Clinically Non-Functioning Pituitary Neuroendocrine Tumor Case Series

Shen et al. retrospectively enrolled 114 patients diagnosed as Clinically Non-Functioning Pituitary Neuroendocrine Tumor with postoperative residual tumors after the first operation, and the diameter of the tumors was greater than 10 mm. Univariate and multivariate analyses were conducted to identify independent clinical risk factors. They identified the optimal sequence to generate an appropriate radiomic score (Rscore) that combined pre- and postoperative radiomic features. Three models were established by logistic regression analysis that combined clinical risk factors and radiomic features (Model 1), single clinical risk factors (Model 2), and single radiomic features (Model 3). The models' predictive performances were evaluated using receiver operator characteristic (ROC) curve analysis and area under curve (AUC) values. A nomogram was developed and evaluated using decision curve analysis. Results: Knosp classification and preoperative tumor volume doubling time (TVDT) were high-risk factors ($p < 0.05$) with odds ratios (ORs) of 2.255 and 0.173. T1WI&T1CE had a higher AUC value (0.954) and generated an Rscore. Ultimately, the AUC of Model 1 {0.929 [95% Confidence interval (CI), 0.865-0.993]} was superior to Model 2 [0.811 (95% CI, 0.704-0.918)] and Model 3 [0.844 (95% CI, 0.748-0.941)] in the training set, which was 0.882 (95% CI, 0.735-1.000), 0.834 (95% CI, 0.676-0.992) and 0.763 (95% CI, 0.569-0.958) in the test set, respectively. Conclusions: We trained a novel radiomics-clinical predictive model for identifying patients with NF-PitNETs at increased risk of postoperative residual tumor regrowth. This model may help optimize individualized and stratified clinical treatment decisions [1].

2022

A retrospective analysis of 137 consecutive patients who underwent transsphenoidal surgery for a nonfunctioning pituitary neuroendocrine tumor between 2008 and 2019. Preoperative (demographics, comorbidities), intraoperative (resection extent, operation time, blood loss volume, cerebrospinal fluid leak, tumor consistency), and postoperative [hematoma, meningitis, diabetes insipidus (DI), hormonal assessment] data were collected, with statistical analysis of each factor performed.

Results: Among the 137 patients, delayed hyponatremia occurred in 31 (22.6%). Multivariate analysis revealed that those with hypertension had a significantly higher likelihood of avoiding delayed hyponatremia ($p = 0.004$). Although no correlations of direct surgical factors with delayed hyponatremia were found, multivariate analysis of indirect surgical factors showed that the presence of a firm tumor, transient DI, and meningitis were significantly associated with delayed hyponatremia ($p = 0.014$, 0.001, and 0.047, respectively). There was also a significant association between severe hyponatremia and the appearance of symptoms ($p = 0.002$).

Conclusion: There was a tendency for hypertension to be associated with delayed hyponatremia avoidance, with indirect surgical factors including tumor consistency, transient DI, and meningitis found to have an influence on delayed hyponatremia. It was concluded that attention should be given to non-hypertensive patients with a firm tumor, transient DI, or meningitis after pituitary surgery, as delayed hyponatremia may occur [2].

A prospective series of all patients with an endoscopic transsphenoidal approach for clinically Non-Functioning Pituitary Neuroendocrine Tumor, during the three first years of experience of a newly board-certified neurosurgeon was analyzed. Clinical, radiological, and peri-operative data were collected. The extent of resection (EOR) was determined by formal volumetric analysis. The impact of the learning curve and predictive factors of gross total resection (GTR) were determined.

Fifty-three patients were included in this prospective cohort which was divided in two periods of time ("First period": 30 first cases, and "second period": 23 following cases). Baseline characteristics of the patients in the two periods were similar. The overall occurrence of complications was 22% and was not significantly different in the two periods of time. No patient had a severe neurological complication. Gross total resection was achieved in 70% of patients. The mean Extent of resection was 96%. In a multiple linear regression model, a higher EOR was positively correlated with experience ($p = 0.018$) and negatively correlated with Knosp Score equal to 4 ($p < 0.001$). Predictive factors for GTR were Higher Knosp grade ($p = 0,01$), higher pre-operative volume ($p = 0.03$), and second period of time ($p = 0.01$).

