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Karavitaki, Niki

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Title

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

Authors

Athanasios Fountas*[1,2,3], Aikaterini Lavrentaki*[1,2], Anuradhaa Subramanian[4], Konstantinos A. Toulis[4], Krishnarajah Nirantharakumar[4], Niki Karavitaki[1,2,3]

*AF and AL joint first authors

Affiliations

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

Corresponding author:

Dr. Niki Karavitaki, MSc, PhD, FRCP

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

Tel.: 0121 414 3826

Fax: 0121 415 8712 17

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

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Abstract

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

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

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

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

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

Introduction

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

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

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

Methods

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

Search strategy and eligibility criteria

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

Data extraction

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

Risk of bias assessment

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

Statistical analysis

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

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

For both outcomes (recurrence rates of SCAs and risk of recurrence of SCAs compared with other subtypes of NFPAs) of the meta-analysis, we estimated pooled IRs and RRRs with their 95% CIs. Due to significant variations in the length of follow-up between the included studies, we also conducted analysis accounting for duration of follow-up and we reported recurrence rates per 100 person-years. In addition, we performed a subgroup analysis estimating recurrence rates separately for patients with follow-up less or more than 5 years.

Results

Study identification and description

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

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

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

Risk of bias

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

Recurrence rates of SCAs

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

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

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

Risk of recurrence of SCAs compared with other subtypes of NFPAs

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

Discussion

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

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

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

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

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

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

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

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

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

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

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

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

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Legends for figures and tables

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

Figure 1: Flowchart showing the study selection process.

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

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

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