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Significance of diagnostic laparoscopy and determination of free cancer cells in peritoneal lavage fluid in patients with gastric carcinoma

Značaj dijagnostičke laparoskopije i određivanja slobodnih karcinomskih ćelija u tečnosti za peritonealnu lavažu kod pacijenata sa karcinomom želuca

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Introduction

Common features of gastric cancer (GC) are a late diagnosis, unsatisfactory results of surgical treatment, and poor effects of the oncological treatment [1]. Radical surgery is the only option for treating gastric cancer patients. According to the latest epidemiological data, GC ranks fourth in cancer incidence and mortality worldwide, preceded by lung cancer, liver cancer, and colon cancer [2].

The incidence of GC increases with age, the highest one being among the individuals aged between 50 and 70 years. Five-year survival in Western European countries was 14.3% in 1975, and 31.0% between 2008 and 2014. According to the World Health Organization (WHO) data, 754,000 people around the world died from GC in 2015 [3].

In the same year, in the Republic of Serbia, 1,100 patients (732 males and 368 females) were registered with GC, and 903 patients (587 males and 316 females) died, as indicated by the Cancer Registry data of the Public Health Institute "Dr. Milan Jovanovic Batut" [4].

Two-thirds of patients with GC in the United States present with advanced disease, and the majority have shown no significant findings on physical examinations [5, 6]. These patients have a high risk of metastatic disease in the abdomen at the time of diagnosis. Despite numerous endoscopic and radiological methods used in the preoperative evaluation of GC, metastatic disease was first diagnosed during laparotomy in a significant number of patients (6.7 %) [7].

Concerning the anatomical location, GC is divided into proximal (cardiac cancer) and distal ("non-cardiac" cancer). In Western Europe, for the past 30 years, the incidence of distal cancers has been declining, and the incidence of cardiac cancer has been increasing (8.9%). Cardiac cancers have a generally worse prognosis, a lower five-year survival rate, and higher operative mortality compared to antropyloric gastric cancer [3].

Characteristics of gastric cancer metastases

It is impossible to accurately determine the biological onset of GC. The two main histological subtypes of the disease, the intestinal and the diffuse type, as classified by Lauren, define two distinct entities that have different epidemiology, etiology, pathogenesis, and behavior [8].

Evolutionary changes in the gastric mucosa, going from normal through atrophic, metaplastic, dysplastic to neoplastic lesions for the intestinal type of cancer, take 15 to 20 years.

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Tsukuma et al. [9] have followed 56 patients with early GC that were not operated on for various reasons. They have shown that the average time for the transition from early to advanced GC was 37 months.

The diffuse subtype of GC is more aggressive than the intestinal type. It is often diagnosed in younger patients, more frequently associated with the loss of expression of E-cadherin, and the precancerous lesions are not clearly defined [10–12].

Invasion and metastasis are the most dangerous properties of malignant tumors and are the final phase of the multi-stage carcinogenesis. The outcome of the metastatic process is the result of the interaction between the metastatic cell and various host factors, above all, the immune system. This process implies the isolation of individual or groups of tumor cells from the primary tumor, their entry into the lymph and/or blood vessels, and the retention of these cells in small blood vessels of the target organs [13, 14].

Moreover, as in other human cancers, gastric tumorigenesis can also be profoundly influenced by epigenetic abnormalities, such as aberrant gene methylation, histone modification, and microRNAs. GC is a complex and molecularly heterogeneous disease involving dysregulation of canonical oncogenic pathways, such as p53, wnt/β-catenin, nuclear factor (NF)-κB, and PI3K/Akt pathways [15, 16]. GC is a disease with an early intra-abdominal spreading and an increase in the incidence of distant metastases during the follow-up. At the time of diagnosis, about 50% of patients have metastatic disease [11].

Metastases spread like other digestive tract cancers, including direct spreading to surrounding tissues and organs (liver, pancreas, diaphragm, spleen, transverse colon, bile ducts), lymphatic pathways (local and remote), hematogenous (liver, lungs, bone, brain) and peritoneal dissemination (surface visceral and parietal metastases, Kruckenberg's tumor). Tumor spreading often occurs simultaneously in different ways. The structure of hematogenous, peritoneal, lymph node metastases, and local recurrences depends on the biological properties and behavior of tumor cells [13, 17, 18].

