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Name of Journal: *World Journal of Gastrointestinal Surgery*

Manuscript NO: 81620

Manuscript Type: ORIGINAL ARTICLE

Retrospective Cohort Study

**Compliance of enhanced recovery after surgery predicting long-term outcome after
hepatectomy for cholangiocarcinoma**

Jongkorkorn C *et al.* ERAS in cholangiocarcinoma

Abstract

BACKGROUND

Enhanced recovery after surgery (ERAS) program has been proved to improve postoperative outcome for many surgical procedures, including liver resection. There was limited evidence regarding the feasibility and benefit of ERAS in patients who underwent liver resection for cholangiocarcinoma.

AIM

To evaluate the feasibility of ERAS in patients who underwent liver resection for cholangiocarcinoma and its association with patient outcomes.

METHODS

We retrospectively analyzed 116 cholangiocarcinoma patients who underwent hepatectomy at Srinagarind Hospital, Khon Kaen University, between January 2015 and December 2016. The primary outcome was the compliance of ERAS. To determine the association between ERAS compliance and outcomes of the patients. Patients were categorized into those adhered more than and equal ($ERAS \geq 50$), and below 50 percent ($ERAS < 50$) of all components. Details on type of surgical procedure, preoperative and postoperative care, tumor location, postoperative laboratory results and survival time were evaluated. The compliance of ERAS was measured by the percentage of ERAS items achieved. The Kaplan-Meier curve was used for survival analysis.

RESULTS

The median percentage of ERAS goals achieved was 40 (+/-12) percent. Fourteen patients (12.1%) were categorized as $ERAS \geq 50$ group, 102 patients were in the $ERAS < 50$ group. Postoperative hospital stay was significantly shorter in $ERAS \geq 50$ group [8.9 d, 95% confidence interval (CI):7.3-10.4] compared with $ERAS < 50$ group (13.7 d, 95%CI: 12.2-15.2), $P = 0.0217$. No hepatobiliary-related complications or in-hospital mortality in $ERAS \geq 50$ group. Overall survival was significantly higher in $ERAS \geq 50$

group. The median survival of the patients in the ERAS < 50 group was 1257 d (95%CI: 853.2-1660.8), whereas that the patients in the ERAS ≥ 50 group was not reached.

CONCLUSION

Overall ERAS compliance for patients who underwent liver resection for cholangiocarcinoma was poor. Greater ERAS compliance could predict in-hospital, short term outcomes and long-term outcome of the patients.

Key Words: Enhanced recovery program after surgery; Cholangiocarcinoma; Hepatectomy; Survival; Enhanced recovery after surgery; Outcome

Jongkorkorn C, Luvira V, Suwanprinya C, Piampatipan K, Leeratanakachorn N, Tipwaratorn T, Titapun A, Srisuk T, Theeragul S, Jarearnrat A, Thanasukarn V, Pugkhem A, Khuntikeo N, Pairojkul C, Kamsa-Ard S, Bhudhisawasdi V. Compliance of enhanced recovery after surgery predicting long-term outcome after hepatectomy for cholangiocarcinoma. *World J Gastrointest Surg* 2023; In press

Core Tip: The present study is the first and the largest study demonstrating the enhanced recovery program after surgery (ERAS) compliance and its association with short term outcomes and long-term outcome of cholangiocarcinoma patients. This study demonstrated that overall ERAS compliance in patients who underwent liver resection for cholangiocarcinoma was poor. The patients with high ERAS compliance were significantly associated with shorter postoperative hospital stay, and, interestingly, longer overall survival.

INTRODUCTION

Enhanced recovery after surgery (ERAS) program has been proven to be beneficial and became the standard of care in colorectal surgery. Over the years, it gains considerable momentum and has been implemented in other surgical specialties^[1], even in

emergency settings^[2]. Since liver resection is a relatively complex surgery, with unique perioperative procedures and complications^[3,4], ERAS in liver resection may be more difficult to implement and has different considerations from other abdominal operations. There are several recommendations and evidence supporting ERAS in liver resection procedures^[5-7].

