RIGHT ANTERIOR SECTIONECTOMY FOR HEPATOCELLULAR CARCINOMA WITH GLISSONEAN PEDICLE APPROACH

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Hepatocellular carcinoma (HCC) is a common primary liver malignancy in Vietnam with a high mortality rate. Right anterior sectionectomy with selective control approach is preferred to the right or the central hepatectomies for HCC, in cirrhotic livers in order to preserve functional liver parenchyma. We carried out a retrospective analysis to evaluate the feasibility and safety of the right anterior sectionectomy at the Vietnam National Cancer Hospital. A retrospective descriptive study was conducted at Vietnam National Cancer Hospital from March 2017 to March 2020. The right anterior sectionectomy study group consisted of 47 patients. The mean patient age was 56.7 years. Of the 47 patients with HCC enrolled in the study, 91.5% were male. Cirrhosis (70.2%) and Hepatitis B virus (HBV) (74.5%) were the predominant chronic liver diseases. Most of the patients had normal preoperative liver function (Child-Pugh A, 97.9%, and MELD scores < 9, 89.4%). The median blood loss was 200 ± 120 mL. There were no intraoperative or postoperative transfusions given. The mean operation time was 182.23 ± 54.07 minutes (min - max: 80 – 340 minutes)(min; max). The median postoperative hospital stay was 7.52 ± 2.25 days (min – max: 5 – 21 days) (min; max). Posthepatectomy liver failure occurred in one case, and there was no perioperative mortality. After a median follow-up time of 33 months, the mean disease-free survival was 37.9 ± 1.9 months. 1-, 2- and 3-year survival rates were 94.7%, 92.1% and 85.0%, respectively.

Keywords: Hepatocellular carcinoma, right anterior sectionectomy, Glissonean pedicleapproachapproach, consecutive pedicles clamping, Pringle maneuver.

I. INTRODUCTION

According to the Global Organization for Research on Cancer (GLOBOCAN), in 2020 there were 905 677 new cases of hepatocellular carcinoma (HCC) and 830 180 deaths worldwide.

Vietnam ranks seventh in the world in terms of incidence with 26 418 cases and seventh in mortality with 25 272 cases.[1] Several treatments are available, including liver resection, transplantation, radiofrequency ablation, transcatheter arterial chemoembolization (TACE), and systemic treatment (Sorafenib, Atezolizumab-Bevacizumab,…) whose indication depends on tumor status (location, number, size) and liver function (Child-Pugh score).

Right anterior sectionectomy using the Glissonean pedicle approachis an anatomical liver resection, which involves segments 5 and 8. With the lesions in the right anterior section, it can optimize the future liver remnant volume when a major hepatectomy (right hepatectomy or central hepatectomy) cannot be performed. As a type of anatomical hepatectomy, right

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anterior sectionectomy improves clearance of intrahepatic metastasis via the portal vein within the resected domain.[2] The Glissonean pedicle approach is an important step in this type of liver resection. The National Cancer Hospital in Hanoi is a leading center for hepatobiliary oncology in Vietnam with over 5000 cases of HCC managed annually, and surgery still has a fundamental position in the therapeutic arsenal, particularly tailored liver resection. The purpose of our study was to evaluate the operativeoutcomes of patients subjected to right anterior sectionectomy in a retrospective analysis.

Surgical techniques

There are three methods of control the Glissonean pedicles: the intrafascial (also called *control method*, introduced by Lortat-Jacob and Honjo),[3] the extrafascial-transfissural (otherwise *intrahepatic technique*, presented by Ton That Tung),[4] and the extrafacial approach (also known as *the extrahepatic Glissonean pedicle isolation*, proposed by Takasaki).[5] In clinical practice, we apply two techniques to dissect the right anterior pedicle: the extrafascial and the extrafacial-transfissural approaches. Following resection, all patients were drained.

1. The extrafascial approach

Step 1: Mobilize the right liver and cholecystectomy after detaching the cystic plate from Lannec's capsule.

Step 2: Dissect the right pedicle and the right anterior pedicle after detaching the hilar plate with Metzenbaum scissors and O'Shaughnessy forceps.

Step 3: Clamp the right anterior pedicle with a tourniquet or a Bulldog clamp, causing change in color of the right anterior section surface.

2. The extrafascial-transfissural approach (Figure 1)

Step 1: Mobilize the right liver and "cystic plate" cholecystectomy.

