

Endoscopic Endonasal Transsphenoidal Surgery (EETS) for PitNETs: Outcomes in a Single Institution Over a Decade

**Jamie ROSEN^{1,2,3}, Zenab SHER², Pratibha NATESH^{1,3}, Mekha KADAVILEVEETIL³,
Miran ALBATAYNEH³, Rudra SHAH³, Mehdi MAQSOOD³, Sanjni BHUDIA²,
Amy HODDER², Henry ANANWUNE², Fatima NOSHAD³, Radu BELTECHI²,
Gregory KALTSAS⁴, Amjad SHAD², Harpal RANDева^{1,3}**

¹ Warwick Medical School, University of Warwick, Medical School Building, Coventry CV4, United Kingdom.
² Department of Neurosurgery, University Hospital Coventry and Warwickshire, Clifford Bridge Rd, Coventry CV2 2DX, United Kingdom.
³ Department of Endocrinology, University Hospital Coventry and Warwickshire, Clifford Bridge Rd, Coventry CV2 2DX, United Kingdom.
⁴ Department of Endocrinology, National and Kapodistrian, University of Athens, Greece.

Correspondence to: Jamie Rosen Bsc
Warwick Medical School, University of Warwick, Medical School Building,
Coventry CV4, United Kingdom
E-MAIL: jamie.rosen@warwick.ac.uk; ORCID: 0009-0005-7505-6871

Submitted: 2025-08-21 Accepted: 2025-12-29 Published online: 2025-12-29

Key words: PitNET; Visual fields; Transsphenoidal surgery; Ki-67

Neuroendocrinol Lett 2025; **46**(7):394-401 PMID: 41565580 460707 © 2025 Neuroendocrinology Letters • www.nel.edu

Abstract

OBJECTIVES: This study aimed to evaluate the outcomes, histopathology and recurrence of pituitary neuroendocrine tumours following Endoscopic Endonasal Transsphenoidal Surgery (EETS) in a single institution, over a period of ten years. **METHODS:** A retrospective, cross-sectional study evaluated our experience and outcomes of EETS in 152 patients between 2013 and 2024. We analysed patient demographics and histopathology, as well as surgical complications. Outcomes such as tumour recurrence and improvement of visual field defects were recorded. **RESULTS:** There were 64 males (42.1%) and 88 female patients (57.9%). Presentations included visual field disturbance, incidentaloma, acromegaly, headaches and Cushing's disease. 133 (87.5%) were macroadenomas and 14 (9.2%) microadenomas. Cavernous sinus invasion was observed in 35 patients (23.0%). Histologically, 72 (47.4%) gonadotroph tumours, 25 (16.4%) somatotroph tumours, 12 (7.9%) non-staining PitNETs/Null cell tumours, 12 (7.9%) corticotroph tumours, 11 (7.2%) plurihormonal tumours, 4 (2.6%) silent corticotroph tumours, 3 (2.0%) cysts, 1 (0.7%) prolactinoma, 1 (0.7%) thyrotroph tumour, and 11 (7.2%) were miscellaneous. Recurrence occurred in 29 (19.1%) patients, out of which 18 (11.8%) required further surgery. 51 (33.6%) patients experienced complications, such as cerebrospinal fluid (CSF) leak in 15 (9.9%) patients. A greater proportion of patients demonstrated normal visual fields postoperatively. Postoperative complications were similar to those reported in literature. Of note, recurrent tumours tended to have a low Ki-67 index of 0-3%.

CONCLUSION: Our findings are in line with those reported in literature, including histopathology of tumour subtypes and surgical complication rates. Visual field defects significantly improved following EETS. We note that predictors of postoperative recurrence cannot rely on the Ki-67 index alone; radiological, biochemical, and other histopathological markers need to be considered.

INTRODUCTION

Pituitary neuroendocrine tumours (PitNETs) are predominantly benign tumours of the anterior pituitary gland, accounting for nearly 15% of intracranial tumours (Ezzat *et al.* 2004). Their usual presentation is either incidental, or due to visual field disturbances or hormonal imbalance. Previously known as pituitary adenomas (PAs), they were renamed as pituitary neuroendocrine tumours (PitNETs) by the World Health Organisation (WHO) in 2022 on the basis of the clinical and biological spectrum of the condition (Asa *et al.* 2022). PitNETs can be classified by various factors, such as size (for example micro- vs macroadenoma), functional status (hormone-secreting versus non-hormone secreting) and invasiveness (Knosp classification for cavernous sinus invasion) (Asa *et al.* 2022; Lenders *et al.* 2023).

