SURVIVAL OUTCOMES OF HEPATECTOMY FOR HEPATOCELLULAR CARCINOMA USING LIGASURE AND KELLY FORCEPS FOR PARENCHYMAL EXCISION COMBINED GLISSONEAN PEDICLE APPROACH: A RETROSPECTIVE SINGLE-CENTRE STUDY

Tran Que Son[1,2,✉], Tran Manh Hung[1,2], Tran Hieu Hoc[1,2]
Trieu Van Truong[1,2], Nguyen Toan Thang[2], Pham Van Tuyen[2]
Nguyen Tuan Thanh[2], Ngo Quang Dinh[2], Bui Thi Minh Hue[2]
Nguyen Van Minh[2], Cu Trung Kien[2], Nguyen Trung Kien[2]
Do Duc Minh[1], Vu Thi Nha[2], Do Quoc Viet[2]
[1]Hanoi Medical University
[2]Bach Mai Hospital

Standard procedures in hepatectomy for hepatocellular carcinoma (HCC) include selective pedicle control and anatomical liver resection. We provide our experience using LigaSure™ and Kelly forceps for parenchymal excision combined with the Glissonian pedicle approach for HCC patients. Sixty-seven patients underwent hepatectomy between June 1st 2016 and May 30th 2020. Prospectively gathered data on surgical outcomes and long-term survival results are given. Minor liver resections comprise 85% of all surgical procedures. The median operative time was 132.1 minutes (range, 102 to 195 mins), and the median intraoperative estimated blood loss was 210 ± 158 (range, 150 – 750) mL. The rate of morbidity was 17.9%, including pleural effusion (13,4%), biliary fistula (0%), liver failure (1.5%), and intra-abdominal bleeding (1.5%). The mean overall survival time by Kaplan – Meier method is 33 ± 0.6 months. The rate of overall survival after 1, 2, and 3 years was 95.5%, 84.5% and 79.4%, respectively. The mean disease-free survival (DFS) time was 25.9 ± 2.1 (months). The recurrence rates after 3 months, 6 months, 12 months, and 24 months were 9.6%, 12.4%, 30.5%, and 42.6%, respectively. Conclusion: In a nation with minimal assets, the Glissonian pedicle approach with the Ligasure and Kelly forceps is a safe and successful method for performing hepatectomy. It permits an anatomical excision with minor morbidity when operated by experienced surgeons.

Keywords: Hepatectomy, Hepatocellular carcinoma, Glissonean, Ligasure, Takasaki approach.

I. INTRODUCTION

In 2018, there were 841,080 newly diagnosed instances of liver cancer, making it the sixth most prevalent cancer overall and the fourth most significant cause of death worldwide due to cancer.[1,2] The 5-year overall survival (OS) rate for HCC patients stands below 20%.[1] Hepatectomy is the most famous radical treatment for hepatic malignancies, which offers resectable patients better survival rates.[3,4] However, hepatectomy is also associated with several complications, such as haemorrhage, acute liver failure, and bile leakage, which can negatively affect survival and mortality rates.[3,5]

One of the effective methods to limit such major complications is applying segmental hepatic vascular occlusion. Ton That Tung

Corresponding author: Tran Que Son
Hanoi Medical University
Email: tranqueson@hmu.edu.vn
Received: 26/12/2022
Accepted: 17/01/2023

introduced a method for dissecting the liver's blood arteries and biliary tract by entering the liver parenchyma directly.[6] This procedure is quite advantageous when operating the liver in cases of cholelithiasis, an extremely prevalent disease in Vietnam. To assure radicalism when removing liver cancer, however, the Glisson sheath that controls the segment of the liver to be excised must be severed.[6] In 1986, Takasaki pioneered the practice of extra fascial Glissonean dissection to maintain control of the Glisson pedicle at the hepatic hilum.[7] This technique has been widely adopted in anatomical resection for hepatocellular carcinoma and other liver tumours.[3,8] This method has certain benefits in hepatectomy, including the accurate assessment of the hepatectomy region, aiding in the safe cutting of the liver, limiting the ischemia of the remaining liver parenchyma, lowering blood loss, and preventing the spread of cancer cells to nearby lobes during surgery. Combining the abovementioned factors could theoretically allow safer and more efficient liver resection.[9-13]

