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Indirizzo Chirurgia Sperimentale e Microchirugia

IRCCS Humanitas Research Hospital – Department of Surgery, Division of Hepatobiliary and General Surgery

Innovazioni tecniche in chirurgia epatobiliare

Utilizzo delle tecniche di modellizzazione 3D nella chirurgia parenchima sparing

Technical innovations in hepatobiliary surgery

Use of fluorescence and 3D modeling techniques in parenchyma sparing surgery

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INTRODUCTION

1. LIMITATIONS OF TRADITIONAL RESECTIVE SURGERY: THE FUTURE LIVER REMNANT

Liver resection represents the first choice in treatment for primary or secondary liver tumors representing the best chance in long-term survival.[1] The extensive use of major hepatectomies increases the risk of post-hepatectomy liver failure (PHLF), which is associated with high frequency of postoperative complications, mortality, and increased hospital stay[2]. To try to minimize the risk of PHLF, a careful and accurate preoperative study of Future Liver Remnant (FLR)[3] in its two facets: volumetric and functional is essential. Information on functional liver reserve is obtained from the measurement of glucuroconjugated and unconjugated bilirubin and coagulation factors: prothrombin rate (PT), fibrinogen or factor I, factor II, factor V (which is not dependent on vitamin K and is not, therefore, reduced in cholestatic jaundice), factors VII and X, and albuminemia. Transaminases: aspartate aminotransferase and alanine aminotransferase, alkaline phosphatases, and gamma-glutamyltranspeptidase (gammaGT) are only indicators of liver distress. If cirrhosis is present, functional reserve is assessed by Child-Pugh classification (which can be by the various centers modified). Further testing can be conducted by exploiting the elimination capacity of indocyanine green: an injection of 0.5 mg/kg is made into a vein in the arm, and hepatic elimination kinetics is studied by withdrawals made sequentially on the contralateral arm[4]. FLR volume is assessed by studying the organ and acquiring data with imaging techniques (CT, MRI) and entering them into continuously updated formulas.[5] The following formula is used: the amount of noncancerous liver to be removed is divided by the total amount of functional liver; the quotient is multiplied by the degree of hepatocellular insufficiency (assessed as follows: patients Child-Paul-Brousse A: 1, Child-Paul-Brousse B: 2 and Child-Paul- Brousse C: 3). The result must be less than 50%. Thus, for Child A patients, the amount of parenchyma that can be sacrificed is no more than 50% of the total noncancerous parenchyma; for Child B patients no more than 25%; and for Child C patients no more than 12.5%. The same calculation can be made for indocyanine green retention of less than 10%, between 10 and 20%, and above 20% at 15 minutes post infusion. It is inferred that what matters is not what is removed as much as what remains. Imaging-deducted volumetric measurements combined with an estimate of liver function contribute to an increasingly objective estimate of the feasibility of hepatectomy. It is possible to estimate the minimum volume of liver parenchyma compatible with survival with 1% of body weight. This is an extrapolation, as these figures have been described on transplants, in cold ischemia and with protective fluid. On a non-cirrhotic liver, the risk of postoperative liver failure is greater if the ratio of residual liver volume to body weight is less than 0.5%.

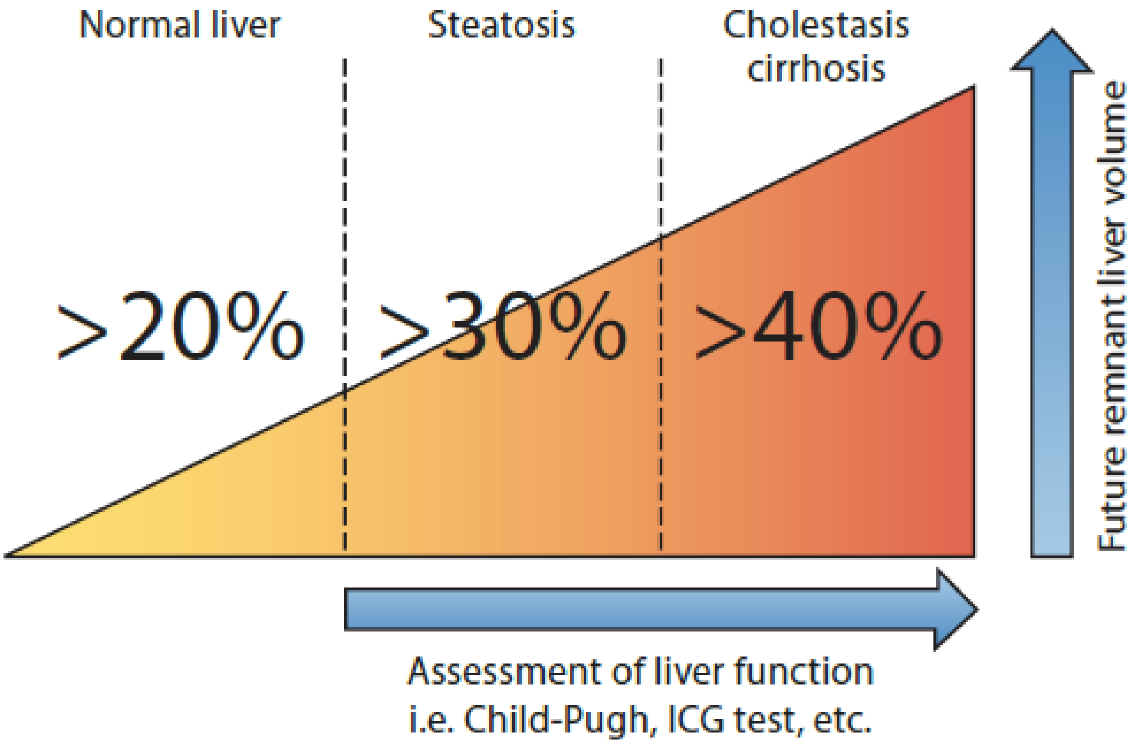

Figura 1: *"How Much Remnant Is Enough in Liver Resection?" Alfredo Guglielmi et al.*

Preserving enough functioning liver is mandatory for its molecular-synthetic function and overall circulatory phagocytic capacity. In conclusion, according to this study, an incidence of PHLF can be obtained. 79 very low at the time when one targets an FLR>26.5% in patients with good liver function and an FLR>31% in those with impaired liver function (preoperative jaundice or neoadjuvant chemotherapy)

2. OVERCOME THE FLR LIMITS: PARENCHYMAL SPARING HEPATECTOMY

Parenchymal sparing hepatectomy (PSH) is a de-escalation strategy that targets only metastasis by minimising the risk of stimulating tumour growth, while enabling iterative interventions. Reducing the loss of healthy parenchyma increases the tolerance of the liver to interval chemotherapy. Technically, PSH could use any type of hepatectomy, providing it is centred on the metastatic load alongside intraoperative ablation.[6] Sparing parenchyma in complex conditions means sparing liver tissue with adequate in- and outflow despite the disease involvement of the major intrahepatic vessel.

