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EDITORIAL

How to identify early complications in patients undergoing distal gastrectomy?

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Abstract

In this editorial we comment on the article by Zhang *et al* published in a recent issue of the *World Journal of Gastrointestinal Surgery*. Gastrectomy with appropriate lymph node dissection is still standard curative treatment in locally advanced gastric cancer. Several studies point out that gastric cancer surgery is a complex procedure that leads to a high risk of morbidity and mortality. Many factors can contribute to the onset of complications with consequent effects on prognosis and increased mortality. The complications can be divided in complications related to anastomosis, to motility and to surgical site infection. The study presented by Zhang B *et al* represent an interesting analysis on the possibility to prevent postoperative morbidity. The study was performed on 131 patients with distal gastric cancer who underwent gastrectomy with D2 lymph node dissection. Of these patients, 16% developed early postoperative complications. The univariate analysis showed that prealbumin level, hypertension, diabetes, history of abdominal surgery, R0 resection, and blood transfusion were factors influencing early postoperative complications after distal gastrectomy. Moreover, the inclusion of the above significant variables in the logistic regression analysis revealed that hypertension, diabetes, a history of abdominal surgery, and blood transfusion were independent predictors of postoperative complications. In conclusion, preoperative and intraoperative factors can be used to establish an early postoperative nomogram model. The results of the study presented by Zhang *et al* suggest that the prediction model can be used to guide the detection of postoperative complications and has clinical reference value.

Key Words: Gastric cancer; Gastrectomy; Lymph node dissection; Morbidity; Mortality;

Surgical site infections

Core Tip: Surgical treatment is still the mainstay of curative gastric cancer treatment. The extent of lymphadenectomy is the only factor that can be influenced by the surgeon. Despite the therapeutic value of lymphadenectomy, mortality and complications are still high in gastric cancer surgery. The study presented by Zhang *et al* represent an interesting analysis on the possibility to prevent post-operative morbidity. The prediction model can be used to guide the detection of early postoperative complications.

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INTRODUCTION

Gastric cancer (GC) represents a global health concern. With more than 1 million new cases every year, it is the fifth most commonly diagnosed cancer worldwide even if there are high incidence regions as East Asia, Eastern Europe, and South America. Although consistent decline in the incidence and mortality rate due to improved living conditions and screening programs in high-incidence areas, mortality rate for GC is still high, ranking as the third leading cause of cancer-related deaths[1]. Also, it is important to mention an increase in the incidence of GC in younger people, usually from high-income countries, indicating a change in the risk and epidemiology of the disease, which should be taken in consideration for future good clinical practice[2].

Early and advanced stage GC present morphological diversity resulting in a large number of classification systems. The staging system most often used for GC is the American Joint Committee on Cancer tumor-node-metastasis (TNM) system, which was last updated in 2017[3]. Staging of primary GC is dependent on the depth of penetration of the primary tumour (Table 1). Typically, GC doesn't spread to distant organs until it reaches the third stage, but it can affect nearby lymph nodes (LN) during the early stages, which holds significance for prognosis[4].

Surgery is the only potentially curative treatment for GC[5-10]. LN dissection is mandatory in the appropriate surgical treatment of GC due to its tendency to metastasize to the regional LNs. A gastrectomy with D2 lymphadenectomy represents the standard of care for the treatment of GC, according to the most current Japanese guidelines.

Which is the most appropriate lymphadenectomy to perform, to offer the best oncological outcome without increasing postoperative morbidity and mortality, is in fact controversial, due to the differences in results between East and West and between high and low volume centres[11]. This aspect is not of negligible importance, since LN metastasis, which can also appear in the early stages of the disease, is one of the most significant prognostic factors in these patients[7,12]. For this reason lymphadenectomy is recommended as the main step of a curative surgical treatment[6,13,14]. According to the TNM staging system[15], the N stage is classified into 5 levels based on the number of metastatic LNs (NX: Regional lymph LNs cannot be assessed; N0: No regional LNs metastasis; N1: Metastasis in 1-2 regional LNs; N2: Metastasis in 3-6 regional LNs; N3: Metastasis in 7 or more regional LNs; N3a, metastasis in 7-15 LNs; N3b, metastasis in > 15 LNs)[16].

