Title: A novel, protective and optimal, flexible liver retraction method with clipping and suturing techniques in laparoscopic gastrectomy for gastric cancer

Short running title: Protective and optimal liver retraction

Authors

Keywords: Gastric cancer · Laparoscopic gastrectomy · Liver retractor

Conflict of interest:

There are no funding sources for this study or any associated financial conflicts.

Total words: 2794

ABSTRACT

Background: Retracting the lateral liver segment during laparoscopic distal gastrectomy is important to achieve an optimal surgical field. However, excessive force may injure the liver, causing liver injuries during perioperative period and a temporary rise in abnormalities of liver function tests after laparoscopic surgery. Since we developed a new liver retraction method, we verified and assessed its safety and usefulness.

Patients and Methods:

This is a retrospective analysis using prospectively compiled retrospective data, we analyzed records in our surgical database in our institute. Consecutive surgical patients
who underwent laparoscopic distal gastrectomy (LDG) for 229 early gastric cancer, were extracted from the database, and the perioperative data were obtained. We divided the 229 patients into two groups depending on whether our liver retraction technique (the Flexible Liver method used, either Flexible liver retraction method with Clipping and Suturing technique (FLICS group)) or Nathanson’s retractor (NR group) was used. After that, one-to-one propensity score matching was performed to align patient backgrounds, and match patients, resulting in the records of 53 pairs of cases were extracted. Serum AST, ALT, CRP and T-Bill were measured at from the database. Operative and postoperative outcomes were assessed, including following the values of serum liver enzymes, total bilirubin, and C-reactive protein until postoperative day 30.

**Results:** There were no significant differences in patient background and characteristics or preoperative examination data after PSM. There was no addition or change of Liver retractor data in the two groups. No serious complications associated with liver retractor retraction were observed in both groups. No postoperative liver failure was observed in all patients, either group.

**Conclusions:** Our new liver retraction technique provided an optimal surgical field without inducing post-operative liver dysfunction. It is a simple, safe, protective new, and effective liver retraction technique.

(301 words)

Key words: Laparoscopic laparoscopic gastrectomy, Gastric gastric cancer, Liver liver retraction, Internal Organ retractor Retractor, Nathanson’s retractor, propensity score-matched analysis.
INTRODUCTION

Laparoscopic distal gastrectomy (LDG) has been widely used for treating patients within Japan since 1991 to treat gastric cancer since 1991 in Japan [1].

Therefore, to avoid this problem, we have devised and enforced a liver retraction method combining internal organ use of an internal retractor with sutures to help lift up by suturing the organ, which we designated flexible liver retraction with clipping and suturing (FLICS).

MATERIALS AND METHODS

Patients and characteristics

This is a retrospective analysis using prospectively. We retrospectively analyzed patient records compiled in our institution's surgical database in our institute. All patients were given sufficient explanations and written informed consents. Consecutive records of consecutive surgical patients who underwent laparoscopic distal gastrectomy (LDG) for gastric cancer, were extracted from the database, and the following data were obtained: patient characteristics (age, sex, performance status, American Society of Anesthesiologists Physical Status Classification [ASA-PS], height, weight, body mass index [BMI, calculated as kg/m²], tumor size, and histology), body weight, body mass index [BMI, weight in kg divided by height in meters squared (kg/m²)], preoperative tumor data (clinical T status, clinical N status, clinical Stage, Lauren classification, presence or absence of pre-operative and preoperative treatment, pre-operative with endoscopic submucosal dissection), preoperative laboratory data (the ALB values [serum albumin], PT, prothrombin time, CRP, C-reactive protein), cT, cN, T-Bil (Total Bilirubin), and T-ALP (Total Alkaline Phosphatase).
Bilirubin), surgical outcomes including intraoperative events (surgical approach, operative time and immediate intraoperative complications), immediate intraoperative complications (if any), postoperative course and laboratory tests of liver function, and mid-term and long-term outcomes. TNM staging was based on the Japanese Classification of Gastric Carcinoma, 3rd English Edition [18].

