

Recurrence in silent corticotroph adenomas after primary treatment: A systematic review and meta-analysis

Karavitaki, Niki

DOI:

[10.1210/jc.2018-01956](https://doi.org/10.1210/jc.2018-01956)

License:

None: All rights reserved

Document Version

Peer reviewed version

Citation for published version (Harvard):

Karavitaki, N 2018, 'Recurrence in silent corticotroph adenomas after primary treatment: A systematic review and meta-analysis', *Journal of Clinical Endocrinology and Metabolism*, vol. 104, no. 4, pp. 1039-1048. <https://doi.org/10.1210/jc.2018-01956>

[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 *The Journal of Clinical Endocrinology & Metabolism* following peer review. The version of record [*The Journal of Clinical Endocrinology & Metabolism*, Volume 104, Issue 4, April 2019, Pages 1039–1048] is available online at: <https://academic.oup.com/jcem/article/104/4/1039/5253711>
<https://doi.org/10.1210/jc.2018-01956>

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 Recurrence in silent corticotroph adenomas after primary treatment: A systematic review and meta-
3 analysis

4

5 **Authors**

6 Athanasios Fountas*^{1,2,3}, Aikaterini Lavrentaki*^{1,2}, Anuradhaa Subramanian⁴, Konstantinos A.
7 Toulis⁴, Krishnarajah Nirantharakumar⁴, Niki Karavitaki^{1,2,3}

8

9 *AF and AL joint first authors

10

11 **Affiliations**

12 ¹Institute of Metabolism and Systems Research, College of Medical and Dental Sciences, University
13 of Birmingham, B15 2TT, Birmingham, UK; ²Centre for Endocrinology, Diabetes and Metabolism,
14 Birmingham Health Partners, Birmingham, B15 2TH, UK; ³Department of Endocrinology, Queen
15 Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, B15 2TH,
16 UK; ⁴Institute of Applied Health Research, College of Medical and Dental Sciences, University of
17 Birmingham, B15 2TT, Birmingham, UK

18

19 **Corresponding author:**

20 Dr. Niki Karavitaki, MSc, PhD, FRCP

21 Institute of Metabolism and Systems Research (IMSR), College of Medical and Dental Sciences,
22 University of Birmingham, IBR Tower, Level 2, Birmingham, B15 2TT, UK

23 Tel.: 0121 414 3826

24 Fax: 0121 415 8712 17

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

26

27 **Short title:** Recurrence in silent corticotroph adenoma – meta-analysis

28

29 **Keywords:** Silent corticotroph adenoma, non-functioning pituitary adenoma, regrowth, recurrence,
30 recurrence rate

31

32 **Total word count:** 3109

33

34 **Funding**

35 This research did not receive any specific grant from any funding agency in the public, commercial or
36 not-for-profit sector.

37

38 **Declaration of interest**

39 There is no conflict of interest that could be perceived as prejudicing the impartiality of the research
40 reported.

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57 **Abstract**

58

59 **Context:** 2017 WHO Classification of Pituitary Tumors grades silent corticotroph adenomas (SCAs)
60 as “high-risk adenomas” due to their aggressive clinical behavior (high probability of recurrence).
61 However, studies comparing recurrence rates of SCAs with other non-functioning pituitary adenoma
62 (NFPAs) subtypes have provided conflicting results.

63 **Objective:** Estimate recurrence rates of SCAs after primary treatment (surgery±radiotherapy) and
64 recurrence rate ratios (RRR) between SCAs and other NFPA subtypes.

65 **Methods:** Systematic review of published literature reporting on outcomes of SCAs up to October 31,
66 2017 was conducted. Recurrence rates, RRRs, 95% confidence intervals (CIs) were estimated from
67 each study and pooled using random effects meta-analysis model.

68 **Results:** For determination of SCAs recurrence rates, 14 studies (low risk of bias, 297 patients) were
69 selected; recurrence rate was 5.96 (95% CI, 4.3-7.84) per 100 person-years. Based on studies with
70 mean follow-up <5 or ≥5 years, 25% (cumulative incidence 0.25; 95% CI, 0.13-0.38) and 31%
71 (cumulative incidence 0.31; 95% CI, 0.23-0.40) of SCAs had recurrence, respectively. Recurrence
72 rates after surgery or surgery+radiotherapy were 5.41 (95% CI, 3.28-7.96) and 4.88 (95% CI, 0.67-
73 11.54) cases per 100 person-years, respectively. Analysis of 10 eligible studies (moderate risk of bias,
74 244 SCAs, 1622 NFPAs) showed no significant RRR (1.44; 95% CI, 0.9-2.33, $p=0.130$) between the
75 groups. Focus on tumors treated solely by surgery also revealed no significant RRR (1.17; 95% CI,
76 0.79-1.75, $p=0.429$).

