https://doi.org/10.22416/1382-4376-2025-35-2-83-94
UDC 616.37-006-07

Outcomes Following Observation of Small Non-Functioning Neuroendocrine Tumors of the Pancreas. Data from the Registry of the Loginov Moscow Clinical Scientific Center

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Aim: to evaluate results of follow-up of patients with pancreatic non-functioning neuroendocrine tumors of the stage T1–T2 using a medical registry.

Materials and methods. A retrospective analysis of the medical registry data of the Loginov Moscow Scientific Center was conducted, which included 312 patients with pancreatic neuroendocrine tumors from 2014 to 2023. Observation was recommended for 115 (36.9 %) patients. The inclusion criteria: diagnosis of pancreatic neuroendocrine tumor; non-functioning tumor status; asymptomatic disease; tumor size less than 3 cm; patient's consent. The exclusion criteria were patient's refusal of observation; tumor growth of more than 3 mm/year of observation; appearance of disease symptoms. Based on the registry data, gender and age of patients, size and location of tumors, TNM stage, tumor growth dynamics (mm/year), biochemical markers of neuroendocrine tumors, and the presence of concomitant pathology were studied. Whole genome sequencing was performed on 53 patients with first diagnosed pancreatic neuroendocrine tumors.

Results. Six patients (5.2 %) were excluded from the study: three refused to be observed, three demonstrated tumor growth. 109 patients diagnosed with non-functioning pancreatic neuroendocrine tumor were included in the analysis: 78 (71.6 %) women and 31 (28.4 %) men aged from 22 to 86 years (58.5 ± 10.8 years) at the time of presentation. The median follow-up time was 34.0 (2.0–86.0) months. The most common location of tumors was in the head of the pancreas — 45.5 % (n = 51). Of the 109 patients observed, 103 were diagnosed with stage T1 tumors (94.5 %), 6 — with T2 (5.5 %). The average tumor size was 11.9 ± 3.8 mm (3.1–29.0 mm) (n = 118). An increase in biochemical markers of neuroendocrine tumors (gastrin, chromogranin A) was associated with atrophic gastritis. Germline mutations were detected in 24.0 % of patients (n = 12). The most common mutations in the sample were the *CHEK2* gene (n = 4).

Conclusions. According to the registry data, active observation is an acceptable tactic for managing patients with T1 non-functioning pancreatic neuroendocrine tumors. Likely it is not the size of the tumor but its growth rate that has prognostic significance, and therefore a protocol for monitoring this group of patients is required. The effect of estrogens on tumor growth inhibition and the role of *CHEK2* gene mutations are perspectives for future research.

Keywords: neuroendocrine tumors, pancreatic NETs, tactics, active observation, registry

Conflict of interest: the authors declare no conflict of interest.

For citation: Khatkov I.E., Salimgereeva D.A., Feidorov I.Yu., Konyakhina A.A., Petrova A.L. Outcomes Following Observation of Small Non-Functioning Neuroendocrine Tumors of the Pancreas. Data from the Registry of the Loginov Moscow Clinical Scientific Center. Russian Journal of Gastroenterology, Hepatology, Coloproctology. 2025;35(2):83–94. https://doi.org/10.22416/1382-4376-2025-35-2-83-94

Результаты наблюдения пациентов при нефункционирующих нейроэндокринных опухолях поджелудочной железы малых размеров. Данные регистра МКНЦ им. А.С. Логинова

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Цель исследования: оценить результаты наблюдения за больными нефункционирующими нейроэндокринными опухолями поджелудочной железы стадии T1–T2 с использованием медицинского регистра.

Материалы и методы. Проведен ретроспективный анализ данных регистра МКНЦ им. А.С. Логинова, который с 2014 по 2023 г. включил 312 больных панкреатическими нейроэндокринными опухолями. Тактика

активного наблюдения была рекомендована 115 (36,9 %) пациентам. Критериями включения в исследование явились: установленный диагноз нейроэндокринной опухоли поджелудочной железы; нефункционирующий статус опухоли; бессимптомность заболевания; размер опухоли до 3 см; согласие пациента. Критериями исключения явились: отказ пациента от активного наблюдения; рост опухоли более чем на 3 мм за год наблюдения; появление симптомов заболевания. На основании данных регистра изучен пол, возраст пациентов, размер и локализация опухолей, стадия по TNM, их рост в динамике (мм/год), биохимические маркеры нейроэндокринных опухолей, наличие сопутствующей патологии. Наблюдаемым с впервые выявленной опухолью (*n* = 53) выполнено полногеномное секвенирование.

Результаты. Из исследования исключены 6 (5,2 %) пациентов: трое отказались от наблюдения, у трех выявлен значимый рост опухоли. В анализ были включены 109 пациентов с клиническим диагнозом нефункционирующей нейроэндокринной опухоли поджелудочной железы: 78 (71,6 %) женщин и 31 (28,4 %) мужчина в возрасте на момент обращения от 22 до 86 лет (58,5 ± 10,8 года). Медиана времени наблюдения составила 34,0 (2,0–86,0) месяца. Наиболее часто опухоли локализовались в головке поджелудочной железы — 45,5 % (*n* = 51). Из 109 наблюдаемых у 103 (94,5 %) чел. стадия опухоли определена как T1, у 6 (5,5 %) — T2. Средний размер опухолей составил 11,9 ± 3,8 мм (3,1–29,0 мм) (n = 118). Повышение биохимических маркеров нейроэндокринных опухолей гастрина, хромогранина А у наблюдаемых было связано с наличием атрофического гастрита. Герминальные мутации выявлены у 24,0 % пациентов (*n* = 12). Наиболее часто в выборке встречались мутации гена *CHEK2* (*n* = 4).

Выводы. По данным регистра, активное наблюдение — допустимая тактика ведения больных панкреатическими нефункционирующими нейроэндокринными опухолями стадии T1. Вероятно, прогностической значимостью обладает не размер, а скорость роста опухоли, в связи с чем необходимо создание протокола наблюдения этой группы больных. Влияние эстрогенов на сдерживание роста опухоли и изучение роли мутаций в гене *CHEK2* являются дальнейшими перспективами для изучения.

