

DIAGNOSTIC AND TREATMENT METHODS

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**INTERVENTIONAL METHODS
FOR TREATING CHRONIC PAIN SYNDROME
IN ONCOLOGICAL PRACTICE:
A SYSTEMATIC REVIEW**

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Currently, chronic pain syndrome (CPS) is considered an independent pathology holding significant importance in cancer patients. It has been established that at the early stage of malignant neoplasms (MN), patients experience chronic pain in 35-47% of cases, during full manifestations the number goes up to 78%, and in 98% of patients with generalized forms of malignant neoplasms, chronic pain is the dominant symptom. Despite numerous studies devoted to CPS in oncology, this problem remains relevant.

Purpose of the Study: conducting a systematic review of the literature based on the results of using interventional methods for treating CPS in oncological practice.

Materials and Methods: the authors carried out a systematic search on the subject for articles in English and Russian published between January 1970 and December 2023 using the following databases: Medline, Cochrane Library, and eLibrary.

Results: the systematic review included 15 studies that used interventional treatments for cancer-related CPS. We have established that the use of the analyzed methods in most cases has provided a sufficient level of pain relief in patients with CPS.

Conclusion. Based on the results of the systematic review, we see that there is a need to develop specialized criteria for choosing an interventional method and creating an algorithm for treating drug-resistant CPS in oncology patients.

Keywords: chronic pain syndrome, cancer pain, neurolysis of the celiac plexus, neurodestruction, neuromodulation, palliative care, malignant neoplasm

Introduction. In the last decade, there has been a trend toward increased morbidity and mortality from malignant neoplasms (MN) [7, 8]. According to the Global Cancer database Observatory (GLOBOCAN), newly diagnosed cases of MN are expected to increase by 47% (28.4 million) by 2040 with a steady increase in patients with chronic pain syndrome (CPS) caused by the tumor process.

CPS in oncological practice is one of the main symptoms causing emotional and physical suffering in patients with cancer. It has been established that in 78-90% of patients with generalized forms of MN, pain is the leading symptom of the underlying disease, which significantly reduces their quality of life, representing a serious medical and social problem [7, 23].

The International Association for the Study of Pain (IASP) has developed a new classification, which provides for the etiology and pathogenesis of CPS in MN [9].

In the treatment of pain, narcotic and non-narcotic analgesics are used according to the three-step WHO Analgesic Ladder [1, 2]. Data from studies of pain therapy indicate that its effectiveness reaches 35-80%. If the analgesic ladder is insufficiently effective, WHO recommends using interventional methods in treating CPS [1, 3, 5, 21]. Such methods of treating CPS can be divided into two categories: neuromodulation and neurodestruction [1-3, 8]. We have analyzed and systemized the information on using neuromodulation and neurodestruction methods in CPS in cancer patients for the basis of this study.

Purpose of the Study: conducting a systematic review of the literature based on the results of using interventional methods for treating CPS in oncological practice.

Materials and Methods. Search and Selection Strategy for Literary Data.

The authors have carried out a systematic search of specialized literature in Russian and English using Medline, Cochrane Library, and eLibrary databases published between January 1970 and December 2023 on interventional methods of treating CPS in cancer patients. The search was carried out using the following keywords for English-language databases: "neurolysis of the celiac plexus", "intrathecal opioid administration in the treatment of pain in cancer patients", "peripheral nerve blocks for oncology", and for eLibrary: "celiac plexus neurolysis", "morphine pumps in oncology", "peripheral blockades in oncology". The data obtained were assessed by two independent experts, and any disagreements between the experts were resolved through group discussion. At the second and third stages, we have analyzed abstracts and articles that did not meet the inclusion criteria were excluded. We have also examined full-text publications (Figure).

This study was carried out in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [28].

Criteria for Selecting Literary Sources:

(1) The study includes retrospective and prospective cohort studies, case-control studies, systematic reviews, and clinical cases studying minimally invasive surgical interventions for the treatment of CPS in oncology practice.

(2) Types of interventions: percutaneous and transgastric celiac plexus neurolysis, implantable programmable morphine pumps, peripheral nerve plexus blocks.

