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EVOLUTION OF CLINICAL AND HORMONAL PARAMETERS IN PATIENTS WITH SOMATOTROPHIC PITUITARY ADENOMAS AFTER RADIOTHERAPY

Z.Yu. Khalimova [1], S.S. Issaeva [2], N.S. Zhuravleva [3], Sh.A. Abdumannopova [4]

1 DSc, Professor Deputy Director for Science, Head of the Neuroendocrinology and Pituitary Surgery Research Laboratory, Republican Specialized Scientific and Practical Medical Center of Endocrinology named after Academician Y.Kh. Turakulov
E-mail: zam-nar777@mail.ru

2 PhD, Doctoral Candidate, Republican Specialized Scientific and Practical Medical Center of Endocrinology named after Academician Y.Kh. Turakulov
E-mail: dr.saodat01@mail.ru

3 Pathologist, Republican Specialized Scientific and Practical Medical Center of Endocrinology named after Academician Y.Kh. Turakulov.

4 Student, Tashkent Medical Academy

ABSTRACT

Objective of the study. To evaluate the clinical and hormonal parameters in patients with somatotrophic pituitary adenomas in the early and long-term periods after radiotherapy. The analysis of the studies showed that hypopituitarism before radiotherapy (RT) was observed in 9.6% of patients with acromegaly. One year after RT, its frequency increased to 19.2% ($p<0.05$), after 2-5 years to 57.1% ($p<0.001$), and after 5-10 years to 68.1% ($p<0.001$). As seen, the degree of hypopituitarism positively correlates ($r=0.57$, Spearman) with the duration of the post-radiotherapy period, requiring the use of replacement hormone therapy. Our research suggests that different cells of the adenohypophysis have varying radiosensitivity. Thyrotrophs are highly sensitive, while corticotrophs are more resistant, which plays an important role in planning the management of patients with acromegaly and determining the outcomes of RT and long-term prognosis.

Key words: growth hormone, insulin-like growth factor-1, acromegaly, pituitary adenoma.

INTRODUCTION

Acromegaly is a chronic disease characterized by the hypersecretion of growth hormone (GH), primarily caused by a pituitary adenoma (4).

The choice of treatment for pituitary adenoma should be made individually, depending on the size and invasiveness of the tumor, its hormonal activity, the severity of visual disturbances, and the patient's overall somatic status (2, 6). Radiation therapy (RT) is considered a primary treatment option for pituitary adenomas, as well as for recurrent tumors, and in cases of ineffective surgical and medical treatment (1). RT is a highly effective treatment for patients with persistent active acromegaly following surgery and/or during conservative therapy (3). RT significantly reduces the frequency of recurrences of giant pituitary adenomas (5).

Furthermore, in our republic, there is currently no established protocol for the diagnosis and management of patients with somatotropic pituitary adenomas in the post-radiation period.

Objective of the Study. To evaluate the clinical and hormonal indicators of patients with somatotropic pituitary adenomas in the early and long-term periods after radiation therapy.

Materials and Methods. The study included 94 patients with somatotropic pituitary adenomas who underwent radiation therapy (RT). All patients underwent clinical, hormonal, biochemical, and imaging studies during the monitoring period.

The average duration of the disease was 9.2 ± 7.8 years, and the follow-up period after RT was 7.36 ± 8.1 years. Of the 94 patients, 26 (27.7%) were men and 68 (72.3%) were women.

Levels of GH, insulin-like growth factor I (IGF-I), prolactin, thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), cortisol, free fractions of thyroxine (T3, T4), estradiol, and testosterone were assessed.

Additionally, the patients were divided into three groups based on the duration of follow-up after RT:

- Group 1: 1 year after RT,
- Group 2: 2-5 years after RT,
- Group 3: 6-10 years after RT (Table 1).

Table 1

Distribution of patients based on the duration of follow-up during RT

Duration of Follow-up	Group 1		Group 2		Group 3	
	Абс	%	Абс	%	Абс	%
Men (n=26)	9	9.57	9	10	8	8,52
Women (n=26)	17	18.09	12	28	39	41.49
Total (n=94)	**26**	**27.66**	**21**	**38**	**47**	**50.01**

Note: The percentage ratio of patients in the third, fifth, and seventh columns is given relative to the total number of patients.

