

## ASSESSMENT OF QUALITY-OF-LIFE INDICATORS IN OPERATED AND NON-OPERATED PATIENTS WITH PRIMARY HYPERPARATHYROIDISM IN A COMPARATIVE ASPECT AT DIFFERENT TIMES

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**Abstract. Introduction.** The clinical picture of primary hyperparathyroidism has changed over the past decades, mainly due to the early detection of hypercalcemia, and often occurs as an asymptomatic or oligosymptomatic disease.

**Aim.** This study aims to evaluate the quality-of-life indicators in operated and non-operated patients with primary hyperparathyroidism in a comparative aspect at various times. **Materials and Methods.** The present study deals with the results of treatment of children who applied to the clinic of the specialized scientific and practical medical center of endocrinology in 2012-2022, 103 children with suspected primary hyperparathyroidism were examined according to anamnesis, outpatient cards, and detailed procedure reports. From among them, 90 children and adolescents with primary hyperparathyroidism were selected, where 50 patients are in the 1<sup>st</sup> group (after surgery) and 40 children and adolescences with primary hyperparathyroidism are in the 2<sup>nd</sup> group (no surgery). Numerical values obtained as a result of scientific research were statistically processed using MS Excel, arithmetic mean (M), mean standard error (m), standard deviation (σ), relative values (% agreement), and Student's t-test (t). **Results and Discussion.** It was found that the quality-of-life indicators in patients with primary hyperparathyroidism were significantly lower than in the control group, to a greater extent due to pain, general health, social functioning, and vitality (p<0.05). Thus, in patients with primary hyperparathyroidism before surgery, a significant violation of both: the physical and mental components of the quality-of-life was established. Further, in the 1<sup>st</sup> group of patients with surgical treatment, in dynamics after 3 and 6 months, all quality-of-life indicators according to SF-36 were significantly closer to the control group in all domains. In the 2<sup>nd</sup> group of patients with conservative treatment in dynamics after 3, 6, 12 months and 10 years, all quality-of-life indicators according to SF-36 remained significantly lower than in the control group in all domains and did not change significantly. **Conclusions.** The results obtained demonstrate the positive effect of surgical treatment from the patient's point of view and confirm the feasibility of assessing the quality of life both at the decision-making stage when choosing a surgical approach, and as part of a comprehensive assessment of the therapy effectiveness in determining the recovery degree of various functioning aspects in patients after surgery.

**Keywords:** primary hyperparathyroidism, children, quality of life.

**For reference:** Nasirova KK, Rikhsieva NT, Urmanova YM, et al. Assessment of quality-of-life indicators in operated and non-operated patients with primary hyperparathyroidism in a comparative aspect at different times. The Bulletin of Contemporary Clinical Medicine. 2024; 17 (4): 127-134. DOI: 10.20969/VSKM.2024.17(4).127-134.

## ОЦЕНКА ПОКАЗАТЕЛЕЙ КАЧЕСТВА ЖИЗНИ У ОПЕРИРОВАННЫХ И НЕОПЕРИРОВАННЫХ ПАЦИЕНТОВ С ПЕРВИЧНЫМ ГИПЕРПАРАТИРЕОЗОМ В СРАВНИТЕЛЬНОМ АСПЕКТЕ В РАЗЛИЧНЫЕ СРОКИ