The philosophy behind PSH includes many surgical strategies aiming to offer minimum sufficient margins to preserve as much liver parenchyma as possible. This approach was thought to be correlated with increased rate of recurrence due to closer margins and a greater amount of at-risk future liver remnant in which metastases could seed. This turned out not to be the case. Data from the present analysis reflect a growing body of evidence that has accumulated over the past decade which have suggested that perhaps more can be achieved with less. For example, almost a decade ago, Pawlik et al. demonstrated that the width of a negative surgical margin after hepatectomy did not affect survival, recurrence risk or site of recurrence.[7] In fact, Adam et al. have suggested that even a microscopically-positive R1 margin does not impact overall survival[8]. PSH is an optimal procedure in this regard, offering less invasiveness with better short-term outcomes than major hepatectomy. More specifically, a recent study demonstrated that PSH for solitary CLM increased the chance of salvage resection for liver recurrence without increasing recurrence in the liver remnant[9,10]. In the same frame, another study demonstrated the striking finding that PSH did not negatively impact on overall, recurrence-free and liver-only recurrence-free survival and was a beneficial factor for candidacy for repeat hepatectomy, without increased risk of recurrence.[9] Moreover, repeat resection in patients with recurrent disease after CLM resection has been shown to offer the potential for long-term disease control without increasing perioperative mortality and morbidity rates.[11] In other words, surgery for recurrent CLM is feasible, with similar morbidity and mortality rates to those of initial or single CLM resections[12–14]. Moreover, PSH can be a reliable choice in the setting of bilateral CLM, with acceptable morbidity, mortality and oncological results.[15] It was also recently shown that PSH seems to be appropriate for deep-placed CLM (>30 mm from the liver surface) since it was performed safely without compromising oncological radicality.[16]

PSH seems to have a role in treatment of advanced CLMs that have a high risk of recurrence because the surgical margins are close to the tumors and residual parenchyma has a high risk of future liver metastases. A recent study in patients with advanced CLM found that PSH did not increase positive surgical margin or liver recurrence in comparison with major hepatectomy. Thus, a parenchymal-sparing approach offers a high rate of salvageability.[10] PSH can increase the number of patients eligible for an operation by halving the resection volume and by increasing the chance of direct operative treatment in patients with ill-located CLM.[16] Moreover, with the application of techniques that induce future liver remnant hypertrophy and liver regeneration[17,18], PSH might offer even superior results in terms of residual liver function. There is a clear trend toward PSH in hepatobiliary centers worldwide as current evidence indicates that tumor biology is the most important predictor of intrahepatic recurrence and survival, rather than the extent of a negative resection margin.[19] Tumor removal avoiding the unnecessary sacrifice of functional parenchyma has been associated with less surgical stress, fewer postoperative complications, uncompromised cancer-related outcomes and higher feasibility of future resections. The increasing evidence supporting PSH has prompted its consideration as the gold-standard surgical approach for CLM.[19]

2.1 GENERAL PRINCIPLES: intrahepatic anatomy to ensure proper in-flow and out-flow

The segmental approach of Couinaud's hepatic anatomy describes a liver divided into eight segments with independent inflow and outflow. The inflow is provided by the hepatic artery and portal vein while the outflow by the suprahepatic veins. In the context of hepatic resective surgery, it is critical to know the venous variants as well as the pattern of venous drainage within the vena cava. This is especially important when en bloc resections of the hepatic veins and part or entire adjacent hepatic segments must be removed due to tumors involving the hepatic veins (HV) at the hepato-caval (CC) confluence. Most frequently, the right HV (RHV) drains segments 5, 6, 7 and 8; the middle HV (MHV) drains segments 4, 5 and 8; and the left HV (LHV) drains segments 2, 3 and 4. However, the sixth segment can have an independent drainage directly into the inferior vena cava(IVC). Although this accessory HV is present in 86-100% of patients, only in less than a quarter of them does it result with a caliber greater than 0.5 cm. This vein is known as inferior right HV (IRHV). Another important anatomical variation is the presence of communicating veins (CVs) connecting adjacent HVs. They have been shown to be present in up to 80% of patients with CLM at the hepatocaval confluence. The finding of IRHV or CVs in adjacent HVs in cases where there is impairment of the hepatocaval confluence may make conservative hepatectomy safe rather than major resection or complex vascular reconstructions.

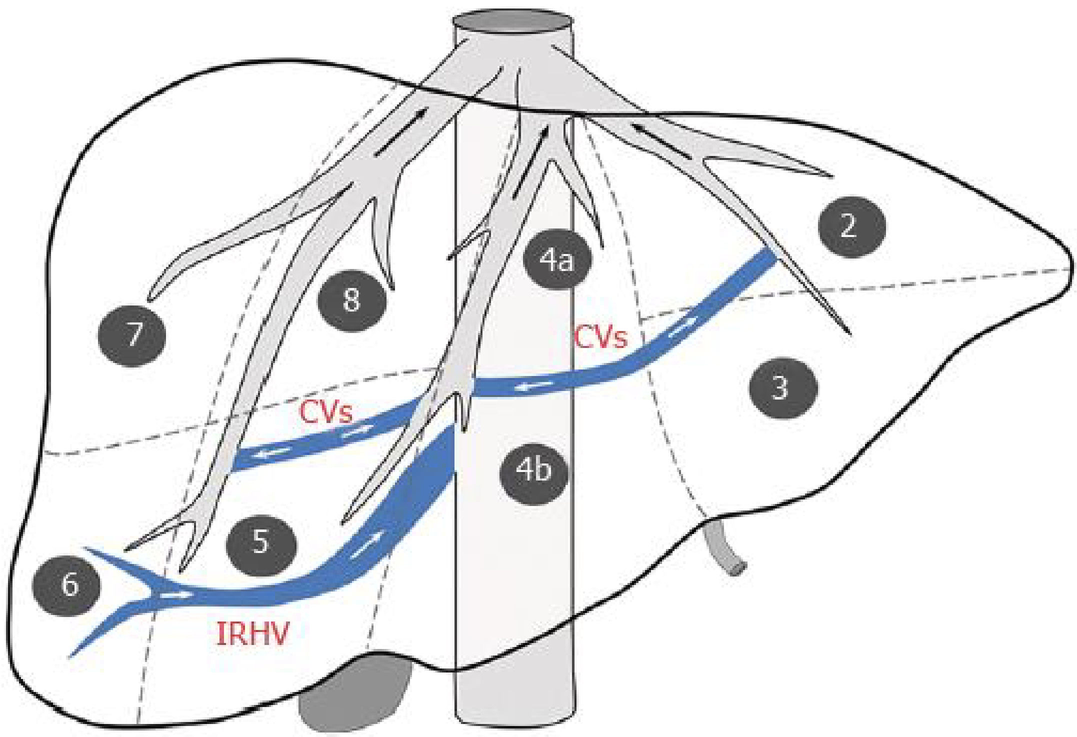

Figure 2: Hepatic segmentation and anatomical variations in hepatic outflow. Communicating hepatic veins; IRHV: Inferior right hepatic vein. Alvarez FA et al. "Parenchymal-sparing liver surgery.105

To ensure the safety of the procedure, an HV can be resected only after intraoperative testing. To make sure of this Torzilli proposes to occlude the HV of the segment to be preserved and see through the ECO-doppler if the portal branches maintain blood flow to the liver (rather than in the hepatofugal direction).[20]

An absolutely important step to support this type of surgery is the selection of patients, who must meet eligibility criteria, declined in 3 points:

1. Risk perspective: it is essential to assess the patient's ability to sustain major abdominal surgery under general anesthesia, evaluation of liver parenchymal status and function. Particular attention should be paid to obese

patients or those undergoing long chemotherapy regimens, modifying the volume of the post-surgical liver remnant (Future Liver Remnant, FLR) according to its quality. In a liver with preserved function, an FLR of 25% of total liver volume is considered sufficient to maintain basic function after resection. In a liver with dysfunction, an FLR of at least 40% of total volume is strongly recommended.