However, the extent of lymphadenectomy has been a controversial topic for a long time with no worldwide consensus as yet. A minimum of 16 LNs has been recommended as an adequate number in radical gastrectomy for GC to ensure reliable N staging. Studies documented that the prognosis is influenced by the number of dissected metastatic LNs. The number of retrieved LNs is a prognostic factor for GC, but the optimal number of retrieved LNs still appears to be controversial. In patients with stage III GC, removal of more than 40 LNs during total gastrectomy has been recommended[17]. According to Lu *et al*[18] , however, the sampling of 21 LNs could represent a superior cut-off point for radical gastrectomy to better determine the prognosis of patients.

The classifications of LNs have been upgraded intermittently since their first publication in 1962. The regional LNs of the stomach are classified into stations numbered from 1 to 20 (Table 2).

The optimal extent of lymphadenectomy has been extensively discussed in the past years. Definitions regarding different types of dissection was made by the Japanese registry data, after mapping the likelihood site of LNs metastasis from each primary tumor location[8]. Multiple levels of dissection are described (Table 3)[19,20]. Moreover, it has been demonstrated that station 4d and 6 metastases were associated with 14v metastasis[21]. For these reasons, station 14v should be dissected during gastrectomy for distal cancer with apparent metastasis to the infra-pyloric LNs.

Since, as stated before, surgery is the cornerstone for treatment of GC, any deviation from the normal postoperative course should be promptly assessed and treated. Despite efforts to reduce postoperative complications for decades, the rate of postoperative complications after curative gastrectomy are still reported to be 10%-20% and severe complications are known to be about 5%-7%[11,22-24].

Table 1 T staging system proposed by the Union for International Cancer Control and the American Joint Committee on Cancer

T category definitions	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*: Intraepithelial tumor without invasion of the lamina propria
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures. T3 tumors also include those extending into the gastrocolic or gastrohepatic ligaments, or into the greater or lesser omentum, without perforation of the visceral peritoneum covering these structures
T4	Tumor invades serosa (visceral peritoneum) or adjacent structures
T4a	Tumor invades serosa (visceral peritoneum)
T4b	Tumor invades adjacent structures such as spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum

The complications can be divided in complications related to anastomosis, to motility and to surgical site infection. Mortality and complications are still high in GC surgery[23,25,26]. Infectious complications such as anastomotic leakage, intraabdominal abscess and pneumonia are serious complications which increase postoperative mortality rate[11,27-29].

NOMOGRAM FOR PREDICTING EARLY POSTOPERATIVE COMPLICATIONS

In a recent issue of the *World Journal of Gastrointestinal Surgery*, Zhang *et al*[30] published the interesting paper. The study presented by Zhang *et al*[30] represent an interesting analysis on the possibility to prevent post-operative morbidity. Although retrospective and short follow up of the cohort, the statistical analysis, based on numerous variables, pinpoints some independent predictors of postoperative complication such hypertension, diabetes, previous abdominal surgery and perioperative blood transfusions[30]. The subsequent calculated nomogram model can be used as a guide to identify patients prone to complications. The study was performed on 131 patients with distal GC who underwent gastrectomy with D2 LN dissection. Of them, 16% of the patients developed early postoperative complications. In these patients, at univariate analysis the authors documented that the factors influencing early postoperative complications after distal gastrectomy are prealbumin level, hypertension, diabetes, history of abdominal surgery, R0 resection, and blood transfusion. Furthermore, the same variables identified in the univariate analysis are independent factors of early postoperative complications after distal gastrectomy in the logistic regression analysis[30].

