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ERAS Protocol for Perioperative Care of Patients Treated with Laparoscopic Nonanatomic Liver Resection for Hepatocellular Carcinoma: The ISMETT Experience

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Abstract

Background: Liver resection (LR) remains the best therapeutic option for patients with early-stage hepatocellular carcinoma (HCC) with preserved hepatic function and who are not eligible for liver transplantation. After its inception, the enhanced recovery after surgery (ERAS) protocol was widely used for treating patients with liver cancer, although there are still no clear indications for improving upon it in both open and laparoscopic surgery.
Objective: This study aims to describe our institute's experience in the application of the ERAS protocol in a cohort of HCC patients, and to explore possible factors that could have an impact on postoperative outcomes.
Materials and Methods: We retrospectively analyzed our experience with LR performed from September 2017 to January 2020 in patients treated with ERAS protocol, focusing on describing impact on postoperative nutrition, analgesic requirements, and length of hospitalization. Demographics, operative factors, and postoperative complications of patients were reviewed.
Results: During the study period, 89 HCC patients were eligible for LR, and 75% of patients presented with liver cirrhosis. The most prevalent among etiologic factors was hepatitis C virus infection (53 patients out of 89, 60%), followed by nonalcoholic steatohepatitis (18 patients, 20%). The median age was 70 years. Liver cirrhosis did not have an impact on postoperative course of patients. Patients who underwent laparoscopic surgery and nonanatomic LR experienced low complication rates, shorter length of stay, and shorter time of intravenous analgesic requirements.
Conclusions: Continual refinement with ERAS protocol for treating HCC patients based on perioperative counseling and surgical decision-making is crucial to guarantee low complication rates, and reduce patient morbidity and time for recovery.

Keywords: hepatocellular carcinoma, laparoscopic liver resection, ERAS, outcome

Introduction

Hepatocellular carcinoma (HCC) is the most common form of liver cancer, ranking fourth among cancer-related causes of death. The current challenging epidemiology of long-term hepatitis clinical pictures has been shown to cause cirrhosis and HCC, in especially in elderly patients.[1,2] Liver resection (LR) is carried out as a valid option to bridge the stay on the waiting list for transplantation of patients with end-stage liver disease (ESLD), and has helped dramatically mitigate the scarcity of donor pool for the past decade.[3–5] Since hepatectomy for HCC is a surgical procedure performed in otherwise elderly patients with or without ESLD, in which manipulation of vessels can cause life-threatening bleeding,[6,7] in recent decades efforts have been made to implement the enhanced recovery after surgery (ERAS) protocol.[8,9]

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It has been widely introduced for treating patients with liver cancer, but there are still no clear indications for improving upon it in both open and laparoscopic surgery in terms of complication rates and, moreover, making the surgery faster and safer, reducing length of hospital stay (LOS), and controlling pain.[10,11] Since the implementation of the ERAS protocol for minimally invasive abdominal and thoracic surgical procedures at our institute, we have involved anesthesiologists, surgeons, skilled nurses, and physical and respiratory therapists in a multidisciplinary team. Our experience with ERAS is described elsewhere.[12–14] The aim of this study is to describe our experience in the application of the ERAS protocol in a cohort of HCC patients, and to explore possible factors that could have an impact on postoperative outcomes.

Materials and Methods

Study population and ERAS protocol pathways

All consecutively recruited patients with a radiological diagnosis of HCC admitted to our institution from September 1, 2017 to January 31, 2020, and treated with ERAS protocol for undergoing radical LR were included in this single-center retrospective study. Institutional research review board approval was granted by IRCCS ISMETT, and good clinical and research practices were adopted. Disease staging and clinical pictures were evaluated with the following variables: dosage of alpha-fetoprotein level, complete serum laboratories, and physical examination, as well as radiological diagnosis. Multidetector computed tomography scans of the abdomen, pelvis, and chest were done within 1 month before surgery, and, during the follow up: every 3 months for the first year after LR, and every 6 months after the first year, for quantifying the HCC size, number of lesions, and exact locations, and to exclude concomitant new lesions.

