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Liver Dysfunction After Use of Nathanson Retractor During Laparoscopic Gastrectomy for Gastric Cancer

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Abstract

Background: Cardiopulmonary complications and liver dysfunction are also specific complications and problems associated with laparoscopic surgery. The main causes of postoperative liver dysfunction, which may often occur after laparoscopic surgery, include carbon dioxide pneumoperitoneum and ligation of the aberrant left hepatic artery. Hepatic steatosis may develop as a natural consequence of neoadjuvant therapy, although rarely, owing to chemotherapy. Nathanson retractor may cause a prolonged elevation in liver enzymes of these patients compared with those who do not receive neoadjuvant therapy.

Materials and Methods: The data of 151 patients who underwent laparoscopic radical gastrectomy between January 2017 and January 2022 for histologically proven primary gastric cancer in our clinic were retrospectively reviewed.

Results: The mean length of hospital stay was 6.21 days. The mean time normalization of the aspartate aminotransferase (AST) value was 2.45 ± 1.83 (range, 0–12) days postoperatively. The analysis of the correlation between the preoperative and postoperative 1-day values of alanine aminotransferase (ALT) and AST revealed a significant difference between the preoperative and postoperative 1-day median values of both parameters ($P < .001$). Each one unit increase in ALT led to an increase of 0.338 days in the length of intensive care stay and an increase of 0.345 days in the overall length of hospital stay. As the time to normalization of the AST value increased, the length of both intensive care stay and hospital stay increased. Each one unit increase in AST resulted in an increase of 0.316 days in the length of intensive care stay and an increase of 0.376 days in the overall length of hospital stay.

Conclusion: Alternative retraction methods can be used safely in laparoscopic surgery for gastric cancer patients receiving neoadjuvant therapy. We are of the opinion that the Nathanson retractor should be used only during dissection of the relevant regions to shorten the intraoperative intermittent release or the time of use.

Keywords: gastric cancer, liver retractor, laparoscopic surgery

Introduction

Laparoscopic gastrectomy for gastric cancer has rapidly gained popularity in recent years. Studies have reported many clinical benefits of laparoscopic gastrectomy.[1,2] On the contrary, cardiopulmonary complications and liver dysfunction are also specific complications and problems associated with laparoscopic surgery. The main causes of postoperative liver dysfunction, which may often occur after laparoscopic surgery, include carbon dioxide pneumoperitoneum and ligation of the aberrant left hepatic artery.[3–5] Recent studies have suggested that liver retraction with liver retractors may also affect this condition.[6–9] The liver retraction technique using the Nathanson liver retractor are becoming widespread in laparoscopic gastrectomy. Nathanson liver retractor has been known to cause compression-

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induced hepatic vascular stasis, leading to postoperative elevations in liver enzyme levels.[10] There are few studies in the literature investigating the effects of Nathanson retractors and their clinical significance.[10,11]

Hepatic steatosis may develop as a natural consequence of neoadjuvant therapy, although rarely, owing to chemotherapy.[12] The Nathanson retractor may cause a prolonged elevation in liver enzymes of these patients compared with those who do not receive neoadjuvant therapy. This may result in more examinations, prolonged length of hospital stay, more complications, later reinitiation of oral intake, and more cost. In addition, chronic liver diseases such as severe fatty liver disease are believed to increase the risk of ischemic liver injury.[13,14] This study evaluated the postoperative effects of the Nathanson retractor in gastric cancer patients receiving neoadjuvant therapy.

Materials and Methods

Ethical statement

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Since our study is a retrospective study, it was carried out within the knowledge of the university administration.

The data of 151 patients who underwent laparoscopic radical gastrectomy between January 2017 and January 2022 for histologically proven primary gastric cancer in our clinic were retrospectively reviewed. Five patients with known chronic liver disease (chronic hepatitis, cirrhosis, etc.), 1 patient with perioperative liver metastasis, 2 patients who underwent cholecystectomy, and 2 patients with gallbladder stones on preoperative imaging were excluded from the study. The study included patients who underwent laparoscopic gastrectomy for primary gastric cancer, who did not undergo additional organ resection, and in whom the Nathanson retractor was used for liver retraction. Patients were divided into two groups: the neoadjuvant therapy group and the non-neoadjuvant therapy group. Clinicopathological findings, including demographic data, operative time, length of intensive care and hospital stay, and postoperative complications were evaluated. Postoperative complications were classified according to the Clavien–Dindo Classification. Laboratory results were acquired from the patient database and recorded as preoperative and postoperative days 1, 3, and 5.

