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REVIEW

The role of 3D printing, virtual and augmented reality in liver surgery: The technological imperative!

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ABSTRACT

Technological innovation has been proven a valuable tool in the modern era of liver surgery. 3-dimensional (3D) printing along with virtual and augmented reality (VR and AR), as part of this technological development, can contribute to avoid high-risk complications during liver surgery. More specific, in terms of liver transplantation, small-for-size and large-for-size syndromes can be avoidable with timely utilization of these modalities, by measuring the volume of both the donor's liver and recipient's abdomen. Additionally, artificial bio-printed livers have the potential to minimize the shortage of grafts, yet this novelty needs further development. The same artificial livers can participate in clinical trials of drugs' hepatotoxicity, removing the risk from living human beings. In hepatic resection, the employment of VR can help hepatobiliary surgeons identify and comprehend the complexity of the anatomic structures of liver parenchyma, especially the related vessels and biliary branches. VR and AR represent new alternatives for the traditional 3D printed models, especially after the increasing availability of relevant medical applications outweighing the disadvantages of 2D models. Apart from their surgical applications, VR and AR can play a valuable role with regards to medical education, not only for medical students, but also for surgical trainees as several studies have shown. Certain limitations, such as those associated with the cost and the time required to generate a 3D prototype, tent to be eliminated due to VR and AR. Unambiguously, further evolution of this technology will lead to wider application for the best of patients' care and perfection of surgical outcomes.

Key words: 3D printing, virtual reality, augmented reality, liver surgery; liver transplantation, large-for-size syndrome

INTRODUCTION

Liver surgery, including liver resection and liver transplantation, has evolved radically over the last few decades. Hepatic surgery demands meticulous attention to detail so that high-risk complications be avoided. Technological innovations have played a key role in that evolution, not only for clinical, but also for educational purposes. The unique anatomical structure of the liver necessitates the preoperative planning and simulation of liver anatomy including the intrahepatic liver vessels.[1] At present, 3-dimensional (3D) printing along with virtual and augmented reality (VR and AR) represent the most cutting-edge technologies providing this information to the surgeons.[2] Technically, 3D printing is the process of creating a solid object of any shape based on a digital model having already proved its efficacy in several fields of surgery,[3–5] providing a bridge between digital 3D models and the real world. VR and AR eliminate the necessity of a tangible model,

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yet their daily clinical usage is deficient due to lack of task realism.[6] In this review, we will illustrate not only the current but also the future applications of these technological innovations in liver surgery, discussing possible disadvantages that might have.

FROM 2D TO 3D TECHNOLOGY

Through the years, hepatobiliary surgeons tried to use technological innovations to achieve better operative results. At first, computed tomography (CT) and abdominal ultrasound were utilized for assessing liver anatomy before or during the operation. However, both of them produce a 2D image which is far less superior than a 3D one.[7] The creation of a real-sized 3D printing model commences with the images extracted from a contrast CT scan and converted to a stereolithography (STL/SLA) file format with a 3D image analysis system.[8] In addition to the dataset of dynamic CT, drip infusion cholangiography CT can be used. The extracted files provide the input data to the 3D printer and the 3D solid object is independently created by additive manufacturing using acrylic-based photopolymer resin.[8] A 3D printer works similarly to a traditional printer, however instead of placing a single layer of ink on paper, the machine lays down successive thin layers of a material to form a 3D object.[9] In our case, the solid object is a replica such as liver graft for liver transplantation or liver resection.[10] The thickness and positional relationship of each vessel can be adjusted and any unnecessary structures can be deleted.[8] By selecting carefully different casting materials and dyes, an assortment of colors, transparencies, textures and consistencies can be produced.[11] Recently, Boedecker *et al.* have developed a virtual reality application which enables the presentation and interaction of preoperative 3D liver models in a comfort way, gaining positive feedback from a few hepatobiliary surgeons.[12] Further prospective trials are necessary to evaluate this interesting technology extension.

