DDS–SIRC COOPERATIVE CONFERENCES

There is a Great Future in Plastics: Personalised Approach to the Management of Hilar Cholangiocarcinoma Using a 3-D-Printed Liver Model

Zoe LARGHI LAUREIRO [1] *, Simone NOVELLI [2][3] *, Quirino LAI [1], Gianluca MENNINI [1], Vito D'ANDREA [4], Paolo GAUDENZI [2], Franco MARINOZZI [2], Cornelius ENGELMANN [3], Raj MOOKARJE [3], Dimitri RAPTIS [3], Massimo ROSSI [1], *and* Rajiv JALAN [3]

1. Department of General Surgery and Organ Transplantation, La Sapienza University of Rome, Rome, Italy;
2. Department of Mechanical and Aerospace Engineering, La Sapienza University of Rome, Rome, Italy;
3. Institute for Liver and Digestive Health, University College London, Royal Free Campus, Rowland Hill Street, London, United Kingdom;
4. Department of Surgical Sciences, La Sapienza University of Rome, Rome, Italy.

Author contributions:
* Zoe LARGHI LAUREIRO and **Simone NOVELLI** equally contributed to the present article.

Keywords: Klatskin tumor, thrombosis, surgical planning, 3-D printing

Conflict-of-interest statement: The authors have no conflict of interest to declare.

***Correspondence to*:**
Quirino LAI,   MD PhD
Department of General Surgery and Organ Transplantation,
La Sapienza University, Viale del Policlinico 155, 00161 Rome, Italy.
lai.quirino@libero.it
Telephone: +39-349 3020126   Fax: +39-06 499701

ABSTRACT

In recent years, three-dimensional (3-D) printing technology has become a standard tool that is used in several medical applications such as education, surgical training simulation and planning, and doctor-patient communication. Although liver surgery is ideally complemented by the use of pre-operative 3-D-printed models, only a few publications have addressed this topic. We report the case of a 29-year old Caucasian woman admitted for a Klatskin tumor infiltrating the right portal vein requiring surgery that required complex vascular reconstruction. A life-sized liver model with colorful plastic vessels and realistic looking tumor was created with the aim of planning an optimal surgical approach. According to the 3-D model, we performed a right hepatic trisectionectomy, also removing *en-bloc* the tract of portal vein encased by the tumor and the neoplastic thrombus, followed by a complex vascular reconstruction between the main portal vein and the left portal branch. After 22 months of follow-up, the patient was alive and continuing chemotherapy. The use of the 3-D models in liver surgery helps clarify several useful pre-operative issues. The accuracy of the model regarding anatomical findings was high. In the case of complex vascular reconstruction strategies, rational use of 3-D printing technology should be implemented.

CASE REPORT AND EVOLUTION

A 29-year old Caucasian woman was admitted in our Center due to worsening jaundice. At hospitalization, patient blood tests showed marked signs of cholestasis, with a total bilirubin level=5.8 mg/dL (normal values [NV] <1.0 mg/dL) and gamma GT=457 IU/L (NV=5-36 IU/L). During the hospital stay, we observed a progressive deterioration of the patient's clinical status, with severe anorexia and progressively increasing total bilirubin values (peak=11.0 mg/dL). A CT scan showed a 20x38mm mass at the level of the biliary confluence, extending to the biliary ducts of segments V and VI, with diffuse dilatation of the intrahepatic biliary tree (**Figure 1A**). Moreover, a tumor thrombus was observed involving the right portal vein and

the portal branches of segments V and VIII (**Figures 1B** and **1C**). Three days before surgery, an external biliary drain was placed at the level of the left liver. Liver volumetry predicted that the future liver remnant was >30%. In consideration of the complexity of the case, we decided to print a three-dimensional (3-D) model of the patient's liver based on a 3-D reconstruction of the imaging studies [**Fig. 1D**].

