Liver Resections in a High-Volume Center: Form Standard Procedures to Extreme Surgery and Ultrasound-guided Resections

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Abbreviations:

CLM – colorectal liver metastases
FLR – future liver remnant
HCC – hepatocellular carcinoma
IVC – inferior vena cava
LHV – left hepatic vein
LR – liver resection
MHV – middle hepatic vein
MSOF – multiple system and organ
failure
PVL – portal vein ligation
RHV – right hepatic vein
TLV – total liver volume

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Rezumat

Rezecțiile hepatice într-un centru terțiar: de la proceduri standard la chirurgia extremă și rezecții ecoghidate

Introducere: Rezecția hepatică este tratamentul de elecție pentru majoritatea leziunilor focale hepatice benigne și maligne, și în cazuri selecționate de traumatisme hepatice. Puține alte metode terapeutice pot egala eficiența rezecției hepatice în cazuri selecționate, cum ar fi transplantul hepatic pentru carcinom hepatocelular și terapiile de ablație tumorală pentru carcinomul hepatocelular sau metastaze de mici dimensiuni. Lucrarea de față analizează experiența centrului nostru în rezecții hepatice, analizând indicațiile, tehnicile chirurgicale și rezultatele postoperatorii imediate.

Material și Metodă: În perioada Ianuarie 2000 - Decembrie 2016, în Centrul de Chirurgie Generală și Transplant Hepatic "Dan Setlacec" s-au efectuat 3165 rezecții hepatice la 3016 pacienți; pacienții cu rezecții hepatice pentru donare de grefă în vederea transplantului hepatic au fost excluși din analiză. Vârsta mediană a fost de 56 ani (medie 58, interval 1-88), cu un raport bărbați/femei de 1524/1492 și raport adulți/copii de 2973/43.

Rezultate: Indicația principală de rezecție hepatică au fost tumorile maligne (2372 cazuri; 74,9%), din care cele mai frecvente au fost

metastaze hepatice colorectale (952 cazuri; 30,1%) și carcinomul hepatocellular (575 cazuri, 18,2%). Numărul maxim de tumori rezecate per pacient a fost de 21, iar diametrul median a celei mai mari tumori rezecate a fost de 40mm (medie 51mm; range 3-250). Rata de rezecții hepatice majore a fost de 18,6% (588 cazuri); în 789 cazuri (24,9%) s-au realizat rezecții hepatice anatomice. Timpul operator median a fost de 180 minute (media 204; interval 45-920). Pierderile sanguine intraoperatorii mediane au fost de 500ml (media 850; interval 500-9500), cu o rată de transfuzii de 41,6% (1316 cazuri). Rata de morbiditate a fost de 40,1% (1270 cazuri), iar cea de complicații majore (cel puțin clasa IIIa Dindo-Clavien) a fost de 13,2% (418 cazuri). Rata de mortalitate a fost de 4,2% (127 pts).

Concluzii: Pentru a obține rezultate optime, cu morbiditate și mortalitate reduse, rezecțiile hepatice trebuie realizate în centre supraspecializate.

Cuvinte cheie: rezecție hepatică, tehnici chirurgicale, leziuni hepatice focale, experiența single-center

Abstract

Background: Liver resection (LR) is the treatment of choice for most benign and malignant focal liver lesions, as well as in selected patients with liver trauma. Few other therapies can compete with LR in selected cases, such as liver transplantation in hepatocellular carcinoma (HCC) and ablative therapies in small HCCs or liver metastases. The present paper analyses a single center experience in LR, reviewing the indications of LR, the operative techniques and their short-term results.

Material and Method: Between January 2000 and December 2016, in "Dan Setlacec" Center of General Surgery and Liver Transplantation were performed 3165 LRs in 3016 patients, for pathologic conditions of the liver. In the present series, liver resections for living-donor liver transplantation were excluded. The median age of the patients was 56 years (mean 58 years; range 1-88), with male/female ratio 1524/1492 and adult/pediatric patient ratio 2973/43.

Results: Malignant lesions were the main indication for LR (2372 LRs; 74.9%). Among these, colorectal liver metastases were the most frequent indication (952 LRs; 30.1%), followed by hepatocellular carcinoma (575 patients, 18.2%). The highest number of resected tumors per patient was 21, and the median diameter of the largest tumor was 40 mm (mean 51 mm; range 3-250). Major resections rate was 18.6% (588 LRs) and anatomical LRs were performed in 789 patients (24.9%). The median operative time was 180 minutes (mean 204 minutes; range 45-920). The median blood loss was 500 ml (mean 850 ml; range 500-9500), with a transfusion rate of 41.6% (1316 LRs). The morbidity rate was 40.1% (1270 LRs) and the rate of major complications (Dindo-Clavien IIIa or more) was 13.2% (418 LRs). Mortality rate was 4.2% (127 pts).

Conclusion: LRs should be performed in specialized high-volume centers to achieve the best results (low morbidity and mortality rates).

Key words: liver resection, surgical techniques, focal liver lesions, single-center experience

Background

Liver resection (LR) has long been regarded as one of the most difficult and challenging procedure in general surgery, due to the historical increased rates of postoperative morbidity and

mortality. Moreover, major hepatectomies (resection of 3 or more liver segments) were initially associated with morbidity and mortality rates exceeding 50% and 10%, respectively (1). Because of the continuous advancements in preoperative imaging and intraoperative devices, as well as

refinement in surgical techniques and intensive care procedures, the morbidity and mortality rates decreased over the last decades, while the indications of LR extended. Consequently, nowadays LR became a standardized procedure with morbidity rates up to 30%, mortality rates less than 5% and blood transfusion rates lower than 50% (2,3,4). Although significant improvements have been achieved during the past decades, postoperative bleeding, bile leak, liver failure and sepsis related to the cut-surface abscess still remain the most common challenges for a successful LR. The present paper analyses a single center experience in LR over a 17 years period, focusing on the indications of LR, operative techniques and the short-term results that were achieved.