The choice of radiological data contributing to the final 3D model depends on how well each hepatic structure is displayed by collected scans.[13] In most cases, the CT images are able to depict the hepatic artery due to the arterial contrast, but other liver structures might be poorly visualized.[13] In this occasion, magnetic resonance imaging (MRI) and multidetector CT scan can be employed, with the latter producing images of acceptable resolution in thin, 3-mm slices.[13] Obtaining thinner slices with MRI entails higher cost and prolonged time. Various liver specific contrast agents are available for use with MRI or multidetector CT scan, in order to maximize the imaging quality.[13]

In a systematic review, Witowski *et al.* showed that the approach to create 3D models varied significantly in several aspects.[14] The most popular fabrication method was the PolyJet/MultiJet technique, followed by the selective laser sintering (SLS) and finally the fused deposition modeling (FDM).[14] All biomaterials for 3D printing are harmless to human body and strong and rigid enough to maintain their shape while fitting the liver graft to the 3D printed model.[15] The choice of technique was crucial on the final model along with time and printing cost. They underlined that, although the PolyJet and SLS technologies allow relatively easy and quick print times, their availability is limited and the costs of creating models on those machines may be significantly higher compared to using of the FDM method.[14] They also noted that the Polyjet method provides great material printing with multiple material in a straightforward manner.[14]

Undoubtedly, complex surgeries such as hepatic resection, living donor liver transplantation (LDLT) and minimally invasive procedures require profound knowledge of patients' unique anatomy (Table 1)[14]. 3D imaging is much more efficient than traditional 2D, as it allows easy calculation of the venocongestive region.[16] A major drawback of 3D imaging is the visualization of images through a 2D computer screen, which limits the sense of depth. The development of 3D printing can provide surgeons with a real indication of depth and also give the chance to manipulate the printed liver with their hands contributing to better understanding of the anatomy and its variations. As a potential alternative or adjunct to standard medical imaging techniques of CT scan and MRI, 3D printing can provide greater intuitive navigation for critical areas and also add tactile feedback.[14] The transparency of the material used for the liver parenchyma and specific color codes for vascular and biliary structures respectively, provide also important and detailed information for surgical outcomes.[7]

Briefly, the American Society for Testing and Materials International (ASTM International) recognizes seven main categories of 3D printers, classified by their materials and curing systems.[17] These are:

- Vat photopolymerization, which involves the use of a photopolymer resin, such as STL/SLA that uses ultraviolet laser to cure resin layer by layer
- Material jetting, which resembles the function of an inkjet paper printer, where the orienting material is dropped through small-diameter nozzles
- Binder jetting, which uses two base materials, a chalk powder and a liquid binder
- Material extrusion that works with thermoplastic filaments through a heating chamber, like FDM
- Powder bed fusion (also known as Selective Laser

Sintering) uses a laser in order to fuse the powdered material

- Sheet lamination
- Direct energy deposition[17]

Figure 1 and Figure 2 depict 3D liver models manufactured at the Department of Rural and Surveying Engineering in Thessaloniki.

LIVER TRANSPLANTATION

LDLT has led to the expansion of the donor pool as an alternative to deceased donor liver transplantation (DLDT), given the scarcity of liver grafts.[18] Minor hepatectomy (*e.g.*, left lateral sectionectomy, [LLS], is typically performed for pediatric LDLT and major hepatectomy (left hepatectomy or right hepatectomy) for adult LDLT. Nevertheless, LDLT is a high-risk procedure, correlated with several abdominal and biliary complications.[19] In LDLT, it is extremely important to calculate accurately the volume of a procured liver graft and plan the resection route. Accurately determining liver volume even with volumetry can be difficult and challenging. There are several factors that may create a discrepancy between the pre-transplant expected liver volume and the actual volume, such as the drainage of intrahepatic blood after procurement, dehydration of the perfused liver by hypertonic preservation solution as well as the loss of perfusion pressure after explanting the procured liver.[20,21] The clinical application of 3D printing and virtual reality might lead to a more accurate assessment of the expected liver volume. Zein *et al.* in Cleveland Clinic, Ohio, were the first who successfully reproduced prototype models of human livers based on patients' CT scans and MRI imaging.[7] They replicated the native livers of 6 patients, 3 living donors and 3 respective recipients who underwent LDLT with mean dimensional errors of less than 4 mm for the entire model and less than 1.3 mm for vascular diameters.[7]

