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Gastric cancer with high risk of intraperitoneal progression: clinical course and current treatments

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ABSTRACT

Locally advanced gastric cancer with a high risk of intraperitoneal progression is characterized by poor prognosis. After radical surgery, most patients die during the first two years post-operation as a result of disease progression. The prevailing type of progression and the leading cause of death in patients with gastric cancer is implantation metastasis.

The main risk factors for peritoneal carcinomatosis in such patients include: gastric tumor invasion into serosa, the presence of tumor cells in peritoneal washings, the largeness of the tumor as accompanied by extensive serous lesions, infiltrative type of tumor growth, histological variants of gastric cancer prone to implantation metastasis and metastatic lesions in regional lymph nodes. Systemic chemotherapy does not provide effective eradication of subclinical peritoneal carcinomatosis in patients with locally advanced gastric cancer.

The vast majority of patients who suffer from locally advanced gastric cancer and run a high risk of implantation metastasis are characterized by subclinical peritoneal dissemination at primary diagnosis, which means a rapidly fatal prognosis for such patients. In recent years, however, the paradigm of treatment of locally advanced gastric cancer has changed: a combination of surgery and adjuvant hyperthermic intraperitoneal chemotherapy is used increasingly, and presents an alternative to the previously accepted surgery only approach. It is also likely to increase the survival rate.

INTRODUCTION

Locally advanced gastric cancer (GC) (T3-4 N+ M0) is characterized by a poor prognosis [1]. Therefore, even after radical surgery, most patients die during the first two years post-operation as a result of disease progression [2]. The prevailing type of GC progression is implantation metastasis [3,4], which probably comes about due to the presence of a microscopic pool of tumor cells in the peritoneum before the time of surgery [5] or because of intraoperative peritoneal dissemination [6]. Of note, metachronous peritoneal carcinomatosis (PC) develops after radical surgery in 50% of all patients with a tumor invasion of serosa [7]. Peritoneal carcinomatosis is the leading cause of death in GC patients, with an average median survival of 6 months after the diagnosis of intraperitoneal recurrence [8].

The problem of intraperitoneal metachronous progression of GC after surgical treatment has been relevant for gastric surgery since the first surgeries for cancer. Indeed, after the

first gastrectomy (performed by T. Billroth, in 1881), the patient lived for 4 months and died of disease progression; the autopsy showed widespread metastases in the omentum, as well as metastases in the liver [9].

According to current literature data, PC occurs in 38-60% of all patients after radical surgery for GC [10,11]. The crucial risk factors for PC development in these patients include: tumor invasion into the gastric serosa [12], the presence of tumor cells in peritoneal lavage [13], the largeness of the tumor and the accompaniment of extensive serosa lesions [4,14], infiltrative type of tumor growth [15], histological variants of GC prone to implantation metastasis [16] and metastatic lesions of regional lymph nodes [17].

The depth of tumor invasion in the wall of a cavernous organ is without doubt the critical factor of implantation metastasis. Invasion of the gastric serosa is an independent adverse prognostic factor which determines the possibility of dissemination of tumor cells in the abdomen and the subsequent rapid fatal prognosis [14,18]. According to Roviello *et al.* [17], intraperitoneal recurrence after surgical treatment

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took place in 69% of all patients with serosa invasion and GC of the diffuse type. Statistically, categories T4a/4b (serosa invasion/ingrowth into adjacent organs – according to TNM-7th edition 2009 [19]) are likely to correlate with the level of intraperitoneal progression and a sharp decrease in the survival rate [20]. However, even if there was no invasion of the gastric serosa, metachronous PC developed in 37% of all patients [21]. The mechanisms of intraperitoneal progression in this case may be connected with both tumor cell migration through unaffected layers of the wall of the stomach and their intraoperative dissemination because of the intersection of lymphatic vessels in the course of lymphadenectomy [22]. A clear connection between PC development and radical surgery/depth of invasion of the primary gastric tumor is shown in a study by S. N. Nered [23]: in the case of pT1 tumors, the intraperitoneal recurrence rate was 12.5%, in the case of pT2 – 29.6% and in the case of ingrowth into serosa, it exponentially increased to 46.2%. In addition, the depth of invasion also affected the length of disease-free period – in the case of pT1, the average life expectancy before PC detection was 54.7 months, whereas in case of pT4a, it was 19.8 months. Metachronous peritoneal carcinomatosis is characterized by the shortest disease-free period in comparison with other ways of GC progression [24].