Demographics, operative factors, and postoperative complications of patients were reviewed. Our approach, which emphasizes parenchyma-sparing-based laparoscopic and open LR, has been previously reported.[15,16] Preoperative counseling was conducted beginning at the first outpatient clinic surgical visit, and patients received information on the ERAS protocol, and offered specific rehabilitation and dietary evaluations. On the day of surgery, a preoperative maltodextrin nutritional supplement was administered, and solid diet was maintained until 6 hours before surgery. During the intraoperative time, and after specific consent, the patients underwent a careful restriction of fluids, preoperative ultrashort antibiotic prophylaxis, epidural catheter placement, and epidural analgesic drug administration (bupivacaine 2%) during surgery.

Patients left the operating room without nasogastric tube, and then started to sip water, after performing physical and respiratory consults to obtain a rapid mobilization for 2 hours the day of surgery. Intravenous (IV) fluids were administered only 24–36 hours after surgery. After dosages of prothrombin time, activated partial thromboplastin time, and international normalized ratio, patients were treated with subcutaneous administration of low molecular weight heparin anticoagulation on postoperative day (POD) one to prevent deep vein thrombosis. As discharge criteria, no temperature, stable hemodynamics, active bowel sounds or at least one bowel movement, and autonomous walking and eating were entered into the clinical charts to permit the patients' discharge.

Statistical analysis

Continuous variables are described in terms of median and interquartile range (IQR), whereas categorical ones are described in terms of frequencies and percentages. Differences between groups were tested by means of the Mann–Whitney *U* test for continuous variables, and Pearson's chi-square or Fisher's exact test, as appropriate, for categorical ones. To evaluate the potential association between patient characteristics and the probability of postoperative complications, single-variable logistic regression models were employed, whereas standard linear regression models were used for LOS, number of PODs from surgery to full bowel function recovery, and number of PODs to the interruption of IV analgesia administration. All analyses were done with the R Statistical computing environment, version 3.6.3.

Results

Since the introduction of the ERAS protocol for hepatic surgery patients at our institute (September 1, 2017) to January 31, 2020, 89 patients with a diagnosis of HCC were identified as eligible for surgical resection. Sixty-nine (78%) were male, median age was 70 years; the most prevalent among etiologic factors was hepatitis C virus infection (53/89, 60%), followed by nonalcoholic steatohepatitis (18 patients, 20%). Seventy-five percent of patients presented with liver cirrhosis. Solid diet was maintained until 6 hours before surgery for 79 (89%) patients; maltodextrin nutritional supplement was administered to 76 (85%) patients (800 mL the evening before surgery and 400 mL 2 hours before induction of anesthesia). Sixty-nine patients (78%) were treated with nonanatomic resections. Laparoscopic approach was initially chosen for 56 patients; however, in 14 cases, due to difficulties in reaching the tumor lesions, or to previous surgery[17] and HCCs located in unfavorable segments,[15] conversion to open surgery was necessary.

Several patient characteristics stratified between laparoscopic and open surgery are described in Table 1. With respect to age, gender, body mass index, presence of cirrhosis, etiology, and American Society of Anesthesiologists (ASA) class, there was relatively little difference between patients treated with a laparoscopic approach and those treated with open surgery. Expected differences were found in terms of type and extent of resection, the need for an associated extrahepatic resection, and intraoperative analgesia.

Postoperative clinical course

Overall, 15 patients (17%) had postoperative complications (Table 2). One patient had a cardiopulmonary arrest, which required intensive care unit management, and 1 had a bowel perforation that required an emergency surgical intervention. All the others were nonsevere complications that were solved pharmacologically. Open surgery had a significantly higher rate of postoperative complication (26% versus 7%, $P = .025$). No patient had biliary complications, or posthepatectomy liver failure, and no one died or needed to be readmitted to the hospital. Median length of stay was 4 days (mean: 5.8, IQR: [4.0, 5.0], range: [2.0, 33.0]), and was significantly higher for patients who underwent open surgery (median: 5.0, IQR [4.0, 6.0] days versus 4.0 [3.0, 4.0], $P < .001$, Table 2). Fourteen patients needed postoperative nasogastric tube for at most 2 days; resumption of liquid and solid diet occurred at day 1 and 2, respectively, for all but 5 patients.