Despite a number of evidences supporting using ERAS in liver surgery, most of them did not focus specifically on liver resection for cholangiocarcinoma, which has several unique features including: (1) The requirement of major-anatomic liver resection; (2) Being non-cirrhotic but having a tense liver from various degree of biliary obstruction; and (3) In selected cases, require biliary-enteric anastomosis^[8,9]. There was limited evidence regarding the feasibility and benefit of ERAS in patients who underwent hepatic resection for cholangiocarcinoma. Although the feasibility of applying ERAS in patients who underwent hepatic resection for cholangiocarcinoma were demonstrated by Yip *et al*^[10] and Quinn *et al*^[8], the association between ERAS compliance and outcomes of the patients, both short and long term outcomes, had not been reported. We, therefore, aimed to evaluate the feasibility of ERAS in patients who underwent hepatic resection for cholangiocarcinoma, and determine its association with outcomes of the patients.

MATERIALS AND METHODS

Study population

All patients undergoing hepatic resection for cholangiocarcinoma at Srinagarind Hospital, Khon Kaen University (Khon Kaen, Thailand) between January 2015 and December 2016. This study was a comparative study. We retrospectively reviewed the prospectively maintained medical and pathological records of 116 histologically-confirmed cholangiocarcinoma. During the study period, our team was aware of ERAS of all abdominal operations but did not fully implement a formal ERAS protocol to hepatobiliary surgery.

Preoperative preparation

All patients with radiologically diagnosed cholangiocarcinoma received a common preoperative protocol, which included: (1) Resectability evaluation by reviewing cross-sectional imaging and patient status. The criteria of resectability included: (1) Good performance status (ECOG 0-1); (2) Absence of distant organ or lymph node metastasis on preoperative imaging; and (3) Sufficient volume of expected future liver remnant; (2) Blood examination: Complete blood count, liver tests, coagulogram, hepatitis panels, and tumor markers; and (3) Preoperative biliary drainage of future liver remnants, either endoscopically or percutaneously, in the patients with obstructive jaundice with the aim to reduce serum total bilirubin to below 10 mg/dL. All patients were admitted to the hospital at least one day before the operation. All clinical, laboratory, and radiological data were rechecked at the time of the admission.

Operative procedure

During the study period, we performed all liver resection by open surgery. Mirror-L incision was used in all cases. The type of liver resection was determined by the extent of the tumor, with plans to achieve at least all gross tumor removal. To optimize the surgical margin, surgeons preferred major hepatic resection to minor hepatic resection, which was performed only in patients with intraoperatively found limited future liver function. Liver parenchyma transection techniques and method of vascular inflow occlusion depended on the surgeon's preference. Biliary-enteric anastomosis, if needed, encompassed ante-colic hepatico-jejunostomy in all cases.

Postoperative care plan

After surgery, all patients were admitted to the intensive care unit until their conditions were stable and able to be extubated. Patients were allowed to be discharged from the hospital when on a full oral diet, received adequate pain controls, and demonstrated acceptable clinical and laboratory results. All patients were followed up in the hepatobiliary clinic with their respective attending surgeon at 2 wk after discharge.

ERAS assessing item

Adherence to ERAS components were recorded. During the study period, our hepatobiliary team had not fully implemented a formal ERAS protocol. Our protocol, as detailed in Table 1, contained 17 components, including preoperative counseling, preoperative fasting and preoperative carbohydrates load, pre-anesthetic anxiolytic, venous thromboembolism (VTE) prophylaxis, antimicrobial prophylaxis and skin preparation, prophylactic nasogastric intubation, preventing intraoperative hypothermia, fluid management, prophylactic abdominal drainage, early mobilization, postoperative glycemic control, preventing postoperative nausea and vomiting (PONV), multimodal analgesia, initial oral analgesic drug at postoperative day 1 (POD1), early NG tube removal at POD 1, postoperative nutrition and early oral intake, and removal of urinary catheter at POD 2. Patients were then categorized into those who adhered to more than and equal 50 percent ($ERAS \geq 50$), and below 50 percent ($ERAS < 50$) of all ERAS components.