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**Реферат. Введение.** Клиническая картина первичного гиперпаратиреоза изменилась за последние десятилетия в основном за счет раннего выявления гиперкальциемии, и часто протекает как бессимптомное или малосимптомное заболевание. **Цель** – оценить показатели качества жизни у оперированных и неоперированных пациентов с первичным гиперпаратиреозом в сравнительном аспекте в различные сроки. **Материал и методы.** Настоящее исследование посвящено изучению результатов лечения детей, обратившихся в клинику эндокринологии по поводу первичного гиперпаратиреоза в 2012-2022 годах. За этот период обследовано 103 ребенка с подозрением на первичный гиперпаратиреоз по анамнезу, амбулаторным картам и операционным журналам. Из них было отобрано 90 детей и подростков с первичным гиперпаратиреозом, при этом 50 больных – это пациенты первой группы (с операцией) и 40 детей и подростков с первичным гиперпаратиреозом – вторая группа (без операции). Статистическую обработку числовых значений, полученных в результате научных исследований, проводили с использованием программы MS Excel, среднее арифметическое значение (M), среднюю стандартную ошибку (m), среднеквадратичное отклонение (б), относительные значения (% совпадения), критерий Стьюдента (t). **Результаты и их обсуждение.** Было установлено, что показатели качества жизни у больных с первичным гиперпаратиреозом значимо ниже, чем у контрольной группы, в большей степени за счет боли, общего здоровья, социального функционирования и жизнеспособности ( $p < 0,05$ ). Таким образом, у больных с первичным гиперпаратиреозом до операции установлено существенное нарушение как физической, так и психической составляющих качества жизни. Далее в первой группе пациентов с хирургическим лечением в динамике через 3 и 6 мес. все показатели качества жизни по SF – 36 достоверно приближались к группе контроля по всем доменам. Во второй группе пациентов с консервативным лечением в динамике через 3, 6, 12 мес. и 10 лет все показатели качества жизни по SF – 36 оставались достоверно ниже группы контроля по всем доменам и достоверно не менялись. **Заключение.** Полученные результаты демонстрируют положительный эффект хирургического лечения с точки зрения пациента и подтверждают целесообразность оценки качества жизни как на этапе принятия решения при выборе хирургической тактики, так и в составе комплексной оценки эффективности терапии при определении степени восстановления разных аспектов функционирования у пациентов после операции.

**Ключевые слова:** первичный гиперпаратиреоз, дети, качество жизни.

**Для ссылки:** Насырова Х.К., Рихсиева Н.Т., Наримова Г.Д., [и др.]. Оценка показателей качества жизни у оперированных и неоперированных пациентов с первичным гиперпаратиреозом в сравнительном аспекте в различные сроки // Вестник современной клинической медицины. – 2024. – Т. 17, вып. 4. – С.127–134. DOI: 10.20969/VSKM.2024.17(4).127-134.

**Relevance.** Primary hyperparathyroidism (PHPT) was first described 90 years ago, almost simultaneously in Europe and the USA [1]. PHPT is a common endocrine disease characterized by hypercalcemia and elevated or inappropriately normal levels of parathyroid hormone (PTH). PHPT results from excessive secretion of PTH by one or more parathyroid glands. PHPT is caused by solitary parathyroid adenoma in 80% of cases, while hyperplasia of all 4 glands accounts for 10–15%, multiple adenomas in 5%, and parathyroid cancer in <1% of cases. Incidence estimates for PHPT range from 0.4 to 82 cases per 100,000 [2-4]. Prior to the routine measurement of serum calcium levels in the 1970s, PHPT was a rare and symptomatic disease. When routine assessment of serum calcium levels became widespread, cases of unrecognized, asymptomatic PHPT were identified, resulting in an initial five-fold increase in the incidence [5]. Thereafter, the PHPT incidence declined in the US until 1998, when another sharp increase was noted [3,6,7], associated with the introduction of osteoporosis screening guidelines and targeted testing of patients with osteoporosis [7,8,9]. The PHPT

incidence increases with age and is higher in women and African Americans than in men and other racial groups, respectively [2]. Half of all patients with PHPT are postmenopausal women, although the disease can occur at any age [8]. PHPT is often diagnosed in the first decade after menopause, consistent with the known action of estrogen on the skeleton, which counteracts the hypercalcemic effects of excess PTH in the bones.

The underlying cause of sporadic PHPT is unknown in most cases. Ionizing radiation, especially in childhood, is a risk factor [9,10]. Chronic use of lithium, which reduces the sensitivity of the parathyroid glands to calcium, is also associated with the development of PHPT [10]. The genetic pathogenesis of PHPT is unclear in most patients. Cell cycle regulating genes are considered important given the clonal nature of sporadic parathyroid adenomas. Two such genes documented as contributing to the development of PHPT are CCND1 (which encodes for cyclin D1) and MEN1 (which encodes for menin). Somatic mutations in MEN-1 occur in 12-35% of sporadic adenomas, while rearrangement or overexpression of CCND 1 may occur in 20–40% of cases [11,12,13]. Recent studies have

also identified the involvement of CDC73, CTNNB1, CDKN1B, and AIP (which encodes an aryl hydrocarbon (AH) receptor interacting protein) in a small percentage of adenomas [13,14,15].

In hereditary or familial forms of PHPT, which account for about 5-10% of cases, germline mutations have been identified in some causative genes [15,16,17].

