

Original Article/Liver

Outcomes of central hepatectomy versus extended hepatectomy

Jenny Chan^a, Luke Bradshaw^{a,b}, Nezor Houli^b, Laurence Weinberg^c, Marcos V Perini^a, Michael Fink^a, Vijayaragavan Muralidharan^a, Graham Starkey^a, Robert Jones^a, Bao Zhong Wang^a, Christopher Christophi^a, Mehrdad Nikfarjam^{a,*}

^a Department of Surgery, University of Melbourne, Austin Health, Heidelberg, Melbourne, Victoria, Australia

^b Department of Surgery, University of Melbourne, Northern Health, Epping, Victoria, Australia

^c Department of Anaesthesia, University of Melbourne, Austin Health, Heidelberg, Melbourne, Victoria, Australia

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ABSTRACT

Background: Central hepatectomy (CH) is more difficult than extended hepatectomy (EH) and is associated with greater morbidity. In this modern era of liver management with aims to prevent post-hepatectomy liver failure (PHLF), there is a need to assess outcomes of CH as a parenchyma-sparing procedure for centrally located liver tumors.

Methods: A total of 178 major liver resections performed by specialist surgeons from two Australian tertiary institutions between June 2009 and March 2017 were reviewed. Eleven patients had CH and 24 had EH over this study period. Indications and perioperative outcomes were compared between the groups.

Results: The main indication for performing CH was colorectal liver metastases. There was no perioperative mortality in the CH group and four (16.7%) in the EH group ($P=0.285$). No group differences were found in median operative time [CH vs. EH: 450 min (290–840) vs. 523 min (310–860), $P=0.328$], intraoperative blood loss [850 mL (400–1500) vs. 650 mL (100–2000), $P=0.746$] or patients requiring intraoperative blood transfusion [1 (9.1%) vs. 7 (30.4%), $P=0.227$]. There was a trend towards fewer hepatectomy-specific complications in the CH group [3 (27.3%) vs. 13 (54.2%), $P=0.167$], including PHLF (CH vs. EH: 0 vs. 29.2%, $P=0.072$). Median length of stay was similar between groups [CH vs. EH: 9 days (5–23) vs. 12 days (4–85), $P=0.244$].

Conclusions: CH has equivalent postoperative outcomes to EH. There is a trend towards fewer hepatectomy-specific complications, including PHLF. In appropriate patients, CH may be considered as a safe parenchyma-sparing alternative to EH.

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Introduction

Liver resection remains the only curative treatment for various liver lesions. Centrally located liver tumors (CLLT) are difficult to resect due to the complexity related to their anatomical location [1]. CLLT have traditionally been treated by extended hepatectomy (EH), with the removal of more than four contiguous liver segments. The main concern with EH is increased risk of post-hepatectomy liver failure (PHLF) due to inadequate liver remnant (FLR) resulting from extensive parenchymal resection (60%–85%) [2,3].

Central hepatectomy (CH) may achieve equivalent oncological results to EH while preserving greater FLR in selected pa-

tients [1,4–11]. CH is a segment-oriented parenchyma-sparing procedure, defined as *en bloc* resection of Couinaud segments 4a, 4b, 5 and 8 (i.e., right anterior and left medial sections) with or without resection of segment 1. It is also known in the literature as mesohepatectomy [1,4–6,12], central bisectionectomy [7,13] and central bisegmentectomy [14].

The main theoretical advantage of CH is preserving a larger volume of liver parenchyma in the FLR, thereby reducing the risk of PHLF. It is a complex procedure not widely undertaken due to the perception of higher risk attributed to proximity to hilar structures, creation of two major transection planes, therefore a larger transection area with potentially increased bleeding and risk of bile leak [1,6]. Evidence supporting this perception of higher risk remains somewhat controversial [8]. The majority of studies on CH originate from East Asia [1,7–9,13] involving mostly patients with hepatocellular carcinoma (HCC) with only a handful from Western countries [4,5,10,11].

* Corresponding author.

E-mail address: m.nikfarjam@unimelb.edu.au (M. Nikfarjam).

We present the first Australian series to report the results of CH in comparison with EH. The purpose of this study is to investigate the indications and perioperative outcomes of patients with CLLT following CH and compare with EH to determine any group differences.