Surgical team's attention could be focused, for instance, on predicting factors such as biomarkers which can be easily assessed. Among complications, the most fearsome is the anastomotic leakage considering the impact on postoperative course, oncological treatment and functional outcome[30]. Occurrence rates from 2% to 14% of all gastrectomy, usually 7 d after surgery[30]. C-reactive protein have already been tested to have high sensitivity for the detection of anastomotic leakage in different types of surgery[31-34]. Procalcitonin elevation was detected as a marker for surgical/infectious complications after esophagectomy or gastrectomy. The first study that prospectively and systematically analyzed procalcitonin as an early laboratory marker of anastomotic leakage concluded it was not superior to C-reactive protein as a predictor of anastomotic leakage[35].

In GC surgery, anastomotic leakage is a complication that occurs especially after total gastrectomy at the level of the esophago-jejunal anastomosis. An anastomotic leakage occurred in 4 our patients (2.1%), and was fatal in one case[11]. Other studies report an incidence of dehiscence in 8.6%[29] and 14.7% of patients[36]. The anastomotic leakage is responsible for an increase in the length of hospital stay, even lasting more than 40 d[37].

In relation to the reconstruction adopted, duodenal dehiscence result from the failure of the suture on the duodenal stump; this results in leakage of biliary-pancreatic secretion from the duodenal lumen into the abdominal cavity. Zhang *et al*[30] observed duodenal dehiscence in 19.1% of their cases. The incidence of duodenal dehiscence is on average around 3%[38], with mortality rate on average 11%[39].

If there is drainage near the dehiscence, the secretion is partially or totally conducted to the outside. The fistula is defined as "low flow rate", if the secretion drained externally is < 200 mL/d, or "high flow rate", if the secretion amounts to > 200 mL/d. This distinction has a prognostic value, as closure of the dehiscence can frequently be achieved with exclusive conservative treatment when the fistula has a low flow rate. Usually, mortality was almost zero if the fistula had a low flow rate, but around 40% if it had a high flow rate[38].

Table 2 Anatomical definitions of lymph node stations

Station	Definition
1	Right paracardial lymph nodes, including those along the first branch of the ascending limb of the left gastric artery
2	Left paracardial lymph nodes including those along the esophago-cardiac branch of the left subphrenic artery
3	3a Lesser curvature lymph nodes along the branches of the left gastric artery
	3b Lesser curvature lymph nodes along the 2nd branch and distal part of the right gastric artery
4	4sa Left greater curvature lymph nodes along the short gastric arteries (perigastric area)
	4sb Left greater curvature lymph nodes along the left gastroepiploic artery (perigastric area)
	4d Right greater curvature lymph nodes along the 2nd branch and distal part of the right gastroepiploic artery
5	Suprapyloric lymph nodes along the 1st branch and proximal part of the right gastric artery
6	Infrapyloric lymph nodes along the first branch and proximal part of the right gastroepiploic artery down to the confluence of the right gastroepiploic vein and the anterior superior pancreatoduodenal vein
7	Lymph nodes along the trunk of left gastric artery between its root and the origin of its ascending branch
8	8a Anterosuperior lymph nodes along the common hepatic artery
	8p Posterior lymph nodes along the common hepatic artery
9	Coeliac artery
10	Splenic hilar lymph nodes including those adjacent to the splenic artery distal to the pancreatic tail, and those on the roots of the short gastric arteries and those along the left gastroepiploic artery proximal to its 1st gastric branch
11	11p Proximal splenic artery lymph nodes from its origin to halfway between its origin and the pancreatic tail end
	11d Distal splenic artery lymph nodes from halfway between its origin and the pancreatic tail end to the end of the pancreatic tail
12	12a Hepatoduodenal ligament lymph nodes along the proper hepatic artery, in the caudal half between the confluence of the right and left hepatic ducts and the upper border of the pancreas
	12b Hepatoduodenal ligament lymph nodes along the bile duct, in the caudal half between the confluence of the right and left hepatic ducts and the upper border of the pancreas
	12p Hepatoduodenal ligament lymph nodes along the portal vein in the caudal half between the confluence of the right and left hepatic ducts and the upper border of the pancreas
13	Lymph nodes on the posterior surface of the pancreatic head cranial to the duodenal papilla
14	Lymph nodes along the superior mesenteric vein
15	Lymph nodes along the middle colic vessels
16	16a1 Paraaortic lymph nodes in the diaphragmatic aortic hiatus
	16a2 Paraaortic lymph nodes between the upper margin of the origin of the celiac artery and the lower border of the left renal vein
	16b1 Paraaortic lymph nodes between the lower border of the left renal vein and the upper border of the origin of the inferior mesenteric artery
	16b2 Paraaortic lymph nodes between the upper border of the origin of the inferior mesenteric artery and the aortic bifurcation
17	Lymph nodes on the anterior surface of the pancreatic head beneath the pancreatic sheath
18	Lymph nodes along the inferior border of the pancreatic body
19	Infradiaphragmatic lymph nodes predominantly along the subphrenic artery
20	Paraesophageal lymph nodes in the diaphragmatic esophageal hiatus

