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SURGICAL AND COMBINED TREATMENT OF LOCALLY ADVANCED GASTRIC CANCER

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ANNOTATION:
In the study, pancreatic involvement was observed in 91.2% of cases in T4 gastric cancer. Moreover, with the same frequency (34.5%), ingrowth into the pancreas was combined with damage to the transverse colon and around vessels. The prognostic factors that determine the survival of patients with T4 gastric cancer remain unclear. Data on the immediate results of combined operations performed for locally pervasive gastric cancer vary considerably in the literature. The frequency of postoperative complications ranges from 5 to 59.4%, postoperative mortality - from 3.3 to 24.2%. The optimal surgical tactics for the treatment of patients with locally widespread gastric cancer has not been determined. Not only the indications for combined resections and palliative interventions remain controversial, but also the immediate and long-term results of treatment, which determines the relevance of continuing research.
Key words: stomach cancer; locally widespread; combined operations; palliative gastrectomy.

Introduction

At present, the concept of "locally advanced gastric cancer" has not yet been fully formed in the literature and is interpreted differently by different authors.

In addition to the above condition, the presence of at least one metastatic regional lymph node (T3-4N0M0, T1-4N1-3M0) is considered sufficient, classifying gastric tumors corresponding to stages II, IIIA and HIB of the disease as locally advanced (the authors used the 5th edition of the classification of the International Union Against Cancer [27]).

A number of researchers believe that locally advanced cancer is a "tumor with a greater prevalence than early cancer." In this case, the authors understand early cancer as cases with a prevalence of T1N0-2M0, while locally advanced cancer includes T2-4N0-3M0 stages.

In addition to the above formulations, at present a large number of authors [17, 24] understand the term “locally advanced cancer” as the lesion of the entire thickness of the gastric wall shown in Figure 1 with histologically verified ingrowth into adjacent structures (symbol pT4) in the absence of distant metastases.

Understanding that, from a biological point of view, from the position of assessing the probability of relapse of the disease, the prognosis of survival of patients with gastric cancer, any of these definitions has a rational kernel, we still use the last definition in our work, considering local spread as the ingrowth of a gastric tumor into neighboring structures. We consider this definition to be the most convenient from a practical point of view, it outlines a relatively homogeneous group of patients who require combined operations with resection of neighboring organs to achieve radical intervention.

The term "ingrowth" itself is also not always interpreted unambiguously. Some authors considered the initial stage of ingrowth to be the adhesion of a gastric tumor to the peritoneum of an adjacent organ. Zhang X. et al. (2017) wrote about the existence of both true and false ingrowth. By false, the author understood the same adhesion. Wang Y. et al. (2018) considered two variants of false ingrowth: in addition to adhesion, he described the development of an inflammatory infiltrate near the stomach with the involvement of adjacent organs. Yang B. et al. (2021) identified adhesion, false (the presence of a pronounced parablastomatous infiltrate) and true ingrowth, arguing that adhesion and ingrowth are successive stages of a single process.

According to various authors [17], true tumor ingrowth into resected organs is confirmed histologically in 39.8% of patients. Smyth E. C. et al. (2020) report that in their study, true ingrowth was confirmed in only 14% of cases. The survival rate of patients with histologically confirmed tumor ingrowth is worse than with adhesion to surrounding tissues [14, 21]. The number of patients “with ingrowth” who survived the observation periods after combined interventions is approximately 1.5 times less compared to the group of patients “with adhesion” [27].

In addition, the literature describes cases of gastric cancer growing into the gallbladder and ducts, lungs, spine and spinal cord, large vessels (portal and cava veins, aorta) and thoracic duct [21, 27].

A number of researchers [1, 4,] have expressed the opinion that the involvement of various organs by a gastric tumor has different effects on the immediate and remote results of surgical treatment. At the same time, data on the frequency of tumor spread to surrounding organs vary quite significantly.

According to the authors [39], in locally advanced cancer, adjacent structures are affected by gastric tumors with the following frequency: pancreas - 28.7%, liver - 27.2%, mesentery of the transverse colon - 20.7%, retroperitoneal space - 5.6%, diaphragm - 5.1%, small intestine and its mesentery - 3.7%), colon - 2.7%, spleen - 0.9%, large vessels (aorta, portal or vena cava) - 0.9%.

