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Comparison of the predictive power of morphological and therapeutic stratification predictors of monohormonal somatotroph pituitary tumors in patients with acromegaly

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Abstract

Introduction. Given the heterogeneity of somatotroph tumors (STs), it is important to study diverse predictors of morphological identification and sensitivity to first-generation somatostatin receptor ligands (fg-SRLs).

Aim. Comparative analysis of the prognostic significance of predictors of STs pathomorphological status and the prospects for using fg-SRLs in patients with acromegaly.

Materials and methods. A retrospective analysis of the long-term efficacy of fg-SRLs was conducted in 634 patients with acromegaly. Treatment outcomes were compared with baseline clinical examination data, pharmacotherapeutic testing (PharmT) results (n = 496), cytological and immunohistochemical analysis data (n = 104), as well as quantitative indicators of relative tumor signal intensity (RTSI) on T2- and T1-weighted MRI (n = 106).

Results. Among the markers of morphological stratification of STs, the most informative are: age at diagnosis (AUC 0.686), tumor volume and maximum diameter (0.664 and 0.665), expression of the 2nd subtype of somatostatin receptors (SSTR2; 0.816), the difference and ratio of SSTR2 and SSTR5 (0.826 and 0.808), the proportion of cells with antibodies to GH (0.932) and with fibrous bodies (FB; 0.962), tumor cell composition (0.935), RTSI on T2-, T1- and (T2-T1)-weighted MRI (WI; 0.878, 0.822 and 0.918). Predictors of fg-SRLs efficacy include: volume and maximum diameter of STs (0.640 and 0.649), baseline IGF-1 index value (0.637), absolute and relative expression of SSTR2 (0.673, 0.688 and 0.713), proportion of cells with FB (0.698), tumor cell composition (0.742), results of RTSI on T2- and (T2-T1)-WI (0.684 and 0.636) and PharmT (%ΔIGF-1 after 3-6 months – 0.840-0.849). The successful use of pegvisomant in patients refractory to fg-SRLs has been demonstrated.

Conclusion. Priority predictors of the morphofunctional status of STs and the long-term effectiveness of fg-SRLs simplifying the differential diagnosis of the relevant histotype and facilitating the management of acromegaly treatment have been identified.

Keywords: acromegaly, precision medicine, somatotroph tumors, IGF-1 index, the 2nd subtype of somatostatin receptors, fibrous bodies, T2-weighted MRI, first-generation somatostatin receptor ligands, pegvisomant

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Сравнение предсказательной силы предикторов морфологической и терапевтической стратификации моногормональных соматотрофных опухолей гипофиза у пациентов с акромегалией

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Резюме

Введение. В условиях гетерогенности соматотрофных опухолей (СО) актуальным является изучение разноплановых предикторов морфологической идентификации и чувствительности к аналогам соматостатина 1-го поколения (АС1).

Цель. Сделать сравнительный анализ прогностической значимости предикторов патоморфологического статуса СО и перспективности использования АС1 у пациентов с акромегалией.

Материалы и методы. Проведен ретроспективный анализ отдаленной эффективности АС1 у 634 пациентов с акромегалией. Результаты лечения сопоставлялись с исходными данными клинического обследования, результатами фармакотерапевтического тестирования (ФармТ) (n = 496), данными цитологического и иммуногистохимического анализа (n = 104), а также количественными показателями относительной интенсивности опухолевого сигнала (ОИОС) на Т2- и Т1-взвешенных изображениях (ВИ) при МРТ (n = 106).

Результаты. Среди маркеров морфологической стратификации СО наиболее информативными являются: возраст диагноза (AUC 0,686), объем и максимальный диаметр опухоли (0,664 и 0,665), экспрессия 2-го подтипа (п/т) соматостатиновых рецепторов (СР; 0,816), разница и соотношение 2-го и 5-го п/т СР (0,826 и 0,808), пропорция клеток с АТ к ГР (0,932) и с фиброзными тельцами (ФТ; 0,962), клеточный состав опухоли (0,935), ОИОС на Т2-, Т1- и (Т2-Т1)-ВИ (0,878, 0,822 и 0,918). К предикторам эффективности АС1 относятся: объем и максимальный диаметр СО (0,640 и 0,649), исходная величина ИФР-1 индекса (0,637), абсолютная и относительная экспрессия 2-го п/т СР (0,673, 0,688 и 0,713), пропорция клеток с ФТ (0,698), клеточный состав опухоли (0,742), результаты ОИОС на Т2- и (Т2-Т1)-ВИ (0,684 и 0,636) и ФармТ (%ΔИФР-1 через 3–6 мес. – 0,840–0,849). Показано успешное использование пэгвисоманта у пациентов с рефрактерностью к АС1.

Выводы. Выделены приоритетные предикторы морфофункционального статуса СО и долгосрочной эффективности АС1, упрощающие дифференциально-диагностический поиск актуального гистотипа и обеспечивающие управление лечением акромегалии.

Ключевые слова: акромегалия, прецизионная медицина, соматотрофные опухоли, ИФР-1 индекс, 2-й подтип соматостатиновых рецепторов, фиброзные тельца, Т2-взвешенные изображения, аналоги соматостатина 1-го поколения, пэгвисомант

Для цитирования: Пронин ЕВ, Анциферов МБ, Пронин ВС, Петряйкин АВ, Алексеева ТМ, Тамаева СМ. Сравнение предсказательной силы предикторов морфологической и терапевтической стратификации моногормональных соматотрофных опухолей гипофиза у пациентов с акромегалией. *Медицинский совет*. 2025;19(16):259–273. https://doi.org/10.21518/ms2025-457.

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INTRODUCTION

Somatotroph tumors (STs), which are the leading cause of pituitary gigantism and acromegaly, account for 15–20% of all neuroendocrine neoplasms of the adenohypophysis (PitNET). The heterogeneous composition of STs, delayed diagnosis and undifferentiated treatment contribute to the pathological prolongation of elevated levels of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) in the blood, leading to the development of life-threatening systemic and metabolic disorders [1, 2].

The current undifferentiated approach of prescribing first-generation somatostatin receptor ligands (fg-SRLs) as first-line treatment results in biochemical remission in only 30–50% of patients in the non-selective group, indicating a costly treatment regimen with unpredictable outcomes. Therapeutic failures are due to the existing multiplicity of GH-secreting neoplasms, which differ in pathogenesis, degree of terminal differentiation, hormonal profile, nature of receptor expression and selective sensitivity to target drugs [3, 4].

The 5th WHO classification of pituitary adenomas from 2022 identifies seven sporadic and genetically determined histotypes of neuroendocrine GH-secreting tumors belonging to the PIT1-dependent family. Among the identified morphotypes, the following are distinguished: pure (monohormonal) densely and sparsely granulated somatotroph tumors (DGSTs and SGSTs), monocellular mammosomatotroph tumors, bicellular somatotroph-lactotroph tumors, mature plurihormonal and immature tumors of the PIT1 line, as well as acidophilic tumors from stem cells [5]. The diversity of histological variants of STs together with the absence of valid predictors of morphofunctional status significantly complicate the differential diagnosis and are an obstacle to achieving the expected control of acromegaly.