The presence of free tumor cells in the peritoneal cavity is another independent negative prognostic factor of locally advanced GC [25]. According to the results of peritoneal lavage cytology in patients with T4a/4b tumors, cancer cells are found in 10% [13] – 44% [26] of all cases. Moreover, according to Bando et al. [25], 5% of patients without macroscopic serosa invasion had positive peritoneal lavage. It is natural that there is a close connection between the affected area of the gastric serosa and the frequency of positive cytologic findings. Thus, according to Iceguchi et al. [27], if the area of peritoneal lesion is smaller than 10 cm^2, free tumor cells are detected in the lavage in 17.3% of all cases, whereas if it is bigger than 20 cm^2, they are detected in 68.5% of all cases. Kaibara et al. [26] also observed a significant difference in positive peritoneal lavage between patients whose affected area of the serosa is smaller than 10 cm^2, and whose that is bigger than 20 cm^2 – 22% and 72%, respectively. Adachi et al. [28] add that the 5-year survival of patients with tumor diameter below and above 10 cm is 42% and 14%, respectively. Bando et al. [25] state that a serosa infiltration which is more than 2.5 cm in diameter is an independent predicative factor of peritoneal GC recurrence. Other studies have noted that the highest occurrence of metachronous PC is observed in patients with total circular lesion of the stomach – 64.9% [23]. This situation often accompanies undifferentiated and colloid carcinomas [29].

Extended lymph node dissection at the time of the surgical treatment of GC can contribute to intraperitoneal dissemination of tumor cells, especially in cases of wide lymphogenous spread of the primary tumor [23]. On the other hand, the positive effect of extended lymphadenectomy D2 on survival, which is becoming common today, is eliminated by the rapid development of metachronous PC. Indeed, it has been shown that surgery with D2-lymphadenectomy in cases of GC with a high risk of implantation metastasis does not increase survival [4].

Thus, the presence of free tumor cells in the peritoneum determines a clear negative prognosis for patients – in one study, none of the patients survived during a 3-year follow-up period after radical surgery [30]. This result stands in agreement with the study of Bentrem et al. [13] wherein the median overall survival for patients who have positive results of intraoperative peritoneal lavage cytology is 14.8 months, whereas in the case of the negative cytological conclusion it is 98.5 months. Furthermore, La Torre et al. [22] report a median survival of 19 months in patients with positive peritoneal lavage, against 38 months in patients with negative lavage. Therefore, many authors believe that the presence of tumor cells in peritoneal lavage from GC patients is a sign of tumor dissemination, and this situation calls for palliative treatment regardless of the extent of interventions performed [31]. Thus, according to the clinical classification of the Japanese Gastric Cancer Association (JGCA), in contrast to the 2002 version of TNM-classification of the Union for International Cancer Control (UICC), these patients are definitely stratified to stage IV of the disease [32]. Therefore, intraoperative cytological examination of peritoneal lavage is a routine procedure in Japan today. In the TNM-7th edition 2009, the peritoneal lavage category was introduced – positive lavage being viewed as a sign of distant metastases [19].

To assess the degree of risk of implantation dissemination, it is necessary to take into account the histological structure and macroscopic appearance of the primary tumor. In terms of the features of metastasis in patients with locally advanced GC and disease progression after surgery, implantation metastasis usually develops in cases of colloid (65%), undifferentiated and poorly differentiated (52-54%) cancers. Well- and moderately-differentiated adenocarcinoma rarely accompanies PC (17.3-27%), but it hides a high risk of hematogenous metastasis to the liver (47.9-52%), while at colloid, cancer liver metastases occur only in 9,6% of cases [33]. The histological grade of GC also affects the time of disease progression, so the shortest disease-free survival (11-14.5 months) is observed in patients with poorly differentiated adenocarcinoma, colloid and undifferentiated cancer [21].