77 **Conclusions:** Based on studies with mean follow-up ≥5 years, 31% of SCAs have recurrence. No
78 evidence supporting higher recurrence risk of SCAs compared with other NFPA subtypes was found.

79

80

81

82

83

84

85 **Introduction**

86

87 Silent corticotroph adenomas (SCAs) are pituitary neuroendocrine tumors (PitNETs) (1)
88 demonstrating positive immunostaining for adrenocorticotrophic hormone (ACTH) but not associated
89 with clinical or biochemical evidence of cortisol excess. They arise from adenohypophyseal cells of
90 Tpit lineage and account for 3-19% of non-functioning pituitary adenomas (NFPAs) (2-4). In contrast
91 to Cushing’s disease which is mostly attributed to microadenomas, SCAs are diagnosed when they are
92 large enough to cause pressure effects to surrounding structures necessitating surgical resection,
93 ultimately leading to their pathological diagnosis (5,6).

94 Traditionally, SCAs have been considered as aggressive lesions and, based on the 2017 WHO
95 Classification of Pituitary Tumors, they are recognized as “high-risk pituitary adenomas” (3); this
96 concept has mostly relied on studies reporting higher recurrence rates compared with other subtypes
97 of NFPA (7-11), potentially leading for low threshold decisions on offering early adjuvant
98 radiotherapy (RT). On the other hand, a number of series have not confirmed this (12-19) supporting
99 the view that imaging follow-up and radiotherapy protocols at initial presentation should not differ
100 from those adopted for other NFPA subtypes. These points, combined with the small number of cases
101 included in each study (even in those from large pituitary centers) due to the rarity of this adenoma
102 subtype and the differences in the follow-up duration between SCAs and other NFPAs within the
103 same study (8,10), suggest that robust evidence on the long-term clinical behavior of SCAs after
104 primary treatment is still lacking.

105 In order to elucidate these controversial data and address reliably this topic, we conducted a
106 systematic review and meta-analysis of published literature reporting on outcomes of SCAs; our first
107 aim was to estimate the recurrence rates of SCAs after surgery followed or not by adjuvant RT, and
108 our second objective was to clarify if SCAs carry a higher risk of recurrence after primary treatment
109 compared to other subtypes of NFPAs.

110

111

112

113 **Methods**

114

115 This systematic review and meta-analysis was conducted based on an *a priori* protocol, registered on
116 PROSPERO (international database of prospectively registered systematic reviews, registration
117 number CRD42017053862). The methods and results of the review are reported according to the
118 Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (20).

119

120 *Search strategy and eligibility criteria*

121 A systematic search of Medline, Embase and Cochrane Library Central databases was conducted to
122 identify relevant articles published up to October 31, 2017. A detailed search strategy was developed
123 by the study investigators with input from an information specialist (Supplementary Figure 1) (21).
124 The reference lists of all retrieved articles were also included in the literature research/citation
125 tracking. Only articles published in English were included, whilst duplicate studies and those with
126 overlapping populations were excluded. Two independent reviewers (A.F. and A.L.) screened the
127 initial search results for titles and abstracts pertaining to the research questions and then performed a
128 full-text assessment of the potentially eligible published studies. Discrepancies in reviewers'
129 selections were resolved through discussion and consensus with a third reviewer (N.K.). Eligible
130 studies were randomized controlled, non-randomized controlled, prospective and retrospective cohort,
131 case-control and case series (with ≥ 5 cases) reporting on recurrence/regrowth rates of SCAs. Review
132 articles, letters, commentaries and meeting abstracts were excluded. For the first review question,
133 eligible studies were those including human subjects with SCA managed primarily by surgery
134 followed or not by adjuvant RT. For the second review question, eligible studies were those
135 comparing outcomes of human subjects with SCA ("exposed" cohort) with other subtypes of NFPA
136 ("unexposed" cohort) managed primarily by surgery followed or not by adjuvant RT. Any article was
137 excluded: i) if it was not reporting on recurrence/regrowth rates, ii) if imaging follow-up was
138 unknown or less than 6 months. Recurrence/regrowth was defined as radiological progress of the
139 tumor (increase in size of residual tumor or regrowth of adenoma when previously no residual tumor
140 mass was present).

141

142 *Data extraction*

143 Data from the selected studies were extracted independently by two investigators (A.F. and A.L.) and
144 are presented in a standardized table. The information extracted from each article included: first
145 author and year of publication, comparison group (patients with other subtypes of NFPA), number of
146 patients in each cohort, age at diagnosis of the adenoma, follow-up duration and recurrence rates (in
147 crude numbers and as a proportion). Data are also presented separately for two subgroups of patients:
148 those treated and those not treated with adjuvant RT.

