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Quantitative MR-derived biomarkers as predictors of function and histotype in adenohypophyseal tumours

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Running title: Pre-treatment MRI biomarkers of adenohypophyseal tumour phenotype

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Abstract

Introduction:

Magnetic Resonance Imaging (MRI) is the main modality to diagnose adenohypophyseal tumours, while biochemical assessment of pituitary hormones allows for their functional classification. In this retrospective exploratory cohort study, we investigated if quantitative differences in tumour MR signal intensity could be utilised to predict the function and histotype.

Methods:

Clinically acquired pre-treatment MRI images were retrospectively analysed in 67 clinically non-functioning gonadotropinomas (NFG), 38 somatotropinomas; and 16 medically treated giant macroprolactinomas. Mean T1- and T2-weighted signal intensity (SI) values were determined for each tumour and normalised against either centrum semiovale white matter (WM) or CSF to derive relative T1W and T2W SI values and the relative tumour T2/T1 SI ratio. Inter-group differences in quantitative MR parameters were compared, and the power of each parameter to discriminate tumour type and subtype was assessed using the area under the receiver operator characteristic curve (AUROC). In resected somatotropinomas, the relationship between tumour granulation status, relative MR SI values and biochemical data was also compared.

Results:

Compared to somatotropinomas, NFG and macroprolactinomas displayed higher relative T2W SI ($p<0.001$) and higher relative tumour T2/T1 SI ratio values ($p<0.001$, ANOVA). Compared to intermediate/densely granulated tumours, sparsely granulated somatotropinomas were larger ($p=0.006$, Mann-Whitney U test), had higher relative T2W SI ($p\leq0.005$) and higher relative tumour T2/T1 SI ratios ($p\leq0.001$, 2-tailed *t*-test). Relative tumour T2W SI values and relative tumour T2/T1 ratio values demonstrated good discriminatory power in differentiating NFG from somatotropinoma (AUROC = 0.87 - 0.94) and predicting somatotropinoma subtypes (AUROC = 0.87 - 0.95).

Conclusion:

Quantitative SI-based MR parameters derived using clinical acquisition MRI protocols may help non-invasively discriminate the functional status of adenohypophyseal tumours and the histological subtype of somatotropinomas.

Introduction:

Tumours of adenohypophyseal cells account for around 10% of all intracranial neoplasms and approximately 90% of all sellar tumours [1]. About 60% are clinically functioning causing signs and symptoms due to hormone hypersecretion [2]. Adenohypophyseal tumours are classified by histotype based on their immunoprofile, and by hormone secretion, size and extension. Magnetic Resonance Imaging (MRI) and assessment of endocrine function are the 'gold standard' for pre-operative assessment of sellar tumours [3]. Lactotroph and some growth hormone (GH) secreting tumours can respond to medical therapy [4]. Surgery is the treatment of choice for clinically non-functioning tumours. [5].

The role of MRI in predicting the endocrine status of adenohypophyseal tumours is not clear, with studies utilising both qualitative and quantitative methods to assess MRI signal characteristics. Most reports have qualitatively assessed differences in MR characteristics between tumour types and subtypes by visual inspection, categorizing tumours as hypo-, iso-, or hyperintense relative to either normal brain or the pituitary gland [6–10]. Such qualitative methods are quick and readily accessible to the expert reader but they lack standardisation and reproducibility as they are subject to inter-observer variability [11]. Some studies have proposed the use of T1-weighted and T2-weighted signal intensity (SI) values normalised to an internal reference region [12,13]. In an early low field (0.5T) MRI study by Lundin et al. [12], tumour T1W SI values measured from a single tumour slice and normalised against the corpus callosum, were found to be higher in functioning than in non-functional tumours. To date, however, there have been no large studies assessing quantitative differences in T1 and T2 SI based measures between clinically non-functioning and functioning adenohypophyseal tumours.

We analysed a single centre retrospective cohort of previously acquired MRI scans to assess whether quantitative differences in signal intensity could predict the functional status and histological subtypes of tumours of adenohypophyseal cells. We also sought to establish amongst a cohort of functioning somatotropinomas if differences in these derived quantitative MR parameters can be used to predict subtype (i.e. densely versus sparsely granulated) and post-operative endocrine remission.

Methods:

Patient identification

This was a retrospective exploratory cohort study. Ethical approval for the study had been granted by the local research ethics committee (REC Reference, 17/EE/0488). Patients were identified retrospectively from the clinical database at Salford Royal NHS Foundation Trust, Manchester UK. The database consisted of patients with pituitary lesions who had undergone surgical treatment over a period of ten years, and patients who had undergone medical treatment for a prolactinoma over this same period.

Data from three cohorts of adult patients were recruited into the study: i) Patients with non-functioning gonadotropinomas (NFG) who had no biochemical or clinical evidence of hormone hypersecretion and had undergone surgery; ii) Patients with clinical and biochemical evidence of acromegaly who had undergone primary surgical resection without pre-operative medical therapy, and; iii) patients with prolactinomas who had undergone medical treatment only.

Inclusion/exclusion criteria

The original slides were reviewed for this study by an experienced neuropathologist (FR). In an attempt to avoid mixed tumour types, only tumours expressing FSH and/or LH beta subunit were included in the non-functioning cohort. Clinically silent corticotrophinomas and silent somatotropinomas were excluded [14]. Only somatotropinoma with clinical and biochemical evidence of acromegaly as defined by the 2017 WHO classification of pituitary tumours were included [2]. On histopathology somatotropinomas were classified as sparsely granulated, densely granulated or intermediate type based on GH expression and the presence and extent of fibrous bodies seen with the immunoreaction for cytokeratin CAM5.2 [15]. Mammosomatotroph and plurihormonal tumours containing growth hormone positive cells and clinically causing acromegaly were also excluded. All prolactinomas at our centre are medically managed at first and only approximately 5% require surgery due to intolerance/ineffectiveness of dopamine agonists. For the group of prolactinomas, only patients with pre-treatment prolactin levels greater than 10,000 mU/L and neuroimaging and biochemical response to

dopamine agonists were included. Because tissue confirmation of the histotype was not available for these medically treated patients, the latter selection criteria aimed to minimize the inclusion of lactotroph tumours with mixed phenotype such as lactotroph/somatrotroph and plurihormonal tumours. .