Step 2: Identify the access to liver parenchyma. Ideally, perform extrahepatic dissection and clamp the right Glisonnean pedicle to expose a demarcated line between the right and the left livers. Otherwise, in complicated cases, utilize the main portal fissure.

Step 3: Create a parenchymal transection along the demarcated boundary or the main portal fissure to approach the right anterior pedicle using Cavitron Ultrasonic Surgical Aspirator (CUSA).

Step 4: Clamp the right anterior pedicle and locate the right anterior section ischemic zone.

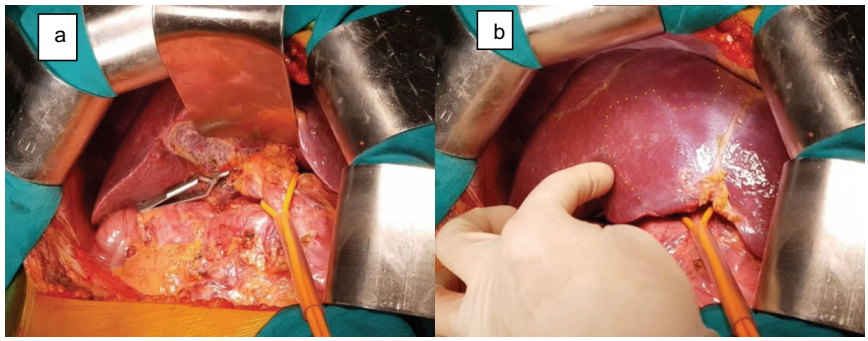

Figure 1a. Isolation of the right anterior pedicle by extrafascial-transfissural approach

a. "Cystic plate" cholecystectomy and clamp the right pedicle;

b. Demarcated line between the right and the left liver (yellow dots);

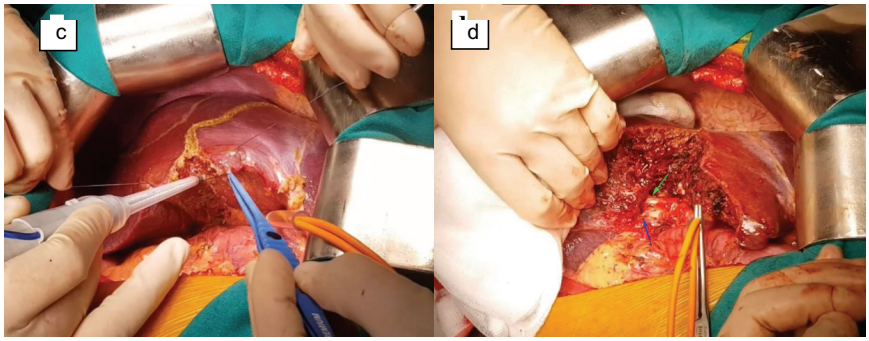

Figure 1b. Isolation of the right anterior pedicle by extrafascial-transfissural approach.

c. Parenchymal transection along the boundary;

d. Identify the right anterior pedicle (green arrow) and the right posterior pedicle (blue arrow).

II. MATERIALS AND METHODS

1. Patients

Our study was conducted from March 2017 to March 2020 in the Department of Hepatobiliary and Pancreatic Surgery, National Cancer Hospital (Hanoi, Vietnam). Patients were recruited with informed consent if they

1) underwent right anterior sectionectomy for hepatocellular carcinoma;

2) presented cirrhosis (or not) but optimum liver function (Child-Pugh score A-B);

3) without invasion to the hepatic veins and/or portal vein (tunor thrombosis); and

4) did not have extrahepatic metastasis or second cancer.

Patients who suffered emergency surgery for a rupture of the tumor, or had recurrent hepatocellular carcinoma, or lacked comprehensive medical record were excluded. According to the guidelines for diagnosis and treatment of HCC of the Ministry of Health in Vietnam, diagnosis of HCC is based on 4 criteria (Table 4): imaging diagnosis, serum AFP level, chronic liver disease, and pathologic evidence.[7]

2. Methods

Our study was a retrospective observational study. The sample size was taken by convenience sampling method. 47 patients who underwent right anterior sectionectomies for hepatocellular carcinoma and met all criteria were included for analysis.

3. Data collection

Information on demographic characteristics, physical examination, laboratory results, imaging reports, operative and postoperative parameters was collected from medical records. Postoperative complications were defined according to the Clavien-Dindo Classification.[6] Follow-up was conducted via telephone interviews and medical surveillance.

