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Liver resections between 2014 and 2020 in the Lausanne University Hospital, Switzerland

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Abstract: Lausanne University Hospital is in the Francophone part of Switzerland and services a catchment population of about 1 million people. We recorded and analyzed baseline characteristics and surgical outcomes for 400 consecutive patients who underwent liver resection there between January 2014 and February 2020. Their pathological results were primary liver cancer (including hepatocellular carcinoma and intrahepatic cholangiocarcinoma): 21.8%, extrahepatic cholangiocarcinoma (including perihilar cholangiocarcinoma and gallbladder cancer): 5.3%, liver metastases: 51.8%, echinococcosis: 10.8%, adenoma: 3.0%, and other diagnoses: 7.5%. Global morbidity rate (Clavien-Dindo classification ≥ 1) was 45.5% with major complication (Clavien-Dindo classification ≥ 3) identified in 81 patients (20.3%). Of the 400 patients, two died within 30 days of surgery (0.5%) and five died within 90 days (1.3%). The 2017-2019 subgroup had a significantly greater percentage of patients aged ≥ 75 years (20.5%) than did the 2014-2016 subgroup (10.9%; $p = 0.011$) and a higher percentage of laparoscopic procedures than the earlier subgroup (2014-2016: 9.2%, 2017-2019: 32.5%; $p < 0.001$). We conclude that as the patient population ages, preoperative management and surgical techniques should be constantly improved.

***Keywords*:** liver cancer, hepatocellular carcinoma, liver metastases, liver resection

Introduction

Switzerland is a relatively small country, with 8.54 million inhabitants. It has a high longevity rate. Lausanne University Hospital is located in the Francophone part of Switzerland, with a catchment population of about 1 million people.

Overall age-standardized cancer mortality is about 140/10,000 in men and 85/10,000 in women. Among causes of cancer-related deaths worldwide, liver cancers rank fifth in men and ninth in women (*1*). Colon, rectum and anal cancers have high mortality rates in both men and women in Switzerland (*1*), approximately 30% of patients present with synchronous or metachronous liver metastasis during their disease course. Both primary liver cancer and liver metastases are typically treated with liver resection.

Switzerland is also an endemic area of alveolar echinococcosis (AE), a zoonotic tapeworm disease caused by *Echinococcus multilocularis* (*2-4*). Carnivores (mainly red foxes in urban areas) serve as definitive hosts for adult tapeworms and their herbivorous prey (mainly rodents) acts as intermediate hosts for metacestodes. Humans are generally not directly involved in the transmission but can become accidental hosts. As the parasite growth pattern resembles a malignant tumor, treatment of AE often requires interventional radiology, liver surgery and antiparasitic chemotherapy (*5,6*).

As surgical techniques, multimodal strategies and perioperative management have improved, liver surgery has become safer. Mortality rates have decreased from 10-20% to near zero in the past two decades (*7-11*), which has allowed safer resections even in elderly patients (*12,13*). In particular, laparoscopic liver resections have dramatically increased in the past decade (*14,15*).

Here, we report the characteristics and results of liver resections between 2014-2020, in the Department of Visceral Surgery at Lausanne University Hospital, Switzerland.

Methods

This retrospective study was approved by the local ethics committee and registered (registration number CER-VD 2020-00968). Written informed consent was obtained from all patients.

Patient selection

We recorded and analyzed baseline characteristics and surgical results of the 400 consecutive patients who underwent liver resections at Lausanne University Hospital between January 2014 and February 2020.

Preoperative management

Preoperative assessment included routine clinical and laboratory examinations (hematology, clinical chemistry, liver function tests, tumor markers, coagulation), volumetric computed tomography (CT) to manage surgical strategy (including need for preoperative portal vein embolization), and characterize the future remnant liver.

Chest and abdominal contrast-enhanced CT and magnetic resonance imaging with Gd-EOB-DTPA (Bayer Schering Pharma, Berlin, Germany) were also routinely performed. Therapeutic strategies were discussed in weekly multidisciplinary tumor board meetings. Major hepatectomies were defined as resections of three or more Couinaud's segments. Since July 2013, all patients scheduled for liver resections in our institution were enrolled in our enhanced recovery after surgery (ERAS) program (*16*).

Postoperative data and patient follow-up

We defined 1- and 3-month morbidity and mortality as postoperative complications and death within 30 days and 90 days after surgery, respectively. Postoperative complications were staged using the Clavien-Dindo classification (*17*). Patients were examined at the outpatient clinic at 1 and 3 months after surgery. Subsequent follow-up was performed either by the patient's general practitioner or in our institution. Follow-up included clinical examination, tumor markers levels, serological tests, and imaging. Recurrence was diagnosed based on imaging findings, clinical data, and/or histopathological studies.

