

A case of metachronous ascending colon cancer and synchronous primary rectal and duodenal cancer in a patient with Lynch syndrome

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Multiple primary malignant tumours (MPMTs) are defined as the simultaneous or sequential occurrence of two or more primary malignant tumours in a single patient, which may originate from the same organ, paired organs, different parts of the same system, or different organs. Synchronous MPMTs develop within 6 months of the primary tumour, while metachronous ones occur more than 6 months later. The available sources have no information on metachronous or synchronous colorectal and duodenal cancer.

OBJECTIVE — to present treatment outcomes of a rare case of metachronous ascending colon cancer and synchronous primary rectal and duodenal cancer in a patient with Lynch syndrome.

A male patient, born in 1963, underwent a right-sided hemicolectomy for ascending colon mucinous adenocarcinoma — stage III (pT_{4p}N₁M₀) — in 2002. In the summer of 2022, he complained of pain in the right hypochondrium, nausea, general weakness, and blood in the stool. The examination revealed the presence of synchronous primary cancer in the rectosigmoid section and duodenal cancer. The decision to proceed with a two-stage surgical intervention was based on the partial colonic obstruction. The first stage (September 08, 2022) included the anterior resection of the rectum with sigmo-recto anastomosis (pT_{4c}N_{2b}M₀, stage III, R-0). The patient flatly refused chemotherapy and independently underwent a course of outpatient treatment using Dr. A. I. Potopalsky's method. The second stage (December 08, 2022) included the resection of a portion of the descending and lower horizontal parts of the duodenum with duodeno-duodenoanastomosis, followed by Roux-en-Y gastrojejunostomy. The procedure entailed stitching the stomach in the prepyloric section, performing a cholecystectomy, and draining the abdominal cavity (duodenal adenocarcinoma with free margins: R-0). The patient was diagnosed with Lynch syndrome based on immunohistochemistry screening results and genetic studies. At the control CT scan 1.9 months after the last operation, there were no signs of prolongatio morbi. A rare case of synchronous rectal and duodenal cancer, demonstrating favourable treatment outcomes after two-stage surgery without standard adjuvant therapy, is described. The patient independently underwent a treatment course using Dr. A. I. Potopalsky's method. Despite the lack of evidence supporting the effectiveness of this technique, its impact cannot be disregarded. Patient follow-up is ongoing; therefore, the results may change in the future.

KEYWORDS

metachronous cancer, synchronous primary rectal and duodenal cancer, surgical treatment, adjuvant therapy, Lynch syndrome.

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Multiple primary malignant tumours (MPMTs) are described as two or more primary malignant tumours that develop simultaneously or sequentially in the same patient. They may originate from the same organ, paired organs, different parts of the same system, or different organs of different systems [1]. The diagnostic criteria for MPMTs

require each tumour to exhibit clear malignant histopathological changes, have an independent morpho-embryogenetic pathological type, and not be an invasion or metastasis of a second tumour type. MPMTs are classified as metachronous and synchronous tumours. Synchronous MPMTs are defined as the second primary tumour occurring

within 6 months after the first primary tumour, and metachronous MPMTs are defined as the second primary tumour occurring later than 6 months after the diagnosis of the first tumour [14]. MPMTs were first described by Billroth in 1889, and the first report was published by Warren and Gates in 1932 [1]. A literature review of 1,104,269 cancer patients showed that the incidence of MPMTs ranges from 0.73 % to 11.7 % [10].

Double MPMTs are most commonly diagnosed [2, 3], but three to five MPMTs are also found [4–7]. The combinations of the locations of the first and second primary cancers can manifest in a variety of ways. Excluding breast and genital cancers in women, the most common primary cancers are thyroid, lung, colon, renal cell, bladder, rectal, and stomach cancers. The most common second primary cancers are lung, thyroid, rectal, bladder, colon, liver, and renal cell cancers [8]. According to Yang XB et al. [8], out of the total number of MPMT cases, 1,678 (88.2 %) were metachronous, and 224 (11.8 %) were synchronous [9]. In men, among synchronous cancers, the incidence of colon cancer was the highest among first primary cancers (15.1 %), and the incidence of rectal cancer was the highest among second primary cancers (21.0 %) [9].