Vascular invasion and metastases in lymph nodes in patients with advanced cancer are an independent risk factor for the development of synchronous and metachronous metastases in the liver [13]. Clinical-pathological studies have shown that the total incidence of metastases of GC in the abdominal lymph nodes is between 60% and 80%, on the peritoneal surface some 30% to 50%, and in the liver 25% to 40% [16–18]. The incidence of lymph node metastases is independent of the pathohistological type of tumor and is significantly associated with the degree of tumor invasion of the wall of the stomach [17].

Liver metastases are more common in patients with intestinal tumor type (50% to 70% vs. 3% to 30% for diffuse type), while peritoneal dissemination is most common in patients with the diffuse type of gastric cancer (45% to 75% vs. 10% to 30% for intestinal type) [16–18].

Peritoneal dissemination excludes surgical treatment of GC and is the most common cause of death in patients with GC. Peritoneal dissemination will occur despite curative resection in about 50% of patients with serosal invasion [17–19].

Diagnostic laparoscopy

The preoperative staging of gastric cancer makes use of chest X-ray, upper endoscopy, barium upper gastrointestinal examination, ultrasound of the upper abdomen (US), endoscopic ultrasonography, computerized tomography (CT) of the chest, upper abdomen, and small pelvis, laparoscopy, magnetic resonance (MR) and computer positron emission tomography (PET CT).

Despite all this, there is still no clear definition of what has to be done in the preoperative staging of GC. In recent years, the treatment of gastrointestinal tumors has become more complex and involves different treatment modalities such as neoadjuvant chemotherapy (HT), adjuvant HT, palliative systemic HT, or symptomatic treatment. In order to determine the optimal type of therapy, it is necessary to establish the stage of the disease more precisely at the time of diagnosis.

In spite of the significant technological advances in the development of highly sophisticated radiological equipment, peritoneal dissemination and lymph node metastasis are quite common in most patients diagnosed during laparotomy [20]. Laparoscopic exploration allows us to visualize the primary tumor, detect metastatic superficial metastases that cannot be diagnosed by other morphological methods (CT, MR, PET-CT), regional nodal metastases, peritoneal metastases, and free cancer cells in the peritoneal fluid [7, 21].

In the retrospective study of Tourani et al. [22], carried out in Australia with 199 GC patients included, diagnostic laparoscopy (DL) with peritoneal lavage in 19% of cases changed the treatment strategy of these patients.

DL significantly reduces unnecessary laparotomy in patients with an advanced stage of the disease [23–34]. In addition, it selects patients with advanced disease for various preoperative treatment modalities.

In the study of Stell et al. [32], the sensitivity of DL in detecting liver metastases was 96%, while the sensitivity of CT was 52% and US was 37%. In the diagnosis of peritoneal metastases, DL sensitivity was 69%, that of CT was 8% and for US it was 23%. The use of PET-CT for peritoneal metastases diagnosis in GC is also controversial, in view of the reported PET-CT poor sensitivity [33].

Absolute contraindications for laparoscopic exploration are severe coagulopathy and a high risk for surgery in general anesthesia. Relative contraindications include previous laparotomy, morbid obesity, and pregnancy. DL is a safe method in the preoperative staging of gastric cancer [31]. In the study by Muntean et al. [25], morbidity during DL was 2.2%, and mortality was 0%. During the monitoring period, no "port site" metastases were registered.

In a 1996 retrospective study by Adamek et al. [35], morbidity and mortality of DL in 747 patients were analyzed over a nine-year period. Eleven patients (1.5%) had serious complications, and one patient (0.13%) died after DL.

Table 1

Recommendations for staging laparoscopy from various professional societies

Society	Country of origin	Recommendation
SAGES [3]	USA	Patients with T3 or T4 gastric cancer without evidence of lymph node or distant metastases on high-quality preoperative imaging
ESMO [19]	Europe	All patients with resectable gastric cancer (III, Grade B)
S3 Guidelines [20]	Germany	Patients with advanced-stage gastric cancer (cT3-cT4); (II–III, Grade B)
GIRCG [21]	Italy	Cases deemed to be at risk of peritoneal carcinomatosis not visible or doubtful at CT examination
SEOM [24]	France	All patients with potentially resectable gastric cancer
JGCA [25]	Japan	Patients with clinical stage II-III prior to neo-adjuvant treatment

SAGES – Society of American Gastrointestinal and Endoscopic Surgeons; ESMO – European Society for Medical Oncology; GIRCG – The Italian Research Group for Gastric Cancer; SEOM – Spanish Society of Clinical Oncology; JGCA – Japanese Gastric Cancer Association; CT – computed tomography.