Patients

A total of 3016 patients underwent 3165 LRs in “Dan Setlacec” Center of General Surgery and Liver Transplantation, Fundeni Clinical Institute during the last 17 years (from January 2000 to December 2016). The median age of the patients was 56 years (mean 58 years, range 1-88) and the male/female ratio was 1524/1492. At the time of LR, 2973 patients (98.6%) were at least 18 years-old, while 43 patients (1.4%) younger than 18 years-old. In 12 patients, LR was performed after previous portal vein ligation (PVL). A two-stage procedure was performed in 5 pts (0.1%), 3 of them undergoing PVL during the first stage. In one patient the resectability was achieved by an ALPPS procedure (Associated Liver Partition and PVL for Staged hepatectomy). A subgroup of 132 patients (4.2%) underwent repeat LRs: in 115 patients (3.6%) was performed one re-resection, while 12 patients (0.5%) received two re-resections.

The proportion of LRs (out of all operations performed in the center during the mentioned period of time) represented 5.4% (3165 LRs out of 58948 operations). To assess the trend of LRs' proportion over the time, the entire period was divided in four intervals (*Table 1*). The number of LRs progressively increased during this period and also the proportion of LRs significantly

Table 1. Evolvement of LR (number and percentage) overtime

Year	All operations (No of cases)	Liver resections (No of cases)	%
2000-2004	16909	541	3.2
2005-2008	15449	821	5.3
2009-2012	13263	787	5.9
2013-2016	13327	1016	7.6
TOTAL	58948	3165	5.4

increased from the first to the last interval (3.2% in the first interval vs. 7.6% in the last interval, $p < 0.01$) (*Table 1*).

Methods

We analyzed an HPB database with data collected prospectively (preoperative and intraoperative data) and retrospectively (postoperative data) from the medical records of patients undergoing LR in our center during the last 17 years. Patient demographics, indications for LR, intraoperative data (tumor location, type of LR, the use of vascular control methods, procedures associated with LR, the amount of blood loss, blood transfusion requirements, duration of surgery), pathologic report (number of lesions, largest tumor size and histological type) and postoperative data (type of postoperative complications and mortality within 90 days from surgery) were recorded and analyzed. Several surgical teams operated along the time, the two main teams being led by Professor Irinel Popescu and Associate Professor Mihnea Ionescu, respectively. In order to evaluate different changes in surgical treatment and outcomes along the time, the entire period was divided in 4 intervals, as it was presented above (*Table 1*).

Study end-points

The primary end-point was the short-term surgical outcome, consisting in morbidity and mortality rates. Morbidity is defined as any postoperative complication occurring in the first 90 postoperative days (POD) and mortality represents any death occurring during the first 90 POD. The postoperative complications were graded according to Dindo-Clavien classifica-

tion; major morbidity included all complications classified between IIIA and V. The secondary end-point of the study was the evaluation of the types of LR used in the present series.

Preoperative Evaluation

The protocol of preoperative imaging included contrast-enhanced CT scan of the thorax, abdomen and pelvis and/or contrast-enhanced magnetic resonance imaging (MRI) in case of uncertain diagnosis or in patients who cannot tolerate CT scan. When distant metastases were suspected, bone scintigraphy and/or FDG-PET were considered.

Liver function tests, tumor markers (CEA, CA 19-9, AFP) and viral hepatitis tests were performed in all patients diagnosed with liver masses. Moreover, upper GI endoscopy and colonoscopy were also routinely performed.

In patients with normal liver parenchyma and good performance status, LR was recommended when preoperatively it was anticipated the ability to perform an R0 resection and the volume of future liver remnant (FLR) exceeded 25-30% of total liver volume (TLV). In patients with chemotherapy induced steatohepatitis or sinusoidal obstruction syndrome, as well as in patients with chronic hepatitis, LR was performed when FLR volume was higher than 40% of TLV. Child A cirrhotic patients, with platelets count of more than 100.000/mm³ and no ascites, were considered for LR if FLR volume exceeded 40-50% of TLV. When intra-operative evaluation revealed macro-nodular liver cirrhosis, LR was precluded, usually being performed an ablative therapy (radiofrequency, microwaves, alcohol injection). In patients with multiple malignant liver tumors which cannot be entirely resected, to increase the possibility of complete clearance of the liver, LR was associated with different methods of tumor ablation.

For each patient with malignant liver tumors, the decision of LR was established by a multidisciplinary team, including surgeons, radiologists, oncologists, pathologists and gastroenterologists.

Surgical Technique

Most LRs were performed by open approach, while minimal invasive approach (laparoscopic or robotic) was used in selected cases. Anatomical LRs were classified according to the anatomical nomenclature of Brisbane 2000 terminology for liver anatomy and resections (5). Major LR was defined as the removal of at least three segments. All established surgical techniques were used: anatomical/non-anatomical hepatectomies, major/minor resections, extra/ intra-glissonian approaches, LRs with/without prior liver mobilization, ultrasound-guided LRs, two-stage LRs, ALPPS approach and ex-situ LRs. Moreover, all established methods for parenchyma transection were deployed, according to the team preference and the status of liver parenchyma: clamp crushing method (Kellyclasia) (6), combined unipolar and bipolar cautery (for simultaneous hemostasis while transaction) (7), electrothermal bipolar vessel sealing (8), harmonic scalpel (9), radiofrequency /microwave device (including Habib 4x device) (10), cavitron ultrasonic surgical aspirator (CUSA) (11) and endo-GIA vascular staplers (12). The first 3 described methods were most frequently used in the present series, similar to many centers around the world (3) (4). Since none of these methods clearly proved its superiority (13), the parenchyma transection technique depends on the surgical team preference and the status of liver parenchyma. Vascular control, consisting in Pringle maneuver and total vascular exclusion, was also used according to team preference and hemodynamic tolerance, in order to reduce the blood loss during LR. The most common used methods to control bleeding on the cut-surface of the liver were ligatures, sutures, monopolar, bipolar and/or argon electrocoagulation, radiofrequency ablation, fibrin sealant patch, hemostatic powder and the newly implemented method using autologous fibrin sealant.

