Review Article

Management of postoperative complications of lymphadenectomy

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Abstract: Gastric cancer remains a disease with poor prognosis, mainly due to its late diagnosis. Surgery remains as the only treatment with curative intent, where the goal is radical resection with free-margin gastrectomy and extended lymphadenectomy. Over the last two decades there has been an improvement on postoperative outcomes. However, complications rate is still not negligible even in high volume specialized centers and are directly related mainly to the type of gastric resection: total or subtotal, combined with adjacent organs resection and the extension of lymphadenectomy (D1, D2 and D3). The aim of this study is to analyze the complications specific-related to lymphadenectomy in gastric cancer surgery.

Keywords: Gastric cancer; lymphadenectomy; management of complications; stomach neoplasm

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Introduction

In respect to gastric cancer, surgery remains the only treatment with curative intent, mostly when is associated with early diagnosis. Radical resection with free-margin and extended lymphadenectomy is the preferred surgical strategy in Eastern Asian centers and most specialized Western centers (1).

Despite over the last two decades there has been an improvement on postoperative outcomes, complications rate is still not negligible even in high volume centers and is directly related mainly to the gastric resection: total or subtotal, combined or not with adjacent organs resection (2-4). Total gastrectomy has been associated with higher morbidity when compared with subtotal gastrectomy (5). Likewise, splenectomy and distal pancreatectomy provide higher incidence of surgical complications and higher mortality (6). Zilberstein *et al.* reported a morbidity rate of 39% and 9.1% mortality rate for patients who underwent gastrectomy associated with splenectomy, which was significantly higher than patients who were treated without combined resection of adjacent organs (P<0.001) (2). Although some studies have reported that D2 lymphadenectomy when compared with limited lymphadenectomy (D1) is associated with higher morbidity and mortality and does not provide better long-term overall survival, recent reports have shown that extended (D2) and super-extended (D3) lymphadenectomy does not involve higher postoperative complications risks and mortality, especially when pancreatosplenectomy is not performed along with D2 node dissection (3,7,8). Yet, 15 years after the conclusion of its accrual, the Dutch trial finally reported a significant decrease of recurrence after D2 lymphadenectomy (9). Thus, this type of lymphadenectomy is considered in Eastern Asia, as well in many Western centers as the standard procedure in gastric cancer surgery.

The aim of this study is to analyze the complications specific-related to lymphadenectomy in gastric cancer surgery. Morbidity directly correlated to gastrectomy such as duodenal stump fistula, anastomotic leakage and stricture are not the scope of the present article and therefore were not analyzed.

Material and methods

A literature review was performed using Medline/PubMed, Cochrane Library and SciELO with the following descriptors: gastric cancer, lymphadenectomy, management of complications, stomach neoplasm. The language used for the research was English.

Lymph node stations and lymphadenectomy

The lymphatic nodes of the stomach were organized in a very useful classification by the Japanese Gastric Cancer Association (JGCA): according to this classification, lymph nodes (LN) draining gastric tumors are divided into 20 stations, plus stations number 110, 111 and 112. They are classified into three groups depending on their proximity to the stomach. In this nodal station system, LNs closer to the stomach (stations No. 1–6) and along the left gastric artery (station No. 7), are defined as group 1 or N1; LNs along the common hepatic artery (station No. 8), celiac trunk (station No. 9), splenic artery (station No. 11) and hepatoduodenal ligament (station No. 12) are defined as group 2, or N2. The others (10-17) are defined as N3 and N4 group.

Previously, to perform the lymphadenectomy according to the Japanese school, this lymph node resection was defined according to the location of the tumor penetration degree in the gastric wall and histological type (18,19). Recently, the type of lymphadenectomy was adopted according to the gastrectomy performed (total or subtotal), considering D1 lymphadenectomy when removing nodes N1 and D2 when, in addition to the N1 LN, are also removed the nodes from the N2 group (20). This methodology to guide the removal of LN is based on studies of lymphatic involvement in various tumor types (location, tumor penetration degree in the gastric wall and histologic type), associating it with the observed survival according to the dissection performed (10).