4. Statistical analysis

We used Student's T-test for continuous variables, non-parametric test for median parameter, and χ^2 test or Fisher's exact test for categorical variables. Overall and disease-free survival were obtained using the Kaplan-Meier method. Data were analyzed using SPSS Statistics version 22.0 for Windows.

5. Research ethical approval

This study was approved by the research ethics committees of National Cancer Hospital (Hanoi, Vietnam).

III. RESULTS

Our study included 43 men (91.5%) and 4 females with a median age of 56,7 years. Hepatitis B virus (HBV) was reported in 35 patients (74.5%) and 33 (70.2%) had liver cirrhosis. HCC was incidentally detected in 24 cases (51.1%) during an abdominal imaging test for other complaints. While half of the patients (51.1%) were asymptomatic, abdominal pain was the main symptom in 21 cases (44,7%). Serum AFP levels were greater than 400 ng/mL in 11 patients (23.4%), increased but lower than 400 ng/mL in 17 (36.2%), and normal in 19 (40.4%). Regarding the severity of liver cirrhosis based on Child-Pugh score, almost all the cases (97.9%) were classified with Child-Pugh A, 1 (2.1%) with early Child-Pugh B (7 points). 42 patients (89.4%) had a MELD score below 9. The platelet count was above 100 G/L in the entire group. Venous thrombosis was not detected in any patient. 45 cases (95.7%) were diagnosed with a single tumor; 2 (4.3%) with two tumors located both in the right anterior section. Patient demographics and preoperative data for all patients are shown in Table 1.

A total of 47 patients received right anterior sectionectomy by laparotomy. Intraoperative exploration found ascites in 1 case (2.1%). To control the right anterior pedicle, the extrafascial approach (*the extrahepatic Glissonean pedicle isolation*) was executed in 35 cases (74.5%) and the extrafascial-transfissural approach in 12 (25.5%). The intermittent Pringle maneuver was carried out in 40 patients (85.1%), while the consecutive right and left pedicles clamping was performed in 7 patients (14.9%). Concerning tumor size, 44 patients (93.62%) had tumors < 5 cm and 3 (6.38) had tumors ≥ 5 cm. The mean hemorrhage was 200 ± 120 mL, no patient required any intraoperative transfusion. An injury to the right posterior bile duct has occurred in 1 case (2.1%). One patient experienced posthepatectomy liver failure (PHLF). No patient required reoperation. The average postoperative hospital stay was 7.5 ± 2.3 days. The drain was removed after 6 ± 1 days. There was no 30-day mortality. Surgical pathology report showed lesions well-differentiated HCC in 6 cases (12.8%), moderately differentiated HCC in 33 (70.2%), and poorly differentiated in 8 (17.0%). Intraoperative and postoperative data for all patients are provided in Tables 2 and 3, respectively.

The median follow-up time was 33 months. At the time of data collection, there had been 5 deaths (13.2%), tumor recurrence was the main cause of death (3 patients). 1-, 2- and 3-year survival rates were 94.7%, 92.1% and 85.0%, respectively. The mean overall survival was 47.0 ± 2.1 months. Tumor recurrence appeared in 21.1% of patients, including intrahepatic recurrence in 18.4% and extrahepatic metastasis in 5.3% (lung only). 1-, 2- and 3-year disease-free survival were 91.7%, 83.4% and 75.9%, respectively. The mean disease-free survival was 37.9 ± 1.9 months.

Table 1. Clinical characteristics of patients in study (n = 47)

Male, *n* (%)	43 (91.5)
Age, years, median (range)	56.7 ± 11.8 (24 - 80)
Risk factor, *n* (%)	
Cirrhosis	33 (70.2)
HBV	35 (74.5)
HCV	0
Alcohol	17 (36.2)
Nonalcoholic fatty liver disease	0
Tobacco	10 (21.3)
Clinical manifestations, *n* (%)	
Asymptomatic	24 (51.1)
Upper abdominal pain	21 (44.7)
Jaundice	2 (4.2)
Liver function, *n* (%)	
Child-Pugh A	46 (97.9)
Child-Pugh B	1 (2.1)
MELD score, median (range)	7.1 ± 1.1 (6 - 10)
MELD score, *n* (%)	
< 9	42 (89.4)
9 - 10	5 (10.6)
> 10	0 (0)
Alpha Fetoprotein, *n* (%)	
< 20 ng/mL	19 (40.4)
20 – 400 ng/mL	17 (36.2)
> 400 ng/mL	11 (23.4)