Methods

Patients

CH and EH were done by specialist surgeons from two high-volume Hepatopancreatobiliary centres in Victoria, Australia. The procedures were undertaken between June 2009 and March 2017. Data was obtained from prospectively maintained databases and retrospective interrogation of hospital clinical records. These included operations and anaesthetic reports, radiology and laboratory test results, inpatient clinical care notes, outpatient and referral letters and histopathology results. The study was approved by the Austin Human Research Ethics Committee.

Preoperative assessment

Demographic data including sex, age, comorbid conditions, surgical indication and American Society of Anesthesiologists physical status classification were recorded. Neoadjuvant therapy including portal vein embolization (PVE), trans-arterial chemoembolization (TACE) and chemotherapy were noted. The workup of surgical candidates involved full blood examination, liver function and biochemical tests and coagulation screen. Contrast enhanced triple phase computed tomography (CT) of the abdomen and pelvis was routinely performed to evaluate the anatomy, size and location of tumors. CT of the thorax, contrast enhanced magnetic resonance imaging of the liver and whole body positron emission tomography (FDG-PET) were used to complete the staging process. All patients were discussed and consensus opinion reached in a multidisciplinary team including hepatobiliary surgeons, specialist radiologists, oncologists and pathologists. CH was elected if tumors were in the central segments of the liver and when the FLR was deemed inadequate after EH. Sometimes EH was required when the location of tumor would necessitate resection of major right sided inflow (right portal vein) or outflow (right hepatic vein). Formal volumetric assessment of the FLR was performed in selected patients with CT volumetry when it was considered that the FLR may be inadequate. Functional assessment was also performed in certain patients with indocyanine green clearance test at 15 min as part of a study investigating the assessment of liver function in patients undergoing liver resection.

Operative details

Patients underwent general anaesthesia with standardized protocols including low central venous pressure (<5 mmHg), restrictive fluid management, intravenous broad spectrum antibiotic and deep vein thrombosis prophylaxis. EH was defined as the resection of more than four contiguous liver segments (hemihepatectomy plus a significant proportion of adjacent segments). Synchronous multi-visceral operations and additional procedures were noted. Operative outcomes were recorded including procedure time, estimated blood loss, intraoperative blood transfusion requirements and vascular control method.

Surgical approach to central hepatectomy

All operations were performed by hepatobiliary surgeons and anaesthetists. Full mobilization of both lobes of the liver was performed in cases when caudate lobe resection was required. A

radical porta hepatis dissection and lymphadenectomy was performed when indicated. Intraoperative ultrasonography was undertaken routinely as a final staging procedure to identify lesion(s) and the relationship to surrounding vascular and biliary structures and to exclude additional lesions not seen on preoperative imaging. Cholecystectomy was performed if the gallbladder was present. CH was generally commenced by extrahepatic ligation and division of vessels and ducts to segments 4, 5 and 8 and the middle hepatic vein. Transection lines were marked along the right of the falciform ligament (i.e., border of segments 2 and 3) and in the plane between right anterior (segments 5 and 8) and posterior sections (segments 6 and 7). Parenchymal transection was achieved with one or a combination of Cavitron ultrasonic aspirator, LigaSure™, harmonic Scalpel, vascular staplers or ERBE® water-jet. The instrument used was at the discretion of the primary operating surgeon. Intermittent complete or hemihepatic Pringle maneuver was used when required. Following completion of parenchymal transection, a final check for haemostasis was undertaken. The falciform ligament was sutured back to the anterior abdominal wall, the abdomen was washed out with saline and an abdominal drain was placed adjacent to cut surfaces. Topical haemostatic agents were applied to the resection margins and Sefrafilm® adhesion barrier was used in selected patients on the liver surface. Mass closure of the abdomen was usually undertaken with looped polydioxanone sutures with or without interrupted 1/0 nylon. The subcutaneous tissues were irrigated with a pulsed lavage device. Skin was closed with 3/0 monocryl or staples and dressings applied.

Postoperative management

Patients were transferred to a high dependency unit (HDU) or intensive care unit (ICU) following the procedure and subsequently transferred to the ward. Their postoperative management followed a liver resection protocol designed for standardized care. Abdominal drain output was recorded in all cases. Perioperative mortality was defined as death during surgery or hospitalization or within 30 days after surgery. Complications were defined as any unexpected events requiring intervention (e.g., drainage, antibiotics) and were graded according to the Clavien–Dindo classification [15]. PHLF was defined according to International Study Group of Liver Surgery as increased international normalized ratio and hyperbilirubinaemia (bilirubin >50 μmol/L) at or after postoperative day 5 [16]. Comprehensive complication index (CCI) [17] was used to assess severity of events using the online calculator (http://www.assessurgery.com/about_cci-calculator/).