Parathyroidectomy (PTE) is a modern method for the PHPT treatment, and the concept of treatment effectiveness is very important for an endocrinologist. The main goal of treatment is to bring the patients' quality of life (QoL) to the level of healthy population. There are some scientific studies of this aspect of the problem, and the criteria for the effective surgical treatment of PHPT in terms of quality of life have not been developed. Therefore, today the assessment of "quality of life" is one of the primary tasks of contemporary medicine [18,19].

The concept of QoL is characterized by the ability of a person to act in accordance with their position and be satisfied with life in various respects. At the same time, the concept of QoL is based on an assessment of a person's ability to subjectively perceive the level of their well-being in physical, mental, social, and economic relations. Therefore, it is necessary to carefully study the condition of sick children with PHPT at different times after PTE: physical and sexual development, mental and social state, ability to work, in general, QoL associated with the health of patients [20,21].

The clinical picture of PHPT has changed over the past decades, mainly due to the early detection of hypercalcemia, and often occurs as an asymptomatic or oligosymptomatic disease. The symptoms of PHPT are varied and often non-specific and include musculoskeletal symptoms (decreased muscle strength and joint pain), neuropsychiatric symptoms (e.g., anxiety, depression/mood changes, fatigue, and memory problems), and gastrointestinal discomfort, including constipation. All these factors can potentially affect the quality of life (QoL) [22,23,24].

**Aim of the study** is to evaluate the quality-of-life indicators in operated and non-operated patients with primary hyperparathyroidism in a comparative aspect at different times.

**Materials and methods.** The present study deals with investigating the results of treatment of children

who applied to the clinic of the the specialized scientific and practical medical center of endocrinology for PHPT in 1999-2014. During this period, 103 children with suspected PHPT were examined according to anamneses, outpatient cards, and detailed procedure reports (Table 1).

In the subsequent dispensary observation, there were 90 patients with PHPT aged 3 to 15 years, who were treated in an inpatient setting, and then observed by us on an outpatient basis. 50 of them were treated surgically, 40 refused surgeries for various reasons and received antiresorptive therapy. Hereditary diseases were also identified among patients (13-12.6%) examined with suspected PHPT. Fig. 1 shows the study design.

The plan for examining patients with suspected PHPT included collecting complaints, obstetric anamnesis, case and family history, physical examination, and laboratory and instrumental diagnostics. In all patients, PHPT was diagnosed in accordance with standard algorithms.

In the conditions of the biochemical and hormonal laboratory of the specialized scientific and practical medical center of endocrinology under the Ministry of Health of the Republic of Uzbekistan, we carried out a number of studies, clinical recommendations, namely, the determination of parathyroid hormone in the blood serum by alkaline phosphatase (AP), total and ionized calcium, etc.

Instrumental research methods included ECG, parathyroid gland (PTC) ultrasound, X-ray densitometry of the body, radioisotope scintigraphy, and SPECT with Te99.

Numerical values obtained as a result of scientific research were statistically processed using MS Excel, arithmetic mean (M), mean standard error (m), standard deviation ( $\sigma$ ), relative values (% agreement), and Student's t-test (t). The difference between the mean values was considered significant at a significance level of  $R < 0.05$ .

The duration of the study ranged from 1-3-6 months to 1 year in the early postoperative period and 5-10-15 years in the long-term period.

**Results and Discussion.** We performed an analysis of changes in quality-of-life indicators in the compared

Table 1  
Distribution of pediatric patients with primary hyperparathyroidism by gender and age

Таблица 1  
Распределение больных детей с первичным гиперпаратиреозом по полу и возрасту

PHPT nosological form	3-6 years		7-12 years		13-15 years		Total		
	B	G	B	G	B	G	B	G	Abs (%)
Renal form	16	0	13	6	8	2	37	8	45(43.6%)
Bone form	4	1	2	5	7	12	13	18	31(30.3%)
Mixed form	1	1	2	2	4	4	7	7	14(13.5%)
Inheritance diseases	4	3	1	2	2	1	7	6	13(12.6%)
Control							5	5	10
<b>Total</b>	<b>25</b>	<b>5</b>	<b>18</b>	<b>15</b>	<b>21</b>	<b>19</b>	<b>64</b>	<b>39</b>	<b>103(100%)</b>