Clinically, duodenal dehiscence manifests itself more frequently between the 4th and 6th postoperative day with the change to a greenish shade of straw color, which normally has the serum collected in the sac connected to the peri-duodenal drainage. The biochemical test shows a concentration of amylase, lipase and bilirubin at least double that of serum. If the drainage has been removed before dehiscence occurs, the secretion collects in Morrison's lodge. Extensive effusions also reach the supra-hepatic site, the right parieto-colic shower and to a lesser extent the cable of Douglas and the folds of the mesentery. In this case the diagnosis is made after first performing an abdominal computed tomography (CT) scan, motivated by intermittent fever, and delayed intestinal canalization, and subsequently a percutaneous drainage.

An important cause of dehiscence is the excessive devascularization of the duodenal stump, which involves the failure of one or more points in an area of fragmented necrosis with consequent filtration of liquids. The problem typically manifests itself between the 5th and 6th postoperative day, probably in relation to the timing of the evolution of the necrosis and the resumption of peristalsis. The enzymes of the biliary-pancreatic secretion degrade the collagen on the

Table 3 Extent of systematic lymphadenectomy in distal gastrectomy

Lymph nodes dissection	Lymph node station, *n*
D0	Lymphadenectomy less than D1
D1	1, 3, 4sb, 4d, 5, 6 and 7
D1+	1, 3, 4sb, 4d, 5, 6, 7, 8a and 9
D2	1, 3, 4sb, 4d, 5, 6, 7, 8a, 9, 11p and 12a

D: Extent of lymph nodes dissection.

lines of the anastomosis and aggravate the damage. Other possible causes of dehiscence are the accidental cauterization of the duodenal wall and the increased intraluminal pressure produced by the secretions that accumulate in case of prolonged duodenal hypokinesia.

The metabolic alterations caused by duodenal dehiscence can quickly lead to patient death. Initially, continuous fever occurs with possible peaks preceded by leukocytosis, tachycardia, persistent peristaltic silence, meteorism, diffuse or localized abdominal tenderness. If drainage of secretions to the outside is adequate, antibiotic treatment can control sepsis, but nutritional status must also be considered.

In some cases, the area of dehiscence adheres to the surgical wound; the enteric secretion forms a subcutaneous collection, which subsequently opens to the outside, creating the so-called "enterocutaneous fistula". More frequently, the secretion tends to be delimited by the tissue reaction in a collection varying in size between the right hemidiaphragm and the pelvic cavity, partially filtering outwards *via* drainage. Factors that prolong the duration of a fistula are malnutrition, epithelialization of the passage, a high flow rate, a short path, a previous exposure to radiation, distal obstruction of the duodenal lumen, age over 60 years and concomitant pathologies[38].