To improve the accuracy of quantitative assessment of the MR images, tumours measuring less than 5mm in maximal dimension, tumours with significant macrocystic and/or haemorrhagic change, and tumours that were previously irradiated were excluded. Corticotrophinomas, which are typically small (<1cm) and difficult to accurately delineate on pre-treatment MRI, were also excluded [16].

MR image analysis

All patients included in this study had undergone imaging on one of five different 1.5T MR scanners (Siemens Avanto, Siemens Aera, Phillips Intera, GE optima MR450W and GE Signa Excite) before surgery or medical treatment. Anonymised pre-treatment MR images for each patient included in the study were exported to a university workstation for further analysis. After bias correcting each image for B1 field intensity variation [17], coronal T1W, T2W and where available post-contrast T1W images were co-registered using SPM12 prior to analysis [18].

Tumours were manually segmented on the co-registered T2W, T1W and post-contrast coronal T1W coronal images using the region of interest tool within ITK-snap [19]. A perimetry based method for tumour delineation and volume measurement was used as it has been reported to have superior accuracy compared to largest area or maximal axis measurements [20]. Care was taken during delineation to avoid normal structures (e.g. cavernous sinus, optic apparatus, large vessels) and the results of segmentation were reviewed and where necessary, edited by an experienced pituitary neurosurgeon (KG). Using the whole tumour object masks the mean absolute T1W and T2W SI values for each tumour were derived and validated against values obtained using a multiple region of interest (ROI) method whereby multiple small ROIs were placed within the central part of each tumour on consecutive image slices. To assess the intra-observer repeatability of each tumour measurement, a blinded second measurement was also undertaken one month later for fifteen tumours in each cohort.

Delineation of white matter and CSF reference regions

Relative SI ratios, adjusted to the signal intensity within each patient's normal appearing white matter or CSF were determined. Using the circular ROI tool within ITK-SNAP [19], appropriately sized circular ROIs were placed in multiple contiguous coronal image sections within the normal appearing white matter of the centrum semiovale (WM) and within the CSF of the lateral ventricles for each patient. The size of the circular ROIs was adjusted for each individual patient, so that partial volume effects from neighbouring voxels was minimized. Regions of T2 white matter hyperintensity and enlarged perivascular spaces within the centrum semiovale, were avoided in ROI delineation [21], along with choroid plexus and regions of flow void within the CSF [22]. The extracted mean T1W and T2W SI values for both the WM and CSF reference regions were then used to determine tumour/WM and tumour/CSF T1W and T2W SI ratios. As an additional marker, the relative tumour T2/T1 SI ratios ($SI_{Ratio\text{-}rel)}$ were determined, where:

Tumour T2/T1 $SI_{Ratio\text{-}Rel} = \frac{(Tumour\ T2W\ SI / Reference\ ROI\ T2W\ SI)}{(Tumour\ T1W\ SI / Reference\ ROI\ T1W\ SI)}$

for WM and CSF reference ROI respectively.

In addition to the quantitative parameters described above, somatotropinomas were classified qualitatively as either hypo- or hyperintense relative to normal appearing white matter on mid-sagittal coronal T2 weighted images. Classification was based on visual inspection by an observer (DL), and verified by a second observer (KG). At time of classification both observers were blinded to clinical data and the quantitative SI ratio values for each tumour.

Biochemical data and remission rates:

For all tumour cohorts serum prolactin levels were analysed using the Siemens ADVIA Centaur two-site sandwich immunoassay (Siemens Diagnostics, Tarrytown, USA) and expressed as mU/L. For somatotropinomas, pre-operative baseline insulin-like growth factor-1 (IGF-1) levels and GH nadir levels during a pre-operative oral glucose tolerance test (OGTT) were analysed [23]. Plasma IGF-1 levels were determined by chemi-luminescent immunoassay (Siemens Immulite 2000 IGF-1, Deerfield, IL, USA.), expressed as percentage increase compared with the upper limit of normal (% ULN) [24]. GH was assayed by chemiluminescent immunoassay utilizing the Siemens Immulite 2000 GH Assay (lower detection threshold, 0.05 mcg/l; analytical sensitivity, 0.001 mcg/l). GH units were expressed in mass units (mcg/L) [25].

All trans-sphenoidal surgeries were undertaken by one surgeon (KG), using an endoscopic trans-sphenoidal approach as previously described [26]. All patients with NFG and somatotropinomas underwent surgery, while those with prolactinomas were managed medically with dopamine agonists.

In somatotropinomas, surgical debulking was attempted in selected patients where the preoperative MRI scan revealed an invasive tumour with circumferential tumour extension around the carotid arteries. In all other cases, gross total resection was attempted, irrespective of tumour size. Parasellar extension or encroachment of the tumour towards the cavernous sinus in relation to the intracavernous carotid artery (ICA) was classified on MRI before surgery using the Knosp grade (Grades 0 - IV) [20,27]. Postoperatively, all patients with somatotropinomas underwent testing of the GH axis (GH nadir on OGTT and IGF-1) at regular intervals [23,26]. When early testing suggested residual tumour, as also supported by findings on a repeat MR scan, further re-exploratory surgery at 2–4 weeks postoperatively was undertaken in some patients. For somatotropinomas, definition of disease remission was according to the 2010 Consensus criteria and required both a GH nadir of ≤0.4mcg/L on OGTT, and a normal age- and gender-adjusted IGF-1 [28]. Borderline remission was defined as meeting only one of the above criteria, and these cases were considered to be not in remission [28].