2. Technical feasibility: abdominal imaging is crucial in establishing resectability and planning the optimal surgical procedure. Although R0 resection of any colorectal liver metastasis (CLM) is the preferred therapeutic option, it should be mentioned that when candidating patients for parenchymal-sparing hepatectomy (PSH), a combination of resection of most lesions and radiofrequency ablation of those located in unfavorable areas may be considered in some patients to offer them the best possible survival.

3. Oncologic perspective: the evaluation of extrahepatic disease and its resectability as well as the response to preoperative systemic therapy in patients with suboptimal prognostic factors is particularly considered, as they are the ones who will benefit most from this approach.

In conclusion, combining acceptable patient risk with a safe technical proposal and a rational oncologic indication should be the goal of the liver surgeon when selecting patients for PSH.

3.2 SURGICAL PRINCIPLES OF PSH

A study from the Memorial Sloan Kettering Center reported a significant decrease in the median number of liver segments resected over the years from 4 to 2, with a simultaneous decrease in mortality rate from 5.2 to 1.6%.[21] Some authors also report how PSH is associated with significant decreases in postoperative morbidity: Jarnagin et al showed how the rate of liver-related complications were closely dependent on the number of segments resected.[22] In fact, liver function postoperative is well preserved in PSH, with a significantly lower and a significantly longer prothrombin time than those patients who had received a major resection.[23] Moreover, with the application of techniques that induce future liver remnant hypertrophy and liver regeneration[17], PSH might offer even superior results in terms of residual liver function. There is a clear trend toward PSH in hepatobiliary centers worldwide as current evidence indicates that tumor biology is the most important predictor of intrahepatic recurrence and survival, rather than the extent of a negative resection margin.[19] Tumor removal avoiding the unnecessary sacrifice of functional parenchyma has been associated with less surgical stress, fewer postoperative complications, uncompromised cancer-related outcomes and higher feasibility of future resections.

3.3 ONCOLOGICAL PRINCIPLES OF PSH

In cases of rectal colon liver metastasis, the spread through portal branches of micrometastases is uncommon. Vigano' et al.[24] demonstrate how the depth of negative surgical margins does not influence the risk of local recurrence or survival: the recurrence rate in patients treated with R0 margins had no significant difference compared with those treated with vascular R1, i.e., after a vascular detachment, in which the tumor is exposed. The possibility of doing a detachment is thus legitimized vascular, increasing not only the number of possible resections but also their safety. Leaving as much parenchyma as possible represents a great advantage because it increases the possibility of repeating hepatectomy in case of hepatic recurrence. Between 60 percent and 70 percent of patients undergoing liver resection for CLM will develop disease recurrence. Studies report improved overall survival for patients treated with PSH rather than with the major resections, due precisely to the increased chance of undergoing salvage hepatectomy in case of recurrence. Mise et al. have recently compared the long-term outcomes of patients with a single CLM<3 cm treated with or without PSH.[9] In this cohort of patients with uniform tumor characteristics, the Authors confirmed this hypothesis (long-term overall survival: 72.4% vs 42%, P=0.047) and a higher rate of reoperation (68% vs 24%, P<0.01) in the PSH group.

3.4 ULTRASOUND-GUIDED LIVER SURGERY

Intraoperative ultrasonography (IOUS) plays a key role in modern liver surgery, not only to study the disease more accurately, but especially as a guide in resection.[25] The extensive use of IOUS makes it possible to maximize the sparing of healthy parenchyma. It makes it possible to precisely identify the location and number of lesions, showing the relationships between them and major vascular structures that can be followed real time.

PSH is more a philosophy than a surgical technique that encompasses a wide range of liver resections, ranging from small, nonanatomic wedge resections, to complex atypical resections, to segmentectomy or subsegmentectomy. The type of resection that is chosen is primarily based on the need to sacrifice glissonian vessels and/or pedicles. It seems obvious, therefore, that meticulous ultrasound exploration of the liver is a fundamental prerequisite for modern liver surgery.

It is very important to be methodical in the use of IOUS in order to examine the parenchyma completely and accurately. 2 standardized explorations are recommended: the first in order to assess the hepatic anatomy; the second for intraoperative staging: in this step the relationships between tumor and vasculature are carefully evaluated. IOUS makes it possible to measure the distance between metastatic nodules and vessels and, in case of vessel adhesion, to define the extent of the contact surface longitudinally and circumferentially. Vessels in contact with the tumor should be well explored for signs of infiltration such as the presence of neoplastic thrombi or endoluminal growth of the tumor.

Having dealt with this information, the surgeon will decide which vessel to spare and which not to spare, thus planning the extent of resection. If vascular infiltration is suspected, the vessel should be ligated and dissected to achieve an R0 resection. The lesion can be dissected from the vessel, even if a very thin surgical margin is achieved. This explains how knowledge of the hepatic inflow and outflow, thanks also to intraoperative echo, is crucial in determining surgical feasibility. A third exploration is necessary: this is the true ultrasound guide for any resection. This exploration focuses on the lesion to be removed and its relationship to the hepatic skeleton. It is possible to draw on the liver with the electrosurgery the map of the area obtained by IOUS i.e., the line of resection. During parenchyma resection, IOUS allows monitoring the correctness of the resection plan to maintain an adequate surgical margin and to avoid injury to major vascular structures. Finally, IOUS can be used to assess proper drainage of the hepatic remnant. Inflow and outflow are evaluated in the search for ischemic or congestive areas. At the end of resection, the cut surface can also be probed in the search for remaining lesions. Although resection of small and superficial metastases often does not require dissection or pedicle ligation, the importance of IOUS should not be underestimated. Indeed, it allows us to assess the distance of the vessels and if they need to be ligated, it allows us to choose the appropriate distance between the resection line and the projection of the metastasis. Multiple atypical bilobar resections, perhaps associated with segmentectomy or subsegmentectomy, are often impractical without IOUS-mediated planning and its constant guidance. If IOUS shows no signs of infiltration or limited contact with a vessel, the lesions can be dissected thus allowing sparing of the vessel itself. Ultrasound guidance makes it possible to reach the appropriate vein at the correct angle. In cases of focal infiltration, suprahepatic veins can be partially resected en bloc with the tumor and reconstructed with a direct suture or patch. Cases with multiple lesions, involving various hepatic veins and glissonian pedicles, can often be treated with limited resection, which is infeasible without IOUS guidance. Regarding MLC, an anatomic segmentectomy is performed when an entire glissonian pedicle must be sacrificed to leave no ischemic areas. Sacrifice of a hepatic vein may require resection of the entire segment drained by it. The difficulty of segmentectomy lies in the lack of landmarks on the hepatic surface to guide the resection. Over the years many methods have been proposed: Makuuchi et al utilized a portal injection of indigo carmine that stained the area thus becoming visible on the organ surface.[26] Torzilli et al proposed portal branch compression, with or withour indocyanine green use, i.e., after identifying by IOUS the portal branch afferent to the segment to be sacrificed, the branch is compressed between the probe and a finger inducing a transient ischemia of the downstream parenchyma resulting in a color change on the organ surface. The area can then be demarcated with an electrosurgical scalpel.[27–29] Another technique proposed by Machado et al requires a small hepatic incision to isolate the second- or third-order branches of the pedicles. After ligating them, the resection would follow the ischemic line formed on the surface of the liver.[30]