In developing nations with low-to-middle income, such as Vietnam, liver resection facilities are restricted. We usually use Kelly forceps, LigaSure™ or Harmonic Scalpel without Cavitron Ultrasonic Surgical Aspirator (CUSA). Therefore, we conducted this study to evaluate the short-term and long-term outcomes of hepatectomy using Kelly forceps and LigaSure™ combined with the Glissonean pedicle approach. The initial results and obstacles encountered using this method will provide invaluable experiences for colleagues in Vietnam and worldwide.

II. METHODS

1. Study design and patients

A retrospective study was conducted on 67 patients who underwent hepatectomy at the Department of General Surgery, Bach Mai Hospital, from January 2016 to March 2019.

The selection criteria were patients (i) diagnosed with primary liver cancer, (ii) whose lesions localized on one side of the liver (left or right), and (iii) with future remnant liver volume measured on the 64-slice CT scan (dm3) to body weight (kg) > 0.8% (for right liver resection). Exclusion criteria were liver resections requiring concomitant bowel resection or hepatic resection with radiofrequency ablation during surgery for other kinds of lesions in the liver.

2. Follow-up and data collection

Routine preoperative evaluations, including blood tests, abdominal computed tomography (CT) scans, and upper GI, were performed to define the tumour location clearly.

Demographic data collected included (i) general information: age, gender, history of liver diseases and past liver-directed therapy; (ii) laboratory tests using Child-Pugh classification; (iii) tumour characteristics: site, size, number, and Barcelona Clinic Liver Cancer (BCLC) staging; (iv) technical characteristics and complications included operative time, estimated blood loss, packed red blood cell transfusion, the day return to diet, hospitalization, morbidity, and mortality.

Postoperative complications were evaluated according to the Clavien-Dindo classification system[14]: Postoperative liver insufficiency was defined as prothrombin < 50% and bilirubin > 50 µmol on the postoperative day 5;[15] Postoperative hemorrhage is defined as considerable blood loss from drainage, hematoma, or blood fluid or active hemorrhage detected by ultrasound or CT scan, and hemoglobin level is decreased 3 g/dl compared with immediately postoperative level;[16] Using the International Study Group of Liver Disease (ISGLS) criteria, bile leakage was defined as a bilirubin concentration in the drain fluid at least three times the serum bilirubin

concentration measured at the same time) from postoperative day three onwards or the need for reintervention (radiologic or surgical) for biliary collections or peritonitis.[17] Mortality was defined as any problems or deaths occurring during or within 90 days following surgery.

All patients were re-examined one month after discharge and followed up every 3 months with blood biochemistry (liver function), tumour markers, and abdominal ultrasound. Abdominal computed tomography (CT) scans were indicated every six months or when tumour recurrence was suspected. The long-term outcomes included disease-free survival (DFS) and OS in months based on Kaplan-Meier charts. The recurrent treatment methods for patients should be the following: TACE, radiofrequency ablation, surgery, and symptomatic treatment. The last follow-up evaluation was in June 2020 or up to the time of death.

3. Surgical technique

A team of digestive and hepatobiliary surgeons, with more than 60 cases of liver resection experienced by each person.

Patients were positioned supine, and their right arm or both arms were perpendicular horizontally to the body. The main surgeon and technician are on the right side, and the others are on the left. An upper midline, J-shape, or Mercedes incision was used depending on the size and location of the lesions. After placement of the Kent retractor, the abdomen was carefully explored for any contraindications for curative resection. Liver mobilization included dividing the round and falciform ligaments and exposing the anterior surface of the suprahepatic inferior vena cava and root of three hepatic veins depending on the type of liver resection.

Extrahepatic extra fascial using Takasaki's technique, Glissonean dissection was performed: Following cholecystectomy, the lesser omentum is opened to expose the liver hilum. At the bifurcation, care is taken to ligate all small branches to segment 4 to prevent bile leakage and hemorrhage. Exposed are three major Glissonean pedicles (left, right anterior, and right posterior). The Pringle manoeuvre can be selectively used during this step. As in the original Takasaki's approach, the pedicle is taped and temporarily occluded instead of early division before parenchymal transection.