Note: PHPT - primary hyperparathyroidism

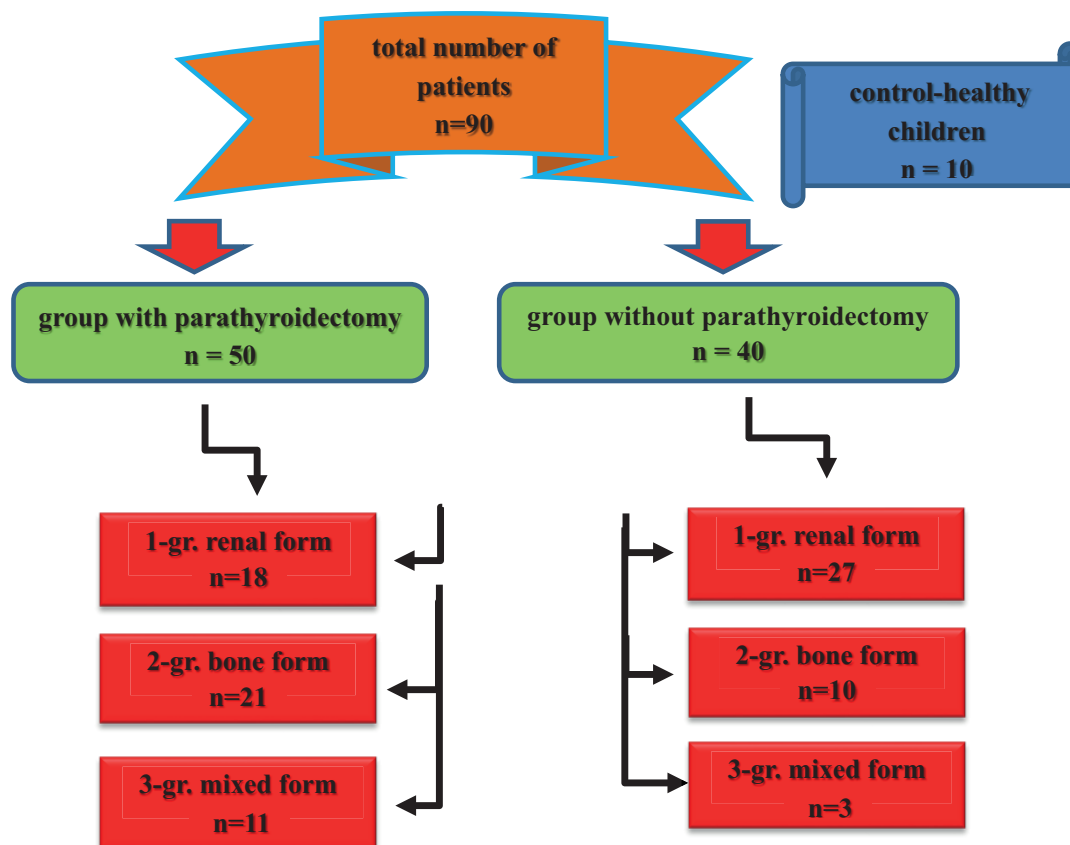


Fig. 1. Study design.  
Рис.1. Дизайн исследования.

groups before, in the early and late postoperative period according to the PAS (parathyroid assessment of symptom score) questionnaire. In the pre- and postoperative period and during the current study,

patients used the visualization scale (VAS) to assess their condition (table 2).

As can be seen from Table 2, in patients of group 1, there was a significant decrease in the clinical symptoms

