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HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY (HIPEC) IS AN EFFECTIVE METHOD OF TREATMENT FOR ABDOMINAL CAVITY CARCINOMATOSIS (LITERATURE REVIEW)

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Abstract:

One of the frequent options for the progression of malignant neoplasms of various localizations is carcinomatosis with tumor cells affecting the serous membranes - the peritoneum, omentum, parietal and / or visceral pleura, meninges of the brain. Peritoneal carcinomatosis, according to various sources, develops in at least 20-35% of patients with primary malignant tumors as a result of transcoelomic spread of tumor cells of intra-abdominal organs. Intraperitoneal chemotherapy HIPEC is one of the highly effective methods of drug antitumor therapy, which involves the introduction of heated chemotherapy drugs into the tumor lesion. The technique provides the most complete destruction of cancer cells, increases the overall and relapse-free survival of cancer patients.

Keywords: Carcinomatosis, Intraperitoneal Chemotherapy, Hyperthermia, HIPEC, Overall And Disease-Free Survival.

According to the implantation theory of carcinomatosis, tumor cells separated from the primary malignant tumor and further spread through the serous cavities with the serous fluid contained in them act as its source [7]. It is believed that the main trigger underlying carcinomatosis is the loss of intercellular adhesion factors by tumor cells. In particular, tumors of the gastrointestinal tract are complicated by carcinomatosis in 30-40% of cases, of which pancreatic cancer is approximately 40%, gastric cancer is 30-40%, appendix cancer is up to 30-100%, colorectal cancer is up to 10% [6]. A significant proportion of cases of peritoneal carcinomatosis is associated with malignant neoplasms of the female genital organs, primarily ovarian cancer. It is known that at the time of diagnosis of ovarian carcinoma, peritoneal carcinomatosis is present in 65-70% of patients [11]. Other sources of development of peritoneal carcinomatosis are primary malignant neoplasms of the peritoneum, such as peritoneal mesothelioma [6], and a group of malignant neoplasms with an unknown primary location. A separate, relatively small group of tumor lesions of the peritoneum with clinical and morphological characteristics similar to carcinomatosis is peritoneal sarcomatosis, which occurs in no more than 2-5%, and casuistic cases of peritoneal dissemination of benign mesenchymal neoplasms [2]. In most cases, the spread of malignant cells in the peritoneum is considered as an unfavorable prognostic factor, this form of tumor progression is practically not amenable to surgical correction, and the existing approaches in chemotherapy can alleviate the patient's condition only for a short time [1].

According to the literature analysis, many authors distinguish 6 main groups of diseases complicated by the development of peritoneal carcinomatosis:

1. Neoplasms of the gastrointestinal tract:
• malignant neoplasms of the stomach, small intestine and appendix, colorectal cancer;
• malignant neoplasms of the pancreas.
2. Neoplasms of the pelvic organs:
• malignant neoplasms of the ovaries, fallopian tubes, cervix and body of the uterus;
3. Neoplasms of the hepato-biliary system:
• hepatocellular cancer, malignant neoplasms of the gallbladder.
4. Primary tumors of the peritoneum (peritoneal mesothelioma).
5. Neoplasms without a primary identified focus.
6. Neoplasms of mesenchymal origin, giving dissemination in the peritoneum and having clinical and morphological characteristics similar to carcinomatosis (lymphomas, sarcomas) [13].

The frequency of peritoneal carcinomatosis has been proven to depend not only on the primary localization of the tumor, but also on its size, depth of invasion, histotype, and degree of differentiation. In particular, if the intestinal type of gastric cancer (GC) is accompanied by carcinomatosis in no more than 10-30% of patients, then with diffuse GC this complication occurs in at least 45-60% of cases. Poorly differentiated tumors, as well as neoplasms that grow into the serous membrane, are much more often complicated by carcinomatosis. With relapses, carcinomatosis occurs in at least 40-65% [4;9].