NFPA surgery can be safe and efficient during the learning period. Dedicated intensive learning, careful patient selection, and multidisciplinary work are key to shortening the learning curve and achieving satisfactory results [3].

2021

There were four surgeons who operated 126 cases, 17 of them reoperations. The average age of the patients was 49 years old. The average length of stay was 13 days, and the average operating time was 134 min. Visual field defect was the most common presenting symptom. Almost all the tumors were classified as pituitary macroadenoma which invaded one or two sellar walls. Total or near total tumor removal was the most extended resection. There were 61 cases of developed early diabetes insipidus (DI), but only 12 cases continue to long-term DI. Seven cases were meningitis. Three cases were death. Out of 83 patients who had preoperative intact hypothalamic-pituitary-adrenal (HPA) axis and hypothalamic-pituitary thyroidal (HPT) axis, 2 and 3 of them developed postoperative impaired HPA and HPT axis in that order. In addition, among 45 patients who had preoperative impaired HPA and HPT axis, 6 of them achieved postoperative endocrinological normalization.

In preoperative intact pituitary hormone patients, the total or near total tumor removal of Non-Functioning Pituitary Neuroendocrine Tumor may have hypopituitarism during the early postoperative period but gradually returned to normal during the 4-6 month postoperative period [4].

2019

In a retrospective cohort study of NFPMA patients treated surgically and followed periodically between 2015 and 2017 in a tertiary care center in Iran. Descriptive analysis was performed applying appropriate tests. Binary logistic regression models were used to determine the predictive factors for subtotal resection (STR) and hormonal recovery. Data were analyzed by Stata software.

A total of 71 patients with a mean age of 50.6 ± 1.4 years were studied. The mean diameter of the adenoma was 26.8 ± 1.1 mm. The most frequent symptoms were headache (85.75%), visual field defect (VFD) (78.3%), and hypogonadism (40.3%). Gross total resection (GTR) was achieved in 45.1%.

Preoperative hypopituitarism was observed in 50.7% of patients. Recovery of at least one axis occurred in 36.1% of the patients suffering from hypopituitarism preoperatively, while new-onset postoperative hormonal deficiency appeared in 14.3% of patients. Multivariate analyses showing preoperative tumor size (OR = 38.2; P = 0.008) and cavernous sinus extension (OR = 13.4; P = 0.020) were predictors of STR. Moreover, hormonal recovery was observed not to be related to age, gender, tumor size, or the extent of tumor resection.

Tumor size and cavernous sinus extension are the main predictors for STR. Notably, recovery of the gonadal axis in a large proportion of patients supports the surgical resection of NFPAM in patients suffering from gonadal deficiency, even in the absence of visual field defect (VFD) [5].

2018

Gan et al., retrospectively reviewed 117 patients with nonfunctioning pituitary neuroendocrine tumors (NFPAs) and chiasm compression in the Peking Union Medical College Hospital Beijing, China from January 2013 to December 2016. The quantitative relationships between suprasellar extension (SSE) on sagittal and coronal MRI sections and visual function, including visual acuity and visual fields, were analyzed. The cut-off value of SSE to predict visual field defect (VFD) was calculated by receiver operating characteristic curves. The mean deviation (MD) value was used to quantitatively analyze the visual fields, and multiple linear regression analysis was performed to investigate risk factors of VFD.

Among 117 NFPA patients, 77 (65.8%) had VFD, and the mean visual acuity was 0.42 ± 0.38 logMAR. The cut-off value of the sagittal SSE was 14.0 mm, with 77.9% sensitivity and 80.0% specificity. The cut-off value of the coronal SSE was 15.8 mm, with 81.8% sensitivity and 85.0% specificity. The values of SSE on two MRI sections were correlated with visual acuity ($p < 0.001$) and the MD ($p < 0.001$). Multiple linear regression analysis demonstrated that SSE on sagittal views ($p < 0.001$), SSE on coronal views ($p < 0.001$), duration of the disease ($p = 0.027$) and apoplexy ($p = 0.036$) were related to the degree of visual field damage.

VFD of NFPA patients with chiasm compression can be predicted by SSE on an MRI scan. There is a linear correlation between the SSE and MD values [6].

