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Factors Associated With Post-Surgical Recurrence Of Pituitary Adenoma: A Systematic Review

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ABSTRACT

Pituitary adenomas, benign intracranial tumors with an incidence of 4-7 per 100,000 annually, are categorized into non-functioning (NFPA) and functioning pituitary adenomas (FPA). Despite surgery being the primary treatment, recurrence remains a significant challenge, with rates of 53% at 5 years and up to 80% at 10 years for incomplete resections. This systematic review evaluates factors associated with postoperative recurrence to enhance understanding and improve outcomes. A literature search was conducted in PubMed and ScienceDirect, covering studies from the past 15 years up to August 8, 2024. Inclusion criteria were patients aged >18 years who underwent pituitary adenoma resection, with at least one year of follow-up and involving 30 or more subjects. Studies with repeated surgeries and non-English articles were excluded. Keywords included ("pituitary" OR "hypophys*") AND ("tumo*" OR "adenoma") AND "recur*" AND "factor*". Quality assessment used the Newcastle-Ottawa Scale. From 7,322 articles, eleven studies met the criteria, totaling 2,814 subjects. These studies varied in design, including retrospective and cohort studies, focusing on both NFPA and FPA. Key findings highlight that tumor size, invasiveness, hormonal activity, and extent of resection significantly influence recurrence. Larger tumors and those with cavernous sinus invasion present higher recurrence risks. Molecular markers like Ki-67 and p53, along with surgical factors, are crucial in predicting recurrence. This review identifies key factors associated with pituitary adenoma recurrence post-surgery. Incorporating these into clinical practice may aid in developing personalized management plans and improving outcomes. Further research is needed to refine predictive models and strategies for long-term disease control.

1. INTRODUCTION

Pituitary adenomas are benign, mostly slow-growing intracranial neoplasms, with an incidence of clinically relevant tumor of 4-7 per 100.000 person annually [1]. The 2019 CBTRUS statistical report placed pituitary adenoma as the second most frequent primary brain tumor in the United States, accounPleting for 16,8% of all primary brain and other CNS tumors, preceded only by meningioma, followed by glioblastoma [2].

Pituitary adenomas can be categorized into non-functioning pituitary adenomas (NFPA) and functioning pituitary adenomas. NFPA comprises 15%-30% of pituitary adenomas and may present with loss of vision and hypopituitarism, among other symptoms [3], [4]. On the other hand, half of these tumors are hormone-secreting or functioning adenomas, which account for 46%-64% of cases. Frequently secreted hormones include prolactin (32%-51%), growth hormone (GH) (9%-11%), adrenocorticotropic hormone (ACTH) (3%-6%), and the least frequent (<1%) are thyroid-stimulating hormone (TSH) and gonadotropin-secreting hormone [5].

Surgery is usually the first-line treatment in cases of large NFPA, when there is a clinically significant compression of the optic nerve and most secreting adenomas, with the exception of prolactinoma [1], [5]. Complete resection of pituitary adenomas can be challenging due to a number of factors such as size, location, consistency, and invasiveness. In these cases of incomplete resection, tumor progression or recurrence (p/r) is inevitable, in which 53% p/r rate is reported at 5 years and 80% at 10 years [1], [6]. However, even in the case of complete resection, pituitary adenomas still hold a high long-term recurrence rate of approximately 7%-12% at 10 years [1].

Higher recurrency means longer follow-up periods and multiple hospitalizations, which increases the healthcare burden. In many cases, patients require lifelong treatment from a multidisciplinary team, especially those with endocrine disturbances, resulting in higher costs. Patients with pituitary adenoma also report impairments in health-related quality of life (HRQoL) and a high disease burden. The associated factors were greater self-perceived disease bother and need for support, worse mental and physical health status, and healthcare environment (including patients living alone) [7], [8]. The impact of brain tumor diagnosis is significant, either for the patient themselves or their family, and can affect the quality of life through disease progression and the effects of treatment. Lack of information is one of the unmet needs of patients and their families. Improving the delivery of information and enhancing communication among patients, families, and healthcare providers is key to building good neurooncological care [9], [10]. Defining factors associated with pituitary adenoma recurrence can be one of them, so that neurosurgeons can communicate and prepare patients for the possibility of their treatment options and prognosis of their disease. This systematic review aimed to evaluate the prognostic factors associated with postsurgical recurrence of pituitary adenoma.