In our center, the normal reference range for aspartate aminotransferase (AST) and alanine aminotransferase (ALT) is 0–50 IU/L. The details of the laparoscopic gastrectomy technique we used have been described in the previous studies.[15] We performed standard D2 dissection on all patients included in the study and used a Nathanson retractor for liver retraction (Fig. 1).

Statistical analysis

Statistical Package for Social Sciences (SPSS) version 22.00 software was used for the analysis of the study data. Descriptive statistics were provided as numbers and percentages for categorical data and as mean, standard deviation, standard error, and minimum–maximum values for continuous data. In statistical analyses, Pearson's chi-squared test was used for categorical data, whereas Mann–Whitney *U* and Spearman's correlation tests were used in nonparametric conditions. A value of $P < .05$ was considered statistically significant.

Results

Of the 151 patients included in the study, 48 (34%) were men and 93 (66%) were women. The patients were aged between 28 and 72 years, with a mean age of 61.31 ± 11.72 years. The analysis of the tumors by location showed that the most frequent tumor type was antral tumor with 44%, followed by corpus (37.6%), cardia (15.6%), fundus (2.1%), and diffuse type (0.7%), respectively. Although the most common pathological subtype was adenocarcinoma (78%) in patients, the pathological subtypes of signet ring, mucinous, adenosquamous, and neuroendocrine were also present. Eighty-nine patients (63.1%) underwent subtotal gastrectomy, and 52 patients (36.9%) underwent total gastrectomy procedures. The mean operative time was 162.7 minutes. The mean postoperative stay in the intensive care unit was 1.98

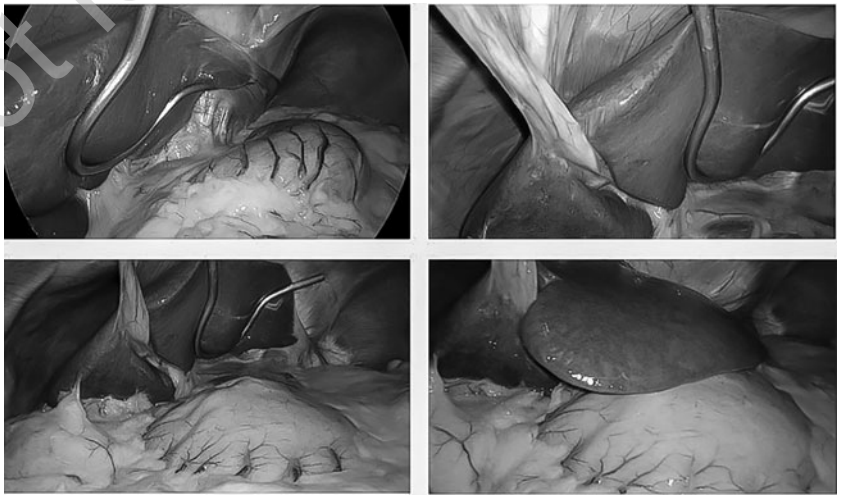


FIG. 1. Liver and Nathanson retractor in a patient who received neoadjuvant therapy.