There is also no consensus in the literature regarding the morphological characteristics of the tumor in locally advanced gastric cancer that potentially affect the prognosis of the disease. Some authors [1, 9] argue that, despite extensive invasion into adjacent organs and tissues, locally advanced gastric cancer is characterized by fairly favorable morphological features: exophytic tumor growth predominates, as well as differentiated forms of adenocarcinoma. Others [10], on the contrary, report predominantly infiltrative tumors with a low degree of histopathological differentiation. In a study among patients with locally advanced gastric cancer, high and low degrees of histopathological differentiation of the tumor occurred with the same frequency [2, 27].

Thus, at present, there is no unified understanding in the literature about the characteristics of tumor growth in locally advanced gastric cancer, namely: the frequency of invasion into other organs and tissues, as well as the predominant macroscopic and histological tumor variants.

Currently, only surgery is recognized as a potentially radical method of treating gastric cancer, since this tumor has pronounced chemoresistance [13, 41].

If, in the case of localized stages of the disease, the absolute majority of authors are inclined to surgical treatment in various variants, then in the case of widespread forms (which include locally advanced and metastatic gastric cancer), the question remains open.

Considering the peculiarities of tumor process prevalence in the majority of patients with locally advanced gastric cancer, one can expect a significant influence of the surgical method on the remote treatment results compared to the population of metastatic cancer, since in this case the theoretically assumed generalization of the tumor process is obvious. Among patients of this category, there are separate groups, surgical treatment of which is justified both from the point of view of improving the quality of life and increasing its duration. Identification of such groups on the basis of determining prognostic factors is a primary task.

Features of surgical treatment of patients with locally advanced gastric cancer

Traditionally, all interventions undertaken in relation to gastric cancer are divided into radical and palliative. In the literature, a division of operations, according to the UICC classification, into three groups, designated by the generally accepted symbol R (from the English Residual tumor) is often used. The first group (R0) includes interventions in the absence of macroscopic and microscopic residual tumor. The second (R1) - interventions performed visually in a radical volume, but the morphological examination of the surgical material of which showed the presence of a microscopic residual tumor, more often along the resection line. The third (R2) - includes operations leaving a macroscopic residual tumor.

The 1998 JGCA classification also takes into account the depth of tumor invasion and the degree of lymphogenous metastasis in combination with the volume of lymph node dissection when determining the nature of the intervention performed. According to this classification, the following are distinguished: radical operations (type A) - in the absence of residual tumor with a high probability of complete cure; conditionally radical operations (type B) - in the absence of residual tumor, but with a high probability of the presence of subclinical tumor foci; palliative operations (type C) - in the presence of residual tumor. In the case of locally advanced gastric cancer T4, the Japanese classification classifies interventions characterized by the absence of residual tumor only as type B (conditionally radical) operations.

One of the main ways to reduce the frequency of unresectable locally advanced gastric cancer is to increase the volume of surgery by monoblock resection of adjacent organs of the stomach involved in the tumor process, i.e. performing combined interventions [6, 27, 38]. Combined surgery in the case of a locally advanced process allows us to hope for performing a radical (R0) intervention. In addition, the question of true tumor invasion or a perifocal inflammatory process can be finally resolved only by morphological examination of the preparation removed during the combined intervention.

For a long time, palliative surgery was the main surgical treatment option for widespread stomach cancer. The attitude towards combined interventions was cautious. According to a number of authors [17, 23], expanding the scope of surgery by removing or resecting organs adjacent to the stomach, in

addition to high postoperative mortality, was accompanied by worse long-term results compared to standard methods.

In the last two decades, increased surgical activity has made the goal of surgical intervention no longer the elimination of complications of the tumor process, but the most complete removal of the tumor during extended and combined operations. The attitude towards combined operations has changed, the indications for them have been expanded. Thus, Roberts M. E. et al. (2019), who previously expressed an opinion on the inappropriateness of combined interventions in the presence of metastases in two or more groups of lymph nodes, even of the first order of metastasis (N1), currently adheres to aggressive surgical tactics, recommending extended combined interventions, up to multivisceral resections [25, 27]. According to Rodriquenz M. G. et al. (2020), the widespread use of combined interventions (up to 62.5% of all operations) reduced the incidence of local recurrence by 4 times (from 19.7% to 4.8%) in gastric cancer.