Pancreatic fistula (PF)

Universally, there is no definition accepted of PF. Some authors emphasize on the amylase content of the drainage fluid, while others are more concerned about the aspect and volume of the drain output, as well its duration. Anyway, postoperative PF may be defined as a leak from the pancreatic ductal system around the pancreas which contains pancreatic enzymes fluids that are originated from the scarified pancreatic parenchyma.

The incidence of PF may vary from 0% to 20% (11,12). In fact, PF is one of the most frequent major complications after gastrectomy associated with pancreatosplenectomy and with extended lymphadenectomy. When it occurs, commonly is followed by contamination/infection, resulting in peripancreatic abscess. Another very worrying situation is secondary hemorrhage from major arteries damaged by contamination, which can be sometimes fatal (13,14).

Early recognition and prediction of risk factors are mandatory for decreasing morbidity and mortality. Routine intra-cavitary drainage at the time of gastrectomy with periodic amylase concentration dosage of the fluid could be useful for detection and management of such postoperative complication. It is acceptable for the diagnosis of PF any measurable volume of fluid after the third postoperative day, with an amylase concentration three times higher than the normal serum value (15-17). Iwata *et al.* reported that pancreas-related complications are highly unlikely to be observed when amylase concentration is less than 1,000 IU/L, with a negative predictive value of 97.7% (21).

PF onset is related to surgical trauma with direct injury to pancreatic parenchyma. It is also associated with pancreatosplenectomy followed by D2 gastrectomy, with an increased postoperative morbidity and mortality. Therefore, resection of the pancreas and the spleen are only acceptable when there is direct extension of disease to these organs (22). Yu *et al.* analyzing 900 consecutives radical gastrectomies, reported a postoperative PF rate of 3.3%. Risk factors were total gastrectomy, combined resection and open surgery (23). Nobuoka *et al.* analyzed the causes of PF on 740 gastric cancer patients who underwent total gastrectomy and reported that BMI and total gastrectomy with pancreatosplenectomy are the influencing factors (13). Katai *et al.* associated besides obesity, older age and dissection along the distal splenic artery as risk factors (17).

The development of PF involves mainly two affairs: prevention and treatment. Prophylactic drain after gastrectomy with extended lymphadenectomy allows monitoring bleeding and the occurrence of pancreatic or any other leakage. Attention must be taken regarding the place and time to remove these drains from the patient. It is reported the increased risk for infections and others complications such as enteric fistulas for drains left in place for too long (24,25).

Conservative treatment for PF is effective in around 80% of cases. Nonetheless, patients with high output leakage and signs of severe sepsis or hemorrhage should undergo to surgery. In order to diminish pancreatic exocrine function,

total oral fasting and parenteral nutrition are the initial clinical management of PF. This simple therapy may work in several patients, with spontaneous closure of the fistula. In some cases, the administration of pancreatic inhibitors function such as octreotide and somatostatin may be useful, not to prevent PF, but to reduce the amount of outflowing (26). Contamination of PF occurs very often. Therefore, according to patient's clinical condition, broad spectrum antibiotics therapy is recommended until sepsis is controlled (27). In case that all these measures fail to reduce the fistula output, an alternative is to perform sphincterotomy or transampullary stenting with endoscopic retrograde pancreatography, which might be thorny in patients submitted to gastrectomy and duodenal exclusion (28).

Most patients with PF will benefit from conservative treatment. Nevertheless, surgery is imperative for patients with marked clinical worsening, inefficient percutaneous drainage of abscesses, vascular complications, progressive sepsis, oncoming organ failure, etc. These situations are commonly associated with elevated postoperative mortality (29).

