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# Three-dimensional printing of liver tumors using CT data: proof of concept morphological study

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**Abstract**

*Introduction*: Hepatocellular carcinoma (HCC) currently represents a major health concern, mainly for its shifting pre-existing conditions that in turn lead to late diagnosis, thus increasing the mortality rate. An improved training of medical personnel involved in diagnosis, staging and the management of treatment is required. *Aim*: We thus aimed to transition tumor view from two-dimensional, on-screen, methods to real, palpatory three-dimensional (3D) representations that can be printed using generally available tools, thus approachable in virtually any medical setting worldwide. *Materials and Methods*: After obtaining ethical clearance, we included imaging contrast-enhanced data from 10 confirmed cases of HCC that we translated into a 3D computer render of the tumor with as much morphological data as possible. In addition, we simulated the inner structure of each tumor, simulating different stiffness levels across their respective surfaces, in order to better gauge possible necrosis or vascular particularities. This translated into 3D printed models that were obtained by using commercially available materials, experimenting with different filling methods in order to better simulate the stiffness of the lesion. *Results*: We administered a structured questionnaire to 43 students and 12 resident doctors (gastroenterologists and surgeons) that manage HCC cases. We assessed tumor morphology and the usefulness of the proposed model in everyday practice and evaluated their use in an academic environment. *Conclusions*: The proposed method provides a cheap alternative to costly medical simulators, providing both curricular advantages as well as integrating well into normal HCC medical management.

***Keywords***: hepatocellular carcinoma, three-dimensional printing, tumor reconstruction, computed tomography, magnetic resonance.

## Introduction

Hepatocellular carcinoma (HCC) represents the most common primary malignancy of the liver [1, 2]. Since its appearance is linked with a number of pre-existing conditions, identifying "at risk" populations seemed feasible at some point [3–5]. Involvement of viral hepatitis and subsequent cirrhosis was proven in large-scale studies [6–8]; however, modern epidemics such as non-alcoholic liver disease (associated with diabetes) [9–11], the ever-growing impact of alcohol consumption – even in regions previously unaffected by this harmful behavior – gave way to new candidates for HCC. Modern therapies for liver infections will most likely gradually decrease the number of HCC cases derived from viral hepatitis or cirrhosis, while the new pandemics quoted above may keep the prevalence constant [12, 13].

In this context, even though it has a slow progression, HCC it is still related to a large number of deaths every year, and any patients often are diagnosed in an unresectable stage [14]. Surgery remains the most effective resolution, either by performing a lobectomy or a full liver transplant [1, 2, 14]. However, both techniques may be associated with a higher morbidity rate due to technical difficulty when performing the procedure. Tumor location and anatomical structure of intrahepatic vessels vary from case to case, which highlights the importance of a proper tumor rendering before surgery [15]. In addition, there are few centers where liver surgery is regularly performed; therefore, training the medical staff for such procedures remains challenging for most [16, 17].

Contrast-aided computed tomography (CT) and magnetic resonance imaging (MRI) are the main options for tumor diagnosis and staging of HCC [3, 18], with an important quantification of tumor load, even though they only offer one-dimensional or two-dimensional (2D) measurement suggestions. Several solutions for semi-quantitative diagnosis were recently developed (especially when performing contrast-enhanced ultrasound), using the pattern of contrast uptake and the characteristics of tumor architecture when viewed during the main phases of these investigations [19–21].

Another factor to take into account is tumor morpho-

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logy, as the study of tissue stiffness and exterior analysis of intra-tumoral vasculature often reveals problematic areas of necrosis or a high density of vascular structures [14, 15]. Being able to correctly reproduce a scale-accurate model of the formation, along with basic data on its deformability and exterior appearance, may provide the clinician additional data when planning an intervention or when studying other options for treatment (trans-arterial chemoembolization, alcohol injection or temperature-dependent local therapies) [22, 23].

On the other hand, providing a three-dimensional (3D) tumor profile ensures some advantages, such as a more accurate measurement of tumor formation or better gauging of irregular tumor formations [24]. Along with the embedment of 3D printing technology in the medical field, the anatomy of each patient may be initially rendered on a printed monitor, thus providing a better understanding of the pathology with new contributions to therapeutic approaches. Moreover, this technique offers a more personalized approach, as each case may benefit from a 3D printing reconstruction [24].

