# CASE REPORT OF THE PATIENT WITH FOUR MULTIPLE PRIMARY MALIGNANT TUMORS IN THE DUODENUM AND COLON

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Currently, the occurrence of multiple primary malignant tumors is one of the complex and poorly understood issues of oncology. After the diagnosis of malignant neoplasm is established, the risk of a new primary, non-metastatic tumor increases in a patient. The paper presents a case report of the patient with four multiple primary malignant tumors in the duodenum and colon. Synchronous cancer of the cecum and rectosigmoid junction occurred after 9 months of the duodenal cancer pancreatoduodenal resection, photodynamic therapy, and 12 multiagent chemotherapy courses. The patient received 8 courses of chemotherapy with capecitabine, during which cancer progression was reported, and 16 multiagent chemotherapy courses. Two years later rectal cancer occurred, due to which rectal re-resection was conducted, along with 4 multiagent chemotherapy courses and target therapy. This clinical case emphasizes that it is necessary to perform additional assessment when treating patients with synchronous or metachronous multiple primary tumors to ensure the timely diagnosis and multidisciplinary approach to treatment of cancer patients.

**Keywords:** duodenal adenocarcinoma, rectal adenocarcinoma, rectosigmoid adenocarcinoma, cecal adenocarcinoma, multiple primary malignant tumors

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# КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ ПАЦИЕНТА С ЧЕТЫРЬМЯ ПЕРВИЧНО-МНОЖЕСТВЕННЫМИ ЗЛОКАЧЕСТВЕННЫМИ ОПУХОЛЯМИ ДВЕНАДЦАТИПЕРСТНОЙ И ТОЛСТОЙ КИШКИ

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В настоящее время одной из сложных и малоизученных проблем онкологии является возникновение первично-множественных злокачественных опухолей. После установления диагноза злокачественного новообразования у пациентов возрастает риск появления новой первичной неметастатической опухоли. В статье представлено клиническое наблюдение пациента с четырьмя первично-множественными злокачественными опухолями двенадцатиперстной и толстой кишки. Через 9 месяцев после панкреатодуоденальной резекции рака двенадцатиперстной кишки, фотодинамической терапии и 12 курсов ПХТ возник синхронный рак слепой кишки и ректосигмоидного соединения. Проведено 8 курсов химиотерапии капецитобином, на фоне которой отмечено прогрессирование процесса, и 16 курсов ПХТ. Спустя 2 года возник рак прямой кишки, по поводу которого выполнили резекцию прямой кишки, 4 курса ПХТ и таргетную терапию. Данный клинический случай акцентирует внимание на необходимости дополнительных исследований в области терапии пациентов с синхронными или метахронными первичными множественными опухолями, обеспечение своевременной диагностики и мультидисциплинарного подхода к лечению у онкологических пациентов.

**Ключевые слова:** аденокарцинома двенадцатиперстной кишки, аденокарцинома прямой кишки, аденокарционома ректосигмоидного соединения, аденокарцинома слепой кишки, первично-множественные злокачественные опухоли

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After the diagnosis of malignant neoplasm is established, the risk of a new primary, non-metastatic tumor (multiple primary malignant tumor, MPMT) increases in a patient. MPMTs are found in 2–17% of individuals, who have undergone treatment due to the first tumor; their risk of developing MPMT is increased 1.1–1.6-fold relative to the general population [1]. The first mention of MPMT dates back to 1793, when J. Pearson reported the case of metachronous cancer in both breasts and the uterus [2]. In 1947, N.N. Petrov added the description of primary multiplicity criteria in the first Soviet clinical oncology guidelines: "tumors shall not be neither metastatic, brought by the flow of lymph, blood or across the serous cavities, nor imprints developed from contact" [3].

Today, two most common definitions presented in the Surveillance Epidemiology and End Results (SEER) and the International Association of Cancer Registries and International Agency for Research on Cancer (IACR/IARC) are used. According to the guidelines of the SEER database, a 2-month interval should be used for differentiation of synchronous and metachronous MPMTs. At the same time, International Agency for Research on Cancer (IARC) suggests to consider tumors synchronous, when these are diagnosed with an interval less than 6 months (or metachronous, when the interval exceeds 6 months), provided that the tumors are localized in different organs [4].