Ключевые слова: нейроэндокринные опухоли, НЭО ПЖ, тактика, активное наблюдение, регистр

Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

Для цитирования: Хатьков И.Е., Салимгереева Д.А., Фейдоров И.Ю., Коняхина А.А., Петрова А.А. Результаты наблюдения пациентов при нефункционирующих нейроэндокринных опухолях поджелудочной железы малых размеров. Данные регистра МКНЦ им. А.С. Логинова. Российский журнал гастроэнтерологии, гепатологии, колопроктологии. 2025;35(2):83–94. https://doi.org/10.22416/1382-4376-2025-35-2-83-94

Introduction

It is widely accepted that pancreatic neuroendocrine tumors (PNETs) represent a heterogeneous group of rare neoplasms. While the heterogeneity of these tumors is becoming increasingly apparent to clinicians, their rarity is, conversely, decreasing. The incidence of PNETs, particularly small asymptomatic tumors, has risen due to the availability of advanced diagnostic techniques. For instance, in the United States, the incidence of neuroendocrine tumors measuring less than 2 cm has increased by 710.4 % over 22 years [1]. The heterogeneity of pancreatic neuroendocrine tumors determines different prognoses for the diseases, according to which it is necessary to specifically determine the treatment strategy for the patient.

The existence PNETs has been recognized by the scientific community for less than a century [2]. During this time, its classification has undergone radical changes, which may indicate that the biology of these tumors remains unclear, and therefore it is not always easy to determine the optimal management strategy for patients. In particular, the tactics for patients with non-functioning asymptomatic localized tumors (without clinical manifestations, small sized and difficult to verify) remain unclear. To date, there is no way to determine why, all else being equal, some of these tumors will continue to grow and gain the ability to metastasize, despite maintaining differentiation, while others will remain the same size, demonstrating a clinically benign course of the disease. The reliable criteria for malignant potential in NETs remain signs of infiltrative growth and metastasis.

Currently, there are no published prospective randomized studies comparing observation and surgical treatment for PNETs. International clinical guidelines provide ambiguous answers regarding the management of such neoplasms, while national recommendations do not address this issue at all [3]. These guidelines are based on data from heterogeneous retrospective studies; consequently, a critical objective of scientific inquiry is to establish criteria for selecting patients for either active observation or surgical intervention.

Thus, the necessity of developing a protocol of observation for patients with small, localized non-functioning pancreatic neuroendocrine tumors is evident. The protocol could improve treatment outcomes for this category of patients.

Aim of the study

To evaluate the results of follow-up of patients with pancreatic non-functioning neuroendocrine tumors of stage T1–T2 using a medical registry

Materials and methods

This study is based on data from the medical registry of the Loginov Moscow Clinical Scientific Center. Patient enrollment into the registry commenced in 2014 and included individuals who received consultations from endocrine surgeons, oncologists, and clinical diagnostic specialists, contingent upon the patient's consent for personal data processing. The patient recruitment region comprises subjects of the Russian Federation.

Clinical diagnoses and treatment strategies were determined by an interdisciplinary oncology consilium at the Loginov Moscow Clinical Scientific Center, which included the following specialists: oncologist, endocrine surgeon, pancreatic surgeon, radiology specialist, and radiation therapist. Subsequently, the data were organized on the platform for online project management for clinical monitoring, Quinta Clinical. As of December 1, 2023, the registry contained data on 312 patients with pancreatic neuroendocrine tumors.

Functional tumors were diagnosed in 77 (24.7 %) cases, while non-functional tumors were observed in 235 (75.3 %) cases. The strategy of active observation was recommended for 115 (36.9 %) patients, while surgical treatment alone was proposed for 104 (33.3 %) patients, systemic drug treatment — only for 47 (15.1 %) patients, and combined treatment — for 46 (14.7 %) patients.

Inclusion criteria for the study were as follows: age over 18 years; a confirmed diagnosis of pancreatic neuroendocrine tumor; non-functional tumor status; asymptomatic disease (absence of clinical and laboratory-instrumental signs of biliary or pancreatic hypertension, duodenal obstruction, or other complications); tumor size up to 2 cm or up to 3 cm in cases where surgical treatment was precluded due to severe comorbidities, pregnancy, or the patient's categorical refusal of surgery; and patient's consent to the proposed management strategy.

Exclusion criteria: the patient's refusal of active observation; tumor growth exceeding 3 mm during the year of observation; and the appearance of disease symptoms.

During the observation period, 6 (5.2 %) patients were excluded from the group of 115 being monitored: three (2.6 %) opted for surgical treatment instead of active observation, and three (2.6 %) were excluded due to tumor growth. Radical surgical treatment was performed for those cases.

A total of 109 patients were included in the study (Fig. 1), comprising 103 patients with stage T1 tumors and 6 patients with stage T2 tumors.

The term "active observation" was defined as a comprehensive patient assessment strategy designed to identify criteria for exclusion from monitoring and referral for surgical treatment at least once every 12 months.