2. Method

2.1 Search Strategy

We performed literature research over the last 15 years until 8th of August 2024 using the PubMed and ScienceDirect databases. Our study population included patients with a history of pituitary adenoma resection, in which we analyzed the risk factors associated with tumor recurrence. We included data from both functional and non-functional pituitary adenomas, with subjects aged > 18 years, with a minimal follow-up period of one year, and studies with 30 or more subjects. Studies with repeated surgeries and non-English articles were excluded.

We used the following keywords: (("pituitary" OR "hypophys*") AND ("tumo*" OR "adenoma")) AND "recur*" AND "factor* Initial searching found 7,322 articles from PubMed and ScienceDirect. Two reviewers independently screened the titles of the identified studies, and the remaining articles were divided equally by the authors for abstract reading to determine whether the study was relevant to the research question. The full text of the selected studies was then appraised to determine its eligibility for analysis based on the completeness of the study data. Any inconsistencies were resolved through discussion with the first author.

2.2 Quality Assessment

The selected articles were appraised by two independent reviewers using Newcastle-Ottawa Scale (NOS) checklist for non-randomized studies. Any disagreement was resolved by discussion between the two reviewers or consultation with other author.

3. Result

3.1 Search Result

Detailed process of article selection is presented in Figure 1. After article screening and appraisal, eleven articles are included in this systematic review.