A tumor infiltrating a suprahepatic vein near the hepatocaval confluence has for years required major hepatectomy. This is no longer acceptable in many cases: in fact, there are many alternatives that allow blood outflow from the territory of the closed hepatic vein. First, the presence of an accessory hepatic vein, evidenced in preoperative work up and confirmed with IOUS, may be viable solution. The communicating veins described by Torzilli et al. can be identified intraoperatively by color Doppler or even power Doppler.[20] During the operation, color Doppler is used to check for the presence of CVs between the suprahepatic vein that has to be resected and the adjacent suprahepatic vein. If they are not noticed, one attempt to clamp the suprahepatic vein that is to be resected, this maneuver allows perfusion of the communicating veins that are usually found to be collapsed in a physiological state.

THESIS RATIONALE

Preoperative FLR estimation is mandatory in major hepatectomy (MH). As alternative, the parenchyma-sparing strategy has been proposed assuming that, in this way, the FLR would be adequate.[9,25] However, pushing this policy to patients with multiple bilobar colorectal liver metastases (CLM),[16] encompassing also the CLM-vessel detachment (R1vasc)[31], the adequacy of FLR may not obvious and its predictability become relevant.

However, the FLR estimation in an R1vasc-OSH setting just adopting the so-called "hand-trace technique", the manual plotting of resection areas on each CT/MRI scans, is unfeasible. The introduction of three-dimensional (3D) virtual cast may facilitate the FLR estimation by allowing the preoperative simulation of the planned surgical procedure. Several reports have emphasized the usefulness of preoperative 3D modeling of the liver resections.[32–34] However, no reports foresee its role in R1vasc-OSH.

This study reports the first experience using 3D virtual cast for preoperative FLR prediction in patients undergoing R1Vasc-OSH for multiple bilobar and deep-located CLMs. Its reliability and clinical value were evaluated.

END-POINTS

The primary endpoint was to verify the predictability of the FLR using the 3D virtual cast in a group of patients undergoing to R1vasc-OSH for multiple bilobar CLMs.

The secondary endpoint was to validate these preliminary data by comparing the FLR between patients who had R1vasc-OSH after 3D virtual cast with a matched group who had R1vasc-OSH without 3D simulation.

The tertiary endpoint was to evaluate the learning curve on 3D FLR estimation in order to define its feasibility and reproducibility. This aspect was evaluated by comparing the FLR estimation performed according with surgeon’s seniority (more or less the 5 years as team leader).

METHODS

1. TERMINOLOGY AND DEFINITION

Liver anatomy and surgical procedures were classified according to Brisbane terminology.[35]

Liver resections involving at least three adjacent segments were defined as MH.

Operative mortality was defined as death within 90 days after surgery or anyway during the hospital stay. All postoperative complications were graded according to the Clavien-Dindo classification.[36]

PLF was defined according to the International Study Group of Liver Surgery (ISGLS) criteria.[37]

Chemotherapy response was monitored by using the Response Evaluation Criteria in Solid Tumors (RECIST).[38]

2. STUDY POPULATION

We analyze all subjects candidate for liver resection from January, 2010 to October, 2020 at a major tertiary center.

Eligible patients were those scheduled for a R1vasc-OSH because carrier of ≥4 bilobar CLMs with at least one lesion in contact with 1st /2nd order portal pedicles (P-zone) or hepatic veins (HV) within 4 cm from their caval confluence (H-zone) and scheduled for detachment.

3. DATA COLLECTION

Data were collected retrospectively using paper and digital medical records, operative records, reports of follow-up visits, and telephone interviews with the patient or family members.

The data collected were:

- Demographic and clinico-pathological data: age, sex
- Chemotherapy data: type, number of cycles, response (stable disease, progressing disease, regressing disease, complete response)
- Pathology data: number of metastases, synchronous disease, bilobar disease, localization, maximum diameter.
- Data related to operative procedures: type of procedure performed, number of resection areas, vascular R1 procedure, operative time, clamping time, blood loss, transfusion
- Post-operative data: 90-day mortality, overall morbidity, major morbidity, postoperative liver failure, in-hospital stay.

4. PREOPERATIVE SIMULATION AND PREOPERATIVE WORK-UP

Preoperative volumetric analysis was performed using a 3D simulation system (Synapse Vincent 3D software; Fujifilm, Tokyo, Japan), based on a contrast-enhanced computed tomography (CT) sliced 1 mm thick and performed within 4 weeks before surgery. The CT images were uploaded to the Synapse workstation, and each 3D-vcast and analysis was performed by one expert hepatobiliary surgeon. 3D planning of the surgical procedures relied on our established parenchyma-sparing policy based on: 1) CLM-vessel detachment in case of contact with P-zone or H-zone major intrahepatic vessels; 2) detection and mapping of the communicating veins (CV) in the event HV has to be sectioned (20). The adequate FLR cut-off was set at 40% of the total liver volume for all patients independently on the amount of preoperative chemotherapy was administered. The software calculated the tumor volume and the amount of blood contained in the portal vein and HV of the virtually determined specimen.

Magnetic resonance imaging (MRI) using hepatospecific contrast media was also done in all patients, although could not be used for the virtual cast with the available version of the software. Positron emission tomography-CT was routinely performed to disclose associated extrahepatic disease (21). Preoperative chemotherapy was administered when CLMs were initially unresectable or marginally resectable (i.e. inability to remove all CLMs with a sufficient FLR), or in a perioperative setting (combination of preoperative and postoperative chemotherapy) according to decisions taken during a weekly multidisciplinary meeting. Patients receiving preoperative chemotherapy were restaged after 4–6 cycles and scheduled for surgery if disease response or stabilization was confirmed.

5. SURGICAL TECNIQUE

An intraoperative ultrasound (IOUS)-guided parenchyma-sparing approach was systematically performed as previously described (22-24). Detachment of CLM from Glissonean pedicles was performed if no signs of infiltration were further confirmed at IOUS. Similarly, tumor detachment from HV at the caval confluence was systematically pursued otherwise partial vascular resection and reconstruction was performed as previously described (11). Parenchymal transection was performed using the crush-clamping method under intermittent pedicle clamping. Glissonean pedicles and HV detachment was done using blunt dissection with Metzenbaum scissors. Vessels thicker than 2 mm were ligated with 3-0 sutures.