Results of the Study. It is known that normalization of GH and IGF-I levels should be accompanied by corresponding neurohormonal and clinical changes. Therefore, the next phase of our research was the study of the dynamics of neurohormonal and clinical indicators at various time points after radiation therapy (RT).

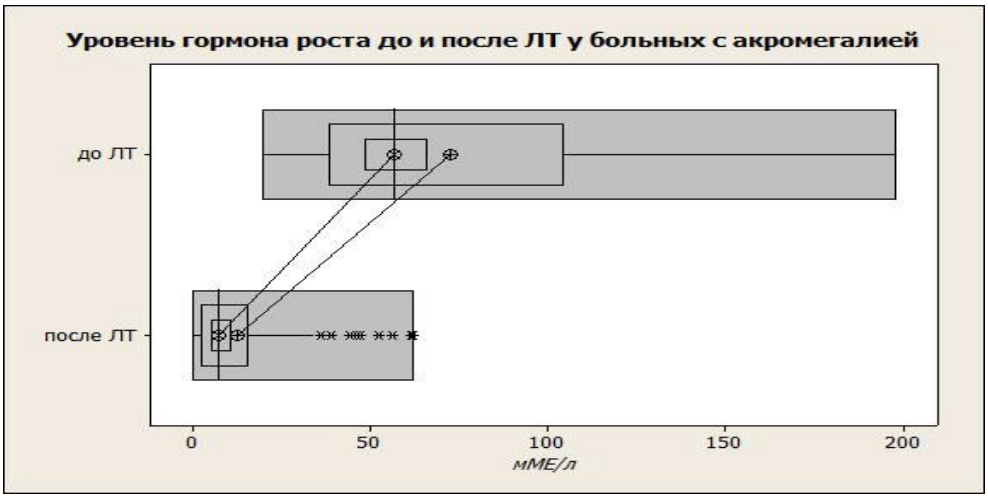

Fig. 1. GH levels before and after RT in patients with acromegaly

The overall GH level during RT showed the following changes: the average GH level before RT was 72.9±45.8 mIU/l (range=178.3; max=198; min=19.7; quartiles Q1=38.5; median=57.1; Q3=104.6), and after RT, this level significantly decreased to 12.6±14.4 mIU/l (p=0.001).

The statistical analysis results indicate that in 93 cases, the GH values after RT were lower than the GH values before RT, with one case showing equal values for both variables. The standardized value (Z) was -8.374, which significantly exceeds the corresponding value obtained earlier for the sign test. The significance level p = 0.001 indicates the statistical reliability of the differences.

Now, let's consider the dynamics of GH and IGF-I at different follow-up periods. As shown in the diagrams, in all groups, a significant decrease in GH levels was observed after RT (p=0.001). In Group I, before RT, the median GH level was 50.5 mIU/l, and the average was 62±36.6 mIU/l (range=150.1; max=170.5; min=20.4; quartiles Q1=44; median=50.5; Q3=61.4). One year after RT, the average level decreased to 20±16.8 mIU/l (range=61.9; max=62.1; min=0.24; quartiles Q1=7.4; median=14.5; Q3=34.6).

In Group II, a significant decrease in GH after RT was observed, reducing by 8 times to 9.08±13.8 mIU/l (p=0.001). In Group III, the GH level before and after RT was 78.7±46.2 mIU/l and 10.04±11.9 mIU/l (p=0.001), respectively.

Due to the lack of medication treatment and follow-up after RT, a relapse occurred in 2 patients in the distant period after RT with acromegaly. Therefore, in Group III, the decrease in growth hormone levels did not exceed that in Group II.