Statistical analysis:

Statistical software program Stata was used to undertake all statistical analyses. Normality and homogeneity of variance for all continuous variables was assessed using the Shapiro-Wilk and Levene test respectively. Differences in patient age, tumour size and quantitative MR derived parameters between the three tumour subgroups (NFG, somatotropinomas and prolactinomas) were compared using a one-way ANOVA with Bonferroni correction. For non-parametric data the Kruskal–Wallis test with adjustment for multiple comparisons was used.

For the somatotropinoma cohort, differences in tumour size, quantitative MR derived parameters and biochemical data were compared against somatotropinoma subtype (intermediate/densely Vs sparsely granulated), biochemical remission status (remission Vs not in remission), and between T2 hypo- and hyperintense tumours (as assessed through visual inspection) using either a two-tailed t-test or the Mann-Whitney U test for non-parametric data. Differences in categorical variables (gender, Knosp grade) and remission rate post trans-sphenoidal surgery between intermediate/densely and sparsely granulated somatotropinomas and between T2 hypo- and hyperintense tumours were assessed using Fisher's exact test.

The ability of each MR parameter (including tumour size) to predict tumour functional status and somatotropinoma subtype was assessed through logistic regression analysis and calculation of the area under the receiver operator characteristic curve (AUROC). Statistical differences between ROC curves were evaluated using the DeLong's test for two correlated ROC curves [29] (Stata package *roccomp*). The MR parameter with the highest AUROC value for predicting histological type or somatotropinoma subtype was then chosen and the optimal threshold value for this imaging metric was then derived using Youden's index (Sensitivity + Specificity – 1) [30]. Pre-treatment predictors of somatropinoma biochemical remission post trans-sphenoidal surgery were similarly assessed through use of an AUROC analysis and multiple logistic regression with Knosp grade, tumour subtype, biochemical data and quantitative MR parameters as independent predictors. Bland-Altman analysis [31] was used to assess the agreement between the whole tumour and ROI derived mean SI values. For assessing the intra-observer repeatability of volumetric tumour measurements, Bland-Altman analysis and the intraclass correlation coefficient (ICC) was used.

Results:

Patient demographics and histological subtype

A CONSORT diagram detailing included/excluded patients is shown in **supplementary Figure 1**. Sixty-seven patients with NFG, 38 patients with somatotropinoma and 16 patients with macroprolactinoma were included in this study (total N=121). Seven patients had sparsely granulated somatotropinoma and 31 patients had either intermediate (6 patients) or densely granulated tumours (25 patients). In somatotropinomas (N=38) biochemical remission post-surgery was achieved in 26 (68%) and 12 (32%) patients did not achieve remission according to the 2010 consensus criteria.

Patient demographics and baseline characteristics across non-functioning/ functioning tumour groups are shown in **Table 1**. Patients with NFG were older than patients with macroprolactinoma (p=0.001) and somatotropinoma (Kruskal-Wallis test, p<0.001). NFG were larger than somatotropinomas but the difference was not statistically significant (p=0.11, Kruskal-Wallis test). All included prolactinomas were greater than 1cm in maximum diameter and displayed significantly larger volumes than either NFG (p=0.001) or somatotropinomas (Kruskal-Wallis test, p<0.001). Compared to excluded tumours with a prolactin level <10,000 mU/L (n=12), patients within the included macroprolactinoma cohort were older (Mann-Whitney U test, p<0.001), predominantly male (Fisher's exact test, p=0.27) and displayed greater tumour size (Mann-Whitney U test, p<0.001) and higher tumour invasiveness as measured through Knosp grade (Fisher's exact test, p<0.001, **supplementary Table 1**).

Gonadotroph, somatotrotroph and macroprolactinoma types

As shown in **Table 2**, derivation of relative SI ratios using both reference regions demonstrated significantly lower Tumour/WM and Tumour/CSF T2W SI ratio values in somatotropinomas compared to both NFG (ANOVA, p<0.001) and macroprolactinomas (ANOVA, p<0.001, **Fig. 1A**). Somatotropinomas also displayed higher relative Tumour/CSF T1W SI ratio values compared to NFG (ANOVA, p<0.001) and macroprolactinomas (p<0.001; **Table 2**). Comparison of mean relative tumour T2/T1 SI ratio values demonstrated that somatotropinomas displayed significantly lower T2/T1 ratios than NFG or macroprolactinomas (ANOVA, p<0.001; **Fig. 1B**). Compared to NFG, macroprolactinomas demonstrated lower Tumour/CSF T1W SI ratio values (95% CI mean difference 0.04, 0.31, ANOVA, p=0.11) and a non-significant decrease in Tumour/WM and Tumour/CSF T2W SI ratio values (ANOVA, p>0.05). Representative coronal T1W and T2W MR images of NFG, macroprolactinoma and somatotropinomas tumour subtypes are shown in **Fig. 1C**.

Densely versus sparsely granulated somatotropinomas

The results of subtype analysis are shown in **Table 3** and **4.** Sparsely granulated tumours were significantly larger than intermediate/densely granulated tumours (Mann-Whitney U test, p=0.006) and demonstrated significantly higher Knosp grade (Fisher's exact test, p=0.03, **Table 3**). Pre-op IGF-1 and GH nadir levels were comparable across the two tumour groups (**Table 3**). Sparsely granulated tumours had significantly higher relative T2W SI values (2-tailed *t*-test, p≤0.005**, Fig. 2A**), and higher relative tumour T2/T1 SI ratio values (2-tailed *t*-test, p≤0.001, **Fig. 2B**) compared to the intermediate/ densely granulated group. Representative case examples of coronal T1W and T2W MR image sections of a sparsely and densely granulated somatotropinoma are shown in **Fig. 2C**.

