS: stable tumor on imaging
14	RT	10 years after RT: stable tumor on imaging
15	TSS and stereotactic radiosurgery	6 years after stereotactic radiosurgery: reduction in tumor size on imaging
16	Gamma knife	9 years after gamma knife: stable tumor on imaging
17	TSS and chemotherapy (capecitabine and lomustine)	Died shortly after TSS
18	TSS, chemotherapy (capecitabine and lomustine), temozolomide	Stable for 2 years followed by increase in size treated with cabergoline and TSS Died 6 years after TSS due to tumor progression

696 TSS: transsphenoidal surgery, RT: radiotherapy

697 **Figure 1.**



698
699
700

701

702

703

