Introduction

Laparoscopic radical gastrectomy with lymph node dissection has widely penetrated to East Asian countries, where incidence of gastric cancer occurrence is higher than the rest of the world. In the latest guidelines (English 4th version) published by the Japanese Gastric Cancer Association (1), laparoscopic distal gastrectomy for cStage I disease is regarded as one of the options in daily practice in the latest Japanese guidelines; however its applicability to more advanced disease (Stage II/III) is still under debate. Actually, operative techniques of laparoscopic D2 dissection is being matured, but still, necessity of total omentectomy, splenic hilar dissection, management of bulky nodes or large primary tumor, high-level anastomosis in esophageal invasion cases, and extensive peritoneal lavage can be raised as technical limitations. In the future perspective, further technological innovation, including next generation surgical robot, may help surgeons overcome these difficulties. Currently, three large-scaled randomized phase-III clinical trials are ongoing in East Asia, in which patients’ accruals have been already completed. With coming long-term outcomes of these well-designed studies, oncological validity of laparoscopic approach will be adequately elucidated.

Technical difficulties or limitation for application of LS to AGC

Total omentectomy

In the latest Japanese guidelines, it is mentioned that total omentectomy combined with D2 lymph node dissection is recommended in the treatment of patients with T3 or
T4 infiltration (1). Furthermore, historically, bursectomy, which removes the whole sac of the bursa omentalis, including the anterior leaf of transverse colon mesentry as well as the anterior capsule of pancreas body for prophylactic local control in addition to total omentectomy, had been performed by some experienced surgeons in Japan (2). The theoretical rationale for bursectomy is to reduce the risk of peritoneal recurrences by removing the peritoneum which might contain micrometastases. Bursectomy had been thought to be effective for tumors with serosal exposure positive cases, especially for those located on the posterior wall. Recently, the primary result of JCOG1001 (UMIN000003688) has been published in ASCO 2017 meeting (3), which demonstrated no survival difference between omentectomy versus bursectomy for T3/T4 tumors diagnoses with surgical findings, though bursectomy was not related with increased morbidity or mortality. Thus, now bursectomy is not recommended as a standard procedure for AGC in Japan. Performing complete bursectomy seemed a huge hurdle for LS; in contrast total omentectomy seems not impossible for experienced surgeons. Beyond this discussion, currently there is a clinical question, whether even omentectomy is really necessary for all of the AGC. If partial omentectomy is enough for some population of AGC, the hurdle for LS will be further reduced. However, several researchers insisted that in some metastatic nodes extra-nodal expansion is recognized, which means cancer cell spread out of lymph node capsule to the adjacent adipose tissue (4,5). This might be one of the rationales for performing omentectomy in AGC. It is also well known that extra-nodal expansion is a poor prognostic factor (4), thus further investigation for this phenomenon should be conducted to conclude whether routine omentectomy is necessary or not.

**Splenic hilar dissection for proximal gastric cancer**

For proximal advanced cancer, lymph node dissection around the splenic hilar region has been thought to be indispensable. In Japanese guidelines, No. 10 nodal station has been long time included within the extent of D2 dissection in the treatment of proximal AGC (1). From historical aspect, splenectomy has been employed as a tool to completely remove No. 10 and No. 11d lymph node stations, even as a prophylactic intent in Japan. In 2016, the final result of JCOG 0110 (UMINC000000004) has been disclosed (6), which compared splenectomy versus non-splenectomy for proximal AGC not invading the greater curvature line. Finally, there was no difference in long-term survival rate; moreover splenectomy group was associated with increased incidence of morbidity. Therefore, splenectomy is not recommended as a standard treatment now, unless tumors involve the greater curvature line. Following these results, nowadays, there is a consensus in Japan that complete lymph node dissection of No. 10/11d is not required for most of proximal AGC. If so, LS may be an ideal intervention for performing such procedures, because there is no need to struggle with complicated anatomy. Even if splenic hilar dissection is required for tumors invading the greater curvature line, in principle, laparoscopic approach has a potential advantage for maneuvers in deep operative fields like the splenic hilum. Additionally recent progress of three-dimensional computed tomography provides us helpful images of anatomical reconstruction of the splenic hilum, which has a marked anatomical diversity depending on individuals (7). However, for some tough cases, such as invading the splenogastric ligament or the pancreas tail, applicability or safety of laparoscopic maneuver seems still questionable.