Although 3D printing and virtual reality techniques are suitable for adult-to-adult LDLT, they can be valuable in the setting of pediatric LDLT.[11] If the pre-transplantation volumetry overestimates the volume of a procured liver, then a probable small-for-size syndrome may complicate the operation resulting to graft loss.[11] Moreover, the remnant liver of the donor must be sufficient for postoperative liver regeneration. On the other hand, a graft-to-recipient weight ratio > 4.0 is associated with increased risk of large-for-size syndrome, yet a sculptured graft can be implanted in the upper right abdominal cavity of a child in case the vasculature is properly aligned.[22] Generally, in large-for-size syndrome, the transplanted graft cannot be placed in a tiny abdominal cavity and it is associated with significantly increased risk for vascular complications such as portal vein and hepatic artery thrombosis.[11] These complications may arise from hemodynamic imbalance of the graft due to possible compression from the abdominal wall. When height and weight are not so different between the donor and the recipient, the graft usually fits into the recipient's abdomen. Nevertheless, the risk is increased in small-sized patients, particularly females. In deceased donor liver transplantation, size mismatch can occur due to limited evaluation of both the donor and the recipient, when they are operated in different hospitals.[15] In these cases, the transplant team should decide whether the graft is in adequate size based barely on visual examination.[15]

Technology of 3D printing with virtual reality can prevent all the above with the concomitant printing of both the graft and the recipient's abdomen. Soejima *et al.* in Fukuoka, Japan, created a real-sized 3D printing model of a LLS graft from a living donor with the associated abdominal cavity of an 11-month-old recipient.[10] The actual weight of the replica of LLS was almost compatible with the estimated graft volume as measured by conventional 3D volumetry.[10] Preoperative simulation by using the 3D prototype gave the surgeons a real sense of the size of the reduced graft which was too large to be transplanted to the initial form.[10] As a result, a small segment of the replica was trimmed off and then the remnant portion was fitted to the recipient's replica well.[10] A reduction of the LLS graft was later performed in situ which corresponded to a graft-to-weight-ratio of 3.8%.[10] The authors concluded that 3D printing can be very effective for the prevention of large-for-size syndrome in pediatric LDLT.[10] More recently, a group in Tapei, Taiwan, used 3D printing for medial segment graft in pediatric LT, in an effort to avoid injury to the right hepatic lobe and the lateral segment which can be used for another two recipients.[23] Compared to the standard pediatric liver transplantation, medial segment graft has two dissection planes and much more complex vascular and biliary anatomy which increase the risk of complications.[23] Park *et al.* in Seoul, South Korea, also endorsed 3D printing model by using it in 16 patients (adults and children) to prevent large-for-size syndrome.[15]

3D BIOPRINTING

Shortage of liver donors is the most crucial barrier to the broader application of liver transplantation. A novel idea is the use of artificial bio-printed livers consisting of available hepatic cells, yet it is quite demanding task due to low viability of hepatocytes.[24] Human-induced pluripotent stem cells are the ideal cells to use for this application due to their ability to self-renew indefinitely. The method involves scaffolds as matrices to load cells. These scaffolds can be fabricated from either naturally

Table 1: Indications of 3-dimensional printing in the field of liver surgery

Indication	3D printing role
Living donor liver transplantation	Presurgical planning of donor resection and evaluation of graft volume to the recipient's abdomen
Liver transplantation	Minimize current shortage of organs with synthetic liver graft by bioprinting
Drug hepatotoxicity	Evaluation of drug hepatotoxicity with synthetic bio-printed livers
Liver tumor	Presurgical plan of tumor resection
Medical education	Fabrication of suitable organs for anatomy and surgical education for medical students and trainees