There is still no consensus when DL should be done. Table 1 lists DL indications according to different national associations.

The rate of DL doubled between 1998 and 2005. Despite the increased use of laparoscopy, occult metastases were identified in a similar proportion of patients [36, 37].

One of the key dilemmas is whether DL should be used as a special diagnostic procedure or immediately prior to the planned curative surgical resection (if there are no macroscopically visible metastases in the liver and peritoneum, and if the cytological examination of the peritoneal lavage fluid (PLF) excludes malignant cells). This mainly depends on the work organization in each hospital, as well as on how long it takes to obtain cytology results of a PLF. In our country, only a few hospitals have a cytology department. Therefore, DL is mostly based on a macroscopic examination (cytological examination of the peritoneal lavage is not a routine procedure). Further development of cytology as a science and an increase in the number of cytologists in our country would significantly improve diagnostic and therapeutic procedures, reduce morbidity (unnecessary laparotomy, unnecessary "curative" resections), and hospitalization costs in patients with advanced malignant digestive diseases.

The patients with metastatic disease (occult or otherwise) do not benefit from resection. Additionally, the minimal morbidity of DL argues strongly in favor of its widespread adoption in the management of patients with gastric cancer.

DL should be performed before chemotherapy for patients in whom a neoadjuvant approach is considered. Washing might increase the accuracy of DL [37].

DL is also used to evaluate the effects of systemic and neoadjuvant HT in patients with advanced GC [36–40].

The cost-effectiveness of DL for GC patients is highly dependent on the patient and the results of the diagnostic examination, and it is higher for locally advanced disease or in detecting peritoneal and superficial liver lesions [41].

Enhanced outreach and education of surgeons may help increase the use of DL in practice.

DL should be used in the following patients: patients with T3, T4 tumor of the stomach (determined by CT or EUS examination); patients with T2, N2 (certain CT or EUS examinations) with a diffuse type tumor greater than 5 cm in diameter; patients with gastric tumors, ascites, and negative cytological findings on malignant cells (sample taken percutaneously) regardless of T stage; patients treated with systemic or neo-adjuvant chemotherapy to evaluate the effects of the treatment [36–40].

DL should not be performed in the following cases: GC complicated by obstruction, bleeding or perforation; early GC; multiple previous laparotomies; in clearly diagnosed distant metastases (liver, lungs, bones, etc.) by other morphological methods [36–40].

Significance of free cancer cells detection in peritoneal lavage fluid (PLF) in patients with gastric carcinoma

Cytological analysis of PLF is an inexpensive and reliable method of testing the presence of free cancer cells (FCC) in the peritoneal cavity.

Laboratory methods for malignant cell detection in the aspirate include conventional cytology and reverse transcriptase-polymerase chain reaction (rt-PCR) [42, 43].

Cancer cells are found as single or groups of cells – epithelial type with all the morphological characteristics of malignant cells (enlarged nuclei of irregular shape, irregular chromatin structure, and prominent nucleolus) [42].

The first step in the development of peritoneal metastases is the detachment of cancer cells from the primary tumor invading serosa, followed by their peritoneal cavity spread.

The hypothesis that FCC play a significant role in the occurrence of peritoneal metastases is justified by the fact that postoperative metastases are present in almost all patients with free cancer cells proven during operative treatment of gastric cancer, even in those with potentially curative resection [42].

The possibility of finding FCC is increased with the degree of serosa involvement and the size of the surface of the affected serosa [42–45].

According to the multivariate analyses, the size of the tumor, the depth of the stomach wall of invasion, and the presence of metastases in lymph nodes are the most important prognostic factors in terms of patient survival [44–46].

Suzuki et al. [47] found that 50% of patients with GC greater than 14 cm had cancer cells in the PLF.

Kostić et al. [48] found that patients with tumor diameters less than or equal to 5 cm did not have FCC in PLF, while 30.95% of patients with cancer diameters greater than 5 cm had a positive cytological finding. This study has also shown

that tumor size is statistically highly significant for the frequency of a positive cytological finding. Positive cytological findings in patients with diffuse gastric cancer were 31.25% and 10.71% in patients with intestinal tumor type. The risk for the presence of FCC is 56 times higher in GC patients with serosal invasion (T3 and T4) than in those with T1 and T2 tumors and as much as 60 times higher in patients with tumor greater than 5 cm in relation to patients with tumors less than or equal to 5 cm.