During the initial consultation, the indications and contraindications for implementing the active observation strategy were evaluated. If a patient met the inclusion criteria for the study, their data were recorded in a medical registry, and the patient was placed into the active

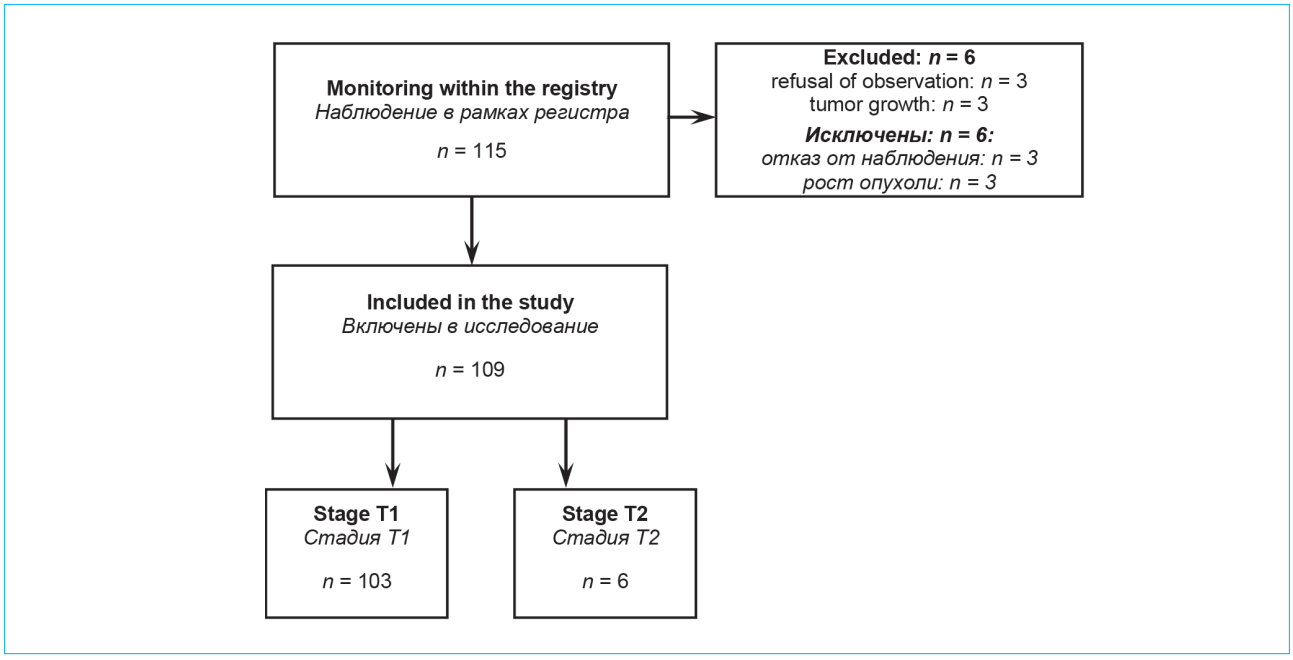

Figure 1. Study design

Рисунок 1. Дизайн исследования

observation group with a comprehensive assessment interval scheduled for at least once every 12 months.

Within the framework of active observation, the minimal set of monitoring examinations included:

1) an examination by a surgeon or a telemedicine consultation when an in-person visit was not feasible, aimed at evaluating complaints, identifying clinical symptoms of the tumor or its hormonal activity, collecting medical history, and performing a physical examination;

2) monitoring of laboratory parameters, including complete blood count and biochemical blood analysis (alanine aminotransferase, aspartate aminotransferase, bilirubin, alpha-amylase, total protein);

3) evaluation of instrumental imaging methods to visualize the tumor, which included multislice computed tomography (MSCT) with intravenous contrast in 98 (89.9 %) cases, magnetic resonance imaging (MRI) of the abdominal cavity — in 8 (7.3 %) cases, and endoscopic ultrasonography — in 3 (2.8 %) cases. The duration of observation without disease progression and the dynamics of tumor growth measured to tenths of millimeters were documented.

During follow-up examinations, MSCT or MRI images were assessed by both an endocrine surgeon and a radiology specialist. In cases where endoscopic ultrasonography was performed, the findings of the examination were also evaluated. In 7 (6.4 %) cases, imaging results from different modalities (MRI and MSCT) were compared at least once during the observation period.

Optional examination methods included:

1) evaluation of biochemical markers of NETs and hormones (chromogranin A, serotonin, gastrin, parathyroid hormone, calcitonin, adrenocorticotropic hormone), including cases of hereditary syndrome;

2) positron emission tomography/computed tomography (PET/CT) with ^{68}Ga-DOTA-TATE — conducted in 17 (15.6 %) patients;

3) MRI of the brain was recommended for patients with suspected or confirmed genetic syndromes, which was performed annually in two cases (1.8 % of all observed patients);

4) ultrasound of the thyroid and parathyroid glands was recommended for patients with suspected or confirmed genetic syndromes, as well as in those with previously known thyroid diseases, with ultrasound data available for 29 (26.6 %) patients.

An analysis of patient demographics, specifically gender and age, as well as tumor size and localization, was conducted. The stage of tumors was determined according to the TNM classification established by the International Union for Cancer Control (UICC) in 2009. Tumor growth was evaluated in millimeters over one year. Size assessments were performed using the RadiAnt DICOM Viewer software, offering precision to tenths of millimeters, in case images were available. In cases where access to images was unavailable, data from the provided descriptions of CT scans were included in the registry. However, only imaging was evaluated during follow-up examinations. In instances where contraindications to MSCT existed, tumor growth was similarly assessed through MRI or endoscopic ultrasonography data.

Comorbidities were evaluated based on laboratory and instrumental examination results, consultative conclusions from specialists, and provided medical documentation. The presence of multiple endocrine neoplasia syndromes was confirmed by identifying mutations in specific genes through molecular genetic testing.

Since 2022, genetic testing has been performed on 50 patients with newly diagnosed T1 PNETs utilizing next-generation sequencing via the EVOGEN-GENOME panel. The presence of germline mutations was determined.

The study of biochemical markers in neuroendocrine tumors was conducted. A comprehensive analysis of the registered data from laboratory tests was performed, focusing on the levels of chromogranin A, gastrin, and serotonin in peripheral blood. Chromogranin A levels were available for 83 (76.1 %) out of 109 patients. Concurrently, gastrin levels were assessed in 64 (58.7 %) subjects and serotonin levels in 63 (57.8 %) patients. An elevated marker level was defined as a concentration exceeding the laboratory reference value by more than two-fold.