Generally speaking, 3D imaging offers a better understanding of tumor characteristics involving nearby structures as well as vascularization developing a tumor preoperative planning suggesting a new alternative for both physician and patient [24, 25]. A major outcome is considered the transition from 2D computer screen interpretation, which might limit the therapeutic technique to a spatial recognition by 3D imaging, which might allow a better guidance for liver resections tumors. Another possible application of such techniques may be in the field of education. Physical interaction with accurate representations of the tumor, with the added benefit of a deformable inner structure that gives the tumor further realism, may help training doctors in different stages or programs to better understand the disease and better integrate the knowledge in their curricula [26–30].

Due to the availability of 3D printing technology, several research centers have used printed patterns of the liver to simulate the resection of hepatocellular carcinoma in a preoperative status [28–31]. However, 3D model printing has not really been put into practice due to the laborious printing process, and due to the high cost of 3D printers. This may change in coming years, as new methods are devised and the technology gradually becomes more accessible to more countries.

### Aim

Our aim was to devise a simple, cheap and reproducible method to provide personalized 3D representations of liver tumors, complete with stiffness data, for easy interaction and assessment.

## Patients, Materials and Methods

### Patients

Between May and July 2018, 10 consecutive patients admitted in the Gastroenterology Clinic of the University of Medicine and Pharmacy of Craiova, Romania, were assessed with contrast-enhanced CT and MRI as part of HCC diagnostic work-up.

All patients were informed that no identifying data would be collected and agreed on providing the anonymized imaging recordings. This study did not interfere in any way with their usual diagnostic and treatment plan and the study complied with all international regulations, receiving the approval of the Ethical Board of the University. The same physicians who supervised the procedures also interpreted the results, and a team of gastroenterologists, imagists, pathologists and surgeons concluded on the HCC diagnosis.

### Digital rendering of the 3D models of the tumors

We exported the digital imaging and communications in medicine (DICOM) files from the multiple phase examinations on mobile transfer media, then imported into a free-to-use application – InVesalius (Renato Archer Information Technology Center, Brazil) version 3.1.1, running on a Windows mobile workstation (Intel Pentium i7 processor, NVIDIA graphic card, 16 GB RAM memory and 256 GB SSD storage). The software could produce a digital 1:1 ratio 3D surface of the HCC formation from the selected area of interest (AOI) on each frame, in three different planes. The MRI and CT scans recorded scans at 1.5 cm intervals on the *Z*-axis, in order to obtain an accurate 3D reconstruction of the tumor mass (Figure 1).

The AOI was obtained semi-automatically by using adjusted presets for soft tissue, as well as manual editing of the tumor outline under the supervision of the radiologist, in order to ensure the optimum fidelity of the 3D reconstruction. For some of the patients, a second selection was made to highlight necrosis inside the HCC mass. Once we obtained the AOI, we used the built-in feature to compile the computerized 3D surface render of the tumor, that we exported as a "stereolithography – *.STL*" digital file.

The *.STL* file obtained was later imported into Autodesk Meshmixer (Autodesk Inc., USA) in order to further adjust the features of the tumor model and edit its structure to simulate elasticity. In order to try and replicate the difference in consistency of the tumors regions (a more dense outline and the interior liquid necrosis), we transformed the tumor files into hollow shells with a 2 mm exterior and interior wall to isolate the two regions. In the next step, we used the MeshMixer's built-in lattice hex grid pattern to fill the space between the two walls.

### 3D printing process

The *.STL* files obtained from MeshMixer were imported into the Up Studio (Tiertime Technology Co., Ltd., Beijing, China) software package for preprocessing. For printing, the software directly controlled an UP BOX+ filament 3D printer (Tiertime) featuring an enclosed cabinet and fully controllable temperature and printing scan speed conditions. For effective printing, we utilized the 1.75 mm diameter nGen_Flex black flexible filament (ColorFabb, Belfeld, The Netherlands), printed with 35 mm/s, extruder temperature of $260^0$C, and with the build platform temperature of $60^0$C. We used a layer thickness of 0.2 mm, defined the objects filling as "hollow objects", and the thickness of the surface consisted of two printed layers. When we have set the objects not to be considered as empty shells, the printer followed the internal structure of the tumors, as defined within the texture of the original CT scan.