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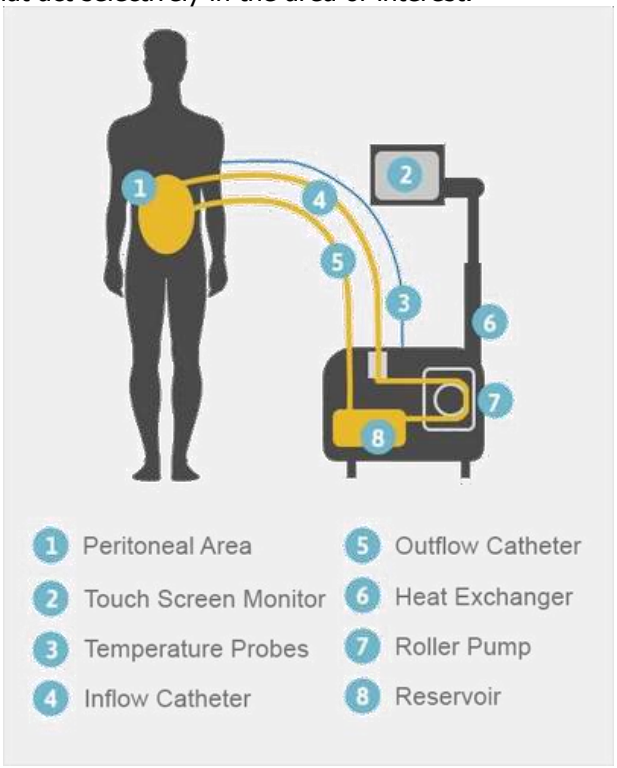
Intra-abdominal or intraperitoneal hyperthermic chemotherapy, or HIPEC for short, is a modern method of treating peritoneal carcinomatosis (tumor lesion), which helps to significantly prolong the patient's life. HIPEC is a combination of two methods of antitumor treatment: hyperthermia - an increase in body temperature simultaneously with chemotherapy, and in fact, prolonged washing with a cytostatic solution heated to 42-43 ° C of the internal organs and the sheets of peritoneum covering them [10,12].

After performing cytoreductive surgery, all its microscopic remnants are removed using intraperitoneal chemotherapy, the main goal of which is to eradicate any remaining free cancer cells. This is a specialized chemotherapeutic method that uses a combination of the actions of a drug and chemotherapy that act selectively in the area of interest.



Picture 1. Mechanism of HIPEC method.

Intraperitoneal chemotherapy is extremely effective because it overcomes the "abdominal barrier" that prevents chemicals from working best when administered intravenously. This method combines the results, which are due on the one hand to high temperature, on the other hand, anatomical localization. The pathogenetic effect of local hyperthermia is based on the ability of the temperature factor (41-48^{0}C) to cause persistent denaturation of the protein structures of tumor cells, inactivate cellular enzyme systems and DNA synthesis, change the rheological properties of blood with impaired microcirculatory blood flow in the tumor area, and increase the permeability of the cytoplasmic membrane due to activation of lipid peroxidation, which leads to the penetration and deposition of a cytotoxic agent inside the cancer cell itself [8,11].

Anatomical position (intraperitoneal) provides exposure anticancer drugs in high doses, thereby minimizing systemic side effects. The dose can be hundreds (sometimes thousands) times greater than with intravenous administration, due to the abdominal barrier, which does not allow absorption into the systemic circulation [3,13].

The choice of drugs for perioperative intraperitoneal chemotherapy is based on its or their ability to exert a direct cytotoxic effect within a short time interval; this means that its action should not be limited to the phases of cell division. Mitomycin, Doxorubicin and Cisplatin meet these essential requirements. Above this, the action of drugs is potentiated by simultaneous hyperthermia. With the simultaneous intraoperative use of cytostatics and hyperthermia, the maximum cytostatic effect is achieved.

1. Mitomycin (MMC): MMC is an anticancer antibiotic that specifically inhibits DNA synthesis. It was found that the toxic effect on cancer cells under hypoxic conditions (with a lack of oxygen in the surrounding tissues and low pH in the cells) increases. MMC does not have cell cycle specificity. The concentration advantage between intraperitoneal and intravenous administration is 20:1. Approximately 70 0/0 doses are adsorbed in the abdominal cavity within 1 hour. About 70-80 0/0 of the drug is excreted in the urine. The recommended dose of MMS for intraperitoneal use corresponds to the dose recommended for intravenous administration.