Table 1. Baseline Characteristics of 89 Hepatocellular Carcinoma Patients Who Underwent Partial Hepatic Resection[a]

	Laparoscopic surgery	*Open surgery*	*Overall*
n	42	47	89
Age, median [IQR]	69.5 [61.0, 73.0]	71.0 [65.5, 75.5]	70.0 [64.0, 74.0]
Gender, male, *n* (%)	34 (81)	35 (74)	69 (78)
BMI, kg/m^2, median [IQR]	25.3 [23.2, 31.1]	26.1 [23.6, 29.7]	25.7 [23.3, 30.1]
Liver cirrhosis, *n* (%)	34 (81)	33 (70)	67 (75)
Etiologic factors, *n* (%)			
HCV infection	28 (67)	25 (53)	53 (60)
Nonalcoholic steatohepatitis	7 (17)	11 (23)	18 (20)
Alcoholic steatohepatitis	4 (10)	3 (6)	7 (8)
HBV infection	3 (7)	2 (4)	5 (6)
HCC on healthy liver	0 (0)	6 (13)	6 (7)
Solid diet within 6 hours before surgery (%)	37 (88)	42 (89)	79 (89)
Maltodextrin administration, *n* (%)	38 (90)	38 (81)	76 (85)
ASA class, *n* (%)			
1	0 (0)	0 (0)	0 (0)
2	5 (12)	5 (11)	10 (11)
3	30 (71)	40 (85)	70 (79)
4	7 (17)	2 (4)	9 (10)
Type of liver resection, *n* (%)			
Right hepatectomy	0 (0)	3 (6)	3 (3)
Left lobectomy	0 (0)	4 (9)	4 (4)
Bisegmentectomy	0 (0)	2 (4)	2 (2)
Segmentectomy	4 (10)	7 (15)	11 (12)
Multiple wedge resection	1 (2)	6 (13)	7 (8)
Single wedge resection	37 (88)	25 (53)	62 (70)
Number of hepatic wedges removed, *n* (%)			
0 (purely anatomic)	3 (7)	16 (34)	19 (21)
1	38 (90)	25 (53)	63 (71)
2	1 (2)	5 (11)	6 (7)
3	0 (0)	1 (2)	1 (1)
Number of anatomically removed segments			
0 (nonanatomic)	38 (90)	31 (66)	69 (78)
1	3 (7)	7 (15)	10 (11)
2	1 (2)	6 (13)	7 (8)
3 or more	0 (0)	3 (6)	3 (3)
Conversion to open surgery, *n* (%)	0 (0)	14 (30)	14 (16)
Associated extrahepatic resection, *n* (%)			
Cholecystectomy	2 (5)	7 (15)	9 (10)
Partial colectomy	0 (0)	1 (2)	1 (1)
Partial diaphragm resection	0 (0)	1 (2)	1 (1)
Adjuvant intraoperative analgesia, *n* (%)			
IV	15 (36)	7 (15)	22 (25)
Epidural analgesia	21 (50)	38 (81)	59 (66)
Local infiltration analgesia	6 (14)	2 (4)	8 (9)

[a]Values reported as median [IQR] or as *n* (%) depending on the categorical or numerical nature of the variable.
ASA class, American Society of Anesthesiologists classification; BMI, body mass index; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IQR, interquartile range; IV, intravenous.

Median times to recovery were 3.0 days (IQR: [0.0, 4.0]) for urinary catheter removal, 2.0 days (IQR: [2.0, 3.0]) for interruption of IV analgesia administration, 4.0 days (IQR: [3.0, 6.0]) for surgical drain removal, 2.0 days (IQR: [2.0, 2.0]) for the return of bowel sounds, and 4.0 days (IQR: [3.0, 5.0]) for full bowel function recovery (IQR: [4.0, 5.0]).

As could be expected, patients treated with open surgery had statistically significant higher recovery times in terms of nasogastric tube removal, urinary catheter removal, IV analgesia interruption, and surgical drain removal. As could also be expected, the need for a more complex surgery appeared to be associated with a worse clinical course. Patients with the need for an extrahepatic-associated resection had a higher probability of developing complications (odds ratio: 5.7, 95% confidence interval [CI]: 1.4–22.5, $P = .012$, Table 3), a longer hospital stay (estimated mean difference 5.9 days, 95% CI: 2.7–9.1, $P < .001$), and need for an endovenous analgesic treatment for longer time (estimated mean difference 3.1 days, 95% CI: 1.3–4.9, $P < .001$).

Full bowel function recovery was significantly affected by age of the patient (Beta = 0.03, 95% CI: 0.01–0.60, $P = .049$), nonalcoholic steatohepatitis etiology (estimated mean difference 0.9 days, 95% CI: 1.2–1.6, $P = .016$), and ASA class (Beta = 0.9, 95% CI: 0.3–1.5, $P = .005$).

