



Laparoscopic splenic hilar lymph node dissection for advanced gastric cancer: to be or not to be

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Abstract: The incidence of proximal gastric cancer has increased in both the East and the West. Although some novel reconstructions like double-tract or double-flap anti-reflux procedure related to proximal gastrectomy are promising, total radical gastrectomy still accounts for a significant portion of these procedures. D2 radical gastrectomy is the globally accepted standard surgical procedure for advanced gastric cancer, and lymph node (LN) dissection is considered as the critical point of radical surgery and closely related to the prognosis. The splenic hilar LNs (No. 10) are LNs that need to be removed during standard D2 surgery for proximal and total gastrectomy. Lymphadenectomy does not only provide valuable information on the prognosis of gastric cancer, but the thoroughness of the sweep itself is directly related to postoperative survival. The incidence of splenic hilar LN (No. 10) metastasis rate is not high. Although the LN metastasis pathway around the spleen is complicated, the feasibility of laparoscopic splenic hilar LN dissection in locally advanced gastric cancer has been verified. However, these results are mostly from small volume clinical studies, and the fact is that the dissection of the splenic hilar is technique-demanding even for open surgery. The rational strategy for LN dissection for surgeons is still controversial. For splenic LN dissection in radical gastric cancer surgery, whether to select individualized splenic LN dissection for those patients highly suspected of clinical metastasis or to advocate the evidence-based strategy and neglect dissection in lower risk patients to avoid over-removing of LNs, is a vital question that needs to be clarified.

Keywords: Gastric cancer; laparoscopic; lymph node dissection (LN dissection); spleen-preserving; splenic hilar

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Introduction

For the surgical treatment of advanced gastric cancer, radical gastrectomy with standard D2 lymph node (LN) dissection is still the preferred procedure. Regarding the proper range of D2 dissection, the No. 10 LN is defined by the Japanese Gastric Cancer Association (JGCA) as the LN around the splenic hilum. Although many studies focus

on this, there is still significant controversy and varying conclusions. According to common thinking, splenectomy appears to be mandatory for performing *en bloc* dissection of the No. 10 LN and No. 11 LN along the splenic artery. This special issue was stressed by the 5th edition of the latest Japanese Gastric Cancer Treatment guideline (Clinical Questions 4, CQ4), which firmly concluded that spleen

resection should not be recommended for advanced gastric cancer when the tumor is not infiltrated into the greater curvature.

The initial content of splenectomy in radical gastrectomy is to complete a thorough splenic hilar LN dissection, which had become increasingly sidelined as accumulating cognition on spleen as an important immune organ (1), and emerging evidences indicated that splenectomy carries high risks of morbidity and mortality, even negative effects on the prognosis of gastric cancer patients (2). Taken together of the potential risks and benefits, it is obvious to understand that splenectomy solely for the purpose of hilum LN dissection is not recommended.

In recent years, gastric cancer has tended to migrate proximally (3), and the incidence of proximal gastric cancer has increased (4). The metastatic rate of the splenic hilar LNs for gastric cancers in the middle-upper or one-third was about 8.8% to 20.9% according to the reported data (5,6). For the surgical treatment of advanced gastric cancer, radical gastrectomy with standard D2 LN dissections is still the popular choice.

Spleen-preserving splenic hilar lymphadenectomy was initially designed to achieve the purpose of both adequate LN dissection and the function preservation of spleen by Schwarz (7) in 2002, and the first laparoscopic spleen-preserving hilar LN dissection was introduced by Hyung (8) until 2008. Since then, studies concerning this problem had gained popularity and many spleen-preserving methods had been reported (9-12), and results of these studies basically suggested that this procedure is feasible and safe with non-inferior oncological results. Moreover, this compromise type of splenic hilar LN dissection not only provide important criterion for tumor staging (13), but the sweeping procedure itself is also considered to be an independent prognostic factor (14).

Pros and cons of the surgical technique: when Japan meets China

The JCOG0110 trial (15) was launched by the Japan Clinical Oncology Group (JCOG) to evaluate splenectomy in total gastrectomy for proximal gastric carcinoma. The apparently irrefutable conclusion of this trial was revealed in 2017 (16). However, the results of this trial should be objectively analyzed. Most medical centers in Japan perform *en bloc* dissection of the No. 10 LN by simultaneous resection of the spleen, and most Japanese scholars consider spleen-preserving hilar LN dissection as

D1+ surgery instead of D2 radical surgery. Thus, it is easy to understand why the JCOG0110 trial divided the study group into splenectomy and spleen-preserving groups, but the conclusion was otherwise about whether to include No. 10 LN or not. The result of the JCOG0110 trial provided clues and important evidence for hilar LN dissection, and was interpreted as indicating a lack of significant difference in the survival between the two groups, but did confirm a difference in pancreatic leakage (significance, 12.6% *vs.* 2.4%). However, it should be noted that only 14.1% (71/505) of the enrolled gastric cancer patients were at the early stage, and the information of these patients might have affected the final analysis of the survival curves of the two groups.