Data obtained from esophagogastroduodenoscopy (EGD) were recorded for 42 (45.2 %) patients. The condition of the gastric mucosa was evaluated, and in cases where endoscopic signs of gastritis were present, the presence of atrophy was assessed. Among 42 patients, three relevant markers of neuroendocrine tumors were studied in 28 individuals.

Statistical analysis was conducted using SPSS Statistics 26 software. Descriptive statistics for nominal variables were provided as absolute and relative values (percentages, %). For the analysis of quantitative variables, median and mean values were utilized. When the distribution of data conformed to a normal distribution, the mean was used as the measure of central tendency; otherwise, the median was reported. Normality of distribution was assessed using the Kolmogorov — Smirnov and Shapiro — Wilk tests. To evaluate the variability of quantitative variables in the general population, the standard deviation (σ) was calculated. The χ^2 test was employed to explore the relationships between categorical variables, assessing the

Table 1. Patient characteristics at the time of data analysis
Таблица 1. Характеристики пациентов на момент анализа данных

Parameter / *Параметр*	Value / *Значение*
Age, years / *Возраст, лет*	62.0 (29.0–90.0)
Females, *n* (%) / *Женщины, n (%)*	78 (71.6 %)
Median of the observation time, months *Медиана времени наблюдения, мес.*	34.0 (2.0–86.0)
Average tumor size, mm ± sd *Средний размер опухолей, мм ± sd* head / *головка* body / *тело* tail / *хвост*	11.7 ± 3.8 11.5 ± 3.2 10.8 ± 3.2 12.1 ± 2.6
Localization, *n* (%) / *Локализация, n (%)* head / *головка* body / *тело* tail / *хвост*	 51 (45.5 %) 26 (23.2 %) 35 (31.3 %)
Multiple tumors of the pancreas, *n* (%) *Множественные опухоли поджелудочной железы, n (%)*	8 (7.3 %)
Elevated levels of biochemical markers, *n* (%) *Повышенный уровень биохимических маркеров, n (%)*	12 (11.0 %)

significance of the associations. Hypothesis testing was performed using the t-distribution, and the null hypothesis was rejected when $p < 0.05$.

Results

A total of 109 patients were included in the study, comprising 78 (71.6 %) women and 31 (28.4 %) men. A majority of the patients were female ($p < 0.001$) in both groups: T1 stage group — 74 (71.8 %) patients, T2 stage group — 4 (66.7 %) patients.

The mean age of patients at the time of consultation was 58.5 years (ranging from 22.0 to 86.0 years), with a standard deviation of 13.4 (Fig. 1A). The average age of patients registered as of December 1, 2023, was 62.0 years (ranging from 29.0 to 90.0 years), with a standard deviation of 13.8 (Fig. 1B).

The primary characteristics of the patients are presented in Table 1.

The median follow-up time was 34.0 months (range: 2.0 to 86.0 months) for the overall group and for the subgroup with small neuroendocrine tumors at T1 stage. The follow-up time in the larger tumor group at T2 stage was 34.5 months (range: 17.0 to 67.0 months). At the time of data analysis, all patients remained under observation, and no patients were lost to follow-up.

The dynamics of patients enrollment in the registry are illustrated in Figure 3.

The average tumor size was 11.7 mm (range: 3.1 to 29.0 mm; $n = 118$, accounting for the presence of multiple tumors in patients; standard deviation (sd) — 4.7) (Fig. 4). The average size of small

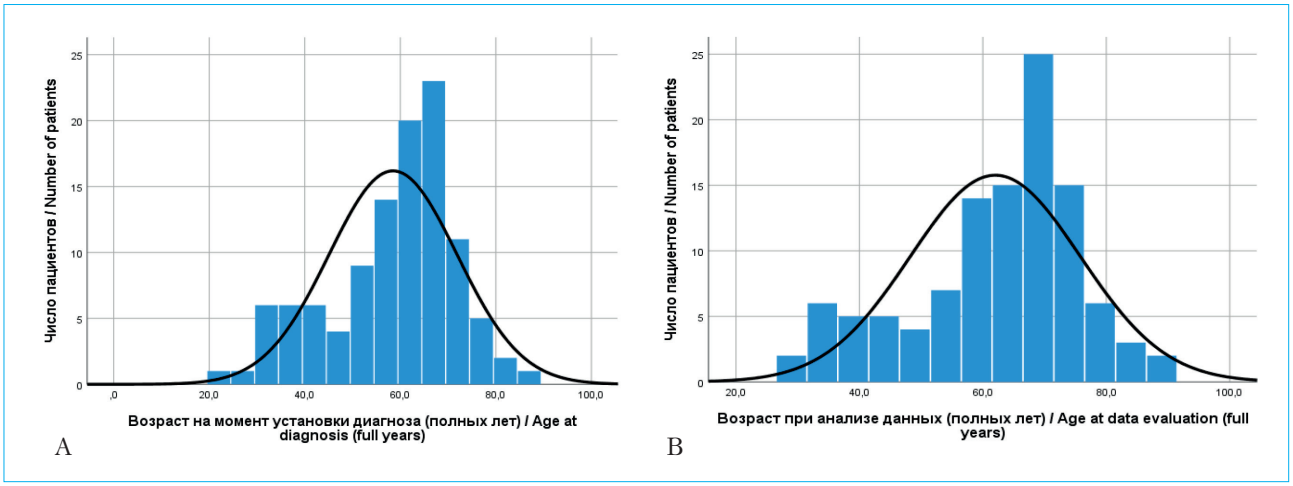

Figure 2. Distribution of patients' ages: A — at the time of diagnosis; B — at the time of data analysis

Рисунок 2. Распределение возраста пациентов: A — на момент установки диагноза; B — на момент анализа данных