Statistical analysis

Data are expressed as median (range) unless otherwise specified. A statistical software package (SPSS version 23.0; IBM, Armonk, NY, USA) was used for statistical analysis. Comparisons between categorical variables were determined by Chi-square test or Fisher's exact test where appropriate. Continuous variables were assessed by *t* test or Mann–Whitney *U* test according to data distribution. A *P* value <0.05 was considered statistically significant.

Results

Patient characteristics

A total of 178 major liver resections were reviewed from June 2009 to March 2017. Eleven (6.2%) patients had CH and 24 (13.5%) had EH among the reviewed patients. Table 1 summarizes the characteristics of patients. There were no differences in age, sex or body mass index between the CH and EH groups and none

Table 1

Characteristics and preoperative laboratory test results of patients who underwent central hepatectomy (CH) compared with extended hepatectomy (EH).

| Characteristics | CH (n = 11) | EH (n = 24) | P value |
|---|------------------|------------------------|--------------|
| Sex (M/F) | 9/2 | 16/8 | 0.447 |
| Age (yr) | 66.0 (23.0–81.0) | 58.5 (31.0–80.0) | 0.696 |
| BMI (kg/m ²) ^a | 25.0 (19.8–44.0) | 25.1 (18.3–35.9) | 0.984 |
| Comorbidities^a | | | |
| Hypertension | 6 (54.5%) | 6 (26.1%) | 0.138 |
| Ischaemic heart disease | 1 (9.1%) | 1 (4.3%) | 1.000 |
| Diabetes mellitus | 2 (18.2%) | 4 (17.4%) | 1.000 |
| Chronic kidney disease | 1 (9.1%) | 0 | 0.324 |
| Other medical condition | 1 (9.1%) | 5 (21.7%) | 0.638 |
| Surgical indication | | | 0.291 |
| Hepatocellular carcinoma | 0 | 5 (20.8%) | 0.157 |
| Cholangiocarcinoma | 1 (9.1%) | 7 (29.2%) ^b | 0.387 |
| Gallbladder carcinoma | 0 | 1 (4.2%) | 1.000 |
| Colorectal liver metastases | 9 (81.8%) | 8 (33.3%) | 0.012 |
| Other liver metastases | 0 | 3 (12.5%) | 0.536 |
| Benign | 1 (9.1%) | 1 (4.2%) | 0.536 |
| ASA classification^a | | | 0.160 |
| Class I | 0 | 3 (13.0%) | |
| Class II | 1 (9.1%) | 6 (26.1%) | |
| Class III | 10 (90.9%) | 12 (52.2%) | |
| Class IV | 0 | 2 (8.7%) | |
| Preoperative treatment^a | | | 0.030 |
| Portal vein embolization | 1 (9.1%) | 9 (39.1%) | 0.113 |
| Trans-arterial chemoembolisation | 0 | 4 (17.4%) | 0.280 |
| Hemoglobin (g/L) ^a | 130 (108–162) | 135 (100–154) | 0.645 |
| Platelet ($\times 10^9/L$) ^a | 204 (124–343) | 280 (95–859) | 0.021 |
| ALT (U/L) ^a | 23 (10–100) | 40 (12–686) | 0.028 |
| ALP (U/L) ^a | 96 (54–793) | 219 (92–1402) | 0.001 |
| GGT (U/L) ^a | 29 (10–243) | 301 (12–2766) | 0.001 |
| Bilirubin ($\mu\text{mol/L}$) ^a | 8 (5–26) | 13 (4–431) | 0.158 |
| Albumin (g/L) ^a | 38 (35–48) | 37 (22–47) | 0.088 |
| Creatinine ($\mu\text{mol/L}$) ^a | 88 (42–298) | 64 (38–120) | 0.051 |
| eGFR (mL/min/1.73 m ²) ^a | | | 0.258 |
| >90 | 3 (27.3%) | 11 (55.0%) | |
| ≤90 | 8 (72.7%) | 9 (45.0%) | |

^a Missing data, BMI (EH, 4), comorbidities (EH, 1), ASA classification (EH, 1), preoperative treatment (EH, 1), hemoglobin (EH, 1), platelet and creatinine (EH, 1), ALT (EH, 6), ALP (EH, 5), GGT (CH, 1; EH, 5), albumin (EH, 2), bilirubin (EH, 6), eGFR (EH, 4).

