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Peritoneal Carcinomatosis in Patients with Locally Advanced Colon Cancer: Literature Review

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Aim: to analyse and systematise available literature data on the diagnosis and treatment of patients with locally advanced colon cancer with peritoneal carcinomatosis.

Key points. Even the obvious and rapid progress in the development of surgical and medicinal methods of treating patients with locally advanced colon cancer does not yet guarantee a complete cure. From 4 to 7 % of patients after radical resection report the progression of the disease — peritoneal carcinomatosis. The proportion of patients with isolated peritoneal lesions is about 2 %. This percentage of detection of peritoneal carcinomatosis at an early stage is directly related to the insufficient effectiveness of diagnostic methods, both laboratory and instrumental. To date, surgeons have accumulated quite a wealth of experience in performing diagnostic operations. Laparoscopy is a minimally invasive diagnostic tool and plays an important role in assessing the degree of dissemination, as it allows detailed visualization of the peritoneal surface, performing abdominal biopsies/flushes, and calculating the peritoneal carcinomatosis index (PCI).

The issue of early diagnosis of isolated peritoneal carcinomatosis is still relevant. and one of the most accurate methods of diagnosing small-focal peritoneal carcinomatosis is a repeated diagnostic operation (second look). Given the direct relationship between the severity of peritoneal spread and survival, it can be assumed that early detection of peritoneal carcinomatosis will increase the proportion of patients suitable for radical treatment and improve survival. To date, a sufficient number of studies have been conducted comparing the immediate and long-term results of treating patients with colorectal cancer using various combinations of cytoreductive surgery with/without hyperthermic intraperitoneal chemotherapy and/or systemic chemotherapy.

Conclusion. Evaluation of the current results of the randomized clinical trials in patients with peritoneal carcinomatosis of colon origin, treated with chemotherapy and in combination with targeted therapy, show fairly good results in overall and relapse-free survival.

Keywords: peritoneal carcinomatosis, colon cancer, HIPEC, cytoreductive surgery, chemotherapy, carcinomatosis index
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Перитонеальный канцероматоз у больных местнораспространенным раком толстой кишки: обзор литературы

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Цель: представить систематизированный анализ данных публикаций о методах диагностики и лечения больных местнораспространенным раком толстой кишки с перитонеальным канцероматозом.

Основные положения. Даже очевидный и стремительный прогресс хирургических и лекарственных методов лечения больных местнораспространенным раком толстой кишки пока не гарантирует полного излечения. От 4 до 7 % больных после радикальной резекции отмечают прогрессирование заболевания — перитонеальный канцероматоз. Доля пациентов с изолированным поражением брюшины составляет порядка 2 % — такой процент выявления перитонеального канцероматоза на ранней стадии напрямую связан с недостаточной эффективностью диагностических методов, как лабораторных, так и инструментальных. На сегодняшний день хирургами накоплен богатый опыт проведения диагностических операций. Лапароскопия является мини-инвазивным диагностическим инструментом и играет важную роль в оценке степени диссеминации, поскольку позволяет детально визуализировать поверхность брюшины, выполнить биопсию/смывы брюшной полости, а также подсчитать индекс перитонеального канцероматоза (peritoneal carcinomatosis index, PCI).

Вопрос ранней диагностики изолированного перитонеального канцероматоза по-прежнему актуален. И одним из точных методов диагностики мелкоочагового перитонеального канцероматоза является повторная диагностическая операция («second look»). Учитывая прямую связь между степенью тяжести перитонеального распространения и выживаемостью, можно предположить, что выявление перитонеального канцероматоза на ранней стадии увеличит долю пациентов, подходящих для радикального лечения, и улучшит выживаемость. К настоящему моменту проведено достаточное количество исследований, сравнивающих непосредственные и отдаленные результаты лечения больных колоректальным раком с применением различных комбинаций циторедуктивной хирургии с гипертермической интраперитонеальной химиотерапией и без таковой и/или системной химиотерапии.

Заключение. Анализ результатов крупных рандомизированных исследований у пациентов с колоректальным раком, осложненным перитонеальным канцероматозом, с применением химиотерапии и в комбинации с таргетной терапией показывает хорошие результаты общей и безрецидивной выживаемости.