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Table 1. Demographic Distribution of All Patients

Age, years, mean ± SD (range)	61.31 ± 11.72 (28–82)
Gender, *n* (%)	
Male	48 (34)
Female	93 (66)
Neoadjuvant therapy, *n* (%)	
Yes	112 (79.4)
No	29 (20.6)
Location, *n* (%)	
Corpus	53 (37.6)
Antrum	62 (44)
Cardia	22 (15.6)
Fundus	3 (2.1)
Diffuse	1 (0.7)
Pathology, *n* (%)	
Adenocarcinoma	110 (78)
Signet ring cell	24 (17)
Adenosquamous	1 (0.7)
Neuroendocrine	1 (0.7)
Mucinous	5 (3.5)
Clavien–Dindo, *n* (%)	
CDC 1	113 (80.1)
CDC 2	8 (5.7)
CDC 3	14 (9.9)
CDC 4	4 (2.8)
CDC 5	2 (1.4)
Operation, *n* (%)	
Subtotal	89 (63.1)
Total	52 (36.9)
N stage	
N0	54 (38.3)
N1	21 (14.9)
N2	28 (19.9)
N3	38 (27)
T stage	
T1	19 (13.5)
T2	17 (12.1)
T3	65 (46.1)
T4	40 (28.4)
Operative time, minutes, mean ± SD (range)	162.70 ± 26.01 (110–250)
Preoperative ALT, IU/L, mean ± SD (range)	22.05 ± 19.14 (2–143)
Preoperative AST, IU/L, mean ± SD (range)	29.26 ± 33.18 (8–212)
Postoperative 1-day ALT, IU/L, mean ± SD (range)	121.39 ± 140 (9–889)
Postoperative 1-day AST, IU/L, mean ± SD (range)	120.72 ± 116.80 (16–873)
Time to ALT normalization, days, mean ± SD (range)	2.42 ± 2.17 (0–11)
Time to AST normalization, days, mean ± SD (range)	2.45 ± 1.83 (0–12)
Length of intensive care stay, days, mean ± SD (range)	1.98 ± 2.80 (0–32)
Length of hospital stay, days, mean ± SD (range)	6.21 ± 2.78 (5–35)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CDC, Clavien–Dindo classification; SD, standard deviation.

days. The mean length of hospital stay was 6.21 days (Table 1).

The analysis of the patients by their ALT values revealed a mean preoperative ALT value of 22.05. The mean postoperative 1-day ALT value was 121.39. The mean time to normalization of ALT value was 2.42 days after the operation. The mean preoperative AST value was 2.42 ± 2.17 (range, 0–11). The mean postoperative 1-day AST value was 120.72. The mean time to normalization of AST value was 2.45 ± 1.83 (range, 0–12) days after the operation. The analysis of the correlation between the preoperative and postoperative 1-day values of ALT and AST showed a significant difference between the preoperative and postoperative 1-day median values of both parameters ($P < .001$).

Although the median preoperative ALT/AST value was 17/20, the median postoperative 1-day value was found to be 75/92 (Table 2). There were 29 (20.6%) patients who received neoadjuvant therapy and 112 (79.4%) patients who did not. The data were statistically significant for the postoperative period, and those who received neoadjuvant therapy had a more increase in ALT/AST values ($P = .001$, $P < .001$, respectively). The normalization process of ALT/AST was found to be longer in patients who received neoadjuvant therapy, with an increase in the length of intensive care and hospital stay of these patients (Table 3).

The Clavien–Dindo Classification was used to classify the postoperative complications of the patients. Of the patients, 80.1% developed grade 1 complications according to the Clavien–Dindo Classification, with none of them being significant. The patients who developed grade 2 complications and required additional medical treatment or blood transfusion constituted 5.7% of the patients. Moreover, 9.9% of the patients who required surgical intervention had grade 3 complications. Single/multiorgan failure (grade 4) developed in 2.8% of patients. Two patients who constituted 1.4% of the portion died (grade 5).

The time to normalization of ALT value was weakly correlated with the length of intensive care stay and was moderately correlated with the length of hospital stay. As the time to normalization of ALT value increased, the length of both intensive care unit and hospital stay increased. Each one unit increase in ALT led to an increase of 0.338 days in the length of intensive care stay and an increase of 0.345 days in the overall length of hospital stay (Table 4).

Similarly, a statistically significant correlation was found between the AST value and the length of hospital and intensive care stay. There was a moderate correlation between the AST value and the length of both intensive care and hospital stay. As the time to normalization of AST value increased, the length of both intensive care and hospital stay increased. Each one unit increase in AST resulted in an increase of 0.316 days in the length of intensive care stay and an increase of 0.376 days in the overall length of hospital stay (Table 5).