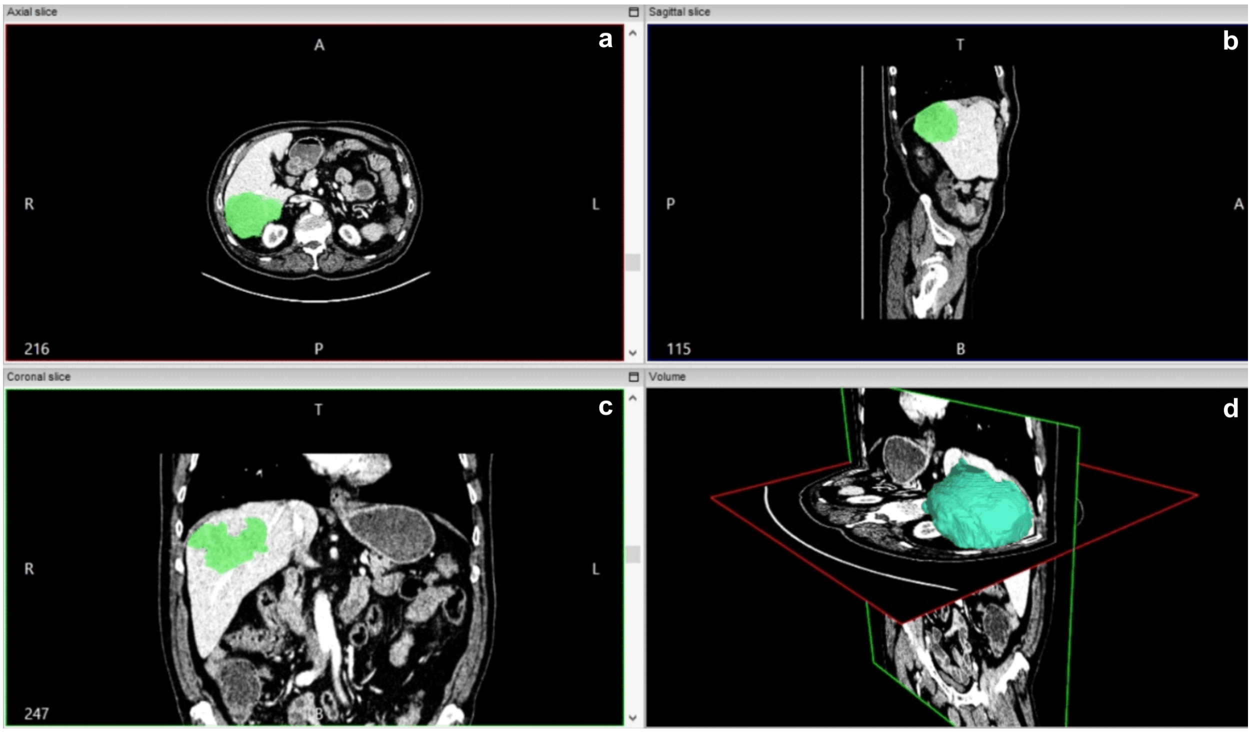



**Figure 1 –** ***(a–d) The 3D rendering software interface, showing the tumor in the three axes and the reconstructed 3D tumor model, as defined by the operator by using presents and custom filters for tissue density and texture. 3D: Three-dimensional.***

### Questionnaire evaluation of the educational value of the model

Finally, we have devised a structured questionnaire designed to assess the usefulness of the 3D printed model, which we have administered to a group of students and learning physicians, after they interacted with the printed items for one hour.

## Results

### Patient characteristics

The basic characteristics of the patients from whom we reconstructed the tumors can be found in Table 1.