Small intestine cancer (SIC) is a rare malignant tumor: it is found in about 0.6% of cancer cases and 3–6% of GIT tumor cases; SIC mortality is 0.3% of the total number of fatal outcomes in cancer patients reported all over the world. In 31.6% of cases, early-stage SIC is diagnosed. Overall (5-year) survival rate of patients having localized small intestine cancer reaches 84.8%. According to statistics, the average annual increase in the number of new SIC cases was 2.2% in 2012–2021, while mortality rate increased by an average of 2% annually in 2013–2022 [5, 6]. Primary malignant tumors of the duodenum are rare. These constitute about 61% of all small intestine cancer cases [7]. According to the WHO data, colorectal cancer (CC) ranks second among all causes of cancer mortality all over the world. In 2020, more than 1.9 million new CC cases were reported, and the rate of deaths from this disorder exceeded 930,000 cases [7].

The authors of one retrospective study analyzed 55 CC cases [8] and noted that gastric cancer was the most common malignant neoplasm associated with CC (20% of cases). Next in prevalence were esophageal cancer, uterine cancer and lung cancer; only one patient was diagnosed with duodenal cancer that was found first, while CC was found more than 6 months later [8].

The paper presents a case report of the patient with four multiple primary malignant tumors in the duodenum and colon.

## Clinical case description

Female patient L. aged 56 years stays at the cancer hospital in Azov. In 2020, examination conducted due to complaints of weight loss, yellowing of the skin, and itching, revealed a duodenal tumor (based on the EGD data of August 10, 2020): infiltrative and ulcerative c-r in the retrobulbar parts of the duodenum, moderately differentiated adenocarcinoma determined in biopsy specimens, MRI features of tumor lesion of the duodenal wall, head of the pancreas, and parapancreatic tissue. Examination yielded no data confirming other malignant neoplasms; fibrocolonoscopy conducted on August 10, 2020 revealed a polyp 30 cm from the anus. The following diagnosis was established: duodenal cancer cT4N0M0 st. IIb, clinical group 2, obstructive jaundice. Percutaneous transhepatic cholangiostomy was performed on August 13, 2020; the following surgical intervention took place after the bilirubin level were back to normal (total bilirubin 8.8 μmol/L) and preoperative preparation was completed on August 21, 2020: laparotomy, gastro-pancreatoduodenal resection, cholecystectomy with an intraoperative photodynamic therapy session on the bed of the tumor removed. Postoperative period proceeded without complications; the patient received supportive drug therapy that included preventive antibiotics and antithrombotic agents.

The following report was obtained after the surgical material histological examination conducted on August 28, 2020: poorly differentiated adenocarcinoma G3 — high grade with mucosal ulceration, extension into all intestinal wall layers, pancreatic tissue invasion, necrotic foci, lymphoid infiltration along the tumor periphery, perineural invasion, presence of tumor emboli in lymphatic and blood vessels. Sinus histiocytosis, follicular hyperplasia were found in 12 lymph nodes assessed. There was chronic inflammation in the intestinal wall, outside the tumor. There were ectatic acini with the dilated lumen outside the pancreatic tumor. The resection margin showed no signs of tumor growth (Fig. 1).

The following diagnosis was established: duodenal cancer extending into the pancreas pT4bN0M0 st. IIB, clinical group 2.

According to the chemotherapist's advice dated September 15, 2020, the patient was recommended FOLFOX-6 adjuvant multiagent chemotherapy with a satisfactory condition of the patient, complete blood counts and blood biochemistry panel within normal range, after consulting a general practitioner and a cardiologist (if there were no contraindications) throughout 6 months after surgery: 2-h infusion of oxaliplatin (85 mg/m$^2$) on day 1, intravenous leucovarin 400 (mg/m$^2$) throughout 2 h with the subsequent bolus of intravenous 5-fluorouracil (400 mg/m$^2$) and 46-h infusion of 5-fluorouracil (2400 mg/m$^2$). The interval was 14 days. In October–March 2021, a total of 12 FOLFOX-6 adjuvant multiagent chemotherapy courses were conducted.

The complaints of constipation, tenesmus, mucus discharge from the rectum during bowel movements, fatigue arose almost immediately after the multiple multiagent chemotherapy courses were completed. Two tumors were revealed based on the fibrocolonoscopy data dated April 29, 2021: in the rectosigmoid junction and ascending colon. Report of the histological examination conducted on May 17, 2021: G2 adenocarcinoma (ascending colon), G2 adenocarcinoma (rectosigmoid junction). Abdominal ultrasonography dated April 29, 2021: structural alteration of the left peritoneal lymph