Timely intraspecific stratification is particularly relevant for the most common DGSTs and SGSTs, whose clinical course and treatment have fundamental differences. DGSTs are observed in 50% of cases and consist of highly differentiated eosinophilic cells characterized by the cytoplasmic presence of multiple large GH-containing granules, high expression of the 2nd subtype (s/t) of somatostatin receptors (SSTR), a small number of cells (<8%) containing fibrous bodies (FB), and a low Ki-67 proliferative index (<3%). The characteristics of tumor development include late onset, usually intrasellar tumor growth, a high content of secretory cells and good sensitivity to the antisecretory and antitumor effects of fg-SRLs.

SGSTs, occurring in approximately 30% of cases, are formed from poorly differentiated chromophobic cells that have lost (or not acquired) species differentiation, which manifests itself in a depleted granular pattern, low positivity of AB to GH, low SSTR2 expression and a high proportion of cells with FB (⩾70%). As a rule, SGSTs manifest at a young age, are characterized by high proliferative activity, invasive growth, a tendency to recur, and resistance to fg-SRLs. Due to the established practice of non-selective selection of therapeutic drugs, adequate treatment of this morphotype is delayed, which negatively affects the therapeutic prognosis [6, 7].

In recent years, intermediate tumors (ITs) have been identified among monohormonal STs. These tumors consist of a mixture of weakly eosinophilic and chromophobic cells and differ from DGSTs in their lower SSTR2 expression and increased proportion (9–69%) of cells with FB. These cell-mixed tumors are characterized by the absence of GNAS mutation, a specific DNA methylation profile, lower SSTR2 expression and the presence of receptors for insulin-like glucose-dependent polypeptide with a paradoxical response to glucose loading. Additional co-expression of LH, FSH and the transcription factor SF1 served as the basis for identifying this histotype as a multilineage (or somatotroph-gonadotroph) tumor. Despite obvious genotypic features, ITs are conditionally included in the DGSTs, but differ in their reduced response to fg-SRLs [8, 9].

Thus, additional consideration of cell composition allows us to distinguish specific histotypes of pure STs: eosinophilic tumors (ETs), mixed intermediate tumors (ITs) and chromophobic tumors (CTs), differing in ultrastructural composition, the severity of relative SSTR2 and SSTR5 expression and, accordingly, high, moderate or low sensitivity to fg-SRLs (*Fig. 1*) [7].

Given the phenotypic differences, it seems obvious that the formal prescription of fg-SRLs as a first-line drug (without taking into account the receptor characteristics of tumor cells) does not allow achieving total control of acromegaly, condemning half of patients to the need for additional treatment options [10]. The best results are observed in the treatment of patients with DGSTs, which is associated with predominantly high SSTR2 expression. In contrast, in patients with SGSTs, prolonged and high-dose monotherapy with fg-SRLs stops from achieving biochemical remission and does not prevent further progression of systemic and metabolic complications [11].

To optimize the pharmacotherapy of acromegaly, international experts have proposed a transition from the empirical «trial and error» method to precision medicine using valid biomarkers of biological behavior of GH and their susceptibility to targeted drugs [12]. Currently, there is a wide range of diverse clinical, hormonal, radiological and morphological indicators for tumor identification and treatment outcome, many of which, unfortunately, have not been implemented in clinical practice due to the lack of unified diagnostic protocols and a single prognostic concept [13, 14].

First of all, this concerns biomarkers of the morphofunctional status of the STs, which determines the characteristics of biological behavior and the effectiveness of planned pharmacotherapy with fg-SRLs. The morphological method using immunohistochemical analysis (IHA) is the «gold standard» for diagnosis, against which the prognostic significance of other predictors is determined [15, 16].

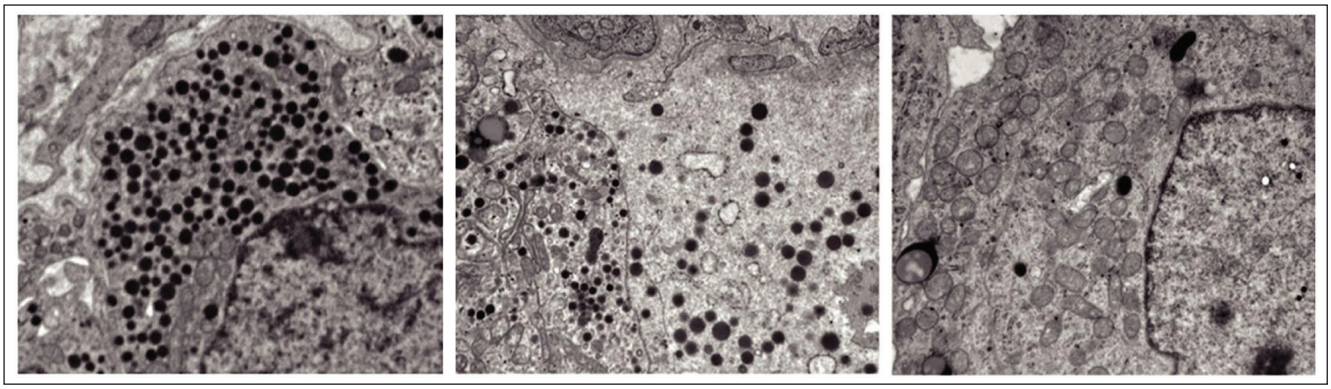
A relatively new diagnostic option that allows for the subclassification of STs at the preoperative stage is the quantitative assessment of the relative tumor signal intensity (RTSI) on T2- and T1-weighted MRI (WI). Foreign and pilot domestic studies have confirmed that DGST is characterized by a hypointense signal, while SGST is characterized by a hyperintense signal on T2- and (T2-T1)-WI [17, 18].

A useful option is pharmacotherapeutic testing (PharmT) with an assessment of the percentage decrease in IGF-1 (%ΔIGF-1) compared to baseline after 3-6 months of treatment with fg-SRLs. The GR nadir value or %ΔIGF-1 can be used to indirectly assess the receptor phenotype and the integrity of postreceptor mechanisms in tumor cells, which is particularly important in the early stages of DT with fg-SRLs [13, 19, 20].

Among the combined list of known predictors of morphological status and sensitivity to fg-SRLs, patient- and tumor-oriented biomarkers can be distinguished. The first group includes: patient age, age at diagnosis, gender, BMI, duration of the latent period, baseline levels of GH and IGF-1, effective doses and duration of fg-SRLs treatment. The second group includes: visual analysis of tumor characteristics (volume, maximum diameter, degree of invasion according to Knosp and Hardy), morphological diagnosis (DGST or SGST), cytological and ultrastructural parameters (cell composition, granular pattern, proportion of cells with FB, comparative SSTR2 and SSTR5 expression, Ki-67 proliferation index), radiological indicators (RTSI on T2- and T1-WI, radiomic tumor characteristics), functional tests (results of tests with octreotide and PharmT) [21-23]. Due to the existing abundance of diverse biomarkers, it is important to stratify diagnostic "tools" taking into account the target objectives and predictive power.

The aim of this study is to compare the prognostic significance of available patient- and tumor-oriented predictors of morphological diagnosis and the prospects for using fg-SRLs in patients with acromegaly.