**Bulky positive nodes or large primary tumor**

Probably, majority of surgeons may agree that laparoscopic procedure has limitation to manage tumors with bulky metastasis-positive nodes or large primary tumors (type 3 tumors > 8 cm or type 4), with concerns of spillage of cancer cells by manipulation with endoscopic forceps. Especially, loss of tactile sense seems to be an important limitation of laparoscopic procedures compared to open surgery. For such cases, currently effectiveness of neoadjuvant chemotherapy using powerful modern regimen is under investigation by several prospective clinical studies. LS for patients treated by neoadjuvant chemotherapy in advance is also technically demanding, because after such treatment unusual tissue fibrosis or edema sometimes exists, which may further increase surgical difficulty.

**Esophageal invasion**

This situation is also significantly increase surgical difficulty. Visibility around the lower mediastinal space via the esophageal hiatus using laparoscopic magnified view seems preferable for dissection. Actually, some researchers emphasized the feasibility and effectiveness of laparoscopic procedures for tumors with gastric cancer with esophageal invasion or adenocarcinoma at the esophagogastric junction.
However, still, intracorporeal anastomosis at the high-level in the lower mediastinum seems challenging even for skilled surgeons. In our institutions, for such cases, linear-stapled esophagojejunal anastomosis, overlap method (11), is basically selected, with widening the esophageal hiatus by division of the diaphragmatic crus. Compared to circular-stapled method, linear-stapled method provides much better visibility during the anastomosis due to smaller shaft of the device. Presently, such procedures should be performed only by well-experienced surgical team.

Peritoneal lavage

Some investigator emphasized the impact of extensive intraoperative peritoneal lavage using a large amount of saline solution for preventing peritoneal recurrences, which theological basis is to reduce free cancer cell in the peritoneal cavity. Actually, some prospective clinical studies are ongoing to evaluate the survival impact of this prophylactic simple treatment. LS can provide an excellent magnified view, but such a gross procedure seems to be a weak point. Sending a large amount of saline solution is not difficult, but shaking the intestines well in the peritoneal cavity or complete evacuation of the solution using current available laparoscopic device seems more difficult compared to open surgery. If positive impact of extensive peritoneal lavage is verified by the ongoing trials, some effective laparoscopic measures should be developed.

Table 1 Current ongoing large-scaled randomized clinical studies comparing laparoscopic versus open distal gastrectomy for advanced gastric cancer conducted in East Asian countries

<table>
<thead>
<tr>
<th>Items</th>
<th>CLASS-01</th>
<th>KLASS-02</th>
<th>JLSSG-0901</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country</td>
<td>China</td>
<td>Korea</td>
<td>Japan</td>
</tr>
<tr>
<td>Sample size</td>
<td>1,056</td>
<td>1,050</td>
<td>500</td>
</tr>
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<td>Eligibility</td>
<td>cT2-4a, N0-3</td>
<td>cT2-4a, N0-3</td>
<td>cT2-4, N0-2</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>3-year DFS</td>
<td>3-year RFS</td>
<td>5-year RFS</td>
</tr>
<tr>
<td>Secondary endpoint</td>
<td>Morbidity &amp; mortality</td>
<td>Morbidity &amp; mortality</td>
<td>OS</td>
</tr>
<tr>
<td>Recurrence pattern</td>
<td>3-year OS</td>
<td>3-year OS</td>
<td>Morbidity</td>
</tr>
<tr>
<td>Postoperative recovery course</td>
<td>Postoperative recovery index</td>
<td>Conversion rate</td>
<td></td>
</tr>
<tr>
<td>Inflammatory &amp; immune response</td>
<td>QoL</td>
<td>Recurrence pattern</td>
<td></td>
</tr>
<tr>
<td>Non-inferior margin</td>
<td>10%</td>
<td>5%</td>
<td>8%</td>
</tr>
<tr>
<td>Completion of patients’ enrollment</td>
<td>Dec 2014</td>
<td>Apr 2015</td>
<td>Aug 2016</td>
</tr>
</tbody>
</table>

DFS, disease free survival; RFS, relapse free survival; OS, overall survival; QoL, quality of life; LN, lymph node.