Ключевые слова: перитонеальный канцероматоз, рак толстой кишки, HIPEC, циторедуктивная хирургия, химиотерапия, индекс канцероматоза

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Introduction

According to WHO data, colorectal cancer ranks fourth in global incidence and third in global mortality [1]. Despite significant progress in surgical and pharmacological treatments, disease progression — peritoneal carcinomatosis — is diagnosed in 4–7 % of cases even after radical resection [2, 3]. To fully assess the extent of peritoneal involvement, diagnostic laparotomy/laparoscopy is performed, and the Peritoneal Cancer Index (PCI), developed by P. Jacquet and P.H. Sugarbaker, is calculated. This index divides the abdominal cavity and pelvis into n regions.

Adequate assessment of peritoneal involvement requires meticulous adhesiolysis (if adhesions are present). The presence and size of lesions are evaluated: no lesions — LS0; lesions up to 0.5 cm — LS1; lesions up to 5.0 cm — LS2; lesions over 5 cm — LS3. If lesions coalesce, forming a continuous peritoneal lesion extending from the abdominal cavity into the pelvis, it is classified as LS3. Radiologists also use this index when calculating clinical PCI [4].

Analysis of data from patients participating in randomized prospective studies on metastatic colon cancer treatment outcomes (ARCAD database) revealed that peritoneal carcinomatosis occurs in 13 % of patients, with isolated peritoneal involvement found in only 1.8 % of cases [5]. J. Franko et al. determined that isolated peritoneal carcinomatosis is characterized not only by the presence of *BRAF* gene mutation (18 % vs. 9 %) and female sex (46 % vs. 37 %), but also by the primary tumor location in the proximal colon (38 % vs. 16 %), metachronous metastasis (67 % vs. 34 %), and poor performance status at the time of metastatic diagnosis (11 % vs. 5 %), compared to metastases in other organs [5].

According to Y. Klaver et al., peritoneal dissemination is a poor prognostic factor: the median survival of such patients without appropriate treatment is only about 5 months, while with systemic chemotherapy based on 5-fluorouracil and leucovorin, it ranges from 5.2 to 12.6 months [6].

Russian clinical guidelines stipulate adjuvant chemotherapy for patients with pT4-N0 or pT1-3N$^+$ cancer, as well as for patients with colon cancer pT3N0M0 in the presence of negative prognostic factors, namely:

- surgery performed under conditions of bowel obstruction or peritonitis;
- surgery with inadequate lymph node dissection (< 12 lymph nodes removed);
- poorly differentiated tumor;
- lymphovascular/perineural invasion;
- tumor budding;
- postoperative carcinoembryonic antigen > 2.35 ng/mL (level of evidence — C).

Adjuvant chemotherapy with the XELOX regimen for 3 months or FOLFOX for 6 months is prescribed for colon cancer pT4N0M0, regardless of microsatellite instability status. The same treatment regimen applies to pT1-3N+M0 cancer. Upon completion of the course, a follow-up examination is performed. In case of disease progression and isolated peritoneal metastases, the possibility of peritoneal metastasectomy should be considered after achieving remission following 2–6 months of systemic therapy [7]. A similar adjuvant chemotherapy regimen is described in the

RUSCO 2023 guidelines [8]. But is everything really so clear-cut from a practical standpoint?

Non-invasive diagnosis of peritoneal carcinomatosis

The proportion of patients with isolated peritoneal involvement is approximately 2 %. The low detection rate of peritoneal carcinomatosis at an early stage is due to the insufficient effectiveness of diagnostic methods, both laboratory and instrumental [9]. According to C. Dromain et al., the sensitivity of computed tomography for detecting peritoneal metastases ranges from 60 to 79 %, but falls below 30 % if the size of peritoneal lesions is less than 5 mm [9]. Consequently, peritoneal carcinomatosis is often detected at a late stage, when peritoneal metastasectomy — cytoreductive surgery or optimal cytoreduction — is feasible as a first step in only 20–25 % of patients [10].

Results of a meta-analysis by A. Laghi et al., which included 22 studies and 954 patients, showed that the diagnostic accuracy for peritoneal carcinomatosis was 83 %. The authors' comparative analysis of computed tomography and positron emission tomography did not reveal fundamentally significant differences between the methods in detecting peritoneal carcinomatosis. However, the sensitivity and specificity of positron emission tomography were higher than those of conventional computed tomography — 82 and 93 % vs. 66 and 77 %, respectively. A correlation was also noted between the levels of the clinical peritoneal cancer index (C-PCI) and the surgical one (S-PCI). Nevertheless, computed tomography underestimation of the extent of peritoneal metastasis is reported at 12–33 % [11]. An evaluation of the effectiveness of magnetic resonance imaging, based on the study by Y. Satoh et al., showed that the sensitivity of positron emission tomography (89 %) was higher than that of magnetic resonance imaging (56 %) and computed tomography (76 %). The sensitivity of diffusion-weighted magnetic resonance imaging (DWI-MRI) was comparable to that of positron emission tomography — 84 % [12]. Thus, computed tomography undoubtedly offers advantages over other imaging methods in diagnosing peritoneal carcinomatosis, yet it demonstrates low sensitivity for detecting isolated peritoneal carcinomatosis.