Parenchymal transection using forceps and Ligasure: transection of the parenchymal is followed by intrahepatic division of Glissonean pedicles. The demarcation line is marked on the surface after the colour change after clamping the Glissonean pedicle. The transaction is performed by clamp-crush technique (Kelly forceps, LigaSure™ Blunt Tip Open Sealer/ Divider) following the demarcation line. Vascular and biliary structures are dissected and ligated at the resection line. Additionally, hepatic veins are separated inside the liver parenchyma. Afterwards, the hepatic veins are sutured and ligated with a prolene 4.0 suture.

Bile leak test at the resection margin using two methods: A white abdominal gauze pad is firmly applied on the cut surface during 5 - 10 minutes. A bile leak signified by yellow spots on the gauze pad is then controlled.

4. Statistical analyses

Categorical data were summarised using the number and percentage of cases. Median and IQR, or rates, are used to convey values. Mean, and standard deviation (SD) were were used for continuous variables. The OS of cancer patients was determined using the Kaplan-Meier algorithm, and group comparisons were assessed using the log-rank test, which was statistically significant when $p < 0.05$. All statistical analyses were performed using SPSS 20.0 software (SPSS Inc., Chicago, IL).

All patients were informed about the procedure, risks, and advantages of hepatectomy. Written informed consent was obtained from all patients before participation, and ethics approval was obtained from the Human Subjects Protection Committee of Bach Mai Hospital: 3377/QĐ-BM (31/10/2016).

This study is reported in line with the STROCSS 2019 criteria.[18]

III. RESULTS

Table 1. Preoperative characteristics of participants

Characteristic	Finding
Ag $\bar{x}$ ± SD (min-max)	56.3 ± 11.6 (30 - 76)
Sex, male/female ratio	6.4/1
Viral hepatitis types B, n (%)	37 (55.6)
Child-Pugh A, n (%)	67 (100)
Histological differentiation, n (%)	
Poorly differentiated	7 (10.4)
Moderately	34 (50.7)
Well	26 (38.9)
pTNM stage, n (%)	
Stage 1	12 (17.9)
Stage 2	42 (62.7)
Stage 3	13 (19.4)

The median age was 56.3 years (range 30 - 76). The proportion of male patients is 6.4 times higher than that of female patients. The prevalence of hepatitis B virus infection is 55.6%. Liver function before surgery with 100% Child-Pugh A. Tumor stages 1, 2, and 3 were 17.9%, 62.7% and 19.4%, respectively.

Table 2. Perioperative characteristics

Characteristic	Finding
Major hepatic resection, n (%), time $\bar{x}$ ± SD)	10 (14.9)
Right hepatectomy	3 (4.4), 130 ± 21.2
Left hepatectomy	4 (5.9), 130 ± 42.4
Central hepatectomy (segment 4,5,8)	3 (4.4), 160 ± 34.6
Minor hepatic resection, n (%), time $\bar{x}$ ± SD)	57 (85.1)
Posterior section	14 (20.9), 135 ± 40.6
Lateral section	10 (14.9), 94 ± 17.1

Characteristic	Finding
Segments 5, 6	14 (20.9), 134.3 ± 36.5
One segment	19 (28.6), 105 ± 57.7
Blood los $\bar{x}$: SD (mL), range	210 ± 158 (150 - 750)
Blood transfusion, n (% $\bar{x}$: SD (mL)	8 (11.9), 542.9 ± 184.1
Morbidity, n (%)	
Liver failure	1 (1.5)
Residual fluid collection	1 (1.5)
Pleural effusion	9 (13.4)
Intra-abdominal bleeding	1 (1.5)
Clavien-Dindo grade, n (%)	
II	9 (75)
IIIa	2 (16.7)
IIIb	1 (8.3)
Mortality, n (%)	0 (0)
Postoperative hospital stay (days $\bar{x}$:SD (range)	12.8 ± 6.1 (6 - 38)

Minor liver resections comprise 85% of all surgical procedures. Different methods of liver resection had varying operating times, with an average operative time of 132.1 minutes. The average hospitalization lasted 12.8 days. The mortality rate was 17.9%.