Figure 1. Electron micrographs of eosinophilic, intermediate and chromophobe tumor cells [7]
Рисунок 1. Электронные микрофотографии клеток эозинофильных, промежуточного типа и хромофобных опухолей [7]



MATERIALS AND METHODS

A retrospective study included 634 patients with acromegaly (197 men) receiving prolonged forms of fg-SRLs (lanreotide 120 mg/28–56 days; octreotide 20-30 mg/28 days) as primary or secondary DT. The IGF-1 index, reflecting the ratio of IGF-1 to the upper limit of normal (IGF-1/ULN), was used for the initial and dynamic assessment of somatotroph function. The criterion for drug control was an IGF-1 index value ⩽1. The age at diagnosis was 47.9 ± 13.8 years, the baseline IGF-1 index value was 2.7 ± 1.2, the baseline tumor volume was 4.7 ± 13.4 cm^3, the duration of DT was 77.8 ± 52.7 months, and the IGF-1 index value at the last visit was 1.2 ± 0.7. PharmT which consisted of assessing the percentage decrease in IGF-1 levels (%ΔIGF-1) 3 and 6 months after the start of treatment with fg-SRLs was also performed.

Surgical treatment was performed in 402 patients (63.4%). Morphological examination (including IHA) of tumor material was performed in 104 patients at National Medical Research Center of Endocrinology of the Ministry of Health of Russian Federation. Microscopy revealed tumors consisting of eosinophilic cells (ETs); mixed-cell intermediate tumors (ITs) and tumors of chromophobe cells (CTs). During IHA, AB to GH, prolactin, Ki-67, cytokeratin (CAM 5.2), and SSTR2 and SSTR5 were evaluated. The severity of SSTR2 and SSTR5 expression in points was determined using IRS (Immunoreactive Score) scale [24]. The proportion of cells with FB was stratified according to the ordinal scale by A. Obary et al.: 1 point – <8%, 2 – 9–69%, 3 – ⩾70% of cells [25]. DGST was identified in 48 patients and SGST – in 56 patients.

Contrast-enhanced MRI was performed at Scientific and Practical Clinical Center for Diagnostics and Telemedicine Technologies. The pituitary tumor volume was determined using Di Chiro & Nelson formula. In 106 patients, the tumor signal intensity on T2- and T1-WI was assessed quantitatively relative to the gray matter of the brain with an additional calculation of the T2-T1 coefficient. The calculation formula is presented in early study [18].

Statistical analysis was performed using the statistical software packages Statistica 12.5 and SPSS Statistics 23. Measures of central tendency and dispersion of quantitative characteristics with normal distribution are presented as the arithmetic mean (M) and standard deviation (SD), and for quantitative characteristics that differ from normal distribution, as the median (Me) and interquartile range (25^{th} and 75^{th} percentiles). When comparing two independent groups using parametric and nonparametric methods, Student's t-test and the Mann-Whitney test were used. The analysis of dependencies was performed using Spearman's rank correlation coefficient (r). To evaluate the predictive power of prognostic models, the ROC curve analysis method was used to determine the area under the curve (AUC), sensitivity (Se), and specificity (Sp). Prognostic models with AUC >0.6 were taken into account. The k-means method was used to perform cluster analysis. Differences were considered statistically significant at $p < 0.05$.

RESULTS

In the analyzed cohort of patients, acromegaly control with normalization of the IGF-1 index (⩽1) against the background of long-term use of fg-SRLs was achieved in only 51% of cases, indicating insufficient effectiveness of empirical pharmacotherapy. *Table 1* presents the results of treatment with fg-SRLs, volumetric and ultrastructural characteristics of STs, taking into account cell composition.

The presented results indicate the presence of reliable phenotypic differences between monomorphic eosinophilic and chromophobic tumors, which confirms the diagnostic significance of determining the cell composition that defines the morphofunctional status of STs. Thus, tumors composed of eosinophilic cells are initially smaller in size, have a higher proportion of AB to GH cells, high SSTR2 expression, a low proportion of FB cells, low Ki-67 content, and high DT efficacy of fg-SRLs. In contrast, somatotroph tumors consisting of chromophobic cells are characterized by directly opposite volumetric, ultrastructural, and therapeutic indicators.

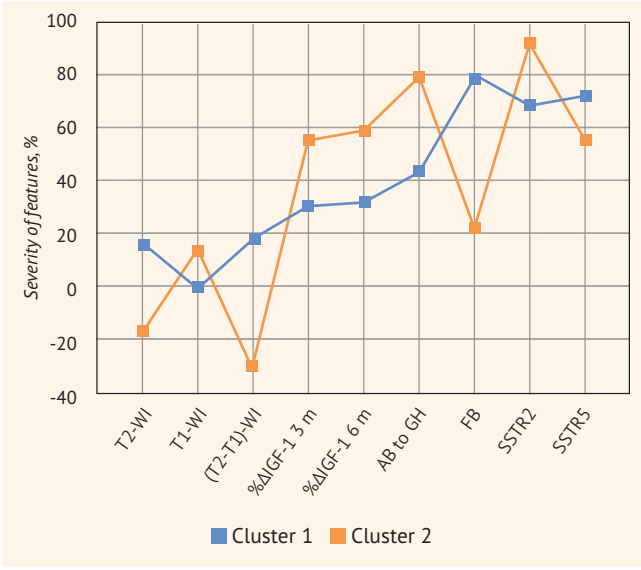
To identify patterns in the grouping of features associated with pathomorphological diagnosis, a procedure was used to cluster clinical, morphological, radiological and therapeutic biomarkers in 104 patients (*Fig. 2, Table 2*).

Table 1. Volumetric and immunohistochemical characteristics of tumors, taking into account cell composition [M (SD)]
Таблица 1. Объемные и иммуногистохимические характеристики опухолей с учетом клеточного состава [M (SD)]

Morphological diagnosis	Cell composition	Final IGF-1 index	Tumor volume (cm^3)	AB to GH (%)	Ki-67 (%)	FB (points)	SSTR2 (points on IRS)	SSTR5 (points on IRS)
DGST	ET (1)	0.86 (0.27)	2.6 (5.9)	86.7 (12.7)	3.9 (2.2)	1.2 (0.4)	10.8 (2.3)	4.4 (3.2)
	IT (2)	1.1 (0.4)	3.8 (5.7)	73.1 (29.1)	4.5 (3.4)	1.9 (0.8)	8.7 (3.5)	5.6 (3.1)
SGST	CT (3)	1.7 (0.7)	10.1 (11.6)	36.7 (16.5)	8.9 (5.4)	2.9 (0.4)	5.7 (3.6)	6.0 (3.1)
p		$p^{1-2} = 0.089$ **$p^{1-3} = 0.004$** **$p^{2-3} = 0.0008$**	$p^{1-2} = 0.48$ **$p^{1-3} = 0.0149$** **$p^{2-3} = 0.0094$**	**$p^{1-2} = 0.0129$** **p^{1-3*}** **p^{2-3*}**	$p^{1-2} = 0.495$ **$p^{1-3} = 0.0012$** **$p^{2-3} = 0.0011$**	**$p^{1-2} = 0.0006$** **p^{1-3*}** **p^{2-3*}**	**$p^{1-2} = 0.0235$** **p^{1-3*}** **$p^{2-3} = 0.0013$**	$p^{1-2} = 0.2059$ $p^{1-3} = 0.0916$ $p^{2-3} = 0.6163$

Note: p* – p < 0,0001
Here and further in tables and figures: AB – antibodies, GH – growth hormone, FT – fibrous bodies, SSTR – somatostatin receptors, s/t – subtype, DGST – densely granulated somatotroph tumor, SGST – sparsely granulated somatotroph tumor, ET – eosinophilic tumor, IT – intermediate tumor, CT – chromophobic tumor, fg-SRLs – first-generation somatostatin receptor ligands, WI – weighted imaging, %ΔIGF -1 – percentage of IGF-1 level reduction, RTSI – relative tumor signal intensity.