Invasive diagnostic methods for peritoneal carcinomatosis

The issue of early diagnosis of isolated peritoneal carcinomatosis remains relevant today. One method for diagnosing small-focus peritoneal carcinomatosis is a second-look diagnostic surgery. This concept was first described by W.O. Griffen Jr. et al. in 1948 and was based on performing repeat diagnostic surgeries in patients with a high risk of recurrence or peritoneal dissemination despite radical surgery for the primary tumor [13].

Today, the world has accumulated quite a wealth of experience in the use of diagnostic operations. Diagnostic laparoscopy is a minimally invasive diagnostic tool and plays a crucial role in detecting and assessing peritoneal carcinomatosis progression, as it allows detailed visualization of the peritoneal surface, performance of biopsies/peritoneal washings, and calculation of the PCI. Nevertheless, results from the multicenter prospective study by I. Thomassen et al., involving 6687 patients, showed that during primary tumor surgeries performed laparoscopically, peritoneal carcinomatosis was diagnosed less frequently than with traditional open surgery. Peritoneal carcinomatosis was diagnosed in 1.4 % of patients undergoing laparoscopic resection, in 5.0 % undergoing open surgery, and in 3.3 % requiring conversion ($p < 0.001$) [14].

Methods for imaging during minimally invasive diagnostics continue to be refined. French researchers led by H. Najah in 2017 evaluated the effectiveness of chromoendoscopy (Fujinon Intelligent Chromo Endoscopy, FICE) in 13 patients with peritoneal carcinomatosis confirmed by computed tomography. The researchers identified the optimal setting (channel 2 out of 9 possible) for detailed visualization of peritoneal vascular architecture ($p < 0.001$), differentiation between adjacent organs ($p < 0.001$), and detection of peritoneal carcinomatosis ($p < 0.001$) [15].

E. Lieto et al. in their study demonstrated the effectiveness of intraoperative visualization using Indocyanine Green Fluorescence Imaging (ICG-FI), which increased the sensitivity of the method from 72.4 % (when using traditional diagnostic procedures) to 96.9 % (when using ICG-FI). The PCI also increased (from 7 to 10) with a reported specificity of 60–100 % ($p = 0.027$). This technique proved less effective for mucinous tumors, though [16].

The study by N.J. Harlaar et al. pioneered the use of a tumor-targeted molecular fluorescent agent (bevacizumab conjugated with the near-infrared dye IRDye800CW, which binds to VEGF-A). Results showed 100 % sensitivity and specificity up to 54 % [17].

According to results from the study by J. Segelman et al. involving 11,124 patients,

peritoneal metastases were detected in 8.3 % of patients, with metachronous peritoneal carcinomatosis diagnosed in 4.3 % of cases. Multivariate analysis identified independent predictors of metachronous peritoneal carcinomatosis:

- tumor location in the right colon (OR = 1.77; 95% CI: 1.31–2.39; $p = 0.002$);
- pT4 tumors (OR = 9.98; 95% CI: 3.10–32.11; $p < 0.001$ for T4);
- N^+ status with pathological examination of fewer than 12 lymph nodes (OR = 7.41; 95% CI: 4.78–11.51; $p < 0.001$):
- tumor perforation (OR = 2.11; 95% CI: 1.66–2.69; $p < 0.001$);
- non-radical removal of the primary tumor (OR = 2.75; 95% CI: 2.10–3.61; $p < 0.001$).

The study also noted that patients over 70 years old had a reduced risk of metachronous peritoneal carcinomatosis (OR = 0.69; 95% CI: 0.55–0.87; $p = 0.003$) [18].