The process of model development consisted of four major phases: object segmentation, 3-D model digital rendering, the 3-D printing process, and finishing and assembly with silicone curing (**Figure 2A**). The cost of production of the model was € 1,200, requiring a total development time of ~ 35 hours. The model was delivered two days before surgery to the surgical team scheduled to perform the procedure. The outcome of the process was a life-sized liver model with colorful plastic vessels and a realistic-appearing tumor (**Figure 2B**).

Using the model, we had the opportunity to visually and tactilely inspect the liver, discussing the case and planning the optimal operative approach. According to the observed results, we performed a right trisectionectomy, also removing the tract of portal vein encased by the tumor and the thrombus *en-bloc* (**Figures 3A** and **3B**). The vasculature connecting the main portal vein and the left portal branch was reconstructed (**Figures 4A-D**). Lastly, a hepaticojejunostomy was placed. The operative time was 230 minutes, with intraoperative blood loss of 120 mL. At pathology, an R0 resection was confirmed of a hilar cholangiocarcinoma arising from the right bile duct (Bismuth type IIIa) with microvascular invasion. Tumor thrombus extension involved the right portal vein and the branches for segments V and VIII. TNM pathological staging was pT2 pN0 G2. After surgery, the clinical course was complicated by a chylous fistula that was treated conservatively. The patient was discharged on the 22nd postoperative day with post-operative adjuvant chemotherapy. Twenty-two months after surgery, the patient is alive without any evidence of recurrence.

A briefing among surgeons was performed with the aim of elucidating the quality of the model used. The recently-proposed questionnaire by Streba et al. was adopted (**1**). Eight different questions were asked regarding similarity with the actual tissue, weight, shape, and size accuracy, the ease of maneuvering or interacting with the model, and improved anatomic knowledge or management planning. According to the observed results, the model was not similar to the actual tissue or liver weight. On the contrary, the printed model had accurate dimensions. Moreover, the model was straightforward to use, providing ample opportunity for interaction, obtaining detailed anatomical knowledge of the patient, and most importantly to design a "tailored" pre-operative management plan. Shape accuracy and ease of maneuvering the model or its parts were in intermediate agreement (**Table 1**).

DISCUSSION

In recent years, 3-D printing technology has become more available to a broader audience due to the rapid growth of commercial 3-D printers and the growing experience with this technology (**2**). Use of 3-D printed models has been proposed in medicine as a useful tool in the fields of education, surgical training simulation, patient-doctor communication, diagnosis, and pathological classification (**3-5**). More specifically, 3-D printing facilitates the creation of accurate anatomical models in relatively simply, easing the planning of complex surgical procedures (**6-8**). Thus, information in regard to anatomical aspects such as structural depth, topological characteristics, and spatial relationships becomes understandable, facilitated by the visualization and the manipulation of physical 3-D printed models. 3-D printing is already extensively used in maxillofacial and orthopedic surgery (**9-10**), although several other subspecialties are discovering its benefits (**11-13**). Among them, liver surgery should emerge as one of the preeminent candidates for reaping great advantages from the creation of 3-D-printed models (**14-16**). Deep understanding of liver anatomy prior to surgery is of

paramount importance to preoperative planning of any liver resection, primarily in cases of anatomical abnormalities or vascular tumor encasement (**17-18**).

We reported in the present study a case of 3-D printing technology successfully adopted in the surgical planning of a Klatskin tumor resection requiring complex vascular reconstruction. To date, < 20 cases of hepatic resection supported by pre-operative 3-D technology have been reported (**14-16**). We identified three systematic reviews that address this argument (**14-16**), one of them explicitly focusing on the contribution of 3-D models to surgical planning (**16**). To our knowledge, only one case of 3-D reconstruction for hilar cholangiocellular cancer has been reported (**19**), but the present study is the first one showing the use of a 3-D model for pre-operative planning of the surgical strategy used for cholangiocarcinoma resection.