Endoscopic Endonasal Transsphenoidal Surgery (EETS) is a minimally invasive surgical technique preferred to resect PitNETs in most cases (Yu *et al.* 2018). The transcranial approach is now only reserved for complex PitNETs associated with significant suprasellar extension or those not accessible via the endonasal approach. Medical management is the first line of treatment for prolactinomas (Melmed *et al.* 2011). EETS is done to remove functioning tumours such as

in acromegaly, Cushing's disease, thyrotroph tumours, medication-resistant prolactinomas and non-functioning pituitary neuroendocrine tumours (NF-PitNET) that are associated with significant visual field disturbances. Most common complications following EETS include cerebrospinal fluid (CSF) leakage and diabetes insipidus (DI) which is now more accurately renamed to Arginine vasopressin deficiency (AVP-D) (Stefanidis *et al.* 2022). The recurrence of PitNETs can be predicted on the basis of the extent of tumour invasion and histological markers (Lu *et al.* 2022).

The aim of this study was to evaluate the outcomes associated with EETS for 152 PitNETs at a tertiary hospital in the United Kingdom (UK). We analysed the histology of PitNET types, the recurrence data in relation to Ki-67 index, as well as surgical complications of EETS, with the objective being to compare them to known rates reported in current literature.

METHODS

A retrospective analysis of 152 pituitary surgeries that were performed at a single institution between 2013 and 2024 was done using the electronic patient database. We did not include craniopharyngiomas in this study. All patients underwent endocrine, ophthalmological and neuroradiological assessments prior to surgery. Surgeries were performed by neurosurgeons, with the nasal approach often being carried out by Ear, Nose and Throat (ENT) surgeons. All authors complied with the ARRIVE guidelines (Percie du Sert *et al.* 2020).

Primary outcomes assessed patient demographics such as age and sex, as well as postoperative surgical complications of CSF leakage and tumour recurrence. Secondary outcomes looked at the extent of resection and visual field improvement.

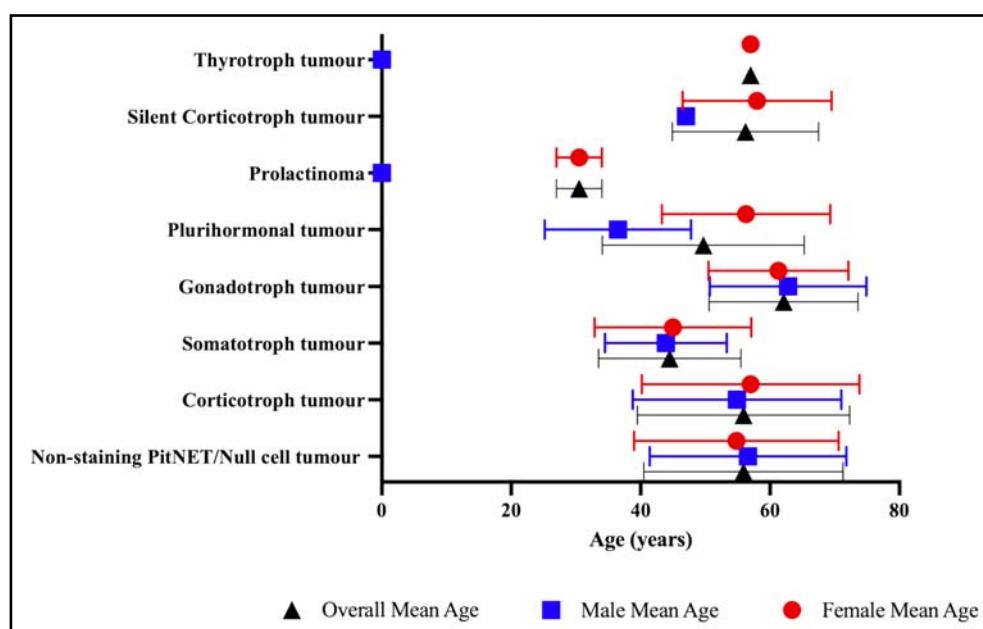


Fig. 1. Mean patient age at diagnosis of PitNET

Endocrine assessment

Preoperatively, all the patients underwent assessment of thyroid-stimulating hormone (TSH), free T4 (FT4), free T3 (FT3), cortisol, and adrenocorticotropic hormone (ACTH) in cases of secondary adrenal insufficiency or Cushing's disease; insulin-like growth factor 1 (IgF1); luteinising hormone (LH); follicle-stimulating hormone (FSH); prolactin; testosterone; and electrolytes. Acromegaly patients underwent oral glucose tolerance tests to assess the growth hormone response (GH) and IgF1. Patients with suspected Cushing's disease were subjected to an overnight dexamethasone suppression test, 24-hour urine-free cortisol measurement, late night salivary cortisol and inferior petrosal sinus sampling. Serum and urine osmolality, urea and electrolytes and urine sodium were checked if there were symptoms of DI/AVP-D and syndrome of inappropriate antidiuretic hormone secretion (SIADH). Six weeks after surgery, patients underwent short synacthen test, thyroid function tests, electrolytes, and IgF1. Patients with acromegaly underwent an oral glucose tolerance test to assess remission. Cushing's disease patients had an overnight dexamethasone suppression test and 24-hour urine-free cortisol.