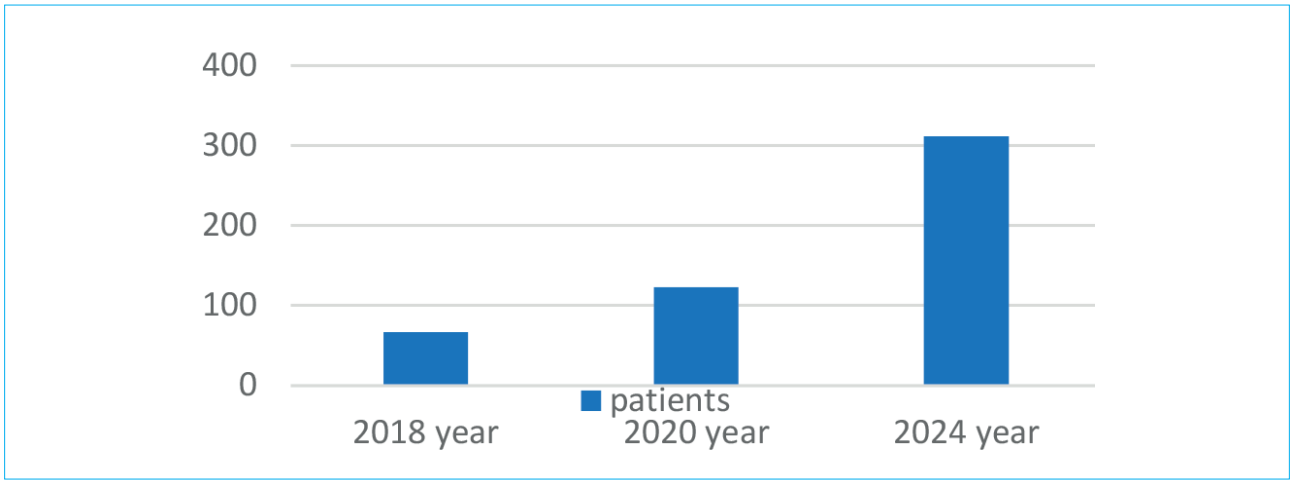

Figure 3. Dynamics of inclusion of patients in the registry

Рисунок 3. Динамика включения пациентов в регистр

non-functioning tumors was 11.1 mm (n = 112, considering the presence of multiple tumors in some patients; sd = 3.9).

Among the tumors analyzed, 45.5 % were located in the head of the pancreas (n = 51; average size — 11.5 mm; sd = 3.2). Tumors in the tail accounted for 31.3 % (n = 35; average size — 12.1 mm; sd = 2.6), 23.2 % were found in the body of the pancreas (n = 26; average size — 10.8 mm; sd = 3.2). In the group of patients with T2 stage tumors, the average tumor size was 23.7 mm (sd = 2.7). Among these, 83.3 % were located in the head of the pancreas (n = 5; average size — 24.0 mm; sd = 2.8), while 16.7 % were found in the tail (n = 1; size — 22.0 mm). As shown in Figure 5, the average tumor sizes did not differ significantly across various regions of the pancreas ($p > 0.05$).

Among the 103 patients with T1 tumors, 8 (7.8 %) exhibited multiple lesions in the pancreas, whereas none were found in the T2 tumor group (0 %). Thus, multiple tumors were observed in 7.3 % of all participants. Of these patients, three (37.5 %) developed multiple tumors in the context of type 1 multiple endocrine neoplasia (MEN-1). Overall, MEN-1 syndrome was identified in 5 patients (4.8 % of the T1 stage group).

Tumor growth of 3 mm or more was noted in the first year of follow-up after diagnosis in three patients (2.6 %), prompting timely removal from observation and radical surgical intervention. No signs of disease progression were observed in any patients. The postoperative follow-up duration ranged from 9 to 53 months.