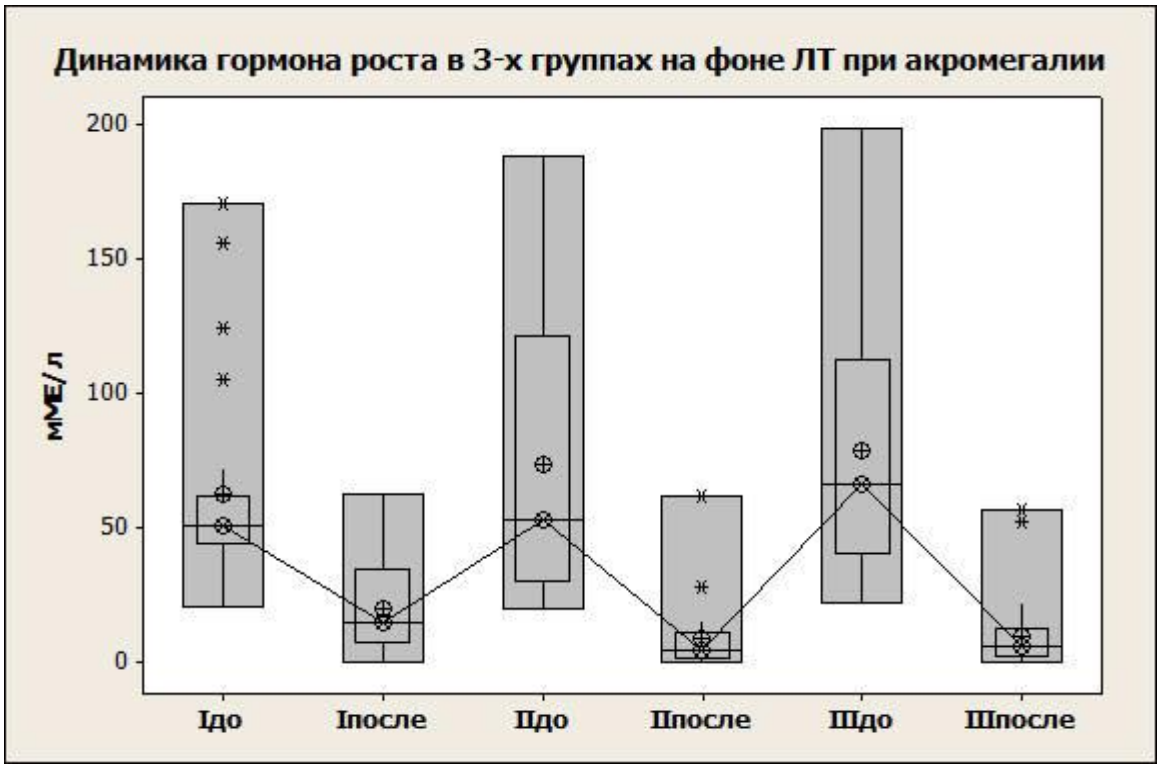

Fig. 2. Average daily GH levels at different time points after radiation therapy (p=0.001)

The analysis shows that overall, before RT, the GH level was not suppressed in 20.2% of patients (p=0.005), was suppressed but not to normal levels in 22.3% (p=0.008), and remission was achieved in 57.5% (p=0.018).

One year after RT, 38.4% of patients had no suppression of GH (p=0.005), while 34.6% had subnormal suppression, with an average of 12.1±6.54 mIU/l (p=0.008). Remission was observed in only 27% of patients (p=0.018).

After 2-5 years, GH was not suppressed in 9.5% of cases (p=0.10), was suppressed subnormally in 23.8% (p=0.04), and remission was achieved in 66.7% of patients (p=0.001).

Six to ten years after RT, the GH level decreased as follows: it was not suppressed, or suppressed but not to normal levels in 7 (15%) patients, with an average of 32.6±26.89 mIU/l and 13.7±8.7 mIU/l, respectively (p=0.005 and p=0.008). In 70.2% of patients, remission was achieved, and the GH level was 1.4±1.2 mIU/l (p=0.001).