**Table 1 –** ***Characteristics of the patient group***

| | | Males | Females | Total |
|---|---|---|---|---|
| **Preexisting condition** | *HBV cirrhosis* | 2 | 1 | 3 |
| | *HCV cirrhosis* | 1 | 1 | 2 |
| | *HBV + HCV cirrhosis* | 1 | 0 | 1 |
| | *HCV hepatitis* | 1 | 0 | 1 |
| | *Alcohol consumption* | 2 | 0 | 2 |
| | *NAFLD* | 0 | 1 | 1 |
| | Total | 7 | 3 | 10 |
| **Age groups** | *50–60 years old* | 2 | 1 | 3 |
| | *60–70 years old* | 3 | 2 | 5 |
| | *70–80 years old* | 2 | 0 | 2 |
| | Total | 7 | 3 | 10 |

HBV: Hepatitis B virus; HCV: Hepatitis C virus; NAFLD: Nonalcoholic fatty liver disease.

We did not choose an age group or a specific gender over the other. Viral cirrhosis was the main cause of HCC in our group (six cases – three from B virus, one with D viral co-infection, two cases with C virus and one with both B and C viral infection). Alcoholic liver disease was the cause for HCC in two patients and one had no history of viral infection or alcohol intake, having type 2 diabetes, obesity and previously diagnosed non-alcoholic fatty liver disease (NAFLD). Finally, one patient had viral C hepatitis, with no signs of liver cirrhosis.

### Morphology of 3D printed tumors

We have printed 16 tumors in total, from 10 patients. Some lesions were printed by using two different printing technologies (Figures 2 and 3). The first method considered the surface to be composed of two layers that were successively printed, relying on the internal mesh structure as a base skeleton to sustain tumor mass (Figure 4). Tumor morphology was thus respected in detail, with minimal laceration of the exterior wall. Interaction was appropriate and the printing resolution was sufficient to include all exterior detail. The deformability of the tumor inner structure varied depending on the exterior structure of the 3D printed formation.

The second method we employed relied on the original CT scan, defining the tumor wall as expressed by the inner structure of the tumor (Figure 5), rather than leaving an empty inside to be filled by the automatically generated hexagonal mesh skeleton. This resulted in a double-layered tumor with varying degrees of "thickness", resulting from actual use of more printing material. This method produced more accurate elastic data; however, the tumor was easily lacerated when it was larger in size, thus this method being only applicable to smaller lesions. We found the exterior wall structure more coarse, with more palpatory information but not necessarily reproducing actual elements of the tumor.

We present some additional rendering techniques in Figure 6, which were used as intermediate stages in defining the tumor model for later printing.

### Assessment of interaction based on a structured questionnaire

We administered a structured questionnaire to a group of 43 students and 12 resident physicians (in gastroenterology and surgery, eight gastroenterologists), who interacted with all tumors for one hour. All students had completed the questionnaires. The synthetic results are presented in Tables 2 and 3. They also had the CT and/or MRI images shown to them during the same session. Two expert gastroenterologists and one surgeon supervised the interaction and provided aid and the necessary explanations.

**Figure 2 –** ***Different examples of the same tumor, printed through the two different procedures. The difference between the two printing methods can be seen upon examining the outer texture.***