Ophthalmological assessment

Goldmann visual field (GVF) assessment was performed before and after surgery in patients with macroadenomas. Preoperative and postoperative visual field status was categorised as normal, abnormal, or not recorded. Descriptive statistics were generated for each

Tab. 1. Baseline demographics and presenting complaints of the study cohort

Value	N (%)
Sex	
Male	64 (42.1%)
Female	88 (57.9%)
Mean age at surgery (Years, SD)	56.5 ± 14.9
Age range at surgery (Years)	19-86
Ethnicity	
Asian	7 (4.6%)
Black	8 (5.3%)
White	121 (79.6%)
Other	6 (3.9%)
Not Recorded	10 (6.6%)
Presenting complaints	
Visual field disturbances	70 (46.1%)
Incidentaloma	38 (25%)
Acromegalic features	25 (16.4%)
Headaches	13 (8.6%)
Features of Cushing's disease	6 (3.9%)

timepoint. To evaluate overall changes in the distribution of visual field categories following surgery, a chi-square test of independence was performed comparing preoperative and postoperative visual field defects. This analysis assessed whether the postoperative distribution differed significantly from the preoperative distribution. Statistical significance was defined as $p < 0.05$.

Neuroradiology

Dedicated pituitary magnetic resonance imaging (MRI) with intravenous contrast was performed for most of the patients. Those who had MRI non-compatible pacemakers had computed tomography (CT) of the pituitary gland. Three months postoperatively, all the patients underwent dedicated pituitary imaging.

Knosp Classification

We classified the tumours using the Knosp classification. This categorises cavernous sinus invasion in relation to the intracavernous internal carotid artery, from grade 0 (no invasion) to grade 4 (complete encasement) (Knosp *et al.* 1993).

Endoscopic Transsphenoidal Surgical Technique

The surgery is carried out in three parts, as per the standard surgical technique. In the nasal stage, the endoscope is introduced into the nasal cavity. The sphenoidal stage then involves removal of any septi and exposure of the sellar protuberance, through an anterior sphenoidotomy. The sellar stage involves removal of the lesion through an opening in the sellar floor. Resection of tumour is completed with bimanual technique using ring curettes and suction. Closure then ensues, with reconstruction of the defect in the sellar floor.

Extent of Resection

More than 95% of tumour removal on post-operative imaging was determined to be a gross total resection. More than 80% of tumour removed was taken as subtotal resection, and if less than 80% of the lesion was resected, this was deemed a partial resection (Tanji *et al.* 2020).

Histopathology

The histology of the surgical samples was analysed by neuropathologists.

Statistical analysis

Statistical analysis was performed using Microsoft Excel (version 16.91) and Prism (version 10.4.1). The results are presented as whole numbers, percentages, means, standard deviations (SD) and ranges. The overall mean age at diagnosis and the mean age of male and female were also calculated along with their standard deviations.

We examined the association between extent of resection and tumour recurrence. Resection was categorised as total, subtotal, or partial. For statistical

Tab. 2. Preoperative and postoperative visual field findings

Value	N (%)
Preoperative visual fields	
Normal	75 (49.3%)
Abnormal	70 (46.1%)
Not recorded	7 (4.6%)
Postoperative visual fields	
Normal	121 (79.6%)
Abnormal	16 (10.5%)
Not recorded	15 (9.9%)

analysis, subtotal and partial resections were grouped together and compared with total resection. Recurrence was defined as radiologically or clinically confirmed regrowth. Categorical variables were compared using χ^2 tests with Yates' correction, and Fisher's exact test was used as appropriate. Odds ratios (OR) with 95% confidence intervals (CI) were calculated from 2x2 contingency tables, and a *p*-value < 0.05 was considered statistically significant.

RESULTS

Study population

A total of 152 patients were included, of whom 57.9% were female and 42.1% were male (*p* = 0.052). The mean age was 56.5 ± 14.9 years, and the majority of patients were white caucasian (79.6%). The most frequent presenting complaint was visual field disturbance (70 patients, 46.1%), followed by other symptoms as detailed in Table 1.

The youngest mean age was observed in females with prolactinoma (30.5 ± 3.5 years; Figure 1), while in males it was in those with plurihormonal tumours (36.5 ± 11.3 years). The oldest patients were those with gonadotroph tumours, with mean ages of 62.8 ± 12.1

years in males and 61.3 ± 10.8 years in females. Overall, the mean age across all PitNET patients was 55.9 ± 15.4 years, with subtype means ranging from 30.5 years for prolactinoma to 62.1 years for gonadotroph tumours.

Visual fields

Preoperatively, visual fields were abnormal in 70 patients (46.1%), most commonly bitemporal hemianopia 41 (27.0%). Postoperatively, visual fields normalised in 121 patients (79.6%), remained abnormal in 16 (10.5%), and were not recorded in 15 (9.9%) (Table 2).