149

150 *Risk of bias assessment*

151 The Newcastle-Ottawa Scale (NOS) was used for evaluation of risk of bias of all included
152 observational studies (22). Reviewers assessed independently the selection of studies, as well as the
153 comparability and their outcomes using a rated system: low, moderate and high risk depending on the
154 scoring for each section as presented in NOS assessment. Comparability of studies on the basis of
155 adjuvant RT, extent of tumor removal and length of follow-up was main area of focus. Any scoring
156 discrepancies were resolved through combined reassessment and consensus by all authors.

157

158 *Statistical analysis*

159 We conducted a meta-analysis using the random-effects model described by DerSimonian and Laird
160 (23) to pool incidence rates (IRs) and recurrence rate ratios (RRRs) and their 95% confidence
161 intervals (CIs). The random-effects model was chosen in order to account for heterogeneity across the
162 included studies. For pooling recurrence rates, we performed Freeman-Turkey double arcsine
163 transformation to address variance instability (24,25). When pooling RRRs, fixed continuity
164 correction of 0.1 was used in case a study had no outcome in one of the arms (26). Statistical
165 heterogeneity was tested by Q statistic generated from the χ^2 test, in which p values less than 0.10
166 were considered significant. Heterogeneity was further quantified through the I-squared (I^2) measure
167 with values between 0% and 30% indicating no important heterogeneity, 30% and 60% moderate,
168 60% and 75% substantial, and 75% to 100% considerable heterogeneity (27). I^2 and p values of

169 statistical heterogeneity were given for all analyses. All statistical analyses were performed on Stata
170 v14.0 software (StataCorp. LP, College Station (TX); 2015).

171 For both outcomes (recurrence rates of SCAs and risk of recurrence of SCAs compared with other
172 subtypes of NFPAs) of the meta-analysis, we estimated pooled IRs and RRRs with their 95% CIs.

173 Due to significant variations in the length of follow-up between the included studies, we also
174 conducted analysis accounting for duration of follow-up and we reported recurrence rates per 100
175 person-years. In addition, we performed a subgroup analysis estimating recurrence rates separately for
176 patients with follow-up less or more than 5 years.

177

178

179

180

181

182

183

184

185

186

187

188

189

190

191

192

193

194

195

196

197 **Results**

198

199 *Study identification and description*

200 The systematic search identified 1942 potentially eligible articles. After screening and assessment of
201 eligibility, 14 articles were eligible for the first (8-10,12,13,15-18,28-32) and 10 for the second review
202 question (8-10,12,13,15-18,29). All included studies were observational. The complete study selection
203 process is described in Figure 1.

204 For the calculation of the recurrence rates of SCAs, 297 patients were included with mean follow-up
205 ranging between 2 and 7.4 years. For the assessment of the risk of recurrence of SCAs compared with
206 other subtypes of NFPA, 244 patients with SCAs followed-up for mean periods between 2 and 7.4
207 years were compared to 1622 patients with other NFPA subtypes with mean follow-up duration
208 ranging between 2 and 6.3 years. A summary of the included studies is given in Table 1.

209 Data on recurrence of patients with SCA treated by surgery were extracted from 10 studies
210 (8,12,13,15,17,18,28,30-32) (Supplementary Table 1) (21) and of those offered adjuvant RT from 4
211 studies reporting on this management approach (13,15,28,32) (Supplementary Table 2) (21). For this
212 subgroup analysis, 4 studies of Table 1 had to be excluded: 3 because the impact of adjuvant RT was
213 not assessed separately (9,10,16) and one because administration of adjuvant RT was unknown (29).

214

215 *Risk of bias*

216 Studies contributing with data for the first question of the meta-analysis were at low (except one at
217 moderate) risk of bias (Supplementary Table 3) (21) and those contributing with data for the second
218 question of the meta-analysis were at moderate risk of bias (Supplementary Table 4) (21).

219

220 *Recurrence rates of SCAs*

221 Overall, the recurrence rate of SCAs was 5.96 (95% CI, 4.30-7.84) cases per 100 person-years
222 ($I^2=33.57\%$, $p=0.11$) (Figure 2a). Recurrence rates were 4.88 (95% CI, 0.67-11.54) cases per 100
223 person-years after adjuvant RT ($I^2=33.01\%$, $p=0.21$) and 5.41 (95% CI, 3.28-7.96) cases per 100
224 person-years without adjuvant RT offered ($I^2=36.31\%$, $p=0.12$) (Figure 2b).

225 Given the variable follow-up duration of the patients with SCA in the included articles, recurrence
226 incidences were estimated in two groups: those with mean follow-up <5 years or ≥ 5 years. In the
227 studies that contributed with follow-up <5 years (8 studies), 25% of the patients had recurrence
228 (cumulative incidence 0.25; 95% CI, 0.13-0.38) ($I^2=60.54\%$, $p=0.01$), whilst in those with follow-up
229 ≥ 5 years (6 studies), 31% had recurrence (cumulative incidence 0.31; 95% CI, 0.23-0.400) ($I^2=0.00\%$,
230 $p=0.48$) (Figure 3a).