The study by V.P. Bastiaenen et al. deserves special attention, focusing on patients with colon cancer types pT4aN0M0 and pT4bN0M0. The scientists compared the incidence of peritoneal carcinomatosis in colorectal cancer after surgical treatment. The study included 665 individuals with pT4a and 187 with pT4b tumors of various locations. The median follow-up was 38 months (interquartile range — 23–60). The 5-year cumulative incidence of peritoneal metastases was 24.7 and 12.2 % for pT4a and pT4b categories, respectively ($p = 0.005$). Independent predictors of metachronous peritoneal carcinomatosis were: female sex; tumor location in the right colon; peritumoral abscess; pT4a resection, pN2, R1 resection; presence of signet ring cells; postoperative infectious complications. Local recurrence rates during the same period were identical for pT4a and pT4b cancer (14 %; $p = 0.138$). Distant metastases occurred in 35 and 28 % of the pT4a and pT4b groups, respectively ($p = 0.138$). Five-year recurrence-free survival and overall survival were 54 % vs. 62 % ($p = 0.095$) and 63 % vs. 68 % ($p = 0.148$) for pT4a and pT4b patients, respectively. Thus, it was proven that patients with pT4a colon cancer have a higher risk of metachronous peritoneal carcinomatosis than patients with pT4b. The authors' observation regarding the importance of this finding for early peritoneal carcinomatosis detection, which could in turn change adjuvant treatment strategy, is noteworthy [19].

The multicenter randomized COLOPEC trial, initiated by the group of Dutch scientists, included patients after surgical treatment for colon cancer who had a high risk of peritoneal metastasis spread (T4N0-2M0 or bowel wall perforation). After surgery, 204 patients were divided into two groups: those who received adjuvant hyperthermic intraperitoneal chemotherapy (HIPEC) and those who did not. The primary endpoint was the incidence of peritoneal metastases. To monitor peritoneal carcinomatosis development, delayed diagnostic laparoscopy was performed 18 months after surgical removal of the primary tumor. The statistical hypothesis assumed that in the group receiving intraperitoneal chemotherapy, the incidence of peritoneal carcinomatosis would decrease from 25 to 10 %.

Interim results published in 2019 showed no difference between the groups in peritoneal metastasis incidence or survival until metastasis development (HR = 0.86; 95% CI: 0.51–1.54). The authors concluded that routine use of adjuvant HIPEC does not improve long-term outcomes in patients with pT4 cancer and/or tumor perforation. However, a significant finding was the diagnosis of peritoneal carcinomatosis within nearly two years of follow-up in 21 % of patients, warranting continued research in this direction [20]. By the end of 2023, researchers published the 5-year overall and recurrence-free survival rates. Five-year overall survival for patients receiving combination of systemic chemotherapy and HIPEC (adjuvant chemotherapy + hyperthermic intraperitoneal chemotherapy) followed by adjuvant systemic chemotherapy and patients receiving systemic chemotherapy alone were virtually identical (69.6 % vs. 70.9 %; $p = 0.569$). Recurrence-free survival in the group receiving adjuvant chemotherapy with hyperthermic intraperitoneal chemotherapy was 63.9 %, compared to 63.2 % in the systemic chemotherapy group, with no significant difference found [21].

In 2019, the protocol for the COLOPEC 2 trial was published — the authors decided to focus on early detection of isolated peritoneal carcinomatosis. The aim of this study is to determine the effectiveness of "second-look" surgery and the additional effectiveness of "third-look" surgery after a negative "second-look" in detecting localized peritoneal carcinomatosis in patients after completion of primary treatment for pT4N0-2M0 colon cancer. The study plans to include 389 patients. At 6 and 9 months after primary tumor removal, patients will undergo computed tomography, followed by diagnostic laparoscopy no earlier than 1 month later. It is anticipated that peritoneal carcinomatosis will be detected in 10 % of patients; the remaining patients will be

randomized into two groups: the investigational group will undergo another diagnostic laparoscopy at 18 months, no earlier than 1 month after computed tomography. Patients in the second group will undergo computed tomography only. The researchers hypothesize that "second-look" diagnostic laparoscopy will detect focal peritoneal carcinomatosis in 10 % of patients, and in cases with a negative result, "third-look" diagnostic laparoscopy will detect peritoneal carcinomatosis in an additional 10 % compared to routine follow-up methods for this patient category. Given the direct correlation between the severity of peritoneal disease and survival, it can be assumed that detecting peritoneal carcinomatosis at an early stage will increase the proportion of patients suitable for radical treatment and subsequently improve survival [22].

Undoubtedly, diagnostic laparoscopy combined with various imaging methods offers advantages over radiological diagnostics and represents one of the most promising approaches for detecting isolated peritoneal carcinomatosis. Importantly, careful patient selection for diagnostic laparoscopy is crucial. This requires clear definition of risk factors for peritoneal carcinomatosis development, which should subsequently serve as criteria for patient selection.

Cytoreductive surgery and intraperitoneal chemotherapy as treatment methods for patients with peritoneal metastases

The topic of cytoreductive surgery as a method for local control of peritoneal carcinomatosis cannot be overlooked. It is performed either alone or in combination with hyperthermic intraperitoneal chemotherapy (HIPEC). The safety and efficacy of this approach in routine practice remain controversial to this day.