^b Four intrahepatic and three hilar cholangiocarcinomas. BMI: body mass index; ASA: American society of Anesthesiologists; ALT: alanine aminotransferase; ALP: alkaline phosphatase; GGT: gamma-glutamyl transferase; eGFR: estimated glomerular filtration rate.

of the surgical candidates demonstrated cirrhosis. The surgical indication for CH was either colorectal liver metastases (CRLM) or intrahepatic cholangiocarcinoma. One patient with a history of total pancreatectomy for neuroendocrine tumor (NET) underwent CH for suspicious metastases in segment 8 and the caudate lobe but was found to have a benign hemangioma in the resected specimen. CH was more likely to be elected on patients with CRLM compared with EH (81.8% vs. 33.3%; $P=0.012$). EH patients had a mix of surgical indications. One patient underwent EH for suspected large cystadenoma but was later found to have a large subtotally sclerosed hemangioma. Another EH patient had mixed tumor pathology involving HCC and intrahepatic cholangiocarcinoma. Most patients who had preoperative portal vein embolization (PVE) were from the EH group [CH vs. EH: 1/11 (9.1%) vs. 9/24 (39.1%); $P=0.113$]. The only CH patient who had PVE underwent a non-standard staged liver resection. The median time until surgery after PVE in the EH group was 6.3 weeks (4–11). The EH group was associated with slightly more deranged liver biochemistry compared with the CH group (Table 1).

Operative outcomes

There were no differences between groups in terms of median operative time [CH vs. EH: 450 min (290–840) vs. 522.5 min

(310–860); $P=0.328$], intraoperative blood loss [850 mL (400–1500) vs. 650 mL (100–2000); $P=0.746$] or patients requiring intraoperative blood transfusion [CH vs. EH: 1 (9.1%) vs. 7 (30.4%); $P=0.227$] (Table 2). Six of 11 (54.5%) CH patients had partial or total caudate lobectomy. In the EH group, five patients had multi-visceral resections – a Whipple's procedure, two patients had anterior resections, one had an ileocolic resection and another was a complex case of spindle cell sarcoma. This case involved a nephrectomy, adrenalectomy, vena cava and partial diaphragm excision, requiring cardiopulmonary and veno-venous bypass. Two EH patients were in the final stage of the associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) procedure. In the CH group, intermittent Pringle manoeuvre was used in six patients and selective hemihepatic vascular control was used in three.

Postoperative outcomes

Postoperative outcomes of patients are summarized in Table 2. There was no perioperative mortality in the CH group, but four in the EH group ($P=0.285$). All patients who died had cholangiocarcinoma. Three deaths were from PHLF and one from hemorrhagic shock. The first patient underwent a Whipple's procedure in addition to right EH for locally advanced cholangiocarcinoma with a mass in the hepatic hilum inseparable from the duodenum.

Table 2
Perioperative outcomes of patients who underwent central hepatectomy (CH) vs. extended hepatectomy (EH).