231 After stratifying the studies for both adjuvant RT and length of follow-up, recurrence was detected in
232 22% (cumulative incidence 0.22; 95% CI, 0.03-0.50) of the patients treated only by surgery and
233 followed-up for <5 years (5 studies) ($I^2=76.91\%$, $p=0.00$) and in 31% (cumulative incidence 0.31;
234 95% CI, 0.21-0.42) of those treated only by surgery and followed-up for ≥ 5 years (5 studies)
235 ($I^2=0.36\%$, $p=0.40$) (Figure 3b). There was only one study with data on SCAs treated with adjuvant
236 RT and followed-up for <5 years (28), reporting recurrence in 4 out of 6 patients. Furthermore, 3
237 studies had data on the outcomes of irradiated patients followed-up for ≥ 5 years (13,15,32) but the
238 number of cases was too small ($n=14$) to allow meta-analysis; amongst these 14 patients, 3 had SCAs
239 recurrence.

240

241 *Risk of recurrence of SCAs compared with other subtypes of NFPAs*

242 In our meta-analysis, there was no significant difference in the recurrence rates between SCAs and
243 other subtypes of NFPAs (RRR 1.44; 95% CI, 0.90-2.33, $p=0.13$) ($I^2=64.1\%$, $p=0.003$) (Figure 4a).
244 This was also shown when tumors not offered adjuvant RT were compared (RRR 1.17; 95% CI, 0.79-
245 1.75, $p=0.43$) ($I^2=9.3\%$, $p=0.357$) (Figure 4b). Only one article included SCAs and other subtypes of
246 NFPAs that had received adjuvant RT (15). In this study, recurrences were detected in 2 out of 6
247 SCAs and in 4 out of 20 other NFPAs (mean follow-up 5.2 and 4.2 years, respectively).

248

249

250

251

252

253 Discussion

254

255 In this systematic review and meta-analysis we assessed the recurrence rates of SCAs and their risk of
256 recurrence compared to other subtypes of NFPAs. We found that overall, the recurrence rate of SCAs
257 was 5.96 cases per 100 person-years and, based on studies with mean follow-up ≥ 5 years, 31% of the
258 patients had recurrence. Furthermore, after accounting for length of follow-up, our meta-analysis
259 showed that the rate ratio for recurrence between SCAs and other subtypes of NFPAs was not
260 significantly evident. This was also confirmed when the comparison focused on tumors not offered
261 adjuvant RT following primary surgery.

262 Amongst NFPAs, the group of SCAs has attracted considerable attention due to the traditional
263 concept that they demonstrate a more aggressive clinical behavior and to the fact that they can evolve
264 into Cushing's disease after long intervals of inactivity. The mechanisms of SCA genesis and growth
265 are poorly understood and studies assessing their post-operative outcomes are limited with wide
266 variations in the reported recurrence rates (5,33). This may be attributed to differences in the duration
267 of follow-up, small sample size, review of irradiated and non-irradiated cases together and inclusion
268 of patients already diagnosed with recurrence in the analyses. In order to overcome these limitations,
269 we used strict inclusion and exclusion criteria focusing on cases after primary surgical treatment
270 (combined or not with adjuvant RT) and taking into account the length of follow-up. We also
271 excluded two patients from the Lopez *et al.* series (30) due to uncertainty on the diagnosis of SCA
272 (both had temporary post-operative adrenal insufficiency and one of them had also Cushing's
273 phenotype), as well as two patients from the Alahmadi *et al.* study (12) due to presence of double
274 adenomas (with ACTH and growth hormone staining).

275 We found that recurrence rates were 4.88 (95% CI, 0.67-11.54) and 5.41 (95% CI, 4.10-7.49) cases
276 per 100 person-years with or without adjuvant RT, respectively, with moderate heterogeneity between
277 studies. It is generally accepted that RT is beneficial for long-term NFPA control after surgery
278 (34,35); however, this treatment modality does not prevent tumor regrowth in all patients (36).
279 Notably, the outcomes of SCAs after adjuvant RT were reported in only four studies (13,15,28,32)
280 and direct comparison between the irradiated and non-irradiated groups leading to robust conclusions

281 were not possible. Thus, Bradley *et al.* (13), in a series of 28 patients (one of whom died during the
282 post-operative period and was excluded from our analysis), had recurrence rates of 36% in the non-
283 irradiated and 20% in the irradiated ones (mean follow-up 7.4 years); Webb *et al.* (32), in a study of
284 22 patients, found recurrence rate of 26% in the non-irradiated and 0% in the irradiated ones (mean
285 follow-up 6.1 years). On the other hand, Baldeweg *et al.* (28), in a series of 15 cases, reported 11%
286 and 67% recurrence rates in the non-irradiated and irradiated patients, respectively (mean follow-up
287 4.8 years) and, Cho *et al.* (15), in a study of 28 SCAs, found tumor progression in 23% and 33% of
288 the non-irradiated and irradiated patients, respectively (mean follow-up 5.2 years).