As shown in **supplementary Table 2**, tumours judged to be hyperintense on T2W MR imaging were larger (Mann-Whitney U test, p=0.02), demonstrated significantly higher relative T2W SI values (2-tailed *t*-test, p<0.001), and higher relative tumour T2/T1 SI ratio values (2-tailed *t*-test, p<0.001) compared to the T2 hypointense tumours. Granulation pattern was significantly different between both groups (Fisher's exact test, p<0.001, **supplementary Table 2**) and all T2 hypointense somatotropinoma in our cohort were intermediate/densely granulated.

Differences in tumour size and relative SI ratios between NFG/macroprolactinomas and each somatotropinoma subtype are shown in **supplementary Table 3**. In line with the results for the whole somatotropinoma cohort, densely/intermediate granulated somatotropinomas demonstrated significantly lower relative T2W SI values compared to non-functioning tumours (ANOVA, p<0.001) and macroprolactinomas (ANOVA, p<0.001,

supplementary Table 3). Sparsely granulated somatotropinomas also demonstrated lower Tumour/WM and Tumour/CSF T2W SI ratio values and higher Tumour/CSF T1W SI ratio compared to both NFG and prolactinomas but these differences were not statistically significant (ANOVA, p>0.05).

Post-operative remission in patients with somatotropinoma

Biochemical remission was achieved post-surgery in 26/38 (68%) patients with somatotropinomas. Seven (18%) were not in remission, including three patients who had undergone debulking and a further three patients in whom complete resection was planned but intra-operatively tumour spread into the cavernous sinus and/or bony clivus was discovered. Five (13%) patients had borderline results and thus as per 2010 consensus guidelines these were included in the 'not in remission' group. In 23 patients remission was achieved following the first trans-sphenoidal surgery and three patients went in to remission following a second surgical procedure.

Patients who achieved biochemical remission had significantly lower Knosp grade (Fisher's exact test, p=0.004, **Table 3**), smaller tumours at diagnosis (Mann-Whitney U test, p=0.003, **Table 3**), and higher tumour/WM T1W SI values (2-tailed *t*-test, p=0.03, **Table 5**) than patients not in remission. Those patients with somatotropinomas achieving biochemical remission trended to have densely/intermediate granulated tumours than patients not in remission, although this failed to be significant (Fisher's exact test, p=0.12).

AUROC characteristics

Comparison of the AUROC for each quantitative MR parameter is shown in **supplementary Table 4**. For differentiating NFG from functioning (macroprolactinoma/somatotropinoma) tumours, relative T2W SI ratio values (AUROC = 0.80 - 0.82) and the tumour T2/T1 $SI_{Ratio\text{ - }CSF}$ (AUROC = 0.81) displayed significantly higher AUROC values than either tumour volume (AUROC = 0.67, $p \leq 0.01$) or Knosp grade (AUROC=0.63, p<0.002). Subgroup analysis on 37 patients imaged using the same scanner system (Phillips Intera) demonstrated increased AUROC values for relative T2W SI ratio values (AUROC = 0.83 - 0.89) and relative tumour T2/T1 SI ratio values (AUROC=0.83 – 0.84) in differentiating NFG from functioning tumours.

As shown in **supplementary Table 5** relative tumour T2W SI values (AUROC = 0.87 - 0.94) and relative tumour T2/T1 ratio values (AUROC = 0.89 - 0.95) demonstrated good discriminatory power in differentiating somatotropinoma granulation status. There was no statistically significant difference in the estimated AUROC values across the different MR imaging metrics including tumour size and Knosp grade (p>0.05). Compared to pre-op IGF-1 (AUROC = 0.73, p=0.03) and pre-op GH nadir (AUROC = 0.51, p<0.001) the tumour T2/T1 SI ratio normalised to CSF (T2/T1 $SI_{Ratio\text{-}CSF}$) displayed significantly higher AUROC for differentiating somatotropinoma granulation status. As shown in **Table 6**, at a threshold of 0.18 the tumour T2/T1 $SI_{Ratio\text{ - }CSF}$ had 100% sensitivity and 87.1% specificity for differentiating sparsely from intermediate/densely granulated somatotropinomas.

For predicting remission post trans-sphenoidal surgery (**supplementary Table 5**), tumour size (AUROC = 0.80) and Knosp grade (AUROC = 0.79) had higher (p>0.05) AUROC values than all relative tumour SI measures (AUROC = 0.51 - 0.73) but these differences were not statistically significant.

ROI and whole tumour based methods

The results of Bland Altman analysis comparing the mean absolute T2W and T1W SI values derived using both the whole tumour perimetry approach and the multiple ROI approach are shown in **supplementary figure 2**. The overall limit of agreement (LOA) using the two methods was +/- 20%, and use of the ROI approach generated systematically higher absolute T2W (mean difference = -2.4%) and T1W values (mean difference = -0.8%). Test-retest analysis of tumour volume using manual delineation is shown in **supplementary fig. 2C**. Whilst the second tumour volume estimate was systematically higher (mean difference = -2.9%), this percentage difference decreased with increasing tumour size, and there was overall good repeatability with a single measure absolute difference ICC of 0.99.