After analysing the clinicopathological data from 15,321 patients with malignant neoplasms, Zhai S et al. [11] discovered that the most prevalent MPMTs were malignant neoplasms in the digestive system. MPMTs were more commonly found in the large intestine (colon and rectum), rather than the stomach [12]. Zhu CL and Peng LZ [13] reported the highest frequency of MPMTs in the colon (38.37 %), rectum (33.14 %), and stomach (26.16 %). According to Kato T et al. [15], MPMTs occur in 10.5 % of cases of colorectal cancer, with gastric cancer being the most frequent neoplasm (44.4 %).

We found no case reports of metachronous or synchronous colorectal and duodenal cancer in the available sources.

OBJECTIVE — to present treatment outcomes of a rare case of metachronous ascending colon cancer and synchronous primary rectal and duodenal cancer in a patient with Lynch syndrome.

Patient I., a male born in 1963, received two-stage surgical treatment for synchronous primary rectal and duodenal cancer at the Municipal Non-profit Enterprise «Kyiv City Clinical Hospital of Emergency Medical Care».

In the anamnesis (July 23, 2002), he underwent a right-sided hemicolectomy for ascending colon cancer. Final diagnosis: Colon cancer of stage III, clinical group II ($pT_{4p}N_1M_0$). Pathohistological conclusion: 1. Lymph node — undifferentiated

cancer. 2. Colon area — mucinous adenocarcinoma; involvement of all intestinal membranes.

During the postoperative period, he underwent 6 courses of chemotherapy that included 5-fluorouracil and folic acid. According to the patient, he tolerated chemotherapy poorly, with hepatotoxic and emetogenic manifestations.

In the summer of 2022, the patient complained of moderate pain in the right hypochondrium, hypogastric region, nausea, belching, general weakness, sometimes fresh blood in the stool, occasional difficulty defecating, and abdominal bloating. The diagnosis was established based on the examination data (fibrocolonoscopy and fibrogastroduodenoscopy dated June 4, 2022 and computed tomography (CT) dated August 6, 2022): Synchronous primary cancer of the rectosigmoid colon, complicated by mild bleeding (Fig. 1, 2) and retrobulbar duodenal cancer (Fig. 3, 4).

The biopsy results dated August 4, 2022 indicate a low-grade adenocarcinoma of the colon (G1–G2) according to the previous grading system (ICD-O code: 8140/3) and low-grade adenocarcinoma of the small intestine (G1–G2) according to the previous grading system (ICD-O code: 8140/3).

The decision to proceed with a two-stage surgical intervention was based on the partial colonic obstruction.

In the first stage (September 8, 2022), the patient underwent anterior resection of the rectum with «end-to-end» sigmo-recto anastomosis, debridement, and drainage of the abdominal cavity.

During the surgical procedure, we discovered a circular tumour in the upper ampullary region of the rectum, which had spread to the pararectal tissue. The pararectal, bifurcation and para-aortic lymph nodes were enlarged to 0.5–1.0 cm.

Macroscopic specimen after surgery: The rectum with mesorectal tissue and para-aortic lymph nodes. In the intestine, a circular tumour with disintegration and bleeding, which occludes the lumen by 2/3 and grows into the pararectal tissue.

Clinical diagnosis: Cancer of the upper ampullary part of the rectum ($pT_{4c}N_{2b}M_0$, stage III, R-0), clinical group 2. Mild bleeding from a tumour. Partial colonic obstruction. Duodenal cancer.

Pathohistological conclusion (September 16, 2022): Adenocarcinoma of the rectum with invasion of the muscle layer. Tumour growth is not detected at the edges of the resection. Tumour growth is not detected in the mesenteric lymph nodes and para-aortic lymph nodes.

Due to pre-existing complaints, the patient underwent an outpatient examination following the first stage of surgery.