Evaluation table PAS in patients of group 1

Table 2

Таблица 2

Оценочная таблица PAS у пациентов первой группы

Symptom	Score before surgery	1 month after surgery	12 months after surgery	10 years after surgery
Bone pains	93.4 ± 12.4	82.3 ± 8.2*	9.7 ± 1.6**	2.2 ± 0.8***
Fast fatiguability	98.7 ± 10.8	78.7 ± 8.1*	11.3 ± 2.4**	0.8 ± 0.09***
Mood lability	95.3 ± 9.3	67.2 ± 5.9*	10.7 ± 1.9**	1.9 ± 0.05***
Depression	90.4 ± 11.2	34.8 ± 9.2*	14.8 ± 4.2**	0.9 ± 0.03***
Stomach ache	87.2 ± 9.7	45.2 ± 6.8*	15.4 ± 4.1**	1.2 ± 0.4***
Weakness	92.5 ± 10.3	23.8 ± 3.2*	6.8 ± 1.2**	1.9 ± 0.07***
Irritability	78.3 ± 7.9	31.9 ± 5.4*	12.9 ± 3.2**	0.2 ± 0.04***
Joint pain	94.8 ± 11.8	22.8 ± 3.6*	6.9 ± 1.4**	0.9 ± 0.07***
Forgetfulness	86.8 ± 5.4	54.9 ± 7.8*	23.8 ± 3.2**	2.6 ± 1.4***
Difficulty in standing up from a sitting position	94.8 ± 10.3	23.8 ± 2.9*	10.9 ± 2.2**	1.6 ± 0.9***
Headache	96.3 ± 12.8	34.7 ± 8.2*	10.1 ± 1.7**	1.6 ± 0.4***
Skin itching	47.3 ± 8.3	10.5 ± 1.8*	5.2 ± 1.7**	1.3 ± 0.04***
Thirst	66.7 ± 8.9	23.8 ± 2.4*	10.7 ± 2.4**	1.5 ± 0.05***

Note: \* - reliability of differences, where \* is p < 0.05, \*\* - p < 0.005, \*\*\* - p < 0.0001, PAS - parathyroid assessment of symptom score

of the disease according to the PAS questionnaire as early as a month after surgery ( $p < 0.05$ ) and after 12 months ( $p < 0.005$ ), and a lasting effect persisted after 10 years ( $p < 0.0001$ ).

At the same time, in contrast to patients of group 1, patients of group 2 had the opposite picture. Thus, in this observation group, at various times after discharge from the hospital, a significant improvement in QoL according to the PAS questionnaire was not detected either in the early or in the long-term period (Table 3) ( $p > 0.05$ ). As can be seen from Table 3, there was a trend towards an insignificant increase in the average scores for most of the disease symptoms ( $p > 0.05$ ). Along with this, some symptoms showed a significant increase in mean values, namely an increase in mean scores for irritability, joint pain, difficulty getting up, thirst, and pruritus ( $p < 0.05$ ).

Next, we analyzed the dynamics of quality-of-life indicators in the compared groups before, in the early and late postoperative period according to the questionnaire SF-36 [23].

41 out of 50 patients with PHPT operated between 2010 and 2020 and 33 out of 40 patients without surgery were surveyed using the SF-36 questionnaire. The survey was conducted twice: before and after the operation, in the period from 1, 3 to 6 months and after 10 years. To assess the change in the operated patients' quality of life, the SF-36 questionnaire was used, and to determine the impairment degree of various aspects of the patients' quality of life, the indicators on the scales of this questionnaire for PHPT patients were compared with conditionally healthy respondents (control group) of the same sex and age, without PHPT and with normal phosphorus-calcium metabolism. Responses were

analyzed using the commercially available SF Health Outcomes TM Screening Software (Quality Metric Inc., Lincoln, USA).

In Fig. 2. the QoL indicators of patients of the 1<sup>st</sup> group are given before surgery and 3, 6, 12 months and 10 years after PTE according to the SF-36 questionnaire.

As seen in Fig. 2 the quality-of-life indicators in patients with PHPT are significantly lower than in the control group, to a greater extent due to pain, general health, social functioning, and vitality ( $p < 0.05$ ). Thus, in patients with PHPT before surgery, a significant violation of both the physical and mental components of the quality of life was established [24]. Further, in the 1<sup>st</sup> group of patients with surgical treatment, in dynamics after 3 and 6 months, all QoL indicators according to SF-36 were significantly closer to the control group in all domains [25].

On Fig. 3 the QoL indicators of patients of the 2<sup>nd</sup> group before and after 3, 6, 12 months and 10 years after conservative treatment according to the SF-36 questionnaire are given.

As can be seen in Fig. 3. in the 2<sup>nd</sup> group of conservatively treated patients in dynamics after 3, 6, 12 months and 10 years, all indicators of QoL according to SF-36 remained significantly lower than the control group in all domains and did not change significantly.

Thus, according to our studies of QoL in PHPT patients of the compared groups, successful surgical treatment with normalization of the parathyroid metabolism levels contributes to a significant improvement in the PHPT patients' quality of life of the 1<sup>st</sup> group already in the early stages after surgery and has a lasting effect in the long-term follow-up period [26].