Previous studies and current ongoing multi-institutional large-scaled prospective studies

So far most of available data regarding long-term outcomes are retrospective clinical studies with from small-sized to relative large-sized samples from both western and eastern countries. Majority of them reported that LS was associated with less blood loss, faster recovery of patients, less pain, shorter hospital stay as well as longer operation time (12-16). Some meta-analysis also demonstrated similar results (17). In terms of long-term outcomes of prospective randomized studies, only that of small sample-sized studies is available. Regarding more scientifically reliable clinical studies, multi-institutional prospective randomized phase-III studies are ongoing in East Asian countries (Table 1). In China, CLASS-01 (NCT01609309) has been conducted and patients’ enrollment has been completed (18). Its short-term outcomes were already published, demonstrating no difference between laparoscopic and open group (15.2% vs. 12.9%) in morbidity rate. The primary endpoint of this study is 3-year disease free survival, thus final outcomes is expected to be analyzed in 2018. In Korea, KLASS-02 (NCT01456598) has already completed patients’ enrollment. Its short-term outcomes were disclosed in ASCO 2016 meeting (19), which demonstrated less overall complication rate (16.4%
vs. 24.3%), less use of analgesics, and faster recovery in LS
group. Its final analyses will be done also in 2018. In Japan,
JLSSG 0901 (UMIN000003420) has completed patients’
recruitment in August 2016 (20,21). The result of its phase-
II part has been published, demonstrating feasible outcomes
of LS, with the incidence of pancreatic fistula or anastomotic
leakage as 4.7% and that of the grade 3 or higher morbidity
as 5.8%. Anyway, the long-term outcomes of these three
clinical trials are being waited to obtain clear insight to
answer our clinical questions. Although it is a randomized
phase-II trial, the long-term out of COACT 1001
(NCT01088204) in Korea has been published in 2017 (22).
The primary endpoint of this trial was noncompliance rate
of the lymph node dissection to evaluate feasibility. The
overall noncompliance rate of the lymph node dissection
was not different between two groups, but in the subgroup
analysis, that of LS was significantly higher for cStageIII
disease (52.0% vs. 25.0%). Interestingly, they measured
several parameters for surgical stress, such as IN-6, IL-10
or TNF-α during the perioperative period, but there was
no significant difference between two arms. Similarly, not
prospective studies, but some well-designed retrospective
studies using large-sized cohort have been published, in
which confounding selection bias or background difference
between two interventions have been balanced by method
of propensity score matching. One such Chinese study
demonstrated comparable oncological outcomes in two
arms, but in far-advanced stage (T4aN3b) survival rate in
LS was inferior to open surgery (23). One Korean study also
conducted a similar case-control study, showing comparable
outcomes to open surgery; however the cohort of this study
included small number of StageIII (24).

Future perspective

For reaching conclusion, we should wait for the final results
of abovementioned phase-III trials. It should be noted that
not only survival rate but also difference of recurrence
pattern should be fully accessed to check the presence of
specific tendency in recurrences after LS. Meanwhile, it is
also a fact that surgical techniques are going to be refined
year by year. Super high definition or three-dimensional
images may help surgeons overcome limitation or shorted
their learning curve. Robotic surgical instruments seem
to have potential to cover disadvantages of LS, such as
insufficiency of forceps’ degree of freedom or surgeons’
physiological tremor at the tip of device (25). It is suggested
by experts that the use of a surgical robot may be beneficial
for more complicated procedures, including more advanced
cancer disease. However, presently, scientific evidences are
lacking, and there are still several issues to be solved, such as
longer operation time or expensive cost; therefore emerge
of the next generation surgical robot is expected. Recently,
some researchers emphasized that early initiation of
adjuvant chemotherapy is correlated with better prognosis
in pStageII/III gastric cancer patients (26). It is also worth
evaluating whether faster patients’ recovery obtained by LS
can realize faster initiation of subsequent treatment for the
patients (27).

Conclusions

There are still several unsolved issues regarding expanding
indication of laparoscopic gastrectomy to more AGC
disease. We should evaluate its validity from many aspects
using the data obtained from well-designed clinical studies.
At the same time, we should pay attention to ongoing
 technological development regarding minimal invasive
surgery.

Acknowledgements

None.

Footnote

Conflict of Interest: The authors have no conflicts of interest
to declare.

References

1. Japanese Gastric Cancer Association. Japanese Gastric
Cancer treatment guidelines 2014 (ver.4). Gastric Cancer
of bursectomy in patients with resectable gastric cancer:
interim analysis results of a randomized controlled trial.
of a phase III trial to evaluate bursectomy for patients
with subserosal/serosal gastric cancer (JCOG1001). J Clin
Oncol 2017;35:abstract 5.
is as an indicator of poor prognosis in patients with gastric


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