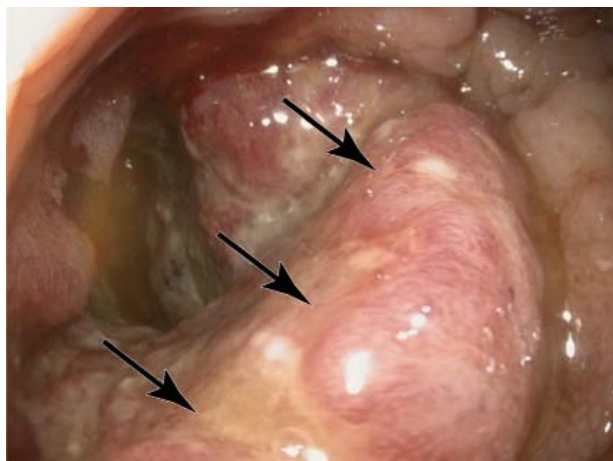


Figure 1. A circular infiltrative tumour of cartilaginous density is determined at 20 cm, occupying half of the intestinal lumen. The tissues here are amorphous, cyanotic, rigid, nodular, and bleed on contact (arrows)

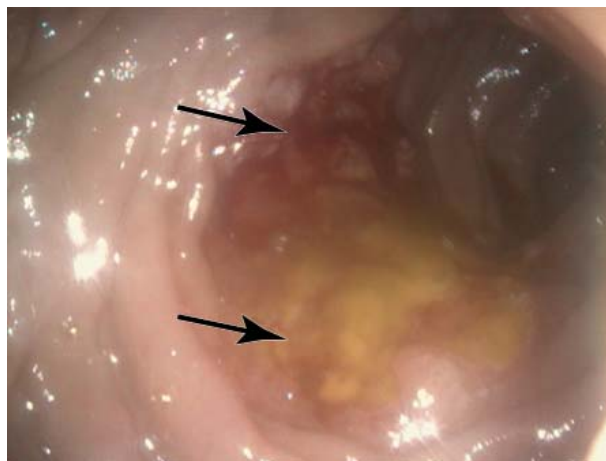


Figure 3. In the area below the major duodenal papilla, a subcircular ulcer-like defect of the duodenum of infiltrative nature with cartilaginous density is visualized, it bleeds on contact, covered with food (the area does not peristaltize). The duodenal patency is observed during endoscopy (arrows)



Figure 2. Preoperative CT reconstruction, 3D visualization. Circular thickening of the rectosigmoid colon wall up to 15 mm. The affected wall has an indistinct, uneven outer contour; the differentiation of the layers is disturbed, and the wall has active contrast enhancement. The surrounding fatty tissue is dense and compacted (arrows)



Figure 4. Preoperative CT reconstruction, 3D visualization. Circular thickening of the wall of the descending and lower horizontal parts of the duodenum up to 10 mm; the lumen of the intestine at this level is unevenly narrowed (arrows)

Fibrogastroduodenoscopy (FGDS) dated October 17, 2022: The esophagus has no abnormalities. There is a moderate amount of secretion in the stomach; the gastric mucosa is focally hyperemic. In the descending part of the duodenum, there is a neoplasia of approximately 4 cm on the lateral wall; the tissues here are cyanotic, amorphous and bleeding, and the edges are nodular. Biopsy (performed previously).

Conclusion: Duodenal neoplasia; FIIC.

After the operation, the patient was prescribed adjuvant chemotherapy. However, due to the potential severe toxic effects the patient had previously experienced from chemotherapy after the first operation, he flatly refused the proposed therapy. Instead, he independently underwent a course of outpatient treatment according to Dr. A.I. Potopalsky's method [16–19].

The patient reported taking Amitozyn for a month (from October 24, 2022 to November 28, 2022), administering 50 mg intravenously in 200 ml of saline every third day, for a total dose of 500 mg. During the first four administrations, hyperthermia was observed to be 37.5–38.5°C, which subsided within 12 hours without the administration of antipyretics. No other reactions to the drug were noted.

An FGDS was conducted on November 28, 2022, in response to the patient's further complaints, subsequent to the first stage of the operation. The esophagus has no abnormalities. A gastric secretion is observed. The duodenal defect in the descending and horizontal sections along the lateral wall has marginally reduced in volume since October 17, 2022; however, its dimensions remain about 4–5 cm. The lumen is unobstructed for the endoscope. The defect measures around 5–7 cm from the pylorus to its proximal margin.

