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Validation of Biological and Clinical Outcome Between with and without Thoracotomy in Liver Resection: A Matched Cohort Study

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Abstract
Background The transthoracic approach in liver resection is a useful option for improving the clearance of and access to the operation field. However, this approach remains controversial due to the threat of increased respiratory complications. The aim of this study was to evaluate the clinical outcomes and biological responses of patients who underwent the transthoracic versus the transabdominal approach in liver resection.
Methods This case-matched cohort study included a total of 127 patients who underwent treatment for hepatocellular carcinoma from June 2006 to December 2007 at the Nihon University Itabashi Hospital. Forty-four (34.6%) patients had the transthoracic approach of liver resection, and the patients were matched on three variables: (1) scale of liver resection, (2) perioperative steroid administration, and (3) pathologically proven liver cirrhosis. The patients were divided into two groups according to the transthoracic ($n = 36$) or transabdominal ($n = 36$) approaches. Clinical outcomes (including respiratory and overall complications) and biological responses (including acute-phase cytokine production and oxygenation) were compared between the two different approaches.
Results The preoperative variables were well matched. However, for the transthoracic group relative to the transabdominal group, the median operative time was significantly longer (median = 402 min [range = 236–661] vs. 330 min [range = 178–697], $P \leq 0.001$), the ischemia time was shorter (65 min [range = 12–223] vs. 76 min [range = 28–247], $P = 0.04$), the level of $AaDO_2$ on POD 1 was higher (66.1 vs. 33.5 Torr, $P = 0.04$), and the IL-6 level in pleural effusions on POD 2 was higher (21,900 pg/ml [range = 6,020–123,000] vs. 866 pg/ml [range = 389–2,210], $P < 0.001$). There was no postoperative mortality and no significant difference between groups in overall morbidity ($P = 0.81$), overall respiratory complications ($P = 0.11$), atelectasis ($P = 0.10$), pleural effusion ($P = 0.06$), pneumonia ($P = 1.00$), and length of postoperative hospital stay ($P = 0.23$).
Conclusion Because of there was no significant difference between transthoracic and transabdominal approaches. We recommend using the transthoracic approach in liver resection.

Introduction

The frequency of postoperative respiratory complications after upper abdominal surgery is around 30%, depending on the operation procedure and the definition of respiratory complications [1–3]. Liver surgery requires a high frequency of thoracotomy, which may lead to increased respiratory complications [4, 5].

The transthoracic approach is a frequently performed procedure and a useful option for obtaining a wide operative field [6, 7]. In the case of tumors located in the right lateral or caudate lobe of the liver, surgeons are forced to

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perform liver mobilization, which entails an inconvenient blockage of sight. The poor sight of the operative field is thought to result in an increased risk of intraoperative bleeding [7, 8]. The advantage of the transthoracic approach to liver resection is that it provides easier access to the zone around the inferior vena cava (IVC) and a potentially quicker response to unanticipated bleeding [7–9].

However, the transthoracic approach is still controversial, and some authors have claimed that it is a more stressful procedure than the transabdominal approach; thus, they propose a different approach without thoracotomy [10–12]. Moreover, previous reports were imbalanced in terms of patient numbers, background disease, operation procedures, and degrees of liver damage [4, 5, 8, 9, 13, 14]. To our knowledge, no study has been published that describes the relationship between the clinical complications of and biological responses to liver resection with or without thoracotomy. Thus, in this study we analyzed three matched variables concerning postoperative outcomes to minimize the bias and assess the biological responses to the two different surgical approaches.

Patients and methods

Patients

The study data were obtained from patients who underwent liver resection for hepatocellular carcinoma. Using minimization methods and PC software, the patients' data were matched for three variables regarding postoperative complications: (1) the scale of liver resection, (2) administration of perioperative steroids, and (3) pathologically proven liver cirrhosis. The 72 patients were divided into two groups: the transabdominal approach group ($n = 36$) and the transthoracic approach group ($n = 36$). These three variables were selected because they have a positive or negative impact on postoperative complications but are not correlated with each other [15–18].

