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MODERN DIAGNOSIS PROBLEMS OF GASTRIC STUMP CANCER

D.N. Păduraru[1,5], Mihaela Handaric[2], Adriana Elena Nica[3,5], S.M. Oprescu[4,5], O. Andronic[5], Oana Adelina Ionescu[5], D. Ion[1,5]

[1]III'rd Departmentof General Surgery, University Emergency Hospital Bucharest, Romania
[2]"Gr. T. Popa" University of Medicine and Pharmacy, Iași, Romania
[3]Department of Anaesthesiology, University Emergency Hospital Bucharest, Romania
[4]IV'rdDepartmentof General Surgery, University Emergency Hospital Bucharest, Romania
[5]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

Summary

Gastric stump cancer represents a malignant tumor which develops after subtotal gastrectomy was performed both for benign and malignant lesions. Worldwide gastric cancer is the second cause of death by cancer. The clinical picture of operated stomach has nonspecific, insidious symptoms which are hard to be included in a clinical entity. Clinical diagnosis can rarely identify suspected GSC in the early stages because symptoms are missing in most cases. A legitimate question is whether gastric stump cancer screening is necessary in patients with a history of subtotal gastrectomy. In conclusion it is particularly important that the clinical examination, but especially with the help of laboratory investigations try to establish early diagnosis, creating thus prerequisites for therapeutic management with better results.
Key words: gastric stump cancer, diagnosis, screening

Résumé

Aspects modernes de diagnostic du cancer du blunt gastrique

Le cancer du blunt gastrique est un néoplasme apparu au site de la résection de l`estomac suivante à une gastrectomie partielle effectuée pour des lésions bénignes aussi que malignes. Une question légitime est de savoir si un programme de dépistage du cancer du blunt gastrique est nécessaire chez les patients qui ont des antécédents de gastrectomie sous-totale. En conclusion il est particulièrement important qu' on essaie d'établir un diagnostic précoce après l`examen clinique, mais surtout à l'aide d'investigations complémentaires, créant ainsi les conditions préalables pour la gestion thérapeutique aux meilleurs résultats.
Mots-clé: cancer de blunt gastrique, le diagnostic, le dépistage

Introduction

Gastric stump cancer (GSC) is a malignant pathology that develops at the site of gastric remnant after subtotal gastrectomy performed for both benign and malignant lesions [1, 2].

A study published in 2015 shows that GSC frequency in patients who underwent partial gastrectomy for peptic ulcer varies between 0.8 and 8.9 % [3]. According yo other authors GSC's incidence varies between 3 and 10% of all gastric cancers [4,5]. In western centers, GSC incidence varies between 2.4 and 6% of all patients with gastric cancers [3-6]. In Japan, the incidence of GSC is situated at 1.2 % of all the gastric cancers [7]. In a recent population-based study conducted in Sweden, the incidence was 0.74 % GSC, being similar to previous reports [8].

Worldwide, gastric cancer is the second leading cause of death related to cancer [9]. Recent progress in terms of methods of diagnosis, minimally invasive treatment techniques and improvement of the perioperative management

Correspondence address: *Dan Nicolae Păduraru, MD, PhD*
General Surgery and Emergency Clinic III, University Emergency Hospital Bucharest, Romania
"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
e-mail: dan.paduraru.nicolae@gmail.com

led to the growth of gastric cancer detection in early stages and decreased morbidity and mortality [2] in this condition.

This article aims to find trends and current recommendations regarding the establishment of early diagnosis of gastric stump cancer.

Material and Method

This study is the result of the analysis of articles published between 2000-2016 regarding the methods and algorithm for diagnosis of gastric stump cancer. The research was conducted in international databases using specific search tools.

Results

Clinical diagnosis

The clinical picture of operated stomach has nonspecific, insidious symptoms which are hard to be included in a clinical entity. Clinical diagnosis can rarely identify suspected GSC in the early stages because symptoms are missing in most cases [10].