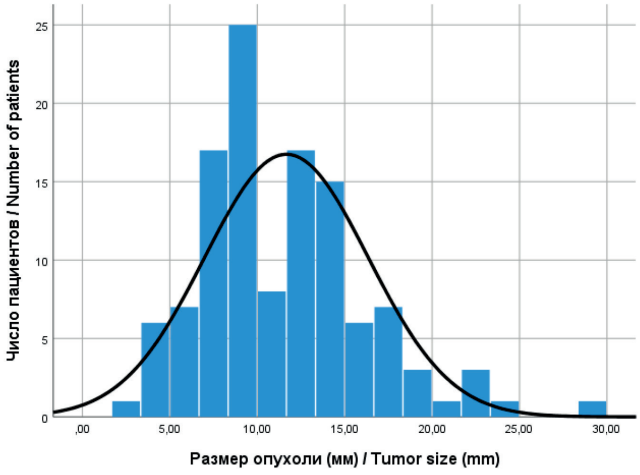

Figure 4. Distribution of tumor sizes

Рисунок 4. Распределение размеров опухолей

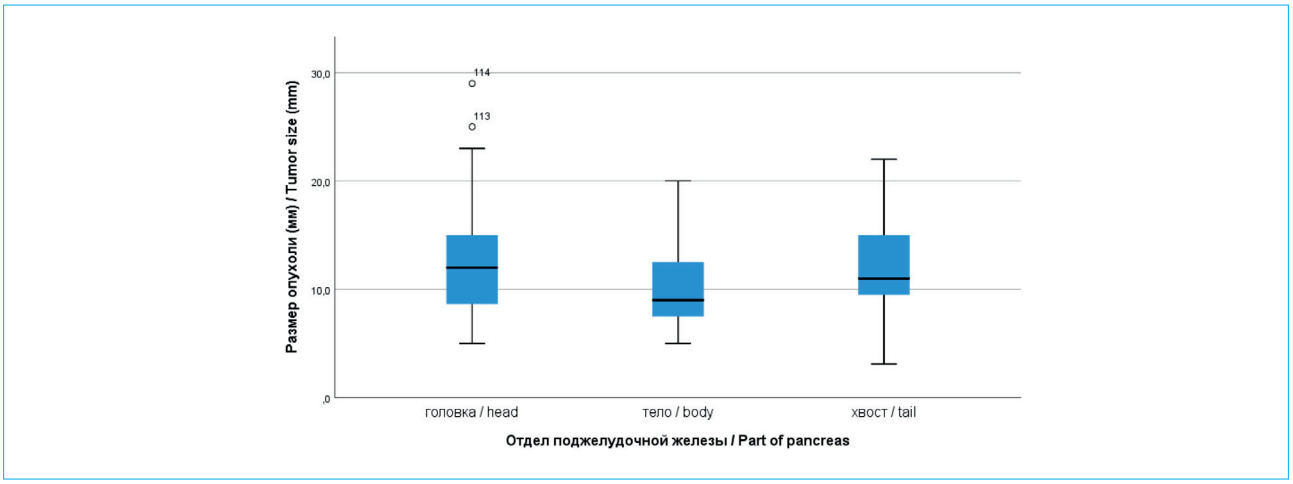

Figure 5. Sizes of tumors in different parts of the pancreas

Рисунок 5. Размеры опухолей в различных отделах поджелудочной железы

Among the concomitant malignancies, breast cancer was most prevalent, affecting 5 patients (4.8 % of all patients; 6.8 % of female patients). Prostate cancer was identified in 4 patients (3.9 % of all patients; 13.8 % of male patients). Three patients had a history of radical surgical treatment for colorectal cancer (2.9 %), two for clear cell kidney cancer (1.9 %), two for thyroid cancer (1.9 %), and two women for endometrial cancer (1.9 % of all patients; 2.7 % of female patients). One patient was under observation for lung cancer, and another for pancreatic adenocarcinoma; additionally, one patient underwent radical treatment for thymoma (histological type unknown). Outside the context of hereditary syndromes, neuroendocrine tumors at non-pancreatic sites were found in two patients (1.9 %). Four patients were monitored for hematological diseases (3.9 %).

Laboratory markers of neuroendocrine tumors. It is widely accepted that the presence of clinically non-functioning pancreatic tumors may lead to an increase in certain neuroendocrine tumor markers, particularly chromogranin A. Data regarding biochemical markers of neuroendocrine tumors (NETs) are presented in Table 2. Among 109 patients observed, reliable information on chromogranin A levels was available for 83 (76.1 %) patients. An elevation in chromogranin A was recorded in 7 (8.4 %) patients. Concurrently, gastrin levels were evaluated in 64 (58.7 %) participants, with elevated gastrin noted in 8 (12.5 %) patients. Both markers were elevated simultaneously in only 3 (4.7 %) patients. Therefore, at least one of the markers was elevated in 12 patients. Serotonin levels were assessed in 63 (57.8 %) patients, with elevated levels observed in two patients (3.2 % of those examined). Notably, the increase in serotonin was isolated; chromogranin A and gastrin were not elevated in these patients. This non-specific elevation in serotonin may be attributed to other causes and may not be associated with the presence of a pancreatic neuroendocrine tumor. For instance, one patient did not adhere to the preparation guidelines for laboratory testing, continuing the use of medications for comorbid conditions — specifically, selective serotonin reuptake inhibitors and proton pump inhibitors — and also reported deviations from the prescribed diet. A second patient experienced recurrent severe attacks of Crohn's disease, which poorly responded to the ongoing therapy. It is worth noting that, in the case of this patient, the severity of the comorbid pathology was the reason for initiating dynamic observation, despite the tumor size exceeding 2 cm, which contradicts current clinical guidelines.

One of the factors provoking an increase in neuroendocrine tumor markers is a series of changes in the gastric mucosa. Specifically, atrophic gastritis or the use of proton pump inhibitors can contribute to this elevation. During the evaluation of data recorded in the registry from esophagogastroduodenoscopy, endoscopic signs of chronic atrophic gastritis were noted in 19 (45.2 %) out of 42 patients. This occurrence was significantly higher ($p < 0.01$) than in the general population, as indicated by a meta-analysis conducted in 2022, which reported an incidence of 25.0 % [4]. Additionally, 6 (14.3 %) patients exhibited signs of non-atrophic gastritis. All 12 patients with elevated levels of chromogranin A and gastrin underwent EGDS, revealing signs of chronic atrophic gastritis in 100 % of those examined.

Furthermore, both complete data from EGDS and molecular marker levels were available for

Table 2. Laboratory markers of neuroendocrine tumors
Таблица 2. Лабораторные маркеры нейроэндокринных опухолей

Biochemical indicators ***Биохимические показатели***	**Number of patients, X (%) for whom information is provided** ***Число пациентов, X (%), для которых представлена информация***	**Number of patients who have experienced an increase in the indicator** ***Число пациентов, у которых зарегистрировано повышение показателя***	
		% of total number ***% от общего числа***	**% of number of patients X** ***% от числа пациентов X***
Chromogranin A *Хромогранин А*	83 (76.1 %)	7 (6.4 %)	7 (8.4 %)
Chromogranin A + gastrin *Хромогранин А + гастрин*	64 (58.7 %)	3 (2.7 %)	3 (4.7 %)
Gastrin *Гастрин*	64 (58.7 %)	8 (7.3 %)	8 (12.5 %)
Serotonin *Серотонин*	63 (57.8 %)	2 (1.8 %)	2 (3.2 %)

33 patients. Among these, chronic atrophic gastritis was confirmed in 19 of the previously described patients (57.6 % of those adequately assessed). The evaluation of the gastric mucosa may play a significant role in determining the causes of elevated neuroendocrine tumor markers in small asymptomatic tumors. There should be consideration for the inclusion of EGDS (preferably with biopsy following the OLGA — Operative Link Gastric Assessment protocol), as well as the determination of antibodies to parietal cells, as standard assessments for patients with pancreatic neuroendocrine tumors.