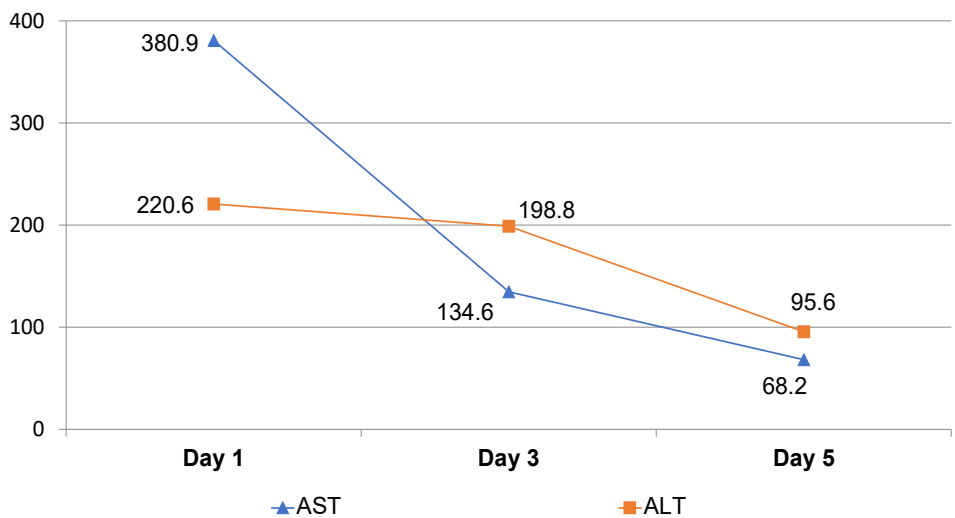

Figure 1. AST and ALT levels in postoperative

The graph shows that AST and ALT levels usually increase on day 1, then gradually decrease on the 3 and 5- days.

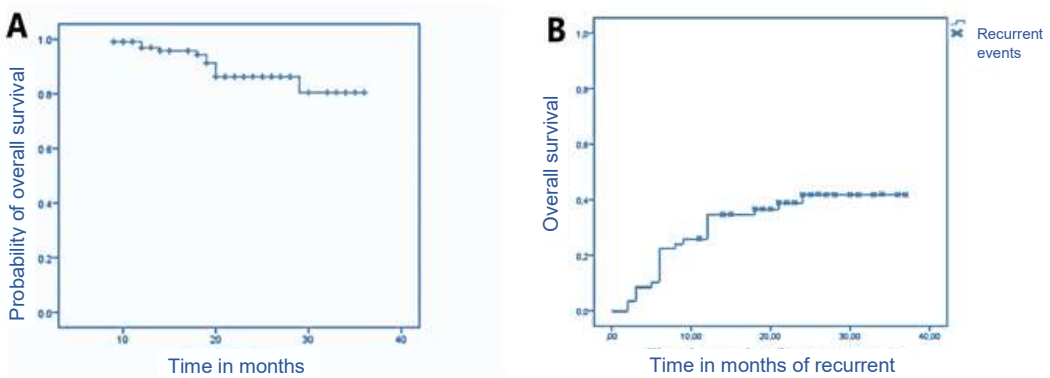

Figure 2. Overall survival (A) and disease-free survival time (B)

The mean overall survival time by Kaplan - Meier method was 33 ± 0.6 months. The percentage of patients with overall survival after 1, 2, and 3 years was 95.5%, 84.5% and 79.4%, respectively. The mean disease-free survival time was 25.9 ± 2.1 (months). The recurrence rates after 3 months, 6 months, 12 months, and 24 months were 9.6%, 12.4%, 30.5%, and 42.6%, respectively.