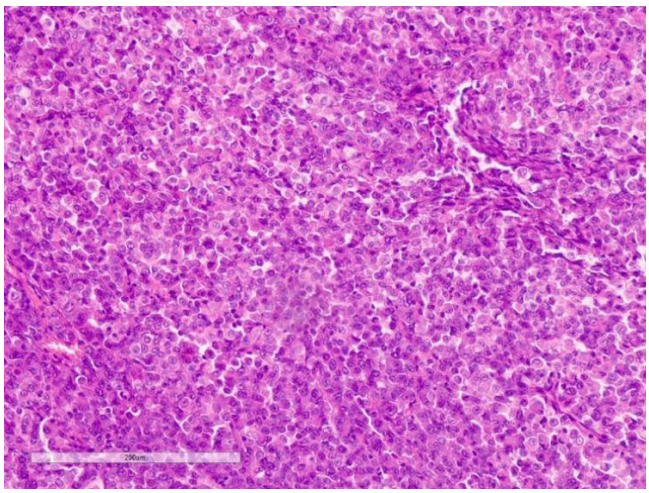

**Fig. 1.** Surgical material: poorly differentiated duodenal adenocarcinoma, G3

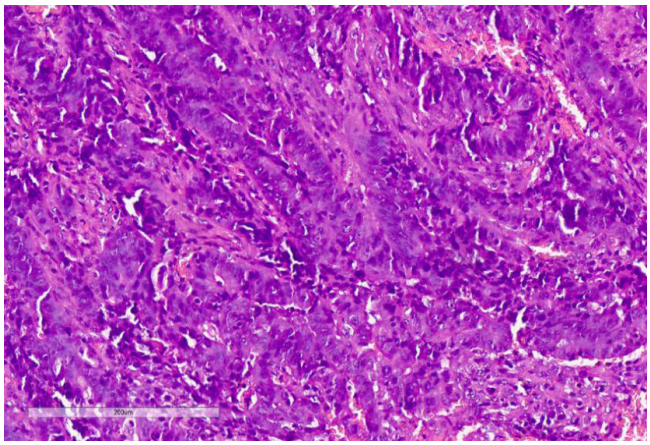

**Fig. 2.** Surgical material. Moderately differentiated adenocarcinoma, G2

nodes. Spiral computed tomography (CT) of the abdomen dated May 18, 2021: diffuse liver changes, condition after pancreatoduodenal resection.

The following surgical procedure was conducted on May 31, 2021: right hemicolectomy, anterio-superior rectal resection. Postoperative period proceeded without complications. Report obtained after the surgical material histological examination conducted on June 7, 2021: G2 adenocarcinoma invading the subserous layer in the cecum; assessment of the regional lymph nodes revealed metastatic lesions in six of those, G2 adenocarcinoma invading the muscular layer was found in the rectosigmoid junction, no metastasis was found in 8 regional lymph nodes. The resection margins showed no signs of tumor growth. The patient was discharged in fair condition (ECOG-1).

The diagnosis of multiple primary metachronous cancer was established: cecal cancer pT2N1M0 st. III, clinical group 2, rectosigmoid cancer pT2N0M0 st. I, clinical group 2, duodenal cancer extending into the pancreas pT4bN0M0 st. IIB; 12 adjuvant multiagent chemotherapy courses.

According to the chemotherapist's advice dated June 12, 2021, the patient was recommended capecitabine chemotherapy courses. A total of 8 capecitabine chemotherapy courses were conducted between July 2021 and January 2022. At the time of treatment, the patient's condition corresponded to the ECOG score 0–1, the treatment courses were accompanied by the 1$^{st}$ degree gastroenterocolitis. Scheduled clinical supervision was accomplished in accordance with the regulations provided.

In May 2022, a year after surgery due to colorectal malignant neoplasms, the next check-up and spiral CT of the abdomen revealed enlarged paraaortic lymph nodes sized up to 16 mm with unclear margins, "obscure" mesentery, no free fluid in the abdominal cavity, which were considered as metastatic lesion of the retroperitoneal lymph nodes.

The council of physicians decided to conduct FOLFIRI anti-cancer drug therapy. In June–August 2022, a total of five FOLFIRI multiagent chemotherapy courses were conducted: irinotecan 180 mg/m$^2$ 300 mg within a day, calcium folinate 680 mg within a day (400 mg/m$^2$), 5-fluorouracil 680 mg within a day, infusional 5-fluorouracil 4100 mg through the microinfusion pump within 46 h (2400 mg/m$^2$).

Spiral CT of the abdomen and pelvis performed on September 20, 2022 revealed metastasis. The patient received 6 FOLFIRI multiagent chemotherapy courses between October 3, 2022 and December 14, 2022.

Based on the results of spiral CT of the chest, abdomen, and pelvis performed on January 23, 2023, a conclusion was drawn about cancer progression due to metastatic lesions in the retroperitoneal and mesenteric lymph nodes.