In locally advanced gastric cancer, a number of authors [6, 31] believe that surgical treatment cannot be considered radical by definition, but only cytoreductive. An opinion is expressed about the initial hidden generalization of the tumor process in such patients [10, 26] revealed tumor cells in the bone marrow and/or peripheral blood in more than half of patients with locally advanced gastric cancer. Observation showed that their presence was associated with the early development of relapse and significantly worsened survival. The results of a study using modern molecular analysis methods [3] have been published, showing the presence of cancer cells in the blood in the early postoperative period in all patients with a depth of tumor invasion of the stomach wall of T4.

Other authors [8, 34] still allow the possibility of radical resections with certain reservations due to the high probability of the presence of unremoved subclinical tumor foci.

Modern aggressive surgical tactics involve expanding the scope of combined interventions to the maximum possible. There are even suggestions about the advisability of left-sided upper abdominal evisceration (LUAE) [29, 36]. This involves en bloc removal of the stomach, spleen, corporocaudal resection of the pancreas, resection of the splenic flexure of the colon, as well as the left adrenal gland and retroperitoneal lymph node dissection of the left subdiaphragmatic space. Sometimes the left lobe of the liver and left kidney are included in the removed complex. At the same time, some authors [28] note an improvement in the long-term results of treatment of locally advanced gastric cancer after LUAE. On the contrary, other researchers [38], studying the results of LUAE, showed that this scope of surgical intervention does not improve patient survival, increasing postoperative mortality.

According to most authors [5, 6], the prognosis for locally advanced gastric cancer remains very pessimistic, and the results of surgical treatment cannot be called satisfactory. There is a fairly frequent (38-60%) refusal of surgical treatment due to the prevalence of the tumor process [15], although in some studies, resectability in case of gastric cancer ingrowth into adjacent organs reaches 73-75% [24, 30]. Even after potentially radical operations, most patients with locally advanced gastric cancer die from tumor progression and recurrence [40]. Many authors argue that the recurrence rate is highest when gastric cancer ingrows into adjacent organs and tissues. In some studies [19], the frequency of locoregional recurrence of gastric cancer in radically operated patients with T4 reached 41% versus 19% with T1-T2. The frequency of hematogenous relapses also increases in locally advanced gastric cancer (up to 54%) [14]. The frequency of relapse in the form of peritoneal dissemination when the tumor invades the serous membrane (T3-T4) reaches 53% versus 10% in T1-T2 [35].

Publications with a comprehensive assessment of the results of radical surgical treatment of locally advanced gastric cancer are few. More often, they are devoted to some individual variants of local spread of gastric tumor to specific neighboring organs and tissues (Chissov V.I. et al., 1981; Adachi Y. et al., 1992; Maehara Y. et al., 2000; Lo S.S. et al., 2002; Ryu S.Y. et al., 2008).

According to some authors [11], the frequency of radical combined interventions is extremely low and does not exceed 19%. Others [94, 123] believe that radical surgical treatment is received by about a third (29.9%) of patients with locally advanced gastric cancer. Still others [41] believe that this figure reaches 53.6-78.3%.

Data on the immediate results of combined operations performed for locally advanced gastric cancer vary significantly in the literature. The frequency of postoperative complications ranges from 5% to 59.4%, postoperative mortality - from 3.3% to 24.2% [16]. Among the most common complications are cardiopulmonary complications, as well as failure of the sutures of the esophageal-intestinal anastomosis [25]. According to some authors [38], with an increase in the volume of combined operations, a significant increase in the frequency of postoperative complications is noted (up to 59.4%), and the leading role in their development is given to the trauma of the intervention, which is understood as a combination of the volume of resection and the duration of the operation [32]. Other researchers [27] argue that this increase is insignificant and amounts to 20.7-21.5%. The third [37] believe that expanding the scope of intervention does not affect the frequency of complications, and complications occur in no more than 6.0% of cases.

Nakahara S. et al. (2007) believe that the main causes of anastomotic suture failure after surgical treatment of patients with locally advanced gastric cancer are: 1) a decrease in the content of protein in the blood plasma, which leads to a slowdown in reparative processes in the anastomotic area; 2) a drop in blood pressure (not associated with massive bleeding) during surgery, which leads to microcirculation disorders in the anastomotic area; 3) impaired food passage against the background of hypoproteinemia and a microcirculation crisis in the absence of selective prophylactic antibacterial therapy, which contributes to the development of anastomotic infection and purulent complications.