Finally, patients who satisfied inclusion criteria were divided into the FLICS group and the NR group. The clinical characteristics and perioperative outcomes were compared between the two groups after propensity score matched (PSM) 

Liver retraction method during LC at our hospital

Nathanson retractor

In use of Nathanson Liver Retractor, the liver retractor in The NR was inserted close to the xiphoid process and then placed near the hepatic hilum under the lateral segment of the liver. Basically, Retractor The retractor was fixed during surgery, and fixation was changed when or repositioned as necessary to provide an adequate surgical field deployment accompanying Liver retraction was necessary. In addition, when If the pressure applied was strong, enough to cause congestion and ischemic findings were observed, weakened or signs of ischemia, the pressure on the liver was weakened.

Flexible liver-retraction method with clipping and suturing techniques (FLICS technique)

Details of the FLICS procedure are shown in Figure 2. When using Along with the Internal Organ Retractor, 48 mm Straight 2-0 PLOLENE prolene sutures (Ethicon Endo-Surgery, Cincinnati, OH, USA) were used for traction.

Under pneumoperitoneum, puncture the right hypochondrium was punctured and lifted the hepatic crown lifted to the right temporal side with using 2-0 PLOLENE the suture. After
dissection of the lesser omentum, Internal Organ Retractor the retractor was inserted into one of the 12-mm trocars, and clipped to the cut edge of lesser omentum was grasped by the applicator. Liver retraction was accomplished by taping from outside external traction on the bodysutures.

It was performed using a logistic regression model and with the following covariates: Age, Sex, ASA-PS, BMI, histology, preoperative laboratory data (ALB, PT, albumin, prothrombin time, CRP, AST, ALT, T-Bil, bilirubin, and ALP), preoperative treatment, Location, with endoscopic submucosal dissection, Lauren classification, and preoperative clinical stage.

Elevations of serum liver enzyme in blood test was enzymes were evaluated based on CTCAE and on the basis of the Common Terminology Criteria for Adverse Events Version [22], with an abnormal value was defined as ≥3 times the upper limit of normal value [22].

Statistical analysis

All statistical calculations were performed with JMP® PRO software (JMP version 13.1.0, SAS Institute, Cary, NC, USA). All values were two-tailed, and P-values <0.05 were considered significant. We used a caliper width of 0.2 of the pooled standard deviation of the logit of the propensity score for PSM.

RESULTS

The Figure 3 depicts the study flow chart is described in Figure 3. Between 2012 January and 2016-December 2016, a total of 1,432 patients with gastric cancer patients.
were admitted to our institution, of whom 434 patients underwent laparoscopic gastrectomy (LDG) for clinical early-stage gastric cancer (cT1N0M0, clinical stage I) were identified in a retrospectively maintained database. The reasons for exclusion criteria before PSM analysis were as follows: multiple records from the study included other organ resections (n = 65), lower clinical stage (n = 67), use of other liver retraction techniques (n = 85). In addition to the above, the patients with liver disease such as hepatitis B virus, hepatitis C virus, and acute viral hepatitis were excluded from the study. Finally, 160 LDG with A, B, or C were included in the study. After PSM, the FLICS and 69 with the NR patients were enrolled in this study.

The clinical characteristics and short-term and long-term outcomes were compared between the two groups after PSM analysis. A total of 106 patients with laparoscopic distal gastrectomy who had undergone LDG for early gastric cancer were included in the study. 53 patients (50%) were included in the FLICS group, and the remaining 53 patients were included in the NR group.

The surgical outcomes of patients undergoing the FLICS group and NR group are detailed in Table 2. In the comparison of surgical characteristics, the shorter median operation time was shorter in the FLICS group than in the NR group (224 min [140–300 min] vs. 262 min [191–336 min], P < 0.001). Both techniques provided a satisfactory view of the working field during laparoscopic distal gastrectomy and LDG. There were no intraoperative complications required any treatments relating to retraction of the liver. Curative resection (R0) was achieved in all patients. The number of patients with:
lymph nodes retrieved did not differ significantly between the two groups ($P = 0.185$).