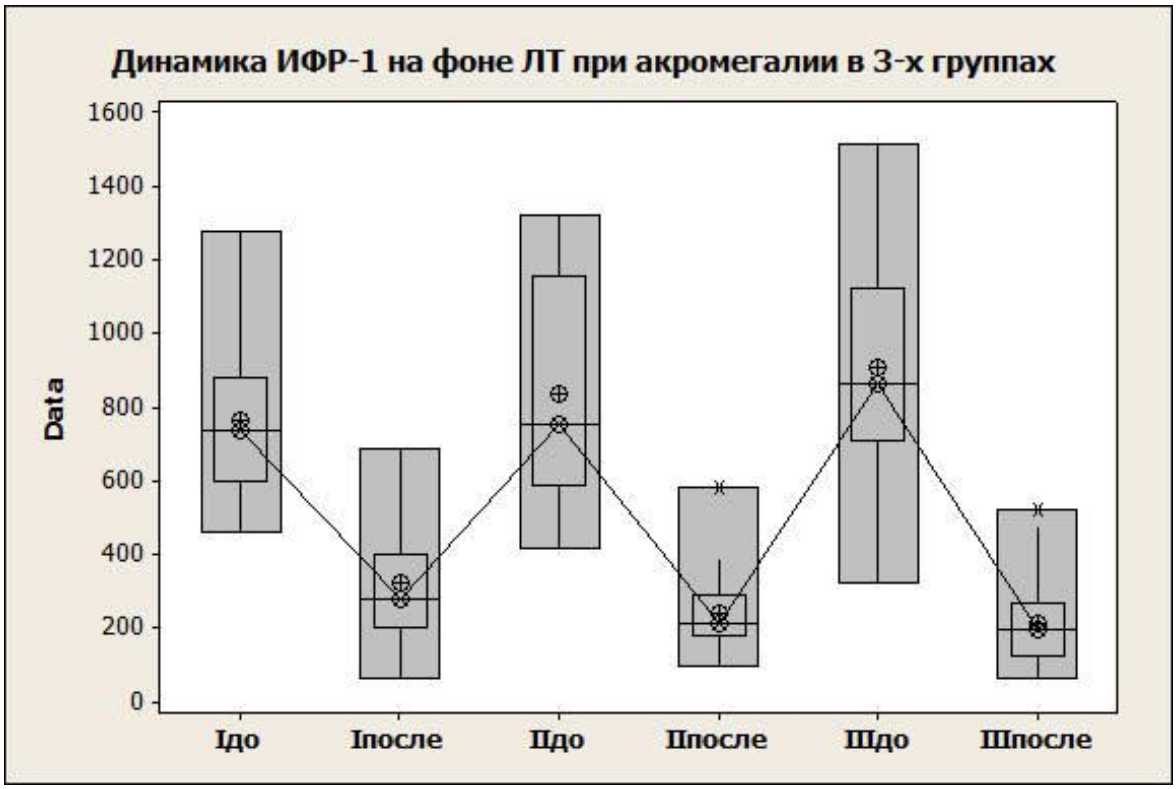

Fig. 3. Average daily IGF-I levels at different time points after radiation therapy (p=0.001).

As shown in Fig. 3, a statistically significant decrease in IGF-I levels was observed in all follow-up periods. In Group I, before RT, the IGF-I level was 763.8±206.3 ng/ml, and after RT, it decreased more than two times, reaching 321.7±165.4 ng/ml (p=0.001). In Group II, the IGF-I levels were 837.9±289.1 ng/ml before RT and 243.4±105.1 ng/ml after RT. In Group III, IGF-I decreased more than four times, reaching 213.4±99.6 ng/ml. Additionally, in both groups, the IGF-I level significantly decreased by 3-4 times (p=0.001). Thus, one year after RT, there is a trend toward positive results.

One year after RT, 77% of patients had no suppression of IGF-I to target values (p=0.001), while 23% showed a reduction in IGF-I to age-specific normal

levels (p<0.01). In Group II, 43% and 57% (p<0.05), and in Group III, 30% and 70% (p<0.01), respectively.

The results of the study indicate that radiation therapy leads to a significant reduction in GH and IGF-I levels in all periods, with particularly significant decreases observed in patients of Group III (p=0.001).