● ***Figure 2.*** Intercluster differences in the severity (in %) of tumor-oriented features
● ***Рисунок 2.*** Межкластерные различия выраженности (%) опухоль-ориентированных признаков



● ***Table 2.*** Comparison of distinctive features of chromophobic (cluster 1) and eosinophilic (cluster 2) tumors (M ± SD)
● ***Таблица 2.*** Сравнение отличительных признаков хромофобных (кластер 1) и эозинофильных (кластер 2) опухолей (M ± SD)

Predictors	Cluster 1 N23	Cluster 2 N20	p
RTSI on T2-WI (%)	17.1 ± 20.9	-16.9 ± 20.3	p*
RTSI on T1-WI (%)	-1.2 ± 12.2	14.1 ± 14.2	p*
RTSI on (T2-T1)-WI (%)	18.3 ± 30.3	-30.8 ± 23.7	p*
%ΔIGF-1 after 3 months	30.5 ± 24.4	55.0 ± 22.9	0.001
%ΔIGF-1 after 6 months	32.0 ± 25.4	59.1 ± 21.4	p*
Proportion of cells with AB to GH (%)	43.7 ± 22.6	79.8 ± 12.2	p*
Proportion of cells with FB (%)	80.0 ± 12.2	20.7 ± 17.9	p*
SSTR2 expression (%)	68.3 ± 27.0	92.3 ± 9.8	p*
SSTR5 expression (%)	72.6 ± 19.8	56.7 ± 32.4	0.034

Note: p* – p<0,0001

During cluster analysis, a set of priority predictors was selected from the above list, the parameters of which are statistically significantly divided into two cluster groups, which together reflect the characteristic features of low- and highly specialized cells of monomorphic STs – CTs and ETs (*Table 1*). Therefore, the complex differences in variables presented in *Table 2* can be used as complementary markers for identifying chromophobic or eosinophilic STs. The results of the clustering served as the basis for including these indicators in the group of tumor-oriented predictors, followed by a comparative determination of their predictive power in relation to the morphological status of STs and response to treatment with fg-SRLs. As for the remaining patients, due to the mixed cellular nature of these tumors, we did not identify any consistent differences suitable for precision subtyping. Given the formal combination of ETs and ITs into a single morphological group (DGST), further evaluation of the prognostic significance of predictive models was performed for DGSTs and SGSTs (*Table 3, Fig. 3*).

As can be seen from *Table 3*, there is a direct dependence between the correlation strength and the prognostic significance of the selected biomarkers.

Among patient-oriented indicators, only age and volume characteristics have acceptable quality as prognostic models, as they allow for approximate prediction of focus groups of patients with DGSTs or SGSTs. Based on the cut-off points, for patients with DGSTs, the approximate passport age is >47 years, the age of diagnosis is >42 years, and the tumor volume is <1.6 cm^3. Patients with SGSTs have the same threshold values for the analyzed characteristics, but with the opposite sign. Regarding gender and hormonal differences, we did not find any significant associations with histological subtypes of STs.

Tumor-oriented predictors included in the previously identified cluster groups have the greatest correlation and prognostic power. Among immunohistochemical and histological indicators, the following have high prognostic significance: absolute SSTR2 expression [r = 0.56 (p*); AUC 0.816], the difference and ratio SSTR2 and SSTR5 [r = 0.57 and 0.54 (p*); AUC 0.826 and 0.808, respectively], the proportion of cells with AB to GH [r = 0.77 (p*); AUC 0.934], the proportion of cells with FB [r = 0.74 (p*); AUC 0.955], cell composition [scores: ET – 1, IT – 2, CT – 3; r = 0.75 (p*); AUC 0.928], percentage of Ki-67 [r = -0.31 (p = 0.003); AUC 0.682].

RTSI values also have high predictive power with regard to the morphological status of STs. For T2-WI, r = -0.65 (p*), AUC 0.878; for (T2-T1)-WI, r = -0.72 (p*), AUC 0.918; for T1-WI, r = 0.55 (p*), AUC 0.822. The corresponding cut-off points <-3.7, <-12 and >4.4 predict the presence of DGST. It is indicative that there is an inverse correlation between RTSI on T2- and (T2-T1)-WI and the proportion of cells with AB to GH [r = -0.64 and -0.67 (p*)], as well as a direct correlation with FB [r = 0.63 and 0.68 (p*)], which fits the concept of the phenomenon of hypo- or hyperintense tumor signal in acromegaly. It is assumed that a hypointense signal is a marker of excessive presence of protein compounds (GH-containing granules) in the cytosol, which is characteristic of DGSTs, while a hyperintense signal, specific for SGSTs, is associated with a low presence of secretory granules and the presence of small cystic degeneration [21]. The combined use of different methods for assessing RTSI confirmed the presence of persistent structural differences between SGSTs and DGSTs (*Fig. 4–6*).

As for the predictive power of PharmT, the correlation between %ΔIGF-1 at 3 and 6 months and morphological status was 0.42 (p*) and 0.36 (p = 0.004); AUC – 0.739 and 0.763, threshold values for differential diagnosis between SGSTs and DGSTs were determined as 35 and 37%, respectively. *Table 4* and *Fig. 7* present a comparison of the prognostic significance of predictors of sensitivity to fg-SRLs.

● ***Table 3.*** Comparison of correlation analysis results and predictive significance of predictor models for morphological status of sparsely (1) or densely (2) granulated somatotroph tumors

● ***Таблица 3.*** Сравнение результатов корреляционного анализа и прогностической значимости предикторных моделей морфологического статуса редко- (1) или плотногранулированных (2) соматотрофных опухолей

morphological status markers	r	p	AUC	Se (%)	Sp (%)	DA (%)	CP
patient-oriented predictors							
Age (years)	0.27	0.012	0.656	66	57	61.5	47
Age at diagnosis (years)	0.32	0.002	0.686	68	54	61	42
Gender	0.008	0.9	0.496				
Initial GH level (ng/ml)	-0.01	0.9	0.490	50	60	55	19
Initial IGF-1 index value	0.045	0.7	0.541	56	47	51.5	2.7
Initial tumor volume (cm^3)	-0.29	0.004	0.664	60	77	68.5	2.8
Maximum diameter (mm)	-0.28	0.004	0.665	68	77	72.5	20
tumor-oriented predictors							
ultrastructural and cytological biomarkers							
SSTR2 expression (points on IRS)	0.56	p*	0.816	82	74	78	7
SSTR5 expression (points on IRS)	-0.21	0.057	0.620	70	51	60.5	5.5
Difference between SSTR2 and SSTR5	0.57	p*	0.826	72	86	79	3.5
SSTR2/SSTR5 ratio	0.54	p*	0.808	81	73	77	1.4
Ki-67 (%)	-0.31	0.003	0.682	67	58	62.5	3.9
Proportion of cells with AB to GH (%)	0.77	p*	0.932	88.5	85	86.7	72
Proportion of cells with FB (points)	-0.74	p*	0.962	92	100	96	2.5
Cell composition (points: 1 – ET, 2 – IT, 3 – CT)	-0.75	p*	0.935	96	85	90.5	1.5
relative tumor signal intensity values on T2-, T1-, (T2-T1)-WI							
RTSI on T2-WI (%)	-0.72	p*	0.878	89	73	81	-3.7
RTSI on T1-WI (%)	0.50	p*	0.822	82	50	66	4.4
RTSI on (T2-T1)-WI (%)	-0.75	p*	0.918	92	69	81.5	-12
percentage decrease in IGF-1 levels after 3-6 months of treatment with fg-SRLs							
%ΔIGF-1 after 3 months	0.42	p*	0.739	76	65	70.5	35
%ΔIGF-1 after 6 months	0.36	0.004	0.763	72	65	68.5	37