Surgical complications classified as **higher** are described in Table 2. Concerning early postoperative complications, more cases (7 cases, 13.2%) were observed in the NR group than in the FLICS group (3 cases, 5.7%), but the difference was not statistically significant ($P = 0.097$) (Table 2). One patient in the NR group (1.9%) had a Clavien–Dindo class III or higher complication, whereas no patients in the FLICS group. In the NR group, one case of complication (anastomotic leakage required reoperation) compared with none in the FLICS group. No liver dysfunction was found in both groups. Curative resection (R0) was performed in all patients. No significant difference in number of retrieved lymph node was observed between the two groups ($P = 0.185$). There was no 30-day mortality or postoperative liver failure in either group.

**Parameters of liver—Liver damage and inflammatory status or inflammation**

After PSM analysis, there were no significant differences in the patient's baseline levels of each liver function test—Circulating at baseline between the two groups. ALT and AST levels increased significantly from baseline within 24–72 hours following operation/surgery in each group. The levels of serum ALT on both groups. On postoperative day 1 (POD1), both serum ALT (Fig. 4a) and AST (Fig. 4b) levels were statistically significantly higher in the NR group than in the FLICS group (Fig. 4a). Furthermore, levels of serum AST on POD 3, 5 and 7 were significant higher in the NR group than in the FLICS group (Fig. 4b). Peak of On the other hand, the total bilirubin levels became the highest on POD 1 and gradually decreased thereafter were also elevated in the first few days, but the levels did not differ significantly from baseline in both groups.

Commented [SE33]: Please note that these two sentences were moved to this paragraph. They are about outcome, not complications, so they did not belong in their original place in the next paragraph on complications.

Commented [SE34]: Please note that mention of the Clavien–Dindo grades of complications is confusing in both text and table. It is particularly difficult to understand the reference to the patient with the anastomotic leak as having a “grade III or higher” complication. Please specify the exact grade—was it III, IV, or V? (You may have chosen a cutoff of grade III for statistical analysis, but when describing the only one that occurred, the grade should be described precisely.) If that complication was the only one that was grade III (or higher), were all the others grade II? If so, they presumably would have required drug treatment other than with the medications allowed for grade I complications.) That seems to be what is indicated in the text, but it should not be stated there that they were “grade II or higher.” Or were some of the complications listed in Table 2 grade I and some grade II? Please clarify these various references to the Clavien–Dindo classifications. One option for Table 2 would be to eliminate the Clavien–Dindo grade III item listed in the table but include a footnote with “Overall surgical complications” stating that the anastomotic leak was grade III but all others were grade II (or grade I or II, if that is correct).

Commented [SE35]: Please consider rounding the percentages to integers. When $n < 100$, using a decimal place implies a greater degree of precision than is possible.

Commented [QA36]: What is the definition of “liver dysfunction”? This should be stated either in the methods or at least at the bottom of the table. I suspect you mean disrupted production of albumin or coagulation factors. However, unless it is stated clearly, it is confusing to read that there was “no liver dysfunction” but the liver enzymes were elevated.

Commented [QA37]: Please note that this abbreviation is unnecessary. We do not measure ALT or AST anywhere else.

Commented [SE38]: Please note that this abbreviation is unnecessary in the text. Having stated “postoperative days” here, every subsequent reference to “day” or “days” will be understood as meaning after the operation. It’s fine to use “POD” in the figures if you want, as that is clearly defined in the legend.