derived or synthetic polymers, and tend to attach, proliferate and expand throughout the entire structure before they develop their own extracellular matrix.[25] For liver bioprinting, investigations suggested that intercellular adhesion was important in order to increase the cell survival rate. In addition, non-parenchymal cells as portal fibroblasts, sinusoidal endothelial cells, hepatic stellate cells and Kuppfer cells play significant roles in certain liver functions.[25] Several groups have described their efforts, revealing a promising alternative technology for liver tissue regeneration and even for artificial liver.[26–29] A crucial factor for enhancing the hepatocyte viability *in vitro* is the biocompatibility of hydrogels and multiple co-cultured cells. Biological complexity, reproducibility and durability of 3D livers are continuously improving with the aid of novel printing procedures such as the NovoGen bio-printing system.[30] Bioprinted liver spheroids embedded in hydrogel can also be utilized in order to protect the cells from the negative effects by shear stress during printing process and recapitulate the volumetric cell-cell interactions.[30] Lastly, 3D bio-printed liver tissues can facilitate the accurate prediction of drug hepatotoxicity and liver injury *in vitro*, as they mimic human liver response to exogenous drugs.[31] Consequently, they can reduce the costs of drug development and attenuate risk in clinical trials when toxicity cannot be evaluated directly in animal models.

LIVER RESECTION

Another key concept of 3D printing and virtual reality is their ability to create structures with visible interior borders[11] and therefore assist with preoperative surgical planning and intraoperative guidance, regarding the more intricate hepatic tumors. *In vivo*, the surgeons are dissecting opaque brown-colored liver paranchyma, with the risk of unproperly resection depending on the surgeon's skills and experience. Consequently, just 1 cm deviation from the preplanned resection line might result in migration into another segment, especially around the hilum.[11]

3D printing can be a valuable tool for the surgeons, especially during curvilinear hepatic resection of right liver, as the right subphrenic dome portion is very deep and resection requires a full mobilization.[11] In a prospective pilot study the use of patient-specific 3D printed livers was compared with conventional 2D images in six consecutive patients with complex liver tumors.[32] In three of the six patients the preoperative plan was altered after the anatomical relationship of the tumor with adjacent structures in the 3D model having been reviewed.[32] Additionally, surgeons felt more confident with use of 3D model for the identification of intra and extrahepatic structures. Souzaki *et al.* reported the successful use of 3D printing in a 3-year-old patient diagnosed with hepatoblastoma.[33] The tumor was adjacent to the portal hepatis while she had undergone neoadjuvant chemotherapy prior to the resection.[33] Cheng *et al.* used 3D printing for further guidance in laparoscopic hepatectomy, adjusting the surgical strategy in 4 out of 24 patients after real-time navigation of 3D technology and indocyanine green fluoroscopy.[34] All final pathological microscopic R0 margins were negative in 3D group, while two out of 30 were positive in the non-R0 group, yet without reaching statistical significance.[34] There were no differences in postoperative complications, mortality, operation time, estimated blood loss and conversion to laparotomy between 3D and non-3D groups.[34] Lastly, a systematic review by Perica *et al.* demonstrated the feasibility and accuracy of 3D printed models in replicating hepatic anatomy and also in preoperative planning and simulation of surgical interventional procedures.[35]

MEDICAL EDUCATION

Beyond clinical contribution, 3D printing, VR and AR can play a major role in medical education. 3D realistic and patient-specific models of different organs may appear superior to 2D and 3D images to medical students and trainees.[36] Jones *et al.* showed the feasibility of creating 3D models of different diseases of various organs for medical education purposes with concomitant surveys of surgical educators and trainees been positive about the project.[37] In a study conducted by Kong *et al.*[38] both 3D printed and 3D virtual reality models were found to significantly improve understanding of the hepatic anatomy when compared to the traditional teaching method. It should be noted however, that there was no significant differences