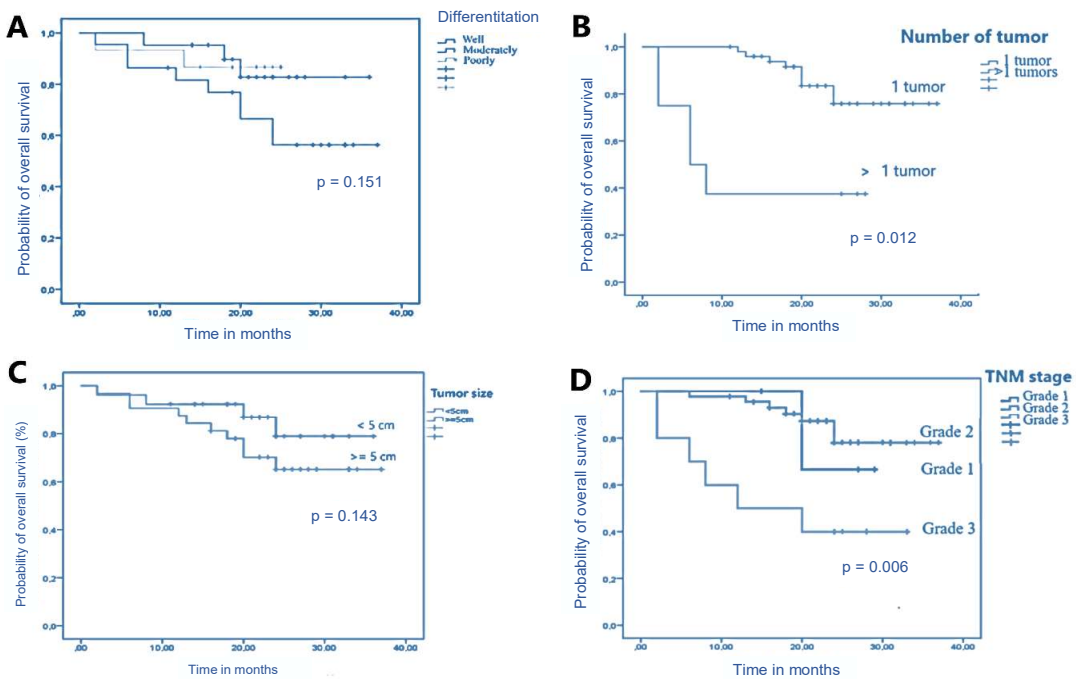

Figure 3. Factors related to overall survival time

According to Kaplan - Meier method, the survival time of the highly differentiated tumour group (Figure 3A) was 27.6 ± 2.4 (months), the group with moderately differentiated tumours: was 33.4 ± 1.9 (months), and the group with low differentiated tumours was 23.5 ± 1.6 (months) (p = 0.151). The survival time of the group of patients with one tumour was 33.8 ±

1.5 months, and the group with many tumours was 13.8 ± 4.1 months (p = 0.012) (Figure 3B). The survival time of patients with tumour size ≥ 5cm was 28.9 ± 3.1 months, and the group with tumour size < 5cm was 31.6 ± 2.3 months (p = 0.143) (Figure 3C). The survival time in stages I, II, and III were 26.3, 33.2, and 18.4 months, respectively (p = 0.006)

IV. DISCUSSION

Liver surgery is still a challenge for surgeons. Jarnagin et al.'s study on 1803 cases of hepatectomy showed that the postoperative mortality rate was 3.1%, but the rate of complications after surgery was 45%.[19] Blood loss and blood transfusion during and after the operation are essential prognosis outcomes in liver resection. Therefore, many authors have proposed vascular control methods to help reduce blood loss in liver resection. In 1908, Pringle first performed total inflow occlusion (clamping of the whole hepatic pedicle) to decrease blood loss. However, this manoeuvre caused complete hepatic parenchyma ischemia and intestinal congestion. Parenchyma damage increased in longer pedicle clamping time, especially in patients with chronic liver diseases. Yamamoto et al., Galperin and Karagiulian, Launois and Jamieson described the Glisson capsule, which surrounds all hepatic arteries, portal hepatic vein, and biliary tract going through into hepatic parenchyma. They proposed the enbloc Glissonean pedicle approach, now called the extrafascial Glissonean approach.[7,11] First, this method not only reduces blood loss in liver resection but also helps to recognize precisely hepatic transection lines based on the ischemic and nonischemic region (demarcation line) in performing selective hepatic inflow vascular control and occlusion. Second, the pedicle exposed after parenchyma transection will create a good space for the surgeon's manipulation. In contrast, the longer resected pedicle length will help pedicle ligation be safer and more accessible. Third, this technique was performed to ensure the radicality of liver cancer surgery. Yamamoto (2001) researched 204 patients who underwent hepatectomy using the pedicle control technique according to Takasaki's approach in liver resection with a tumour size of 5 cm and found the success rate of Glisson pedicle control was one hundred per cent. At the hilar position between the liver parenchyma and the pedicle, the author hypothesises that a thin layer of connective tissue can be readily removed to expose the Glissonean. In the right, left, and anterior segmentectomy, the posterior segment can ligate and sever the Glissonean at the hilum of the liver.[9]