Commented [SE39]: Please note that this was true only for the FLICS group. The graph clearly shows the level in the NR group peaking on day 2. It’s better not to try to describe everything in detail in the text, since the figures show the results so clearly.
**DISCUSSION**

The present study evaluated a demonstrated that FLICS, our new flexible-liver retraction method without was associated with only minimal transient elevation of liver enzymes and did not cause liver injury. During laparoscopic gastrectomy LDG, it is important to establish a good operative field and ensure an adequate working space.

Furthermore, investigation of hepatic injury on postoperative CT caused by use of Nathanson Liver Retractor during a study using computed tomography, liver abnormalities were seen after use of the NR in 14 of 52 (27%) patients who had undergone laparoscopic gastrectomy for cancer and 2 of 11 (18%) who had had laparoscopic upper gastrointestinal surgery revealed some liver abnormality in 27% of LG performed cases and 18% of bariatric surgery [28]. Such damage to the liver is caused by the persistent strong exclusion retraction of the liver, occurring without noticing can result in damage that goes unnoticed intraoperatively [8]. To date, various liver retraction methods have been done and reported to reduce the damage to the liver [12, 17, 29, 30]. Kitajima et al. [17] suggested that reducing liver damage could be prevented when using the NR by limiting the duration of liver retraction and moving the position of periodically repositioning the retractor, or releasing it intermittently could avoid physical pressure by Nathanson Liver Retractor releasing it. Although they demonstrated that their technique was safe and useful effective, it is technically difficult to arrange prepare and it is necessary to set up the

**Commented [SE40]:** Please be consistent in the number of decimal places that you report. There's no need to be so precise. In fact, some journals limit it to two decimal places. The size of the p value is not that important. It is either significant or not significant depending on the significance level you defined.

**Commented [QA41]:** The Discussion is expected to begin with a clear statement of the major findings of your study. Readers are aware of the study question that was stated (although not in question form) at the end of the Introduction. When they reach the Discussion, they expect to see the answer. The Discussion should not repeat the Introduction. We have edited the Discussion as written, but please consider revising it to begin with the main findings followed by further discussion of two to three points you consider most important. Please eliminate the repetition of information that was already stated in the Introduction.

**Commented [SE42]:** Please note that it is better not to state "naked" percentages. Please include number whenever possible. The 27% for those undergoing cancer surgery is a somewhat firmer proportion than the 18% who underwent bariatric surgery, simply because of the difference in the numbers. Care is usually taken with prospective studies to include enough numbers to yield adequate statistical power. This is often not possible in retrospective studies. That does not mean that such studies are invalid. But we should be cautious about generalizing from small numbers. By including the numbers from reference you cite, you help the reader understand how much weight to put on the finding.

**Commented [SE43]:** Please check that this correctly conveys the intended meaning. The original was quite unclear, and the reference's Abstract didn't mention this point. (We did not have access to the full article.) The meaning of "exclusion of the liver" was unclear: I imagine it refers to excluding it from the surgical field but nonsurgical (such as myself) might not understand it.

**Commented [SE44]:** Please note that the wording of this sentence. The original was in part copied verbatim from the Abstract's conclusion. Word-for-word copying must be avoided unless included in quotation marks. However, it's better to restate the ideas in your own words.

**Commented [QA45]:** It is necessary to be more specific here and provide details on why it was difficult.
hepatic relief again during surgery. [1] Our retraction FLICS method can be continuously carry-out steady operative field deployment in order to mobilize the liver to the patient’s upper right side of the patient, but allowing a clear surgical field. It is adaptable by changing the traction on the sutures, allowing adjustment as needed of fixation of the liver is done with leeway, so adaptability is high enough that as well as normal respiratory variation remains. [Other text deleted]

The absence of elevation of fact that increases in liver enzymes enzyme and CRP levels were less marked in the FLICS than the NR group confirms that FLICS is a proof that our safer retraction method is a compulsive excretion method against the liver. We believe that the overall reliability of our results is enhanced by the one-to-one matching of this study are very accurate by groups using PSM to adjust the background factors as much as possible. Moreover, since this method is simple, stable and safe, it is considered to be very useful, which should have reduced the influence of unknown confounders.