Data collection and statistical analysis

The primary outcome of this study was the compliance of ERAS, which was measured by the percentage of ERAS items achieved. We also investigated the association between the ERAS compliance and long term outcomes of the patients. Descriptive analyses were performed and presented as appropriate. Continuous data were analyzed using student's *t*-test. Categorical data were compared using the Pearson χ^2 test. Survival analysis was presented using the Kaplan-Meier curve. Comparison amongst groups were analyzed using a log-rank test. A *P*-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using STATA version 13 (Lakeway, TX, United States).

Ethical consideration

The Institutional Review Board, Office of Human Research Ethics, Khon Kaen University, reviewed and approved this study (HE611590).

RESULTS

There were 116 cholangiocarcinoma patients who underwent hepatic resection during the study period. The median age was 63 (+/- 9.5) years. Male patients outnumbered female patients (62.1% vs 37.9%). None of the patients achieved ERAS goal of at least 80%. The median percentage of ERAS goals achieved was 40 (+/-12) percent. Only 14 patients (12.1%), achieved at least 50 percent of ERAS goal, were categorized as ERAS \geq 50 group. The remaining were categorized as ERAS < 50 group. All of the patients of this cohort achieved goals in three components, including preoperative counseling, antimicrobial prophylaxis and skin preparation, and preventing intraoperative hypothermia. None of the patients achieved goals in preoperative fasting and preoperative carbohydrates load, avoiding NG intubation, avoiding abdominal drainage, and early mobilization. The ERAS items that had a difference in goal achievement between two groups included: Early removal of Foley catheter, early oral dietary intake, early NG tube removal, initiate oral analgesic drug, postoperative glycemic control, prevention of PONV, multimodal analgesia, VTE prophylaxis, pre-anesthetic anxiolytic, and fluid management, as detailed in Figure 1. There were no differences in patients' clinical and operative characteristics between groups, except for the number of male patients in ERAS < 50 group (65.7% vs 35.7%, $P = 0.03$), higher proportion of intrahepatic tumor location (85.7% vs 39.2%, $P = 0.027$) and higher in preoperative serum cholesterol level ($P = 0.0445$) in ERAS \geq 50 group (Table 2).

ERAS and postoperative outcome

The postoperative outcomes are shown in Table 3. There were no hepatobiliary related complications in ERAS \geq 50 group. Postoperative hospital stay was significantly shorter in ERAS \geq 50 group [8.9 d, 95% confidence interval (CI): 7.3-10.4] compared with ERAS < 50 group (13.7 d, 95%CI: 12.2-15.2), $P = 0.0217$. There were no differences in

postoperative laboratory results between two groups, except for serum cholesterol level at POD3 and POD5.

There was no 30-d mortality in this cohort. There were three patients with 60-d mortality, all of which were in the ERAS < 50 group. The patients died on postoperative days 21, 37, and 45 from bleeding aneurysm of right hepatic artery stump, severe pneumonia, and postoperative liver failure, respectively. With the median follow-time of 1241 d, the median survival of this cohort was 1302 d (95%CI: 1130.6-1473.4). There was a statistically significant difference in overall survival between two groups ($P = 0.0187$) (Figure 2A). The median survival of the patients in the ERAS < 50 group was 1257 d (95%CI: 853.2-1660.8), whereas of the patients in the ERAS \geq 50 group was not reached- more than 50 percent of the patient with ERAS \geq 50 were still alive at the time of the last follow-up. The respective 1- and 3-year survival of the patients in ERAS < 50 was 77.5% (95%CI: 63.1-89.1) and 50.9% (95%CI: 37.1-67.9), and of the patients in ERAS \geq 50 group was 100% and 85.7% (95%CI: 53.9-96.2). The survival between the groups seem to differ in both intrahepatic (Figure 2B) and extrahepatic tumor (Figure 2C), but not statistically significant.

DISCUSSION

This study has demonstrated that overall ERAS compliance in patients who underwent liver resection for cholangiocarcinoma was poor. The patients with ERAS \geq 50 were significantly associated with shorter postoperative hospital stay, and, interestingly, longer overall survival.