Measurements

The patients' background data, including preoperative laboratory data, respiratory function, and operation-related data, were examined. Serum levels of interleukin 6 (IL-6) and C-reactive protein (CRP) were measured to evaluate the surgical stress response on the day before surgery, just after surgery on POD (postoperative day) 0, and on PODs 1, 2, 3, 5, and 7. IL-2 levels in the pleural effusions taken from thoracic tubes were routinely measured in the transthoracic group at POD 2. The pleural effusions of the transabdominal group were collected to analyze their IL-2 levels by thoracentesis on POD 2 if the estimated pleural effusion volume was more than 300 ml on ultrasonography. The alveolar-arterial oxygen tension difference ($AaDO_2$) was measured to assess oxygenation and peripheral alveolar injury on PODs 0, 1, 2, 3, 5, and 7. Laboratory tests assessing the recovery of liver function and coagulation activity were also evaluated at the same time.

The pleural effusion was defined by ultrasonography as an estimated volume of more than 300 ml. The atelectasis was defined based on the appearance of chest X-P and was improved by suction with a bronchial fiberscope. Pneumonia was defined on the basis of a positive sputum culture and a requirement for administration of antibiotics. Complications were monitored by a single observer (S.O.) who was not involved in the surgery or the postoperative treatment. The resected specimen was checked by two different pathologists who estimated the degree of cirrhosis after liver resection.

Surgical procedure

The indications and procedures for liver resection were in accordance with Makuuchi's criteria for hepatic functional reserve [19]. Almost all liver transections were performed with intermittent clamping of the hepatoduodenal pedicle (Pringle's maneuver) for 15 min, followed by release for 5 min. Before the liver transection, intraoperative ultrasonography was performed in all patients to confirm the suitability of the operative procedure. When steroids were administered, patients received 500 mg of hydrocortisone immediately before hepatic pedicle clamping, 300 mg on POD 1, 200 mg on POD 2, and 100 mg on POD 3 as described elsewhere [16]. A closed irrigation drain was left in each liver stump. Standard systemic antibiotic therapy with cefazolin (Cefamezin α, Astellas, Japan), a first-generation cephalosporin, was routinely administered immediately before surgery and then given twice daily on PODs 1 through 3. Red blood cell transfusion was performed if the hematocrit level fell to <20.0%. Fresh frozen plasma transfusion was performed if the intraoperative blood loss was >1000 g or the albumin level on POD 2 was >2.6 g/dl.

Statistical analysis

Continuous variables were compared using Student's t-test or the Mann-Whitney U test, and categorical variables were compared using the χ^2 test or Fisher's exact test. Multiple comparisons were made using a one-way repeated-measures analysis of variance (ANOVA). Significance was defined as $P < 0.05$. All of the analyses were performed using JMP 8.0 software (SAS, Cary, NC, USA).

Results

Patients

From July 2006 to August 2007, 187 patients underwent liver resection at the Nihon University Itabashi Hospital. Of these, 127 patients had hepatocellular carcinoma and 44 (34.6%) patients underwent the transthoracic approach of liver resection. The baseline characteristics of the two groups were completely matched for three variables (more than three segments of liver resection, administration of perioperative steroids, and pathological liver cirrhosis) (Table 1). Preoperative laboratory data were not different between the groups, including age, hepatic function, and coagulation activity. Preoperative respiratory function was also similar between the two groups.

The median operative time (median = 402 min [range = 236–661] vs. 330 min [range = 178–697], $P \leq 0.001$) and ischemia time (65 min [range = 12–223] vs. 76 min [range = 28–247], $P = 0.04$) were significantly longer, but intraoperative blood loss was similar (453 mg [range = 94–1,930] vs. 431 mg [range = 178–1,291], $P = 0.28$) between the two groups.