289 It has been previously shown that most of the recurrences in NFPA are detected in the first 5 post-
290 operative years (37,38). After stratifying the studies for modality of primary treatment and duration of
291 follow-up, we found that in the group treated solely by surgery, recurrence was diagnosed in 22% of
292 the patients monitored for <5 years (considerable heterogeneity between studies) and in 31% of those
293 followed-up for ≥ 5 years (no heterogeneity amongst studies). The limited sample size of patients
294 treated by surgery and adjuvant RT did not allow solid determination of the recurrence rates stratified
295 for follow-up duration in this group; further studies are required to elucidate this issue.

296 Interestingly, our meta-analysis did not confirm that SCAs have higher recurrence rates than the other
297 NFPA subtypes (RRR 1.44; 95% CI, 0.9-2.33). Focus on reports with patients offered only surgery
298 supported the same view (RRR 1.17; 95% CI, 0.79-1.75) with no important heterogeneity amongst the
299 studies. In the only available article including patients with both types of adenomas that had been
300 offered adjuvant RT, recurrence rates were 33% for SCAs and 20% for other NFPA during mean
301 observation periods 5.2 and 4.2 years, respectively (15). In this study, conventional fractionated RT
302 was used in 67% of SCAs and 50% of NFPA, whilst gamma knife radiosurgery was offered to 33%
303 and 50% of SCAs and NFPA, respectively; the radiation therapy protocol and the latency time
304 between surgical treatment and adjuvant therapy did not differ between the two groups (15). Langlois
305 *et al.*, found higher adenoma progression rates in a series of 39 SCAs compared with 70 silent
306 gonadotroph adenomas (36% vs. 10%, $p=0.001$) (10). It should be noted, however, that in the latter
307 group, follow-up duration was significantly shorter (mean 6.7 vs 2.7 years). Similar results were also
308 reported in the cohort of Jahangiri *et al.* (9) with 27% of SCAs recurring compared to 7% of NFPA

309 ($p < 0.001$); nonetheless, mean follow-up duration was short (2.4 and 3.1 years, respectively). On the
310 other hand, in studies with similar follow-up length between the two groups (12,15,16), no difference
311 in the recurrence rates was detected.

312 Although our meta-analysis did not find evidence supporting an important increase in risk of
313 recurrence of SCAs compared with other NFPA subtypes, an area potentially raising concerns on the
314 prognosis of these tumors is the reported [in a few (13,15,32) but not in other (9,16) series] aggressive
315 course of a subset of recurrent SCAs which continue to show multiple growths requiring various
316 treatment modalities. Nonetheless, the number of these cases is extremely small and identification of
317 predictive factors in a reliable way is currently not possible. It is of note that in a study by
318 Ioachimescu *et al.* (16) comparing SCAs with other NFPA subtypes, there was no significant
319 difference in the percentage of patients requiring multiple surgeries and RT. Furthermore, malignant
320 transformation of SCAs has been described and this may also be seen in cases with gain in hormone
321 secretion and development of overt Cushing's syndrome (2,5,39,40). In a recent review of all
322 published cases of malignant NFPAs, staining for ACTH was reported in 9 out of 38 patients (23.7%)
323 (41); again, the very small number of total cases make the interpretation of this rate difficult.

324 **Therefore, it would be reasonable to consider that decisions on the management strategies for the total**
325 **group of SCAs should not rely on the outcomes of these rare subgroups of aggressive SCAs.**

326 Potential sources of heterogeneity in our meta-analysis include the variable sample size and follow-up
327 duration of patients between different studies and between groups under comparison within the same
328 study, as well as variations in the radiotherapy techniques/protocols and in the extent of tumor
329 removal/location of residual tumor after primary surgery [which has been reported as a factor
330 predicting recurrence risk in NFPAs (17,42,43)].

331 The strengths of our study include the comprehensive literature search, the strict protocol-driven
332 selection of studies, the duplicate process for study selection and evaluation and the performance of
333 analyses also taking into account the length of follow-up. Limitations include the retrospective,
334 observational nature of the available reports, the moderate to substantial heterogeneity in the meta-
335 analysis of a number of outcomes, the absence of data on pathological/molecular markers of
336 aggressiveness and the small number of cases offered adjuvant RT not allowing sound estimation of

337 outcomes in this subgroup. Finally, given that transcription factor expression analysis was not
338 available, the possibility of inclusion of corticotroph adenohypophyseal cell differentiation tumors in
339 the group of “null cell” NFPAs cannot be excluded. Nonetheless, based on a recent report (44), it is
340 anticipated that only a small proportion of hormone immunonegative adenomas express corticotroph
341 lineage specific transcription factors; future studies will elucidate this field.