With the aim of confirming the usefulness of this tool, we adopted a quantitative/qualitative evaluation of the model using a questionnaire (**1**). According to the observed results, we noted that the model was highly accurate regarding size matching and anatomical characteristics with respect to the actual liver, whereas weight and parenchymal consistency were not accurate, in keeping with prior publications (**19-24**).

Despite the most recent advanced radiological techniques used to reconstruct an excellent 3-D visualization of the liver, it may be difficult to fully understand the anatomical connections between the tumors and the surrounding complex hepatic anatomy. Therefore, 3-D printed models may present greater value compared with ordinary radiological methods alone in preoperative planning and simulation of surgical procedures (**25**).

Apart from this visual superiority, 3-D printed models also provide a valuable tactile experience (**26**). In the present case, the possibility to pre- and intra-operatively manipulate the tool enabled us to visualize in detail the connection of the tumor with the hepatic vascular and biliary structures. A combinatory use of the model and intraoperative ultrasound

improved our capability to identify the optimal dissection plane and level to cut the portal vein for the successive vascular reconstruction, enabling us to obtain an *en-bloc* specimen with minimum tumor manipulation. All of the previously reported data underline that 3-D printed models may be considered extremely valuable in clinical practice notwithstanding their current high costs and lengthy production times that might impair their practicality and feasibility.

Concerning the costs, some studies reported the use of low-cost materials, in which 3-D models created using nylon or polylactic acid polymers cost < USD $100 (**27**). Nevertheless, in the vast majority of cases, the price of a full-sized model ranges from USD $400-$2,000 (**15**). In our experience, we were able to obtain a full-sized organ with a cost of € 1,200 (approximately USD $1,400), within price ranges reported in the literature.

As for the time required to complete the entire 3-D printing process, this latter is typically composed of two different parts. The first, pre-print period, includes semiautomatic or manual segmentation of medical imaging data. This process is generally based on commercially-available software or open-source software tools, requiring up to 15 hours (**22**). The second part, consisting of the actual printing time, generally takes up to 4-5 days (**15**). In the case of scheduled surgery, a longer production time could delay the procedure, which would impair the value of pre-operative model production. In our experience, we were able to produce a tool within two days from the beginning of the pre-print time, a relatively rapid process, which falls within the customary planning interval. The ready availability of the model facilitated presurgical planning, contemporaneously merging all of the information derived from the tool and the radiological images.

We are confident that the diversity of different modalities of 3-D printing model creation proposed in the literature (**15**) will be beneficial. The high concurrence in the process should

incentivize manufacturers to reduce the costs and decrease the time required for the creation of the models.

In summary, we report the use of a 3-D printed model liver intended to faciliatate surgical plannng of a major hepatic resection of an advanced cholangiocarcinoma requiring complex portal reconstruction. Only a small number of printed tools have been reported for the surgical planning of liver tumor resection. Judging from the outcome of our case and that of others, the utility of using 3-D models in complex hepatic cases is evident. The limits of the method are mostly connected with the costs and the produciton time, that like all other technologies, are expected to decline rapidly. In the near future, we are confident that the number of 3-D tools in used in liver surgery will grow exponentially. We hope that as these tools become more widely adopted, controlled studies will be conducted to assess the value of this approach.

KEY MESSAGES

• 3-D printing tools have become more available in surgery.

• The utility of 3-D technology to planning liver surgery is evident, primarily in case of complex vascular reconstructions.

• The limits of the method are chiefly related to the costs and production time, which are expected to rapidly decrease with time.

REFERENCES

1. Streba CT, Popescu S, Pirici D, et al. Three-dimensional printing of liver tumors using CT data: proof of concept morphological study. ***Rom J Morphol Embryol.*** 2018;59:885–893.

2. Martelli N, Serrano C, van den Brink H, et al. Advantages and disadvantages of 3-dimensional printing in surgery: A systematic review. ***Surgery.*** 2016;159:1485–1500.