Treatment is subject to knowledge of the location and extent of the fistula. Ultrasound and/or CT allow you to locate the collections, position one or more 10-14 Fr percutaneous drains inside them and subsequently check their position to ensure optimal drainage. There are no randomized clinical trials demonstrating the superiority of conservative treatment or surgical treatment. However, experience indicates quite clearly that surgical treatment is initially contraindicated since acute tissue inflammation hinders the healing of a new suture. Conservative treatment should therefore be continued for no more than 6-8 wk, *i.e.* until the fistula no longer has any possibility of closing. At the same time, the resolution of acute inflammation will allow a safer surgical approach. This prolonged wait is justifiable in the case of a low-capacity fistula and in the absence of complications.

Another severe complication is pancreatic fistula. We have observed this complication only in a group of patients where more than 35 LNs had been removed[11]. This complication was found to be severe, as reported in the literature [40-42]. Many factors are held responsible for the onset of this fearful and often fatal complication. Among these, obesity, a pancreas with normal texture, intraoperative trauma, and the use of high-energy devices when performing LN dissection are considered the most important risk factors for the development of postoperative pancreatic fistula[40,41].

Other complications, although less serious, are gastrointestinal dysfunctions linked to the reconstruction of intestinal transit after distal gastrectomy and complications of the gallbladder and biliary tract, if the gallbladder is not removed during the gastrectomy operation.

Depending on the type of intestinal transit reconstruction after distal gastrectomy, such as Billroth-II gastrojejunostomy or Roux-en-Y, clinical syndromes of varying severity may occur. Billroth-II reconstruction exposes the patient to bile reflux and gastritis, with disabling symptoms and the risk of cancerization of the residual gastric stump. The operated stomach is considered as a pre-malignant condition and the greatest risk of cancerization occurs 15 years after the operation and especially in reconstruction according to Billroth-II. From a functional point of view, multiple studies in the literature recognize the Roux-en-Y gastrojejunostomy as having the best functional results[43,44]. These are confirmed in recent meta-analyses, so much so that this reconstruction modality has, for years, been the most widespread both after gastric resection and after total gastrectomy. The uniformly positive experience of using the Roux-en-Y jejunal loop for reconstruction after partial or total demolition of the stomach now tends to also replace the Billroth-II technique after gastric resection[45,46].

Another aspect to consider is that relating to biliary and gallbladder complications if the gallbladder is not removed during the distal gastrectomy operation. We always prefer to perform cholecystectomy during gastrectomy, both to avoid inflammatory complications of the gallbladder in the follow-up period and for an easier lymphadenectomy of the hepatoduodenal ligament. In patients with a radical resection, when a D2 lymphadenectomy is performed and the duodenum is excluded in the intestinal reconstruction, cholecystectomy, considered by some to be a non-essential measure, is necessary to avoid gallstone formation and its complications. In this setting, a prophylactic cholecystectomy is necessary for patients with a good cancer prognosis[47-49].

Furthermore, infectious complications may also be a risk factor for GC recurrence[50]. The severity of the complication may also be correlated to the timing of recurrence[51]. Complications in the postoperative period may also result in accelerated hepatic metastasis after GC resection[52]. Postoperative infectious complications were an independent prognostic factor for five-year overall survival after curative gastrectomy. In addition, inflammatory pathways associated with infectious complications have been reported to affect cancer recurrence and treatment. In a recent study of 6585 patients who underwent curative gastrectomy, 5-year survival was 86.0% in uncomplicated patients and 74.1% in patients

with infectious complications. At univariate analysis, the authors documented that infectious complications have a statistically worse survival. It has also been documented that local recurrence, LNs recurrence and distant metastases are significantly associated with infectious complications[53]. In addition to these aspects, it must be considered that patients who experience postoperative infectious complications have a delay in adjuvant chemotherapy. Furthermore, the prolonged duration of hospitalization and the need for additional treatments, such as antibiotics or percutaneous drainage, reduce patient compliance with adjuvant chemotherapy.

CONCLUSION

In conclusion, the results of the study presented by Zhang *et al*[30] suggest that the prediction model can be used to guide the detection of early postoperative complications and has clinical reference value.

FOOTNOTES

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