342 In conclusion, our systematic review and meta-analysis of studies of moderate risk of bias has not
343 confirmed higher risk of SCAs recurrence compared with other NFPA subtypes. Our data point out
344 the need for further methodologically robust (adequately powered, with appropriate adjustment for all
345 possible confounding factors and of prolonged follow-up) studies comparing SCAs with other NFPA
346 subtypes and clarifying their true biological behavior, as well as whether they should be indeed (as per
347 2017 WHO recommendation) classified as high-risk pituitary adenomas. Furthermore, studies
348 particularly looking at the rare subgroups of SCAs with multiple growths and resistance to various
349 treatments, malignant transformation or development of overt Cushing’s aiming to shed light on their
350 pathophysiology and factors predicting their prognosis will be of major significance in the field and
351 will facilitate the development of valuable evidence-based management protocols in the area of
352 PitNETs.

353

354 **Acknowledgments**

355 None

356

357

358

359

360

361

362

363

364

365 **References**

366

- 367 1. Asa SL, Casar-Borota O, Chanson P, Delgrange E, Earls P, Ezzat S, Grossman A, Ikeda H,
368 Inoshita N, Karavitaki N, Korbonits M, Laws ER, Jr., Lopes MB, Maartens N, McCutcheon
369 IE, Mete O, Nishioka H, Raverot G, Roncaroli F, Saeger W, Syro LV, Vasiljevic A, Villa C,
370 Wierinckx A, Trouillas J. From pituitary adenoma to pituitary neuroendocrine tumor
371 (PitNET): an International Pituitary Pathology Club proposal. *Endocr Relat Cancer*
372 2017;24(4):C5-c8
- 373 2. Karavitaki N, Ansorge O, Wass JA. Silent corticotroph adenomas. *Arq Bras Endocrinol*
374 *Metabol* 2007;51(8):1314-1318
- 375 3. Mete O, Lopes MB. Overview of the 2017 WHO Classification of Pituitary Tumors. *Endocr*
376 *Pathol* 2017;28(3):228-243
- 377 4. Cooper O. Silent corticotroph adenomas. *Pituitary* 2015;18(2):225-231
- 378 5. Ben-Shlomo A, Cooper O. Silent corticotroph adenomas. *Pituitary* 2018;21(2):183-193
- 379 6. Lonser RR, Nieman L, Oldfield EH. Cushing's disease: pathobiology, diagnosis, and
380 management. *J Neurosurg* 2017;126(2):404-417
- 381 7. Cohen-Inbar O, Xu Z, Lee CC, Wu CC, Chytka T, Silva D, Sharma M, Radwan H, Grills IS,
382 Nguyen B, Siddiqui Z, Mathieu D, Iorio-Morin C, Wolf A, Cifarelli CP, Cifarelli DT,
383 Lunsford LD, Kondziolka D, Sheehan JP. Prognostic significance of corticotroph staining in
384 radiosurgery for non-functioning pituitary adenomas: a multicenter study. *J Neurooncol*
385 2017;135(1):67-74
- 386 8. Cooper O, Ben-Shlomo A, Bonert V, Bannykh S, Mirocha J, Melmed S. Silent
387 corticogonadotroph adenomas: clinical and cellular characteristics and long-term outcomes.
388 *Horm Cancer* 2010;1(2):80-92
- 389 9. Jahangiri A, Wagner JR, Pekmezci M, Hiniker A, Chang EF, Kunwar S, Blevins L, Aghi MK.
390 A comprehensive long-term retrospective analysis of silent corticotrophic adenomas vs
391 hormone-negative adenomas. *Neurosurgery* 2013;73(1):8-17; discussion 17-18