Genetic testing via next-generation sequencing, employing the EVOGEN-GENOME panel, was performed on 50 patients in the first group with newly diagnosed pancreatic neuroendocrine tumors at stage T1, and 3 (50 %) patients — at stage T2. Germline mutations were identified in 12 (24.0 %) patients. The most frequently encountered mutation in the sample was the *CHEK2* gene mutation, identified in 4 patients (3.9 % of the T1 group or 8.0 % of those examined), which constituted one-third of all patients with identified germline mutations. A mutation in the *MEN1* gene was found in 3 (2.9 %) patients, while in two additional patients, neuroendocrine tumors were discovered during dynamic monitoring due to a previously established diagnosis of Wermer's syndrome. Furthermore, mutations in genes associated with tumor development in humans, including *SDHA, PLA2G2A, ANCD2, BRCA* and *ATM*, were identified in 5 additional patients, with one patient per gene. Notably, within the observation group of patients with larger tumors (n = 6), genetic testing was performed in 3 (50 %) of them, with no germline mutations detected in this subgroup.

Patients not included in the analysis. Three individuals who initially declined active monitoring in favor of surgical treatment and underwent surgeries at other centers were not included in the study. There was no evidence of disease progression after 13.3 ± 6.4 months of postoperative monitoring. The average tumor size measured 11 ± 2.6 mm, with hospitalization durations ranging from 30 to 66 days. All tumors were classified as G1 based on immunohistochemistry of the surgical material.

Patient 1 underwent a pancreatoduodenectomy; data on the early postoperative period is unavailable, but late follow-up indicated exocrine pancreatic insufficiency.

Patient 2 underwent a distal (corpora-caudal) resection of the pancreas; complications during the postoperative period included a grade C pancreatic fistula according to the International Study Group on Pancreatic Fistulas (ISGPS), a grade B intra-abdominal hemorrhage as per ISGPS guidelines, the formation of an abscess in the abdominal cavity, and multiorgan failure (with complications classified as Clavien — Dindo grade IVb).

Patient 3 underwent a laparoscopic distal (corpora-caudal) resection of the pancreas; the postoperative period was complicated by a class C pancreatic fistula and a grade B hemorrhage according to the ISGPS, with the overall complication classified as Clavien — Dindo grade IVa.

Discussion

Analysis of the demographic data from the registry revealed a predominance of female patients, which contrasts with findings from the global literature. It is possible that clinically benign NETs of the pancreas are more characteristic of women due to

the protective effects of estrogens in inhibiting tumor growth. According to research by W. Qiu et al. (2017), the total duration of estrogen exposure significantly correlated with smaller sizes of pancreatic neuroendocrine tumors in a sample of 141 females with confirmed MEN-1 syndrome ($p = 0.043$) [5]. However, a similar analysis has not been conducted for sporadic tumors. Meanwhile, most asymptomatic small neuroendocrine tumors are incidental findings. It can be hypothesized that more frequent screenings of the female population lead to a higher detection rate of NETs. Additionally, one cannot discount the influence of the presence of a prominent mammological center within Loginov Moscow Clinical Scientific Center on the distribution of patients by sex.

The primary method for the initial diagnosis and dynamic assessment of pancreatic neuroendocrine tumors remains contrast-enhanced computed tomography, despite the higher sensitivity of endoscopic ultrasound [6] and the increasing importance of PET/CT with ^{68}Ga-DOTA, which is not routinely used in the case of small sporadic neoplasms [7]. Due to the specific characteristics of contrast enhancement, neuroendocrine tumors may sometimes go completely unnoticed by radiology specialists in non-specialized centers.

Another challenge is the precision of measurements and the operator dependence of the method [8]. Since tumor size can be assessed differently by various specialists and across different slices, it would be optimal to calculate tumor volume, which has already been suggested for the evaluation of malignant tumors in the lungs and parathyroid glands [9, 10]. This methodology would standardize measurements, although it would not entirely eliminate the "human factor". Notably, research is already underway to study the impact not of the total volume of neuroendocrine tumors, but rather the functional volume calculated based on the accumulation of tissue-labeled Ga-68 somatostatin analogs [11]. The application of radiomics and artificial intelligence demonstrates promising data, particularly for the differential diagnosis of small pancreatic neuroendocrine tumors against other indistinguishable tumors, such as solid pseudopapillary tumors, clear cell carcinoma metastases from the kidneys, and ectopic splenic tissue in select cases [12–15], as well as for non-invasive tumor grade evaluation [16, 17].

In our study, the evaluation of tumor size was not standardized; for patients with available CT or MRI images, measurements were made by the researchers. In the absence of imaging data, information was sourced from medical records.

Genetic testing was performed as part of our study on 53 (48.6 %) patients with newly diagnosed neuroendocrine tumors. Germline mutations were identified in 24.0 % of patients, while literature suggests that genetically predisposed tumors account for about 10 % of all neuroendocrine tumors [18]. The most frequently encountered mutations are typically found in the *MEN1* gene. However, in our study, genetic testing revealed mutations in the *CHEK2* gene most often, accounting for 8.0 %, which constituted one-third of all patients with identified germline mutations. When considering data from previously conducted genetic studies (outside the scope of our "cohort"), mutations in the *MEN* gene still represented the majority — two additional patients had already been diagnosed with MEN syndrome when referred for pancreatic tumor evaluation. It is noteworthy that the disease in these two patients manifested as non-pancreatic tumors, with pancreatic neoplasia discovered under already known MEN status. It is possible that in the general population of patients with pancreatic neuroendocrine tumors, the *MEN* gene mutation is not the most common but rather the most detectable due to prominent clinical symptoms. The association of *CHEK2* gene mutations with the development of neuroendocrine neoplasms is not established. In a cohort study by B.L. Bychkovsky et al. (2022) involving 36,817 patients assessed for malignant tumors of various localizations, *CHEK2* mutations were found in 3,783 patients; it was determined that the presence of this mutation is associated with breast, thyroid, and kidney cancers, and to a lesser extent with pancreatic cancer [19]. Nevertheless, there have been clinical cases where patients with neuroendocrine tumors presented with *CHEK2* gene mutations. R.D. Vallera et al. (2022) described a case involving two siblings carrying the *CHEK2* mutation, one of whom had a pituitary adenoma and pancreatic neuroendocrine tumor, while the other had a pheochromocytoma [20]. A meta-analysis conducted by K.Ø. Andersen et al. (2024), involving 225 patients with functioning and non-functioning pancreatic neuroendocrine tumors of grades G1–G2 at various clinical stages (T1–T4), identified a mutation in the *CHEK2* gene in only 4 (1.8 %) patients [21]. In our study, this mutation was observed in tumors at stage T1 and was not recorded in the T2 group. It may be hypothesized that mutations in the *CHEK2* gene are characteristic of small non-functioning tumors or that their presence defines a clinically benign course of the disease.