Conclusion: Duodenal neoplasia; FIIC; positive dynamics.

Regarding the duodenal tumour, the patient was offered surgical intervention in the scope of pancreatoduodenal resection (PDR), which he categorically refused but agreed to tumour excision due to the threat of bleeding.

The second stage of the operation (December 08, 2022) was performed: Resection of part of the descending and lower horizontal section of the duodenum with duodeno-duodenoanastomosis, Roux-en-Y gastrojejunostomy, through-the-stomach stitching in the prepyloric section, cholecystectomy, and drainage of the abdominal cavity. The operation was without complications.

During the revision in the abdominal cavity, the adhesion process was detected, especially pronounced in the right hypochondrium and subhepatic space; small concretions were found in the

gallbladder; and an irregularly shaped, dense tumour measuring 4 × 5 × 3 cm was palpated along the lateral edge in the lower horizontal part of the duodenum. Duodenotomy — the tumour has a glandular structure, easily disintegrates, and bleeds. Regional lymph nodes are not enlarged.

Histopathology report dated December 22, 2022, No. 11436-39: Duodenal adenocarcinoma with free margins (R-0), atrophic cholecystitis, and gallbladder adenosis.

Since the disease exhibited the characteristics typical of Lynch syndrome, additional studies were carried out to confirm it. Initially, immunochemistry (IHC) was used to assess the status of proteins within the mismatch repair (MMR) system. The screening revealed a deficiency (dMMR/MSI-H) characterized by the loss of MSH2 and MSH6, which is typically associated with Lynch syndrome due to an inherited mutation in the MSH2 gene. Genetic tests confirmed the presence of an inherited MSH2 mutation (c.2042C > T, (p.Ala681Val)), thereby validating the diagnosis of Lynch syndrome in the patient.

During the postoperative period, suppuration of the retroperitoneal tissue hematoma was noted, which was managed with antibiotic treatment and hematoma drainage.

After surgery, the patient once more declined the recommended adjuvant chemotherapy. The patient reported undergoing outpatient therapy using Dr. A.I. Potopalsky's method from April 4, 2023, until May 19, 2023.

The patient underwent a similar treatment course in January 2024 [16–19].

Five months after surgical treatment, the patient complained of moderate pain in the epigastric region and heartburn. A gastroscopy was performed (May 16, 2023), during which a superficial peptic ulcer up to 1.5 cm in diameter was detected immediately behind the gastroentero-anastomosis from the side of the small intestine, Fores III. The antrum ends blindly. The afferent loop ends blindly and there are single ligatures. The efferent loop has no abnormalities. The patient underwent an antiulcer therapy course. Control gastroscopy dated June 26, 2023: The ulcer healed. Fifteen months later (September 23, 2024), during FGDS, erosions of the gastrojejunostomosis zone from the side of the small intestine measuring 3–7 mm were detected. The antrum ends blindly and the afferent loop on a segment 15 cm long is unchanged.

After 1.9 months (September 29, 2024), a CT scan of the chest and abdominal cavity, retroperitoneal space, and pelvis was performed with contrast «Tomohexol 350» (120 ml). Interintestinal anastomoses are patent without wall thickening. The

remainder of the colon does not exhibit gross wall thickening. The stomach stump is of sufficient size without wall thickening and the gastrojejunal anastomosis is patent. The afferent loop and duodenal stump are not dilated, without additional pathological formations and wall thickenings.