2016

Over a 5-year period, 305 transsphenoidal surgeries for NFAs performed at The California Center for Pituitary Disorders were retrospectively reviewed. Patients with preoperative endocrine deficits (n = 153, 50%) were significantly older (mean age 60 vs 54 years; $p = 0.004$), more frequently male (65% vs 44%; $p = 0.0005$), and had larger adenomas (2.4 cm vs 2.1 cm; $p = 0.02$) than patients without preoperative deficits (n = 152, 50%). Of patients with preoperative endocrine deficits, 53% exhibited symptoms. Preoperative deficit rates were 26% for the thyroid axis; 20% and 16% for the male and female reproductive axes, respectively; 13% for the adrenocorticotropic hormone (ACTH)/cortisol axis, and 19% for the growth hormone (GH)/insulin-like growth factor-1 (IGF-1) axis. Laboratory normalization rates 6 weeks and 6 months after surgery without hormone replacement were 26% and 36% for male and 13% and 13% for female reproductive axes, respectively; 30% and 49% for the thyroid axis; 3% and 3% for the cortisol axis; and 9% and 22% for the IGF-1 axis ($p < 0.05$). New postoperative endocrine deficits occurred in 42 patients (13.7%). Rates of new deficits by axes were: male reproductive 3% (n = 9), female reproductive 1% (n = 4), thyroid axis 3% (n = 10), cortisol axis 6% (n = 19), and GH/IGF-1 axis 4% (n = 12). Patients who failed to exhibit any endocrine

normalization had lower preoperative gland volumes than those who did not (0.24 cm(3) vs 0.43 cm(3), respectively; $p < 0.05$). Multivariate analyses revealed that no variables predicted new postoperative deficits or normalization of the female reproductive, cortisol, and IGF-1 axes. However, increased preoperative gland volume and younger age predicted the chances of a patient with any preoperative deficit experiencing normalization of at least 1 axis. Younger age and less severe preoperative hormonal deficit predicted normalization of the thyroid and male reproductive axes ($p < 0.05$).

After NFA resection, endocrine normalization rates in this study varied with the hormonal axis and were greater than the incidence of new endocrine diseases. Low preoperative pituitary gland volume precluded recovery. Patient age and the severity of the deficiency influenced the recovery of the thyroid gland and male reproductive axes, the most commonly impaired axes and most likely to normalize postoperatively. This information can be of use in counseling patients with hypopituitarism who undergo NFA surgery [7)].

Case note review of all patients treated for NFPA in University Hospitals Birmingham and Beaumont Hospital Dublin between 1999 and 2014 was performed.

Clinical presentation, treatment strategies, pituitary function and vitality status were recorded in each patient. A multivariate Cox regression model was used to examine the association between hypopituitarism, hormone replacement and premature mortality.

A total of 519 patients were included in the analysis. Median duration of follow-up was 7·0 years (0·5-43). A total of 81 deaths were recorded (15·6%). On multivariate analysis, adrenocorticotropic hormone (ACTH) and gonadotropin (Gn) deficiencies were associated with an increased relative risk of death (OR 2·26, 95% CI 1·15-4·47, P = 0·01 and OR 2·56, 95% CI 1·10-5·96, P = 0·01, respectively). Increased hydrocortisone (HC) (P-trend = 0·02) and lower levothyroxine (LT4) doses (P-trend = 0·03) were associated with increased risk of death. Mortality increased with the degree of pituitary failure observed (P-trend = 0·04).

ACTH and gonadotropin-deficient patients have higher mortality rates compared to those with intact hormonal axes. Excessive HC and suboptimal LT4 replacement may also increase risk of death. Complex associations between hormone deficiency and replacement underpin the increased mortality risk in NFPA patients [8)].

2015

Sixty-six patients were managed conservatively for a mean follow-up period of 4·3 years (range: 1-14·7). Forty-seven (71%) had a macroadenoma, and nineteen (29%) had a microadenoma. Tumour size decreased or remained stable in 40% of macroadenomas and 47% of microadenomas. The median annual growth rate of enlarging macroadenomas and microadenomas was 1·0 mm/year and 0·4 mm/year, respectively. The median annual growth rate of macroadenomas was significantly higher than that of microadenomas (P < 0·01). Sixty-eight percentage of patients with a macroadenoma had pituitary hormone deficiency in one or more axes, compared to 42% of those with a microadenoma.