2. Cisplatin (CDDP): CDDP is a metal complex having a platinum atom in the center, which is surrounded by 2 chlorine atoms and 2 amino groups in the cis position. (cis-diamindichloroplatinum). Its biochemical properties are similar to other bifunctionally alkylating substances that are inserted between DNA strands and form crosslinks between them. Does not have cell cycle specificity. Almost 9594 doses are adsorbed in the abdominal cavity within 1 hour. Cisplatin accumulates in the liver, kidneys and intestines and is excreted through the kidneys. The recommended dose of CDDP for intraperitoneal use is the same as that recommended for intravenous administration.

3. Doxorubicin (DOX): DOX is an anticancer antibiotic that interferes with DNA function, replication, and RNA transcription. The drug is metabolized in the liver and 90% is excreted in the bile, and 10% in the urine. DOX is a highly caustic drug that causes tissue necrosis in high concentrations. Based on the studies performed, a

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Doxorubicin concentration of 10 u/ml was proposed for intraperitoneal hyperthermal chemotherapy [5,13].
Clinical efficacy and safety of the HIPEC method.
Sun J., et al conducted a meta-analysis of randomized controlled trials investigating the benefits of hyperthermic intraperitoneal chemotherapy in patients with serous invasion of gastric cancer. This meta-analysis included 10 RCTs, a total of 1062 patients with gastric cancer in these studies were divided into HIPEC group (n=518) and control group (n=544). A significant improvement in survival was observed in the HIPEC group compared to the mitomycin C control group (RR = 0.75, 95%; CI 0.65–0.86; p < 0.00001). The authors indicate that SSRES shows a lower peritoneal recurrence rate compared with the control group (RR = 0.45, 9594 CI 0.28-0.72; P = 0.001). In conclusion, the authors indicate that the use of HIPEC improves the overall survival of patients who are scheduled for resection of gastric cancer and helps to avoid peritoneal recurrence [11].
Chua T.C., Robertson G., Liauw W., Farrell R., MorrisD.L. conducted a systematic review of intraoperative hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis after cytoreductive surgery for ovarian cancer. According to the study, the mortality rate ranged from 0 to 10%. Median survival after treatment with HIPEC ranged from 22 to 64 months, with median disease-free survival ranging from 10 to 57 months. In patients with optimal cytoreduction, 5-year survival ranged from 12 to 66%. In their conclusions, the authors note that HIPEC may be a viable treatment for peritoneal carcinomatosis in ovarian cancer. [2].
According to Willemien J. van Driel, M.D., Ph.D., Simone N. Koole, M.D., Karolina Sikorska, Ph.D. was a randomized, open-label phase 3 trial of interval cytoreductive surgery with or without HIPEC in patients with International Federation of Gynecology and Obstetrics stage III ovarian, fallopian tube, or peritoneal cancer who had at least stable disease after three cycles of neoadjuvant chemotherapy with carboplatin and paclitaxel. As a result, the median overall survival was 12 months longer among patients treated with HIPEC than among those who did not receive HIPEC, while the median disease-free survival was 3.5 months longer with HIPEC than without HIPEC [13]. In studies by Stefano Cianci, Gaetano Riemma, Carlo Ronsini, In women with recurrent ovarian cancer, the use of HIPEC in addition to cytoreductive surgery and chemotherapy significantly improved 1-year OS compared to non-HIPEC protocols. OS improvement also remained significant at 2, 3, and 5 years, respectively [3].
According to researchers K.D. Huseynov, I.V. Berlev and others, the following results were obtained for ovarian cancerThe mean time to progression of the process directly depended on the volume of cytoreduction. After suboptimal cytoreduction in the experimental group, it was 1.4 months (n = 29), in the control group - 2.1 months (n = 48) (p = 0.67); after optimal - 22.1 months (n = 63) and 4.3 months (n = 32), respectively (p < 0.05). The best result was observed in 16 patients who, after optimal cytoreduction with intraperitoneal hyperthermic chemoperfusion and platinum-containing chemotherapy, are in clinical remission for more than 32 months [14].
When studying quality of life of patients, the authors Huseynov K.D., Berlev I.V., Belyaev A.M. write the following: At the beginning of the follow-up (days 3 and 7), the quality of life indicators (according to the EORTC QLQ-C30 questionnaire) decreased to an average value of 77.34 ± 0.67 points. There was an increase in general weakness, limitation in the performance of daily activities and significant physical exertion, the severity of pain. By the 30th day, these indicators of the quality of life returned to their original values. At the same time, an increase in the indicators of anxiety/depression according to the EQ-5D general questionnaire was recorded exactly by the 30th day of observation, which may be due to the patients' serious worries about their future fate [14].
At present, the world medical community has accumulated extensive clinical experience in hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal carcinomatosis.