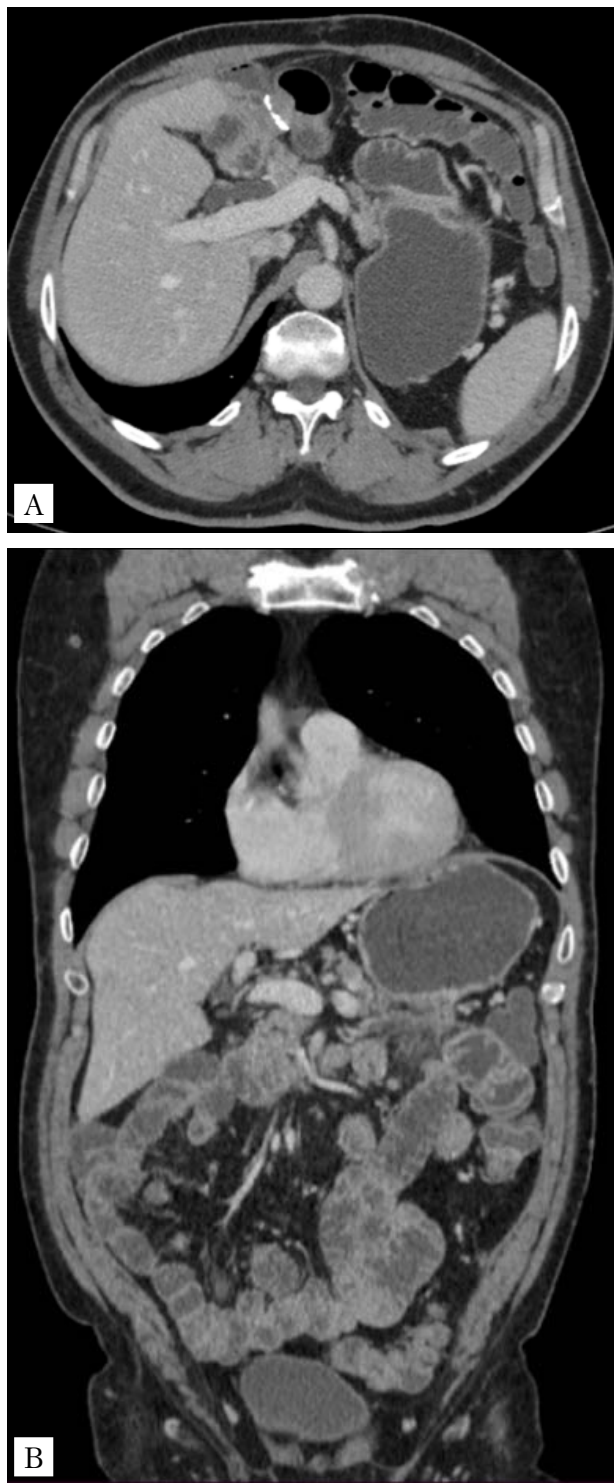


Figure 5. CT scan of the abdominal cavity with contrast, as of October 10, 2024: axial (A) and frontal (B) projection. There are no signs of prolongatio morbi

There are no pathologically enlarged retroperitoneal, mesenteric, pelvic, or inguinal lymph nodes. There is no ascites or pneumoperitoneum. There are no peritoneal implants.

The liver has even contours and normal dimensions. No pathological alterations are noted in the internal structure of the organ.

Bone destructive changes are not determined.

Conclusion: Condition after right-sided hemicolectomy and rectal resection. Condition after duodenal resection for cancer. No CT signs of prolongatio morbi (Fig. 5).

According to the SF-36 Score questionnaire, the patient's quality of life indicators one year and nine months after the last operation correspond to the population norm (table).

The indicators of tumour markers of the gastrointestinal tract CA-242 and pancreas CA 19-9 (as of September 12, 2024) are within normal limits (< 0.5 U/ml and < 1.2 U/ml, respectively).

Discussion

The occurrence of metachronous cancer, first of the colon and then of the rectum, among gastrointestinal MPMTs is a common phenomenon [12, 13]. Such a chronological sequence of malignant tumours was also observed in our patient. However, he was diagnosed with duodenal adenocarcinoma simultaneously with rectal cancer, which is rare ($< 0.5\%$ of all gastrointestinal cancers) [20, 21]. Therefore, the adenocarcinoma was synchronous with respect to rectal cancer and metachronous with respect to colon cancer. Such variants of combinations of multiple carcinomas are not given in the literature.

Table. Patient quality of life indicators 1 year and 9 months after the last surgery according to SF-36 Score

Item	Percentage
Physical functioning	80
Role limitations due to physical health	100
Role limitations due to emotional problems	100
Energy/fatigue	65
Emotional well-being	80
Social functioning	100
Pain	100
General health	70
Health change	75

In the surgical treatment of synchronous cancer, we chose a two-stage strategy. Initially, we removed the rectal tumour due to the presence of partial colonic obstruction and uncertainty about the scope of the operation for duodenal adenocarcinoma.