6. VALIDATION OF 3D ANALYSIS

To validate the 3D analysis, the concordance between the real volume of the specimen and that estimated by the 3D-vcast was evaluated. The volume of specimen was analyzed just after specimen removal by one expert pathologist blinded to 3D analysis data. Similarly, the real volume of the resection specimens remained blinded to the investigators until all patients had been included and analyzed prospectively. To determine real volume, the specimen was placed in a container of water by measuring the volume of displaced liquid. The same tumor volume (computed on the 3D analysis) was excluded from both predicted and real specimen.

For comparing the postoperative complications of patients having virtual R1vasc-OSH (R1vasc-OSHv) with those who had not 3D virtual cast (R1vasc-OSHnv), a propensity score matching was performed. In order to decrease any potential biases due to potential technical improvement, only patients undergone to R1vasc-OSHnv in the last 5 years (n=133) were considered for matching.

7. METHOD FOR THE STEP-WISE TRAINING OF INEXPERIENCED SURGEON ON 3D SIMULATION

A step-wise training method was adopted to educate younger surgeons how to do a virtual cast for FLR estimation in OSH:

a. training on basic techniques of 3D reconstruction including liver anatomy and tumoral mapping;
b. preoperative FLR estimation in anatomical liver resection;
c. preoperative simulation of a virtual surgical planning in OSH.
d. Senior residents (SR: attending the last year of the 5-years long postgraduate school in general surgery) performed the R1vasc-OSHv, by themself, deciding when and which vessels should be divided during dissection according to aforementioned parenchyma-sparing criteria. The surgical planning was classified into increasing levels of difficulty. Virtual casts were recorded, and an experienced surgeon (ES) checked when the trainee was ready for the next step;

e. final feedback from senior surgeon.

8. METHOD FOR THE STEP-WISE TRAINING OF INEXPERIENCED SURGEON ON 3D SIMULATION

Continuous data are presented as median (range). Categorical variables were compared using the $\chi 2$ test, Fisher's exact test and Mann–Whitney U test, as appropriate. Propensity score matching was generated using a logistic regression model on the following covariates considered as potential confounding factors: number of resection areas, number of CLMs, operation time, cumulative clamping time, blood loss, preoperative chemotherapy and number of cycles. R1vasc-OSHv and non-R1vasc-OSHv patients were then matched by these propensity scores with a ratio 1:2. An optimal matching with a caliper size of 0.2 was used to avoid poor matches. Error ratio in prediction of FLR using 3D system during the first and last 10-patients in each young surgeon was compared to identify any differences in performance at the baseline and the end of study period. Proficiency was defined as the point at which the slope of the error ratio curve became less steep and greater overlapped to that experienced surgeon. A p value < 0.05 was considered significant for all tests. All statistical analyses were performed using Stata (version 13, StataCorp LLC).

RESULTS

1. PREDICTABILITY OF 3D FLR ESTIMATION

A total of 30 consecutive R1vasc-OSHv for multiple bilobar CLMs were performed between January 2018 and December 2019 at the author Institute (Humanitas Research Hospital, Milan, Italy). The 3D planned hepatectomies were effectively performed accordingly (Figures 3-4). Median CLMs removed was 12 (4-33), included in a median number of 3 specimens (1-8). Median predicted-FLR (pFLR) and the related percentage in relation to the entire organ once removed the CLM volume were 899 ml (558-1157) and 60% (42-85), while for the real-FLR (rFLR) were 915 ml (566-1777) and 63% (43-87). The median discrepancy between the pFLR and rFLR was -0.6% (range: -25% - +10%; p = 0.504), indicating a slight tendency to preoperatively underestimate the FLR. The difference between the pFLR and the rFLR was more evident in patients with more than 12 CLMs removed (-4.6% vs. +0.2%; p=0.013) (Figure 5A). Differently, a discrepancy between the pFLR and rFLR was not evident according to number of resection areas (1-3 resection areas -0.3% vs >3 resection areas -0.7%; p=0.316) (Figure 5B).

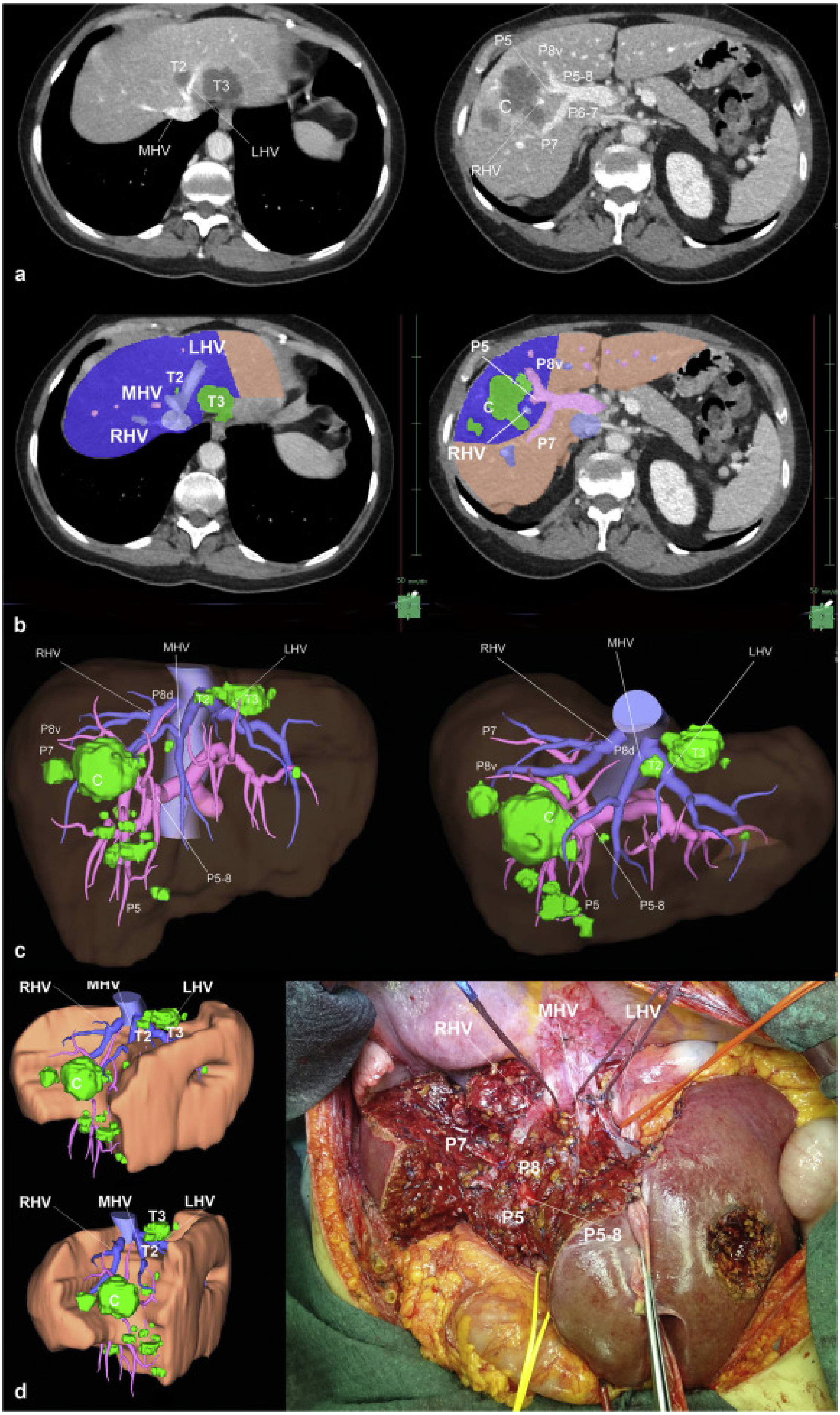
T2
T3
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Figure 3: **(A) CT-scan of a patient with multiple bilobar and deep-located colorectal liver metastases (CLM) of which a cluster of lesions (C) was in contact with the portal branch to S8 (P8) and S5 (P5) at its origin from P5-8, the portal branch to S7 (P7) and the right hepatic vein (RHV), a lesion (T2) in segment 4 superior in contact with both middle (MHV) and left hepatic vein (LHV) and an another (T3) in segment 2 in contact with the left side of LHV at the caval confluence; the CLMs were 18 in total; (B) 3D reconstruction showing lesions location; (C) (*on the left*) 3D virtual cast showing the planned hepatectomy; (*on the right*) the hepatectomy consisted in a wide partial resection of segments 8 and 5, enlarged to the segment 6, segment 7, the paracaval portion of segment 1, segments 4 superior and 2; the tumor in segment 2 involved the LHV which was partially resected and reconstructed by direct suture; all three hepatic veins, P7 and P5-8 were fully exposed on the cut surface; predicted future liver remnant was 631 ml while the real was 637 ml (error ratio -0.5%)**