IN CONCLUSION, we can conclude that the advantages of this method are:
- Hyperthermia increases the penetration of the cytostatic
- Hyperthermia increases the toxicity of the chemotherapeutic agent Heating itself has a cytotoxic effect
- Intraperitoneal chemotherapy destroys free tumor cells and thus prevents their introduction into the wound.
- Intraperitoneal chemotherapy makes it possible to evenly distribute the cytostatic agent in all areas of the peritoneum.
- Due to local action, higher doses of anticancer drugs can be used. Only a small amount of the drug enters the systemic circulation, thereby reducing the risk of side effects.
- High temperature in itself destroys tumor cells due to denaturation (changes in the three-dimensional structure) of proteins and other molecules, disruption of

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DNA synthesis and repair, and important biochemical processes in cells.

• Due to heating, the penetration of the drug into the tumor foci is improved.

• The solution in the peritoneal cavity flushes out loose tumor cells and blood clots on which they can be fixed.

• Inside the tumor foci, the cells may be in a state of hypoxia - oxygen starvation. They are insensitive to radiation therapy, but sensitive to heat.

• High temperature causes tumor cells to multiply actively, due to this, chemotherapy drugs work better on them.

• There is some evidence that heat inhibits the growth of new blood vessels in tumor lesions and stimulates antitumor immunity through the production of heat shock proteins.

BIBLIOGRAPHY:

1. Brucher B.L., Piso P., Verwaal V., Esquivel J., Derraco M., Yonemura Y. Peritoneal carcinomatosis: cytoreductive surgery and HIPEC—overview and basics. Cancer Investig 2012; 30: 209–24. DOI: 10.3109/07357907.2012.654871
2. Chua TC, Robertson G, Liauw W, Farrell R, Yan TD, Morris DL. Intraoperative hyperthermic intraperitoneal chemotherapy after cytoreductive surgery in ovarian cancer peritoneal carcinomatosis: systematic review of current results. J Cancer Res Clin Oncol. 2009 Dec;135(12):1637-45. doi: 10.1007/s00432-009-0667-4. Epub 2009 Aug 23. PMID: 19701772.
3. Cianci S, Riemma G, Ronsini C, De Franciscis P, Torella M, Schiattarella A, La Verde M, Colacurci N. Hyperthermic intraperitoneal chemotherapy (HIPEC) for ovarian cancer recurrence: systematic review and meta-analysis Gland Surg 2020 Aug;9(4):1140-1148 doi: 10.21037/gs-20-335 PMID: 32953629; PMCID: PMC7475376.
4. Glehen O, Kwiatkowski F, Sugarbaker PH, Elias D, Levine EA, De Simone M, Barone R, Yonemura Y, Cavaliere F, Quenet F, Gutman M, Tentes AA, Lorimier G, Bernard JL, Bereder JM, Porcheron J, Gomez-Portilla A, Shen P, Deraco M, Rat P. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. J Clin Oncol. 2004 Aug 15;22(16):3284-92. doi: 10.1200/JCO.2004.10.012. PMID: 15310771
5. Mirnezami R, Mehta AM, Chandrakumaran K, Cecil T, Moran BJ, Carr N, Verwaal VJ, Mohamed F, Mirnezami AH. Cytoreductive surgery in combination with hyperthermic intraperitoneal chemotherapy improves survival in patients with colorectal peritoneal metastases compared with systemic chemotherapy alone. Br J Cancer. 2014 Oct 14;111(8):1500-8. doi: 10.1038/bjc.2014.419. Epub 2014 Sep 16. PMID: 25225906; PMCID: PMC4200082.
6. Mirnezami R, Moran BJ, Harvey K, Cecil T, Chandrakumaran K, Carr N, Mohamed F, Mirnezami AH. Cytoreductive surgery and intraperitoneal chemotherapy for colorectal peritoneal metastases. World J Gastroenterol. 2014 Oct 14;20(38):14018-32. doi: 10.3748/wjg.v20.i38.14018. PMID: 25320542; PMCID: PMC4194588
7. Passot G, Bakrin N, Roux AS, Vaudoyer D, Gilly FN, Glehen O, Cotte E. Quality of life after cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy: a prospective study of 216 patients. Eur J Surg Oncol. 2014 May;40(5):529-535. doi: 10.1016/j.ejso.2013.11.019. Epub 2013 Dec 14. PMID: 24370285
8. Schmid K, Boettcher MI, Pelz JO, Meyer T, Korinth G, Angerer J, Drexler H. Investigations on safety of hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) with Mitomycin C. Eur J Surg Oncol. 2006 Dec;32(10):1222-5. doi: 10.1016/j.ejso.2006.05.011. Epub 2006 Jun 19. PMID: 16784832.
9. Sloothaak DA, Mirck B, Punt CJ, Bemelman WA, van der Bilt JD, D'Hoore A, Tanis PJ. Intraperitoneal chemotherapy as adjuvant treatment to prevent peritoneal carcinomatosis of colorectal cancer origin: a systematic review. BrJ Cancer. 2014 Sep 9;111(6):1112-21. doi: 10.1038/bjc.2014.369. Epub 2014 Jul 15. PMID: 25025964; PMCID: PMC4453838.
10. Spratt JS, Adcock RA, Muskovin M, Sherrill W, McKeown J. Clinical delivery system for intraperitoneal hyperthermic chemotherapy. Cancer Res 1980;40:256-260.
11. Sun J, Song Y, Wang Z, Gao P, Chen X, Xu Y, Liang J, Xu H. Benefits of hyperthermic intraperitoneal chemotherapy for patients with serosal invasion in gastric cancer: a meta-analysis of the randomized controlled trials. BMC Cancer. 2012 Nov 16;12:526. doi:

World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
Volume-13, August 2022
ISSN: 2749-3644

10.1186/1471-2407-12-526. PMID: 23153379; PMCID: PMC3551633.

12. van Driel WJ, Koole SN, Sikorska K, Schagen van Leeuwen JH, Schreuder HWR, Hermans RHM, de Hingh IHJT, van der Velden J, Arts HJ, Massuger LFAG, Aalbers AGJ, Verwaal VJ, Kieffer JM, Van de Vijver KK, van Tinteren H, Aaronson NK, Sonke GS Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer N Engl J Med 2018 Jan 18;378(3):230-240 doi: 10.1056/NEJMoa1708618 PMID: 29342393
13. Verwaal VJ, van Ruth S, de Bree E, van Sloothen GW, van Tinteren H, Boot H, Zoetmulder FA. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer J Clin Oncol 2003 Oct 15;21(20):3737-43 doi: 10.1200/JCO.2003.04.187. PMID: 14551293.
14. Гусейнов К.Д., Берлев И.В., Беляев А.М., Урманчеева А.Ф., Городнова Т.В., Киреева Г.С., Яковлева М.Г., Шихзадаева М.Г. Возможности гипертермической интраперитонеальной интраоперационной химиоперфузии в лечении рецидивирующего рака яичников. Доктор.Ру. 2020; 19(1): 62–68. DOI: 10.31550/1727-2378-2020-19-1-62-68