Several factors are leading to delays in diagnosing this pathology, of which we believe we should mention:

- Absence or presence of nonspecific symptoms in the early stage;
- Frequent confusions with other diseases (recurrence of ulcer or inflammation of the anastomosis) which cause loss of optimal therapeutic moment.
- CBG symptoms are often overlooked by patients as partial gastrectomy leads to the occurrence of gastrointestinal symptoms that patients misinterpret (as symptoms of ulcer recurrence).
- Gastric resection operations can give many symptoms due to decrease of stomach capacity, decrease of the secretion of acid and pepsin, removal of the pylorus.

In most cases, patients get a consultation after a period of unsystemized suffering at first rudimentary but persistent and evolving towards aggravation. The most common location of the lesion is in the stoma, often early symptoms are related to mechanical dysfunction of the anastomosis through which food transit is becoming harder and harder.

The most common symptoms are [11]:

- Abdominal pain or unsystemized upper abdominal pain;
- Early satiety, feeling of gastric distension, sometimes painful;
- Capricious appetite that can go up to partial/ total inappetence, sometimes selective for meat and bread.
- Nausea, bilious-alimentary or alimentary vomiting
- Dysphagia when tumors are located in the upper third of the stomach or the eso-gastric junction. As a natural consequence of difficulties in food, weight loss occurs and progresses rapidly to neoplastic cachexia
- Sometimes GSC can be found starting as an anemic syndrome. Digestive hemorrhage can occur suddenly through hematemesis and / or melena which may require transfusion. In cases when bleeding is chronic, secondary iron deficiency anemia can be installed. This happens frequently because of stomach bleeding after gastric resection, once started, continues worsening in evolution.
- Fatigue.

GSC diagnosis is suggested by dyspepsia, heartburn, progressive weight loss or from an unclear anemic syndrome in a patient who underwent partial gastrectomy for benign or malignant pathology in history.

Clinical diagnosis of GSC is, as it was shown,difficult to establish in early stages because of uncharacteristic symptoms, laboratory investigations being decisive for diagnosis.

Biological tests

Of the tests performed routinely, there are no elements statistically supported by information that would have specifically changed values in GSC [12]. Iron deficiency anemia, moderate or severe is common in most cases, and sometimes causes extensive research leading to the diagnosis [13].

Digestive cancer screening by tumor markers has not proven sensitivity because there are no specific tumor markers for gastric cancer [14]. Carcinoembryonic antigen value in gastric juice in patients with distal gastric resection correlates with the degree of histological changes of gastric mucosa. This means that the determination of CEA may be a potential screening method for the detection of GSC [11].

Status of the stump mucosa after gastrectomy was examined at molecular level. In this regard, Tanigawa reports that the apoptotic index, the level of p53 and Ki-67 are significantly higher in patients treated with Billroth II reconstructive surgery versus those who undergone the procedure Billroth I [14].

Also Nakache et al and Aya et al showed a higher frequency of microsatellite instability in patients with GSC (88.9 %, 43 %) than in those with primary cancer of the upper third of the stomach(20 %, 6 %). In addition, Aya reported both a greater level of microsatellite instability and hMLH1 and hMLH2 frequency inactivation in patients who have undergone Billroth II or Billroth I procedure [15,16].

There is a biological plausibility of the association of gastric remnant and the outstanding risk of developing cancer. This results from both experiments in animal models, and in examining patients with intraluminal bacterial flora proliferation because of gastric acid neutralization after surgery. These anaerobic bacteria convert nitrate from diet to nitrite, carcinogenic N- nitroso compounds precursors [8].

Also persistent bile reflux, a common consequence of gastric surgery, promotes chronic gastritis an eventually-metaplasia, frequently suggested as being a precursor of malignancy [6].

Diagnostic imaging

Upper digestive endoscopy

Upper endoscopy is the investigation with the highest

detection of GSC [16]. For diagnosis in an early stage of GSC it is essential harvesting biopsies from different areas of the gastric stump, even if there is no visible macroscopic tumor.

This allows macroscopic diagnosis and development of biopsies for histopathologic diagnosis of certainty.