Hemorrhage

Postoperative bleeding after radical gastrectomy is either luminal or abdominal, and each requires different diagnostic and treatment approaches according to its origin. Bulky bleeding is a wasting complication and is specific related to extended or super extended lymphadenectomy and may occurs in 0.6–3.6% (30). Luminal bleeding often originates from anastomosis sites and will not need any aggressive therapy. On the other hand, abdominal massive hemorrhage maybe life-threatening if treatment is not initiated promptly. Yang *et al.* investigated 1,875 consecutive patients receiving gastrectomy with extended (D2 or D2 plus) lymphadenectomy. The overall postoperative arterial hemorrhage rate was 1.92%, with a relatively high mortality rate of 33.3%. It is mostly caused by abdominal arterial bleeding, mainly from branches of the celiac trunk, the common hepatic artery and its branches and splenic artery (31). Rupture of abdominal arteries can provoke not only massive abdominal bleeding but also intraluminal bleeding. Abdominal bleeding is usually diagnosed when there is bleeding from the abdominal drain, abdominal distension with radiologic findings or a fall in hemoglobin count. The main factors predisposing to postoperative bleeding is prolonged operation time, obesity and combined organ resection (32). It may happen early (within 24 h after surgery) or late (beyond 24 h after surgery). This last situation is more frequent (80%) and often associated with worse prognosis, due to its correlation with anastomotic leakage, PF and thereafter infection (33). Technical failure is probably the main cause of bleeding in the early postoperative period, whereas arterial wall injury during arterial skeletization maneuvers performed in lymphadenectomy occurs more frequently in the late bleeding period.

Clinical manifestations include bright red bleeding from the drain, pale skin, abdominal pain, distension, tachycardia, hypotension, oliguria and hemodynamic instability. Bedside ultrasonography, paracentesis, CT scan and angiography may be helpful to diagnosis, but will depend on patient's condition, hemodynamic status, amount of bleeding, risk factors and onset time of bleeding. Initial treatment consists in fluid resuscitation and blood transfusion (34,35). In case of a life-threatening situation, immediate re-laparotomy is considered the cornerstone of treatment. However, a less traumatic procedure such as interventional angiography can be useful in many cases, mainly in early postoperative bleeding. Overtly, relative stable hemodynamic conditions are mandatory for indication of this approach. To perform radiological intervention, a team of interventional radiologists must be available 24 h per day. Angiography of the superior mesenteric artery and celiac trunk must be accomplished to try to detect any extravasations of contrast or pseudo-aneurysms. Whenever angiography finds the source of bleeding, artery embolization may stop the bleeding. Another possibility is to place a covered stent graft. The choices between the two methods will depended on the preference of interventional radiologists and anatomic conditions. Salvage re-laparotomy should be undertaken in case of negative finding or failure angiography. Among the options during surgery we can list ligation of bleeding vessels, over sewing the bleeding spots, vascular reconstruction, and organ resection, such as splenectomy. Immediate re-laparotomy can be effective in early postoperative arterial bleeding with admissible results. Still, in the late bleeding phase, re-operation can be challenging due to inflammatory reactions, adhesions, and friability of tissues. Damage control surgery may be used as a heroic attempt when bleeding control failed, primarily for patients who present hypothermia, coagulopathy, and acidosis, also known as the triad of death (36).

Bile duct injury

Great concern must be given to the lymph node dissection of the station No. 12. It is situated along the proper hepatic artery, limited superiorly by the hepatic duct confluence, the bile duct to the right, the hepatoduodenal ligament region to the left and the pancreatic border inferiorly up to the anterior aspect of the portal vein. Due to the proximity of important vascular and bile structures, the risk of surgical complications secondary to iatrogenic injury demands careful dissection of the LN in this region (37,38).

This procedure, when performed by experienced surgeons, has minimal chances of complications. There are isolated reports of intraoperative injury of these structures, such as the hepatic artery, main bile duct and cystic artery with posterior gallbladder necrosis or even bile duct necrosis. Nevertheless, due to low index of such complications, these reports are apart from great comparative studies between D1 *vs.* D2 open lymphadenectomy (14,39).