Additionally, the reported rates of pancreatic leakage are low in other studies concerning the spleen-preserving hilar LN dissection, and the JCOG0110 trial does not include such patients in the study. Moreover, complications of the No. 10 LN dissection should not be seen as completely equivalent to complications related to splenectomy. Therefore, the conclusion that the No. 10 LN dissection was excluded in the D2 station of LN dissection after total gastrectomy of the renewed 5th edition can be rationally understood.

In China, most gastric cancers are found in the advanced stage; splenic hilar LN dissection is more frequently practiced, is taken for granted as the essence of D2 operation, and is considered as routine either when obvious lymphadenomegaly is noted around the splenic hilum and/or splenic artery or when the greater curvature is infiltrated by tumor. In the case of bulky LNs, the removal of the No. 10th LN is of great significance, and this was confirmed by the JCOG0110 and JCOG9501 collaboration study units (17). A similar strategy was also favored by some collaboration units of the JCOG0110 and JCOG9501 trial as a reasonable clinical resolution when metastasis is suspected. What should be noticed is that the JCOG0110 trial is about open surgery, thus the advantages and disadvantages of laparoscopic surgery in advanced gastric cancer still require clarification.

Undefined issues in the current research

As the JCOG0110 trial exclusively examined open gastrectomy, a comparison of the advantages and disadvantages of hilar LN dissection for laparoscopic gastrectomy remains incomplete, and the following four

major problems still need to be thoroughly clarified.

Issue 1: is splenic hilar LN dissection indispensable?

Advanced gastric cancer carries a certain degree of splenic hilar LN metastasis, and the metastasis rate of No. 10 LN was reported to be from 9.8% to 26% in the literature (6). The traditional view was that splenic LN dissection should be recommended for upper 1/3 gastric cancer patients with risk factors (18). In other words, for patients with cT1–T2 mid-upper gastric cancer, restrictive splenic LN dissection should be performed, while for patients with cT3 and above, radical dissection should be performed (19,20). From the oncological perspective, it was of great importance to perform No. 10 LN dissection, and No. 10 LN metastasis was directly related to the prognosis of the patients (21). In a report by Son *et al.*, the 5-year overall survival rate was 54.8% in a negative LN metastasis group and 24.1% in a positive LN metastasis group (22). Meanwhile, patients with positive splenic LN metastasis had poor prognosis, and splenic hilar LNs resembled perigastric LNs which were an independent risk factor in prognosis assessment. However, studies have shown that the prognosis of patients with positive splenic LNs is significantly worse than that of other patients with LN metastasis. Therefore, splenic LN metastasis should be considered as an incurable factor (18). This contrasts studies indicating that splenic hilar LN dissection may have little effect on the degree of radical resection for patients with Siewert type II esophagogastric adenocarcinoma (23).

In the JCOG9501 trial, 199 patients who underwent total gastrectomy were enrolled. Of the 191 patients underwent splenectomy and concomitant removal of the No. 10 LN, 16 patients (8.4%) were pathologically confirmed to be positive for splenic LNs, and 8 patients (4.2%) had a survival period of more than 5 years; these results objectively reflect the vital application value of splenic LN dissection. Given this, we may deduce from the additional result of the JCOG9501 trial, that the benefits of No. 10 LN dissection could outweigh its risks in advanced stage gastric cancer patients.

Issue 2: the proper maneuver of splenic hilar LN dissection, spleen-preserving, or combined splenectomy

The initial concept of extreme gastric cancer operation, represented by the Appleby procedure, involved removing the entire left upper abdominal organs to perform thorough