Statistical analysis

Categorical variables were expressed as *n* (%) and were compared between groups using Fisher's exact test or the chi-square test, as appropriate. Continuous variables were expressed as median (interquartile range [IQR]) and were compared using Wilcoxon's rank test. Overall survival (OS) and disease-free survival were calculated from the initial liver resection. Survival curves were determined using the Kaplan-Meier method and compared using the log-rank test. Values of $p < 0.05$ were considered significant. Statistical analyses were performed using JMP 13.2.0 software (SAS Institute Inc., Cary, NC, USA).

Table 1. Baseline characteristics

Variables	Number (%) *n* = 400
Age, year	
Median; IQR	64; 54-71
Gender	
Male	237 (59.2%)
Female	163 (40.8%)
BMI, kg/m^2	
Median; IQR	24.8; 22.2-28.0
ASA PS classification	
1	12 (3.0%)
2	274 (68.5%)
3	113 (28.3%)
4	1 (0.3%)
Diagnosis	
Primary liver tumor	87 (21.8%)
Extrahepatic cholangiocarcinoma	21 (5.3%)
Liver metastases	207 (51.8%)
Echinococcosis	43 (10.8%)
Adenoma	12 (3.0%)
Others	30 (7.5%)
Preoperative treatment	
None	221 (55.3%)
Neoadjuvant chemotherapy	162 (40.5%)
Radiotherapy	4 (1.0%)
Radio-chemotherapy	13 (3.3%)

Data are presented as median (IQR) or *n* (%). ASA PS classification, American Society of Anesthesiologists physical status classification; BMI, body mass index.

Results

Patients

We reviewed the records of 400 consecutive patients who underwent liver resections between January 2014 and February 2020. Patients' characteristics, including demographic, clinical, and pathological data, are summarized in Table 1. Their median age was 64 years (IQR: 54-71 years); 28.6 % had high American Society of Anesthesiologists physical status classification ≥ 3. Their pathological results were primary liver cancer (including hepatocellular carcinoma and intrahepatic cholangiocarcinoma): 21.8%, extrahepatic cholangiocarcinoma (including perihilar cholangiocarcinoma and gallbladder cancer): 5.3%, liver metastases: 51.8%, echinococcosis: 10.8%, adenoma: 3.0%, and other diagnoses: 7.5%. About 21% of patients had liver resections for benign lesions. Among the liver metastases, 87.0% were of colorectal origin (Table 2). Preoperative treatments (for 44.7%) included neoadjuvant chemotherapy (40.5%), radiotherapy (1.0%), and radio-chemotherapy (3.3%).

Over time, we saw increasing percentages of elderly

Table 2. Details of liver metastases

Liver metastases	Numbers (%) *n* = 207
Colon cancer	120 (58.0%)
Rectal cancer	60 (29.0%)
Intestinal cancer	4 (1.9%)
Breast cancer	5 (2.4%)
GIST	2 (1.0%)
NET	2 (1.0%)
Others	14 (6.8%)

Data are presented as *n* (%). GIST, gastrointestinal stromal tumour; NET, neuroendocrine tumor.

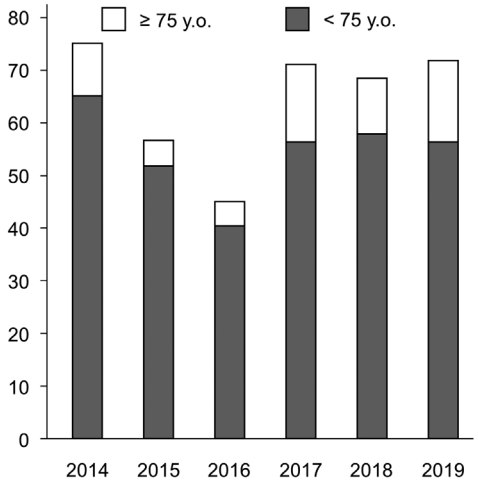

Figure 1. Percentage of hepatectomy in elderly patients. For the later 2017-2019 period, percentages of patients aged ≥ 75 years were 21.4% in 2017, 16.2% in 2018, 22.5% in 2019; and 20.5% in 2017-2019 overall, which was significantly greater than for the earlier 2014-2016 period (10.9%; $p = 0.011$).

patients – *i.e.*, ≥ 75 years old – were receiving liver resections (Figure 1). For the later 2017-2019 period, percentages of patients aged ≥ 75 years were 21.4% in 2017, 16.2% in 2018, 22.5% in 2019; and 20.5% in 2017-2019 overall, which was significantly greater than for the earlier 2014-2016 period (10.9%; $p = 0.011$; Figure 1).