Kaibara et al. [45] found FCC in 22% of patients with infiltration of serosa lesser than 10 cm^2, whereas the presence of FCC reached 72% in patients with infiltration of serosa greater than 20 cm^2.

A positive cytological finding is more often present in non-differentiated *versus* differentiated tumors [49–52].

The length of survival of patients with FCC does not differ significantly from patients with macroscopically visible peritoneal metastases (PM), even after curative resection of gastric cancer [46, 49].

The disease-free survival (DFS) of patients with a positive FCC without clearly seen peritoneal metastases is 13 months, whilst the DFS of patients with peritoneal metastases is about 10 months [47].

In the study by Bentrem et al. [51], the DFS of patients with R0 resection (a total of 371 patients), due to GC and a positive FCC in PLF, was 14.8 months, while patients with negative cytological findings had a DFS of 98.5 months.

A positive FCC in the PLF in the absence of visible peritoneal metastases is not uncommon in patients with gastric cancer and indicates a poor prognosis [49].

Sometimes, in patients with clear peritoneal dissemination, we get a negative finding for cancer cells in the peritoneal fluid.

Nakajima et al. [53] found that 32% of patients with macroscopic peritoneal dissemination did not demonstrate the presence of FCC in the peritoneal fluid. They concluded that such a high rate of false-negative findings is not a technical error but a consequence of the type of implantation of tumor cells into the peritoneum (often deeply implanted in the peritoneum).

The reliability of the cytological analysis of PLF in patients with advanced GC is about 91%, with a lower sensitivity of about 56% and a specificity of about 97% of the method [51].

Since the cytological examination of ascites on malignant cells has low sensitivity, new biomarkers are being examined to diagnose and predict the occurrence of gastric carcinoma peritoneal dissemination [54–57].

In a multicentre prospective study [57], miRNA expression of the genes encoding carcinoembryonic antigen (CEA) and cytokeratin 20 (CK-20), evaluated by RT-PCR, has proven to be useful for the prediction of overall survival and PM in GC. However, the disadvantage of mRNA-based diagnostic methods is the high degradability of mRNA in the course of surgical procedures.

In contrast, miRNAs enclosed in exosomes remain stable and can circulate in body fluids, such as serum, plasma, saliva, urine, breast milk, and tears, for long periods of time [56].

Cytology and molecular diagnostic assays are based on detecting the cancer cells, whereas profiling of miRNAs in PLF may be used for predicting the peritoneal premetastatic phenotype in GC, ensuring more effective preventive and curative measures [57].

The results of some randomized studies show that intraperitoneal chemotherapy is effective in preventing peritoneal recurrence in patients with FCC [58, 59]. Intraperitoneal chemotherapy statistically significantly reduces the incidence of peritoneal dissemination, though without affecting the incidence of liver or other metastases.

Cytological examination of PLF and PCR of PLF on FCC in patients with advanced GC is mandatory during a diagnostic laparoscopy. The presence of FCC in the PLF is a contraindication for curative surgical resection, and such patients are candidates for neoadjuvant chemotherapy [60].

Intraperitoneal FCC can also be found in earlier clinical stages of gastric cancer. In patients with low surgical and oncological risk (no serosa invasion, no lymph nodal spread, moderate or well-differentiated neoplasm), immediate surgery should be performed, and intraoperative peritoneal washing/lavage should be added [61].

The question remains whether it is necessary to do a PLF cytological examination on FCC (considering the pathogenesis of peritoneal metastases) in each patient during the surgical resection of GC, regardless of the stage of the disease. Further studies are necessary to better monitor and treat these patients.

Conclusion

Diagnostic laparoscopy is an important method in the preoperative staging of gastric cancer. Accurate preoperative disease staging is necessary for the optimal treatment of patients with gastric cancer. A cytological examination of the peritoneal lavage fluid is mandatory during the diagnostic laparoscopy in patients with advanced gastric carcinoma without macroscopically visible changes in the peritoneum. Further research on reliable biomarkers in peritoneal lavage fluid is needed to attain more reliable recruitment of patients with a phenotype for probable peritoneal dissemination, enabling a more aggressive therapeutic oncological approach and possibly a longer survival of patients with advanced gastric cancer.

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