Discussion:
In this retrospective exploratory cohort study, we have demonstrated that non-functioning and functioning anterior adenohypophyseal tumours differ in their quantitative T2W signal intensity (SI) characteristics, and that these differences can help differentiate between tumour subtypes. Normalised relative SI ratios demonstrated that somatotropinomas notably densely granulated subtype display lower T2W SI values compared to NFG and a cohort of macroprolactinomas.

Lower T2W SI values in somatotropinomas support the results of earlier studies [7,10,12,13]. Different theories have been formulated to explain such differences [12,13]. Hormone secretion and subsequent shortening of the T2 relaxation rates of nearby water protons was proposed to cause the lower T2W SI seen in functioning compared to non-functioning tumours [7,13,32]. Microscopic cysts and areas of necrosis can occur in adenohypophyseal tumours. Smaller areas of microscopic necrosis in somatotropinoma compared to NFG and prolactinoma may also part explain their comparatively lower T2W SI values [12,33,34]. By contrast, previous studies have suggested that treatment-naïve prolactinomas and NFG display similar intratumoural necrosis [12,33], a finding that may explain the absence of significant quantitative T2W SI differences between these two tumours in our study. Data in the literature on the correlation between fibrosis and T2W SI is contradictory, reporting either no [8,35,36] or inverse correlation [37–39].

The ability of our quantitative T1W and T2W MR parameters to predict the histotype of adenohypophyseal tumours may have some application in their management. Our study demonstrated that the use of a quick, multiple ROI based tumour sampling method offer comparable results and it is conceivable that such a method could be incorporated into MR image analysis software to aid in pre-treatment differentiation of adenohypophyseal tumours. One such application could be to help differentiate NFG with raised prolactin levels due to stalk effect from true prolactinomas. Due to a limited number of surgically resected prolactinomas at our centre, a cohort of medically treated, giant macroprolactinomas that displayed high pre-treatment prolactin levels (>10 000 mU/L) and clear biochemical/radiological response to treatment were included. These observations will therefore require further larger studies with inclusion of a group of smaller prolactinomas with moderate prolactin levels before these findings can be generalised to the wider prolactinoma cohort.

In this quantitative study, we observed that densely granulated somatotropinoma display lower SI values on T2W imaging compared to sparsely granulated tumours, findings consistent with previous qualitative studies [7,10,11,40]. Increased hormone secretion into the tumoural capillary network [41] and an increased abundance of secretory granules in densely granulated somatotropinomas have been previously proposed as reasons behind this feature [13,40,42]. In previous studies it has been shown that sparsely granulated somatotropinomas show less biochemical response to somatostatin analogues (SSA) compared to densely granulated tumours [23,40,43]. Our demonstration that quantitative T2W SI measures can differentiate the subtype of pre-treatment somatotropinomas may therefore be of clinical use to stratify somatotropinoma histological subtypes and thus identify patients who would benefit from pre- operative medical treatment [44]. This lends further support to previous studies which have demonstrated a correlation between tumour T2W SI values at baseline and tumour shrinkage with SSA [11,45]. In this study, all patients with GH secreting tumours underwent trans-sphenoidal surgery as their primary treatment and biochemical remission rates following surgery (68%) are in line with recent publications from specialist pituitary centres [25]. Tumour size, extent of tumour invasion and surgeon experience have all been shown to impact on remission rates post-surgery [25,46] and in this single surgeon study, both higher Knosp grade [27] and larger tumour volume were associated with failure to achieve biochemical remission post-surgery. Whilst sparsely granulated somatotropinomas did demonstrate a trend to lower remission rates, these tumours were also larger.

To our knowledge, this is one of the largest studies investigating quantitative MR parameters across different adenohypophyseal tumour types and subtypes. Due to its retrospective nature, however, the study did suffer from some limitations. Thus patients with limited and/or inadequate imaging were excluded from this study. In addition, we only investigated somatotropinomas and NFG that were surgically resected, focusing the study on larger, non-functioning tumours and somatotropinomas that were suitable for surgical resection rather than

medical therapy. Tumours with significant cystic/haemorrhagic components were excluded to reduce confounding features on the measured MR signal intensities. In the present study patients had been imaged using five different MR scanner vendors, at different times, using different MR scanner protocols and use of relative SI measures obtained from a single scanner improved differentiation between different pituitary subtypes. Larger prospective studies using the same scanner vendor and fixed acquisition are therefore required to better verify our study findings.

Conclusion:
This quantitative MR study demonstrated that non-functioning and functioning adenohyophyseal tumours differ in their quantitative T1W and T2W signal intensity characteristics on pre-treatment MRI, and that these signal intensity differences can be used as potential markers to help non-invasively predict the functional status and certain histotypes.

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Statement of Ethics:
The study was approved by the East of England Research ethics committee (REC Reference, 17/EE/0488). All study procedures were performed in accordance with the ethical standards of the institutional and national research committees and in accordance with the 1964 Helsinki Declaration and its later amendments.

Disclosure Statement:
The authors have no conflicts of interest to declare.

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Author Contributions:
D.L and K.G conceived the study. D.L, F.R, T.K and K.G collected the data. D.L and D.C performed the data analysis. D.L, F.R, T.K, D.C and K.G edited the manuscript, and all authors have read and approved the manuscript.

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Figure legends:

Fig. 1: Comparison of quantitative MR parameters against tumour functional status

a) Boxplot comparison of mean tumour/WM T2W SI ratio against tumour functional status.

** P ≤ 0.05 ** P ≤ 0.01 *** P ≤ 0.001*

b) Boxplot comparison of mean relative tumour T2/T1 SI ratio normalised to centrum semiovale WM (T2/T1 $SI_{Ratio\text{-}WM}$)

c) Pre-treatment coronal T1W and T2W MR images from: 64 yr old patient with a non-functioning gonadotropinoma (**Top**); 53 yr old patient with a macroprolactinoma (**Middle**); 35yr old acromegalic patient with a densely granulated somatotropinoma **(Bottom**). *All patients imaged using a Phillips Intera at 1.5T*

Top left image: ROIs shown within tumour (red), bilateral centrum semiovale (green) and CSF of lateral ventricles (blue).