For instance, results from a multicenter study by D. Elias et al. involving 523 patients showed that using cytoreductive surgery combined with HIPEC achieved a 3-year survival rate of 41 % and a 5-year survival rate of 27 %. Multivariate analysis identified favorable prognostic factors: initially low PCI, absence of lymph node involvement, administration of adjuvant chemotherapy, and achievement of CC-0 cytoreduction. Notably, median survival increased to 32.5 months with complete CC-0 cytoreduction, compared to 18 months with suboptimal cytoreduction [23]. However, contradictions exist — results from other studies indicate that this approach does not increase survival or reduce the rate of peritoneal carcinomatosis progression.

A multicenter randomized phase 3 study by D. Goere et al. assessed the need for repeat "second-look" laparotomy with HIPEC after completing adjuvant chemotherapy. It included 150 patients at high risk for peritoneal carcinomatosis development. All patients underwent radical surgical treatment followed by adjuvant chemotherapy with oxaliplatin and fluoropyrimidines, with or without targeted therapy. Patients without disease progression on computed tomography and with normal tumor marker levels were randomized to either observation or laparotomy with HIPEC. In the surgery group (n = 71), peritoneal metastases were detected in 52.1 % of patients, with a mean PCI of 4 (interquartile range — 0–26). HIPEC with oxaliplatin was performed in 92 % of this group. Grade 3–4 postoperative complications (according to Clavien — Dindo classification) occurred in 41 % of patients. Three-year recurrence-free survival was 51 % in the control group vs. 44 % in the HIPEC group (p = 0.75); three-year overall survival was 80 % vs. 79 % (p = 0.63); and the rate of peritoneal involvement was 32 % vs. 33 % (p = 0.67) [24].

The authors of the multicenter randomized phase 3 PRODIGE 7 trial favor cytoreductive surgery without HIPEC. The study included 265 patients with colorectal cancer and confirmed peritoneal carcinomatosis (PCI < 25). After randomization, 133 patients (Group 1) underwent cytoreductive surgery in combination with HIPEC (oxaliplatin) and 132 underwent cytoreductive surgery alone (Group 2). Optimal cytoreduction (CC-0) was achieved in 89 % of Group 1 and 92 % of Group 2 (p = 0.54). Statistically significant differences were observed in operation duration (median — 365 minutes in Group 1 vs. 300 minutes in Group 2; p = 0.00010) and hospital stay (18 days vs. 13 days; p = 0.0010). No significant difference was found in early postoperative complications (within 1–30 days; 42 % vs. 32 %; p = 0.083). However, the rate of late postoperative complications (within 31–60 days) was higher in the group receiving combination "cytoreductive surgery + HIPEC" than in the group with application of cytoreductive surgery alone (26 % vs. 15 %; p = 0.035). Median follow-up was 63.8 months (interquartile range — 53.0–77.1). Median overall survival was 41.7 months (95% CI: 36.2–53.8) in the "cytoreductive surgery + HIPEC" group and 41 months (95% CI: 35.1–49.7) in the cytoreductive surgery group (HR = 1.00; 95.37 % CI: 0.63–1.58; p = 0.99). According to the authors, given the lack of overall survival benefit from adding

HIPEC to cytoreductive surgery and the higher rate of late postoperative complications with this combination, cytoreductive surgery alone should be considered the cornerstone of treatment for colorectal cancer patients with peritoneal carcinomatosis [25].

Cytoreductive surgery and systemic chemotherapy

To date, a sufficient number of studies have been conducted comparing the immediate and long-term outcomes of treating colorectal cancer patients using various combinations of cytoreductive surgery with/without intraperitoneal chemotherapy and/or systemic chemotherapy.

In our view, the authors of 4 studies included in the meta-analysis by R. Mirnezami et al. chose the most aggressive combination. The meta-analysis used data from 342 patients with confirmed peritoneal carcinomatosis. One group (187 patients) underwent cytoreductive surgery combined with intraperitoneal chemotherapy, while the remaining 155 participants received only systemic chemotherapy. According to the study, the two-year survival rate in the first group (cytoreductive surgery + intraperitoneal chemotherapy) was 61.75 %, compared to 34.5 % in the group receiving only systemic therapy (OR = 2.78; 95% CI: 1.72–4.51; p = 0.001). Similarly, five-year survival was higher in the cytoreductive surgery group (31 % vs. 8.25 %; OR = 4.07; 95% CI: 2.17–7.64; p = 0.001) [26]. The authors found that survival significantly correlated with the completeness of cytoreduction: 5-year survival was 45 %, 8 %, and 0 % in patients undergoing R1 (complete macroscopic tumor removal), R2a (residual tumor nodules < 2.5 mm thick), and R2b resection (residual tumor nodules > 2.5 mm thick), respectively.