Endoscopically, we can appreciate the location, expansion of the disease, the existence (or not) of an undamaged portion of the stomach, elements which, besides establishing conclusive diagnosis, help shape the surgical decision to be adopted.

In 2011, a study published by JJ Mezhir et al authors reports the following locations of tumors objectified in endoscopic examination: the anastomotic area 69 %, esophageal - gastric junction 10%, cardia 8%, the gastric body (stump) 13% diffuse 1% [17].

In a recent study published by Huang et al., most patients had malignant lesions at the anastomotic area (59.64 %) and the average tumor size was 4.0 cm [7].

In 2014, Di Leo et al. classifies GSC in terms of tumor localization in [18]:

- Anastomotic when the bulk of the tumor involves the anastomotic area;
- Extra- anastomotic when the tumor is located outside the area of the anastomosis;
- Diffuse when the tumor involves the entire gastric stump.

Note that in this study GSC definition refers to tumors that occur in the gastric stump up to 5 years or more after distal gastric resection for ulcer. Tumors diagnosed as recurrence after distal gastrectomy for cancer were not included in the study noted According to this classification, the percentage values obtained were: 40 % anastomotic area, the extra- anastomotic area 42 %, 18 % diffuse [18].

It was found that tumor localizations differ depending on the surgical technique [19]:

- in patients with Billroth II gastrectomy GSCdevelops especially in the anastomotic area, at the gastric stump, regardless of the initial character of the disease;
- in patients with Billroth I gastrectomy tumor is mostly commonlocalized at the body of the gastric stump.

Endoscopic ultrasound can put out with an accuracy of 85 % the degree of infiltration in the gastric wall and nearby organs [4].

Lymphatic metastasis diagnosis is more difficult. With the help of an endoscopic ultrasound it can get a diagnostic accuracy of 65-87 % (stage I) [20].

It is important to harvest biopsies from several areas of the gastric stump even if there is no visible macroscopic tumor in order to get a correct diagnosis of GSC in an early stage.

In a study published in 2015, Huang et al. rank GSC in histologically differentiated and undifferentiated [7]:

- Differentiated type includes: papillary adenocarcinoma, well / moderately differentiated adenocarcinoma;
- Undifferentiated type includes: poorly differentiated or undifferentiated adenocarcinoma, squamous seal cell carcinoma.

In another study published in 2014, Di Leo et al classified GSC by means of histology according to Lauren's criteria [18].

Lauren's system is the most useful and widely used method of classifying gastric adenocarcinoma, which separate them based on histological appearance in:

- Intestinal adenocarcinoma typically occurs in a precancerous lesion known such as gastric atrophy and intestinal metaplasia. Men are more commonly affected than women, and the incidence of intestinal type of gastric adenocarcinoma increases with age. Intestinal type is well differentiated with a tendency to form glands. Metastasis is hematogenous in this case.
- Diffuse gastric adenocarcinoma is poorly differentiated, not forming glands and is composed of signet ring cells.

Evolutionary changes in tumoral histology between the early stages and the locally advanced stage of disease are important and suggest that the onset of stump cancer is the intestinal type of adenocarcinoma and it changes in diffuse type in the course of the evolution to locally advanced stage.

In this regard are mentioned the results reported by Tanigawa et al., after histology study of GSC. Of the 304 patients with GSC in early stage of disease, 72.4 % were diagnosed with intestinal type of adenocarcinoma (well or moderately differentiated adenocarcinoma), while in the late stage of disease this histological type felt to 42 2% among the 521 patients studied.

This trend was observed regardless of the location of the tumors [14]. It is suggested so that the onset of GSC shows intestinal histology and it changes in the diffuse type during evolution toward advanced stages of the disease. Obvious histological tumoral changes in the current study may indicate a typical clone evolution model during progression of GSC.

GSC is usually diagnosed in an advanced stage [7]. Early diagnosis may be difficult because most patients are asymptomatic, but also because it is rarely suspected. It is particularly important that the clinical examination, but especially with the help of laboratory investigations to try to establish early diagnosis, thus creating prerequisites for therapeutic management with better results [10].