Trends of alveolar-arterial oxygen tension differences ($AaDO_2$) after liver resection

There were no significant differences regarding the preoperative $AaDO_2$ between the two groups (14.3 Torr [range = −6.0 to 35.2] vs. 13.6 Torr [range = −8.2 to 46.9], $P = 0.54$) (Fig. 1). The median $AaDO_2$ values were twice as much on POD 1 in the transthoracic group; however, this was the only time point that was significantly different between the groups (66.1 vs. 33.5 Torr, $P = 0.04$). Both for trends and for each time point, no significant differences between the two groups were observed for levels of alanine aminotransferase ($P = 0.41$), aspartate aminotransferase ($P = 0.39$), total bilirubin ($P = 0.68$), and prothrombin ($P = 0.71$) (Fig. 2).

Inflammatory response

There was no significant difference in serum IL-6 levels between the two groups at any time points tested (Table 2). In the transabdominal group, 13 patients had confirmed pleural effusion on POD 2 by ultrasonography, and their IL-6 levels were examined by thoracentesis. The IL-6

Table 1 Patients background data

	Transthoracic group (n = 36)	Transabdominal group (n = 36)	P value
Matched variables[a]			
Hepatectomy more than 3 segments	9	9	1.00
Administration of perioperative steroids	19	19	1.00
Pathological liver cirrhosis	6	6	1.00
Preoperative laboratory data			
Age	66 (40–78)	70 (35–80)	0.08
Platelets (10^3/dl)	19.5 (8.5–51.8)	20.2 (7.2–41.8)	0.65
Albumin (g/dl)	3.9 (2.9–4.6)	3.9 (2.6–4.8)	0.16
Total bilirubin (mg/dl)	0.6 (0.2–2.5)	0.6 (0.3–1.9)	0.43
Alanine aminotransferase (IU/L)	34 (14–153)	30 (15–100)	0.16
ICG-R15 (min)	9.4 (2.9–19.8)	9.9 (2.0–33.9)	0.31
Prothrombin time (%)	100 (76–100)	100 (83–100)	0.67
Preoperative respiratory function			
%VC (%)	101.3 (61.9–154.3)	93.7 (66.9–133.1)	0.62
$FEV_{1.0}$ (%)	73.4 (48.4–88.7)	76.4 (44.4–97.6)	0.26
PaO_2 (mmHg)	84.7 (64.4–109.0)	82.3 (63.0–116.1)	0.64
$PaCO_2$ (mmHg)	39.7 (27.6–49.0)	37.5 (29.9–44.7)	0.69
Base excess (pg/ml)	1.5 (–5.1–6.6)	1.8 (–3.7–6.2)	0.82
Saturation (%)	96.1(94.0–99.6)	96.4 (93.4–100)	0.88
Operation related data			
Operative time (min)	402 (236–661)	330 (178–697)	<0.001
Ischemia time (min.)	65 (12–223)	76 (28–247)	0.04
Blood loss (g)	453 (94–1,930)	431 (68–1,291)	0.28

[a] Values for matched variables are number of patients; other values are median with range in parentheses

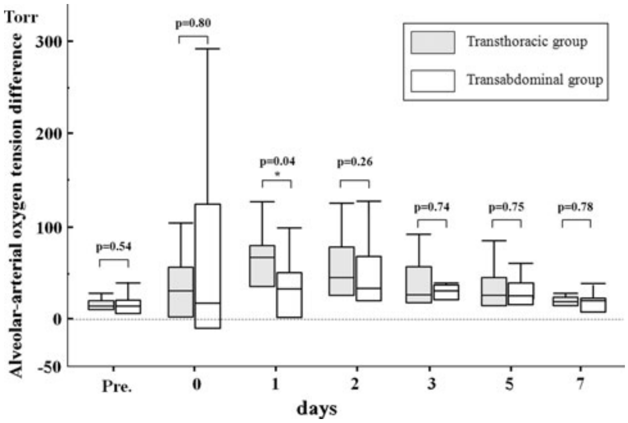

Fig. 1 Trends of alveolar-arterial oxygen tension differences after liver resection. Preoperative $AaDO_2$ was not significantly different between the two groups. The median $AaDO_2$ on POD 1 alone was significantly different (66.1 vs. 33.5 Torr, $P = 0.04$)