Discussion

Liver retraction is vital for safe laparoscopic gastric cancer surgery in terms of the exploration of lymph node stations numbered 1, 3, 5, 8, and 12 during lesser curvature and D2 lymph node dissection. There are different techniques for

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Table 2. Analysis of Preoperative and Postoperative 1-Day Alanine Aminotransferase And Aspartate Aminotransferase

Variables	*Preoperative*	*Postoperative*	*P*
ALT, IU/L, mean ± SD, median (range)	22.05 ± 19.14, 17 (2–143)	121.39 ± 140, 75 (9–889)	<.001[a]
AST, IU/L, mean ± SD, median (range)	29.26 ± 33.18, 20 (8–212)	120.72 ± 116.80, 92 (16–873)	<.001[a]

[a]Wilcoxon signed-rank test.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; SD, standard deviation.

Table 3. Association Between Neoadjuvant Chemoradiotherapy and Clinicopathological Factors

	No. of patients (%)		
Clinicopathological factors	*Neoadjuvant therapy Yes (112)*	*Neoadjuvant therapy No (29)*	P
Operative time, minute, median (range)	150 (110–250)	170 (120–230)	**.006**
Preoperative ALT, IU/L, median (range)	16 (2–143)	20 (5–69)	**.018**
Preoperative AST, IU/L, median (range)	19 (8–212)	26 (13–207)	**.005**
Postoperative 1-day ALT, IU/L, median (range)	64 (9–889)	121 (22–856)	**.001**
Postoperative 1-day AST, IU/L, median (range)	69.5 (16–787)	126 (49–873)	**<.001**
Time to ALT normalization, days, median (range)	2 (0–11)	3 (0–11)	**<.001**
Time to AST normalization, days, median (range)	2 (0–6)	4 (2–12)	**<.001**
Length of intensive care stay, days (range)	1 (0–32)	3 (2–4)	**<.001**
Length of hospital stay, days, median (range)	5 (5–35)	8 (7–9)	**<.001**

Bold values are statistically significant.
χ^2: Chi-squared test, §: Mann–Whitney *U*-test.
ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 4. Correlation and Regression Analysis of Time to Alanine Aminotransferase Normalization Between Length of Intensive Care and Hospital Stay

Correlation

Clinicopathological factors	N	*rho*	P
(1) Length of intensive care stay	141	0.394	**<0.001**
(2) Length of hospital stay	141	0.427	**<0.001**

Regression

Dependent variable	*Independent variable*	B	*95% CI for* B	t	R^2	P
(1) Length of intensive care stay	Time to ALT	0.338	0.233–0.640	4.235	0.114	**<.001**
(2) Length of hospital stay	normalization	0.345	0.240–0.643	4.332	0.119	**<.001**

Bold values are statistically significant.
ALT, alanine aminotransferase; CI, confidence interval.

Table 5. Correlation and Regression Analysis of Time to Aspartate Aminotransferase Normalization Between Length of Intensive Care and Hospital Stay

Correlation

Clinicopathological factors	N	*Rho*	P
(1) Length of intensive care stay	141	0.511	**<0.001**
(2) Length of hospital stay	141	0.472	**<0.001**

Regression

Dependent variable	*Independent variable*	B	*95% CI for* B	t	R^2	P
(1) Length of intensive care stay	Time to AST normalization	0.316	0.240–0.726	3.923	0.100	**<.001**
(2) Length of hospital stay		0.376	0.335–0.806	4.790	0.142	**<.001**

Bold values are statistically significant.
AST, aspartate aminotransferase; CI, confidence interval.

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liver retraction. Among these, the liver retraction technique using the Nathanson liver retractor is one of the most preferred techniques owing to its ease of use. As in many centers, we have been using Nathanson liver retractors in our clinic since 2014.