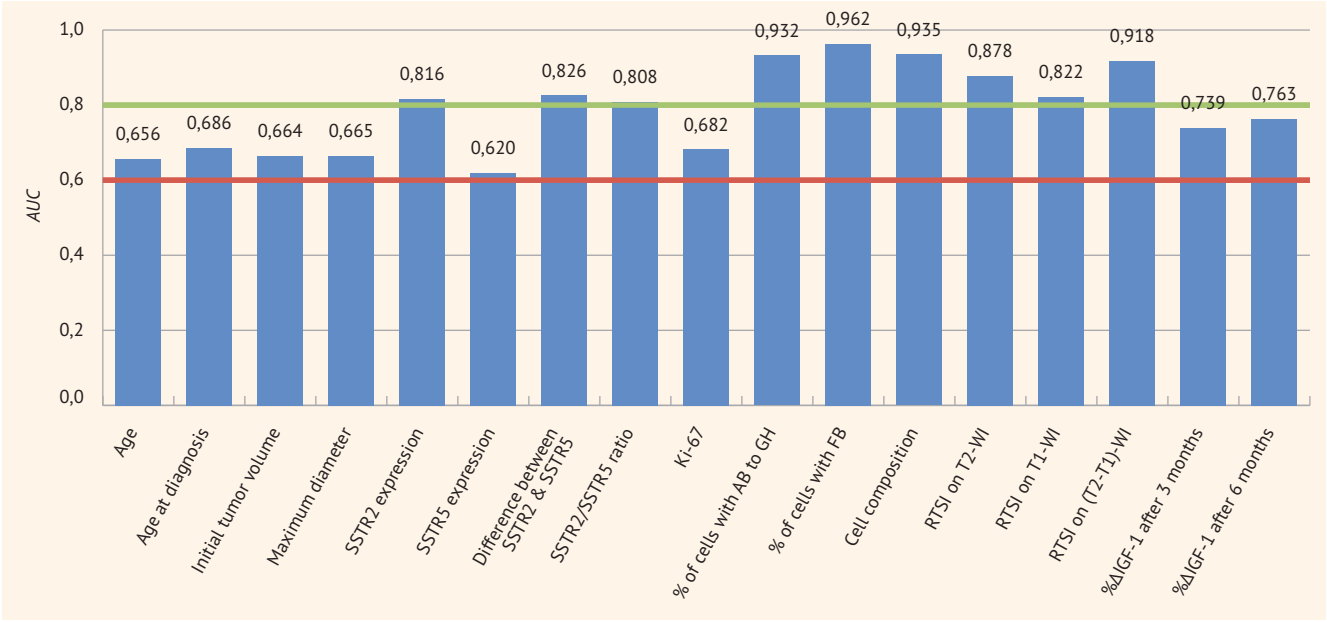
Note: r – Spearman's correlation coefficient, AUC – Area Under the Curve; Se – sensitivity; Sp – specificity; DA – diagnostic accuracy; CP – cut-off point; p* – p < 0,0001

The data in *Table 4* indicate the weak predictive power of patient-oriented markers. Neither age nor gender indicators allow us to assess the quality of treatment outcomes. Only the baseline level of the IGF-1 index and the volumetric characteristics of the STs can be taken into account to predict the effectiveness/ineffectiveness of treatment with fg-SRLs, which is consistent with the data from S. Petersenn et al. [19].

The prognostic capabilities of morphological markers are somewhat higher. The strongest correlation with the final value of the IGF-1 index and the prognostic power of the treatment outcome are observed in the indicators of tumor cell composition [r = 0.57 (p*); AUC 0.792], SSTR2 expression [r = -0.36 (p = 0.004); AUC 0.673], the difference and ratio of SSTR2 and SSTR5 [r = -0.49 and r = -0.52 (p*); AUC 0.688 and 0.713, respectively] and Ki-67 values (AUC 0.674). The threshold values for successful treatment with fg-SRLs include eosinophilic tumor cell composition, SSTR2 expression >8 points, difference and ratio between SSTR2 and SSTR5 >3.5 and >1.4, a low proportion of cells with FB (<8%), and a low Ki-67 index (<2.5%). All of the above characteristics correspond to the DGST status and may be useful for deciding on the prospects of secondary or primary DT with fg-SRLs. The greatest correlation strength (r = -0.63 and r = -0.65; p*) and prognostic significance in determining the long-term efficacy of fg-SRLs are the values of %ΔIGF-1 after 3 and 6 months of treatment (AUC 0.840 and 0.849, respectively) with cut-off points

● ***Figure 3.*** Comparison of AUC predictors of morphological status of somatotroph tumors (the red dividing line indicates AUC >0.6; the green line indicates >0.8)

● ***Рисунок 3.*** Сравнение AUC предикторов морфологического статуса соматотрофных опухолей (красная разграничительная линия выделяет AUC > 0,6; зеленая линия – > 0,8)



of 55-56% of the baseline level. Regarding the predictive value of RTSI, we found the moderate quality of prognostic models, which are close to hormonal, volumetric and morphological predictors [AUC T2-WI 0.684; (T2-T1)-WI 0.636]. Nevertheless, it was shown that with a RTSI value on T2-WI of less than -10% or more than 10%, the final value of the IGF-1 index was 1.06 ± 0.5 versus 1.6 ± 0.7 (p = 0.009), which is confirmed by other authors [17].

Thus, sensitivity to fg-SRLs depends on the cell composition of STs, absolute or relative SSTR2 expression and the integrity of postreceptor mechanisms. Since all these options are covered by PharmT, it seems useful to use this diagnostic method clinically in the absence or inconsistency of IHA results.

The diverse biomarkers (and cut-off points) presented in *Table 5* reflect the results of ROC analysis and can be used to verify the histological phenotype of ST and select an appropriate treatment strategy. Below is a clinical illustration of the need for preliminary stratification of patients before prescribing DT. We identified a group of 67 patients (33 M) aged 50 ± 13 years who had undergone non-radical surgery or radiation therapy and had been receiving maximum doses of fg-SRLs for a long time (60 ± 48 months) without a positive effect (IGF-1 index 1.86). According to the results of IHA (n = 33), 25 patients (76%) were diagnosed with SGST, 7 (21%) – with DGST, and 1 – with a somatotroph-lactotroph tumor. SSTR2 expression was 5.9 ± 4.0 points, SSTR2/SSTR5 ratio was 1.1 ± 1.0. In 17 patients, RTSI was studied on T2-WI: in 11 of them (65%) hyperintense (RTSI 17.7 ± 14.3%) tumors were detected, in 6 – hypointense tumors (RTSI -17.4 ± 19.7%). In 65 patients, %ΔIGF-1 after 3 months was 27 ± 21, after 6 months – 26 ± 22, which, along with low SSTR2 expression, indicates the presence of the fg-SRLs-resistant histotype. To achieve control, the GH receptor antagonist pegvisomant (PEG) was prescribed as a second-line drug, which resulted in normalization of the IGF-1 index (0.96) in 77% of patients, which persisted in 18 patients with a reduction in the therapeutic dose (n = 15) or complete discontinuation of fg-SRLs (n = 3). Dynamic monitoring showed no continued growth of the residual tumor. This observation indicates that the combined use of antitumor (fg-SRLs) and antagonistic (PEG) drugs allows for timely control of acromegaly in patients in the resistant group (*Fig. 8*).