GH = somatotropinoma; NFG= non-functioning gonadotropinoma; PRL= macroprolactinoma; SI= signal intensity

Fig. 2: Somatotroph granulation status

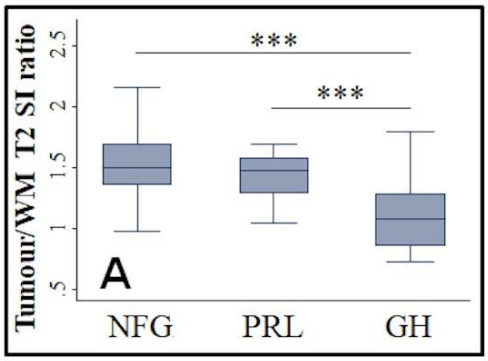
a) Boxplot comparison of pre-treatment mean tumour/WM T2W SI ratio against somatotropinoma granulation status

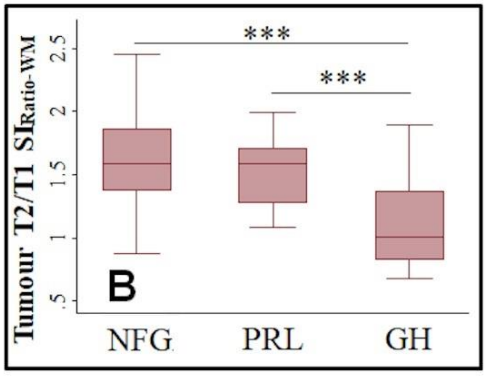
b) Boxplot comparison of pre-treatment mean relative tumour T2/T1 SI ratio normalised to CSF (T2/T1 $SI_{Ratio\text{-}CSF}$)

c) Representative T1W and T2W coronal image sections in in a 26yr old patient with a sparsely granulated tumour (*left*); and a 57yr old patient with a densely granulated tumour (*right, ⁎*). *Both patients imaged with a GE Optima MR450W at 1.5T*

Data shown for 7 sparsely and 31 intermediate/ densely granulated somatotropinomas

Figure 1





*** $P \leq 0.001$

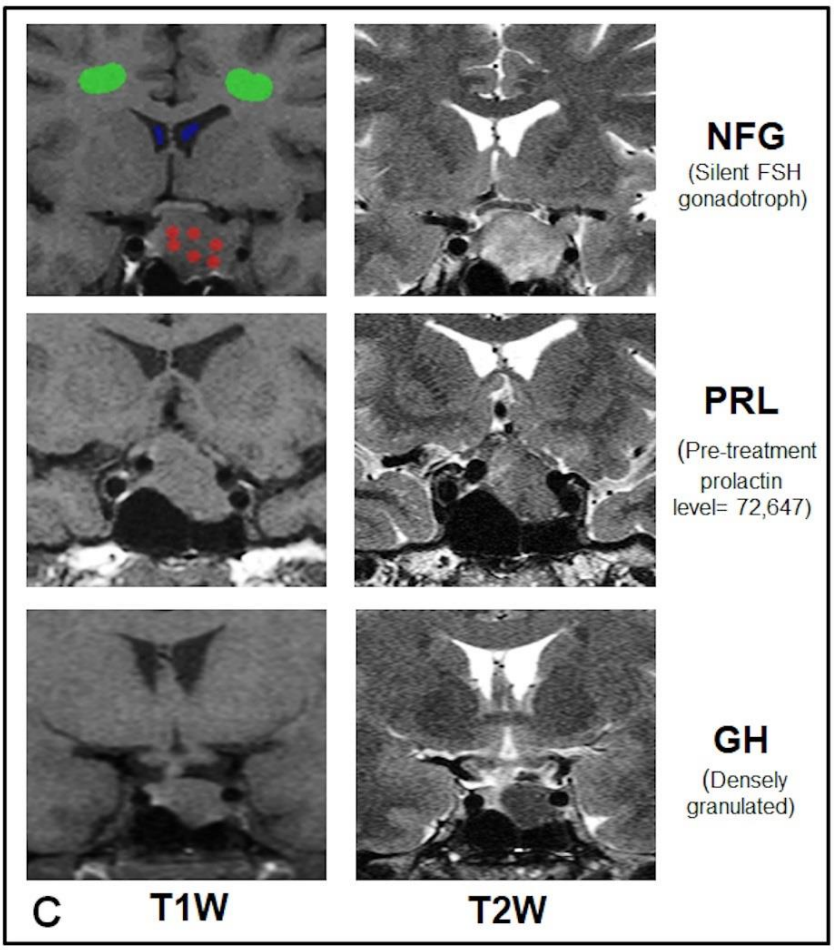
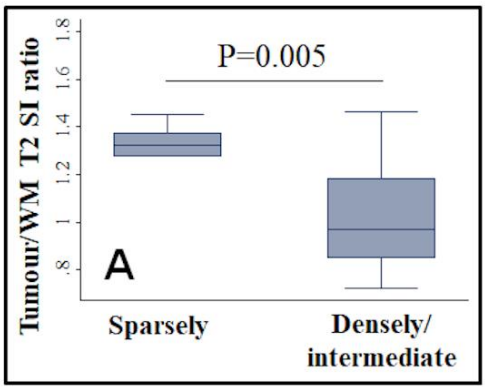
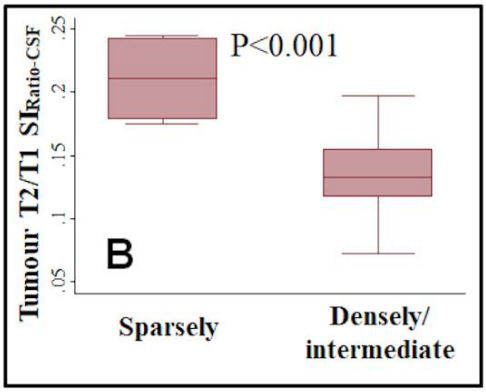