(3) Study design: includes all types of studies describing the use of interventional methods for treating CPS in cancer patients.

Assessing the Risk of Bias and Systematic Error in Studies. The risk of systematic errors was determined us-

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ing the Newcastle-Ottawa Scale (NOS) [30].

Results. Literary Data Search. This systematic review included 15 publications that used interventional methods for treating CPS in oncological practice [1, 4, 5, 6, 10, 11, 14, 15, 17, 18, 20, 22, 24, 26]. The characteristics of the studies included in the systematic review are presented in Table 1.

The systematic review presents the most commonly used methods for treating CPS in oncological practice.

Neuromodulatory Treatment for CPS. Intrathecal and Intraspinal Opioids Administration. Neuromodulatory treatment methods include intrathecal and epidural administration of opioids [23, 27, 29]. For the first time in 1979, Wang et al. applied and proved the effectiveness of intrathecal morphine injections in treating CPS in cancer patients. The main advantage of such methods of administration is adequate pain relief with low doses of opioids and a long effective period, which significantly reduces the likelihood of developing adverse drug effects [25]. This therapy positively affects the gelatinous substance of the dorsal horns of the spinal cord [5, 20, 23].

When choosing a method of interventional treatment of CPS, there has to be a detailed selection of patients, which includes determining the general somatic and mental status, the etiology and pathogenesis of CPS, as well as the predicted life expectancy [11, 14].

Percutaneous implantable epidural catheters today are in most cases used in the early postoperative period to relieve acute pain, and they are also used for a test study before installing long-term intrathecal therapy with a morphine pump, especially with a relatively unfavorable prognosis (less than 3 months) [20, 23]. The disadvantages of these devices include local and generalized infection, migration, kinking, and obstruction of catheters [5, 14]. In the work published by Hsieh et al., the authors have assessed the effectiveness and safety of epidural opioid administration in cancer patients with end-stage cancer. The systematic review included 9 randomized trials (n=340) and 15 observational studies (n=926). The authors found that epidural administration of opioids in combination with local anesthetics or adjuvants had the best analgesic effect. There was also no significant difference in the dynamics of pain between bolus administration and continuous epidural infusion of morphine [13].

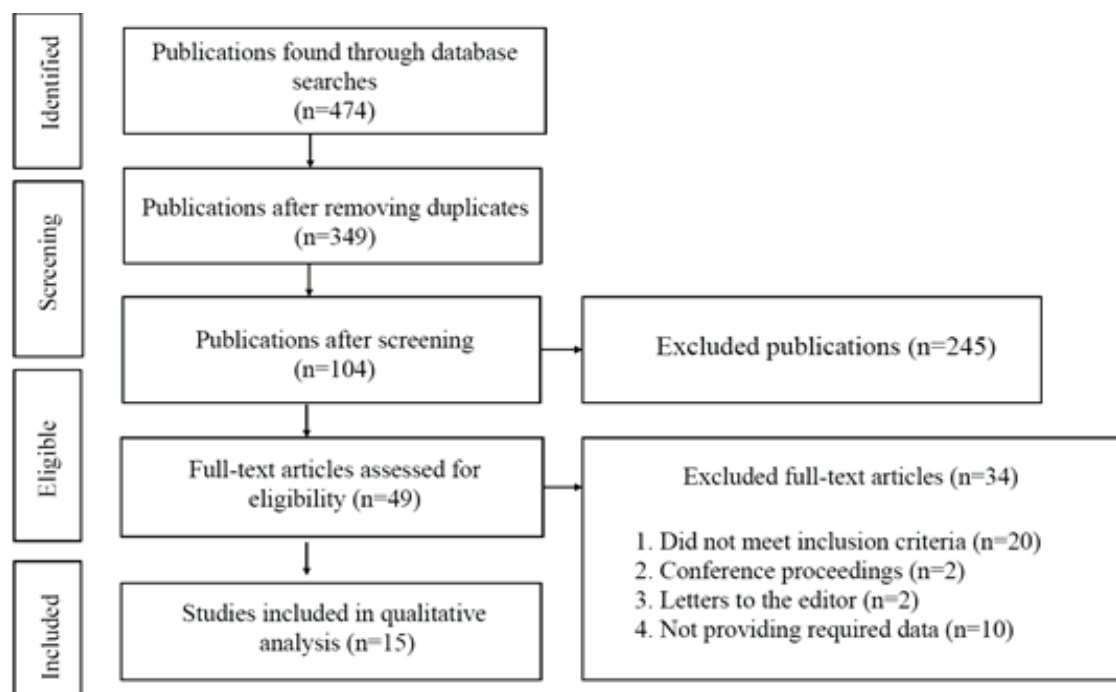
Today, there is also the method of dosed intrathecal administration of opioid analgesics using programmable pumps being successfully applied. One of the advantages of these systems is maintaining lower morphine concentrations in the cerebrospinal fluid [13, 16, 20, 25].