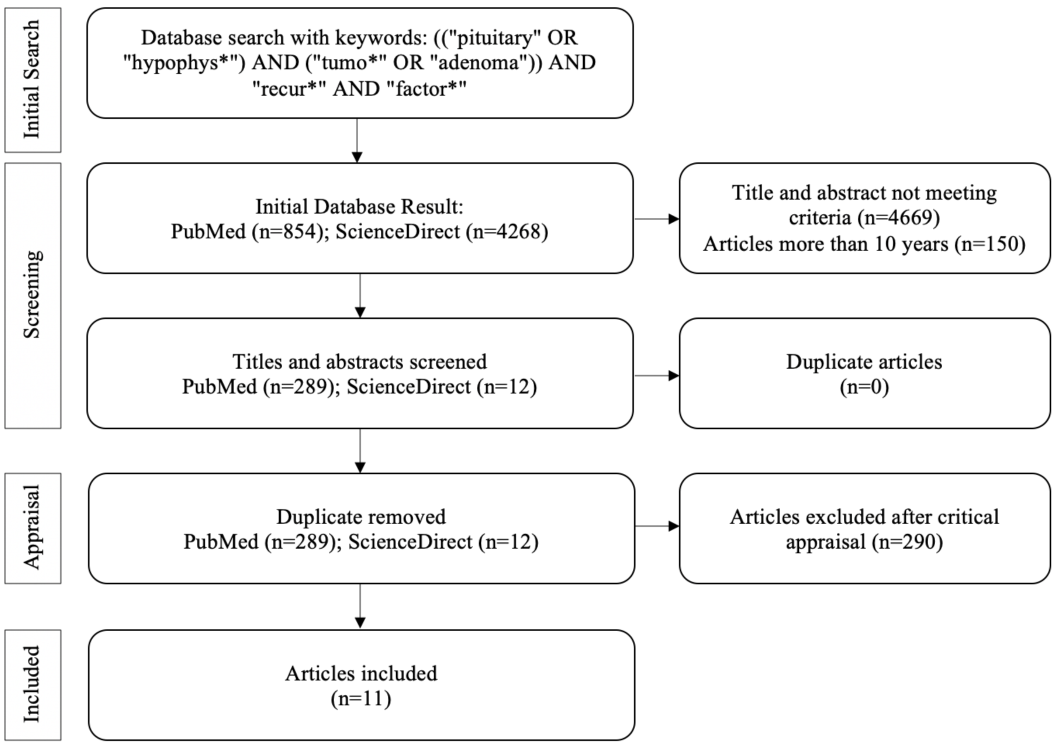

Figure 1. Flowchart of literature search strategy for included studies

3.2 Study Characteristics

Sixteen studies, published between 2014-2024, comprised of 2,814 subjects with pituitary adenoma, were selected. All studies were single-center, and only two were cohort studies, while the rest were retrospective studies. Six studies analyzed both non-functioning pituitary adenoma (NFPA) and functioning pituitary adenoma (FPA), six exclusively studied FPA, and the last four studied NFPA only. While some studies differentiated between progression and recurrence based on the presence of residual tumor after surgery, all studies used MRI as a diagnostic standard for defining growth/recurrency. The characteristics of the eligible studies are summarized in Table 1.

4. Discussions

The recurrence of pituitary adenomas after surgical resection is a multifaceted issue that presents a significant challenge in neurooncology. The findings from this systematic review highlight the complex interplay between tumor biology, patient demographics, molecular markers, and surgical factors in determining the risk of recurrence. This discussion delves deeper into these factors and explores their implications in clinical practice and future research.

4.1 Tumor Characteristics and Recurrence

The intrinsic characteristics of pituitary adenomas, particularly tumor size, invasiveness, and hormonal activity, are pivotal for determining the risk of recurrence. Larger tumors, especially those greater than 10 mm in diameter, have consistently been associated with higher recurrence rates. This is likely due to the difficulty in achieving complete surgical resection of larger tumors, which often extend into surrounding structures, making total removal challenging. According to [11], larger adenomas, particularly those with cavernous sinus invasion, pose a significant challenge for surgeons, as they often result in residual tumor tissue being left behind, which increases the risk of recurrence.

In addition to size, invasiveness of the tumor into the surrounding structures, such as the cavernous sinus or suprasellar region, is a critical factor. According to [14], tumors that exhibit parasellar extension are particularly susceptible to recurrence as a result of the anatomical intricacy and the vicinity of crucial neurovascular structures, which restrict the extent of safe resection. This highlights the need for preoperative imaging modalities like MRI to assess the degree of invasion and plan surgical approaches accordingly.

Hormone-secreting tumors, such as those producing adrenocorticotropic hormone (ACTH) or growth hormone (GH), also present unique challenges. According to [16], functional adenomas, especially those that secrete ACTH, have a higher likelihood of recurrence. The hypersecretion of hormones not only drives tumor growth but also complicates postoperative management, as even small residual tumor tissue can lead to a resurgence of clinical symptoms, necessitating further intervention.

4.2 Molecular and Histopathological Markers

Molecular and histopathological markers have emerged as important prognostic tools to assess the risk of pituitary adenoma recurrence. The proliferation marker Ki-67, which indicates cellular proliferation, has been extensively studied and is widely regarded as a predictor of tumor aggressiveness and recurrence. Higher Ki-67 indices, as indicated by [12], [18] are strongly associated with increased recurrence rates, particularly in functional adenomas. This suggests that Ki-67 should be routinely assessed in surgical specimens to guide postoperative surveillance strategies.

Moreover, overexpression of p53, a tumor suppressor protein, has been associated with more aggressive tumor behavior and higher recurrence rates. A recent study conducted by [27] and others revealed that the presence of p53 in pituitary adenomas is associated with a poorer prognosis, especially in non-functional adenomas. This highlights the potential role of p53 as a biomarker for identifying patients at higher risk of recurrence who may benefit from closer follow-up or adjuvant therapies.