There are numerous techniques for dissecting liver parenchyma, including Kelly forceps, Harmonic Scalpel, Ligasure, and CUSA. In this study, liver parenchyma was examined using the Ligasure and Kelly forceps, both of which were readily available at our hospital. During transecting hepatic parenchyma, all patients underwent right or left Glissonean pedicle occlusion combined Pringle manoeuvre technique. In our study, this was produced by two methods. First is Glissonean pedicle occlusion of resected part of the liver that revealed the demarcation line. This method is helpful for posterior, anterior sectionectomy, or segmentectomy of the right liver because it is difficult to determine the exact transaction line. Second, we also transected parenchyma based on hepatic landmarks and fissures described by Ton That Tung but do not need to dissect and occlude the Glissonean pedicle of resected part of the liver such as lateral segmentectomy, segment 4, segment 6+7, or only one segment such as S5, S6, S7, S8. This is a simple

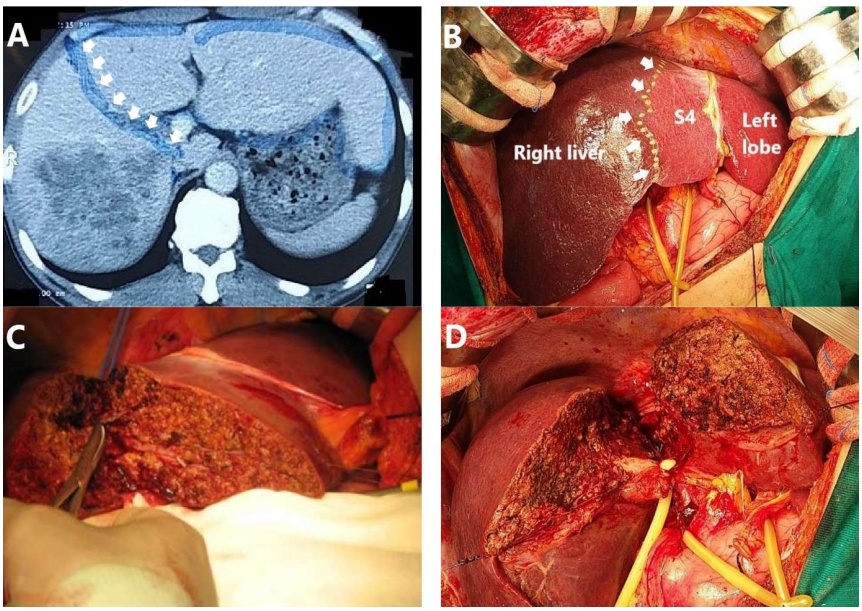

Figure 4. Right hepatectomy for HCC with selective pedicle control combined Pringle manoeuvre. *Source: Patient Vu Duc M, 59 years old, code C22/366 – 2018. A - Right liver tumor on computed tomography and predicted liver resection (white arrow); B - Anemic right liver after controlling the right hepatic Glissonean; C - Resection of liver parenchyma by Kelly forceps; D- Liver parenchyma, right-, and left hepatic Glissonean*

