

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

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1 **Title**

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

4

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28

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57 **Abstract**

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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.

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85 **Introduction**

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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.

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113 **Methods**

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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  $\geq 5$  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.

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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  $\chi^2$  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.

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197 **Results**

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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  $\geq 5$  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  $\geq 5$  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  $\geq 5$  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  $\geq 5$  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).

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253 **Discussion**

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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  $\geq 5$  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  $\geq 5$  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 NFPA, 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 NFPA (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

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355 None

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502 **Legends for figures and tables**

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

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

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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*).

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