A chi-square test of independence was performed to compare the distribution of visual field status before and after surgery. The overall distribution differed significantly between timepoints ($\chi^2(2) = 47.6$, *p* < 0.001). Postoperatively, a greater proportion of patients demonstrated normal visual fields and fewer had abnormal fields compared with the preoperative distribution.

Knosp score and extent of resection

Cavernous sinus invasion was determined by the Knosp score. A total of 119 patients (78.3%) had low Knosp grades (0–2), while cavernous sinus invasion (Knosp ≥3) was observed in 35 patients (23.0%). Gross total resection was achieved in 101 patients (66.4%), with the remaining 50 patients (32.9%) undergoing subtotal or partial resection (Table 3).

Histopathology of PitNETs

Histopathology was categorised into 10 tumour subtypes (Table 4):

Non-staining/Null cell PitNET

These are the cohort of tumours which did not demonstrate any hormonal staining. Twelve (7.9%) patients had non-staining/Null cell PitNET. No patients underwent a 2nd or 3rd surgery or pituitary radiotherapy, and 8 (5.3%) had a Ki-67 index ≤3%.

Corticotroph tumours

Twelve (7.9%) patients had corticotroph tumours. Of the 12 patients, 5 (3.3%) had a preoperative clinical diagnosis of Cushing's disease. Biochemical remission occurred in 3 (2.0%) Cushing's disease patients. Two (1.3%) of the corticotroph tumour patients underwent a 2nd or 3rd surgery, and 2 (1.3%) had radiotherapy.

Somatotroph tumours

Twenty-five patients (16.4%) had somatotroph tumours, and all had a preoperative clinical diagnosis of acromegaly. Twenty-two (14.5%) were macroadenomas, and 3 (2.0%) were microadenomas. Seven (4.6%) patients had biochemical recurrence, and all were treated with somatostatin analogues. Two (1.3%) patients were treated with Pegvisomant, and 1 (0.7%) of these started on Pasireotide due to Pegvisomant intolerance. Two

Tab. 3. Knosp Score & Extent of Resection

Value	N (%)
Knosp Score	
Grade 0	101 (66.4%)
Grade 1	8 (5.3%)
Grade 2	10 (6.6%)
Grade 3	22 (14.5%)
Grade 4	11 (7.2%)
Extent of Resection	
Total (>95%)	101 (66.4%)
Subtotal (>80%)	31 (20.4%)
Partial (<80%)	19 (12.5%)
Lost to follow-up	1 (0.7%)

Tab. 4. PitNET histopathology and tumour size

Histology	N (%)
Gonadotroph tumours	72 (47.4%)
Somatotroph tumours	25 (16.4%)
Non-staining PitNET/Null cell tumour	12 (7.9%)
Corticotroph tumours	12 (7.9%)
Plurihormonal tumours	11 (7.2%)
ACTH, LH and FSH	1 (0.7%)
ACTH, GH, FSH and LH	1 (0.7%)
GH and ACTH	1 (0.7%)
GH and Prolactin	7 (4.6%)
FSH, GH and Prolactin	1 (0.7%)
Silent Corticotroph tumours	4 (2.6%)
Prolactinoma	1 (0.7%)
Thyrotroph tumours	1 (0.7%)
Cyst	3 (2.0%)
Miscellaneous	11 (7.2%)
Ki-67 Index	
0-2	72 (47.4%)
2.1-3	19 (12.5%)
>3.1	16 (10.5%)
Not Recorded	45 (29.6%)
Tumour Size	
Macroadenoma (>1 cm)	133 (87.5%)
Microadenoma (<1 cm)	14 (9.2%)
Giant Adenoma (>4 cm)	16 (10.5%)
Not applicable (N/A)	5 (3.3%)

(1.3%) patients were moved to different hospitals, and we were unaware if they had experienced any recurrence. Four (2.6%) underwent a 2nd or 3rd surgery, and 3 (2.0%) received radiotherapy.

Gonadotroph tumours

Seventy-two patients (47.4%) had gonadotroph tumours. All had a preoperative clinical diagnosis of NF-PitNET. The Ki-67 index was $\leq 3\%$ in 49 patients (32.2%) and $>3.1\%$ in 9 (5.9%). Ten patients (6.6%) required a second or third surgery, and 7 (4.6%) received radiotherapy.

Plurihormonal tumours

Eleven patients (7.2%) had plurihormonal tumours. Five patients (3.3%) were clinically diagnosed with acromegaly, 5 (3.3%) with NF-PitNET, and 1 (0.7%) with Cushing's disease. Tumour staining was variable: 1 (0.7%) stained for ACTH, LH and FSH; 1 (0.7%) for ACTH, GH, FSH and LH; 1 (0.7%) for GH and ACTH; 7 (4.6%) for GH and prolactin; and 1 (0.7%) for FSH, GH and prolactin. Ki-67 indices were $\leq 3\%$ in

Tab. 5. Preoperative hormone deficiencies

Value	N (%)
Growth hormone deficiency (GHD)	12 (7.9%)
Secondary hypothyroidism	59 (38.8%)
Secondary hypogonadism	36 (23.7%)
Secondary adrenal Insufficiency	46 (30.3%)

7 patients (4.6%) and $>3.1\%$ in 1 (0.7%). One patient (0.7%) required a second or third surgery, and 2 (1.3%) received radiotherapy.