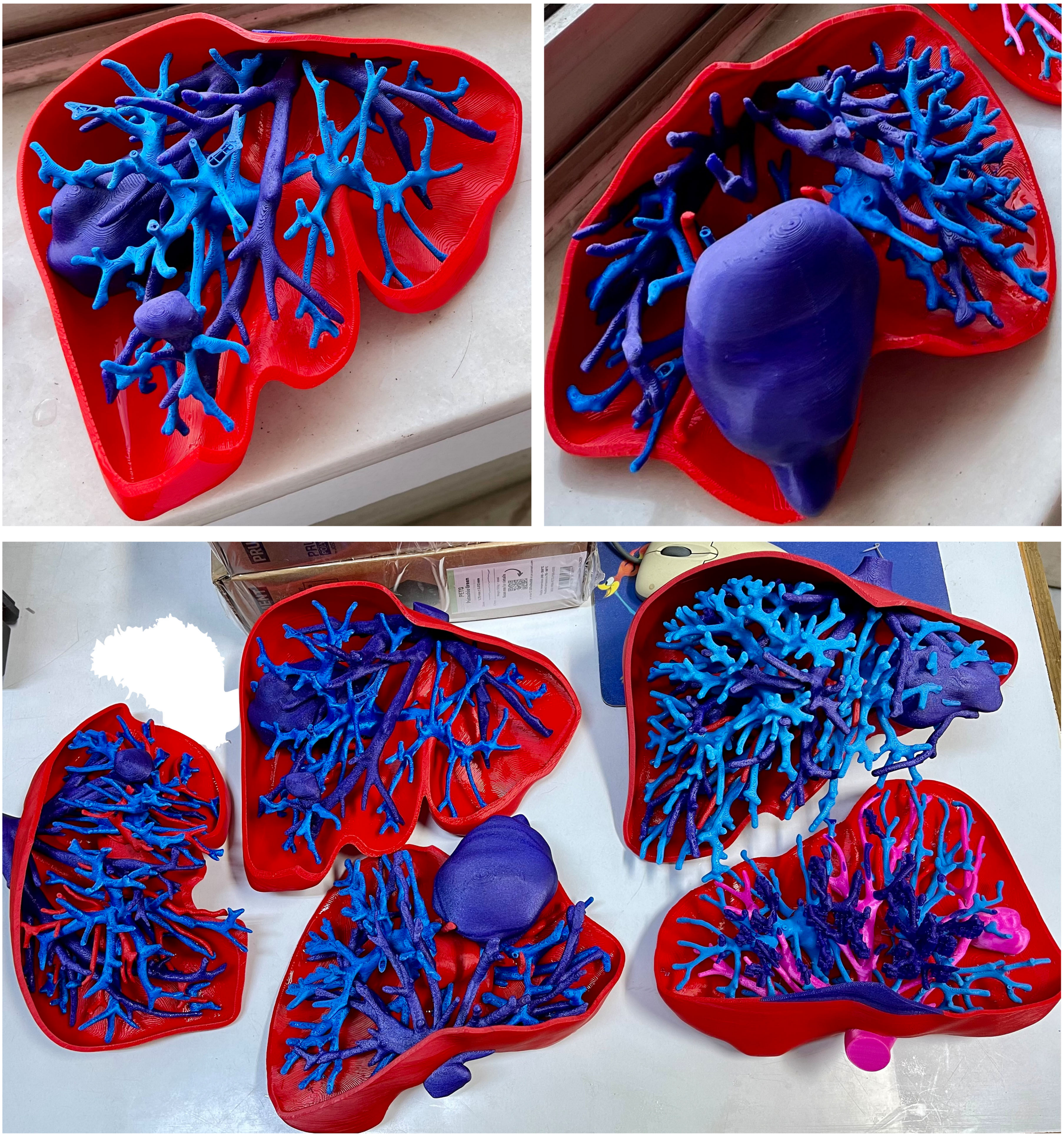

Figure 1. 3D printed model with fused deposition modeling (FDM) technology. Blue: portal vein; purple: hepatic vein and liver tumor; red: hepatic artery and liver parenchyma.

between 3D printed models and 3D visualization in each index of assessment.[38] Immersive virtual reality can improve medical education due to the interactive use and the possibility to interact with multiple participants and over distances.[12] The same conclusion was drawn. from another study that evaluated virtual reality training in 57 medical students and 35 resident surgeons.[39] Should the cost for 3D decreases over time on account of increasing competition and market pressures, 3D printers will become available in most medical schools and academic centers providing the anatomic models with necessary information for surgical education.[39]

In another study, Javan and Jeman developed a 3D printed liver model that contained, apart from the hepatic parenchyma and the associated vessels, abscesses

Figure 2. 3D printed model with fused deposition modeling technology combined with Mosaic Pallete 2s machine. pink: hepatic vein, green: portal vein, red: liver parenchyma and arteries, white: supportive structure. **A**. 3D model inside the printer. **B**. 3D model outside the printer. **C**. 3D liver model with fused deposition model technology and resin fill. **D**. Previous model before the resin-fill. **E** and **F**. 3D liver model with fused deposition model technology. blue: portal vein; purple: hepatic vein and liver tumor; red: hepatic artery and liver parenchyma; the transparent segment represents half of the hepatic parenchyma and complements the rest of the model.