Postoperative care for liver resection had many unique challenges that had a large impact on the physiologic outcomes, such as having a large abdominal incision that requires the use of spinal anesthesia, significant intraoperative hemodynamic disturbance, and having a decreased liver volume postoperatively. These factors explain why overall ERAS compliance is lower compared to other abdominal operations, despite the fact that this group of patients might gain the most benefit from ERAS implementation. We initially intended to use 80 percent ERAS adherence as the

cut point for categorizing the patients. However, at the time of the study, there was poor compliance to the ERAS protocol and none of the cases were able to achieve more than 80 percent of ERAS components. Consequently, a cut point at 50 percent ERAS was used instead. In the future, when ERAS is more routinely adopted, a higher cut point for components achieved may result in more tiers and more pronounced difference in patient outcomes. It should be noted that some ERAS components might not be suitable for cholangiocarcinoma resection, including the omission of nasogastric tube and abdominal drainage^[8]. In our study, none of the patients achieved these component goals. Gastric dilation during the operation would preclude a good exposure of the operative field. Liver transection created a large raw surface of the liver that could cause postoperative bleeding and bile collection, therefore placement of abdominal drainage almost unavoidable. Instead, several intraoperative manners should be further evaluated and considered to be ERAS components, such as intraoperative vascular inflow occlusion, controlling of CVP, and IVC clamping^[9,11]. These make liver transection safer, and would enhance patient recovery. We found that ERAS components that showed difference in compliance between the groups were mostly related to analgesic and dietary- related components. This finding is compatible with previous study^[12]. These components could be modified easily without any additional costs, and should be prioritized for implementation. Effective pain management might be a key to successfully enhance recovery after liver resection. Lower postoperative pain, incorporated with early removal of Foley catheter, leads to early mobilization and, subsequently, early returns of bowel movement^[8]. Concerning the delayed oral intake in the patients with extrahepatic cholangiocarcinoma, whose require biliary-enteric anastomosis, preclude enhanced recovery. This leads to several delays, including oral analgesia, NG tube removal, mobilization, and, ultimately, recovery. This explains why we found a higher proportion in extrahepatic cholangiocarcinoma in the ERAS < 50 group. Improvement of ERAS for liver resection is crucial. Since a number of cases is required for achieving the optimal recovery and compliance^[13], the large center with high number of cholangiocarcinoma cases should be the initiator of ERAS development.

Since 2016, we were able to consistently apply these ERAS components: Pre-anesthetic anxiolytic, VTE prophylaxis, preventing intraoperative hypothermia, preventing PONV, Early NG tube removal at POD1, and early oral intake. Moreover, we started to perform minimally invasive surgery for liver resection procedure.

Another way in which operative outcomes could be improved is through laparoscopic surgery, as previous studies have shown that laparoscopic liver resection is associated with shorter length of stay^[14]. Therefore, ERAS in laparoscopic liver resection should be considered separately from open liver resection. Since laparoscopic liver resection is typically performed in selected patients that required less complicated operative procedure, our study was intentionally conducted when all cholangiocarcinoma cases, at our center, received open resection in order to minimize selection bias.

Recent evidence from other randomized controlled trials reaffirmed that the ERAS protocol for patients who underwent liver resection was associated with decreased LOS and lower overall morbidity^[15-17]. Our study confirmed that these findings are also valid in cholangiocarcinoma patients. We found that the patients with higher ERAS compliance had significantly shorter LOS. This is comparable with a previous report, which stated that patients undergoing major liver resection that were on ERAS protocol experienced the greatest benefit in terms of decreased LOS and decreased rate of 30-d complications^[12]. Alteration of postoperative liver tests could be used as an indicator for liver recovery and risk of postoperative liver failure^[4]. In our study, the postoperative serum cholesterol level was significantly higher in the ERAS ≥ 50 group. It might indirectly indicate that liver recovery is faster in this group. Other explanations include: (1) The patients in this group already had higher cholesterol level preoperatively; (2) Higher proportion of intrahepatic tumors, which require less extensive liver resection. None of our patients in the ERAS ≥ 50 group experienced hepatobiliary-related complications. There might be synergistic effects between absences of complication and achieving ERAS goals. Both of them promote patient recovery and, ultimately, shorten LOS. One study reported that even in high risk or with postoperative major

complication, high ERAS compliance was achievable^[8]. However, it is safe to say that achievement of ERAS ≥ 50 can be used to predict in-hospital, postoperative hepatobiliary-related complications, especially postoperative liver failure.