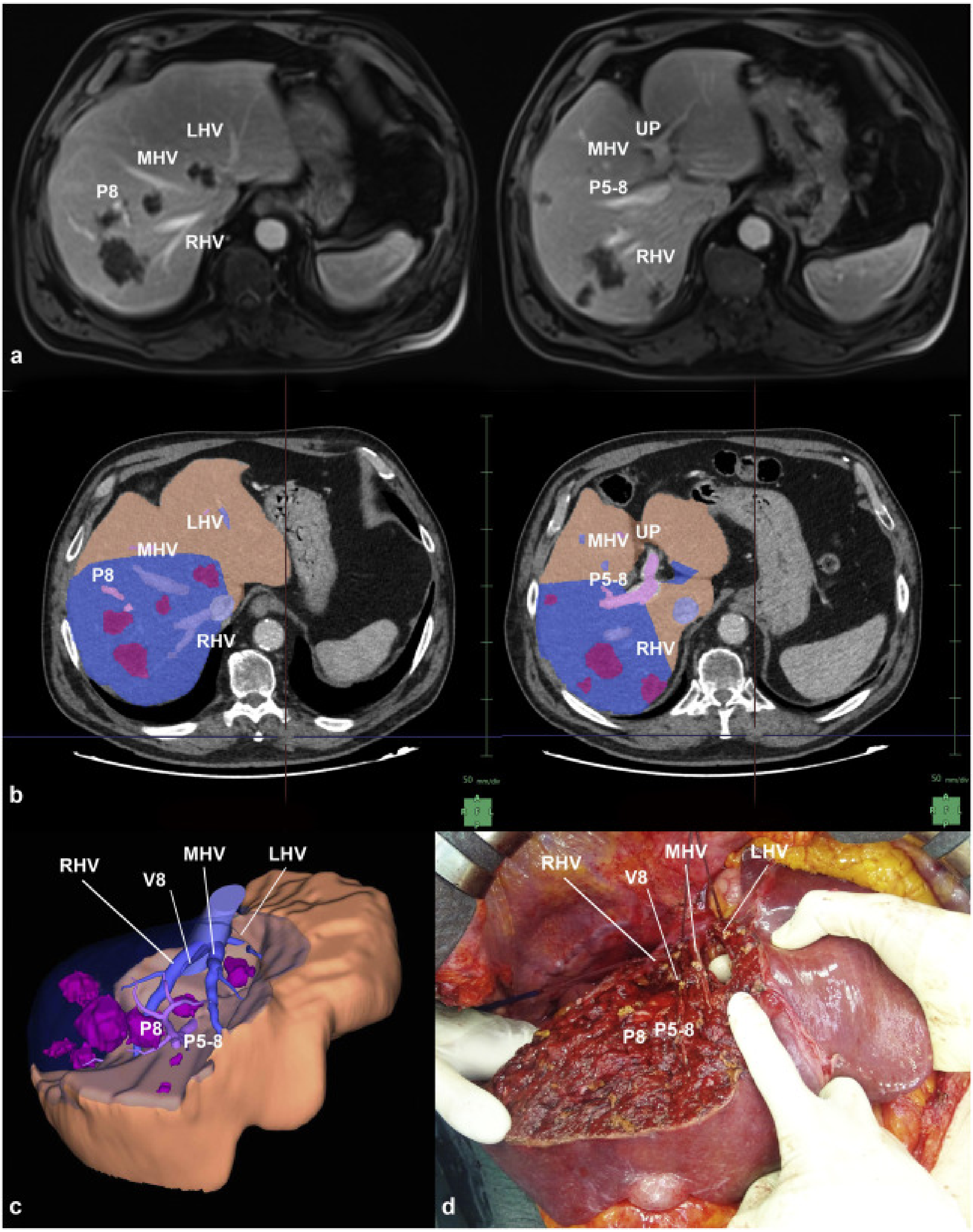


Figure 4: (A) MRI-scan of a patient with multiple bilobar and deep-located colorectal liver metastases in contact with all three hepatic veins at their caval confluence, the portal pedicle to S8 (P8) at its origin from P5-8; the CLMs were 11 in total; (B) 3D virtual cast showing the planned hepatectomy; (C) the hepatectomy consisted in a wide partial resection of segments 4 superior, 8 and 5, enlarged to the segment 6, segment 7, the paracaval portion of segment 1; all three hepatic veins, P8 and P5-8 were fully exposed on the cut surface; predicted future liver remnant was 994 ml while the real was 1006 ml (error ratio -0.7%)

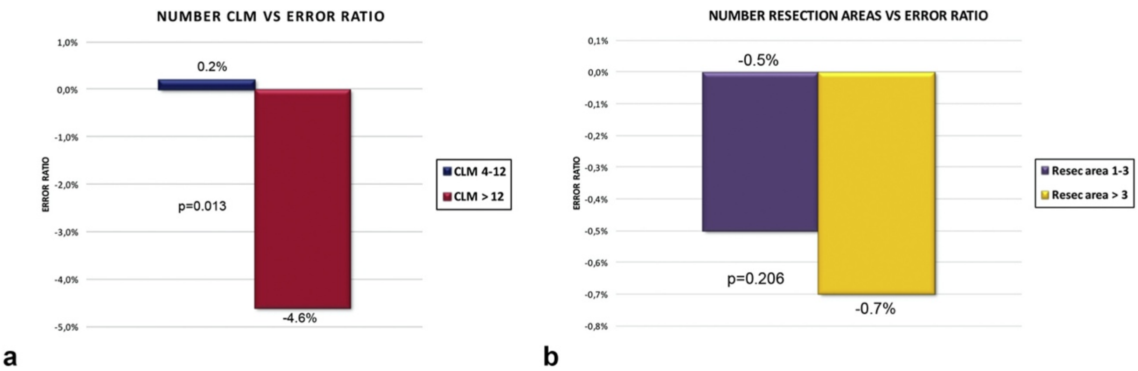


Figure 5: **Error ratio in prediction of future liver remnant using 3D system according to number of colorectal liver metastasis (A) and number of resection areas (B). Ratio values are expressed as median.**