LN dissection. However, function-preserving surgery has gradually gained attention over the last three decades, so nowadays even combined resection of the spleen and pancreatic tail is thought to be too aggressive, as it entails certain rates of mortality and morbidity (24). The significance of simultaneous pancreaticosplenectomy or splenectomy along total gastrectomy has also been evaluated, and the study concluded that such radical procedures were not obligatory for splenic hilar LN dissection (25). As for isolated splenectomy with the pancreatic tail preservation, which once represented the mainstream option for splenic hilar LN dissection and was subsequently replaced by spleen and pancreas preservation lymphadenectomy, the results showed that the postoperative survival rate was comparable in the preservation group, but the complication rate and mortality were much lower than those in the combined resection group (26). Recently, for the setting of tumors involved in the greater curvature or in relatively young patients without serosal exposure, splenectomy is thought to have a survival benefit according to results from single Japanese center (27). Older age, prolonged operation time, and pancreas resection constituted the main risk factors for the increase of complications after splenectomy (28). With the continuous improvement of surgical techniques, and the in-depth development of clinical research, the important physiological functions of the spleen have gradually gained attention (29), and the preservation of the splenic LNs by preserving the pancreas and spleen is the current surgical consensus. However, the “Real World” situation may not be exactly the same as the clinical studies (30), when we are in the era of individualized treatment and precision medicine, especially taken into consideration of spot case of hilum recurrence (31) of spleen-preserving LNs dissection that also reported by Japanese scholars.

The spleen-preserving hilar LN dissection can be divided into either *in situ* dissection or ectopic dissection, with the former being very easy to understand, and the latter requiring the mobilization of the spleen from its normal anatomical position through an incision to the extracorporeal space to offer LN dissection (18,32). In traditional open surgery, to achieve a dissection of the splenic hilar LN completely, the surgeon can generally dissociate the spleen and pancreatic tail and drag it out of the abdominal cavity, in a process named “pull-out dissection” or “extracorporeal/*ex-situ* dissection” (32). However, this unique method is technically difficult in obese patients or when extensive omental adhesion is encountered. Also, there may be cases where the spleen

cannot be pulled out (33). As for the *in situ* splenic hilar LN dissection or the intracorporeal dissection, the surgical field may be confined by the narrow space when the spleen is in a deep position. The capsule of the spleen is brittle and prone to be torn when the topographic anatomy and adjacent relationship are complicated, so splenic hilar LN dissection is often a condition demanding technique and cannot be routinely performed (34). Also, spleen-preserving hilar LN dissection is rarely conducted, and splenectomy is seen as mandatory.

With the extensive development of laparoscopic surgery, surgeons have gained a deeper understanding of the spleen area anatomy (35,36). Through multi-dimensional and multidisciplinary research such as three-dimensional (3D) vascular reconstruction and membrane anatomy, it is more safe and feasible to preserve the splenic LNs while retaining the spleen. In contrast to open surgery, laparoscopic surgery is more precise in the identification of the perigastric fascia and fascial space, blood vessels, and their branches during lymphadenectomy. LNs along the splenic vessels and its branches can be easily exposed by the visibly enlarged views of the surgical field. As a result, accurate partial block LN sample or efficient *en bloc* lymphadenectomy can be easily achieved. Compared with open surgery, laparoscopic splenic hilar LN dissection is supposed to have smaller incisions, less trauma, shorter operation time and an even higher percentage of spleen preservation, without the need to sacrifice the integrity of radical LN dissection (37). Therefore, laparoscopy has certain advantages in the preservation of the spleen and in the dissection of hilar LNs, with one study reporting no significant difference in short-term efficacy between LN dissection and resection of the spleen (8).

Computer tomography reconstruction may serve as guidance and facilitate laparoscopic spleen-preserving splenic LN dissection (38). Laparoscopic spleen preservation with dissection of the 10th LN was initiated by Korean scholars in 2005 (39). After more than 10 years of development, it has been confirmed that laparoscopic LN dissection can be successfully performed by means of laparoscopic surgery even for advanced gastric cancer. Furthermore, the outcome of LN dissection has been demonstrated not to be inferior to open surgery in the case of adopting surgical methods of concomitant splenectomy. In particular, Lin *et al.* (40) made many meaningful contributions to the work of laparoscopic splenic LN dissection and accumulated reliable, evidence-based medical

evidence. Taken together, laparoscopic LN dissection is an advanced minimally invasive procedure that can be mastered after appropriate learning.

Issue 3: in the view of fluorescence laparoscopy or 3D technical display and the era of precise medicine

The Japanese gastric cancer treatment guidelines include laparoscopic surgery for advanced gastric cancer as a research strategy, and routine clinical application is not recommended (41). However, China has more proportion of gastric cancer patients in advanced stages as compared with Japan, and so it is easy to comprehend why many Chinese clinical trials favor advanced gastric cancer, and more stress and focus is put on it (42). Preliminary findings from these clinical studies suggest that laparoscopic D2 LN dissection is safe and feasible for advanced gastric cancer, and long-term survival is comparable to that of open surgery (43-45). However, the current level of evidence is still low and needs to be interpreted with caution, and laparoscopic total gastrectomy D2 LN dissection still faces the problem of splenic hilar LN dissection. In minimally invasive surgery, the surgeon's lack of hand touch and flexibility, along with a dependence on the assistant's exposure skills, make it more difficult to dissect the splenic LNs than in open surgery. Nevertheless, the magnification effect of the laparoscopic imaging system can clearly show the fascial space and blood vessels which, to a certain extent, may compensate for the lack of tactility (46). At present, the evidence for laparoscopic or robotic splenic hilar LN dissection is still limited to retrospective clinical analysis. Although the results show that laparoscopic or robotic splenic hilar LN dissection is safe and feasible, it requires superb surgical skills, well-rounded team and a certain learning curve (47,48), to cope with some unexpected emergency situations during this scrupulous operation (49). The safety, when compared with the efficacy of open surgery, and the impact on oncology endpoints need to be further validated in prospective randomized controlled trials in the future (50).