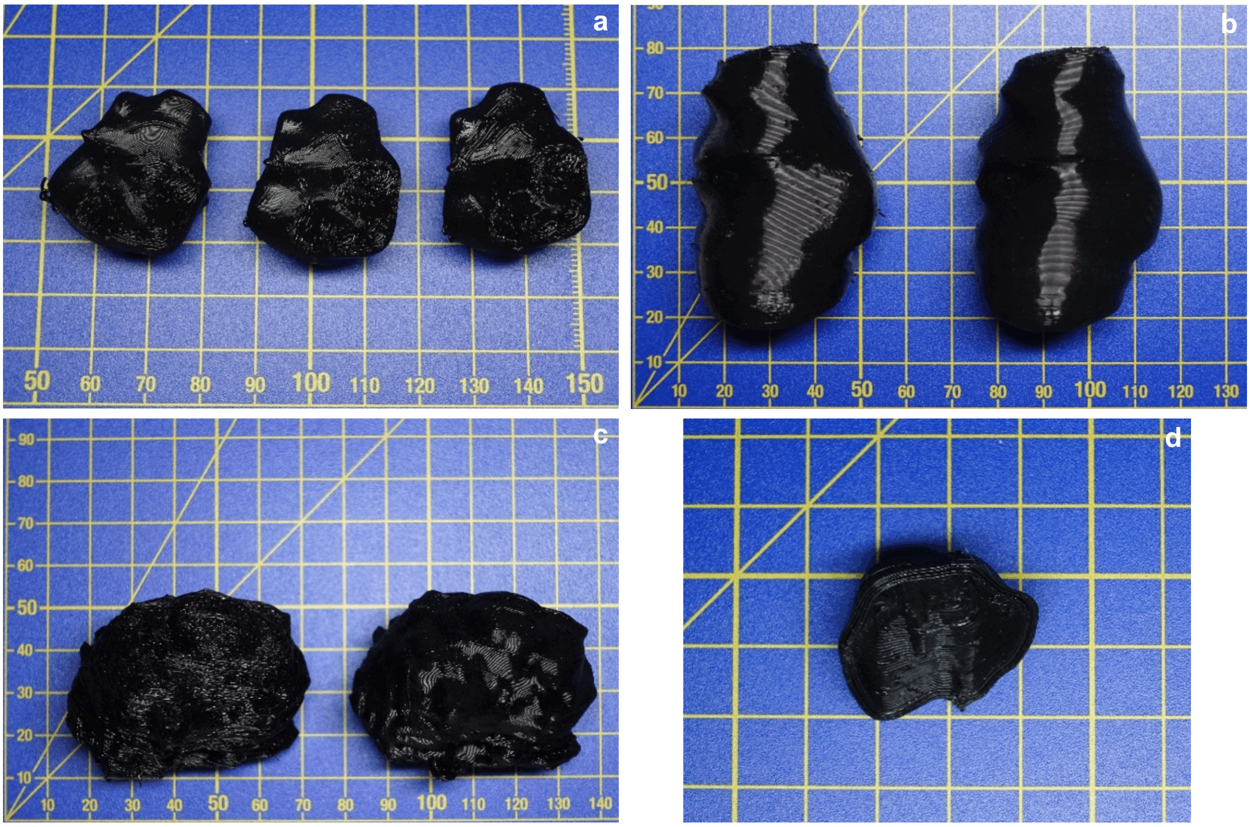
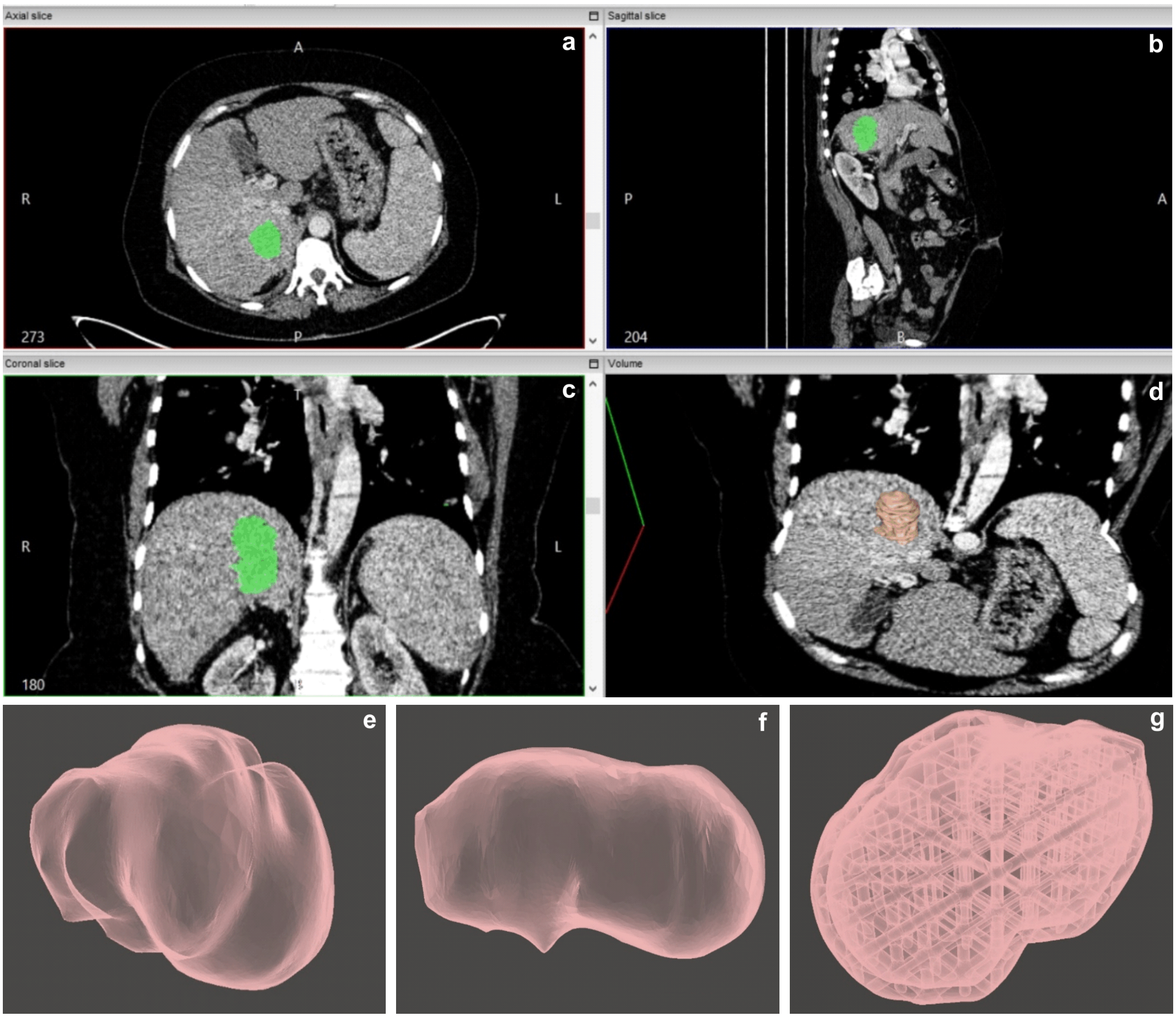