2. VALIDATION OF 3D VIRTUAL CAST IN R1VASC-OSH

After propensity score matching, the total cohort comprised 90 patients: 30 patients comprised the R1vasc-OSHv group and 60 patients comprised the R1vasc-OSHnv. As shown in Table 1, the 2 groups of patients were well matched for number of resection areas, number of CLMs, operative time, cumulative clamping time, blood loss, preoperative chemotherapy and number of cycles. Patients' characteristics, surgical procedures and postoperative outcomes are summarized in Table 1 and Table 2. Postoperative mortality was nil in both groups while postoperative complication rate was 10% in R1vasc-OSHv and 50% in other group (p-value 0.042). Patients in R1vasc-OSHv group had lower major postoperative complications (Dindo-Clavien III-IV) compared to non-R1vasc-OSHv (0% vs 18%, p-value 0.014). PLF occurred in 1 (3%) patient of R1vasc-OSHv group and in 11 (18%) patients of non-R1vasc-OSHv group (p-value 0.055).

Table 1 Patients' characteristics

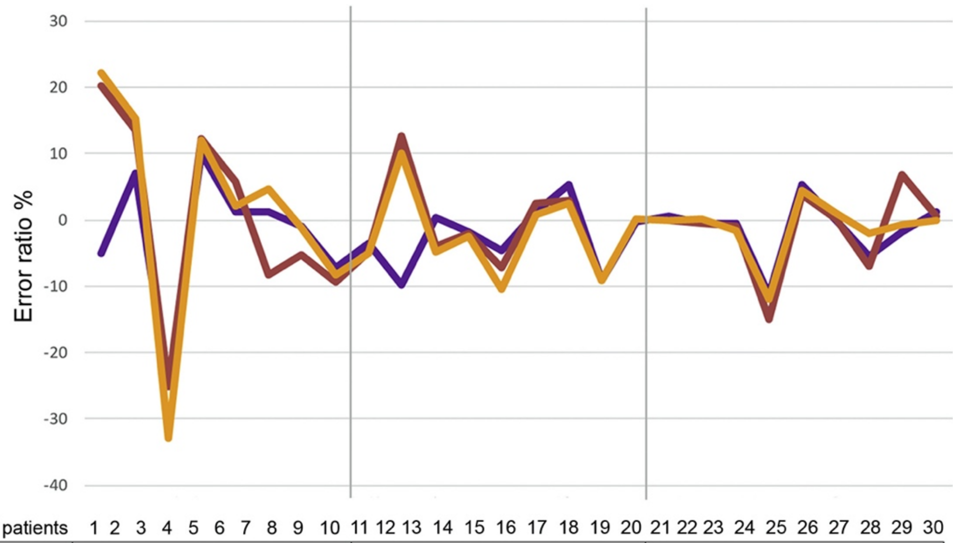
	Virtual e-OSH (n=30)	No Virtual e-OSH (n=60)	p-value
Gender, ratio			
Female:Male	10:20	27:33	
Age, median (range)	52 (32-69)	62 (30-75)	ns
Prior chemotherapy, n. (%)	30 (100)	60 (100)	ns
FOLFOX	17 (57)	33 (55)	ns
FOLFIRI	13 (43)	27 (45)	ns
Ass. Bevacizumab	28 (93)	24 (40)	**0.0001**
Ass. Cetuximab	2 (7)	12 (2)	ns
Number of cycles, median (range)	9 (4-12)	8 (3-26)	ns
Responders (SD + PR)* , n. (%)	30 (100)	60 (100)	ns
Number of CLM, median (range)	12 (4-33)	12 (4-38)	ns
4-12	14 (47)	28 (47)	
≥ 12	16 (53)	32 (53)	
Synchronous, n. (%)	27 (90)	55 (92)	ns
Bilobar CLM, n. (%)	30 (100)	60 (100)	ns
CLM location, n. (%)			
P-zone	4 (13)	6 (10)	ns
H-zone	10 (34)	27 (45)	ns
Bilateral H and/or P zone	16 (53)	27 (45)	ns
Largest diameter > 50 mm, n. (%)	4 (13)	14 (23)	ns

Table 2 Surgical procedures and postoperative outcome

	Virtual e-OSH (n=30)	No Virtual e-OSH (n=60)	p-value
Surgical procedure, n. (%)			
Major hepatectomy	-	-	
Minor anatomical resection			
Sectionectomy + multiple LR	1 (3)	11 (18)	ns
Segmentectomy + multiple LR	-	5 (8)	ns
Limited resection			
Single resection area	3 (10)	3 (5)	ns
≥ 2 resection areas	26 (87)	41 (68)	ns
Number of resection areas, median (range)	3 (1-8)	5 (2-9)	ns
R1vasc procedure	30 (100)	50 (83)	**0.027**
Operative time, median (range)	534 (446-683)	620 (456-717)	ns
Clamping time, median (range)	143 (91-236)	155 (104-208)	ns
Blood loss, median (range)	700 (200-1200)	750 (300-1500)	ns
Blood transfusion, n. (%)	3 (10)	13 (22)	ns
Postoperative outcome, n. (%)			
90-day mortality	**-**	**-**	
Overall morbidity	3 (10)	30 (50)	**0.042**
Major morbidity (Dindo-Clavien III-IV)	-	11 (18)	**0.014**
Postoperative liver failure (ISGLS grade)	1 (3)	11 (18)	ns
Grade A	1 (3)	3 (5)	ns
Grade B	-	2 (3)	ns
Grade C	-	6 (10)	ns
Bile leakage	1 (3)	7 (12)	ns
Ascite	4 (13)	1 (3)	ns
In-hospital stay (day), median (range)	10 (6-27)	10 (7-21)	ns

3. LEARNING CURVE EFFECT ON 3D VIRTUAL CAST

The 3D planned R1vasc-OSH were effectively performed by two senior residents accordingly. Not statistically differences in error ratio were observed in both senior residents between the beginning and the end of the study (SR-1 p=0.870; SR-2 p=0.391). However, the learning curve showed as the discrepancy between the FLR predicted by SR and ES progressively decreased (greater overlapping of the curves) (Figure 6). The graph showed that both SRs reached a steady state error ratio after approximately 16 consecutive cases (Figure 6). Similarly, to the whole series, a slight tendency to preoperatively underestimate the FLR was more evident in patients with more than 12 CLMs (Figure 7A). Differently, discordant results were observed between the two SRs according to the number of resection areas (Figure 7B).