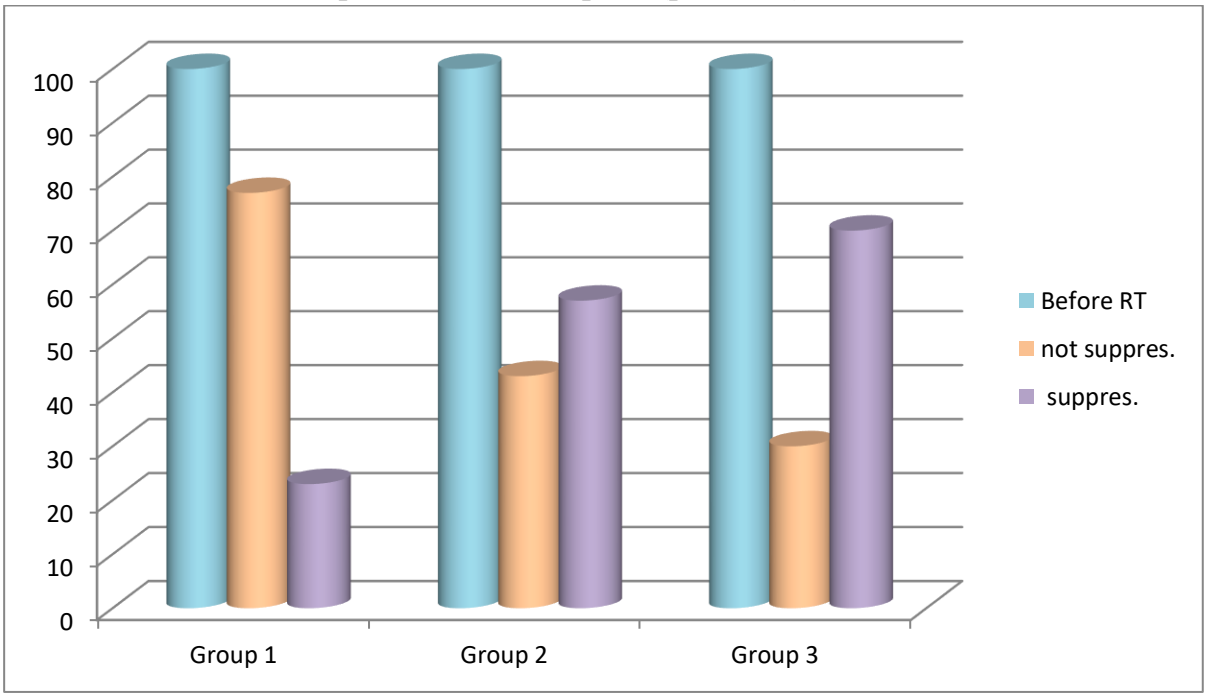

Fig. 4. IGF-I levels at different time points of RT in acromegaly

Table 2

Dynamics of hormonal indicators during radiation therapy (RT)

	Group I, n=26		Group II, n=21		Group III, n=47	
	Before RT	After RT	Before RT	After RT	Before RT	After RT
TSH (мME/l)	2,2±1,4	2±1,2	2,8±1,5	0,7±0,5*	2,4±1,9	0,5±0,4**
Thyroxine (нг/дл)	1,47±0,6	1,3±0,9	1,5±0,4	1,2±0,5	1,6±0,4	1,1±0,8*
Prolactin (ng/ml)	20,8±7,6	31,7±16,8	11,5±5,2	26±15,3*	28,7±11,3	59,9±17,3**
FSH (ME/l)	5,4±5	3,3±2,5*	4,4±2,5	2,6±1,3*	3,5±1,9	1,6±0,7**
LH (ME/l)	3,2±2,4	2,9±1,8	2,7±1,9	1,7±0,9*	1,9±0,3	0,8±0,4**
Cortisol (nmol/l)	484±195	403,8±123	382,3±171	289,1±88,6	591,9±99,6	197,4±53***

One of the early hormonal disorders was hyperprolactinemic condition, which was observed before RT in groups I, II, and III in 15.4% (mean 20.8±7.6 ng/ml), 4.8% (11.5±5.2 ng/ml), and 23.4% (28.7±11.3 ng/ml) of patients, respectively. Furthermore, the frequency of hyperprolactinemic states progressively increased (up to 2 times) after RT, reaching 23.1% (31.7±16.8 ng/ml) ($p<0.10$), 14.3% (31.7±16.8 ng/ml), and 46.8% (59.9±17.3 ng/ml) ($p<0.05$) in the three groups, respectively. This is due to the dose-dependent radiation damage to the pituitary stalk and pituitary structures, leading to impaired regulation and secretion of prolactin through dopamine transport.

The results of the analysis of adenohypophysial insufficiency show that in group I, before RT, the following hormonal disturbances were found: a decrease in thyroid hormone (T4) in 23.1% (1.47±0.6 ng/dl), cortisol in 30.1% (484±195 nmol/l), LH in 19.2% (3.2±2.4 IU/l), and FSH in 11.5% (5.4±5 IU/l) of patients. After one year, these indicators changed as follows: 30.1% (1.3±0.9 ng/dl) ($p<0.01$), 30.8% (403.8±123 nmol/l), 34.6% (2.9±1.8 IU/l), and 23.1% (3.3±2.5 IU/l) ($p<0.05$), respectively. In group II, before RT, decreased thyroid function was found in 19.1% (1.5±0.4 ng/dl), adrenal function in 28.6% (382.3±171 nmol/l), LH in 28.6% (2.7±1.9 IU/l), and FSH in 23.8% (4.4±2.5 IU/l) of patients.