Results from one such study demonstrated the advantage of cytoreductive surgery over systemic chemotherapy. This meta-analysis included 20 studies, pooling data from 3137 colorectal cancer patients diagnosed with resectable peritoneal and liver metastases. According to M.C.E. Polderdijk et al., the median overall survival for these patients undergoing cytoreductive surgery was 26.4 months (95% CI: 22.4–30.4), with overall 3-year and 5-year survival rates of 34 and 25 %, respectively. In patients with isolated peritoneal involvement, the postoperative complication rate was lower (22 %) than in the group with both liver and parietal peritoneal metastases (40 %), a statistically significant difference (p = 0.0014). However, mortality rates and reoperation rates did not differ significantly (p = 0.2744). The authors conclude that combined surgery for peritoneal and synchronous liver metastases is an acceptable approach and leads to improved survival compared to systemic therapy administered upon progression [27].

Results of a retrospective analysis conducted by D.J. Repullo et al. in Belgium between 2008 and 2017 demonstrated the advantage of using cytoreductive surgery combined with intraperitoneal chemotherapy in patients with colorectal peritoneal metastases. The study included 125 patients with peritoneal carcinomatosis: in Group 1 (n = 67), cytoreductive surgery with intraperitoneal chemotherapy in combination with intraoperative systemic chemotherapy was performed, and in Group 2 (n = 56), only cytoreductive surgery with intraperitoneal chemotherapy was performed. Median follow-up was 54 ± 5 months. Overall survival at 1, 3, and 5 years in Group 1 was 98, 59 and 35 % compared to 97, 77, and 56 % in Group 2 (HR = 1.46; 95% CI: 0.87–2.47; p = 0.155). The 1-, 3-, and 5-year recurrence-free survival in Group 1 was 47, 13 and 6 % compared to 58, 29 and 26 % in Group 2, respectively (HR = 1.22; 95% CI: 0.78–1.92; p = 0.376) [28].

The role of systemic drug therapy

At this stage, oncologists face a challenging task — stabilizing and achieving maximum possible regression of peritoneal carcinomatosis, assessed as a reduction in the PCI level. Accomplishing this task, in turn, will enable the implementation of surgical treatment methods and, consequently, improve overall survival. According to results from a meta-analysis conducted by R. Marques et al., which included 8 randomized studies with a total of 1772 patients, the use of the FOLFOXIRI regimen led to an increase in the objective response rate (objective response rate — 60.6 % vs. 47.6 %; complete response — 7.3 % vs. 4.1 % with FOLFOX/FOLFIRI). The authors concluded that using the FOLFOXIRI regimen increased the rate of cytoreductive surgeries achieving complete cytoreduction (CC-0) (18.2 % vs. 8.7 %; p = 0.03) [29].

Unresectable metastatic disease

The situation is considerably more complex for treating unresectable metastatic colorectal cancer and patients with negative mutational status. However, administering systemic chemotherapy while considering the location of the primary tumor relative to the colon, along with assessing mutational status, contributes to improved overall survival when the most effective

Table 1. Clinical studies on the treatment of patients using various combinations of cytoreductive surgery, hyperthermic intraperitoneal chemotherapy and systemic chemotherapy

Таблица 1. Клинические исследования по лечению больных с применением различных комбинаций циторедуктивной хирургии, гипертермической внутрибрюшной химиотерапии и системной химиотерапии