3. Cai B, Kanagasuntheram R, Bay BH, et al. The Effects of a Functional Three-dimensional (3-D) Printed Knee Joint Simulator in Improving Anatomical Spatial Knowledge. *Anat Sci Educ.* 2019;12:610–618.

4. Jones DG. Three-Dimensional Printing in Anatomy Education: Assessing Potential Ethical Dimensions. *Anat Sci Educ.* 2019;12:435–443.

5. Gomes EN, Dias RR, Rocha BA, et al. Use of 3-D Printing in Preoperative Planning and Training for Aortic Endovascular Repair and Aortic Valve Disease. *Braz J Cardiovasc Surg.* 2018;33:490–495.

6. Chen Y, Jia X, Qiang M,et al. Computer-Assisted Virtual Surgical Technology Versus Three-Dimensional Printing Technology in Preoperative Planning for Displaced Three and Four-Part Fractures of the Proximal End of the Humerus. *J Bone Joint Surg Am.* 2018;100:1960–1968.

7. Bhadra D, Shah NC, Arora A, et al. Deducing a surgical dilemma using a novel three dimensional printing technique. *J Conserv Dent.* 2018;21:582–585.

8. Chandak P, Byrne N, Coleman A, et al. Patient-specific 3-D Printing: A Novel Technique for Complex Pediatric Renal Transplantation. *Ann Surg.* 2019;269:e18–e23.

9. Lal H, Patralekh MK. 3-D printing and its applications in orthopaedic trauma: A technological marvel. *J Clin Orthop Trauma.* 2018;9:260–268.

10. Wauters LD, Miguel-Moragas JS, Mommaerts MY. Classification of Computer-Aided Design-Computer-Aided Manufacturing Applications for the Reconstruction of Cranio-Maxillo-Facial Defects. *J Craniofac Surg.* 2015;26:2329–2333.

11. Lin J, Zhou Z, Guan J, et al. Using Three-Dimensional Printing to Create Individualized Cranial Nerve Models for Skull Base Tumor Surgery. *World Neurosurg.* 2018;120:e142–e152.

12. Hummelink S, Verhulst AC, Maal TJJ, et al. Applications and limitations of using patient-specific 3-D printed molds in autologous breast reconstruction. *Eur J Plast Surg.* 2018;41:571–576.

13. Soejima Y, Taguchi T, Sugimoto M, et al. Three-dimensional printing and biotexture modeling for preoperative simulation in living donor liver transplantation for small infants. *Liver Transpl.* 2016;22:1610–1614.

14. Witowski JS, Coles-Black J, Zuzak TZ, et al. 3-D Printing in Liver Surgery: A Systematic Review. *Telemed J E Health.* 2017;23:943–947.

15. Perica ER, Sun Z. A Systematic Review of Three-Dimensional Printing in Liver Disease. *J Digit Imaging.* 2018;31:692–701.

16. Soon DS, Chae MP, Pilgrim CH, et al. 3-D haptic modelling for preoperative planning of hepatic resection: A systematic review. *Ann Med Surg (Lond).* 2016;10:1–7.

17. Yang T, Lin S, Xie Q, et al. Impact of 3-D printing technology on the comprehension of surgical liver anatomy. *Surg Endosc.* 2019;33;41141–41147.

18. Xiang N, Fang C, Fan Y, et al. Application of liver three-dimensional printing in hepatectomy for complex massive hepatocarcinoma with rare variations of portal vein: preliminary experience. *Int J Clin Exp Med.* 2015;8:18873–18878.

19. Takagi K, Nanashima A, Abo T, et al. Three-dimensional printing model of liver for operative simulation in perihilar cholangiocarcinoma. *Hepatogastroenterology.* 2014;61:2315–2316.

20. Zein NN, Hanouneh IA, Bishop PD, et al. Three-dimensional print of a liver for preoperative planning in living donor liver transplantation. *Liver Transpl.* 2013;19:1304–1310.

21. Bucking TM, Hill E, Robertson JL, et al. From medical imaging data to 3-D printed anatomical models. *Plos One.* 2017;12:e0178540.