Receptor profiling, including the expression of somatostatin receptors (SSTRs), corticotropin-releasing hormone receptors (CRHR1), and proliferation markers such as MKI67, has also shown promise for predicting recurrence. According to [24], the presence of high levels of SSTR1 and CRHR1 expression was linked to a lower likelihood of recurrence, particularly in GH-secreting adenomas. This finding suggests that receptor-targeted therapies could be beneficial in reducing recurrence in these patients.

4.3 Surgical Factors and Extent of Resection

Extent of resection (EOR) remains one of the most significant determinants of postoperative recurrence. Achieving gross total resection (GTR) is the primary surgical goal because it significantly reduces the risk of recurrence. However, the ability to achieve GTR is often limited by tumor size, invasiveness, and proximity to critical structures, such as the optic chiasm, carotid arteries, and cavernous sinus. [13] highlighted that incomplete resection, particularly in cases with cavernous sinus invasion, was a strong predictor of recurrence, emphasizing the need for meticulous surgical planning and execution.

In some cases, subtotal resection may be unavoidable because of the risk of damage to critical structures. This necessitates a balanced approach, in which the surgeon must weigh the benefits of attempting GTR against the potential for causing neurological deficits. Additionally, advances in surgical techniques, such as endoscopic transsphenoidal surgery, have improved visualization and access to pituitary tumors, allowing for more precise resection. However, as noted by [28] even with these advances, the risk of residual tumor remains, particularly in complex cases, underscoring the importance of postoperative imaging to assess resection status and plan further management.

4.4 Patient Demographics and Clinical Factors

Patient demographics, including age, sex, and hormonal status have also been shown to influence recurrence rates. Younger age at diagnosis is associated with a higher likelihood of recurrence, as noted by [15]. This may be due to the more aggressive nature of adenomas in younger individuals, or it could reflect longer follow-up periods, which allows more time for recurrence to be detected. The role of sex in recurrence is less clear, with some studies suggesting a higher recurrence rate in males, while others report no significant sex differences. This variability may be due to differences in tumor subtypes or hormonal influences.

Hormonal factors play a critical role in the recurrence of functional adenomas. For instance, higher preoperative ACTH levels in silent corticotroph adenomas, as reported by [16], are indicative of a more aggressive tumor phenotype and a higher risk of recurrence. Similarly, elevated postoperative cortisol levels, particularly in the early days following surgery, have been associated with increased recurrence rates in functional pituitary adenomas (FPAs), as noted by [22]. This suggests that close hormonal monitoring postoperatively is essential for early detection of recurrence and timely intervention.

4.5 Grading Systems and Predictive Models

The development of grading systems and predictive models has significantly advanced the ability to stratify patients according to their risk of recurrence. Trouillas classification, which incorporates tumor size, invasion, and proliferation markers, has been validated in several studies as a reliable predictor of recurrence. [17], [20] demonstrated that the Trouillas' grading system, when combined with additional factors such as Ki-67 and p53, provides a comprehensive risk assessment tool that can guide postoperative management.

Moreover, the integration of molecular and imaging biomarkers into predictive models holds promise in improving the accuracy of recurrence risk stratification. In line with the findings of [29], the use of MRI-based radiomics, which assesses imaging features at the voxel level, has demonstrated significant potential in predicting tumor behavior and recurrence. These advances suggest that future models will likely incorporate a combination of clinical, histopathological, and imaging data to provide a more individualized risk assessment for patients with pituitary adenomas.

4.6 Limitations and Future Directions

This systematic review offers valuable insights but has several limitations. Many included studies were retrospective, introducing biases in data collection and interpretation. Additionally, variations in study design, patient populations, and follow-up durations complicate direct comparisons, limiting the findings' generalizability. Future research should prioritize prospective multicenter studies with standardized data collection, imaging, and molecular analysis protocols. This approach would better validate prognostic factors and aid in developing predictive models applicable across various clinical settings. Moreover, the impact of adjuvant therapies like radiotherapy and medical therapy on reducing recurrence rates requires further investigation, especially for high-risk patients ineligible for complete surgical resection.