Table 2. Operative characteristics of patients (n = 47)

Extrafacial approach, *n* (%)	35 (74.5)
Extrafascial-transfissural approach, *n* (%)	12 (25.5)
Pedicle clamping time, minutes, median (range)	30 ± 11

Intermittent Pringle maneuver, *n* (%)	40 (85.1)
Consecutive right and left pedicles clamping, *n* (%)	7 (14.9)
Operation time, minutes, median (range)	182.2 ± 54.1
Median hemorrhage, mL (range)	200 ± 120
Complications intraoperative, *n* (%)	1 (2.1)

Table 3. Postoperative characteristics of patients (n = 47)

Postoperative complications, *n* (%)	
Liver failure	1 (2.1)
Infection	0
Bleeding	0
Postoperative hospital stay, days (range)	7.5 ± 2.3
Drain remove, postoperative days (range)	6 ± 1
Mortality within 30 days, *n* (%)	0

Table 4. Criteria of diagnosis HCC of the Ministry of Health of Vietnam 2020

Typical characteristics of HCC on dynamic contrast enhancement CT or MRI; AFP ≥ 400 ng/ml
Typical characteristics of HCC on dynamic contrast enhancement CT or MRI; elevated AFP level (< 400 ng/ml); risk factors (cirrhosis, HBV, and/or HCV infection)
Pathologic evidence of HCC

IV. DISCUSSION

HCC is a primary liver malignancy that predominantly develops on underlying liver cirrhosis. According to the Asian Pacific Association for the Study of the Liver (APASL), the risk factors of HCC include cirrhosis, HBV, hepatitis C, nonalcoholic fatty liver disease (NAFLD), Budd–Chiari syndrome, alcoholism, tobacco, and aflatoxin B1.[7] Most patients arrived at an advanced stage, generally, liver resection is possible in less than one-third of cases. According to the guidelines for diagnosis and treatment of HCC of the Ministry of Health in Vietnam, diagnosis of HCC is based on 4 criteria (Table 4): imaging diagnosis, serum AFP level, chronic liver disease, and pathologic evidence.[8] The best candidates for surgical resection are patients in whom tumors can be completely removed by liver resection (anatomical or non-anatomical), adequate future remnant liver volume (measurement of liver volumes with imaging techniques is required before major hepatectomy when resection concerns at least 50% of the total liver volume), preserved liver function as evaluated by Child-Pugh score (A and B) without metastasis. In our center, MELD scores is not usually used for assessing the liver function in patients undergoing hepatectomy. Because liver resection for HCC is normally limited to patients with moderate liver dysfunction and

without cirrhosis, this model may have difficulty discriminating the risk of complications and the mortality in this group of patients for indication of hepatic resection.[9,10] Furthermore, in some rare cases, patients with portal vein thrombosis located on the ipsilateral side of the tumor could be considered for hepatic resection. Although targeted agents and checkpoint inhibitors (Sorafenid) is the recommended treatment for advanced stage with portal invasion,[8,11] its high health costs restrain the application of this option in Vietnam. The surgery represents an alternative therapeutic approach with a good safety and effectiveness profile, for selected cases, for tumor thrombus distal to the second-order branches of portal vein and invasion of the second-order branches of portal vein.[12,13]

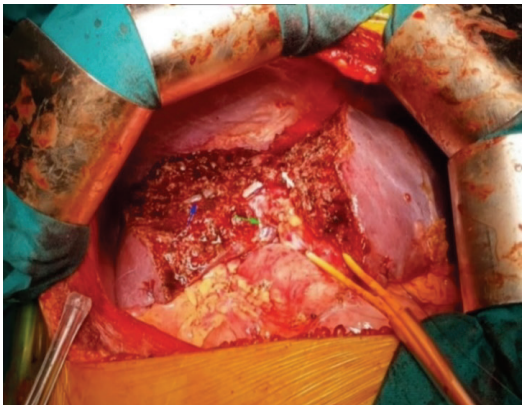

Figure 2. Hepatic parenchymal transection planes after resection of the right anterior section

Right hepatic vein (blue arrow), stump of the resected right anterior pedicle (green arrow).