Radiology

In the past radiological imaging methods of investigation were the first laboratory tests used in exploration of operated stomach which showed some symptoms.

Radiological examination can identify malfunctioning stoma, of the anastomosis' mouth, gastro - jejunal or duodenal. Often, due to infiltration,orientation of anastomosis' mouth is changed, with reflux in the afferent loop [21].

Radiological exploration may reveal more suggestive aspects of GSC:

- Malignant ulcer on the small curvature of the gastric stump or anastomosis mouth;
- Ulcero vegetant mass on the remnant stomach;
- Early gastric stump cancer;
- Gastric stump cancer;
- Cancer of the fundus away from the anastomosis mouth.

Computed tomography

Computed tomography can identify tumors in the gastric

stump, but more important it can accurately assess the anatomical extent and metastases of the tumor whose existence has already been endoscopically proven.

Upper abdominal ultrasound

It can give details of the whole, especially in advanced cases, invading the liver, pancreas, perigastric.

Screening

Development of endoscopic technology and regularly endoscopic surveillance allows clinicians to detect GSC in an early stage, which could improve the poor prognosis of these patients.

Since treatment outcomes in patients with advanced CBG are unsatisfactory, endoscopic monitoring can offer surgery the chance to practice a curative resection consecutively with good postoperative results.

Because of the predisposition of gastric stump to be the headquarters of developing a cancer, but also because of the lack of symptoms in early stage of disease, endoscopic screening is essential in detecting GSC. It was found that patients who were regularly monitored after primary surgery had a better survival rate [22].

Early detection of GSC is possible if endoscopy is performed regularly along with harvesting gastric biopsies in patients with partial gastrectomy. This has an important impact on postoperative survival [23].

Periodic endoscopic exploration of the gastric stump is, as it was shown, essential. This enables early diagnosis and curative treatment of GSC. However, an excessively intense follow-up program does not appear to be beneficial to the patient [24].

Both early diagnosis of GSC and improving prognosis depend in a large measure on the duration of monitoring. Thus, annual endoscopic surveillance is recommended for a period of at least 12 years after distal gastrectomy and after this period, endoscopic surveillance is recommended every two years [23].

Thorough endoscopic examination should be performed on the suture line and the wall of the gastric stump after Billroth I type of reconstruction, respectively on the anastomosis area in patients who undergone Billroth II reconstruction. [24]

Greene reported an incidence of 2.5 % of GSC in a group of 163 patients where endoscopic screening was performed after partial gastrectomy. In this study, patients who refused screening had shown advanced stages of disease at diagnosis and the postoperative results were modest [25].

After Morgagni et. al, monitoring during the first 5 years after surgery includes clinical examination, ultrasound, tumor markers every 6 months and annual endoscopy. After this, patients will be reassessed once a year [24].

According to literature, the time between first surgery and diagnosing GSC is between 6.8 and 7.5 years for patients initially treated for cancer and 20 years for those who had benign lesions. It is worth noticing the significant difference between these two time intervals [25].

Some authors believe that all patients should be included in a screening program after a period between 15 and 20 years after distal gastrectomy. Moreover, any patient with gastrointestinal or ulcer disease symptoms should undergo an endoscopy. After initial endoscopy, a range between 3 and 5 years seems to be sufficient, but if dysplasia is detected annual endoscopy is recommended [5,13,23].

After partial gastrectomy, endoscopic surveillance should be done starting with the 15th year of the surgery in order to detect an early stage of GSC and improve the prognosis of patients [26-28].

Growing incidence of GSC suggests that patients previously treated by gastric resection should undergo a surveillance program throughout life in order to maximize a potential detection of dysplasia or cancer of the gastric stump in an early stage.

CONCLUSIONS

GSC is usually diagnosed at an advanced stage. Early diagnosis can be difficult because most patients are asymptomatic, but also because it is rarely suspected. It is particularly important that the clinical examination, but especially with the help of laboratory investigations to try to establish early diagnosis, thus creating prerequisites for therapeutic management with better results.

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