5. Conclusion

This systematic review identified several key factors associated with the recurrence of pituitary adenomas following surgical resection. Tumor size, invasiveness, molecular markers, extent of resection, and patient demographics play significant roles in determining the likelihood of recurrence. The findings underscore the importance of a multidisciplinary approach to the management of pituitary adenomas, incorporating detailed preoperative assessment, meticulous surgical techniques, and close postoperative monitoring, particularly in high-risk patients.

Moreover, the integration of molecular markers and advanced imaging techniques into predictive models offers potential for more personalized treatment strategies. By identifying patients at a higher risk of recurrence, clinicians can tailor postoperative management, including the use of adjuvant therapies and more frequent monitoring, to improve the long-term outcomes. Further research is needed to refine these predictive models and to develop evidence-based guidelines for the management of recurrent pituitary adenomas.

In conclusion, although significant progress has been made in understanding the factors associated with pituitary adenoma recurrence, there remains a need for ongoing research to address the challenges of tumor heterogeneity, incomplete resection, and the development of targeted therapies. By continuing to build on the insights gained from such studies, the goal of achieving long-term disease control in patients with pituitary adenomas may become increasingly attainable.

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Table 1. Characteristic of Eligible Studies

No	Author	Year	# of Samples	Follow-up Time	Recurrence Rate (N; %)	Age at diagnosis/surgery (year)	Time to recurrence/ progression (months)	Tumor Type
1	[11]	2014	64	24,3 yrs[a]	6; 9,4%	46,7 ± 116,7[a]	N/A	NFPA, FPA

2	[12]	2014	47	5,2 (3 – 8,5) yrs[b]	N/A	40,8 (17 – 73)[b]	N/A	FPA
3	[13]	2016	289	4 (1 – 12,6) yrs[b]	47; 16,3%	51 (15 – 79)[b]	N/A	NFPA
4	[14]	2016	50	N/A*	17; 34,0%	34,8 ± 16,4[a]	N/A	NFPA, FPA
5	[15]	2017	123	48 (31 – 86) mos[b]	36; 29,3%	57 (45 – 69)[bΔ]	44,5 (22 – 80)[b†] 48 (12 – 96)[b‡]	NFPA
6	[16]	2018	39	6,4 ± 5,9 yrs[a]	14; 35,9%	50 ± 14[a]	44 ± 37[a]	FPA
7	[17]	2018	120	48 (5 – 187) mos[b]	38; 31,67%	56,4 ± 15,0[a]	N/A	NFPA, FPA
8	[18]	2018	30	4 (1 – 6,1) yrs[b]	17; 56,7%	N/A	N/A	NFPA
9	[19]	2019	30	45 mos[a]	19; 63,3%	53 (46,5 – 59,5)[b]	24[b]	NFPA
10	[20]	2019	566	5,8 yrs[a]	60; 10,6%	49,8 ± 15,5[a]	64,8 (4 – 210)[b]	NFPA, FPA
11	[21]	2020	1066	65,6 mos[a]	116; 10,9%	50,7 ± 15,9[a]	47,9 (0,3 – 208,8)[b]	NFPA, FPA
12	[22]	2021	39	24 (4 – 79) mos[b]	1; 3%	37 (8 – 75)[b]	N/A	FPA
13	[23]	2021	172	5 yrs[s]	70; 40,7%	53 ± 12,7[a]	N/A	NFPA, FPA
14	[24]	2022	60	52 (24 – 152) mos[b]	12; 20%	40 ± 19[a]	N/A	FPA
15	[25]	2023	64	25,5 ± 8,24 mos[a]	19; 29%	41,6 ± 12,68[a]	N/A	FPA
16	[26]	2023	55	2,73 ± 2,11 yrs[a]	17; 30,99%	44,6 ± 14,1[a]	N/A	FPA