The work of narcotic analgesics administered intrathecally is inhibiting the release of neurotransmitters by opioid receptors located in lamina II of the dor-

sal horn of the spinal cord. Programmable pumps are suitable for patients with a life expectancy of more than 6 months [21, 23]. Complications of such analgesia include urinary retention, sweating, nausea, vomiting, euphoria, central depression, orthostatic hypotension, and tachyphylaxis [4, 13, 14].

In the study Carvajal et al. The results of surgical treatment of 93 patients with pancreatic MN were studied: in 70 cases, a programmable morphine pump was implanted and in 23, ports and external pumps were implanted. All patients received a mixture of morphine and analgesics – ropivacaine (n=89), ziconotide (n=75), clonidine (n=25). Median survival was 91 days. The authors found that a halving of pain was noted by 78.8% of patients with an implanted system and 44.4% of patients with external pumps and ports [5].

In a multicenter prospective study on 1403 oncology respondents with CPS, the effectiveness and safety of intrathecal therapy with opioid analgesics was assessed. The most common locations of MN were lungs, breast, colon/rectum, pancreas, and prostate. The authors assessed life expectancy after pump implantation: six-year life expectancy was 39%, one-year – 24%, two-year – 16%, three-year – 11%, ten-year – 5%. The authors managed to collect information about the dynamics of pain severity from 283 patients. It was found that intrathecal administration of opioids reduced pain



Search and selection strategy for the systematic review

General Characteristics of Studies included in the Systematic Review

Authors	Number of patients	Average age of patients	Study design	Level of evidence	Newcastle-Ottawa Scale score	Interventional treatment method	Observation timeframe (months)
Carvajal et al., 2018 [5]	93	61.1	Retrospective	3	2	Implantable programmable morphine pumps	3
Stearns et al, 2020 [20]	1403	59	Prospective, cohort	3	6	Implantable programmable morphine pumps	12
Pacheco-Feijóo et al., 2023 [17]	-	-	Meta-analysis	1	6	Transgastric neurolysis of the celiac plexus	-
Gevorkyan T. G. et al., 2023 [1]	12	-	Retrospective, cohort	3	2	Transgastric neurolysis of the celiac plexus	2
Koulouris et al., 2021 [15]	727	-	Systematic review and meta-analysis	1	6	Transgastric neurolysis of the celiac plexus	-
Wong et al., 2007 [22]	25	55	Retrospective, cohort	3	3	Intercostal blocks	1
Darabad et al., 2020 [10]	3	65	Clinical case	3	-	Selective blockade of the stellate ganglion	3
Luo et al., 2022 [26]	-	-	Literature review	5	-	Puncture interventions on the stellate ganglion	-
Motoyama et al., 2023 [24]	1	55	Clinical case	3	-	Transgastric neurolysis of the celiac plexus	-
Sakamoto et al., 2010 [18]	67	-	Retrospective, cohort	3	2	Transgastric neurolysis of the celiac plexus	1
Capozza et al, 2021 [23]	-	-	Literature review	5	-	Implantable programmable morphine pumps	-
Bentley et al., 2014 [4]	5	64	Retrospective, cohort	3	2	Implantable programmable morphine pumps	3
Candido et al., 2017 [6]	-	-	Literature review	1	-	Neurolysis of the celiac plexus, selective blocks	-
Zheng et al., [11]	54	66.40±18.52	Prospective, cohort	3	3	Implantable programmable morphine pumps	3
Duarte et al., [14]	3043	-	Meta-analysis	1	6	Implantable programmable morphine pumps	16

levels and maintained the effect after 6 (n = 103) and 12 (n = 55) months. There was also an improvement in the quality of life according to the EuroQol -5 D questionnaire (n = 41) 6 months after the procedure. In 3.2% of patients, complications associated with the operation of the pump were registered that required its replacement [20].