Patients with NFPAs without optic chiasm compression can be managed conservatively. All patients

need pituitary function assessment, irrespective of tumour size. These findings provide clinically relevant data for the management of patients with NFPAs [9].

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546 patients operated for a macroNFA between 1963 and 2011 were studied. Mortality data were retrieved through the National Health Service Central Register and hospital records and recorded as standardized mortality ratio (SMR). Mortality was estimated for the total and various subgroups with clinical follow-up data.

Median follow-up was 8 years (range 1 month-48.5 years). SMR was 3.6 [95% confidence interval (CI), 2.9-4.5], for those operated before 1990, 4.7 (95% CI, 2.7-7.6) and for those after 1990, 3.5 (95% CI, 2.8-4.4). Main causes of death were cardio/cerebrovascular (33.7%), infections (30.1%) and malignancy (28.9%). Cox regression analysis demonstrated that only age at diagnosis remained an independent predictor of mortality (Hazard Ratio 1.10; 95% CI, 1.07-1.13, $p<0.001$) whereas sex, presentation with acute apoplexy, extent of tumour removal, radiotherapy, recurrence, untreated GH deficiency, FSH/LH deficiency, ACTH deficiency, TSH deficiency and treatment with desmopressin had no impact.

Despite the improvement of treatments over the last three decades, the mortality of patients with NFAs in our series remains high. Apart from age, factors related with the management/outcome of the tumour are not independent predictors, and pituitary hormone deficits managed with the currently-used substitution protocols do not adversely affect mortality [10].

A HRQoL questionnaire (15D) was sent to all patients (n=161) having undergone transsphenoidal surgery for NFPA in the years 2000 to 2010 at the Helsinki University Hospital. The 15D score and dimension scores of the study population (n=137) were compared with those of a large (n=4967) gender- and age-standardised control population. Possible independent predictors of HRQoL in the patients were estimated with multivariate regression analysis.

Postoperatively, 56.9% of the patients had normal visual function. After a mean follow-up of 7.4 ± 3.2 years (mean ± SD), 62% suffered from hypopituitarism. Overall HRQoL was near-normal in patients compared to controls (15D scores 0.885 ± 0.114 vs. 0.903 ± 0.093, respectively, $p=0.07$). On single dimensions, patients had impaired vision and sexual activity (both $p<0.0005$), more depression and distress (both $p<0.005$) and less discomfort and symptoms ($p<0.05$). Age, body mass index, diabetes, depression and reoperation were independent predictors of impaired HRQoL (all $p< 0.05$). Thyroxine substitution was associated with impaired and hydrocortisone and testosterone substitution (males only) with better HRQoL (all $p< 0.05$).

This recent series of NFPA patients demonstrates that overall HRQoL is near-normal after medium term follow-up; the most impaired dimensions were in vision and sexual activity. Comorbidities are strong predictors of impaired HRQoL [11].

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160 patients operated via pure endoscopic endonasally. Presenting symptoms, results of neurological and visual examination, levels of pituitary hormones, results of radiological examinations, adenoma sizes, rates of resection, results of postoperative visual examination, and pituitary hormone levels at follow-up were recorded to establish the appropriate approach, operative criteria, and outcomes of patients with Non-Functioning Pituitary Neuroendocrine Tumor.

Headache was the presenting symptom in 87.5% of the patients. Thirty-three percent had visual loss and visual examination carried out in the whole study population revealed a visual field defect in 47.5% of the subjects. While only 16.25% of the patients presented with endocrinological symptoms, 52.5% had abnormal anterior pituitary hormone levels. Regarding the adenoma size56 patients had macroadenoma (35%), 84 (52.5%) had mesoadenoma and 20 patients had giant adenoma. The grosstotal resection was achieved in majority (90%) of the patients and in the remaining group subtotal resection could be done. The rate of total resection was lower in giant adenomas and recurrences. Visual symptoms and anterior pituitary hormone levels improved in 27 and 42 patients, respectively following the operation.