Although this retractor provides a good operational field of view, it has been associated with hepatic cell damage, elevated liver enzymes, and transient postoperative liver dysfunction in some studies on laparoscopic gastric cancer surgery, fundoplication, or gastric bypass.[16,17] This may prolong the length of hospital stay, affect postoperative pain scores, prolong the reinitiation of oral intake, and increase costs. The role of neoadjuvant therapy in the treatment of gastric cancer is gradually increasing. Hepatic steatosis may develop as a natural consequence of neoadjuvant therapy, although rarely, owing to chemotherapy.

Patients with gastrointestinal cancer are usually treated with regimens containing 5FU, oxaliplatin, and irinotecan. Chemotherapy drugs such as 5FU, platinum derivatives, and taxanes have been shown to induce oxidative stress in normal hepatocytes, leading to the accumulation of lipid globules and hepatic steatosis.[18,19] The use of the Nathanson retractor in these patients may cause longer term elevated levels of liver enzymes compared with those who do not receive neoadjuvant therapy, resulting in more investigations, longer length of hospital stay, and more complications. Therefore, transient postoperative liver dysfunction should be prevented as much as possible in these patients by intraoperative maneuvers. In such patients, the Nathanson retractor can be loosened intermittently every half an hour, repositioned, or used only during D2 dissection by avoiding any color change in the liver parenchyma.[20] These measures can prevent postoperative complications, shorten the length of hospital stay, and prevent frequent postoperative blood collections, which can increase patient anxiety.

Our study demonstrated a significant increase in postoperative serum levels of ALT and AST in both groups (with and without a history of neoadjuvant therapy) of patients who underwent laparoscopic gastric adenocarcinoma surgery using a Nathanson liver retractor. Postoperative 1-day serum levels of ALT and AST tended to be higher in the neoadjuvant therapy group than in the group that did not receive neoadjuvant therapy. The length of hospital and intensive care stay was significantly longer in patients with a history of neoadjuvant therapy. The evaluation of the patients in our study revealed that none of them had liver infarction.

However, care should be exerted when performing intraoperative maneuvers in patients with fatty liver disease because severe liver infarction has been reported in a few cases where the Nathanson liver retractor was used.[10,21] We are of the opinion that serious complications can be prevented by simple modifications to be made during laparoscopic surgery for gastric cancer in patients with a history of neoadjuvant therapy.

In the literature, factors such as anesthetic agents, patient position, rough manipulation of the liver, ligation of the aberrant left hepatic artery, and pneumoperitoneum have been reported as possible causes of transient liver enzyme elevation after laparoscopic surgery.[15,22–24] Among these factors, anesthetic agents and patient positioning were the same in all patients in our study, and patients with an aberrant left hepatic artery were not included in our study.

Our study has some limitations that may affect the results. The retrospective, single-center design, and the small sample size are major limitations of our study. Some of the patients included coincide with the early stages of our learning curve, and because we did not categorize patients into subtotal and total gastrectomy groups, we acknowledge that potential variations in operating time between the groups were not well controlled. We routinely measured AST and ALT early in our practice; therefore it is possible that length of stay was affected by our enhanced concern for these enzyme abnormalities. We decided to perform blood tests based on the clinical status of the patient.

In addition, we did not evaluate the level of hepatic steatosis preoperatively. However, to the best of our knowledge, there is no study in the literature investigating the changes caused by Nathanson retractors in gastric cancer patients. Considering the lack of data in the literature, we believe there is value in reporting the results from our series study.

In conclusion, we recommend alternative retraction techniques in laparoscopic surgery for gastric cancer patients who have received neoadjuvant therapy. We are of the opinion that the Nathanson retractor should be used only during dissection of the relevant regions to shorten the time of intraoperative liver compression. Although postoperative liver dysfunction is transient, we believe such precautions may reduce intensive care and overall hospital length of stay in these patients.

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Authors' Contributions

Conceptualization: S.C., Data curation: S.T., S.E., C.A. Formal analysis: B.M. Funding acquisition: none. Investigation: A.E.U. Methodology: S.C., S.T. Software: S.E. Visualization: S.D. Writing—original draft: S.E., S.T. Writing—review and editing: A.E.U., S.C.

Disclosure Statement

No competing financial interests exist.

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