Author, year ***Автор, год***	***n***	**Treatment regimen** ***Схема лечения***	**Postoperative complications / mortality, %** ***Послеоперационные осложнения / летальность, %***	**3-/5-year overall survival rate, %** ***3-/5-летняя общая выживаемость, %***	**3-/5-year disease-free survival rate, %** ***3-/5-летняя безрецидивная выживаемость, %***
D. Elias et al., 2010 [23]	523	CRS + HIPEC *ЦРХ + HIPEC*	31/3.3	–/27	–/10
D. Goere et al., 2020 [24]	150	aCT / *aXT* + «second look» + HIPEC	41/0	79/–	44/–
F. Quénet et al., 2017 [25] (PRODIGE 7)	265	CRS vs. CRS + HIPEC *ЦРХ vs. ЦРХ + HIPEC*	42/2 vs. 32/3	–/39 vs. –/29	–/14.8 vs. –/13.1
R. Mirnezami et al., 2014 [26]	342	CRS + HIPEC vs. CT *ЦРХ + HIPEC vs. XT*	72/7 vs. 8/6	61.75/31 vs. 34.5/8.25	–/– vs. –/–
M.C.E. Polderdijk et al., 2022 [27]	3137	CRS + HIPEC *ЦРХ + HIPEC*	39.9/5.3	14.4/–	33.9/24.6
J. Repullo et al., 2021 [28]	137	nCT + CRS + HIPEC vs. CRS + HIPEC *нХТ + ЦРХ + HIPEC vs. ЦРХ + HIPEC*	81.1/93.2 vs. 1/1	59/35 vs. 77/56	13/6 vs. 20/26

Note: *CRS — cytoreductive surgery; HIPEC — hyperthermic intraperitoneal chemotherapy; CT — chemotherapy; aCT — adjuvant chemotherapy; nCT — neoadjuvant chemotherapy; "second look" — repeat diagnostic surgery.*

Примечание: *ЦРХ — циторедуктивная хирургия; HIPEC — гипертермическая внутрибрюшная химиотерапия; ХТ — химиотерапия; аХТ — адъювантная химиотерапия; нХТ — неоадъювантная химиотерапия; «second look» — повторная диагностическая операция.*

systemic chemotherapy regimen is selected. This is supported by data from several studies. The authors of the multicenter phase III randomized TRIBE study report that superior progression-free survival (23.7 months vs. 31 months; $p = 0.010$) and overall survival were achieved with "FOLFOXIRI + bevacizumab" therapy only in patients with primary tumors located in the right colon. For right-sided tumors, the FOLFOXIRI regimen without bevacizumab was effective regardless of mutational status [30].

The work by J. Holch et al., which pooled results from 13 randomized clinical trials, merits attention. A meta-analysis of the PRIME and CRYSTAL studies shows that primary tumor location is a prognostic factor for improved survival when using anti-EGFR (epidermal growth factor receptor) antibody targeted therapy combined with standard chemotherapy in patients with RAS wild-type tumors (overall survival, hazard ratio for left-sided location — 0.69; 95% CI: 0.58–0.83; $p < 0.0001$; hazard ratio for right-sided location — 0.96; 95% CI: 0.68–1.35; $p = 0.802$).

A meta-analysis of the FIRE-3/AIO KRK0306, CALGB/SWOG 80405, and PEAK studies showed that patients with left-sided RAS wild-type tumors had increased overall survival when treated with anti-EGFR targeted therapy compared to anti-VEGF (vascular endothelial growth factor) targeted therapy (HR = 0.71; 95% CI: 0.58–0.85; $p = 0.0003$). For right-sided tumors, the use of bevacizumab was numerically associated with longer survival (HR = 1.3; 95% CI: 0.97–1.74; $p = 0.081$). This meta-analysis demonstrates that primary tumor location has prognostic significance in metastatic colorectal cancer. Furthermore, it confirms the conclusion that anti-EGFR antibody therapy should be used for patients with left-sided RAS wild-type metastatic

colorectal cancer. For right-sided metastatic colorectal cancer, chemotherapy combined with bevacizumab is also a treatment option; however, in the researchers' opinion, the most effective option for this patient category remains to be determined [10].

A. Avallone et al. presented results from the randomized phase II IMPROVE trial, based on data from patients with unresectable, previously untreated RAS/BRAF wild-type metastatic colorectal cancer. They compared the efficacy of continuous "FOLFIRI + panitumumab" treatment until progression vs. administering the same regimen for 8 cycles followed by a treatment-free interval until progression, after which another 8 cycles were administered until progression occurred. The primary endpoint was 1-year progression-free survival. Patients received

Table 2. Clinical trials for the treatment of patients with unresectable metastatic colorectal cancer
Таблица 2. Клинические исследования по лечению больных с нерезектабельным метастатическим колоректальным раком