levels in the pleural effusions on POD 2 were significantly elevated in the transthoracic group compared to those of the transabdominal group (21,900 pg/ml [range = 6,020–123,000] vs. 866 pg/ml [range = 389–2,210], $P < 0.001$). For serum IL-10, levels just after surgery (POD 0) (16.5 pg/ml [range =2.0–152.0] vs. 7.0 pg/ml [range = 2.0–128.0], $P < 0.001$) were significantly higher in the transthoracic group than in the transabdominal group. However, perioperative CRP levels were similar between the groups at each time point.

Postoperative complications

There was no postoperative mortality, and no significant differences were observed in overall complications between the two groups (36.1 vs. 38.9%, $P = 0.81$) (Table 3). Overall respiratory complications (19.4 vs. 36.1%, $P = 0.11$), atelectasis (16.7 vs. 33.3%, $P = 0.10$), pleural effusion (16.7 vs. 36.1%, $P = 0.06$), and pneumonia (2.8 vs. 2.8%, $P = 1.00$) did not differ between the two groups. Other nonrespiratory complications were also similar between the groups. There was also no significant difference in the length of postoperative hospital stay

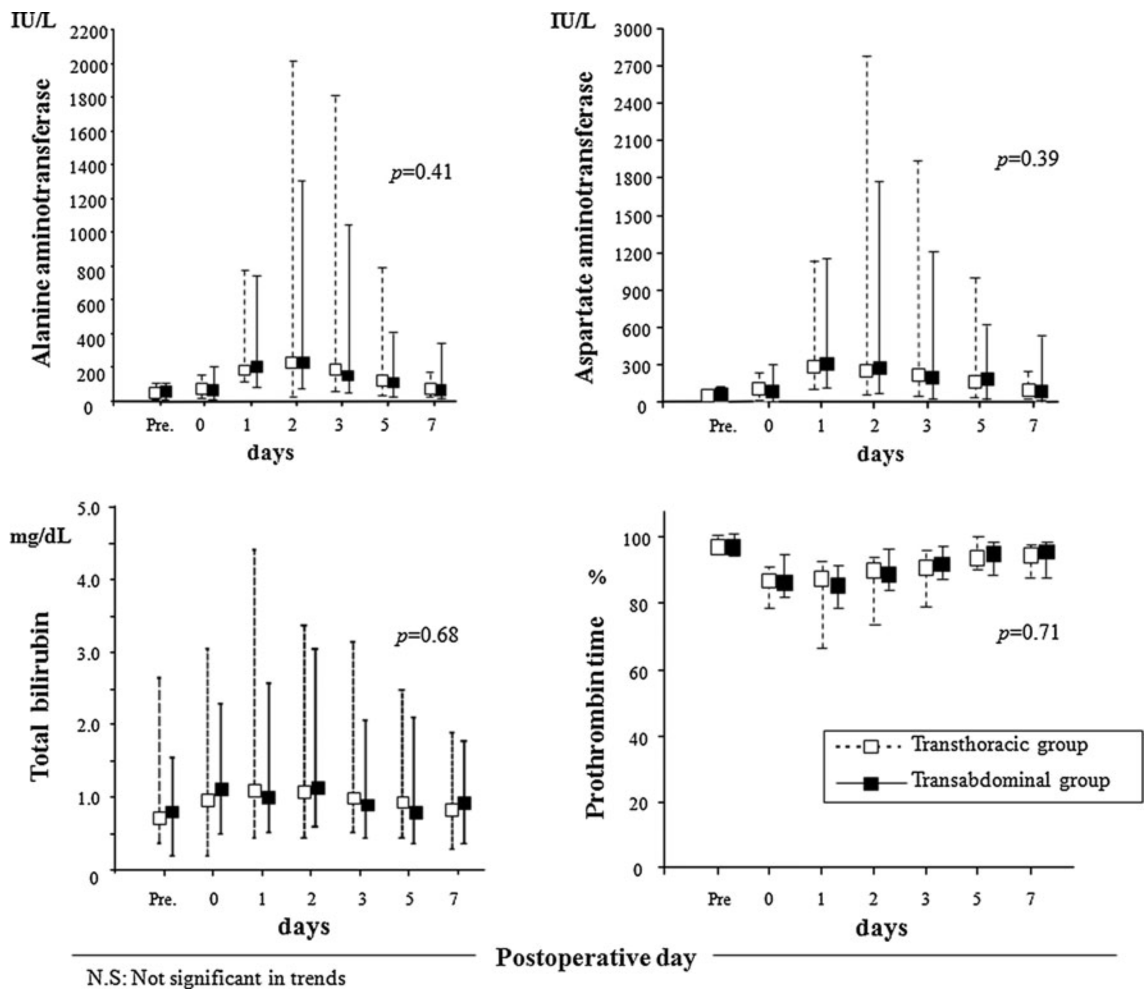

Fig. 2 Trends of postoperative liver function recovery after liver resection. The trends of postoperative recovery of liver function and coagulation activity are shown. The peak levels of each variable occurred around POD 2; thereafter, they gradually recovered by POD 7

Table 2 Inflammatory response

	Transthoracic group ($n = 36$)	Transabdominal group ($n = 36$)	*P* value
Serum IL-6 (pg/ml)			
Preoperation	2.7 (0.8–42.9)	2.9 (0.4–23.1)	0.71