Diffuse or scirrhous GC, according to Lauren's classification, is characterized by a high risk of implantation metastasis – 31% of all cases were accompanied by PC, whereas with regard to the so-called intestinal or differentiated type, peritoneal dissemination was observed in only 6% of all patients. At that, no clear difference in the frequency of lymphogenous metastasis was revealed between the two types of GC [28]. The macroscopic appearance of GC also points to the risk of implantation dissemination. Thus, GC type I according to Borrmann's classification (1926) (an exophytic tumor) is accompanied by PC in 6.2% of all patients with a progressing disease, type II (saucer-shaped cancer) – in 23.4%, type III (ulcerative-infiltrative cancer) – in 48.1% and type IV (diffuse, or infiltrating, cancer) – in 61.4% of all patients [23].

Thus, in a considerable number of patients, locally advanced GC with a high risk of implantation metastasis

is accompanied by subclinical peritoneal dissemination at diagnosis, as shown by PC manifestation within the first months or years after treatment. Therefore, it is clear that these patients require combined therapy.

For a long time, hopes of adjuvant chemotherapy of GC had no confirmation in randomized studies [34]. For example, two meta-analyses of randomized studies of previous years showed no increase in survival due to the use of systemic adjuvant chemotherapy in patients with resectable GC [35,36]. However, in 2006, the results of MAGIC research [10] were published. Herein, it was evident that doctors had definitely managed to increase the 5-year survival rate in patients who underwent preoperative and postoperative ECF chemotherapy (from 23% to 36%) when compared to a surgery group of patients. This approach is currently the national standard of GC treatment in the UK and in some EU countries. A detailed analysis of the data of this research shows that the percentage of patients with a high risk of implantation metastasis in the study groups is small – only about 20% of all patients had tumor diameter bigger than 8 cm. In a North-American multicenter study – SWOG 9008 (INT 0116) – patients were randomized for surgery and for combined therapy by fluorouracil/leucovorin postoperative chemotherapy before, during, and after radiation therapy (45 Gy). In the study group, the 5-year survival rate was increased to 15% of all patients [11]. Of note, while the percentage of patients with T4a tumors in the study group was high (about 60%), only 64% managed to complete the combined therapy due to its toxicity. Today, this GC therapy is standard in the US and Canada. In Japan, the national standard of GC treatment is based on the results of the randomized study, ACTS-GC, published by Sacuramoto et al. in 2007, which confirmed the growth of 3-year survival in 10% of all patients who received systemic adjuvant chemotherapy S1 [37]. In addition, a statistically significant reduction in the incidence of metachronous lymphogenous and peritoneal metastases was received in the study group, but the frequency of implantation metastasis decreased inconsiderably (from 15.8% in the surgical treatment group, to 11.2% in the combined therapy group).

In 2007, the results of phase II of a clinical study (the Borrmann JCOG 0210-study) of the use of neoadjuvant chemotherapy S1 + cisplatin in patients with locally advanced GC types 3 – 4 were published. In this, 3-year survival was achieved in 26% of all patients [38]. Moreover, the application of the same chemotherapy regimen in patients with seropositive GC allowed a 3-year survival in 43% of all patients [39], however, serosa invasion was pathomorphologically confirmed in only 61% of the studied patients.

Thus, systemic chemotherapy does not provide effective eradication of subclinical PC in patients with locally advanced GC with a high risk of implantation progression. Potential factors causing relatively poor results of combined therapy in such patients include relatively low sensitivity of GC to chemotherapy and the supply of inadequate doses of drugs directly to tumor microdeposits in the peritoneum [40].