22. Perica E, Sun Z. Patient-specific three-dimensional printing for presurgical planning in hepatocellular carcinoma treatment. *Quant Imaging Med Surg.* 2017;7:668–677.

23. Takao H, Amemiya S, Shibata E, et al. Three-dimensional printing of hollow portal vein stenosis models: a feasibility study. *J Vasc Interv Radiol.* 2016;27:1755–1758.

24. Choi YR, Kim JH, Park SJ, et al. Therapeutic response assessment using 3-D ultrasound for hepatic metastasis from colorectal cancer: application of a personalized, 3-D-printed tumor model using CT images. *Plos One.* 2017;12:e0182596.

25. Javan R, Herrin D, Tangestanipoor A. Understanding spatially complex segmental and branch anatomy using 3-D printing: liver, lung, prostate, coronary arteries, and circle of Willis. *Acad Radiol.* 2016;23:1183–1189.

26. Matsumoto JS, Morris JM, Foley TA, et al. Three-dimensional physical modeling: applications and experience at Mayo clinic. *Radiographics.* 2015; 35:1989–2006.

27. Watson RA. A low-cost surgical application of additive fabrication. *J Surg Educ.* 2014;71:14–17.

TABLES

Table 1. Quality evaluation of the 3-D printed model provided by the surgical team.

Question	Strongly disagree	Disagree	Partially agree	Agree	Strongly agree
Texture feels natural	YES	NO	NO	NO	NO
Weight accuracy	YES	NO	NO	NO	NO
Shape accuracy	NO	NO	NO	YES	NO
Size accuracy	NO	NO	NO	NO	YES
Easy to maneuver	NO	NO	YES	NO	NO
Easy to interact with	NO	NO	NO	NO	YES
Improve anatomic knowledge	NO	NO	NO	NO	YES
Improve management decisions	NO	NO	NO	NO	YES

FIGURES

Figure 1.

Figure 1A. CT scan showing the Klatskin tumor (red arrow) encasing the right portal vein

Figure 1B. 3-D coronal reconstruction of the liver derived from the CT scan images. The tumor corresponds to the yellow area.

Figure 1C. 3-D coronal only vascular reconstruction of the liver (hepatic parenchyma digitally removed) derived from the CT scan images. The tumor corresponds to the yellow area.