Right anterior sectionectomy, as anatomical liver resection, involves resection of segments 5 and 8 according to Couinaud's classification.[9] Although the risk of bile leakage increases with two parenchymal transection planes, it is preferred to use this hepatectomy to optimize the future liver remnant volume and avoid significant anatomical changes for the lesions in the right anterior section (Figure 2). In 1998, Ken Takasaki described the Glissonean pedicle transection method for hepatic resection (otherwise known as the extrafascial approach), approaching the main and sectional Glissonean pedicles after detaching the hilar plate from the segment 4b. Thus, the Glissonean pedicles can be detached and controlled from the liver parenchyma without liver dissection.[10] In 2017, Sugioka et al. have proposed a novel comprehensive surgical anatomy of the liver with the Laennec's capsule that covers the entire surface of the liver, the intrahepatic parenchyma surrounding the Glissonean pedicles, and the major hepatic veins.[11] This work contributed to standardizing the surgical technique of Glissonean pedicle transection proposed by Takasaki. In our study, we applied Takasaki's technique to approach the right anterior pedicle. However, this approach is not always easy to carry out.

Following are three examples. First, dissection of the right anterior pedicle was more difficult when the tumor deformed the parenchyma at the hilum. Second, the right main pedicle is divided into the right anterior pedicle so deep in the parenchyma, the sectional pedicle dissection becomes hazardous with hemorrhage and potential vascular and biliary injuries. Third, an anatomical variation was recorded in 1 case: the segment 4 pedicle derived from the right anterior pedicle. If we had applied the extrafascial approach, segment 4 would have been sacrificed. Therefore, we performed the extrafascial-transfissural approach as a modified technique for right anterior pedicle control, inspired by Ton That Tung's intrahepatic technique.[4] Dissection of the hepatic parenchyma is carried out along the main portal fissure or preferably the boundary between the left and the right livers (if the right pedicle can be controlled by Takasaki's

technique) to expose the right anterior pedicle. So, the Glissonean pedicle approachapproach (extrafascial and extrafascial-transfissural) helps to reach the right anterior pedicle rapidly and reduces operation time. While a careful dissection of Glissonean pedicles is essential for a safe hepatic inflow control and the anatomical hepatectomy, an adapted surgical strategy is a *sine qua non* of successful operation.

An adequate vascular clamping may facilitate the liver resection and have an impact on operative time, so should be adapted to the situation and surgical strategy. Liang et al. demonstrated that operative time is longer with intermittent Pringle maneuver than with continuous hemihepatic clamping.[12] In our study, the mean operation time was 182 min, compared to several reports of Kwon *et al*.,[13] Makuuchi *et al.*,[14] and Kim *et al.*[15] on right anterior sectionectomy (156 min, 412 min, and 331 min, respectively). We applied two techniques of vascular inflow occlusion according to the actual circumstance: the consecutive right and left pedicles clamping and the intermittent Pringle maneuver (clamping periods of 15 minutes separated by 5-minute periods of declamping). In the extrafascial approach, if the right, the left, and the right anterior pedicles are controlled without difficulty, the first technique is preferred. The left pedicle is clamped by a tourniquet during left-side parenchymal transection to reduce bleeding. And at the time of right-side transection, the right pedicle is temporarily occluded. The consecutive right and left pedicles clamping may reduce ischemic injury and ensure a continuous parenchymal transection, thus saving time. On the other hand, if the tumor is located adjacent to the hilar plate or infiltrates this region, hindering the approach of the main and the sectoral pedicles, we opt for the extrafascial-transfissural approach and the second clamping technique. Once the demarcated line between two hemiliver is identified, the hepatoduodenal ligament is clamped *en masse* before initiating the left-side parenchymal transection, isolating the right anterior pedicle and finishing with the right-side parenchymal transection. At any time a complicated situation occurs, the intermittent Pringle maneuver is justified to control hemorrhage.

Despite an unexpected injury to the right posterior bile duct during the right-side parenchymal transection, no bile leakage was recorded in this series. This complication was accounted for 15% in some reports.[18] After identification of the biliary injury at the cut liver surface, we carried out a reconstruction with a 5-0 Prolene suture. The patient was discharged favorably on post operative day5. Attention must be paid to biliary injury during Glisonnean pedicle dissection at any rate.