Technically demanding LRs (complex LRs) were defined based on the following criteria:

- Tumor characteristics: at least 10 cm diameter and/or more than 3 bilobar lesions;

- Status of the liver parenchyma: cirrhosis;
- Type of LR: resection of the middle segments (segments 4, 5, 8), right posterior sectionectomy (segments 6, 7), right posterior sectionectomy extended to the right anterior section and/or segment 1, isolated segmentectomy 1, transverse hepatectomy (segments 4, 5, 6), non-anatomical extended hemihepatectomies, trisectionectomies, two-stage hepatectomies, ALPPS;
- Associated resections: portal/ hepatic artery/ inferior vena cava resection and reconstruction, biliary resection and reconstruction, other organ(s) resections;

Short-term Outcome

All postoperative complications that occurred in the first 90 POD were recorded and classified according to Dindo-Clavien classification (14). Complications leading to life-threatening conditions (grade IIIA and above) were considered as major morbidity; these included postoperative bleeding, abscess, sepsis, any organ failure. Complications with no fatal potential were considered minor, (Dindo-Clavien grade I-II). Liver-related complications were defined as all complications directly related to the LR, such as bile leak, cut-surface hematoma or abscess, hemoperitoneum, ascites, liver failure. The major complication rate was calculated based the most severe complication for each LR. Operative mortality was defined as death during surgical procedure or within 90 POD.

Statistical Analysis

Continuous parameters were expressed as median, mean and ranges. Categorical variables were expressed in absolute number and percentage. The Mann-Whitney test was used to compare nonparametric data and the Chi-square test or Fisher's exact test were applied for analysis of categorical variables. The level of statistical significance was set at p value < 0.05 .

Results

Indications for LR

The majority of resected lesions were malignant (2372 LRs; 74.9%); among these, colorectal liver metastases (CLM) were the most frequent tumors (952 LRs; 30.1%), followed by hepatocellular carcinoma (HCC) (575 tumors, 18.2%). Benign tumors represented 24% of resected cases (658 LRs), hemangioma being the most frequent (305 LRs; 9.6%). 1.1% LRs were performed for liver trauma (Table 2).

The incidence of LRs performed for malignant lesions increased overtime, from 67.7% (in 2000-2004) to 76.8% (in 2013-2016) ($p=0.03$). Contrarily, the incidence of non-malignant lesions decreased overtime: from 32.3% (in 2000-2004) to 23.2% (in 2013-2016) ($p=0.02$) (Fig. 1). The incidence of LRs performed for colorectal liver metastases, non-colorectal liver metastases and intrahepatic cholangiocarcinoma significantly increased overtime: from 25.0% to 29.7% ($p=0.04$), from 9.6% to 13.2% ($p=0.05$) and from 1.3% to 2.9% ($p=0.01$), respectively.

Table 2. Type of resected lesions (pathologic diagnosis)

Tumor type	No of cases	%
Malignant tumors	2372	74.9
Colorectal liver metastases	952	30.1
Hepatocellular carcinoma	575	18.2
Non-colorectal liver metastases	352	11.1
Other malignant tumors	231	7.3
Klatskin tumor	113	3.6
Gallbladder cancer	73	2.3
Peripheral cholangiocarcinoma	61	1.9
Hepatoblastoma	15	0.5
Benign tumors	658	24.0
Haemangioma	305	9.6
Focal nodular hyperplasia	91	3.3
Liver Abscess	81	0.5
Adenoma	73	2.9
Liver hydatid cyst	70	2.3
Biliary cyst	15	2.2
Caroli disease	11	2.6
Localized liver necrosis	6	0.3
Intrahepatic lithiasis	3	0.2
Other benign tumors	104	0.1
Liver trauma	34	1.1
TOTAL	3165	100

Figure 1. Trends of the incidence of malignant and benign lesions overtime

Figure 2. Trends of the incidence of main types of lesions overtime

Conversely, hemangioma (as indication for LR) significantly decreased overtime, from 15.5% to 7.2% ($p=0.01$). Incidence of HCC and Klatskin tumor among patients undergoing LR was relatively stable overtime: from 16.3% to 18.5% ($p=0.5$) and from 4.4% to 3.2% ($p=0.6$), respectively (Fig. 2).

The median number of resected lesions was 1 (mean 1.5; range 1-21); 163 LR (5.1%) were performed for more than 3 lesions. The median diameter of the main lesion was 40 mm (mean 51 mm; range 3-250); 376 LR (11.9%) were performed for lesions larger than 100 mm. Lesions were most frequently located in the right hemiliver (1383 LR; 43.7%) (Table 3).

LR Technique

The open approach was used in 3050 LR (96.4%), while laparoscopic and robotic approach were performed in 77 LR (2.4%) and 38 LR (1.2%), respectively.

Major hepatectomy was performed in 588 patients (18.6% of LR). The rate of major LR

significantly decreased overtime, from 23.8% (216 LR) in 2000-2004, to 16.98% (171 LR) in 2013-2016 ($p=0.04$).

Anatomical resections were performed in 789 cases (24.9%) (Table 4); out of these, 104 (3.3%) had associated limited non-anatomical LR.

According to the above-mentioned criteria, 1495 LR (47.2%) were technically complex hepatectomies (Table 5). The rate of these

Table 4. Type of liver resection (LR)

Type of liver resection	No of pts	%
Major resections	588	18.6
Minor resections	2577	81.4
Anatomical resections	789	24.9
Trisectionectomy	36	1.1
Right hemihepatectomy	243	7.7
Left hemihepatectomy	108	3.4
Central LR (anatomic)	9	0.3
Transversal LR (resection of segment IV, V and VI)	3	0.1
Bisegmentectomy	320	10.1
Posterior right sectionectomy	37	1.2
Anterior right sectionectomy	7	0.2
Isolated segmentectomy I	26	0.8
Non-anatomical resections	2376	75.1
Extended right hemihepatectomy	96	3.0
Extended left hemihepatectomy	101	3.2
Extended bisegmentectomy	11	0.3
Extended right posterior sectionectomy	6	0.2
Central LR (non-anatomic)	25	0.8
Limited non-anatomical resection	2137	67.5

Table 3. Topography of the focal liver lesions

Lesion topography	No of LR	%
Right hemiliver	1383	43.7
Left hemiliver	1022	32.3
Bilobar	726	22.9
Segment 1 (alone)	34	1.1
TOTAL	3165	100.0

Table 5.