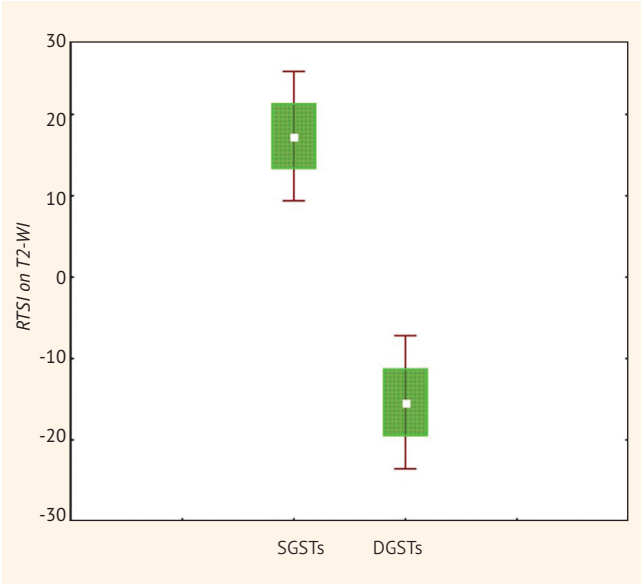
DISCUSSION

Precise differential diagnosis between monohormonal histotypes of STs using valid predictors is of great practical importance, as it allows predicting: 1) the likely biological scenario of disease development; 2) the receptor phenotype and proliferative potential of tumor cells; 3) the risk of recurrence and continued growth; 4) the prospects for planned DT with fg-SRLs. From a clinical standpoint, it is important to identify fg-SRLs-resistant patients in a timely manner in order to select alternative pharmacotherapy. Despite the apparent abundance of candidate predictors, there are currently no unified protocols for hormonal, radiological and immunohistochemical diagnostic methods, nor agreed-upon thresholds that would allow for diagnostic typing and comparison of the results of clinical and scientific studies [26, 27].

First and foremost, this concerns the coordination of the treatment target (TT) with the recommended level of the IGF-1 index ⩽1 as a starting point for determining the prognostic significance of the proposed predictors, which is enshrined in foreign and domestic clinical guidelines [28, 29]. Arbitrary interpretation of acromegaly control parameters

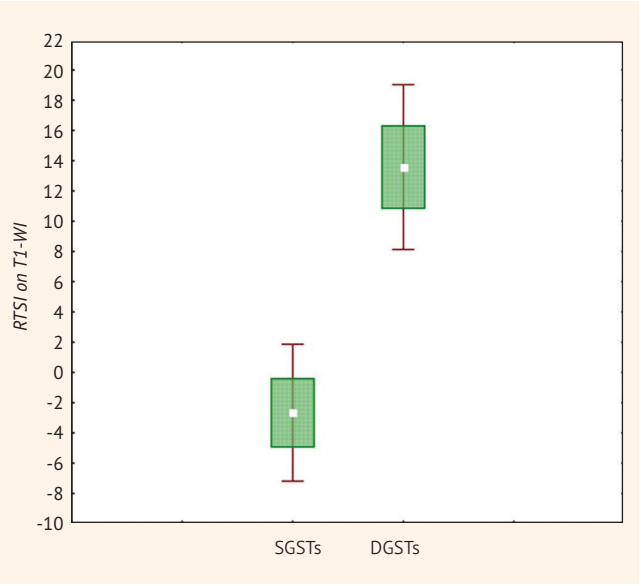
● ***Figure 4.*** Differences in relative tumor signal intensity (%) between sparsely and densely granulated somatotroph tumors on T2-WI [Me (25/75%)]

● ***Рисунок 4.*** Различия в относительной интенсивности опухолевого сигнала (%) между редко- и плотногранулированными соматотрофными опухолями на Т2-ВИ [Me (25/75%)]



● ***Figure 5.*** Differences in relative tumor signal intensity (%) between sparsely and densely granulated somatotroph tumors on T1-WI [Me (25/75%)]

● ***Рисунок 5.*** Различия в относительной интенсивности опухолевого сигнала (%) между редко- и плотногранулированными соматотрофными опухолями на Т1-ВИ [Me (25/75%)]



(IGF-1 index <1.2–1.3) disrupts the threshold scale, reduces the predictive power of biomarkers, and makes it difficult to compare the obtained results [30–32].

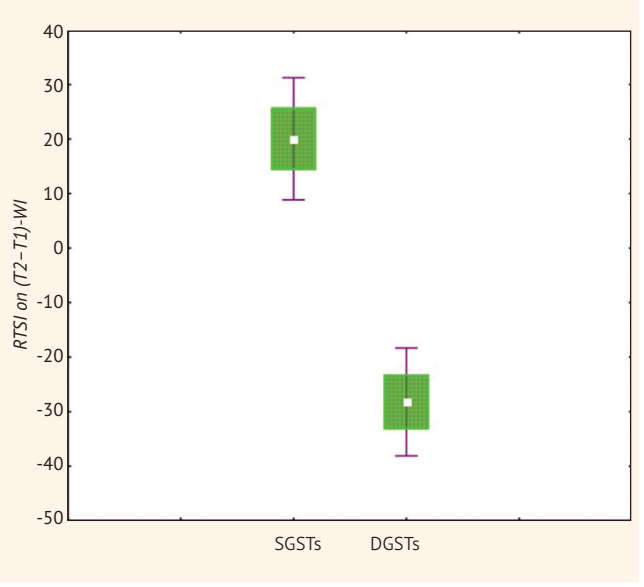
An important aspect is the identification of priority predictors (or predictor groups) with the greatest predictive power. Given the insufficient effectiveness of fg-SRLs in non-selective groups, the largest number of biomarkers is associated with predicting the effectiveness of their long-term use. As follows from the analysis, patient-oriented predictors do not have sufficient predictive power and are therefore often used as part of a comprehensive prognostic model.

Age parameters. The age characteristics of patients remain relevant in indirectly predicting sensitivity to fg-SRLs and the degree of aggressiveness of the tumor formation, which is due to the peculiarities of the manifestation of DGSTs and SGSTs. The higher the passport age, the lower the disease activity and the better the response to fg-SRLs. According to the Spanish registry, the acromegaly phenotype in patients over 65 years of age includes: small adenoma size, GH level <6 ng/ml, moderately elevated IGF-1 index (1.9 ± 0.8), and good sensitivity to fg-SRLs [31]. In the study by E.T. Durmus et al., the following predictors of good sensitivity to fg-SRLs were identified: older age of patients, slight excess of GH and IGF-1 levels, small adenoma size, presence of DGST and hypointense signal on T2-WI. The threshold values for GH and IGF-1 at diagnosis were ⩽8.8 ng/ml and ⩽461.5 ng/ml, respectively, the IGF-1 index value was ⩽1.8, and the tumor volume was ⩽1.11 cm^3 (all p <0.05) [33].