A meta-analysis including 22 studies showed that intrathecal use of opioid analgesics and spinal cord stimulation are effective and safe methods in the treatment of CPS of oncological origin [14].

Neurodestructive methods of treating chronic pain syndrome. Percutaneous and transgastric neurolysis of the celiac plexus. Neurodestructive methods of treating CPS in cancer patients are used when the "analgesic ladder" is ineffective, in patients with uncontrolled pain syndrome [2,20]. The most commonly used neurodestructive methods include neurolysis of the celiac

plexus, peripheral and plexus blockades, laser and radiofrequency destruction of the spinal nerve roots [3,12,17,24].

Neurolysis (neurolysis, neuroablation) is a process of persistent destruction of afferent fibers of the peripheral nervous system (surgical, chemical, thermal), which is based on the introduction of a 96% ethyl alcohol solution into the celiac plexus [12]. The most typical complications of the manipulation are: orthostatic hypotension, diarrhea, post-injection hematoma, pneumothorax, abscess and peritonitis [3,17]. Neurolysis of the celiac plexus is indicated for patients with MN of the upper gastrointestinal tract, mainly with inoperable lesions of the pancreas [18,24].

In a meta-analysis by Pacheco-Feijóo et al. compared the effect of percutaneous endoscopic neurolysis and traditional pharmacological treatment of patients with chronic heart disease and MN localized in the upper abdominal cavity. A

total of 744 publications were examined between 2000 and 2021 in the PubMed, Cochrane, Scopus, Web of Science and Google Scholar databases. Of these, 13 manuscripts were selected for qualitative analysis, 3 of which met the criteria for quantitative synthesis and procedural efficiency. It was found that pain was significantly reduced in the neurolysis group compared to the group that used only pharmacological treatment. Among the side effects of manipulation, orthostatic hypotension, diarrhea and pain at the puncture site were recorded in 21-37% of cases [17].

In a study by Gevorkyan et al., the results of neurolysis in 12 patients with inoperable pancreatic MN associated with CPS were studied retrospectively. The authors reported that in 9 (75%) cases there was a persistent decrease in pain, while in 3 (25%) repeated neurolysis was required due to persistent pain [1].

Transgastric neurolysis of the celiac

plexus under endoscopic ultrasonography control (EUS) is currently one of the most popular methods of treating CPS of the upper gastrointestinal tract, which was introduced in 1966 by Wiersema MJ and Wiersema LM [1].

In a meta-analysis by Koulouris et al., the effectiveness and safety of endoscopic neurolysis for pancreatic MN was studied depending on the needle access point: central, bilateral, or celiac ganglion neurolysis. Of the 136 publications on this topic, 26 were used for full-text qualitative analysis. The authors reported that there was no significant difference in the dynamics of pain reduction between the three access points; the overall reduction in pain after EUS was 68% (61-74%) in the second week after manipulation and 53% (45-62%) in the fourth week [15].

Peripheral Nerve Plexus Blocks.

Peripheral and plexus blocks in oncological practice are used as an additional method of pain relief in combination with the analgesic ladder and are combined with a multimodal approach [3]. Such methods are used for CPS that occurs in innervation of one or more nerves [3, 22, 26].

Intercostal nerve blockade is a common method for relieving CPS that occurs in rib destruction by a metastatic lesion in MN of the breast, lungs, and sternum and is associated with a high probability of pneumothorax. There is practically no information in the specialized literature about the results of using this method. In 2007, a clinical series of 25 patients who underwent neurolytic intercostal blockade was published. It was found that 80% of patients experienced a reduction in pain by more than 50% [22].