Surgical outcomes

Intra- and post- operative outcomes are summarized in Table 3. Median surgical time was 275 minutes (IQR: 190-353 minutes); median estimated blood loss was 600 mL (IQR: 300-1,000 mL). Major and minor hepatectomies were performed in 207 patients (51.8%) and 193 patients (48.2%), respectively. Laparoscopic approaches were used in 22.0% of procedures overall, but were used significantly more in the 2017-2019 period (32.5%) than in the 2014-2016 period (9.2%; $p < 0.001$; Figure 2). Overall morbidity (Clavien-Dindo classification ≥ 1) was 45.5%, with major complications (Clavien-Dindo classification ≥ 3) identified in 81 patients (20.3%), including 32 patients (8.0%) who needed another surgery within the same hospitalization because of biliary fistula (after biliodigestive anastomosis), bilioma, or surgical site infection. Clinically significant post-hepatectomy liver failure (International Study Group of Liver Surgery [ISGLS] grade ≥ B) occurred in 10 patients (2.5%). Two patients (0.5%) died within 30 days, and five (1.3%) died within 90 days after surgery. Median length of hospital stay was 8 days (IQR: 6-14 days).

Overall survival of patients with malignant lesions

Among patients with one or more malignant lesions, the median follow-up period was 15.4 months (IQR: 11.3-29.7 months) for intrahepatic primary tumors, 13.8 months (IQR: 11.9-52.1 months) for liver metastases, and 12.0 months (IQR: 10.0-13.9 months) for extrahepatic cholangiocarcinoma (including

Table 3. Intra- and post- operative outcomes

Variables	Number (%) $n = 400$
Intraoperative outcomes	
Procedure	
Major hepatectomy	207 (51.8%)
Minor hepatectomy	193 (48.2%)
Hepatico-jejunostomy	41 (10.3%)
Venous reconstruction	23 (5.8%)
Approach	
Laparotomy	312 (78.0%)
Laparoscopic	88 (22.0%)
Operative time, min.	
Median; IQR	275; 190-353
Estimated blood loss, ml	
Median; IQR	600; 300-1000
RBC Transfusion	41 (10.3%)
Postoperative morbidity	
Morbidity	182 (45.5%)
Clavien-Dindo classification	
I	14 (3.5%)
II	81 (20.2%)
IIIa	42 (10.5%)
IIIb	17 (4.3%)
IVa	14 (3.5%)
IVb	8 (2.0%)
Clavien-Dindo classification ≥ 3	81 (20.3%)
Re-operation	32 (8.0%)
ISGLS B/C	10 (2.5%)
Mortality	
30-day	2 (0.5%)
90-day	5 (1.3%)
Postoperative length of stay, days	
Median; IQR	8; 6-14

Data are presented as median (IQR) or *n* (%). ISGLS, the posthepatectomy liver failure defined by the International Study Group of Liver Surgery; RBC, red blood cells.

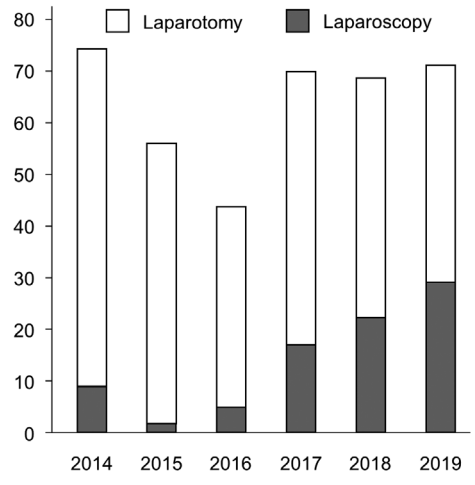

Figure 2. Percentage of laparoscopic/open approach. Laparoscopic approaches were used in 22.0% of procedures overall, but were used significantly more in the 2017-2019 period (32.5%) than in the 2014-2016 period (9.2%; $p < 0.001$).