and tumors in order to allow simulation of interventional procedures such as stent placement during transjugular intrahepatic portosystemic shunt procedure (TIPS), or percutaneous cholecystostomy tube placement.[40] They also created an interactive virtual tutorial on liver anatomy for teaching the segmental anatomy and planning preoperatively the hepatectomy virtually.[40] In spite of 3D's potential for educational purposes, the true challenge is to create patient-specific models depicting each patient's specific anatomical structures in order to represent realistic conditions for clinical application.

LIMITATIONS

This technology can significantly help liver surgeons in the operating field, but it still has certain limitations. 3D printing models are based on imaging so they will be prone to imaging errors. The level of accuracy rendered by these models seems to be highly acceptable with small margins of error compared to the explanted native livers.[7] Secondly, due to its relatively high cost, 3D printing may not be used in routine surgery. The exact cost has not been fixed yet, whereas the actuarial cost of a high-quality full-sized liver model printed with photopolymer resin (TangoPlus) can overcome 2,000$.[10] This number is just an estimate and varies according to the fabrication type, with the PolyJet being the most expensive,[14] while other authors report lower costs (15$).[41] By using low-cost materials like silicon, nylon plastic or polylactic acid costs can be reduced drastically,[42] yet this process requires more manual work in the final phase and is more time consuming due to long curing period[43].

At present, time seems to be against the use of 3D printing, as it usually requires more than a day to generate the 3D prototypes.[11] Until the period of model preparation is shortened, the technique cannot be employed in emergency cases. Progressively shorter development times and better printing technology are likely to expand the use of 3D printing into other medical applications.[14,34] The first challenge is to minimize the considerable amount of time required to complete pre-print process. Data segmentation and editing for 3D printing is subject to users' experience and software environment.[35] As a result, key features for a quicker procedure are proper experience of the software used and understanding of the normal anatomy and pathology of interest.[35] Another solution to reduce time is to print only the hepatic lesions with blood vessels, bile ducts and their branches, excluding any spare liver parenchyma, yet it still remains a lengthy task.[34] Additionally, time can be shortened if multiple 3D printers are used simultaneously or number of slices are lowered.[15] Notably, Park *et al.* manufactured 3D abdominal cavity in less than 10 hours, using an FDM type printer, reporting minimal amount and cost of filaments.[15] Another factor that has to be addressed, is the lack of technicians with the requisite knowledge of interpreting medical imaging. As a result, assistance from expert radiologists and technicians in the early phases of 3D printing research is of paramount importance.[14] The intraoperative application of preoperative 3D imaging is not easy due to the absence of reliable liver surface markers that correspond to hepatic segmentation. Lastly, liver deformity after mobilization during surgery increases the difficulty level of 3D imaging use, so surgeons tend to use ultrasonography and intraoperative cholangiography for localization of vessels and major biliary branches. It could be ideal, if possible, to temporarily transfer the 3D printing graft into the real recipient abdominal cavity after total hepatectomy and observe if it properly fits into the abdomen.[10]

CONCLUSION

In conclusion, VR and AR seem to hold a leading role in terms of liver surgery nowadays. The continuous growth of these technologies, along with their vast range of application they offer, aim to alter radically the healthcare service provision and the surgical education as well. They could be an integral as well as valuable tool of medical education, representing a feasible teaching aid of intricate anatomical concepts, not only for medical students, but for surgery trainees as well. Moreover, their employment prior or during the operation contribute to increase further of safety of liver surgery, availing to a meticulous preoperative plan. Further development is required to attain these goals, with international collaborative efforts and further prospective studies to be able to promote progress in this field.

DECLARATIONS

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Author contributions
Kakos CD, Piachas A, Karolos IA and Tsoulfas G conceived and designed the study, acquired, analyzed, and interpreted the data, drafted, and critically revised the manuscript, and approved the final version of the manuscript.

Conflicts of interest
The authors declare no conflict of interests for this article.

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