| Outcomes | CH (n = 11) | EH (n = 24) | P value |
|---|----------------|----------------|---------|
| Operative time (min) | 450 (290–840) | 523 (310–860) | 0.328 |
| Intraoperative blood loss (mL) ^a | 850 (400–1500) | 650 (100–2000) | 0.746 |
| Intraoperative blood transfusion ^a | 1 (9.1%) | 7 (30.4%) | 0.227 |
| 30-day mortality | 0 | 4 (16.7%) | 0.285 |
| Morbidity | 8 (72.7%) | 19 (79.2%) | 0.685 |
| Hepatectomy-specific complications | 3 (27.3%) | 13 (54.2%) | 0.167 |
| Bile leakage | 1 (9.1%) | 2 (8.3%) | 1.000 |
| Intra-abdominal collection/abscess | 3 (27.3%) | 6 (25.0%) | 1.000 |
| Post-hepatectomy liver failure | 0 | 7 (29.2%) | 0.072 |
| Intra-abdominal hemorrhage | 0 | 2 (8.3%) | 1.000 |
| General/medical complications | 7 (63.6%) | 17 (70.8%) | 0.709 |
| Pulmonary (e.g., pleural effusion) | 1 (9.1%) | 5 (20.8%) | 0.640 |
| Neurologic (e.g., delirium) | 2 (18.2%) | 4 (16.7%) | 1.000 |
| Acute kidney injury | 3 (27.3%) | 7 (29.2%) | 1.000 |
| Anaemia | 2 (18.2%) | 3 (12.5%) | 0.640 |
| Ileus | 0 | 4 (16.7%) | 0.285 |
| Deep venous thrombosis | 0 | 2 (8.3%) | 1.000 |
| Urinary tract infection | 0 | 1 (4.2%) | 1.000 |
| Pericardial tamponade | 0 | 1 (4.2%) | 1.000 |
| Paroxysmal atrial fibrillation | 0 | 1 (4.2%) | 1.000 |
| Cholangitis | 0 | 1 (4.2%) | 1.000 |
| Haematemesis | 0 | 1 (4.2%) | 1.000 |
| Clavien–Dindo classification ≥ Grade III | 3 (27.3%) | 11 (45.8%) | 0.461 |
| Comprehensive complication index (CCI) | 12.2 (0–43.6) | 30.2 (0–100) | 0.103 |
| Length of HDU/ICU stay (d) | 2 (1–7) | 2 (0–13) | 0.912 |
| Overall length of stay (d) ^b | 9 (5–23) | 12 (4–85) | 0.244 |
| ≤14 | 10 (90.9%) | 12 (60.0%) | 0.106 |
| >14 | 1 (9.1%) | 8 (40.0%) | |
| Resection margin ^{a,c} | | | 0.145 |
| R0 | 9 (100%) | 16 (72.7%) | |
| R1 or R2 | 0 | 6 (27.3%) | |

^a Missing data, intraoperative blood loss (CH, 1; EH, 10), intraoperative blood transfusion (EH, 1), resection margin (CH, 1; EH, 1).

^b Excluding mortalities (EH, 4).

^c One CH and one EH patient had a benign tumor in resected specimens. HDU: high dependency unit; ICU: intensive care unit.

He passed away on postoperative day (POD) 13 from abdominal hemorrhage leading to hemorrhagic shock. The second patient was transferred from a regional hospital after pre-arrest in theatre for initial attempt at right EH. This patient later had a complicated intraoperative course involving evacuation of portal vein thrombus and reconstruction of the portal vein twice. This patient had preoperative right PVE eleven weeks prior, however the postoperative course was complicated by ischemic hepatitis and enteritis. She died of liver and renal failure on POD 3. The third patient had hilar cholangiocarcinoma and preoperative PVE eight weeks prior. He died of fulminant liver failure and multi-organ failure on POD 6. The final patient underwent right EH for hilar cholangiocarcinoma without preoperative PVE. His predicted remnant liver volume was 35% and was not recognized to have chronic liver disease. Histology later revealed unrecognized cirrhosis possibly due to obstruction and alcohol consumption and he died of PHLF on POD 13.

The overall morbidity rate was not significantly different [CH vs. EH: 8 (72.7%) vs. 19 (79.2%); $P=0.685$] but there was a trend towards fewer hepatectomy-specific complications in the CH group compared to the EH group [3/11 (27.3%) vs. 13/24 (54.2%); $P=0.167$]. Intra-abdominal collection was the most common hepatectomy-specific complication in CH patients [$n=3$ (27.3%)]. PHLF appeared to occur more often in the EH group (CH vs. EH: 0/11 vs. 7/24; $P=0.072$), although without statistical significance. Bile leakage was documented in one CH patient compared with two EH patients [1 (9.1%) vs. 2 (8.3%); $P=1.00$]. There was a trend towards lower median CCI in the CH group compared with the EH group [12.2 (0–43.6) vs. 30.2 (0–100); $P=0.103$]. Median length of stay was similar between groups [CH vs. EH: 9 days (5–23) vs. 12 days (4–85); $P=0.244$].

Resection margin

Nine of 10 patients with tumor pathology in the CH group had documented margin width, all of which had clear resection margins. The remaining one patient with a history of total pancreatectomy for NET was found to have benign hemangioma in the resected specimen. Twenty-two patients from the EH group had information on margin width, sixteen of whom had clear margins (Table 2).

Discussion

Liver resection generally offers the best potential for cure for patients with resectable hepatic lesions. A major obstacle for curative liver resection is insufficient FLR volume predisposing to PHLF. This is the most common cause of mortality in these patients and is determined by two main factors: small remnant liver volume and poor quality of liver parenchyma [2,16]. Approximately 20% of normal liver parenchyma or a minimum of two Couinaud segments is required for adequate FLR, but this required functional volume increases to 30%–60% in the presence of chemotherapy associated steatohepatitis and 40%–70% in the presence of cirrhosis [2].