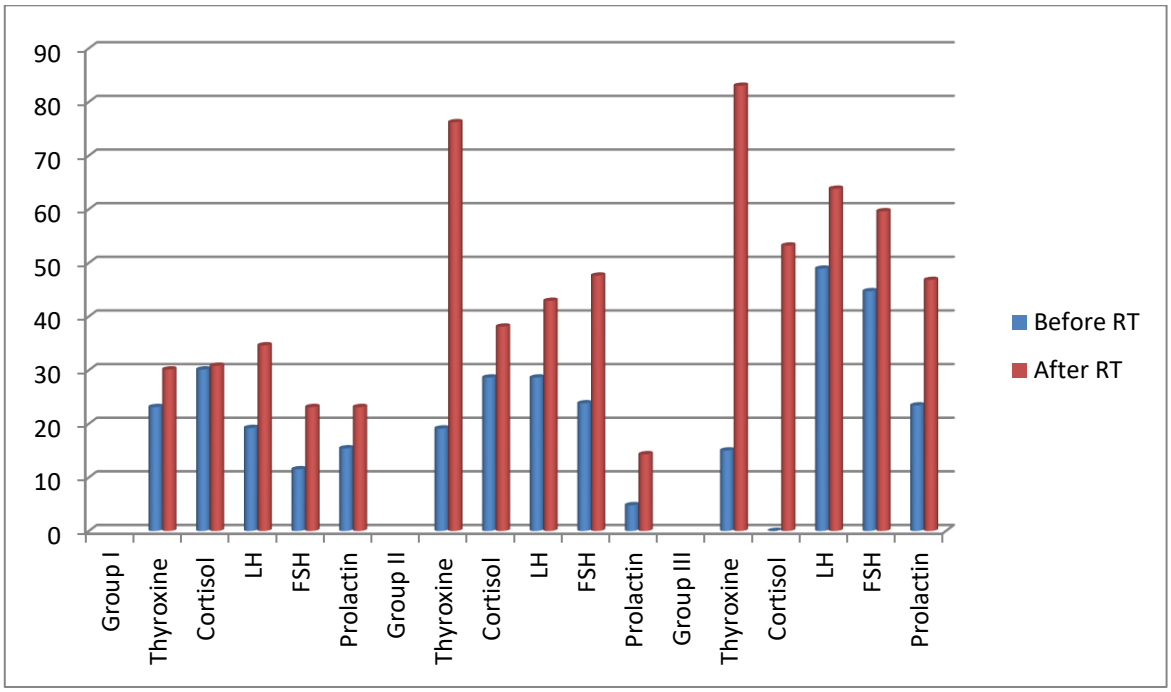

Figure 5. Dynamics of hormone level reduction (increase in prolactin) (%) at various time points after radiation therapy

After 2-5 years, the hormone levels decreased in 76.2% (1.2±0.5 ng/dl) ($p<0.01$), 38.1% (289.1±88.6 nmol/l), 42.9% (1.7±0.9 IU/l) ($p<0.001$), and 47.6% (2.6±1.3 IU/l) ($p<0.01$), respectively. In group III, before RT: 15% (1.6±0.4 ng/dl),

0% (no decrease in cortisol, 591.9±99.6 nmol/l), 48.9% (1.9±0.3 IU/l), and 44.7% (3.5±1.9 IU/l). After 6-10 years, there was a significant decrease in hormones, especially thyroid hormone in 83% (1.1±0.8 ng/dl) ($p<0.05$), 53.2% (197.4±53 nmol/l), 63.8% (0.8±0.4 IU/l), and 59.6% (1.6±0.7 IU/l) ($p<0.001$), respectively.

As shown by our results, with an increase in the observation period after radiation therapy, the frequency of hypopituitarism development progresses. It is noteworthy that the pattern of loss of pituitary tropic functions in patients with somatotropic adenomas is confirmed in our cases. The thyroid-stimulating, gonadotropic, and adrenocorticotropic functions of the pituitary sequentially diminish in these patients.

The results of our studies show a high frequency of decreased thyroid hormone levels, indicating the high sensitivity of thyroid-stimulating cells to radiation. In contrast, adrenocorticotropic cells of the pituitary are radioresistant, which is accompanied by relatively preserved function and a low frequency of secondary adrenal insufficiency in the post-radiation period.