- 392 **10.** Langlois F, Lim DST, Yedinak CG, Cetas I, McCartney S, Cetas J, Dogan A, Fleseriu M.
393 Predictors of silent corticotroph adenoma recurrence; a large retrospective single center study
394 and systematic literature review. *Pituitary* 2018;21(1):32-40
- 395 **11.** Pawlikowski M, Kunert-Radek J, Radek M. "Silent" corticotropinoma. *Neuro Endocrinol Lett*
396 2008;29(3):347-350
- 397 **12.** Alahmadi H, Lee D, Wilson JR, Hayhurst C, Mete O, Gentili F, Asa SL, Zadeh G. Clinical
398 features of silent corticotroph adenomas. *Acta Neurochir (Wien)* 2012;154(8):1493-1498
- 399 **13.** Bradley KJ, Wass JA, Turner HE. Non-functioning pituitary adenomas with positive
400 immunoreactivity for ACTH behave more aggressively than ACTH immunonegative tumours
401 but do not recur more frequently. *Clin Endocrinol (Oxf)* 2003;58(1):59-64
- 402 **14.** Chen SC, Chung WY. Progression rate of silent corticotroph adenomas after stereotactic
403 radiosurgery. In regard to Xu et al. *Int J Radiat Oncol Biol Phys* 2015;91(5):1113-1114
- 404 **15.** Cho HY, Cho SW, Kim SW, Shin CS, Park KS, Kim SY. Silent corticotroph adenomas have
405 unique recurrence characteristics compared with other nonfunctioning pituitary adenomas.
406 *Clin Endocrinol (Oxf)* 2010;72(5):648-653
- 407 **16.** Ioachimescu AG, Eiland L, Chhabra VS, Mastrogianakis GM, Schniederjan MJ, Brat D,
408 Pileggi AV, Oyesiku NM. Silent corticotroph adenomas: Emory University cohort and
409 comparison with ACTH-negative nonfunctioning pituitary adenomas. *Neurosurgery*
410 2012;71(2):296-303; discussion 304
- 411 **17.** Reddy R, Cudlip S, Byrne JV, Karavitaki N, Wass JA. Can we ever stop imaging in surgically
412 treated and radiotherapy-naive patients with non-functioning pituitary adenoma? *Eur J*
413 *Endocrinol* 2011;165(5):739-744
- 414 **18.** Watts AK, Easwaran A, McNeill P, Wang YY, Inder WJ, Caputo C. Younger age is a risk
415 factor for regrowth and recurrence of nonfunctioning pituitary macroadenomas: Results from
416 a single Australian centre. *Clin Endocrinol (Oxf)* 2017;87(3):264-271
- 417 **19.** Ceccato F, Regazzo D, Barbot M, Denaro L, Emanuelli E, Borsetto D, Rolma G, Alessio L,
418 Gardiman MP, Lombardi G, Albiger N, D'Avella D, Scaroni C. Early recognition of

- 419 aggressive pituitary adenomas: a single-centre experience. *Acta Neurochir (Wien)*
420 2018;160(1):49-55
- 421 **20.** Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews
422 and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009;62(10):1006-1012
- 423 **21.** Fountas A, Lavrentaki A, Subramanian A, Toulis KA, Nirantharakumar K, N K. Data from:
424 Recurrence in silent corticotroph adenomas after primary treatment: A systematic review and
425 meta-analysis. UBIRA eData Repository. Deposited 10 September 2018.
426 <https://doi.org/10.25500/eData.bham.00000231>.
- 427 **22.** Wells G, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle–Ottawa
428 Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2013;
429 http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed January, 2018.
- 430 **23.** DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7(3):177-
431 188
- 432 **24.** Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of
433 binomial data. *Archives of public health = Archives belges de sante publique* 2014;72(1):39
- 434 **25.** Freeman M, Tukey J. Transformations Related to the Angular and the Square Root *Ann Math*
435 *Stat* 1950;21(4):607-611
- 436 **26.** Friedrich JO, Adhikari NK, Beyene J. Inclusion of zero total event trials in meta-analyses
437 maintains analytic consistency and incorporates all available data. *BMC Med Res Methodol*
438 2007;75
- 439 **27.** Deeks J, Higgins J, Altman D. Analysing data and undertaking meta-analyses. In: Higgins J,
440 Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions* Chichester,
441 England: John Wiley & Sons; 2008:276-281.
- 442 **28.** Baldeweg SE, Pollock JR, Powell M, Ahlquist J. A spectrum of behaviour in silent
443 corticotroph pituitary adenomas. *Br J Neurosurg* 2005;19(1):38-42
- 444 **29.** Hewedi IH, Osman WM, El Mahdy MM. Differential expression of cyclin D1 in human
445 pituitary tumors: relation to MIB-1 and p27/Kip1 labeling indices. *J Egypt Natl Canc Inst*
446 2011;23(4):171-179