Table 2. Postoperative Clinical Course of 89 Hepatocellular Carcinoma Patients Who Underwent Partial Hepatic Resection[a]

	Laparoscopic surgery[a]	*Open surgery*[a]	P
n	42	47	
Any postoperative complications	3 (7)	12 (26)	.025
Type of complication			
Posthepatectomy liver failure	0 (0)	0 (0)	1.000
Biliary fistula	0 (0)	0 (0)	1.000
Pulmonary complication	1 (2)	3 (6)	.619
Other	2 (5)	10 (21)	.030
Maximum Clavien–Dindo grade			.067
0 (No complication)	39 (93)	35 (74)	
1	3 (7)	5 (11)	
2	0 (0)	5 (11)	
3b	0 (0)	1 (2)	
4	0 (0)	1 (2)	
CCI©	8.7 [8.7, 8.7]	20.9 [8.7, 24.3]	.099
Hospital length of stay	4.0 [3.0, 4.0]	5.0 [4.0, 6.0]	<.001
Postoperative mortality	0 (0)	0 (0)	—
Hospital readmission	0 (0)	0 (0)	—
Postoperative nausea and vomiting	3 (7)	8 (17)	.205
Postoperative recovery days			
Nasogastric tube removal			.005
0 (No postoperative intubation)	40 (95)	35 (74)	
POD 1	1 (2)	11 (23)	
POD 2	1 (2)	1 (2)	
Liquid diet			.057
POD 1	42 (100)	42 (89)	
POD 2	0 (0)	5 (11)	
Resumption of solid diet			.119
POD 1	1 (2)	0 (0)	
POD 2	41 (98)	42 (89)	
POD 3	0 (0)	4 (9)	
POD 4	0 (0)	1 (2)	
Urinary catheter removal (POD)	2.0 [0.0, 3.0]	3.0 [1.5, 5.0]	.003
EV analgesia interruption (POD)	2.0 [1.0, 3.0]	2.0 [2.0, 3.5]	.014
Drain removal (POD)	3.0 [3.0, 5.8]	4.0 [4.0, 8.0]	.003
Return of bowel sounds (POD)	2.0 [1.0, 2.0]	2.0 [2.0, 3.0]	.120
Full bowel function recovery (POD)	4.0 [3.0, 5.0]	4.0 [4.0, 5.0]	.240

[a]Values reported as median [IQR] or as *n* (%) depending on the categorical or numerical nature of the variable.
CCI© values relates to patients with at least one complication.
CCI©, Comprehensive Complication Index; IQR, interquartile range; POD, postoperative day.

Alcoholic steatohepatitis patients required a longer time of IV analgesic treatment (estimated mean difference 3.4 days, 95% CI: 1.2–5.6, $P = .002$).

Notably, liver cirrhosis did not have an impact on postoperative course of patients. Open hepatectomy was associated with a significant postoperative complication profile and LOS, and the use of surgical nonanatomic resection for LR reduced the postoperative LOS (Table 3).

Discussion

Initially developed in the setting of colorectal surgery, ERAS is a multidisciplinary approach aimed at achieving early recovery after surgical procedures, defining standards of preoperative counseling, nutrition, analgesic and anesthetic treatments, and mobilization of the patient. Mainly due to its challenging nature and to the diversity and complexity of patients in terms of both morbidity and mortality,[16] preoperative counseling, perioperative nutrition, preanesthetic medication, antithrombotic prophylaxis, antimicrobial prophylaxis, and skin preparation have been set to ameliorate both open and minimally invasive surgical approach for achieving early mobilization, reducing impact of analgesia adverse effects, and preventing postoperative nausea and vomiting.[18] However, current guidelines focus on noncirrhotic patients, and on patients without additional nonliver surgery, due to the scarcity of data available on the application of ERAS protocols for such patients.[19] In fact, even if ERAS concepts for liver surgery date back to 2008, and several studies have found use of the protocols to be safe and effective in patients undergoing LR, some key elements of the protocol remain controversial.[19–24]