Patients with MN in the head and neck area represent the most vulnerable group with a frequent risk of developing opioid dependence due to the high need for use of narcotic medications. Today, ultrasound-guided blockade of the stellate ganglion is effectively used to relieve pain in this group of patients [3, 26]. This neural structure is located along the lateral border of the C6 and Th1 vertebral bodies, and in some cases on the lower edge of the C6 vertebral body. A contraindication to the blockade is contralateral pneumonectomy, which is accompanied by the risk of pneumothorax [26]. The study by Darabad et al. presents data from 3 patients with head and neck MN who underwent stellate ganglion blockade using 0.25% Bupivacaine. As a result, the authors report a reduction in pain by an average of 5.33 ± 4.16 cm, the effectiveness of which was maintained for up to three months. The authors stated

that there were no complications after the procedure [10].

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CLINICAL EXPERIENCE OF CORRECTION OF THE MOTOR-EVACUATION FUNCTION OF DUODENUM IN ACUTE DESTRUCTIVE PANCREATITIS IN THE FIRST PHASE OF THE DISEASE

The purpose of the study was to clinically evaluate the effectiveness of the treatment tactics we developed using the Dextran-40 colloidal solution in patients with duodenal MEF disorders with ADP in the first phase of the disease. The use of a technique using a colloidal solution of Dextran-40 showed greater effectiveness in terms of the rate of reduction in intraduodenal pressure compared to the standard method of prolonged nasogastrojejunal decompression of the upper gastrointestinal tract used for this purpose. Among other things, this made it possible to improve the immediate results of treatment.

Keywords. Acute pancreatitis, motor-evacuation function, duodenostasis.

Introduction. Currently, the problem of acute destructive pancreatitis (ADP) and its complications is one of the most difficult in modern emergency surgery of the abdominal organs. Despite the successes achieved in improving various diagnostic methods, intensive care tactics, surgical treatment using minimally invasive technologies, mortality in destructive pancreatitis over the last decade remains at a fairly high level and amounts to 15–40% [9], with infected forms and the development of pancreatogenic sepsis can reach 65% [3].

In the pathogenesis of many diseases of the pancreatobiliary system, including acute pancreatitis, a special place is occupied by the problem of impaired motor-evacuation function (MEF) of the duodenum [8]. In the medical literature, this pathology can be described under different names: duodenal stasis, megaduodenum, chronic duodenal obstruction,

duodenal dyskinesia, etc. However, with ADP, unlike many other situations, duodenal stasis (DS) is acute [4]. In addition, DS is an integral part of a more significant process that develops against the background of ADP, which includes intestinal failure syndrome (IFS). In turn, IFS, as some researchers believe [1,2,4,10], is the cause of the development of a wide range of infectious complications in ADP. A non-trivial task is that correction of duodenal MEF in ADP can be carried out over a fairly long period of time, taking into account the phase nature of the disease, the presence or absence of certain forms of complications of the disease, the need for surgical interventions, which can also affect the effectiveness of the corrective measures. All this creates the prerequisites for a more in-depth study of this problem by modern emergency pancreatology, and the search for ways to quickly resolve this issue.

Despite the fact that in our time, significant progress has been made in understanding the general principles of treatment of ADP and some of its complications, the issues of correcting disorders of the MEF of the duodenum remain

unresolved, as we indicated above. At different periods of time, different authors proposed certain methods for correcting disturbances in the MEF of the duodenum in ADP [4,6,8,11,12]. In particular, it was pointed out that the most severe MEF disorders are diagnosed in the initial stages of the disease (I A-B phase). However, to this day, despite regular revisions of clinical recommendations for the treatment of acute pancreatitis and its complications, there are no protocols devoted to the correction of duodenal MEF disorders in ADP. It is for this reason that we tried to evaluate the clinical effectiveness of the treatment tactics used in the clinic in relation to patients who were diagnosed with symptoms of duodenal MEF disorders in the first phase of the disease. It is during this period that a pronounced pathomorphological transformation of pancreatic necrosis occurs, ranging from enzymatic peritonitis and parapancreatitis to peripancreatic infiltrate and the formation of delimited fluid accumulations.

The **aim** of the study – to evaluate the clinical effectiveness of the developed treatment tactics in patients with disorders of the duodenal MEF during ADP in the first phase of the disease.

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