POD 0	201.5 (44.2–1160)	147.0 (33.2–688)	0.08
POD 1	77.7 (16.1–528)	78.8 (10.1–706)	0.93
POD 2	29.5 (4.0–149)	24.2 (3.5–91.7)	0.22
POD 5	19.5 (7.2–124)	18.3 (2.7–102)	0.24
Pleural IL-6 (pg/ml)			
POD 2	21,900 (6,020–123,000)	866 (389–2,210)[a]	<0.001
Serum IL-10 (pg/ml)			
Preoperation	2.0 (2.0–6.0)	2.0 (2.0–6.0)	0.68
POD 0	16.5 (2.0–152.0)	7.0 (2.0–128.0)	<0.001
POD 1	2.0 (2.0–8.3)	2.0 (2.0–7.0)	0.57
C-reactive protein (IU/L)			
Preoperation	0.2 (0.1–6.6)	0.2 (0.1–6.9)	0.23
POD 0	0.7 (0.1–3.6)	0.2 (0.1–5.5)	0.03
POD 1	3.9 (0.1–13.8)	4.0 (1.0–11.8)	0.84
POD 2	8.5 (1.7–26.7)	9.2 (1.6–22.2)	0.53
POD 3	6.8 (1.6–23.2)	7.6 (1.4–18.6)	0.70
POD 5	3.9 (0.6–20.1)	3.8 (0.5–12.0)	0.49
POD 7	3.4 (0.3–15.3)	3.4 (0.5–13.1)	0.43

Values are median with range in parentheses

IL interleukin, *POD* postoperative day

[a] $n = 13$

Table 3 Postoperative outcomes

	Transthoracic group ($n = 36$)	Transabdominal group ($n = 36$)	*P* value
Mortality	0 (0%)	0 (0%)	1.00
Overall complications	13 (36.1%)	14 (38.9%)	0.81
Respiratory complications	7 (19.4%)	13 (36.1%)	0.11
Atelectasis	6 (16.7%)	12 (33.3%)	0.10
Pleural effusion	6 (16.7%)	13 (36.1%)	0.06
Pneumonia	1 (2.8%)	1 (2.8%)	1.00
Other complications			
Reoperation	1 (2.8%)	0 (0%)	0.31
Ascites	3 (8.3%)	2 (5.6%)	0.64
Bile leakage	2 (5.6%)	1 (2.8%)	0.55
Wound infection	8 (22.2%)	6 (16.7%)	0.68
Wound dehiscence	2 (5.6%)	2 (5.6%)	1.00
Others	1 (2.8%)	2 (5.6%)	0.56
Hospital stay (days)[a]	14 (9–54)	13 (8–46)	0.23

Values are the total number of patients

[a] Median with range

between the two groups (14 days [range = 9–54] vs. 13 days [range = 8–46], $P = 0.23$).