Prolactinoma

A clinical and histological diagnosis of microprolactinoma was made in 1 patient (0.7%), and no recurrence was noted.

Silent corticotroph tumours

All four patients (2.6%) had a clinical diagnosis of NF-PitNET, and all (2.6%) had a Ki-67 index $\leq 3\%$. Two (1.3%) underwent a second or third surgery, and 1 (0.7%) received radiotherapy.

Thyrotroph tumours

A total of one patient (0.7%) had a thyrotroph tumour histologically. Their clinical diagnosis was of NF-PitNET. There was no endocrine insufficiency, and the Ki-67 index was $\leq 3\%$. There was no recurrence.

Miscellaneous

Eleven (7.2%) miscellaneous diagnoses were made in our sample. Two (1.3%) had lymphocytic hypophysitis, 1 (0.7%) had diffuse large B-cell lymphoma, 1 (0.7%) had cholesterol crystals with xanthogranulomatous reactions, and 7 (4.6%) did not stain for any pituitary neuroendocrine tumour.

Cysts

Three (2.0%) were Rathke's cleft cysts and no recurrence occurred.

Endocrine abnormalities

All patients underwent pre and postoperative endocrine assessment. Preoperatively, the most frequent abnormality was secondary hypothyroidism, followed by secondary adrenal insufficiency and hypogonadism. GH deficiency was least common (Table 5).

Postoperative complications

Fifty-one patients (33.6%) experienced postoperative complications. The most frequent were cerebrospinal fluid (CSF) leak in 15 patients (9.9%) and DI/AVP-D in 14 patients (9.2%). Other less common complications included cranial nerve palsies, hyponatraemia/SIADH, and meningitis. Additional isolated events involved vascular, sinonasal, or wound complications (Table 6).

Tab. 6. Complications of pituitary surgery

Complication type	N (%)
Bleeding	1 (0.7%)
CN ¹ III palsy	1 (0.7%)
CN VI palsy	4 (2.6%)
CSF leak	15 (9.9%)
CSF leak & Meningitis	1 (0.7%)
Diabetes Insipidus (AVP deficiency)	14 (9.2%)
Epistaxis	1 (0.7%)
Hyponatraemia & SIADH	6 (3.9%)
Meningitis	2 (1.3%)
Pneumocephalus	1 (0.7%)
Stroke	1 (0.7%)
Septal perforation	1 (0.7%)
Sinusitis	2 (1.3%)
Wound leak	1 (0.7%)
Total	51 (33.6%)

¹Cranial nerve

Postoperatively, endocrine dysfunction was observed in 47 patients (30.9%).

Postoperative CSF leak occurred in 16/152 patients (10.5%). Leak frequency was similar between gonadotroph tumours (7/72, 9.7%) and all other tumour subtypes (9/80, 11.3%). There was no significant association between histological subtype and CSF leak ($\chi^2(1) = 0.11, p = 0.74$; OR 0.84, 95% CI 0.31–2.23).

Recurrence of PitNETs

Tumour recurrence occurred in 29 patients (19.1%), of which 18 (11.8%) underwent further surgery. Somatotrophs demonstrated the highest recurrence rate (13/25, 52.0%) compared to gonadotrophs (10/72, 13.9%). Among recurrent cases with available Ki-67 data (18/29, 62.1%), 14 (77.8%) had Ki-67 $\leq 3\%$, compared to 62.6% in the non-recurrent cohort ($\chi^2 = 1.43, p = 0.23$). This paradoxical association, in which low Ki-67 did not protect against recurrence, was statistically non-significant, likely due to Ki-67 data unavailability in 37.9% of recurrent cases and the cohort's advanced mean age (56.5 ± 14.9 years). Adjuvant radiotherapy was administered in seven patients (Table 7).