Table 3

PAS evaluation table in patients of group 2

Таблица 3

Оценочная таблица PAS у пациентов второй группы

Symptom	Evaluation before surgery	1 month after surgery	12 months after surgery	10 years after surgery
Pain in the bones	96.5 ± 9.7	97.7 ± 9.4 ^	97.6 ± 8.8 ^	98.9 ± 8. ^
Fast fatigability	97.2 ± 7.6	98.5 ± 7.9 ^	98.3 ± 8.4 ^	99.5 ± 12.3 ^
Mood lability	98.4 ± 11.7	97.8 ± 8.8 ^	98.8 ± 9.2^	99.1 ± 12.5^
Depression	97.6 ± 9.2	98.3± 8.9^	97.6 ± 8.9^	98.5 ± 8.8^
Stomach ache	89.6 ± 8.4	88.9 ± 7.6^	96.8 ± 12.1^	99.6 ± 8.4^
Weakness	91.5 ± 8.3	93.7 ± 8.8^	96.6 ± 8.7 ^	99.2 ± 7.8^
Irritability	88.9 ± 6.8	88.8 ± 7.4^	92.9 ± 8.3^	97.9 ± 8.4**
Joint pain	95.2 ± 7.3	96.4 ± 5.8^	99.9 ± 5.4^	99.9 ± 8.4*
Forgetfulness	89.8 ± 7.8	91.2 ± 8.9^	93.6 ± 7.4^	97.8 ± 4.8*
Difficulty in standing up from a sitting position	92.4± 6.9	93.7 ± 7.8 ^	95.8 ± 8.2^	99.8 ± 4.9*
Headache	92.7 ± 11.2	94.3 ± 7.8^	95.7 ± 8.3 ^	99.3 ± 8.4 ^
Skin itching	65.8 ± 5.3	66.8 ± 5.8^	74.8 ± 3.8 ^ *	81.3 ± 0.08 ^**
Thirst	87.7 ± 7.3	88.8 ± 9.4 ^	95.6 ± 6.8^*	98.8 ± 8.05^ *

Note: \* - reliability of differences, where  $p < 0.05$  \*, \*\* -  $p < 0.005$ , ^  $p > 0.05$ , PAS – parathyroid assessment of symptom score.