Figure 2





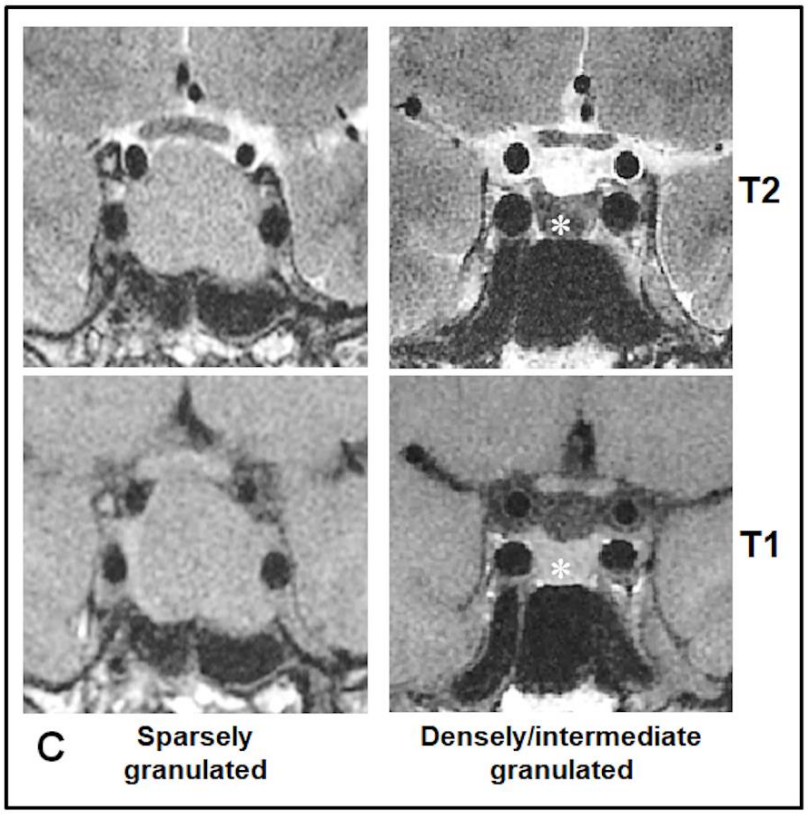


Table 1: Patient demographics and baseline characteristics across non-functioning/ functioning tumour groups

GH = somatotropinoma; NFG= non-functioning gonadotropinoma; PRL=macroprolactinoma; SI= signal intensity

Tumour diameter = maximum diameter of tumour on mid-sagittal coronal T2-weighted image

P value calculated using the Kruskal-Wallis test. For differences in patient gender and Knosp grade, p value determined using Fisher's exact test (*).

Demographic/ biochemical parameter		NFG (N=67)		PRL (N=16)		GH (N=38)		P value
Median age, yrs (IQR)		61.2 (53 -69)		44.1 (32-56)		42.9 (35-57)		<0.001
Sex, N	**Male**	44		11		19		0.24*
	Female	23		5		19		
Median tumour diameter, cm (IQR)		2.31 (1.7-3.0)		2.95 (2.3 -3.9)		1.11 (0.9-1.9)		<0.001
Median tumour size cm^3 (IQR)		4.23 (2.3-9.1)		7.96 (3.1-17.2)		0.87 (0.4-2.7)		<0.001
Knosp Grade, N		*0*	2	*0*	0	*0*	17	<0.001*
		I	13	*I*	1	*I*	8	
		II	17	*II*	5	*II*	6	
		III	24	*III*	1	*III*	3	
		IV	11	*IV*	9	*IV*	4	
Median serum prolactin mU/L (IQR)		341 (167-477)		30461 (17400-90000)		214 (148 – 505)		<0.001

Table 2: Inter-tumour comparison of quantitative MR parameters across non-functioning and functioning tumours

GH = somatotropinoma; NFG= non-functioning gonadotropinoma; PRL=macroprolactinoma; SI= signal intensity
P value calculated using one-way ANOVA. Post hoc analysis of pairwise comparisons was performed using the Bonferroni method.

Tumour MR parameter Within group mean (S.D)	**NFG (N=67)**	**PRL (N=16)**	**GH (N=38)**	**NFG vs PRL**	**NFG vs GH**	**PRL vs GH**
				P value	**P value**	**P value**
Tumour/WM T2W SI ratio	1.55 (0.3)	1.46 (0.3)	1.08 (0.3)	0.74	<0.001	<0.001
Tumour/WM T1W SI ratio	0.98 (0.1)	0.93 (0.1)	1.01 (0.1)	0.47	0.58	0.14
Tumour/CSF T2W SI ratio	0.56 (0.1)	0.53 (0.2)	0.37 (0.1)	0.98	<0.001	<0.001
Tumour/CSF T1W SI ratio	2.20 (0.2)	2.03 (0.3)	2.49 (0.4)	0.11	<0.001	<0.001
Tumour T2/T1 $SI_{Ratio-WM}$	1.61 (0.4)	1.56 (0.4)	1.10 (0.3)	0.85	<0.001	<0.001
Tumour T2/T1 $SI_{Ratio-CSF}$	0.26 (0.06)	0.29 (0.2)	0.15 (0.04)	0.60	<0.001	<0.001

Table 3: Patient demographics and baseline characteristics across somatotropinoma subtypes (N=38)

GH = somatotropinoma; SI= signal intensity; TSS= trans-sphenoidal surgery

Tumour diameter = maximum diameter of tumour on mid-sagittal coronal T2-weighted image

P value calculated using Mann-Whitney U test. For differences in patient gender and Knosp grade, p value determined using Fisher's exact test (*).