technique suitable for medical supplies of most hospitals in Vietnam.[3,12,13] Major blood vessels and the biliary tract were sutured. The portal and hepatic vein were sutured with prolene or monofilament 4.0 sutures. In addition, small blood vessels are excised with Ligasure. For liver function, GOT and GPT average after surgery on days 1, 3, and 5 were higher than the preoperative day. Most increased on day one and gradually decreased on the following tested days. In the research group, no patient died within 30 days of surgery. 17.9% had postoperative complications. Liver failure is the most severe consequence following liver resection. The percentage of liver failure following surgery varies between 1.2% and 32.0%, depending on the author.[12,13,20] In this sample, postoperative liver failure was diagnosed using the “50 - 50” criteria of Balzan and Belghiti (2005): prothrombin ratio of 50% and bilirubin concentration > 50 mol/l on the fifth postoperative day.[21] Early diagnosis of indications of liver failure is crucial for efficient treatment. After resection, just one patient in the study group suffered liver failure, representing 1.5%. Moreover, another patient in the research group had postoperative bleeding complications. The cause of bleeding from the left hepatic artery after surgery on the first day was indicated to re-operate to stop the bleeding. (Table 2).

Most of the authors’ global studies reported a recurrence rate of 70 - 80% after five years.[4,12,13] Many strategies to limit the postoperative recurrence rate of HCC have been applied, such as preoperative chemoembolization, chemotherapy, interferon therapy, and targeted therapy with Sorafenib.[4] Liver transplantation is

the best treatment to decrease the recurrence rate and improve survival time following surgery. According to Sapisochin et al. (2012), the 5-year recurrence rate of HCC in the liver transplant group was only 16% compared with 72% in the hepatectomy group.[22] Due to the difficulty in selecting organs for transplant, the number of liver transplants in Vietnam remains limited and is performed in only a few hospitals. Less than 500 liver transplants have been performed to date, most of which have been performed on brain-dead donors. When analysing the parameters influencing postoperative recurrence, we discovered a correlation between the time of reproduction and the number of tumours, size, differentiation, and numerous tumours surrounding the primary tumour. In Zhang's study (2016), the recurrence rates for the highly differentiated, moderately differentiated, and poorly differentiated groups were calculated to be 29.38, 26.85, and 8.88 months, respectively ($p = 0.006$).[23]

The mean survival time after liver resection was 33 ± 0.8 months, with the overall survival after 1, 2, and 3 years being 96.9%, 86.2% and 80.5, respectively. % (Figure 2A). We found a correlation between survival time and factors such as tumour differentiation, TNM stage, number and size of tumours, and AFP levels in the blood (Figure 3). Zhang's statistics (2016) showed that the mean survival time of the tumour group alone, 2 - 3 tumours, and > 3 tumours was 96.23, 48.08, and 29.11 months, respectively ($p = 0.000$).[23] This suggests that the more tumours in the liver parenchyma, the lower the chances of survival. Therefore, combining many treatment methods and liver transplantation in these subjects is necessary.

This study has limitations because it is a retrospective analysis. Some histopathological results do not provide information related to how many centimetres from the tumour to the resection area. Does the liver resection achieve a radical cure? Therefore, we did not evaluate the relationship between these factors to disease-free and overall survival. The study did not investigate the effects of chemoembolisation of the hepatic artery (TACE), radiofrequency ablation (RFA), reoperation for tumour recurrence, or target cell drugs Sorafenib (Nexavar) on long-term recurrence rates or survival.

V. CONCLUSION

In a nation with minimal assets, the Glissonian pedicle approach with the Ligasure and Kelly forceps is a safe and successful method for hepatectomy. It permits an anatomical excision with a low complication risk and excellent survival rates when operated by experienced surgeons.

Conflicts of interest:

The authors declare no conflict of interest.

Sources of funding: none

Ethical approval: 3377/QD-BM (31/10/2016)

Author contribution: TQS study concept, data collection, data analysis, writing the paper and final editing of the manuscript; TMH, THH, NTT, TVT authoring the article, and final editing of the manuscript; other authors: review literature, final editing of the manuscript.

Research registration: BM-2015-710-118

Guarantor: TQS, MD.PhD

Acknowledgements: We would like to express our deepest gratitude to the Board of Directors, staff of the Department of General Surgery at Bach Mai Hospital, the nutrition center, and the anesthesia and resuscitation department for facilitating the completion of the study.

Provenance and peer review

Not commissioned, externally peer-reviewed

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