Figure 1D. The final version of the 3-D printed model of the liver. The tumor corresponds to the purple area.
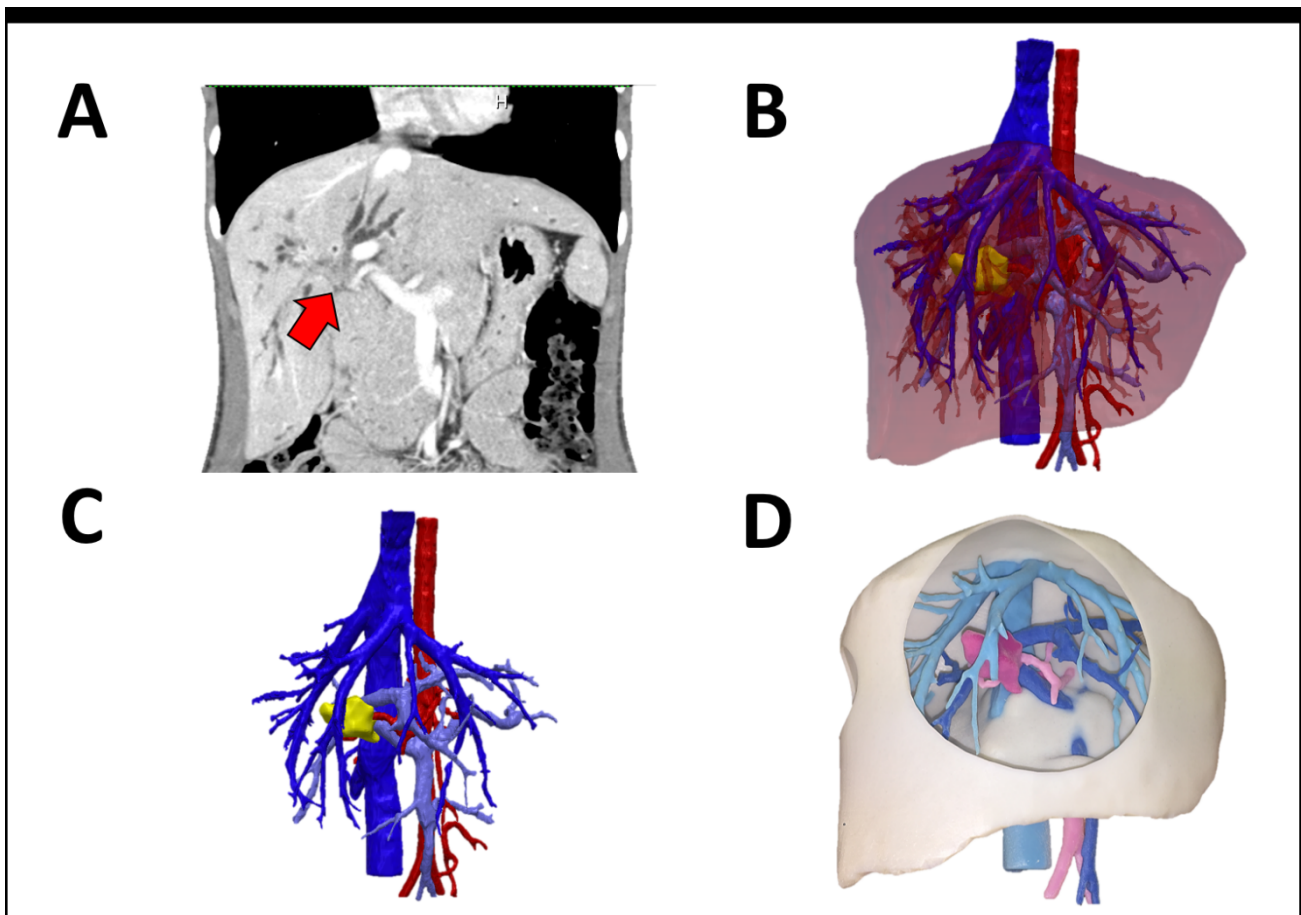
Figure 2

Figure 2 A. The printing process of the 3-D model.

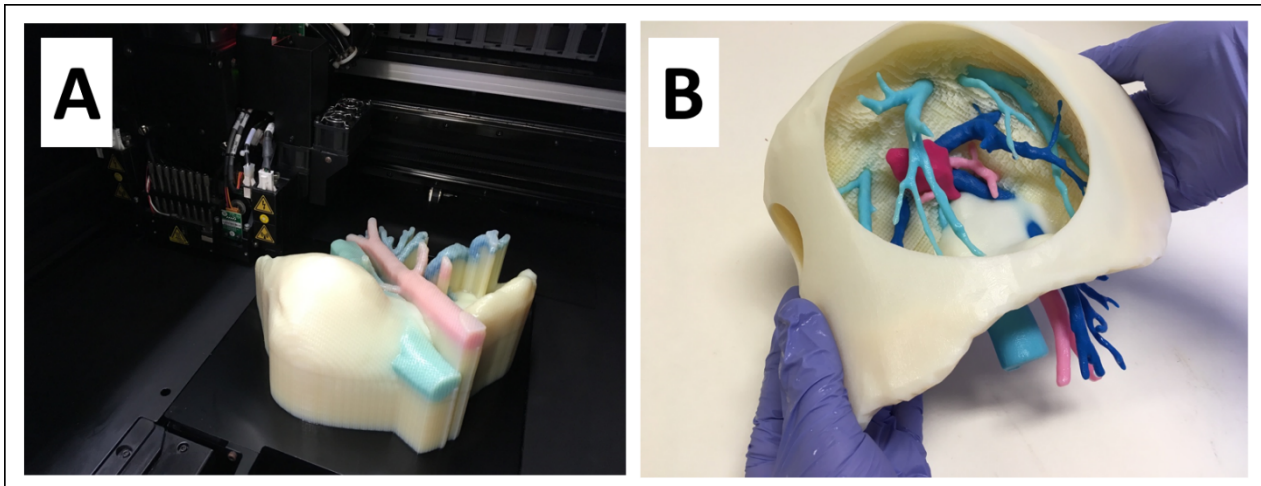**Figure 2B.** The final result of the 3-D printing process.