Author, year ***Автор, год***	***n***	**Primary endpoint** ***Первичная конечная точка***	**Scheme of systemic chemotherapy** ***Схема проведения системной химиотерапии***	**Number of cycles** ***Количество циклов***	**Survival rate, months** ***Выживаемость, мес.***	**Progression-free survival, months** ***Выживаемость без прогрессирования, мес.***
M. Koopman et al., 2006 [34] (CAIRO)	820	Overall survival, stabilization *Общая выживаемость, стабилизация*	Capecitabine, irinotecan, XELOX vs. XELIRI, XELOX *Капецитабин, иринотекан, XELOX vs. XELIRI, XELOX*	6	10.4 vs. 7.8	5.8 vs. 7.7
M. Koopman et al., 2007 [35] (CAIRO2)	755	Overall survival, stabilization *Общая выживаемость, стабилизация*	Capecitabine, oxaliplatin + bevacizumab vs. Capecitabine, oxaliplatin + bevacizumab + cetuximab *Капецитабин, оксалиплатин + бевацизумаб vs. Капецитабин, оксалиплатин + бевацизумаб + цетуксимаб*	9	15.2 vs. 13.9	6.6 vs. 7.2
R.P. Marques et al., 2017 [29] (PROSPERO)	1732	Overall survival, stabilization *Общая выживаемость, стабилизация*	FOLFOXIRI vs. FOLFOX or / *или* FOLFIRI	н.д.	23.4 vs. 16.7	14.1 vs. 9.2
C. Cremolini et al., 2014 [30] (TRIBE)	508	Overall survival, stabilization *Общая выживаемость, стабилизация*	FOLFOXIRI + bevacizumab vs. FOLFIRI + bevacizumab *FOLFOXIRI + бевацизумаб vs. FOLFIRI + бевацизумаб*	12	31.0 vs. 25.8	12.1 vs. 9.7
C. Antoniotti et al., [32] (TRIBE-2)	679	Overall survival, stabilization *Общая выживаемость, стабилизация*	mFOLFOX6 + bevacizumab — progression — FOLFIRI + bevacizumab vs. FOLFOXIRI + bevacizumab *mFOLFOX6 + бевацизумаб — прогрессирование — FOLFIRI + бевацизумаб vs. FOLFOXIRI + бевацизумаб*	8	22.5 vs. 27.4	5.6 vs. 6.2
A. Avallone et al., 2023 [31] (IMPROVE)	137	Progression-free survival, overall survival *Выживаемость без прогрессирования, общая выживаемость*	FOLFIRI + panitumumab (12 months) vs. FOLFIRI + panitumumab (8 cycles), break *FOLFIRI + панитумумаб (12 мес.) vs. FOLFIRI + панитумумаб (8 циклов), перерыв*	8	31.3 vs. 32.2	11.4 vs. 18.1

"FOLFIRI + panitumumab" treatment continuously (Group A, 69 patients) or intermittently (Group B, 67 patients). With a median follow-up of 28 months (interquartile range — 21–37 months), median progression-free survival was 11.4 months (95% CI: 9.1–13.7) in Group A and 18.1 months (95% CI: 6.8–29.3) in Group B. Median progression-free survival for left-sided colon tumors was 11.7 months (95% CI: 9.1–14.3) in Group A and 23.9 months (95% CI: 15.0–32.9) in Group B, compared to 10.7 months (95% CI: 7.3–14.1) and 7.9 months (95% CI: 5.7–10.1) for right-sided tumors. Overall survival was 31.0 months (95% CI: 24.7–37.2) in Group A and 32.2 months (95% CI: 23.6–40.8) in Group B [31].

Thus, administering 8 cycles of first-line with "FOLFIRI + panitumumab" systemic chemotherapy followed by chemotherapy holidays, repeated upon progression, improved progression-free survival compared to treatment with "FOLFIRI + panitumumab" scheme until progression [31].

Conclusion

Computed tomography demonstrates the highest sensitivity compared to other non-invasive diagnostic methods for peritoneal carcinomatosis.

Literature analysis indicates the promise of the "second-look" approach, both alone and in combination with fluorescent technologies, for diagnosing peritoneal carcinomatosis. However, definitive conclusions about the efficacy of any specific method will only be possible after studies involving larger patient cohorts.

The literature review revealed a substantial number of studies dedicated to the problem of peritoneal carcinomatosis in colorectal cancer patients. Researchers compare various combinations of treatment modalities, such as cytoreductive surgery combined with intraperitoneal chemotherapy, and sometimes obtain conflicting results. This indicates that peritoneal carcinomatosis remains and will continue to be a significant challenge in this particularly difficult patient population for the foreseeable future. Performing cytoreductive surgery with intraperitoneal chemotherapy is considered a safe and effective procedure, provided it is conducted in high-tech surgical centers equipped with the necessary resources and experienced personnel.

To date, results from large, randomized studies in patients with colorectal cancer complicated by peritoneal carcinomatosis, utilizing systemic chemotherapy and in combination with targeted therapy, show encouraging overall and recurrence-free survival rates.

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