Extent of resection and recurrence

Overall, recurrence requiring further surgery occurred in 18 patients (11.8%). When considered by detailed resection category, recurrence was observed in 10 patients (6.6%) after total resection, 3 (2.0%) after subtotal resection, and 5 (3.2%) after partial resection. When subtotal and partial resections were combined into one group, recurrence occurred in 8 patients

Tab. 7. Clinically Recurrent PitNETs

Tumour Subtype	N (%)
Recurrent PitNETs	29 (19.1%)
Histopathology	
Non-staining PitNET/Null cell tumour	4 (2.6%)
Corticotroph tumour	1 (0.7%)
Somatotroph tumour	13 (8.6%)
Plurihormonal tumour	1
Gonadotroph tumour	10 (6.6%)
Silent corticotroph tumour	1 (0.7%)
Clinical Diagnosis	
Acromegaly	3 (2.0%)
Cushing's disease	1 (0.7%)
Non-functioning pituitary macroadenoma	25 (16.4%)
Ki-67 Index	
0-2	13 (8.6%)
2.1-3	1 (0.7%)
>3.1	4 (2.6%)
Not recorded	11 (7.2%)
Radiotherapy	
Non-staining PitNET/Null cell tumour	2 (1.3%)
Gonadotroph tumour	4 (2.6%)
Plurihormonal tumour	1 (0.7%)
Undergone 2 nd or 3 rd surgery	18 (11.8%)

following subtotal/partial resection and 10 patients following total resection. Statistical comparison using the chi-square test showed no significant difference in recurrence between the groups ($\chi^2 = 1.18, p = 0.28$).

DISCUSSION

Our study reiterated that there were no significant differences between the incidence of PitNETs in male versus female patients. Seventy (46.1%) patients had visual field disturbances as the initial symptom. Existing evidence indicates that following EETS, 30–40% of patients achieve complete recovery of vision, and 4% experience deterioration of vision (Musken et al. 2017). Similar to other studies, our study showed that bitemporal hemianopia due to chiasmal compression remains the most common visual field disturbance (Ogra et al. 2014). Vision normalised in 121 (79.6%) of our patients following surgery.

Following EETs, the incidence of CSF leakage varies between 1.4% and 16.9% (Slot et al. 2022). The most common postoperative complication in our study was CSF leakage with 15 (9.9%) patients affected; this is similar to that reported in literature (Slot et al. 2022). Of note, our data includes presumed CSF leaks and not

only those confirmed with β 2-transferrin, so the total number of our CSF leaks may be even lower.

Postoperative endocrine dysfunction could be due to damage to the pituitary tissue during surgery, compression of the pituitary tissue by the mass, and a lack of blood supply to the pituitary stalk and portal vessels (Arafah, 1986).

Compared with the transcranial approach, EETS has a lower incidence of complications. However, microscopic resection does not significantly reduce endocrine dysfunction (Møller *et al.* 2020; Wang *et al.* 2022).

Fourteen (9.2%) patients experienced postoperative DI/AVP deficiency. Transient AVP deficiency accounts for 16%, and permanent AVP deficiency accounts for 3% following pituitary surgery (Fountas *et al.* 2024). Our study considered the overall incidence of DI/AVP-D in the early post-operative phase. This is within the rates stated in literature which range from 3 to 66% in surgery for PitNETs (Fountas *et al.* 2024). The incidence of hyponatremia or SIADH and cranial nerve palsies was consistent with the literature (Florea *et al.* 2020; Little *et al.* 2020).

CSF leak risk did not differ across tumour subtypes, suggesting that tumour phenotype is not a major determinant of postoperative leak. This aligns with evidence that anatomical and surgical factors are more influential predictors of post-operative leak than histopathology (Zhou *et al.* 2021).

Despite the established predictive value of Ki-67 $>3\%$ (Losa *et al.* 2000), 77.8% (14/18) of our recurrent tumours with recorded indices measured $\leq 3\%$. This implies limited negative predictive value but must be interpreted with caution: Ki-67 data were missing in 37.9% (11/29) of recurrent cases, creating potential selection bias. While the recurrence in older gonadotrophs (mean 62.1 years) suggests age-related proliferative suppression, our data lacks the age-stratified controls necessary to validate this hypothesis. Furthermore, since neither extent of resection ($p = 0.28$) nor low Ki-67 prevented recurrence, unmeasured biological drivers likely predominate. Consequently, clinicians should not use a low Ki-67 ($\leq 3\%$) to exclude recurrence risk; surveillance intensity must remain rigorous regardless of proliferation index, relying instead on multimodal assessment including Knosp grade and hormonal status.

Recurrence in our cohort was low, and it did not differ significantly based on the extent of resection. When grouped together, subtotal/partial resections had a recurrence rate similar to gross total resections, and the odds of recurrence were essentially unchanged. This suggests that factors beyond surgical extent of resection, such as tumour behaviour or subtype, may play a larger role in driving recurrence. This reiterates that the number of our recurrence events was small and larger studies with longer follow-up would be instrumental to clarify these relationships.

Limitations

This is a retrospective, non-randomised and cross-sectional study. The sample size was small, which may affect the generalisability of the findings. Additionally, postoperative evaluations of endocrine function were incomplete in some cases. Visual field assessments were also missing for certain patients, primarily because these individuals received follow-up care at different hospitals leading to variability in data availability and consistency. These limitations should be considered when interpreting the results. Future studies with a larger sample size, possibly incorporating a regional experience could be more informative. Apart from Ki-67 index, markers such as p53 expression (Cai *et al.* 2021), as well as factors such as the extent of cavernous sinus invasion are of importance in predicting the recurrence of PitNETs. These factors could also be studied to further explain the behaviour of PitNETs.