Figure 3

Figure 3A. A detailed image of the vascular structures observed in the tool: the vascular encasement of the portal system (in dark blue) is clearly observable.

Figure 3B. A scheme explaining the relations between the tumor (in light yellow) and the portal system (in dark blue). The tumor thrombus (in purple) is present along the branches for segments V and VIII. The dashed lines show the places in which the main portal trunk and the left portal branch were interrupted and eventually re-anastomosed.
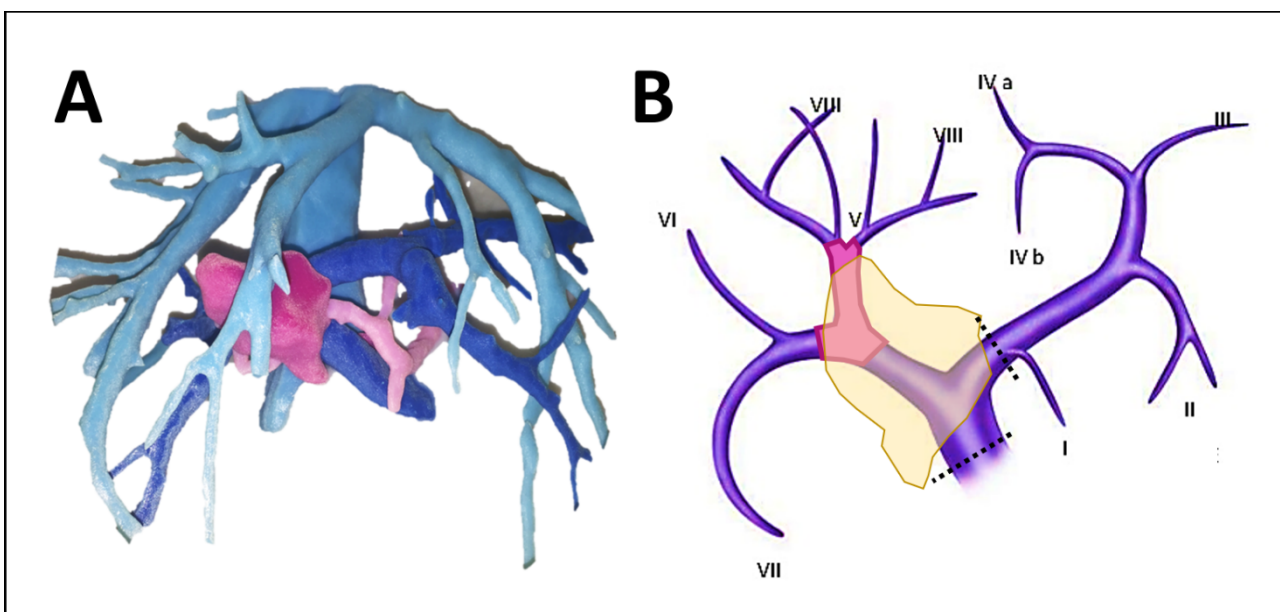
Figure 4

Figure 4A. After the division of the right branch of the hepatic artery and of the common bile duct, the left portal branch is passed using a right angle.

Figure 4B. After the *en-bloc* section of the portal vein, a vascular termino-terminal reconstruction is done between the portal left branch and the distal part of the portal vein.