Although ERAS protocol has been proven to be beneficial amongst patients who underwent liver resection in terms of short-term outcomes^[6,7,12], there was no study demonstrating these associations with long-term outcomes. We demonstrated the association between higher ERAS achieving and longer survival of the patients. This issue had been addressed in other cancers^[18,19]. ERAS improved survival through various ways: (1) Reduction of postoperative stress leads to better immunologic function against the remaining tumor micro-metastases; and (2) Promoting quick recovery prevents the delay of adjuvant treatment. However, since there is no solid evidence of benefit of postoperative adjuvant chemotherapy for resectable cholangiocarcinoma^[20-22], and cholangiocarcinoma is a heterogeneous disease with various progression pathways^[23,24], it could not be concluded that improvement of ERAS compliance leads to an improvement of overall survival of cholangiocarcinoma patients. Even so, higher ERAS achievement could at least be used as a marker of better survival of cholangiocarcinoma patients.

To the best of our knowledge, our study was the first study to demonstrate the association between greater ERAS achievement and long-term outcome of the patients who underwent liver resection. Moreover, this study was the largest study that focuses only on cholangiocarcinoma patients who underwent liver resection by various hepatobiliary surgeons. However, there were several limitations that should be acknowledged. Bias might be introduced through: (1) Being retrospective in nature; (2) Having a short interval of study period when a standard, full- ERAS protocol has not completely been developed. Due to the aforementioned limitations, only a correlation between better ERAS compliance and better outcome can be drawn; we were unable to interpret that better ERAS achievement caused better outcome; and (3) The sample size of the ERAS ≥ 50 group is quite small and could cause a significant type 2 error. Future

prospective study should be conducted with full implementation of ERAS protocol specifically for the cholangiocarcinoma patients to demonstrate this association.

CONCLUSION

Overall ERAS compliance for cholangiocarcinoma was poor. There is a room for improvements of ERAS in patients who underwent liver resection for cholangiocarcinoma. Greater ERAS compliance could predict not only in-hospital, short term outcomes but also long-term outcome of the patients.

ARTICLE HIGHLIGHTS

Research background

Enhanced recovery after surgery (ERAS) protocol has shown to be beneficial to patient outcomes in various abdominal surgeries, including hepatectomy. However, no previous study has demonstrated this association for hepatectomy in cholangiocarcinoma patients.

Research motivation

The present study reviews the ERAS compliance and its association with outcomes of the patients who underwent open liver resection for cholangiocarcinoma during the first period of ERAS implementation.

Research objectives

To demonstrate the association between good ERAS compliance, short term outcomes, and long term outcomes in cholangiocarcinoma patients.

Research methods

Cholangiocarcinoma patients who underwent open hepatectomy between January 2015 and December 2016 were retrospectively analyzed. Patient's compliance to ERAS was measured by the percentage of ERAS items achieved and categorized into more than

and equal to 50 percent (ERAS \geq 50), and below 50 percent (ERAS $<$ 50). Details on operative procedure, patient care, and survival were analyzed.

Research results

A total of 116 patients were identified - 14 patients (12.1%) were categorized as ERAS \geq 50 group, and 102 patients were in the ERAS $<$ 50 group. Postoperative hospital stay was significantly shorter in ERAS \geq 50 group [8.9 d, 95% confidence interval (CI): 7.3-10.4] compared with ERAS $<$ 50 group (13.7 d, 95%CI: 12.2-15.2), $P = 0.0217$. No hepatobiliary-related complications or in-hospital mortality in ERAS \geq 50 group. Overall survival was significantly higher in ERAS \geq 50 group.

Research conclusions

Good ERAS compliance is associated with decreased LOS, decreased morbidity, and better survival.

Research perspectives

Current overall ERAS compliance was poor. Future improvements in ERAS compliance could result in better short term and long term outcomes.

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