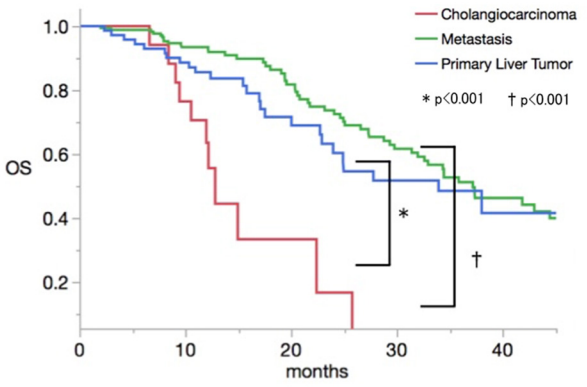

Figure 3. Overall survival of patients with malignant lesions. Extrahepatic cholangiocarcinoma had significantly worse overall survival than did intrahepatic primary liver tumor or liver metastases ($p < 0.001$ for both).

perihilar cholangiocarcinoma and gallbladder cancer); these follow-up periods did not significantly differ ($p = 0.080$). The respective 12-, 24-, and 36-month OS rates were primary liver tumor: 85.6%, 57.5%, and 48.5%; liver metastases: 93.4%, 72.5%, and 51.2%; and cholangiocarcinoma (perihilar cholangiocarcinoma and gallbladder cancer): 63.5%, 16.7%, and 0%. Extrahepatic cholangiocarcinoma had a significantly worse OS than did intrahepatic primary liver tumor or liver metastases ($p < 0.001$ for both; Figure 3).

Discussion

We evaluated results of liver surgery performed at our institution for the period 2014-2020. The major complication rate was 20.3%, and mortality was 0.5% at 30 days and 1.3% at 90 days after surgery – rates similar to those of other European countries.

Globally, hepatocellular carcinoma is the fifth-most common cancer and the second-most common cause of cancer-related death (*18,19*). In parallel, colorectal cancer (CRC) is a growing cause of cancer-associated death, about 30% of patients with CRC develop liver metastases (*20-22*). Although chemotherapy regimens have improved in recent years, liver resection is the main curative treatment for liver malignancies. However, liver failure remains the most feared postoperative complication, and is associated with high mortality (*23-25*). In the present study, significant post-hepatectomy liver failure (ISGLS grade ≥ B) was 2.5% and mortality rate was 0.5% at 30 days and 1.3% at 90 days after surgery in the Lausanne University Hospital. To decrease mortality, many countries have refined their selection criteria, surgical techniques and perioperative management (*26-28*). In our institution, indications for liver resection are mainly based on Makuuchi's criteria (*29*). In other European countries, the Barcelona Clinic of Liver Cancer guideline is most widely used (*30*), and recommends liver resection only for patients without portal hypertension. However, several reports of liver resection in patients with portal hypertension have been published in recent years (*31-34*). Our institution has refined its selection guidelines to avoid excluding patients solely because of portal hypertension. In assessing preoperative liver function and future liver remnant volume and function, we routinely use ICG tests, CT-scan volumetry, portal pressure measurement, and ^{99m}Tc-labeled mebrofenin hepatobiliary scintigraphy (*35,36*). Since 2016, if functional volumetry does not portend a safe liver resection, our group has routinely performed ipsilateral hepatic vein embolization simultaneously with portal vein embolization ("liver venous deprivation"), which we have reported to be safe, as it induces greater and faster future liver remnant hypertrophy than portal vein embolization alone (*37*). We are now studying the relationship of indocyanine green retention rate, ^{99m}Tc-labeled mebrofenin heaptobiliary scintigraphy and portal vein hypertension.

ERAS programs have been shown to improve postoperative outcomes of abdominal, orthopedic, urological and gynecological surgeries (*38,39*). Our institution has used ERAS protocols for liver surgery since July 2013, and had reported financial benefits of ERAS in liver surgery in 2016 (*40,41*). However, in a 2020 systematic review, we concluded that cost-reduction benefits from liver surgery ERAS were still unclear because of the small number of studies and high compliance variability (*42*). As more hospitals use ERAS programs, their utility should become more demonstrable.

We saw significantly more patients aged ≥ 75 years and more laparoscopic resections in the 2017-2019 period than in the earlier 2014-2016 period. Life expectancy continues to increase, in Switzerland and around the world, and surgery in elderly patients is increasingly common as perioperative management and surgical techniques have improved. Although major hepatectomy is no longer contraindicated in this age group (*43*), patients with diabetes have a higher risk of major complications and should be closely monitored in the postoperative course. As the patient pool continues to age, hepatobiliary surgeons will be challenged to improve preoperative evaluation/preparation techniques and preoperative management further, and to develop specific minimally invasive techniques (laparoscopic and/or robotic surgery).

Conclusion

Liver resection has been consistently and safely performed in our institution. As our patient base ages, preoperative management and surgical techniques should be constantly improved. Many innovations and improvements are awaited, especially for evaluation of future liver remnant function and preoperative preparation.

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