- 447 **30.** Lopez JA, Kleinschmidt-Demasters Bk B, Sze CI, Woodmansee WW, Lillehei KO. Silent
448 corticotroph adenomas: further clinical and pathological observations. *Hum Pathol*
449 2004;35(9):1137-1147
- 450 **31.** Tateno T, Izumiyama H, Doi M, Akashi T, Ohno K, Hirata Y. Defective expression of
451 prohormone convertase 1/3 in silent corticotroph adenoma. *Endocr J* 2007;54(5):777-782
- 452 **32.** Webb KM, Laurent JJ, Okonkwo DO, Lopes MB, Vance ML, Laws ER, Jr. Clinical
453 characteristics of silent corticotrophic adenomas and creation of an internet-accessible
454 database to facilitate their multi-institutional study. *Neurosurgery* 2003;53(5):1076-1084;
455 discussion 1084-1075
- 456 **33.** Drummond J, Roncaroli F, Grossman AB, Korbonits M. CLINICAL AND
457 PATHOLOGICAL ASPECTS OF SILENT PITUITARY ADENOMAS. *J Clin Endocrinol*
458 *Metab* 2018;
- 459 **34.** Tampourlou M, Ntali G, Ahmed S, Arlt W, Ayuk J, Byrne JV, Chavda S, Cudlip S, Gittoes
460 N, Grossman A, Mitchell R, O'Reilly MW, Paluzzi A, Toogood A, Wass JAH, Karavitaki N.
461 Outcome of Nonfunctioning Pituitary Adenomas That Regrow After Primary Treatment: A
462 Study From Two Large UK Centers. *J Clin Endocrinol Metab* 2017;102(6):1889-1897
- 463 **35.** Minniti G, Flickinger J, Tolu B, Paolini S. Management of nonfunctioning pituitary tumors:
464 radiotherapy. *Pituitary* 2018;21(2):154-161
- 465 **36.** Dekkers OM, Pereira AM, Romijn JA. Treatment and follow-up of clinically nonfunctioning
466 pituitary macroadenomas. *J Clin Endocrinol Metab* 2008;93(10):3717-3726
- 467 **37.** Roelfsema F, Biermasz NR, Pereira AM. Clinical factors involved in the recurrence of
468 pituitary adenomas after surgical remission: a structured review and meta-analysis. *Pituitary*
469 2012;15(1):71-83
- 470 **38.** Sheehan J, Lee CC, Bodach ME, Tumialan LM, Oyesiku NM, Patil CG, Litvack Z, Zada G,
471 Aghi MK. Congress of Neurological Surgeons Systematic Review and Evidence-Based
472 Guideline for the Management of Patients With Residual or Recurrent Nonfunctioning
473 Pituitary Adenomas. *Neurosurgery* 2016;79(4):E539-540

- 474 **39.** Roncaroli F, Scheithauer BW, Young WF, Horvath E, Kovacs K, Kros JM, Al-Sarraj S,
475 Lloyd RV, Faustini-Fustini M. Silent corticotroph carcinoma of the adenohypophysis: a report
476 of five cases. *Am J Surg Pathol* 2003;27(4):477-486
- 477 **40.** Ceccato F, Lombardi G, Manara R, Emanuelli E, Denaro L, Milanese L, Gardiman MP,
478 Bertorelle R, Scanarini M, D'Avella D, Occhi G, Boscaro M, Zagonel V, Scaroni C.
479 Temozolomide and pasireotide treatment for aggressive pituitary adenoma: expertise at a
480 tertiary care center. *J Neurooncol* 2015;122(1):189-196
- 481 **41.** Lenders N, McCormack A. Malignant transformation in non-functioning pituitary adenomas
482 (pituitary carcinoma). *Pituitary* 2018;21(2):217-229
- 483 **42.** O'Sullivan EP, Woods C, Glynn N, Behan LA, Crowley R, O'Kelly P, Smith D, Thompson
484 CJ, Agha A. The natural history of surgically treated but radiotherapy-naive nonfunctioning
485 pituitary adenomas. *Clin Endocrinol (Oxf)* 2009;71(5):709-714
- 486 **43.** Ratnasingam J, Lenders N, Ong B, Boros S, Russell AW, Inder WJ, Ho KKY. Predictors for
487 secondary therapy after surgical resection of nonfunctioning pituitary adenomas. *Clin*
488 *Endocrinol (Oxf)* 2017;87(6):717-724
- 489 **44.** Nishioka H, Inoshita N, Mete O, Asa SL, Hayashi K, Takeshita A, Fukuhara N, Yamaguchi-
490 Okada M, Takeuchi Y, Yamada S. The Complementary Role of Transcription Factors in the
491 Accurate Diagnosis of Clinically Nonfunctioning Pituitary Adenomas. *Endocr Pathol*
492 2015;26(4):349-355
- 493
494
495
496
497
498
499
500
501

502 **Legends for figures and tables**

503

504 *Table 1:* Characteristics of the included studies for both review questions

505

506 *Figure 1:* Flowchart showing the study selection process.

507

508 *Figure 2:* (a) Recurrence rates of silent corticotroph adenomas per 100 person-years. (b) Recurrence
509 rates of silent corticotroph adenomas managed without or with adjuvant radiotherapy after
510 primary surgery (*IR: incidence rate; CI:confidence intervals*).

511

512 *Figure 3:* (a) Recurrence rates of silent corticotroph adenomas according to mean follow-up (≥ 5 or < 5
513 years). (b) Recurrence rates of silent corticotroph adenomas treated primarily only by
514 surgery according to mean follow-up (≥ 5 or < 5 years) (*CI:confidence intervals*).

515

516 *Figure 4:* (a) Recurrence rate ratios between silent corticotroph adenomas and other subtypes of non-
517 functioning pituitary adenomas. (b) Recurrence rate ratios between silent corticotroph
518 adenomas and other subtypes of non-functioning pituitary adenomas treated primarily only
519 by surgery (*RRR: recurrence rate ratio; SCA: silent corticotroph adenoma, NFPA: non-*
520 *functioning pituitary adenoma; CI:confidence intervals*).

521

522