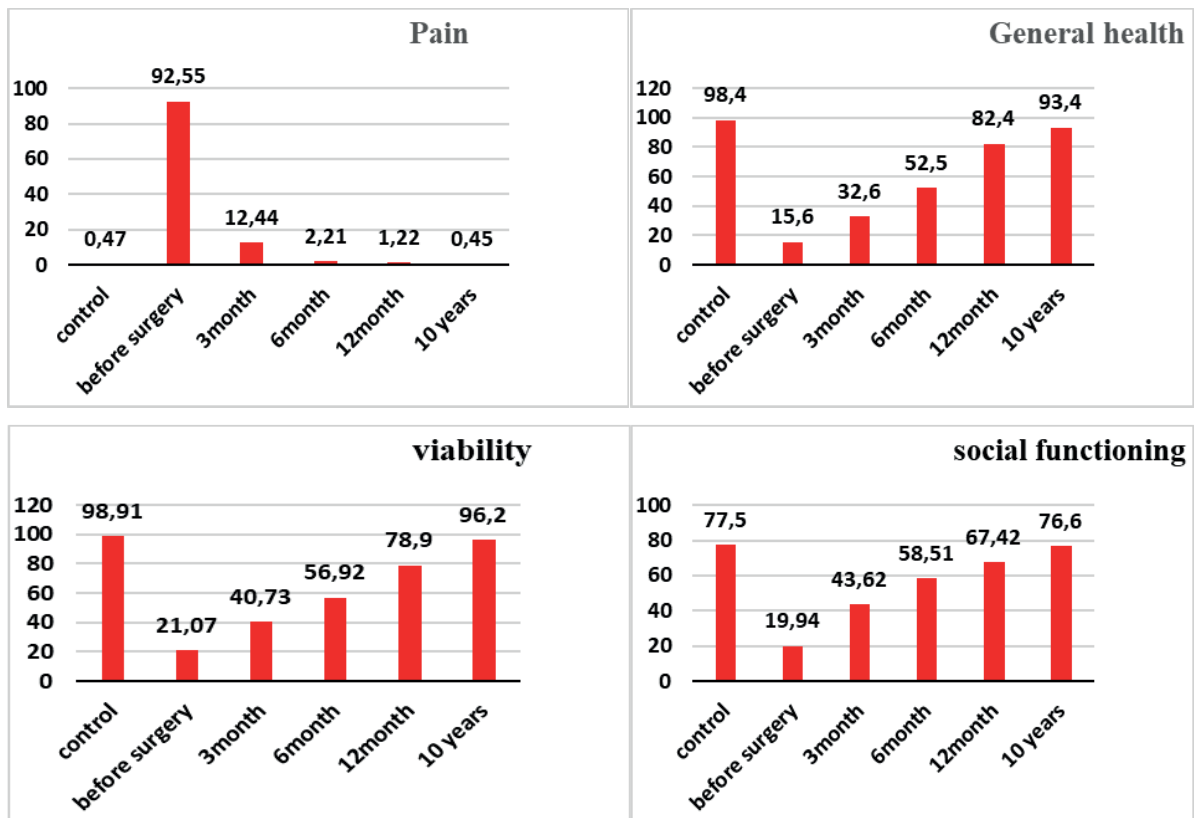


Fig. 2. Quality of life indicators of patients of the 1st group before surgery and 3, 6, 12 months and 10 years after parathyroidectomy according to the SF-36 questionnaire for 4 domains.

Рис. 2. Показатели качества жизни пациентов первой группы до и через 3, 6, 12 месяцев и 10 лет после паратиреоидэктомии по данным опросника SF-36 по 4 доменам.

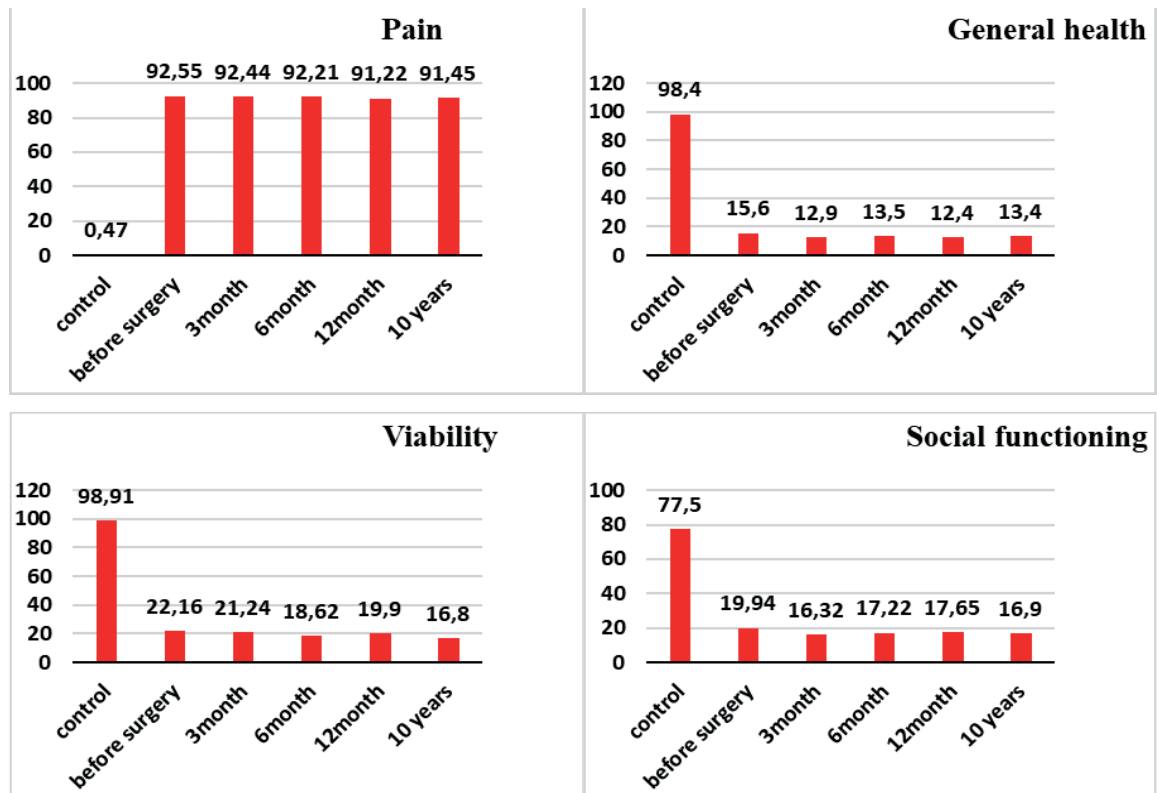


Fig. 3. Quality-of-life indicators of patients in group 2 before and 1, 3 and 6 months after treatment according to the SF-36 questionnaire.