Expert surgeon	-0,9%	-0,5%	-0,6%
Young surgeon 1	-4,9%	-0,3%	0,2%
Young surgeon 2	2%	-0,1%	-0,7%

Figure 6: Learning curve. A grater overlapping of the three curves (young surgeons vs expert surgeon) is shown after approximately 16 3D simulations. The values are expressed as median.

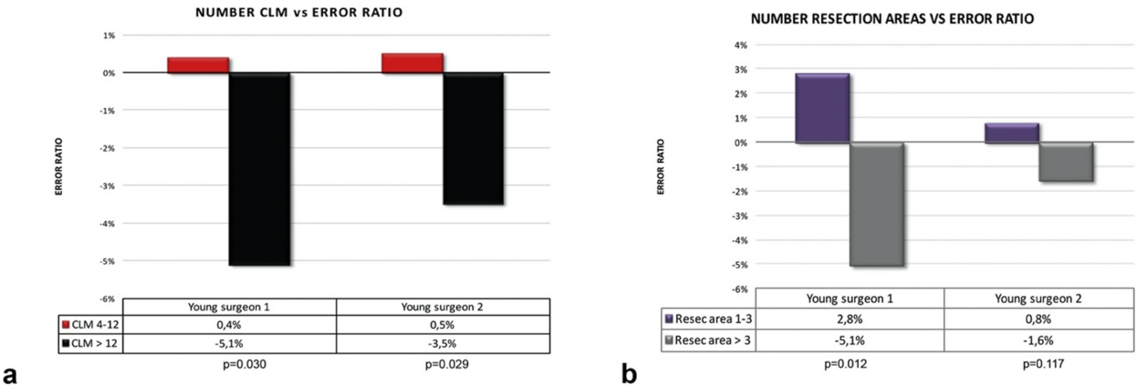


Figure 7: Error ratio in prediction of future liver remnant using 3D system according to number of colorectal liver metastasis (A) and number of resection areas (B) in the two young surgeons. Ratio values are expressed as median.

DISCUSSION

This thesis is part of other studies and clinical protocols underway at the UO of General and Hepatobiliary Surgery at IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy, dealing with various issues concerning the use of modern technologies in liver surgery, particularly for the development of parenchyma-sparing liver surgery.

3D simulation analysis has an increasing interest in liver surgery.[39–41] The present study is the first to assess the clinical impact of 3D-vcast focusing on prediction of FLR in the peculiar setting of R1vasc-OSH for multiple bilobar CLMs. FLR is well known to affect postoperative mortality and morbidity.[42] Then, an accurate preoperative estimation of the FLR is a key factor for successful hepatectomy. To assess the liver volume, the so-called "hand-trace technique", the manual plotting of resection areas on each CT/MRI scans, still remains the gold standard. The planning of anatomical hepatectomy using this method can be relatively easy to perform, and a certain degree of accuracy in the volume estimation can be achieved.[33] The introduction of 3D simulation modalities has standardized the FLR estimation in the anatomical resections by computing the process, limiting the operator-dependence of the hand-trace technique and also speeding up the process. In this sense, several reports support the value of the 3D simulation by showing a good correlation between the real volume of resected liver specimen and that predicted.[32,33,39] Things become more complex when the resections have a multiplanar path (27), and furthermore once they are multiple: for such a condition, the hand-trace estimation of FLR becomes unfeasible. Of course, in case of extremely complex parenchyma-sparing resection featuring the R1vasc-OSH setting[25,31], intraoperative findings may impact the surgeons decision making resulting in a modified strategy. However, a reliable preoperative estimation of the FLR according to the previous planning could act as trustable baseline in the decision making whether and how the strategy could be changed.

Takamoto et al. has recently reported the benefit of virtual hepatectomy in parenchyma-sparing procedures for CLMs.[43] However, most of the patients included had monolateral, and oligometastatic (<3) disease, one fifth of them received a small anatomical resection and another fifth underwent a MH. In the present study, the reliability of 3D-vcast has been tested in predicting the FLR exclusively in patients with bilobar, and deep-located CLMs. Minimal differences resulted between the pFLR and rFLR, with a slight preoperative underestimation (median error ratio was -0.6 %). Some factors can explain this slight difference. First, the resected specimen contains less amount of blood. Second, as said transection plans may be modified based on more accurate surgical interpretation of the vascular anatomy provided by IOUS, including identification of communicating veins as source of new parenchyma-sparing options.[20,44] Indeed, the estimation error increased with the tumor burden. The pFLR resulted 3-4% lower than rFLR in patients with more than 10 CLMs or 3 resection areas. The intraoperative “adjustment” of the planned surgical procedure, aiming to maximize the parenchyma-sparing in these patients, could explain this result and should be object of further evaluations.

Given the feasibility and reliability of pFLR estimation in R1vasc-OSH, its clinical impact remains to be elucidated. Previous studies have reported as 3D simulation improves the performance of anatomical resection in terms of oncological adequacy and postoperative complications.[9,32] The comparison of the 30 R1vasc-OSHv with 60 matched patients who received R1vasc-OSHnv, resulted in 0% mortality for both, but an overall PLF of 3% for the first vs 18% for the latter. Noteworthy, with all grade A in those with R1vasc-OSHv and 16% of grade C in the other (Table 2). Larger analyses are needed, but these data clearly support the advantage provided by the introduction of the preoperative 3D analyses in the unique setting of R1vasc-OSH.

So far, these findings show feasibility and rationale of 3D virtual cast for patients undergoing complex parenchyma-sparing hepatectomy for multiple bilobar CLMs. In our department, a parenchyma-sparing approach is proposed most of the time. However, in advanced tumoral presentation, the preoperative 3D volume estimation given its reliability may help in improving patients' selection and to drive planning of the most adequate treatment. Indeed, volumetric liver analysis using 3D system should be necessary before making a final decision about the extent of liver resection. Indeed, although never occurred in this series, given the reliability of this measurement herein demonstrated, an inadequate pFLR for allowing a R1vasc-OSH could empower the shifting towards staged procedure.

The main potential drawback of this method could be its technically demanding process. The 3D simulation system requires careful preoperative evaluation to select the adequate resection plane considering the tumor location, and liver anatomy. Furthermore, to our knowledge, its reproducibility and real learning curve in R1vasc-OSH has never been studied. To eliminate possibly operator-dependent bias, we investigated the preoperative FLR estimation performed by two SR in general surgery. A constant improvement in predicting FLR was observed: the discrepancy between SR and ES progressively decreased. These data clearly demonstrate a learning curve effect due to technique improvement and standardization, especially for surgical planning, which represents the most difficult part of R1vasc-OSHv. Certainly, an external validation, possibly multi-institutional, would be crucial in substantiating our results.

In conclusion, according to these results, 3D analysis provides a reliable FLR estimation in a clinical setting as the R1vasc-OSH for multiple bilobar and deep-located CLMs, in which to now there was no suitable modality. That in addition to its clinical reliability, and its reproducibility, given a relatively short learning-curve, address to this modality great potentiality in favouring a further spread of a complex but safe and effective procedure as the R1vasc-OSH.

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