In our study, elevated levels of gastrin and chromogranin A in patients with small NETs of the pancreas were associated with the presence of atrophic gastritis. Magnetic evaluation of the gastric mucosa according to the OLGA protocol could provide an objective assessment of atrophy and facilitate the investigation of the relationship between neuroendocrine tumor markers and the presence and severity of chronic atrophic gastritis. To clarify the functional status of the tumor, esophagogastroduodenoscopy with biopsy following the OLGA protocol may be considered for inclusion in the diagnostic plan for patients with PNETs.

In our research, tumor growth was noted in three patients — two men and one woman. The duration of preoperative observation ranged from 3 to 12 months. According to immunohistochemical studies, two tumors were classified as G1, while one was classified as G2. The average follow-up period after surgery at the time of data analysis ranged from 9 to 53 months, with no signs of disease progression observed. The efficacy and safety of the method in this cohort of patients proved to

be high, which undoubtedly warrants further investigation, longer follow-up, and an increased number of observations. The small number of patients exhibiting tumor growth limits the ability to accurately assess their characteristics and differences from the main observation group. Possibly, these data may hold the key to understanding why some tumors exhibit invasive growth and the ability to metastasize while others remain unchanged. In this regard, two of the three patients excluded from the study due to the rate of tumor growth underwent whole-genome sequencing, but the known genetic mutations were not detected.

The limitations of the study included its retrospective descriptive nature (assessment of previously registered data), selective performance of genetic testing (conducted in 53 patients, representing 48.6 % of the cohort), and the lack of a control group.

A comparison group could consist of patients with non-functional PNETs who have undergone surgical treatment as the initial step. However, the authors of this study find it unethical to form a control group for this category of patients, as the potential benefits of surgical intervention are outweighed by the associated risks. Nonetheless, three patients initially opted for surgical treatment over active observation (as described in the Results section), that led to extended hospitalizations and significant complications.

Considering the medical and economic aspects and given the absence of disease progression in both groups, we can hypothesize that the costs associated with active observation for such patients would be comparable to the total expenses incurred from surgical treatment. Although this inquiry was not a primary objective of our study, it undoubtedly holds interest from a healthcare organizational perspective.

At the time of writing, a review of the literature revealed no registered prospective randomized studies comparing surgical treatment and active observation in non-functional tumors measuring less than 2 cm. The ethical justification for such a study at this stage in the examination of neuroendocrine tumors is questionable; directing patients with unchanged pancreatic structures and small asymptomatic tumors toward technically challenging surgeries carries a high risk of developing pancreatic fistulas and life-threatening complications. Conversely, it is feasible to monitor the moment when a tumor becomes hazardous and to initiate surgical intervention, when necessary, prior to the tumor acquiring metastatic potential.

The European Neuroendocrine Tumor Society (ENETS) is conducting a multicenter prospective study to compare the outcomes of surgical treatment in patients with small asymptomatic PNETs measuring less than 2 cm against active observation, referred to as the ASPEN study (Asymptomatic Small Pancreatic Endocrine Neoplasms; NCT03084770). According to interim results published in 2022, the study has enrolled 500 patients with pancreatic neuroendocrine tumors, all measuring less than 2 cm, asymptomatic, and non-functional, confirmed by fine-needle biopsy under endoscopic ultrasound guidance or by PET/CT with Ga-68-DOTA-TATE. Of these, 406 patients were assigned to the active observation group, and 94 — to the surgical treatment group (with surgery being performed at the patient's request in 45 % of cases, $n = 42$). Notably, the presence of regional and distant metastases (i.e., direct indicators of malignancy), as well as dilation of the main pancreatic duct and grade 3 tumors, were not exclusion criteria for the study but rather indications for inclusion in the surgical treatment group. In our opinion, it is not entirely appropriate to compare tumors which benign nature needs to be verified or refuted within the same group as tumors with confirmed malignant potential. On the contrary, the objective of scientific inquiry should be to identify the specific factors that underlie the differences between these two categories.

Despite present limitations, as far as we are concerned, this work represents the largest experience documented in the national literature regarding the observation of small non-functional neuroendocrine tumors.

Conclusions

Active observation of patients with non-functioning pancreatic neuroendocrine tumors staged T1, according to medical registry data, has proven to be an acceptable management strategy for this patient group, provided that control examinations are conducted at appropriate intervals. In specific cases, the strategy of active observation may also be applicable to patients with tumors staged T2.

It is likely that the prognostic significance lies not in the size of the tumor but rather in the rate of its growth, necessitating the development of an observation protocol for this patient group. Tumor growth was documented in 2.6 % of those observed in the study. An analysis of the influence of various factors on tumor development and growth rate would be feasible through larger epidemiological studies.

Further research is required to assess the role of estrogen activity in inhibiting tumor growth, the impact of mutations in the *CHEK2* gene on the genesis of neuroendocrine tumors, and their predictive significance.

The study also demonstrated a correlation between elevated levels of chromogranin A and gastrin in patients with pancreatic neuroendocrine tumors who have chronic atrophic gastritis.

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Проверка верстки и ее согласование с авторским коллективом: Салимгереева Д.А.

Submitted: 02.12.2024 Accepted: 15.03.2025 Published: 30.04.2025
Поступила: 02.12.2024 Принята: 15.03.2025 Опубликована: 30.04.2025

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