Рис. 3. Показатели качества жизни пациентов второй группы до и через 3, 6, 12 месяцев и 10 лет после лечения по данным опросника SF-36 по 4 доменам.

Table 4

**Correlation relationship (R) of PAS questionnaire indicators with laboratory and instrumental indicators**

Таблица 4

**Корреляционная взаимосвязь (R) показателей опросника PAS с лабораторно-инструментальными показателями**

PTH, pg/ml	CT, pg/ml	1.25 VitD <sub>3</sub> , pg/ml	Serum P, mmol/l	Ca <sup>++</sup> , mmol/l	AP, μmol/l	Serum Ca, mmol/l
0.63*	0.51*	0.44	0.27	0.68*	0.56*	0.33

Note: PTH – parathyroid hormone, ALP – alkaline phosphatase, \* – significance of differences, where \* - p < 0.05, PAS - parathyroid assessment of symptom score.

Table 5

**Correlation relationship (R) of the SF-36 questionnaire indicators with laboratory and instrumental indicators**

Таблица 5

**Корреляционная взаимосвязь (R) показателей опросника SF-36 с лабораторно-инструментальными показателями**

PTH, pg/ml	CT, pg/ml	1.25 VitD <sub>3</sub> , pg/ml	Serum P, mmol/l	Ca <sup>++</sup> , mmol/l	AP, μmol/l	Serum Ca, mmol/l
0.68*	0.53*	0.48	0.32	0.63*	0.54*	0.30*

Note: PTH – parathyroid hormone, ALP – alkaline phosphatase, \* – significance of differences, where \* - p < 0.05.

At the same time, it should be noted that out of 40 non-operated patients, 5 (12.5%) patients died in the long term: 2 (40% of 5 patients) developed chronic kidney disease, 1 (20%) acute renal failure, 1 (20%) parathyroid cancer, and 1 (20%) hypercalcemic crisis.

The results obtained demonstrate the positive effect of surgical treatment from the patient's point of view and confirm the feasibility of assessing the quality of life both at the decision-making stage when choosing a surgical approach and as part of a comprehensive assessment of the therapy effectiveness in determining the recovery degree of various functioning aspects in patients after surgery.

We performed a correlation analysis of QOL indicators according to two questionnaires and laboratory data (Tables 4 and 5).

As can be clear from Table 4, a direct correlation was established between the data of the PAS questionnaire and PTH, CT, alkaline phosphatase, and Ca ++.

From Table 5 is clear, a direct correlation was established between the data of the SF-36 questionnaire and PTH, CT, alkaline phosphatase, and Ca ++.

Thus, both questionnaires showed a high correlation with blood markers reflecting the PHPT degree.

Next, we studied the correlation between the two questionnaires. A linear correlation was observed between PAS scores and the physical component of SF-36 [27].

Thus, the use of information obtained based on the SF-36 and PAS questionnaires before and after surgery allows monitoring changes in the PHPT patients' quality of life and assessing the dynamics of physical and psychological functioning, tracking changes in specific aspects of quality of life impaired due to the disease, and monitoring actual symptoms in PHPT patients after treatment [28,29,30].

**Conclusions.** The results obtained demonstrate the positive effect of surgical treatment from the patient's point of view and confirm the feasibility of

assessing the quality of life both at the decision-making stage when choosing a surgical approach and as part of a comprehensive assessment of the therapy effectiveness in determining the recovery degree of various functioning aspects in patients after surgery. A direct correlation was established between the data of the PAS and SF-36 questionnaires with PTH, CT, alkaline phosphatase, and Ca++.

**Transparency of the study.** *The study did not have sponsorship. The authors are solely responsible for the provision of the final version of the manuscript for publication.*

**Declaration of financial or other relationships.** *All authors participated in the conception and design of the study and in the writing of the manuscript. The final version of the manuscript was approved by all the authors. The authors did not receive a fee for the study.*

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