The second stage (surgery for duodenal cancer) was planned after standard adjuvant chemotherapy. However, the patient refused the prescribed treatment and independently underwent an outpatient treatment course according to Dr. A. I. Potopalsky's method [16–19].

After three months, the second stage of operation was performed. Pancreatoduodenal resection was planned. The patient flatly refused the specified volume of surgical intervention, but due to intestinal bleeding, he agreed to resection of the part of the duodenum affected by the tumour. Thus, we performed resection of part of the descending and lower horizontal section of the duodenum with duodeno-duodenoanastomosis, Roux-en-Y gastrojejunostomy, through-the-stomach stitching in the prepyloric section, cholecystectomy, and drainage of the abdominal cavity.

Protective gastric suturing and Roux-en-Y gastroenteroanastomosis were performed to prevent food transit through the duodeno-duodenoanastomosis zone, which made it possible to prevent failure of its sutures.

Roux-en-Y gastroenterostomy presents a higher incidence of anastomotic peptic ulcers. In bariatric surgery, Roux-en-Y anastomotic ulcers are particularly common, accounting for 16 % of cases [22]. This is due to a number of causes, including the action of acid on the mucosa of the small intestine. The Roux-en-Y gastrojejunostomy area is more vulnerable to acid because the alkaline duodenal contents do not neutralize it, unlike other gastrojejunostomies. In our situation, a superficial ulcer up to 1.5 cm in diameter appeared directly below the anastomosis on the small intestine side, five months following surgery. Since the Roux-en-Y anastomosis was performed on the entire stomach, it was probably advisable to reinforce the procedure with a selective proximal vagotomy or selective vagotomy to avoid peptic ulcers. However, the peptic ulcer in this case responds well to standard conservative treatment.

Since the disease exhibited the characteristics typical of Lynch syndrome, namely the occurrence of a tumour at a young age (in our patient at the age of 39 years), most often in the right half of the colon, a high risk of synchronous or metachronous (recurrent) cancer, (as in this case) [23, 24], we conducted additional studies to confirm it after the second stage of the operation. Immunohistochemistry (IHC) was used to assess the status of proteins within the

mismatch repair (MMR) system. The screening revealed a deficiency (dMMR/MSI-H) characterized by the loss of MSH2 and MSH6, which is typically associated with Lynch syndrome due to an inherited mutation in the MSH2 gene. Genetic tests also confirmed the presence of an inherited MSH2 mutation (c.2042C > T, (p.Ala681Val)), which allowed us to diagnose Lynch syndrome in the patient.

Very few studies have identified variants of Lynch syndrome that result in damage to the colon and duodenum. A recent study by Hammoudi N, et al. [25] reported a specific risk of duodenal cancer in Lynch syndrome. The authors identified 154 patients with Lynch syndrome, including 85 patients with MSH2 mutations and 41 patients with MLH1 mutations. Seven of the 154 (4.5 %) had at least one duodenal lesion. Of these 7 patients, three had synchronous colorectal adenocarcinomas. The median age at diagnosis was 58 years (range: 49–73). Twelve lesion locations were: descending duodenum (n = 7), lower part (n = 2), duodenal bulb (n = 1), ampulla (n = 1), and fourth duodenum (n = 1). Three lesions were invasive adenocarcinomas. The incidence of duodenal involvement in patients with pathogenic MSH2 or MLH1 variants was 7.1 % (6 of 85) and 2.4 % (1 of 41), respectively. This suggests that patients with MSH2 mutations tend to have a higher risk of duodenal involvement (RR: 5.17; 95 % CI (0.8–60.07), p = 0.1307).

Amjad AI, et al. [26] reported the diagnosis of squamous cell cancer in the duodenum of a 58-year-old man with Lynch syndrome. Previous malignancies included two metachronous colorectal adenocarcinomas.

In our case, the histological analysis revealed that the synchronous duodenal and rectal tumours were adenocarcinomas, while the metachronous tumour of the right colon was a mucinous adenocarcinoma. We did not find similar variants of Lynch syndrome in the available literature.

Following the second stage, the patient underwent two independent courses of outpatient treatment according to Dr. A. I. Potopalsky's method.