CONCLUSION

The prevalence of pituitary tumours, outcomes of pituitary surgery, extent of resection and recurrence in our relatively small sample over 10 years, are in line with existing literature. We present data which alludes to endoscopic pituitary surgery continuing to be an optimal surgical procedure for the majority of PitNETs. The complication rate and the recurrence rate is low, and in line with known data. We do note, however, that the Ki-67 index needs careful consideration when used to predict the risk of recurrence of PitNETs. This is because most of the tumours which recurred had a low Ki-67 index, in the region of 0-3%. Overall, our data shows that EETS remains the optimal choice of surgical resection of PitNETs, with its low rate of complications and high rate of successful surgical, visual and endocrinological outcomes.

ETHICAL DECLARATIONS

Ethics approval and consent to participate

All methods and procedures in this study were performed in accordance with The Declaration of Helsinki. Ethical clearance was not required as this was a retrospective study. The audit (study) is registered with the audit department at University Hospital Coventry and Warwickshire and the reference number for the audit (study) is 1879.

Consent for publication

Ethics approval was waived by the IRB. This retrospective study has been registered as an audit (study) at University Hospital Coventry and Warwickshire, and the reference number is 1879.

Availability of data and materials

Data is available from the corresponding author upon reasonable request.

Disclosure Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding

No funding received.

Author contributions

J.R - Abstract, data collection, figures and tables, manuscript writing, statistical analysis, results, Reviewed manuscript

Z.S - Manuscript writing, data collection, contribution towards describing postoperative complications, Reviewed manuscript

P.N - Lead PI, Abstract, data collection, discussion, introduction, manuscript writing, methods, project design, results, Reviewed manuscript

M.K - Data collection, Reviewed manuscript

M.A - Data collection, Reviewed manuscript

R.S - Data collection, Reviewed manuscript

M.M - Data collection, Reviewed manuscript

S.B - Data collection, Reviewed manuscript

A.H - Data collection, Reviewed manuscript

H.A - Data collection, Reviewed manuscript

F.N - Data collection, Reviewed manuscript

R.B - Data collection, Reviewed manuscript

G.K - Reviewed and provided recommendation on manuscript.

H.R - Reviewed manuscript

A.S - Project design, Reviewed manuscript

J.R, Z.S., and P.N are joint 1st authors

All authors consent for this manuscript to be published.

Acknowledgements

We would like to acknowledge Mr Shahzada Ahmed and Mr Dheeraj Karamchandani (ENT surgeons).