Tumor size. In a study by L.M. Del Corso et al., the clinical, laboratory and radiological characteristics of patients were evaluated based on the maximum diameter of the adenoma. The authors concluded that a diameter of less than 20 mm is the threshold for predicting lower morbidity and better sensitivity to fg-SRLs (TT: IGF-1 index ⩽1.0) [34]. In a study by M. Shen et al. it is also confirmed that age over 49 years and a maximum tumor diameter of less than 2 cm indicate good sensitivity to fg-SRLs (achievement of the IGF-1 index ⩽1.0 or %ΔIGF-1 >50 after 3 months of treatment was the criterion for a good response to fg-SRLs) [35].

● ***Figure 6.*** Differences in relative tumor signal intensity (%) between sparsely and densely granulated somatotroph tumors on (T2-T1)-WI [Me (25/75%)]

● ***Рисунок 6.*** Различия в относительной интенсивности опухолевого сигнала (%) между редко- и плотногранулированными соматотрофными опухолями на (Т2-Т1)-ВИ [Me (25/75%)]



● ***Table 4.*** Comparison of correlation analysis results and predictive significance of predictor models for sensitivity to first-generation somatostatin receptor ligands
● ***Таблица 4.*** Сопоставление результатов корреляционного анализа и прогностической значимости предикторных моделей чувствительности к аналогам соматостатина 1-го поколения

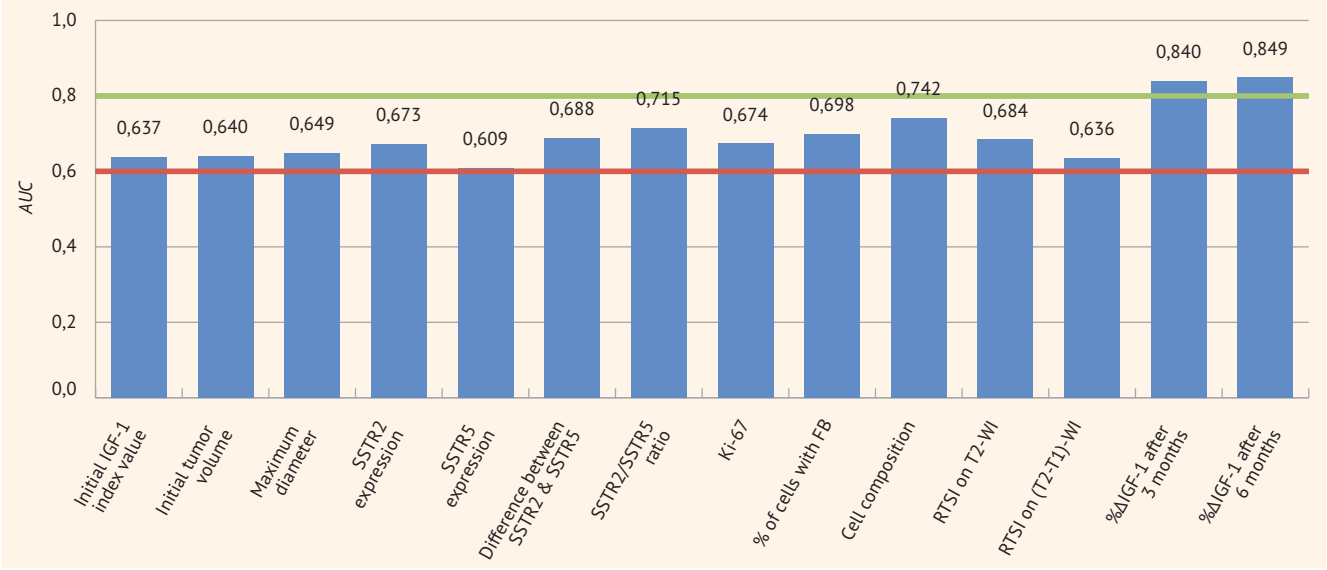
fg-SRLs sensitivity markers	r	p	AUC	Se (%)	Sp (%)	DA (%)	CP
patient-oriented predictors							
Age (years)	-0.07	0.21	0.517	53	50	51.5	60
Age at diagnosis (years)	0.007	0.9	0.515	53	51	52	46
Duration of the latent period (years)	-0.04	0.7	0.560	59	51	55	5.5
Initial GH level (ng/ml)	0.14	0.02	0.576	58	51	54.5	16
Initial IGF-1 index value	0.28	0.001	0.637	63	60	61.5	2.6
Initial tumor volume (cm^3)	0.25	p*	0.640	50	78	64	2.5
Maximum diameter (mm)	0.40	p*	0.649	63	56	59.5	16
Duration of DT (months)	-0.08	0.19	0.612	61	55	58	56
tumor-oriented predictors							
ultrastructural and cytological biomarkers							
SSTR2 expression (points on IRS)	-0.36	0.004	0.673	64	61	62.5	8
SSTR5 expression (points on IRS)	0.26	0.042	0.609	64	57	60.5	6
Difference between SSTR2 and SSTR5	-0.49	p*	0.688	68	68	68	3.5
SSTR2/SSTR5 ratio	-0.52	p*	0.715	71	58	64.5	1.4
Proportion of cells with AB to GH (%)	-0.26	0.045	0.582	62	66	64	72
Proportion of cells with FB (points)	0.37	0.003	0.698	75	73	74	2.5
Ki-67 (%)	-0.01	0.9	0.674	60	76	68	2.5
Cell composition (points: 1 – ET, 2 – IT, 3 – CT)	0.57	p*	0.742	69	76	72.5	2.5
relative tumor signal intensity values on T2-, T1-, (T2-T1)-WI							
RTSI on T2-WI (%)	0.32	0.046	0.684	68	59	63.5	-10
RTSI on (T2-T1)-WI (%)	0.29	0.069	0.636	64	71	67.5	-0.3
percentage decrease in IGF-1 levels after 3-6 months of treatment with fg-SRLs							
%ΔIGF-1 after 3 months	-0.63	p*	0.840	77	83	80	55
%ΔIGF-1 after 6 months	-0.65	p*	0.849	85	86	85.5	56

Note: r – Spearman's correlation coefficient, AUC – Area Under the Curve; Se – sensitivity; Sp – specificity; DA – diagnostic accuracy; CP – cut-off point; p* – p<0,0001

Hormonal activity of STs. In a study by E. Coopmans et al., the prognostic value of a moderate increase in baseline IGF-1 levels and a decrease in IGF-1 levels after 6 months of treatment was emphasized to confirm the prospects for long-term fg-SRLs use. On the other hand, young age and high BMI were associated with a poor prognosis for successful treatment with fg-SRLs (TT: IGF-1 index <1.3). Regarding tumor volume, the smaller it is, the better the sensitivity to fg-SRLs is [30]. According to B. Biagetti et al., the prognostic significance of a comprehensive predictive model of sensitivity to fg-SRLs, including basal levels of GH, IGF-1 index, gender, maximum diameter and BMI, was 0.82 at TT <1.2 [31]. Our results confirm higher prognostic significance of tumor-oriented predictors, which is consistent with the literature data.