Complex LR	No of pts	%
Criteria		
Maximum tumor diameter more than 100 mm	139	4.4
More than 3 bilobar lesions	127	4.0
Liver cirrhosis	285	9.0
Trisectionectomy, right/left extended (non-anatomical) hepatectomy, central LR (anatomical/ non-anatomical), transversal hepatectomy, two-stage hepatectomy, ALPPS	275	8.6
Main bile duct resection	169	5.3
Portal resection	39	1.2
Inferior vena cava resection	11	0.3
Other organ resection	763	24.1
Number of simultaneous criteria		
1	1227	38.8
2	220	7.0
3	36	1.1
4	7	0.2
TOTAL	1495	47.2

procedures increased overtime from 39.9% (216 LRs) in 2000-2004 to 50.3% in 2013-2016 (511 LRs) ($p=0.02$). The types of other organs resections performed simultaneously with LR are resumed in *Table 6*.

Two hundred eighty-five LRs (9%) were performed in cirrhotic patients.

Associated ethanol injection and thermal tumor ablation were used during 26 LRs (0.8%) and 76 LRs (2.4%), respectively.

Intraoperative ultrasound was used for diagnosis and resection guidance in 490 LRs (15.5%) and 137 LRs (4.3%), respectively.

Total vascular exclusion was used in 49 LRs (1.5%).

The median operative time was 180 minutes (mean 204 minutes; range 45-920). The median blood loss was 500 ml (mean 850 ml; range 500-9500). The transfusion rate was 41.6% (1316 operations).

Surgical Outcome

Overall complications rate was 40.1% (1270 LRs) and major morbidity rate was 13.2% (418 LRs). Among all liver-related complications, bile leak was the most frequent (876 LRs; 27.7%), followed by ascites (624 LRs; 19.7%)

Table 6. Associated resections during LRs for focal liver lesions

Associated resections during LR	No of pts	%
Associated organ resection	763	24.1
Liver resection associated with colorectal resection	182	5.8
Associated resection of common bile duct	169	5.3
Associated portal vein resection	39	1.2
Associated resection of inferior vena cava	11	0.3

Table 7. All liver-related complications recorded after LR

Liver-related complications	No of LRs	%
Bile leak	876	27.7
Ascites	624	19.7
Cut surface abscesses	354	11.2
Liver failure	95	3.0
Hemoperitoneum	46	1.5
Cut surface haematoma	28	0.9
Localized liver necrosis	17	0.5
Angiocholitis	8	0.3
Portal vein thrombosis	7	0.2
Arterial thrombosis	5	0.1
Vein graft thrombosis	2	0.1

and cut-surface abscesses (354 LRs; 11.2%) (*Table 7*).

Among major complications, cut-surface abscess was the most frequent complication after LR (44 LRs; 1.4%) (*Table 8*).

Overtime, the major complications rates decreased from 14.7% (80 out of 541 LRs) in 2000-2004 to 11.7% (119 out of 1016 LRs) in 2013-2016 ($p=0.05$).

Overall, mortality rate was 4.2% (127 pts). There were not significantly statistical differences in mortality rates over the 4 periods of time ($p=0.6$).

Discussion

The first documented LR was performed in the XVIIth century by Hildanus for liver trauma and the first elective LR was done by Langenbuch in 1888 (15). The first steps toward establishing the techniques of liver resection were performed at the beginning of the 6th decade of the XXth century, by surgeons like Honjo I (right hepatectomy; 1950) (16),

Table 8. Dindo-Clavien classification of major complications after liver resection (LR)

Organ or System / Main complication	Dindo-Clavien grade					TOTAL	%
	IIIA	IIIB	IVA	IVB	V		
Liver							
Cut surface abscesses	41	3	0	0	0	44	1.4
Hemoperitoneum	0	21	0	0	6	27	0.9
Liver failure	0	0	6	0	13	19	0.6
Bile leakage	16	2	0	0	0	18	0.6
Ascitis	14	1	0	0	0	15	0.5
Localized liver necrosis	1	3	0	0	0	4	0.1
Hepatic artery thrombosis	0	2	0	0	1	3	0.1
Portal vein thrombosis	0	1	0	0	0	1	0.0
Lung							
Pleural effusion	32	1	0	0	0	33	1.0
Respiratory failure	0	0	14	0	11	25	0.8
Bronchial pneumonia	0	0	0	0	1	1	0.0
Digestive system							
Colorectal fistula	0	10	0	0	0	10	0.3
Perforated ulcer	0	3	0	0	0	3	0.1
Small bowel fistula	2	1	0	0	0	3	0.1
Pancreatic fistula	2	0	0	0	0	2	0.1
Bowel obstruction	0	2	0	0	0	2	0.1
Upper digestive hemorrhage	0	0	1	0	0	1	0.0
Gastric fistula	0	1	0	0	0	1	0.0
Kidney							
Kidney failure	4	0	6	0	0	10	0.7
Cardiovascular system							
Pulmonary embolism	7	0	8	0	12	27	0.8
Acute pulmonary edema	0	0	4	0	10	14	0.5
Acute coronary syndrome	6	0	0	0	6	12	0.4
Cardiac arrest	0	0	0	0	3	3	0.1
Neurologic system							
Stroke	0	0	6	0	4	10	0.3
Systemic complications							
MODS	0	0	2	4	51	57	2.0
Sepsis	0	1	5	0	8	14	0.5
Other abdominal complications							
Intra-abdominal abscess	22	6	0	0	1	29	0.9
Evisceration	7	6	0	0	0	13	0.4
Peritonitis	0	11	0	0	0	11	0.3
Wound infection	3	1	0	0	0	4	0.1
Wound bleeding	2	0	0	0	0	2	0.1
TOTAL	159	76	52	4	127	418	13.2
%	5.2	2.3	1.5	0.1	4.2	13.2	

Lortat-Jacob JL (right hepatectomy and extended right hepatectomy; 1952) (17,18) and Couinaud C. (left hemihepatectomy; 1952) (19).