Indocyanine green fluorescence (IGF)

IGF imaging was first reported being applied in sentinel node (SN) mapping in patients with early gastric cancer (51), and was then implemented in laparoscopic sleeve gastrectomy (52) and in the evaluation of serosal invasion. Most recently, IGF LN was used in surgical margin

navigation and LN mapping in gastric cancer (53), but the role of IGF in splenic hilar LN dissection has yet to be clarified (54,55).

3D technique

In the case of LN dissection for the preservation of vascular structure in gastric cancer surgery, intraoperative CT-assisted 3D reconstruction technique was initially applied in gastric cancer surgery to reduce surgical complications and improve the extent of LN dissection (56). Results show that CT-assisted 3D reconstruction technology has a certain guiding significance for displaying perivascular structures; whether this application can be used for splenic LN dissection remains to be clarified by further study (57,58).

The application of the 3D laparoscopic technique has gradually matured. Previous studies have shown that 3D laparoscopic surgery has certain advantages in abdominal surgery (59,60), but the effect of LN dissection is still unclear, and more well-designed trials are warranted to evaluate 3D laparoscopic in gastric cancer surgery (61) with special emphasis on the role of splenic LN dissection.

Issue 4: the perspective of evidence-based medicine

At present, there are still many controversies about splenic hilar LN dissection of gastric cancer. Evidence has mostly been derived from small volume retrospective studies, and results of large randomized controlled trials are lacking (39). Therefore, besides evidence-guided clinical decision-making, the surgeon's experience with splenic hilar LN dissection is also a major consideration. Furthermore, the patient's general condition may also affect the extent and durability of the operation. Taken together the patients' factors, such as general conditions, tumor stage, or anatomy variations, along with the surgeons' factors, such as technical experience or preference, splenic hilar LN dissection can be safely conducted, either through spleen-preserving methods or concomitant splenectomy.

In response to the above controversial issues, more high-quality prospective randomized controlled studies are needed (62), and a higher level of evidence from such studies is eagerly anticipated (16,63).

Prospective

Whether choosing open surgery or laparoscopic surgery, the dissection of the splenic LNs is important for patients with advanced gastric cancer. Results of a single-center

randomized controlled trial from China were revealed recently, which suggest that laparoscopic spleen-preserving splenic hilar lymphadenectomy is a feasible procedure and as safe as open maneuver (63). The development of follow-up technology and the wide application of laparoscopic technology, along with its excellent surgical field magnification, modularized surgical procedures, and fine anatomical operations, have made a thorough splenic hilar LN dissection with the spleen preserved viable. Although the feasibility, safety, and short-term oncology of laparoscopic splenic LN dissection have been supported by evidence-based medical evidence, and the interim report of the first prospective clinical trial (NCT02980861) (63) that evaluate the splenic hilar LN dissection in laparoscopic gastrectomy had just released with positive results, proof of long-term efficacy and high-level RCT studies are still being expected, and the results of China's CLASS-04 trial (NCT02845986) could be important supplementary evidence for this special issue. Meanwhile, the trial for application of laparoscopic total gastrectomy with LN dissection for gastric cancer (KLASS-06) (NCT03385018), a multicenter randomized controlled trial sponsored by the Korean Gastric Cancer Association (KGCA), was launched with the aim of exploring the application of totally laparoscopic gastrectomy with LN dissection for gastric cancer (64). The data of these studies will provide a stronger basis for future research.

Conclusions

As laparoscopic splenic hilar LN dissection requires a long learning curve and a relatively fixed laparoscopic surgery team with sophisticated skills, the leadership of experienced gastrointestinal surgeons is also recommended, to get a more satisfying rate of spleen-preserving hilar LN dissection; splenectomy may also be indicated when swollen non-bulky LNs are noted in the hilar area, or when tumor invades the greater curvature, and the adjacent anatomy of the stomach and spleen is suboptimal. All the options are derived from the oncological point of view and validity of evidence: to be or not to be, that is the question.

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Footnote

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