With the development of laparoscopic techniques for advanced gastric cancer, dissection of station No. 12 has become a great challenge for surgeons. In recent Korean study, Bo *et al.* reviewed 302 patients with complications after laparoscopic D2 gastrectomy for gastric cancer, showing 4.97% intraoperative complications, such as one iatrogenic cystic artery injury leading to gallbladder necrosis and one bile duct lesion, adding up a total of 0.66% complication rate in laparoscopic procedures (40).

When we think about bile duct injury during lymphadenectomy in gastric cancer surgery, two possible scenarios arise: one is the injury identified intra-operatively, which has a better prognosis when is proper corrected. Usually requires simple suture and less often bile duct anastomosis, bile-digestive anastomosis or placement of T-tube. A darker scenario occurs when the iatrogenic injury is not identified immediately and late fistula befalls mainly due to necrosis of the bile duct resulting from thermal injury from the electrocautery. In a certain amount of time, if there is a drain nearby this region, a bile leakage will clinic manifest and may be treated conservatively. Radiological intervention with percutaneous trans-hepatic cholangiography and stent placement might be an option. Patients may develop coliperitoneum, bilioma, infection and peritonitis evolving rapidly to sepsis. Commonly, surgical intervention is required for peritoneal washing and extensive cavity drainage. Primary repair of the bile duct injury may be difficult and will depend on patient's clinical and surgical site condition, expertise of the surgeon and the type of lesion. Final repair of the lesion may be delayed until the patient is in better clinical conditions. Broad-spectrum antibiotics are always recommended.

Despite the low risk of such complications described, surgeons who perform extent lymphadenectomy of this territory must be skilled to perform biliary and vascular repairs, including grafts, vascular reconstruction and bile-digestive anastomosis.

Chylous fistula

Chylous fistula corresponds to the presence of milky peritoneal effusion rich in triglycerides. It is cause by the presence of intestinal or thoracic lymph inside the abdominal cavity and it is developed due to the rupture or obstruction of the lymphatic system. The major causes are traumatic lesions, surgical procedures or malignant obstructions. Other even more rare underlying conditions have been described as leading to chyloperitoneum (41). It is a very rare post-operative complication and its incidence undetermined. In fact, it is related to extended lymphadenectomy and pancreatic manipulation (42).

According to Bostanci *et al.*, lymphatic fistula rate was 11.7% after gastrectomy with D3 lymph node dissection (8), whereas it was as low as 0.3% to 0.7% after D1 or D2 laparoscopic gastrectomy (40,43). Lo *et al.* reported an incidence of chylous fistula of 2.4% when gastrectomy was associated with pancreatosplenectomy (44).

The output of high volume of fluids containing proteins and lymphocytes may increase morbidity and mortality in a previously debilitated population such as post-operative patients. It is included multiple organs dysfunctions related to hypovolemia, loss of electrolytes and infections related to the immunity deterioration.

A multicenter study addressed the management of high-output chylous fistula after D2-lymphadenectomy in patients with gastric cancer. Nine patients out of 436 gastrectomies were detected with chylous fistula. The average amount fistula output was 939 mL per day. The mean time to fistula closure and length of hospital stay were 23 and 24 days, respectively (45).

Initial treatment should always be conservative, with good results in most cases. It consists of low lipid and high medium-chain triglycerides diet. In case of failing, total parenteral nutrition and somatostatin analogs may be used (46). Surgery should be reserved for cases that do not respond to conservative treatment. Bipedal

lymphangiography with lipiodol seems to be a promising tool with resolution rates of the chylous leakage reaching up to 70%, especially when the daily volume of chylous fistula output is less than 500 mL (47). Further clinical research is needed to enhance prevention, diagnosis, and treatment of this relevant surgical problem.

Conclusions

Surgical resection with free margins associated with adequate lymphadenectomy is the cornerstone in gastric cancer surgery. This type of approach offers better overall survival and lower recurrence. Yet, even when performed in specialized high volume center, morbidity is not negligible and is often associated directly to gastric resection and the digestive tract reconstruction. The most common complications related to lymphadenectomy are PF, hemorrhage, chylous ascites and bile duct injury. The surgical team must be prepared to deal with these types of perioperative complications.

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Footnote

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