In general, radiation therapy, followed by dopamine agonist medication therapy in both the short and long-term periods after its administration, contributes to the stabilization of the pathological process in acromegaly, as recommended by the International Consensus (2011).

Hypopituitarism is the most common long-term outcome of radiation therapy. Analysis of the conducted studies showed that hypopituitarism before RT was established in 9.6% of patients with acromegaly. One year after RT, its frequency increased to 19.2% ($p<0.05$), after 2-5 years to 57.1% ($p<0.001$), and after 5-10 years to 68.1% ($p<0.001$). As shown, the degree of hypopituitarism positively correlates ($r=0.57$ by Spearman's test) with the duration of the post-radiation period and requires hormone replacement therapy.

The percentage of secondary hypothyroidism increased over the years and reached 30.8%, 76.2%, and 83%, respectively. Before RT, secondary hypocortisolism was detected in 14.9% of patients. After RT, this figure increased to 30.8% ($p<0.01$), 38%, and 53.2% ($p<0.001$), respectively ($p<0.05$) (Table 3).

The results also show that secondary hypogonadism before RT in group I was observed in 19.2% of cases, after RT in 34.6% ($p<0.10$), after 5 years in 28.6%, and 47.6%, and after 5-10 years in 48.9% and 63.8%, respectively ($p<0.01$).

Our studies indicate that different cells of the adenohypophysis exhibit varying levels of radiosensitivity. Thyrotrophs are highly sensitive, while corticotrophs, in contrast, are more resistant, which plays an important role in planning the management of patients with acromegaly and determining the outcomes of radiation therapy (RT) and long-term prognosis.

It is important to note that before RT, cases of partial optic neuropathy in group I before and after RT showed the same results, which were 46.2%. In group II, these indicators were 61.9% before and 71.4% after RT, and in group III, 49% before and 53.2% after RT. ESS occurred in 9.5% and 23.4% of patients in groups II and III, respectively.

It has been established that with the progression of the disease, the frequency of complications increases, and their course worsens. Therefore, it is crucial to detect the earliest signs of the disease.

Conclusion.

The assessment of long-term outcomes of RT showed that 11.5% of patients experienced hypopituitarism during the pre-radiation period. After RT, with the increase in the post-radiation period, the indicators of hypopituitarism increased: after one year, 19.2%, after 2-5 years, 57.1% ($p<0.10$), and after 6-10 years, 68.1% ($p<0.05$). Different degrees of radiosensitivity in adenohypophysial cells were identified: thyrotrophs were highly sensitive, followed by gonadotrophs, and corticotrophs were more resistant. This was confirmed by the high frequency of secondary hypothyroidism (83%) ($p<0.01$), hypogonadism (63.8%) ($p<0.05$), and hypocortisolism (53.2%) ($p<0.01$) after 6-10 years.

REFERENCES

1. Bex M. Divergence between Growth Hormone and Insulin-Like Growth Factor-I Concentrations in the Follow-Up of Acromegaly. – 2014. –№ 2. – P. 204-209.

2. Bronstein M.D. A consensus on the diagnosis and treatment of acromegaly complications A consensus on the diagnosis and treatment of acromegaly complications // Pituitary. – 2013. – Vol.16. № August – P. 294–302.

3. Hannon M.J., Barkan A.L., Drake W.M. The Role of Radiotherapy in Acromegaly // Neuroendocrinology. – 2016. –Vol.103, № 1. – P. 42–49.

4. Hayashi M. [и др.]. Gamma Knife robotic microradiosurgery of pituitary adenomas invading the cavernous sinus : Treatment concept and results in 89 cases Gamma Knife robotic microradiosurgery of pituitary adenomas invading the cavernous sinus : treatment concept and results established // J Neurooncol. – 2010. –№1. – P.185–194

5. Kosteljanetz M., Feldt-rasmussen U. Fractionated stereotactic radiotherapy in patients with acromegaly : An interim single– Pentre audit Fractionated stereotactic radiotherapy in patients with acromegaly : an interim single– Pentre audit // European Journal of Endocrinology. – 2015. –№ 12. –P. 685–694.

6. Ntali G., Karavitaki N. Recent advances in the management of acromegaly [version 1 ; peer review : 2 approved] // F1000Research. – 2019. – Vol.4, № 5. – P. 1–7.