After undergoing surgical treatment and receiving three courses of treatment according to Dr. A. I. Potopalsky's method, the patient's condition is satisfactory 1.9 months later. The quality-of-life indicators, as measured by the SF-36 questionnaire, align with the population norm, and the tumour markers of the gastrointestinal tract (CA-242) and pancreas (CA 19-9) are within normal limits. There are no signs of *prolongatio morbi*.

The radicality of the surgical intervention can absolutely explain the positive effect of treatment for synchronous rectal and duodenal cancer. At the

same time, the fact that the patient received three courses of the unregistered drug «Amitozyn» also attracts our attention.

Conclusions

A rare case of Lynch syndrome with synchronous primary rectal and duodenal cancer, which exhibited positive treatment outcomes after two-stage surgery without the use of conventional neoadjuvant and adjuvant therapies, is described. Instead, the patient independently received three courses of outpatient treatment according to Dr. A. I. Potopalsky's method. The lack of evidence regarding the effectiveness of this method raises doubt on its contribution to the achieved result, although its impact cannot be entirely disregarded. Patient follow-up is ongoing; therefore, the results may change in the future.

DECLARATION OF INTERESTS

The authors declare that they have no conflicts of interest.

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AUTHORS CONTRIBUTIONS

Work concept and design, writing the manuscript — Y.M. Susak; data collection and analysis — I. M. Leschyshyn, O. M. Lobanova; critical review — Y.M. Susak, I. M. Leschyshyn.

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Випадок метакхронного раку висхідної кишки та синхронного первинного раку прямої і дванадцятипалої кишки

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Множинні первинні злоякісні пухлини (МПЗП) — це дві або більше первинні злоякісні пухлини, які одночасно або послідовно виникли в одного пацієнта. Можуть походити з одного органа, парних органів, різних частин тієї самої системи або з різних органів. Синхронні МПЗП виникають протягом 6 міс після першої пухлини, метакхронні — пізніше 6 міс. Відомостей про метакхронний або синхронний колоректальний рак і рак дванадцятипалої кишки (ДПК) у доступних джерелах не знайдено.

Мета — представити результати лікування рідкісного випадку метакхронного раку висхідної кишки й синхронного первинного раку прямої та дванадцятипалої кишки.

Описано рідкісний випадок синхронного раку прямої та ДПК з позитивними результатами лікування після двоетапного хірургічного втручання без традиційної ад'ювантної терапії. Пацієнт самостійно пройшов курс за методикою доктора А.І. Потопальського. Хоча ефективність цього курсу не має доказової бази, його вплив не можна повністю ігнорувати. Пацієнт, чоловік, 1963 року народження, у 2002 р. переніс правобічну геміколектомію з приводу муцинозної аденокарциноми висхідного відділу товстої кишки III стадії (pT_{4p}N₁M₀). Улітку 2022 р. у нього з'явилися скарги на біль у правому підребер'ї, нудоту, загальну слабкість і домішки крові в калі. Обстеження виявило синхронний первинний рак ректосигмоїдного відділу та рак ДПК. Через часткову низьку кишкову непрохідність ухвалено рішення про двоетапне оперативне втручання. Перший етап (08.09.2022): передня резекція прямої кишки з накладанням сигморектоанастомозу (pT_{4c}N_{2b}M₀, III стадія, R-0). Пацієнт категорично відмовився від хіміотерапії та самостійно в позастаціонарних умовах пройшов курс лікування за методикою доктора А.І. Потопальського. Другий етап (08.12.2022 р.): резекція частини нисхідного та нижньо-горизонтального відділу ДПК із дуодено-дуоденоанастомозом, гастроеюностомія за методом Ру, наскрізне прошивання шлунка в препілоричному відділі, холецистектомія, дренування черевної порожнини (аденокарцинома ДПК, краї вільні: R-0). Під час контрольної комп'ютерної томографії через 1,9 міс після останньої операції ознак prolongatio morbi немає. Спостереження за пацієнтом триває.

Ключові слова: метакхронний рак, синхронний первинний рак прямої та дванадцятипалої кишки, хірургічне лікування, ад'ювантна терапія.