Discussion

In this study we demonstrated that a transthoracic approach in liver resection can be performed safely and without additional risks and that the clinical outcomes and biological responses of patients to liver resection with or without thoracotomy were similar.

Previous reports were imbalanced in terms of patient numbers, background disease, scale of liver resection, and degree of liver damage [4, 5, 8, 9, 13, 14]. To confirm the benefits of a transthoracic approach, a prospective randomized trial is needed. However, to our knowledge, neither a randomized controlled trial (RCT) nor a matched cohort study has been described in the literature. Thus, we performed a matched cohort study to minimize the bias concerning postoperative outcomes for treatment of hepatocellular carcinoma.

The transabdominal approach is useful in two different respects. Tumors located in the right lateral segment, large hamper tumors, and diaphragmatic invasions are hard to treat with only the transabdominal approach [20].

In repeated liver resections, it is also difficult to mobilize the liver because of severe adhesion. The transthoracic approach allows the surgeon easier manipulation and a better view around the IVC; additionally, it enables safe and easy extensive hepatic mobilization [7, 9]. Hepatic vein bleeding can also be controlled more easily by raising the liver with the left hand above the IVC [7].

Previously, the thoracotomy had been thought of as a risk factor for increased postoperative morbidity and mortality [21, 22]; however, the advantages and safety of this procedure have been highlighted in more recent studies [6–9]. Some reports have demonstrated that the transthoracic approach has shorter operative times and less blood loss [5, 13]. However, in our study, the operative time was longer for the transthoracic group, and the intraoperative blood loss was similar between the two groups. We speculate that this discrepancy was due to the matched cohort study of the operation scale. The liver ischemia time was significantly shorter in the transthoracic group than in the transabdominal group. Thus, the transthoracic approach may be potentially beneficial for reducing ischemic damage due to the sufficient mobilization of the liver at the time of liver transection.

The transthoracic approach is known to increase the incidence of pleural effusion [7, 13]; however, in our study, the rate of atelectasis was 16.7 versus 33.3% ($P = 0.11$) and pleural effusion was 16.7 versus 36.1% ($P = 0.10$) for the transthoracic versus transabdominal group. There seemed to be few postoperative respiratory complications when using the transthoracic approach. The atelectasis and pleural effusion were well controlled by continuous thoracic drainage for the first 2 days, and postoperative complications in this early period did not differ between the two groups. Thus, our study revealed that thoracotomy alone did not increase the risk of respiratory complications.

Some authors have argued that the transthoracic approach is associated with greater surgical stress; thus, they recommend a different approach [8–10]. IL-6 levels were used as a simple measure of injury severity and surgical stress in this study. The serum IL-6 levels responded rapidly just after surgery but were unchanged regardless of technique, i.e., with or without thoracotomy. Interestingly, the IL-6 levels in pleural effusions were much higher in the transthoracic group than in the transabdominal group, but this did not correlate with the serum IL-6 levels. Moreover, the $AaDO_2$ value reflects peripheral alveolar injury and surgical stress, and there were no significant differences at any time points measured between the two groups after the operation. These results indicate that thoracotomy alone did not increase surgical stress or alveolar injury. We speculate that unlike thoracic or esophageal surgery, the thoracotomy is only a part of an operative procedure.

The results of the transthoracic approach were comparable to those of the transabdominal approach for all parameters tested. Our results indicate that this procedure might be justified as a useful surgical option, and surgeons need not hesitate to perform thoracotomy in liver resections when the location and condition of the tumor are suitable.

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