However, these initial attempts to perform anatomical liver resections would not be able to standardize the surgical techniques,

because, at that time, the functional anatomy of the liver has not been fully elucidated, yet. A major step forward was made by Claude Couinaud who revealed, based on the intra-hepatic portal distribution, that the liver contains 8 independent anatomical and func-

tional units, called segments (20,21). This initial description of the liver segmentation is, probably, the most important milestone in the development of liver resection, representing the basis of modern functional and surgical liver anatomy (22), although it was further improved by Henri Bismuth (23), Claude Couinaud (24) and the International Hepato-Pancreato-Biliary Association in 2000 (5,25). Furthermore, the Couinaud conception represented the cornerstone for introduction and development of all the types of liver resection techniques.

In Romania, Ioan Balacescu, Amza Jianu and Thoma Ionescu performed the first non-anatomic LR at the beginning of the XXth century (26). Fagarasanu carried out the first left hepatectomy in 1956 (27) and the first right hepatectomy was performed in 1958 by Burghel (28). In 1971, V. E. Bancu et al., who performed the first hepatectomies in Targu Mures, was the first Romanian surgeon who published a paper about the evolution of liver resection techniques toward anatomical hemihepatectomies (29). In 1975, Mihai Stancescu et al. published the first Romanian series of 41 LR (performed between 1960 and 1974) (30). In the early '80s, Vladimir Fluture and Sergiu Duca performed experimental liver transplantation (31) (32). The first large series of LR was reported in 2003 by Irinel Popescu et al., who presented the results of 445 LR performed between 1997 and 2002 in Fundeni Clinical Institute (33). In the same center, there were performed for the first time in Romania the total vascular exclusion for major LR (34), isolated resection of segment 1 (35), two-stage hepatectomy (36), ALPPS (Associating Liver Partition and PVL for Staged hepatectomy) (37) and the ultrasound-guided LR (38). Meanwhile, Ionel Campeanu introduced the extraglissonian approach for anatomical LR (39) and performed anatomic ventral anterior hemisectionectomy (40).

Most authors consider that high-volume centers are those institutions where are performed more than 50 LR per year (41,42). It is known that high-volume centers and high-volume surgeons correlate with improved

outcomes after LR (43,44).

Besides expertise in liver surgery, extensive experience in surgical oncology and gastrointestinal pathology and high-quality diagnostic and interventional radiology are crucial for a high-volume center.

The present series of 3165 LR is one of the largest reported in the literature, so far.

Indications for LR

In our series, the majority of resected liver lesions were malignant (74.9%), similar to the previous reports (from the high-volume centers) on the indications of LR (45).

Despite improvements in chemoembolization, thermal tumor ablation and other treatment modalities, LR remains the procedure of choice for most primary liver tumors (25). Although liver transplantation is the best approach in selected patients with HCC [mainly those with liver cirrhosis and small HCCs (46)], due to the shortage of organs, this approach could not be applied to all these patients.

Another major indication for LR in malignant liver tumors is represented by colorectal liver metastases (CLMs) (47). In patients with CLMs, resection is considered the gold standard treatment offering the highest rates of overall survival (48,49).

The better outcomes of patients undergoing LR for malignant liver tumors led to the extension of criteria for LR in such patients, thus increasing the number of hepatectomies performed for CLMs non-colorectal liver metastases and intrahepatic cholangiocarcinoma (50). Similar trends were observed in the present series, with a statistically significant higher incidence of LR for such indications in the interval 2013-2016 than between 2000-2004.

Conversely, LR for benign lesions decreased overtime, especially for hemangiomas (who continue to represent the most frequently resected benign liver tumor). This decreased prevalence of LR for hemangioma could also be explained by the changing paradigm regarding the indications for its resection.

Thus, in present, it is considered that heman-
giomas should be resected when their
maximum diameter exceeds 10 cm (and not 4-
5 cm as it was recommended in the early
2000s) (51).

Surgical Technique

Operative Approaches

The main approach in our series was open,
usually consisting in a bilateral subcostal inci-
sion with or without upward midline extension;
J incision (52) or upper midline incision were
seldom used. A thoracic extension was rarely
necessary for bulky right hemiliver tumors
invading the diaphragm. A J-incision is another
way to gain good exposure to the whole liver
with the advantage of extension into the
thoracic cavity, if needed. Occasionally, an upper
midline incision is sufficient for a minor hepatic
resection such as a left lateral sectionectomy.

Despite initial concerns about bleeding, air
embolism, tumor seeding (port site and
peritoneal) and oncologic clearance, minimal
invasive approach has been proven efficient in
LR. Moreover, minimal invasive LR insure
shorter hospital stay, less analgesic require-

ment and quicker oral intake, while complica-
tion rate is comparable to open LR (53).
Although initially the laparoscopic approach
was recommended in patients with small focal
lesions (less than 5 cm), limited number of
tumors and favorable topography (segment 2,
3, 4b, 5 or 6; distant to major vascular trunks)
and who do not require vascular/ biliary recon-
struction (54), in the last years, specialized
centers performed on a larger scale major LR
by minimal invasive approach (55). By these
reasons, in our center, beside the minor liver
resections performed by minimally invasive
approach, there were performed also right
hepatectomies, either by laparoscopic or
robotic approach (*Fig. 3*).

Usually, LR was preceded by liver mobiliza-
tion; however, if the right hemiliver was
occupied by a bulky tumor, an anterior
approach without prior mobilization was
preferred. In order to facilitate the hemi
hepatectomies, the hanging maneuver
described by Belghiti et al (56) was used
whenever considered adequate by the
surgeon. Frequently, during right hepatec-
tomies, a modified hanging maneuver was used,
consisting in passing the tape after complete

Figure 3. Robotic right hemihepatectomy
for colorectal liver metastases

right hemiliver mobilization, sectioning the hepatocaval ligament and right small hepatic veins and exposing the right hepatic vein at its confluence with inferior vena cava, thus avoiding the bleeding risk from the blind blunt dissection in front of the IVC.