Figure 4C. Right trisectionectomy: the parenchymal dissection is performed.

Figure 4D. Final view of the operative field showing the retro-hepatic inferior cava vein (*), the stump of the right hepatic vein (yellow arrow) and the anastomosis between the left
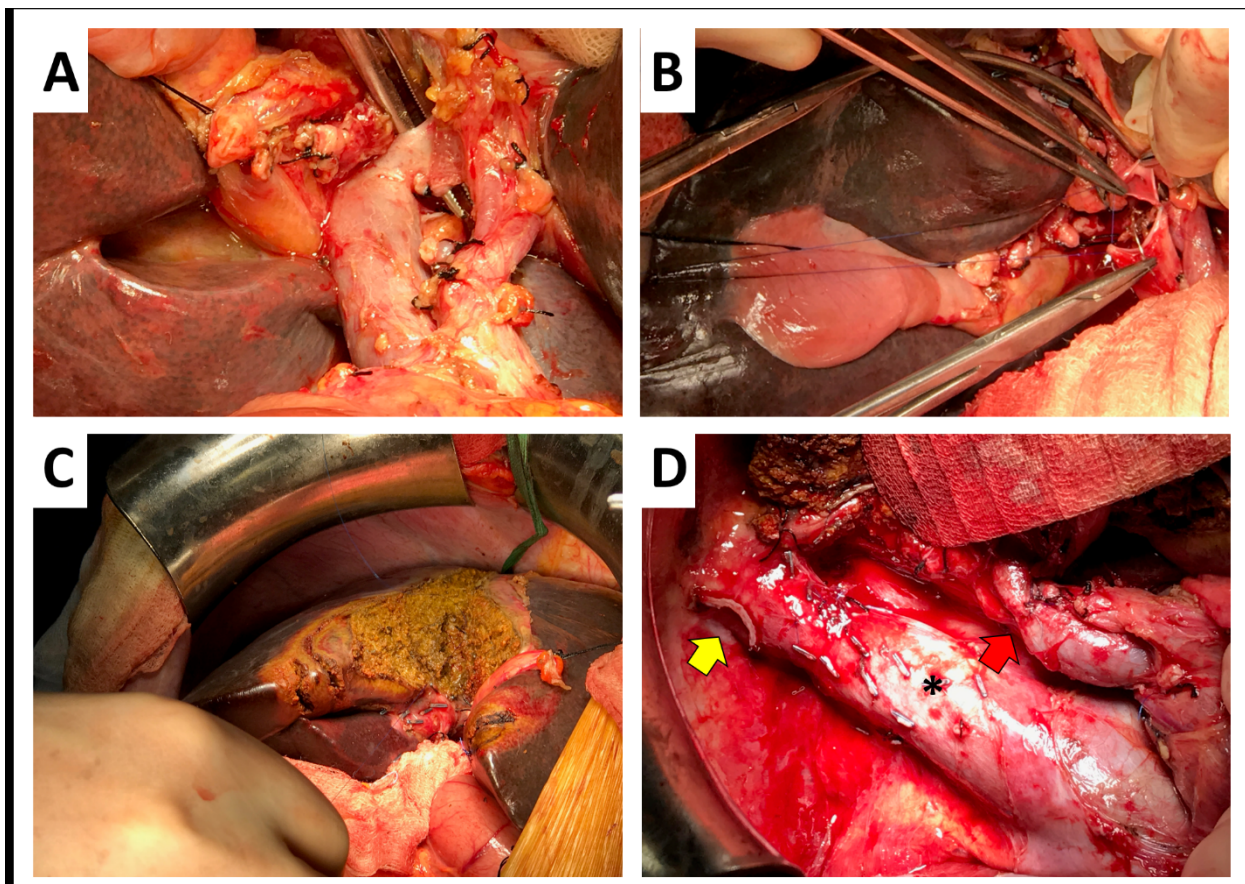
portal branch and the portal vein (red arrow).