One postoperative complication was reported: posthepatectomy liver failure. The patient is diagnosed with grade A PHLF (according to ISGLS) and did not require any change in the clinical management.[16] Right anterior sectionectomy is a minor hepatectomy. As a larger volume of functional liver parenchyma is preserved than in the right hepatectomy and central hepatectomy (segments 4, 5, and 8), the risk of PHLF in cirrhotic patients is low. The predictive risk factors of PHLF can be categorized into patient-related (> 65 years, malnutrition, sepsis, hyperbilirubinemia), liver-related (steatosis, chemotherapeutic agents, extent of cirrhosis/ fibrosis), and surgery-related (excess intraoperative hemorrhage > 1200 mL, transfusion, dissection techniques, insufficient remnant liver volume).[17] Son et al. reported a lower incidence of PHLF in patients with Child-Pugh A cirrhosis undergoing hepatectomy

versus Child-Pugh B (3.7% vs 16.7%; $p < 0.05$); thus Child-Pugh A is a potential candidate for major hepatectomy and Child-Pugh B is reserved for segmentectomy.[18] In our study, right anterior sectionectomy is indicated for patients with Child-Pugh A and Child-Pugh B.

In our study, all patients were classified as BCLC stage A (Early stage – Barcelona Clinic Liver Cancer system) and liver resection represents a recommended approach in this category of patients with optimum liver function.[8] However, this category includes a wide range of patients with different prognoses and subsequently requiring adapted therapeutic strategies according to tumor size, multiple tumors, tumor capsule invasion, alpha fetoprotein level, and presence of microvascular invasion confirmed by postoperative histological examination. Despite surgical resection still being advocated as the first-line treatment, patients with a single HCC nodule > 5 cm may be more appropriately classified as intermediate BCLC stage B because of a worse survival than other patients with BCLC stage A (single tumor 2 - 5 cm, or ≤ 3 nodules each ≤ 3 cm) but similar OS to patients with BCLC stage B.[19] Moreover, large HCC (> 5cm) is singled out for a high postoperative recurrence risk compromising the overall survival and recurrence-free survival.[20,21] The combination strategy involving surgery and neoadjuvant or adjuvant therapy (e.g. TACE) is an interesting approach in this group of patients to improve the long-term outcome. However, the effectiveness of perioperative TACE has remained a controversial subject for early stage HCC. Wang et al reported a greater disease control and survival benefit of a single preoperative TACE treatment than postoperative TACE in patients with large HCC undergoing liver resection.[20] Yamashita *et al* obtained a similar result in favor of preoperative TACE.[22] On the other hand, Ye *et al* indicated that postoperative TACE can effectively prevent tumor recurrence and improve the survival of BCLC early stage with microvascular invasion.[21] But in another study, Jianyong *et al* concluded that preoperative TACE did not prolong long-term overall or tumor-free survival for BCLC stage A.[23]

In Vietnam and developing countries, sectionectomy is currently the most reasonable anatomical liver resection for tumors in the right anterior section to optimize the residual liver volume in patients with impaired liver function because small and early HCCs are not often diagnosed due to limited access to health care. Moreover, even if liver transplantation represents a compelling alternative on appropriate occasions, only a few specialized centers have mastered this technique, and access to transplantation in Vietnam is still very limited due to the lack of available organs and prohibitive costs. But there is coming change. Tailored anatomical resections are conceived, e.g. bisegmentectomy and segmentectomy. While Couinaud adopted a horizontal subdivision of the right anterior section into segments 5 and 8, Ryu and Cho proposed a new and symmetrical concept of liver anatomy in which the right anterior section is divided vertically into the ventral area (*anterior segment*) and dorsal area (*middle segment*) according to the portal ramification and the hepatic venous system.[24,25,26] Fujimoto's report has confirmed this classification and described surgical procedures of hepatectomy including the ventral, dorsal, or even cranio-ventral (Segment 8 ventral) areas of the right anterior section.[27] With intraoperative ultrasound, this concept would drive huge and effective innovation, leading to a safe and curable hepatic surgery.

This study has some limitations. The

number of patients is small and the series are retrospective with a limited follow-up time. Large-scale and prospective studies are required to evaluate the outcomes of right anterior sectionectomy for HCC in the long term.

V. CONCLUSIONS

Right anterior sectionectomy for HCC with Glissonean pedicle approachis a feasible, safe and effective procedure. The Glissonean pedicle approach is an important and useful technique but should be adapted in particular circumstances. We recommend the right anterior sectionectomy for HCC in segments 5 and 8 to minimize the sacrifice of functional liver parenchyma in clinical practice.

Conflict of interest: The authors declare that they have no conflict of interest.

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