Intraoperative Ultrasonography

Intraoperative ultrasound (IOUS) remains an essential tool for hepatobiliary surgeons. The main advantages offered by IOUS are the improved detection of liver tumors and the possibility to guide and assist LR (57). Despite significant advancements in preoperative imaging, such as contrast-enhanced CT scan, MRI and FDG-PET, IOUS still provides essential diagnostic information during operation by detecting new lesions that were not revealed by preoperative imaging methods. The detection of additional tumors during the surgery often changes the scheduled surgical procedure and even the therapeutic management of the patient. IOUS may also assist the LR procedure, by delineating the resection area, guiding the line of transection, marking target vascular structures that should be resected or, by contrary, preserved (58). IOUS could also be used to assess the immediate results after LR, checking the remnant liver for proper vascular flow and tumor-clearance. Thus, IOUS increases the rate of complete tumor clearance increasing the chance of improved survival in patients with malignant liver tumors. In the present series, IOUS guidance was used in 137 LRs (4.3%) (either anatomical or non-anatomical).

Methods for Parenchyma Transection

Regarding the parenchyma transection methods, a recent randomized controlled trial, comparing four different transection methods used in LR, showed that the clamp crushing method remained the most efficient device in terms of resection time, blood loss, and blood transfusion rate, when compared with CUSA, hydrojet and the dissecting sealer. Moreover, this trial revealed that the clamp crushing method was also the least expensive (59). However, the choice of

parenchyma transection method remains a matter of preference and skills on behalf of each surgical team and a matter of cost-effectiveness for the institution.

Intraoperative Blood Loss Control

Despite the recent advances in surgical and anesthetic techniques, blood transfusion is still required in 10–33% of patients undergoing elective LRs (60,61). The need for blood transfusions depends on the amount of blood loss, which is increased by liver cirrhosis or advanced steatosis, as well as by the complexity of LR. In the present series, the overall transfusion rate was 41.6%, slightly higher in comparison to the published data. This could be explained by the relative higher number of patients with liver cirrhosis or requiring major hepatectomies (almost 30%), that were included in this series. Moreover, in this study, emergency LRs (performed for liver trauma and ruptured HCCs or adenomas) were included.

Major bleeding and the subsequent requirements for blood transfusion have been shown to increase the post-operative morbidity and mortality (62,63). Perioperative blood transfusions are also associated with higher recurrence rates and lower survival rates after resection of malignant liver tumors, especially in HCC (64).

Similar to other centers (65), in our institution, vascular control methods (Pringle maneuver, total vascular exclusion) were implemented, to reduce the blood loss and decrease the rate of blood transfusions. In patients included in this series, mostly intermittent (15 to 20 minutes, with 5 minutes breaks) Pringle maneuver was used. Hemihepatic clamping (half-Pringle maneuver), that interrupts the vascular inflow selectively to the hemiliver that is to be resected (66), was used only in few situations. Ischemic preconditioning (devised for protection against subsequent sustained ischemia-reperfusion injury) (67) was also seldom performed. Total vascular exclusion, combining total inflow and outflow occlusion of the liver (68), was performed in selected cases with high risk of bleeding during LR and tolerance to the significant hemodynamic changes (49 LRs; 1.5%) (69). The prompt deployment of this maneuver in

case of torrential hemorrhage during LR was often considered a life-saving procedure. The modified total vascular exclusion, consisting in inflow occlusion associated with extra parenchymal control of hepatic veins, was used in few cases. Lowering the central venous pressure below 5 cm H₂O, in order to decrease the backflow bleeding during LR (70), was not routinely carried out, representing another potential explanation for the relative higher transfusion rate.

In patients with benign lesions, when significant blood loss was anticipated, the autologous blood recovery system (Cell Saver®; Haemonetics) was used, to decrease the need for blood transfusion and improve the short-term outcomes.

The routine use of fibrin sealant for bleeding control and lowering the risk of postoperative bile leak has not been supported by prospective randomized trials although it has been quite extensively used by many centers (71,72). However, in this series, such methods were used, especially when high risk of bleeding and/or bile leak was estimated. Recently, in such instances, autologous fibrin sealant technology (Vivostat®; Alleroed) was employed.

Even though the routine use of abdominal drainage after hepatic surgery has been challenged and many centers do not drain after LR anymore (73) (74), we routinely used drains in such operations, supporting this “old-fashioned” policy.

Extension of LR

In the first years of modern era of liver surgery, major hepatectomies were extensively used to resect malignant liver tumors (3). Because afterward it was observed that the only independent prognostic factors correlated with increased morbidity and mortality were blood loss and the number of resected liver segments, a trend toward replacing major hepatectomies with limited liver resections was observed (3). Thus, in the last decade, most centers favor parenchyma sparing LR instead of major LR. A similar trend is observed in the present series, with a signifi-

cant decrease in proportion of major LR overtime (23.8% in 2000-2004 vs. 16.8% in 2013-2016, p value = 0.04). Besides the lower morbidity and mortality rates associated with parenchyma sparing hepatectomies, another advantage of this approach is the increased likelihood of performing repeat LR for recurrent liver malignancies. This policy to perform repeat LR for recurrent hepatic malignancies represents one of the most important modalities to significantly improve overall survival in patients with CLMs and intrahepatic cholangiocarcinoma (75,76).

The performance of parenchyma sparing hepatectomies was facilitated by the advent of IOUS. This method allows performing segmental oriented anatomical LR, thus avoiding major hepatectomies. The main benefit of this approach was observed in cirrhotic patients with HCC, because the replacement of major hepatectomies by the limited anatomical LR decreased the risk of postoperative liver failure and increased the resectability rates.