Parenchyma-sparing hepatectomy has been identified as an emerging gold standard treatment of CRLM [18]. This technique aims for minimum sufficient margins to achieve R0 resection while maximizing the FLR [18]. Although not defined in the Brisbane 2000 Nomenclature of Hepatic Anatomy and Liver Resections by the International Hepatopancreaticobiliary Association [19], CH is not a new technique and is becoming increasingly used [10,11].

In this present study, there were no statistical differences between groups in terms of demographics. There were no cases of

HCC in our CH study group which differs from the Asian literature [9,12]. CRLM was the main indication for CH, similar to studies from Western countries [5,10,11]. Studies from large series have shown minimal use of PVE in their CH group compared with the EH group [1,10,11]. Similarly in this study, PVE was commonly used in the EH group and only used in one CH patient, which was a non-standard case of staged liver resection.

In our series, the procedure time, intraoperative blood loss and requirement for intraoperative blood transfusion were similar between groups and comparable to current literature [1,4,5,7,10–13]. There was no perioperative mortality in the CH group but four in the EH group. Morbidity associated with CH remained high. Postoperative complication rates in this series were comparable between groups and most similar to a study in 2000 by Scudamore et al. [4]. The overall morbidity after CH was higher than that reported in other studies [1,10,11], possibly a reflection of the small sample size. Despite this, the complications were often medical and of minor clinical significance (grade I or II according to Clavien–Dindo classification).

As previously reported in the literature, bile leakage is a common hepatectomy-specific complication after CH [1,11]. In a recent paper by Ishii et al. [20], CH was identified as an independent risk factor for postoperative bile leakage. Our rate of post-hepatectomy bile leakage falls within the reported range of 1.6%–11% but we did not find any differences in bile leak rate between the CH and EH groups. In addition, a trend towards fewer hepatectomy-specific complications including PHLF was found in the CH group compared with the EH group.

A potential disadvantage of parenchyma-sparing resection techniques is compromising the resection margin. On par with other studies reporting 100% R0 rates [7,13], we also found clear resection margins in patients who underwent CH. It has previously been highlighted that clear resection margins and not width impact on long-term outcomes [7,9]. Our study did not analyze and compare survival outcomes, therefore the oncological safety of CH remains an area for further evaluation given its controversy in the previous study [21].

We contend that CH has equivalent outcomes to EH and the perioperative outcomes of CH in this study are comparable to other centres. The procedure is a safe and effective approach in selected patients with the added advantage of sparing liver parenchyma [1,4,10,11], and perhaps obviate the need for and risks of PVE in certain patients as pointed out by Lee et al. [10].

There are some limitations in this retrospective study of small sample size which therefore lacks in power. There is also a degree of variability in selection of patients and techniques of the operating surgeons. Volumetric assessment was not routinely performed in all patients. The assessment of FLR in the others was subjective. Furthermore, EH was used as an umbrella term to describe resection of more than four contiguous liver segments. This included staged liver resections, ALPPS procedure and formal up-front right and left trisectionectomies. In addition, many patients from both groups had additional procedures and multi-visceral operations. Finally, most patients from the EH group did not have tumors located in such a manner that would be amenable to CH as a resection technique, adding to a selection bias between groups.

In conclusion, patients with CLLT remain a challenging population to treat. Conventional EH usually requires extensive sacrifice of significant viable liver parenchyma, necessitating alternative techniques to minimize parenchymal loss. CH appears to be an alternative to EH in selected patients for CLLT. This study found no major differences in perioperative outcomes when comparing CH to EH, however, there was a trend towards overall fewer hepatectomy-specific complications, including PHLF. In appropriate patients, CH may be a safe option and parenchyma-sparing alternative to EH.

Further longitudinal studies with larger patient cohorts are required to validate CH as an oncologically safe technique.

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Contributors

HN, WL, PMV, FM, MV, SG, JR, WBZ, CC and NM proposed the study. CJ performed the research and wrote the first draft. CJ, BL, HN and WL collected data. CJ analyzed the data. All authors contributed to the design and interpretation of the study and to further drafts. NM is the guarantor.

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Ethical approval

The study was approved by the Austin Human Research Ethics Committee (LNR/15/Austin/321).

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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