[a]Value stated in mean (with or without ± SD)
[b]Value stated in median (with or without range)
*Follow-up period of minimum 10 years, as stated in methodology
ΔMedian age (interquartile range) of total 177 subjects
†Median for regrowth (in residual adenoma)
‡Median for recurrence (in completely resected adenoma)

Table 2. Summary of Studies Finding

No	Author	Tumor Type	Study Conclusion
1	[11]	NFPA, FPA	Amenorrhea and tumor diameter > 10 mm are significant risk factors for radiographic recurrence
2	[12]	FPA	The level of Ki-67 expression was higher among patients with hormonal recurrence The p53 expression level was remarkably higher in patients with radiological recurrence Patients younger than 30 years of age and those with mixed GH-prolactin secreting adenomas had significantly higher hormonal remission and lower radiological recurrence rates.
3	[13]	NFPA	Extent of resection (EOR) and adjuvant radiotherapy are significant prognostic factors for recurrence. Immunohistochemistry (IHC) assay did not yield consistent result
4	[14]	NFPA, FPA	Parasellar invasion is a strong predictive factor for tumor recurrence

5	[15]	NFPA	Residual disease and younger age at presentation is a risk factors for tumor regrowth/recurrence
6	[16]	FPA	Less cystic tumor and higher preoperative ACTH is predictor in silent corticotroph adenoma recurrene
7	[17]	NFPA, FPA	Grade 2b of Trouillas' grading for clinicopathological classification of pituitary adenoma has significantly higher risk than grade 1a
8	[18]	NFPA	Ki-67 and p21 are significantly higher in regrowing tumor
9	[19]	NFPA	Low ADC values/ratio increases risk of progression/recurrence
10	[20]	NFPA, FPA	Trouillas' grading is an independent predictor for pituitary adenoma evolution
11	[21]	NFPA, FPA	The combined evaluation of Trouillas' grading, proliferation indexes and immunohistochemistry appears promising in the prediction of surgical outcome in PitNET
12	[22]	FPA	Larger size of tumor, such as macroadenomas, and higher day 3 cortisol concentration are associated with higher recurrence rates after surgery
13	[23]	NFPA, FPA	Body mass index (BMI) ≥25 kg/m², Knosp classification grade 4, partial tumor resection, a Ki-67 index ≥3%, and a history of smoking are independent risk factors associated with recurrence or progression
14	[24]	FPA	Overexpression of *SSTR1*, *CRHR1*, and *MKI67* are showing significant associates with higher recurrence rate Tumor size, serum prolactin, and post-surgery cortisol level were associated with higher tumor recurrence
15	[25]	FPA	Shorter duration of glucocorticoid (<6 months) were associated with higher recurrence rates. Higher Ki-67 index and postoperative cortisol and ACTH values were not found to be significantly associated with tumor recurrence
16	[26]	FPA	Cavernous sinus invasion, suprasellar extension, and a history of prior operations were significant predictors of tumor recurrence, with intraoperative ACTH levels and postoperative day 1 morning cortisol levels being reliable markers of surgical outcomes.

Table 3. Quality Assessment of Included Studies Based On Newcastle-Ottawa Scale (NOS)

Study	Selection	Comparability	Outcome	Total Stars
[11]	★★★★	★★	★★★	9
[12]	★★★☆	★★	★★★	8
[13]	★★★★	★★	★★★	9
[14]	★★★☆	★★	★★★	8
[15]	★★★★	★★	★★★	9
[16]	★★★★	★★	★★★	9
[17]	★★★★	★★	★★★	9
[18]	★★★☆	★★	★★★	8
[19]	★★★★	★★	★★★	9
[20]	★★★★	★★	★★★	9
[21]	★★★★	★★	★★★	9
[22]	★★★★	★★	★★★	9

[23]	★★★★	★★	★★★	9
[24]	★★★★	★★	★★★	9
[25]	★★★★	★★	★★★	9
[26]	★★★★	★★	★★★	9