Type of LR

Although the debate regarding the preferred type of LR (anatomical vs. non-anatomical) still continues, in present, several conclusions have been established.

Because it was clearly proven that in HCC the tumor spread occurs through portal system, it is obvious the necessity to remove the entire liver segment where the tumor is located (77,78). Thus, the potential tumor cells, spread (via portal branches) within different parts of the tumoral liver segment, will be removed, decreasing the risk of recurrence. The use of IOUS is of tremendous importance to achieve such segmental-oriented LR and the higher number of ultrasound-guided LR reported in this series between 2013 and 2016 is a consequence of the devotion to this procedure.

In contrast, in patients with CLMs, multiple comparative studies investigating the results achieved by anatomical vs. non-anatomical LR revealed similar results regardless the type of hepatectomy (79) (80). Similarly, in patients with intrahepatic cholangiocarcinoma, there is no evidence

that the type of LR influence the long-term outcomes.

By these reasons, in our center, non-anatomical LRs are favored in patients presenting other liver tumors but HCC. Because less than 20% of patients in this series underwent LR for HCC, the percentage of anatomical LRs in the entire series was lower than 25%.

Resection Margins

For liver malignancies, the achievement of a negative resection margin larger than 1 cm was recommended, traditionally. However, the evidence of the last two decades revealed that even narrow resection margins will enable similar overall survival rates if they are negative (R0 resections).

As such, in patients with HCC, several studies revealed that resection margins less than 1 cm did not correlate with significantly higher recurrence rates (81-83). However, whenever possible, in patients with HCC should be performed R0 segmental-oriented hepatectomies.

Similarly, in CLMs, most authors consider that the margin width does not influence the long-term outcomes, as long as a negative margin (R0) is achieved (84,85). These results are explained by the extensive use of efficient adjuvant chemotherapy in these patients. Moreover, in the last years, for CLMs adjacent to intrahepatic vascular structures that should not be resected, CLMs-vessel detachment R1 vascular margin (R1Vasc) was performed (86). Surprisingly, a recent paper revealed the equivalence between R1 vascular resections and R0 LRs (87). Similar conclusions were presented by other recent studies, revealing that an aggressive approach consisting in combined chemotherapy and repeat surgery could achieve similar overall survival rates in patients undergoing R1 LRs vs. R0 hepatectomies (88).

Complex LR

In this study, almost half of LRs were complex (47.2%), meaning that patients often were referred to surgery in advanced stages. The

performance of such complex operations requires highly trained surgical teams, experienced not only in liver surgery, but also in lower GI and upper GI surgery. By this reason, patients with such complex presentations of liver tumors should always be evaluated by a multidisciplinary team, in a highly-specialized center in HPB and digestive surgery.

In present series, the proportion of complex LRs significantly increased overtime, from 39.9% in 2000-2004 to 50.3% in 2013-2016 (p value = 0.02). That reflects that the experience gained overtime in specialized high-volume centers makes possible the use and development of more sophisticated liver resection techniques and the association of hepatectomy with other surgical procedures.

Increase of Resectability

In the present series were included all the strategies aiming to improve the resectability rates in patients with otherwise unresectable liver tumors. Based on the current definition of resectability of liver tumors, the only contraindications for LR are the impossibility to achieve an R0 resection and preserve a sufficient volume of liver parenchyma to avoid postoperative liver failure (25-30% of TLV in patients with normal liver parenchyma or 40% of TLV in patients with chronic hepatopathy or liver cirrhosis) (89) (90).

Currently available strategies to achieve complete clearance of the liver are:

- LR after embolization/ligation of one of the main branches of the portal vein. PVL/embolization usually induces the hypertrophy of the contralateral hemiliver, allowing subsequent performance of a curative-intent LR in patients whose initial FLR was less than 25-30% of TLV (91). The main drawbacks of this approach are insufficient FLR hypertrophy and tumor progression before the achievement of sufficient FLR hypertrophy, which preclude LR in up to 40% of cases (92) (91). In our experience, 26 pts (1.3%) benefited from PVL, out of which 21 (1.2%) were for colorectal liver metastasis. Resectability rate was 55%, similar to

those presented in other series.

- Two-stage hepatectomy (93), recommended in multiple bilobar CLMs, consists in two subsequent hepatectomies. During the first operation are resected the metastases from the less affected hemiliver and, sometimes (when the volume of this hemiliver is less than 25-30% of TLV), is performed ligation of the contralateral portal branch. The second stage is usually performed 4-8 weeks later (when the volume of FLR increased to more than 25-30% of TLV) and consists in resection of the bulk metastatic burden from the contralateral hemiliver (usually by a hemihepatectomy or trisectionectomy) (36,93,94). The drawbacks are the necessity of two operations (each associated with specific morbidity and mortality) and the failure to perform the second stage due to tumor progression in 19-24% patients (94,93). In the present series, there 5 such procedures were performed, 3 with PVL and 2 without.
- ALPPS (Associating Liver Partition and PVL for Staged hepatectomy) procedure is a novel surgical technique that aims

the more rapid and robust hypertrophy of the FLR. It consists in two operations; during the first stage is performed right portal branch ligation and in-situ splitting of the liver parenchyma along the left intersectional plane; in the second stage are resected the right hepatic artery, the right hepatic duct and the RHV and MHV, followed by completion of the right trisectionectomy. After the initial operation, the volume gain usually exceeds 75% and this important hypertrophy of FLR occurs in 7-10 days. In the present series one patient with primary hepatic lymphoma underwent this approach, without postoperative complications. However, the limitations of this technique are related to the increased rates of major morbidity (up to 40%) and mortality (up to 12%) (95)

- Multiple liver resections represent an alternative to the two stage hepatectomy, especially in patients with bilobar liver tumors. The strategy consists in avoidance of major LR (<5%), replacing them with multiple non-anatomical resections,

Figure 4. Non-anatomical LR of segments IV, V and VIII, with segmental resection of middle hepatic vein (MHV). A. deep-located hepatocellular carcinoma (HCC) in segment VIII compressing MHV (arrow head). B. Resection area marked with electrocautery; C. Remnant liver; D. Resected specimen

or segmental oriented minor LR associated with minor non-anatomical resections (Fig. 4). The main criticism is represented by narrow resection margins and even a higher incidence of R1 resections (96).