Demographic/ biochemical parameter		Sparsely granulated GH (n=7)		Densely/intermediate granulated GH (n=31)		P value	No biochemical remission post TSS (n=12)		Biochemical remission post TSS (n=26)		P value
Median Age (IQR)		48.3 (30-69)		47.1 (38-69)		0.96	46.5 (34-67)		49.6 (38-69)		0.62
Sex,N	**Female**	4		15		0.99*	6		13		0.99*
	male	3		16			6		13		
Median tumour diameter, cm (IQR)		2.30 (1.6- 2.8)		1.10 (0.86 – 1.4)		0.02	1.99 (1.2- 2.6)		1.00 (0.8 - 1.3)		0.007
Median Tumour size, c m^3 (IQR)		7.38 (2.4 - 8.4)		0..73 (0.4-1.7)		0.006	3.72 (1.5-7.9)		0.63 (0.4-0.9)		0.003
Knosp grade, N		*0*	1	*0*	16	0.03*	*0*	2	*0*	15	0.004*
		I	1	*I*	7		*I*	3	*I*	5	
		II	1	*II*	5		*II*	1	*II*	5	
		III	1	*III*	2		*III*	2	*III*	1	
		IV	3	*IV*	1		*IV*	4	*IV*	0	
Median pre-op IGF1, % ULN (IQR)		487 (314 - 580)		326 (255 - 427		0.06	357 (300 - 527)		324 (251 - 446)		0.20
Median pre-op growth hormone nadir, mcg/L (IQR)		10.7 (3.8 – 12.5)		9.1 (3.0 – 19.8)		0.94	12.8 (6.1 – 24.2)		6.05 (3 – 12.5)		0.15

Table 4: For somatotropinomas, inter-tumour comparison of quantitative MR parameters by granulation status (N=38)
SI= signal intensity
P value calculated using 2-tailed t-test.

MR parameter Within group mean (+/-S.D)	**Sparsely granulated GH (n=7)**	**Densely/intermediate granulated GH (n=31)**	**P value**
Tumour/WM T2W SI ratio	1.31 (0.1)	1.03 (0.2)	0.005
Tumour/WM T1W SI ratio	0.92 (0.1)	1.03 (0.1)	0.05
Tumour/CSF T2W SI ratio	0.47 (0.1)	0.34 (0.1)	<0.001
Tumour/CSF T1W SI ratio	2.25 (0.3)	2.55 (0.4)	0.07
Tumour T2/T1 $SI_{Ratio-WM}$	1.44 (0.19)	1.02 (0.29)	0.001
Tumour T2/T1 $SI_{Ratio-CSF}$	0.21 (0.03)	0.14 (0.03)	<0.001

Table 5: For somatotropinomas, inter-tumour comparison of quantitative MR parameters and granulation status by post-surgical resection remission status (N=38)

SI= signal intensity; TSS= Trans-sphenoidal surgery
P value calculated using 2-tailed t-test. For *differences in tumour granulation status p value determined using Fisher's exact test (*).*

MR parameter Within group mean (+/-S.D)	**No biochemical remission post TSS (n=12)**		**Biochemical remission post TSS (n=26)**		**P value**
Tumour/WM T2W SI ratio	1.13 (0.2)		1.06 (0.3)		0.39
Tumour/WM T1W SI ratio	0.94 (0.1)		1.04 (0.1)		0.03
Tumour/CSF T2W SI ratio	0.36 (0.1)		0.37 (0.1)		0.82
Tumour/CSF T1W SI ratio	2.38 (0.3)		2.55 (0.4)		0.22
Tumour T2/T1 $SI_{Ratio\text{-}WM}$	1.22 (0.29)		1.04 (0.32)		0.10
Tumour T2/T1 $SI_{Ratio\text{-}CSF}$	0.16 (0.05)		0.15 (0.04)		0.50
Tumour granulation status	Sparsely	4 (33%)	Sparsely	3 (12%)	0.12*
	Densely/ intermediate	8 (66%)	Densely/ intermediate	23 (88%)	

Table 6: Area under the receiver operator characteristic curve (AUROC), sensitivity, and specificity of individual quantitative MR parameters for the prediction of adenohypophyseal tumour functional/granulation status

GH = somatotropinoma; NFG= non-functioning gonadotropinoma; PRL=macroprolactinoma; SI= signal intensity

Optimal cut-off point for each parameter chosen using the Youden's index (J). Sensitivity, specificity and % correctly classified shown.

	Quantitative MR parameter	AUROC (95% confidence interval)	Optimal Threshold value	Sensitivity	Specificity	Correctly classified	Youden's index (J)
NFG vs GH	**Tumour T2/T1 SI Ratio-CSF**	0.94 (0.89 - 0.98)	≥ 0.20	91.0%	86.8%	89.5%	0.78
NFG vs PRL	**Tumour/ CSF T1 W ratio**	0.67 (0.50 – 0.83)	≥ 2.04	80.6%	56.3%	75.9%	0.37
PRL vs GH	**Tumour T2/T1 SI Ratio-CSF**	0.90 (0.81 – 0.99)	≥ 0.22	75.0%	89.5%	85.2%	0.65
Sparsely vs Densely/intermediate GH	**Tumour T2/T1 SI Ratio-CSF**	0.95 (0.88 – 1.00)	≥ 0.18	100.0%	87.1%	89.5%	0.87