Non-Functioning Pituitary Neuroendocrine Tumors present frequently as meso- and giant-adenomas. Patients harboring these tumors may have subclinical visual or hormonal deficits at the time of diagnosis. An early and effective surgical treatment is essential for rapid recovery of visual and/or hormonal deficits, particularly in symptomatic cases [12)].

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56 cases of NFPA with CS invasion treated through an endoscopic endonasal approach (EEA) between 2000 and 2010. The Knosp classification was adopted to describe CS involvement using information from preoperative MRI and intraoperative findings. Extent of resection and surgical outcomes were evaluated on the basis of postoperative contrast-enhanced MRI. Endocrinological improvement and visual outcomes were assessed according to the most recent consensus criteria.

EEA was performed using direct para-septal, trans-ethmoidal-sphenoidal or trans-ethmoidal-pterygoidal-sphenoidal ap- proach. Visual outcomes improved in 30 (81%) patients. Normalization or at least improvement of previous hypopituitarism was obtained in 55% of cases. A gross total resection was achieved in 30.3% of cases. The recurrence-free survival was 87.5%, with a mean follow-up of 61 months (range, 36-166 months). No major intraoperative or postoperative complications occurred.

EEA is a minimally-invasive, safe and effective procedure for the management of NFPA invading the CS. The extent of CS involvement was the main factor limiting the degree of tumor resection. The EEA was able to resolve the mass effect, preser- ving or restoring visual function, and obtaining adequate long-term tumor control [13)].

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84 patients with presumed NFPA were studied retrospectively. Patients were enrolled based on the following criteria: imaging suggestive of pituitary neuroendocrine tumor, absence of any biochemical/clinical evidence of hormonal excess, exclusion of prolactinomas and at least one sequential imaging during the follow-up. Repeated assessment of the pituitary function, visual fields and imaging was performed at regular intervals. The follow-up duration was evaluated from the first and last imaging dates.

In group F (follow-up without surgery, 33 patients), the macroadenomas showed a 15 % probability of tumor growth and reduction. Similar tumor size alterations were observed also for the microadenomas. In group S (surgery, 51 patients), both residual tumors (>1 and <1 cm) following initial surgical resection remain mainly stable until the last imaging.

Based on the given lack of approved medical treatment and the possible risks of surgical intervention in presence of significant comorbidities, the study proposes a conservative approach with a careful

follow-up in patients with NFPAs without visual or neurological abnormalities [14].

In 86 NFA patients, treated between 1987 and 2008 at the University Medical Center Groningen, white-matter lesions (WMLs), cerebral atrophy, brain infarctions and abnormalities of the temporal lobes and hippocampi were assessed on pre- and post-treatment MRI scans in patients treated with (n=47) or without RT.

The median MRI follow-up time for RT patients was 10 (range 1-22) years and 5 (range 1-21) years in patients treated without RT. In RT patients the cumulative incidence of WMLs was significantly lower compared to patients treated without RT (log-rank test RR 0.49, 95% CI 0.25-0.97, p=.042). The cumulative incidences of cerebral atrophy, brain infarctions, abnormalities of the temporal lobes and hippocampi, and the severity of WMLs and cerebral atrophy ratings were not significantly different between the two treatment groups.

Brain abnormalities on MRI are not observed more frequently in NFA patients treated with RT compared to patients treated with surgery-alone. Furthermore, RT was not associated with an increased severity of WMLs and cerebral atrophy ratings in this cohort of NFA patients [15].

1986

The records of 100 patients who had undergone a transsphenoidal procedure for excision of such tumors were reviewed. Immunocytology for pituitary hormones was performed in all cases. The group consisted predominantly of null-cell adenomas, although a small number of prolactinomas and gonadotropic tumors were found. The mean diameter of the tumors at the time of detection was slightly more than 2 cm. In most cases, the presenting symptoms were due to the mass effect of the tumor (that is, visual symptoms in 72 patients, hypopituitarism in 61, headache in 36, and cranial nerve disturbance other than visual loss in 10). Radiation therapy was recommended for patients in whom subtotal removal of the adenoma was expected. Six patients developed symptomatic tumor recurrence, and 10 patients demonstrated radiographic recurrence during the 48 to 100 months (mean 73.4 months) of follow-up observation. Only three of 10 deaths during the follow-up period were due to pituitary disease or treatment [16].

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