REFERENCES

- 1 Arafah BM (1986). Reversible Hypopituitarism in Patients with Large Nonfunctioning Pituitary Adenomas. *J Clin Endocrinol Metab.* **62:** 1173–1179. <https://doi.org/10.1210/jcem-62-6-1173>
- 2 Asa SL, Mete O, Perry A, Osamura RY (2022). Overview of the 2022 WHO Classification of Pituitary Tumors. *Endocr Pathol.* **33:** 6–26. <https://doi.org/10.1007/s12022-022-09703-7>
- 3 Cai X, Zhu J, Yang J, Tang C, Yuan F, Cong Z, et al. (2021). A Nomogram for Preoperatively Predicting the Ki-67 Index of a Pituitary Tumor: A Retrospective Cohort Study. *Front Oncol.* **11:** 687333. <https://doi.org/10.3389/fonc.2021.687333>
- 4 Ezzat S, Asa SL, Couldwell WT, Barr CE, Dodge WE, Vance ML, et al. (2004). The prevalence of pituitary adenomas. *Cancer.* **101:** 613–619. <https://doi.org/10.1002/cncr.20412>
- 5 Florea SM, Graillon T, Cuny T, Gras R, Brue T, Dufour H (2020). Ophthalmoplegic complications in transsphenoidal pituitary surgery. *J Neurosurg.* **133:** 693–701. <https://doi.org/10.3171/2019.5.JNS19782>
- 6 Fountas A, Couliden A, Fernández-García S, Tsermoulias G, Allotey J, Karavitaki N (2024). Central diabetes insipidus (vasopressin deficiency) after surgery for pituitary tumours: a systematic review and meta-analysis. *Eur J Endocrinol.* **191:** S1–S13. <https://doi.org/10.1093/ejendo/lvae084>
- 7 Knosp E, Steiner E, Kitz K, Matula C (1993). Pituitary Adenomas with Invasion of the Cavernous Sinus Space. *Neurosurgery.* **33:** 610–618. <https://doi.org/10.1227/00006123-199310000-00008>
- 8 Lenders NF, Earls PE, Inder WJ, McCormack AI (2023). The evolution in pituitary tumour classification: a clinical perspective. *Endocrine Oncol (Bristol).* **3:** e220079. <https://doi.org/10.1530/EO-22-0079>
- 9 Little AS, Kelly DF, White WL, Gardner PA, Fernandez-Miranda JC, Chicoine MR, et al. (2020). Results of a prospective multicenter controlled study comparing surgical outcomes of microscopic versus fully endoscopic transsphenoidal surgery for nonfunctioning pituitary adenomas: the Transsphenoidal Extent of Resection (TRANSSPHER) Study. *J Neurosurg.* **132:** 1043–1053. <https://doi.org/10.3171/2018.11.JNS181238>
- 10 Losa M, Franzin A, Mangili F, Terreni MR, Barzaghi R, Veglia F, et al. (2000). Proliferation index of nonfunctioning pituitary adenomas: correlations with clinical characteristics and long-term follow-up results. *Neurosurgery.* **47:** 1313–1318.
- 11 Lu L, Wan X, Xu Y, Chen J, Shu K, Lei T (2022). Prognostic Factors for Recurrence in Pituitary Adenomas: Recent Progress and Future Directions. *Diagnostics (Basel).* **12:** 977. <https://doi.org/10.3390/diagnostics12040977>
- 12 Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, et al. (2011). Diagnosis and Treatment of Hyperprolactinemia: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* **96:** 273–288. <https://doi.org/10.1210/jc.2010-1692>
- 13 Møller MW, Andersen MS, Glintborg D, Pedersen CB, Halle B, Kristensen BW, et al. (2020). Endoscopic vs. microscopic transsphenoidal pituitary surgery: a single centre study. *Sci Rep.* **10:** 21942. <https://doi.org/10.1038/s41598-020-78823-z>
- 14 Muskens IS, Zamanipoor Najafabadi AH, Briceno V, Lamba N, Senders JT, et al. (2017). Visual outcomes after endoscopic endonasal pituitary adenoma resection: a systematic review and meta-analysis. *Pituitary.* **20:** 539–552. <https://doi.org/10.1007/s11102-017-0815-9>
- 15 Ogra S, Nichols AD, Styli S, Kaye AH, Savino PJ, Danesh-Meyer HV (2014). Visual acuity and pattern of visual field loss at presentation in pituitary adenoma. *J Clin Neurosci.* **21:** 735–740. <https://doi.org/10.1016/j.jocn.2014.01.005>
- 16 Percie du Sert N, Ahluwalia A, Alam S, Avey MT, Baker M, Browne WJ, et al. (2020). Reporting animal research: Explanation and elaboration for the ARRIVE guidelines 2.0. *PLoS Biol.* **18:** e3000411. <https://doi.org/10.1371/journal.pbio.3000411>
- 17 Slot EMH, Sabaoglu R, Voormolen EHJ, Hoving EW, van Doormaal TPC (2022). Cerebrospinal Fluid Leak after Transsphenoidal Surgery: A Systematic Review and Meta-analysis. *J Neurol Surg B Skull Base.* **83:** e501–e513. <https://doi.org/10.1055/s-0041-1733918>
- 18 Stefanidis P, Kyriakopoulos G, Athanasiou F, Mytareli C, Tzanis G, Korfias S, et al. (2022). Correction: Postoperative complications after endoscope-assisted transsphenoidal surgery for pituitary adenomas: a case series, systematic review, and meta-analysis of the literature. *Hormones.* **21:** 345–345. <https://doi.org/10.1007/s42000-022-00367-w>
- 19 Tanji M, Kataoka H, Kikuchi M, Sakamoto T, Kuwata F, Matsunaga M (2020). Impact of Intraoperative 3-Tesla MRI on Endonasal Endoscopic Pituitary Adenoma Resection and a Proposed New Scoring System for Predicting the Utility of Intraoperative MRI. *Neurol Med Chir (Tokyo).* **60:** 553–562. <https://doi.org/10.2176/nmc.oa.2020-0060>
- 20 Wang X, Li M, Jiang X, Wang F, Ling S, Niu C (2022). Prediction of Higher Ki-67 Index in Pituitary Adenomas by Pre- and Intra-Operative Clinical Characteristics. *Brain Sci.* **12:** 1002. <https://doi.org/10.3390/brainsci12081002>
- 21 Yu S, Du Q, Yao S, Zhang K, Wang J, Zhu Z, Jiang X (2018). Outcomes of endoscopic and microscopic transsphenoidal surgery on non-functioning pituitary adenomas: a systematic review and meta-analysis. *J Cell Mol Med.* **22:** 2023–2027. <https://doi.org/10.1111/jcmm.13445>
- 22 Zhou Z, Zuo F, Chen X, Zhao Q, Luo M, Jiang X, et al. (2021). Risk factors for postoperative cerebrospinal fluid leakage after transsphenoidal surgery for pituitary adenoma: a meta-analysis and systematic review. *BMC Neurol.* **21:** 417. <https://doi.org/10.1186/s12883-021-02440-0>