- Acceptance of resection margins less than 1 cm and even R1 vascular resections also increases the resectability rates, especially in patients with multiple, bilobar liver tumors.
- Conversion to resectability by tumor shrinkage following chemotherapy is useful mainly in patients with large CLMs.
- Replacement of major anatomical hepatectomies with non-anatomical limited LRs. This approach is usually recommended in patients with liver metastases or intrahepatic cholangiocarcinoma. Thus, whenever feasible, hemihepatectomy associated with partial resection of the adjacent section was preferred instead of a trisectionectomy and right posterior sectionectomy associated with partial resection of the anterior section replaced the right hepatectomy. For centrally located tumors (segments 4, 5 and 8), an alternative to the central hepatectomy (trisegmentectomy 4, 5, 8) was a non-anatomical LRs of the

tumors located in these segments (Fig. 5). The performance of such a hepatectomy, which involves segmental resection of the MHV, requires IOUS to detect the presence of compensatory collateral venous circulation to the RHV and LHV (97). By these techniques, as much as possible liver parenchyma is preserved, enabling LR in some patients considered unresectable by conventional LR techniques.

- LR associated with in-situ ablation of less than 3 cm tumors located in the remnant parenchyma significantly improves survival in comparison with palliative treatment.

Postoperative Outcome

For a long period, LR has been associated with high morbidity and mortality rates. Due to the progresses in liver surgery, anesthesiology and intensive care therapy, the short-term outcomes improved during the last three decades. However, the morbidity rates vary among different centers, ranging between 16.2% and 47.7% (98,99). This large range is partially due to the heterogeneity of the published series,

Figure 5. Non-anatomical multiple LR for multiple bilobar hemangioendotelioma (13 lesions). A, B. Resection areas marked with electrocautery; C, D. Remnant liver

with major differences in indications, extension of LR, number of patients with liver cirrhosis and volume-load of the center.

In present series, the overall morbidity was 40.1% and major complications rate was 13.2%, similar to those reported by other high-volume centers during the last two decades. However, the major complications rates decreased from 14.7% (80 out of 541 LR) in 2000-2004 to 11.7% (119 out of 1016 LR) in 2013-2016 ($p=0.05$), as a consequence of the increased experience with LR of both surgical and anesthesia teams.

Among all liver-related complications, bile leaks were the most frequent (27.7%). Among major complications, cut-surface abscesses were the most frequent and most severe complications after LR (1.4%). Liver failure was the most common liver-related complication leading to death: out of 95 LR complicated with liver insufficiency, 54 pts died (56.8%): 13 pts with liver failure only and 41 with MSOF induced by liver failure. Of note, one patient with liver failure after LR was transplanted with a whole liver graft.

Complex LR was the main factor influencing the postoperative outcome, with major complication and mortality rate of 16.9% and 6.6%, respectively, compared to 8.6% and 2.2%, respectively, in patients undergoing non-complex LR ($p=0.01$ and $p<0.01$, respectively). In our opinion, the complexity of LR should always be considered when analyzing the results of a certain series.

The mortality rate after LR varies from 1.5-3.5% in high-volume centers, to 8-24% in low-volume ones (100,101). In our experience, the 30-day and 90-day mortality rates were 3.1% and 4.2%, respectively, which is similar to other high-volume centers.

New Technologies in LR

Technology is an intricate part of the development of liver surgery, starting with preoperative imaging, intraoperative tools, and postoperative intensive care treatments. In preoperative imaging, a recent development that is worth mentioning is the advanced planning tool

Figure 6. MeVis® 3D reconstruction for large cholangiocarcinoma

that provide high-resolution color-coded 3D visualization of the liver parenchyma and its vessels, with corresponding liver segmentation. Moreover, this tool simulates LR scenarios, evaluating the risks of cutting at a given point in the liver. Applied to tumor resection, the software optimizes the shape of the transection plane and allows deciding which vessels need to be reconstructed in order to avoid liver ischemia or congestion. This system was recently implemented in our practice (MeVis®; MeVis Medical Solutions AG) optimizing the planning of 23 LR performed for malignant lesions (*Fig. 6*).

A novel device using real-time intraoperative navigation technology (CAscination®; CAscination AG) provides integration of pre-operative 3D liver models, surgical instruments and intraoperative ultrasound imaging, optimizing the surgical producers, such as LR or thermal ablation. This device was recently introduced in our surgical practice, guiding the LR in 4 patients.

Conclusion

LR involves complex surgical techniques requiring extensive anatomy and radiology knowledge, surgical expertise, adequate endowments and also proper anesthesia and intensive care therapy.

The wide range of operative techniques, instruments and devices involved in LR means that currently there is no clearly superior

established method. The use of a particular technique is determined mainly by the surgeon's preference and by the particular conditions of LR and liver parenchyma status. Thus, many surgeons prefer clamp crushing for parenchyma transection and intermittent Pringle maneuver for vascular control. Nevertheless, liver surgeons should be familiar with all liver resection techniques, vascular control and parenchyma transection methods, because the need to employ alternative ways of performing hepatectomy may often occur.

The advent of surgical and radiological methods able to increase the volume of FLR led to increased resectability rates, over the last two decades. Moreover, modern chemotherapy also contributes to further improvement in resectability rates, by liver tumors shrinkage. The modern chemotherapy protocols entered the clinical practice, the resection margin have become of secondary importance.

The current trend is to perform parenchyma sparing hepatectomies, thus allowing the safe performance of repeat LRs for recurrent liver malignancies. This surgical approach leads to the reduction of morbidity and mortality rates, while increasing overall survival of patients with malignant liver tumors.

LRs should be carried out in specialized high-volume centers, thus achieving lower morbidity and mortality rates. This short-term outcomes improve overtime, due to the greater experience gained by high-volume teams and surgeons.

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