Acknowledgments

Table 1 Baseline characteristics of one-to-one propensity score-matched patients who underwent laparoscopic distal gastrectomy for gastric cancer

<table>
<thead>
<tr>
<th></th>
<th>FLICS group (n = 53)</th>
<th>NR group (n = 53)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67 (34–79)</td>
<td>66 (27–91)</td>
<td>0.994</td>
</tr>
<tr>
<td>ASA-PS(1:2:3)</td>
<td>11 (20.8%): 42 (79.3%): 0</td>
<td>11 (20.8%): 42 (79.3%): 0</td>
<td>0.001</td>
</tr>
</tbody>
</table>

[Other text deleted]
BMI: body mass index, cT: clinical T stage, cN: clinical N stage, ESD: endoscopic submucosal dissection

Table 2 Operative and postoperative outcomes in patients who underwent laparoscopic distal gastrectomy for gastric cancer

<table>
<thead>
<tr>
<th></th>
<th>FLICS group (n = 53)</th>
<th>NR group (n = 53)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reoperation</td>
<td>0</td>
<td>1 (1.9%)</td>
<td>0.237</td>
</tr>
<tr>
<td>Postoperative hospital stay (days)</td>
<td>9.1 ± 1.8</td>
<td>15.1 ± 7.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Overall surgical complications</td>
<td>3 (5.7%)</td>
<td>20 (37.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clavien–Dindo grade &gt;III</td>
<td>0</td>
<td>1* (1.9%)</td>
<td>0.237</td>
</tr>
<tr>
<td>Liver dysfunction</td>
<td>0</td>
<td>0</td>
<td>1.000</td>
</tr>
<tr>
<td>Organ damage (including liver injury)</td>
<td>0</td>
<td>0</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Commented [SE52]: All first-time use abbreviations in main text or peripheral text must be defined.

Commented [SE53]: Please note that you discount this item in discussing the study limitations. Please consider deleting it from the table. If not, please at least mention it in the text of the Results, e.g. “Although the FLICS group had a shorter mean hospital stay, changes in hospital policy during the study period may have influenced this result.”

Commented [SE54]: Please note that this item was indented. When left aligned, it appeared that it referred to all the items indented below it. However, it might be best to delete this item from the table entirely.

Commented [SE55]: As noted above in the text, this required definition.

Commented [SE56]: Please note that this is unclear. Do you mean “gross liver injury”? The fact that enzyme levels were elevated indicates at least microscopic injury.

Commented [SE57]: Please note that the journal requests that figure legends be brief, with no more than 4 or 5 lines. We have revised them to shorten them as much as possible.

Commented [QA58]: Please consider reversing panels a and b in the figure, as well as the descriptions written here in the legend. The intrabdominal schematic should come first. The external tension only makes sense when one understands how the sutures are situated internally.

Commented [SE59]: Please consider reordering the panels so that a-c are the top row, d-f the middle row, and g-i the bottom row. Because readers of English normally read from left to right, the natural tendency is also to look at a figure with multiple panels the same way. It’s initially a bit confusing for the sequence of steps to be oriented vertically rather than horizontally.

Commented [SE60]: Please note that figure 2 is not been cited in the text. Please check.

Commented [SE61]: Please check that this correctly conveys the intended meaning. There was no description for panel a.

**Figure legends**

**Figure 1.** Described: Schematic of the flexible liver retraction with clipping and suturing method of handling 2-0 PLOLINE in extracorporeal operation. (a).

**Figure 2.** Our procedure of Flexible liver retraction with Internal Organ retractor. Puncture the clipping and suturing in situ during laparoscopic distal gastrectomy. (a–c) The right hypochondrium and left hypochondrium is punctured by the suture needle and the hepatic crown lifted to the right temporal side (b–c). After dissection of lesser omentum.

[Other text deleted]