Receptor expression. In a study by M.-D. Ilie et al., a group of 49 patients was examined for the association between

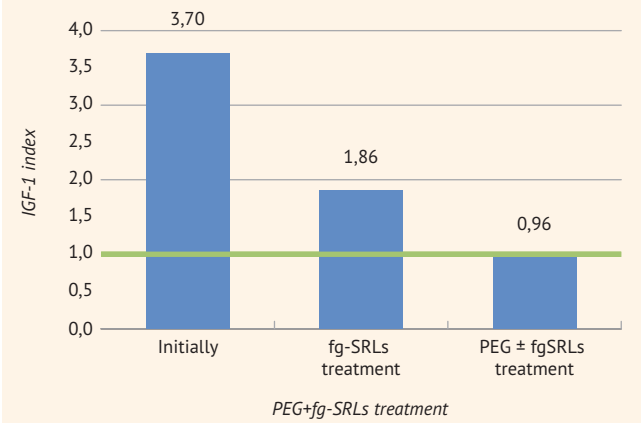
● ***Figure 7.*** Comparison of AUC predictors of sensitivity to first-generation somatostatin receptor ligands (the red dividing line indicates AUC >0.6; the green line indicates >0.8)
● ***Рисунок 7.*** Сравнение AUC предикторов чувствительности к аналогам соматостатина 1-го поколения (красная разграничительная линия выделяет AUC > 0,6; зеленая линия – > 0,8)



● ***Table 5.*** Predictors of sensitivity/refractoriness to first-generation somatostatin receptor ligands, taking into account cut-off points
● ***Таблица 5.*** Предикторы чувствительности/рефрактерности к аналогам соматостатина 1-го поколения с учетом точек отсечения

№	Predictors of sensitivity to fg-SRLs	Predictors of refractoriness to fg-SRLs
1	Presence of DGST	Presence of SGST
2	Presence of an eosinophilic tumor	Presence of a chromophobic tumor
3	SSTR2 expression >8 points on IRS	SSTR2 expression <6 points on IRS
4	Proportion of cells with AB to GH >72 %	Proportion of cells with AB to GH <30 %
5	Absence or low proportion of cells containing FB (<1,5 points)	Proportion of cells with FB >2,5 points
6	%ΔIGF-1 after 3-6 months of DT with fg-SRLs >55	%ΔIGF-1 after 3-6 months of DT with fg-SRLs <30
7	Hypointense tumor signal on T2- and (T2-T1)-WI (RTSI <-10%)	Hyperintense tumor signal on T2- and (T2-T1)-WI (RTSI >10%)

● ***Figure 8.*** Total IGF-1 index values against the background of first-generation somatostatin receptor ligands + pegvisomant pharmacotherapy (Me)
● ***Рисунок 8.*** Значения суммарного ИФР-1 индекса на фоне фармакотерапии аналогами соматостатина 1-го поколения + пэгвисомантом (Me)



PEG – pegvisomant

the severity of SSTR2 and SSTR5 expression, granular pattern, tumor signal intensity on T2-WI (visual method), and sensitivity to fg-SRLs (%ΔIGF-1 >20 after 6 months). It was noted that the value of %ΔIGF-1 after 6 months positively correlated with SSTR2 expression. It was emphasized that DGSTs and intermediate-type tumors had a more pronounced decrease in GH and IGF-1 levels compared to SGSTs. Hyperintense adenomas on T2-WI were characterized by a predominant dominance of SSTR5 and were refractory to fg-SRLs (%ΔIGF-1 ⩽20 after 6 months) [15]. According to O. Casar-Borota et al., the number of SSTR2 expression points according to IRS ⩾7 (on a scale from 0 to 12) can serve as a predictor of normalization of IGF-1 level during fg-SRLs treatment with a sensitivity of 71% and specificity of 100% [36]. Nevertheless, in the article by A.M. Berton et al. it is noted that the combination of high SSTR2 expression with low E-cadherin content is associated with poor efficacy of fg-SRLs (IGF-1 index ⩽1.0), which may be explained by the presence of two independent regulators of sensitivity to this treatment option in tumor cells [37].

Tumor signal intensity. Over the past decade, many studies have confirmed the prognostic significance of quantitative indicators of low or high T2-WI signal intensity associated with tumor sensitivity or refractoriness to fg-SRLs. In a pioneering study by A. Heck et al., the high prognostic power of this method for assessing the possibility of drug control of acromegaly with an AUC of 0.861 was confirmed [38]. In a comparative study by M. Luo et al. it is noted that the presence of a hyperintense signal on T2-WI and reduced SSTR2 expression (<5.4 points on IRS) is significantly associated with a low response to treatment with fg-SRLs (IGF-1 index >1), regardless of histological subtype [39]. The presented data are consistent with our results and indicate the promise of further research.

Diagnostic testing. In a study by S. Petersenn et al., a high prognostic significance was found between the magnitude of reduction in GH and IGF-1 levels after 3 months and long-term outcomes of treatment with fg-SRLs. The AUC values were 0.87 and 0.93, respectively [19]. In a review article by M. Marques-Pamies et al. the high prognostic significance of functional tests with subcutaneous administration of octreotide is emphasized. The dynamics of GH level during a 2- and 6-hour test allows predicting the effectiveness of 3–6 months of fg-SRLs treatment (AUC 0.830 and 0.877, respectively) [40]. In a clinical and morphological study by M.C. Gliga et al., data from 21 patients stratified into sensitive and resistant groups based on the results of 6 months of treatment with fg-SRLs were compared. The separating criterion was an IGF-1 index level < or >1.3. The authors also found no statistically significant age-sex and hormonal differences associated with treatment outcome. According to IHA data, the resistant group was characterized by a higher presence of patients with SGSTs and low SSTR2 expression according to IRS (5.1 vs. 9.4 points). The prognostic power of the severity of SSTR2 expression in predicting sensitivity to fg-SRLs was 0.8, Se – 0.83, Sp – 0.67, cut-off point – 6 points [32]. The study by M. Marazuela et al. confirmed a positive correlation between SSTR2 expression, the reduction in GH and IGF-1 levels and the degree of tumor volume reduction after 6 months of treatment with fg-SRLs. The prognostic significance of SSTR2 expression was 0.650, which coincides with our data [41].

Identification of ST histotype. Accurate determination of the morphological variant of ST is of fundamental importance, as it allows predicting the biological behavior of the tumor, response to DT, and long-term consequences. According to the literature data, DGSTs are characterized by the presence of a hypointense signal on T2-WI, high SSTR2 expression and good sensitivity to fg-SRLs. In contrast, SGSTs, which have a hyperintense tumor signal, low SSTR2 expression, high SSTR5 expression, are refractory to fg-SRLs and therefore require treatment with PEG and/or a second-generation somatostatin receptor ligand [42, 43].

Our work presents a broader range of predictors of the morphofunctional status of monohormonal somatotroph tumors, including assessment of tumor signal intensity on T2-, T1- and (T2-T1)-WI, cell composition, absolute (and relative) SSTR2 expression, percentage of cells with AB to GH, proportion of cells with FB, %ΔIGF-1 after 3-6 months of DT with fg-SRLs, which showed high prognostic significance during clustering and ROC analysis. The proposed threshold values for tumor-oriented biomarkers will optimize the differential diagnostic search and the selection of a target drug.

CONCLUSION

1. Given the heterogeneity of STs, the success of DT depends on the standardization of treatment goals, diagnostic protocols and preliminary predictive stratification of patients.

2. When comparing diverse predictors of the morphofunctional status of STs and sensitivity to fg-SRLs, priority morphological, radiological and therapeutic biomarkers with the greatest prognostic significance were identified.

3. The proposed prognostic models and working tables of threshold values can be used to verify the histotype of STs and select an adequate treatment strategy.

4. Timely diagnosis of the morphotype of STs refractory to treatment with fg-SRLs and early modification of pharmacotherapy with the prescription of PEG allows for stable control of acromegaly in the most complex category of patients with SGSTs.

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