In February 2023, Aflibercept, the targeted drug (tumor angiogenesis inhibitor) was prescribed; in February–July 2023, a total of 5 r. FOLFIRI multiagent chemotherapy courses + target therapy (infusional Aflibercept 4 mg/kg 260 mg within a day) were conducted.

The patient noted health deterioration (nausea, itching, fatigue) when receiving chemotherapy. In September 2023, routine fibrocolonoscopy revealed a polyp in the transverse colon, which was removed by endoscopy. In February 2024, the patient experienced abdominal pain, as well as blood and mucus discharge during bowel movements again. In April 2024, fibrocolonoscopy performed in the residential clinic revealed the fourth malignant tumor localized in the rectum 8 cm from the anus, proximal to which, 13 cm from the anus, a previously formed intestinal anastomosis showing no signs of tumor infiltration was located. Histological assessment revealed a G2 moderately differentiated adenocarcinoma. Spiral CT of the abdomen conducted on April 24, 2024 revealed wall thickening of the rectosigmoid junction, retroperitoneal lymphadenopathy.

Considering the fact that more than 30 chemotherapy courses had been earlier conducted, it was decided to perform surgery. On May 14, 2024 anterior rectal re-resection was performed. G2 adenocarcinoma in the rectal wall with inflammation, ulceration, and hemorrhage was diagnosed based on the surgical material histological examination conducted on May 28, 2024. The tumor infiltrated into the mucous layer, submucous layer, muscular layer, extended into the pararectal adipose tissue showing perineural invasion, invasion of blood vessels. No signs of lymphatic vessel invasion were found. The resection margins (distal and proximal) showed no signs of tumor growth. No components of the tumor were found in12 lymph nodes isolated from the regional adipose tissue (Fig. 2).

Multiple primary synchronous-metachronous cancer of the middle ampullary rectum pT3N0M0, st. IIa, rectal re-resection, duodenal cancer pT4bN0M0, st. IIb, pancreatoduodenal resection, intraoperative photodynamic therapy in 2020, 12 adjuvant multiagent chemotherapy courses, cecal cancer pT2N1M0 st. III, rectosigmoid cancer pT2N0M0 st. I. In 2021, right hemicolectomy and anterior rectal resection were performed, 8 capecitabine monotherapy courses and 16 multiagent chemotherapy courses were conducted.

According to the chemotherapist's advice dated May 26, 2024, FOLFIRI anti-cancer drug therapy + target therapy with Aflibercept was indicated. The next course started on day 15.

In June–August 2024, a total of 4 FOLFIRI anti-cancer therapy courses + target therapy with Aflibercept were conducted.

During the chemotherapy courses, the patient assessed her condition as satisfactory, she noted increased fatigue and occasional nausea.

### Clinical case discussion

Today, the causes of MPMTs are poorly understood. It is assumed that these are affected by several factors, such as advances in early diagnosis and treatment of malignant neoplasms, screening, and scheduled diagnostic tests following identification of the first tumor, due to which the second and subsequent tumors are identified, and the cancer patients' life expectancy increases. It is also important to note the early use of specific anti-tumor treatment, especially the methods having a damaging effect on DNA (radiation therapy and chemotherapy) and used for treatment of the first malignant neoplasm: the immune status deterioration associated with

such treatment can be a ground for the development of subsequent tumors [9]. Furthermore, genetic susceptibility and exposure to environmental factors can play an important role.

A retrospective trial conducted at the Korean cancer center involved analysis of the data of 96,174 adult patients diagnosed with their first cancer in 2003–2022. Among them 87,338 were diagnosed with a single primary malignant neoplasm, while in 8836 patients (9% of the total number) two or more neoplasms were identified. The analysis of median latency period showed that in 44% of patients with multiple primary tumors the second malignant tumor was identified within 1–5 years after the first one. A similar trend was reported for subsequent cancers: 40% of third and 42% of fourth primary tumors were diagnosed within 1–5 years after the previous diagnosis. The decrease in time to the emergence of new tumors: the median interval between the first and second malignant tumors was 4.1 years, between the second and third ones — 2.1 years, between the third and fourth ones — 1.6 years [9].

## CONCLUSION

This clinical case emphasizes the importance of prolonged monitoring and regular check-ups for early detection of new malignant tumors after completion of treatment of the first malignant neoplasm. The timely diagnosis and intense surgical treatment can considerably improve the outcome in such patients. In this regard, it is extremely important to ensure the systematic long-term follow-up in order to reveal new malignant neoplasms in such patients. Additional tests are required, especially when treating patients with synchronous or metachronous multiple primary tumors. Furthermore, it is necessary to more thoroughly assess the effects of previous treatment on the outcome, anti-tumor therapy efficacy, and potential toxic effects.

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