In the international scientific literature of reference, it is well understood how to identify the best surgical procedure by analyzing clear clinical outcomes both in the setting of hepatobiliary surgery and in liver transplantation.[25–30] Otherwise, LR is a valid therapeutic strategy for elderly patients, who cannot be referred to a transplant program because of the potential severe complications associated with transplantation. In contrast, ESLD may limit interventional options to HCC

Table 3. Univariate Statistical Models for Probability of Any Postoperative Complication, Length of Hospital Stay, Time to Bowel Function Recovery, and Time to Intravenous Analgesia Requirements

	Any complication			Length of stay			Bowel function recovery (POD)			IV analgesia interruption (POD)		
	OR	*95% CI*	P	*Beta*	*95% CI*	P	*Beta*	*95% CI*	P	*Beta*	*95% CI*	P
Gender, male	0.51	0.15 to 1.83	.275	−0.36	−3.08 to 2.36	.793	0.29	−0.39 to 0.98	.398	−0.02	−1.51 to 1.46	.975
Age, years	0.99	0.93 to 1.05	.681	−0.01	−0.14 to 0.12	.863	0.03	0.01 to 060	.049	−0.04	−0.11 to 0.03	.290
BMI	1.02	0.91 to 1.14	.684	0.05	−0.18 to 0.28	.652	0.03	−0.03 to 0.09	.324	−0.05	−0.17 to 0.08	.472
Liver cirrhosis	1.38	0.39 to 6.54	.643	−0.24	−2.87 to 2.4	.858	0.14	−0.52 to 0.81	.667	0.2	−1.24 to 1.63	.784
HCV infection	1.02	0.33 to 3.33	.969	−0.16	−2.48 to 2.16	.890	−0.54	−1.12 to 0.03	.064	−0.38	−1.64 to 0.88	.554
Alcoholic steatohepatitis	0.81	0.04 to 5.27	.850	1.44	−2.78 to 5.65	.500	0.47	−0.6 to 1.53	.385	3.44	1.26 to 5.62	.002
Nonalcoholic steatohepatitis	0.98	0.21 to 3.59	.981	−1.59	−4.40 to 1.23	.265	0.86	0.17 to 1.55	.016	−0.9	−2.43 to 0.63	.244
ASA class	0.5	0.15 to 1.67	.264	−0.85	−3.31 to 1.6	.492	0.87	0.27 to 1.46	.005	−0.85	−2.18 to 0.48	.206
Extrahepatic resection	5.67	1.41 to 22.54	.012	5.91	2.69 to 9.13	<.001	0.65	−0.21 to 1.52	.135	3.10	1.33 to 4.86	<.001
Laparoscopic surgery	0.22	0.04 to 0.77	.029	−3.63	−5.77 to −1.48	.001	−0.31	−0.88 to 0.26	.280	−1.21	−2.43 to −0.10	.05
Nonanatomic resection	0.51	0.15 to 1.81	.275	−3.65	−6.26 to −1.04	.007	0.03	0.65 to 0.72	.920	−0.28	−1.77 to 1.20	.707

ASA class, American Society of Anesthesiologists classification; BMI, body mass index; CI, confidence interval; HCV, hepatitis C virus; IV, intravenous; OR, odds ratio; POD, postoperative day.

treatment, influence pharmacokinetics of anticancer drugs, and render patients susceptible to hepatotoxicity, adding a risk for morbidity and mortality.[31] In the setting of these fragile patients, the key point is clearly to assess the patient's physical and mental characteristics because in the elderly there are often cognitive deficits or dementia during the ERAS preoperative counseling that can hinder compliance with and the adoption of therapies.

A specific assessment by a multidisciplinary team of aforementioned specialists, specifically trained for the care of cancer patients, and meeting to review individual clinical cases, must estimate the life expectancy and, above all, the social and family living conditions. An aggressive treatment plan for a patient who lives alone needs adequate health and family organization. The elderly HCC patient needs a personalized path based not only on the anatomic profile of the tumor staging, but also on his perceived experience and psychophysical conditions, because even a mild depression can make it difficult to undergo powerful cancer treatments.[5,7] The patient is taught to understand the fundamentals of pre- and postoperative care, and does better in the postoperative rehabilitation process. Nonanatomic LR in patients with reduced liver function has been found to be feasible and safe, and has not been found to be a significant independent factor for recurrence-free survival. Our experience suggests that, in this light, laparoscopic surgery may reduce the impact of surgery on the patient, and allows extension of the indications for patients with a reduced performance status.[18,32,33]

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