Because gastric cancer is a relatively chemo-resistant tumor, it is now hoped to increase the effectiveness of combined therapy by changing modes of administration of chemotherapeutic agents and by using modulation techniques of chemotherapeutic intervention [41].

The first report on intra-abdominal chemotherapy was published in 1955, by Weisberger et al. [42]. The first report of intraperitoneal chemotherapy for GC was published by Kimura in 1979 [43]. The combination of intraperitoneal administration of chemotherapeutic agents and local hyperthermia was first applied by the American surgeon Spratt et al. in 1980, to treat a pseudomixoma peritonei [44]. Later, this treatment option was called hyperthermic intraperitoneal chemotherapy (HIPEC).

Pharmacokinetic studies show that at intraperitoneal administration of cytostatic agents of high molecular weight (mitomycin, cisplatin, doxorubicin etc.), the gradient of their concentration remains high for a long time due to the existence of the peritoneal-plasma barrier. This situation allows for the creating of a high concentration of chemotherapeutic agents in the peritoneum with low systemic toxicity [45].

One of the promising directions of using hyperthermic intraperitoneal chemotherapy in oncology is its use in the adjuvant mode for patients with locally advanced GC with a high risk of implantation progression [46]. Thus, Fujimoto et al. [47] present the results of a combined therapy of 71 GC patients with a high risk of implantation metastasis with the use of HIPEC (mitomycin, 90 min at 44.0-45.0°C), which allowed achieving 2-, 4- and 8-year survival in the study group at the level of 88%, 76% and 62%, whereas in the control group, survival rates were 77%, 58% and 49%, respectively.

The results of a randomized controlled study of extended gastrectomy combined with HIPEC in an adjuvant mode (mitomycin 30 mg + cisplatin 300 mg, 90 min at 42.0-43.0°C) are presented by Yonemura et al. [48]. In the combined therapy group, the 5-year survival rate reached 61%, as against 42% in the surgery group. The authors conclude that HIPEC is effective in the prevention of PC progression after GC radical surgery.

Kim et al. [49] find that after interventions with D1 perigastric lymphadenectomy, the rate of intraperitoneal recurrence is 33.3%, while after lymph node dissection D2, it increases to 46.7%. This level of increase is attributed to the intraperitoneal dissemination of tumor cells as a result of the intersection of a large number of lymphatic ducts. However, not a single case of metachronous PC development and the highest follow-up indices were recorded after interventions with lymph node dissection D2 combined with HIPEC. Indeed, GC intraperitoneal recurrence rate in cases of using HIPEC after radical surgery ranges from 0-5% to 39%, whereas in the control group it is 48-59%, according to different authors [49,47].

In 2004, the Cochrane Collaboration performed a meta-analysis of 11 prospective randomized studies of the effectiveness of adjuvant intraperitoneal chemotherapy use in radically operated patients suffering from locally advanced GC [50]. The total number of study patients was 1,161. This meta-analysis statistically showed that combined therapy was more effective than that used in the control group. The best results of general and disease-free survival were obtained in cases where HIPEC was used.

In 2007, results of another meta-analysis of randomized studies of adjuvant intraperitoneal chemotherapy of resectable GS were published. It presents a cooperative analysis of the results of treatment of over 1.6 thousand patients within 13 randomized studies which have the highest level of evidence and were selected from 106 reports found in literature [51]. The results of this meta-analysis show that HIPEC alone or in combination with normothermic intraperitoneal chemotherapy is associated with a statistically significant survival rate growth.

In conclusion, the analysis of literature data shows that the vast majority of patients who suffer from locally advanced GC and run a high risk of implantation metastasis are characterized by subclinical peritoneal dissemination at primary diagnosis, which means a rapidly fatal prognosis for such patients. In recent years, however, the paradigm of treatment of locally advanced GC has changed: a combination of surgery and adjuvant HIPEC is used increasingly, and this presents an alternative to the previously accepted exclusively surgical method. It is also likely to increase the survival rate.

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