Many authors [17] see the cause of serious cardiovascular complications in the fact that during traumatic long-term operations for widespread gastric cancer, the content of catecholamines in the blood plasma increases excessively, which leads to a disruption in the nutrition of the myocardium, the occurrence of arrhythmias and increased platelet aggregation.

According to Maier M. K. et al. (2007), one of the most significant risk factors for complications in the postoperative period is the need to perform pancreatic resection. The authors believe that when performing such a resection, the surgeon is highly likely to encounter specific complications associated with the high proteolytic properties of pancreatic juice (postoperative pancreatitis, pancreatic necrosis, formation of an external pancreatic fistula). Another factor complicating the postoperative period and worsening the quality of life of patients is impaired glucose tolerance up to the development of insulin-dependent diabetes mellitus.

The main cause of mortality (up to 36% of cases) is peritonitis due to failure of the sutures of the esophagojejunostomy and esophagogastrostomy (Davydov M.I. et al., 1998; Zherlov G.K. et al., 2003).

The 5-year survival rate of patients with locally advanced gastric cancer after radical combined interventions in a number of studies is absent [5] or low - 12.7-25.0% [36]. Other authors [21] report a 5-year survival rate after extended combined operations at the level of 34.1-49.3%.

Prognostic factors determining the survival of patients with T4 gastric cancer remain unclear [27, 38]. According to some authors [16, 22], no dependence of long-term surgical treatment results on the number of adjacent organs resected and the organ resected was found. Not all researchers agree with this.

The most significant factors include the macroscopic type of tumor growth and the presence of regional metastases, which reduce the 5-year survival rate to 13.6%. At the same time, according to the same authors, in patients with T4 gastric cancer with non-infiltrative types of tumor growth and no metastases in the regional lymph nodes, the 5-year survival rate after combined NA interventions was 100%. I. Scientists [17] did not note any differences in survival after radical and palliative combined operations for diffuse-infiltrative tumor growth (type IV according to Bohrmann).

As for the volume of intervention on the stomach, the opinions of the authors also differ. Some researchers [9, 33] believe that the long-term results after various volumes of combined procedures with the correct establishment of indications are practically identical, others claim that the results are more favorable with distal resection, less so with gastrectomy. Some authors [6] generally consider it unacceptable to perform gastric resection in locally advanced cancer.

Speaking about the results of surgical treatment of locally advanced gastric cancer, it is impossible not to note that the frequency of postoperative complications and mortality, survival rates also depend on the profile of the institution in which they are performed, on the qualifications and experience of medical specialists providing assistance to such patients [12, 24]. Many authors [20, 24] note an improvement in the immediate results of treatment of patients with locally advanced gastric cancer with sufficient experience in performing combined operations, maximally developed surgical and anesthetic techniques.

A significant number of patients cannot receive specialized care in oncology departments of hospitals, oncology dispensaries and institutes, since the number of such patients significantly exceeds the bed capacity of specialized institutions. A comparative analysis of the periods of relapse-free progression of the disease showed that after treatment in specialized departments this period is reliably twice as long [10, 18].

An audit of the quality of surgical care for patients with gastric cancer in the UK found that the level of such care in general surgical clinics is unsatisfactory - with a high level of postoperative complications (49%), mortality (20%) and a high frequency of residual tumor masses along the resection line (36.6%) [40]. A serious problem [6] is the emergency hospitalization of patients in this category in surgical departments due to complications of gastric cancer and the implementation of interventions that are sometimes inadequate from the point of view of classical oncology.

Conclusions

The results of surgical treatment of locally advanced cancer cannot be considered satisfactory. There is a fairly frequent (38-60%) refusal of surgical treatment, due to the prevalence of the tumor process. Radical interventions in relation to such patients, according to various authors, are performed in 19-53.6% of cases. Even after potentially radical operations, the majority of patients with locally advanced gastric cancer die from tumor progression and relapse.

The solution to this problem is complicated by the fact that the concept of "locally advanced cancer" has not yet been fully formed in the literature, although a large number of authors still understand this term as a lesion of the entire thickness of the stomach wall with histologically verified ingrowth into adjacent

structures in the absence of distant metastases. There is also no consensus on the morphological features of gastric cancer in a locally advanced process: the frequency of invasion into various organs and tissues, the predominant macroscopic and histological variants of gastric tumors.

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