**Figure 3 –** ***(a–d) Different examples of tumors, printed through the two procedures, as described. We could observed improved texture and aspect of the exterior wall once the inner structure was automatically filled by the printer, with a generated hexagonal mesh.***



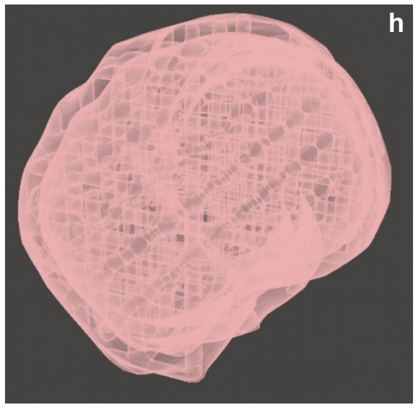




**Figure 4 –** ***(a–h) 3D rendering of a tumor by using a pre-defined inner skeleton, as extracted from CT data reconstructed in the described software. We could simulate the different texture densities by altering the structure of the sustaining skeleton. 3D: Three-dimensional; CT: Computed tomography.***

We found that all students considered the 3D printed models satisfactory in terms of size and shape representation. The majority found the weight to be as expected, with a higher percentage of partial agreement (16, 37.2%) and eight (18.6%) in disagreement. Compared to these answers, training doctors found all physical characteristics of the tumor models to be satisfactory (only 2/12 – 16.6%). A major issue identified through the questionnaire was the texture – as the printing technique required vertical layering of the material, the texture was different from expectation and did not feel organic or regular (16 responders – 37.2% – in the students group, 10 – 83.3% – in the training doctors group). However, tumor morphology was unaffected; both the students and training doctors found the model easy to interact.

Moreover, the model was found useful for gaining further insight about particular aspects of tumor morphology, with a high chance of increasing knowledge regarding each individual aspect (only three students in disagreement, no doctors). Further decisions of practicing training physicians were found to be more likely to be influenced by the interaction (all 12 in agreement, of whom six strongly agree).

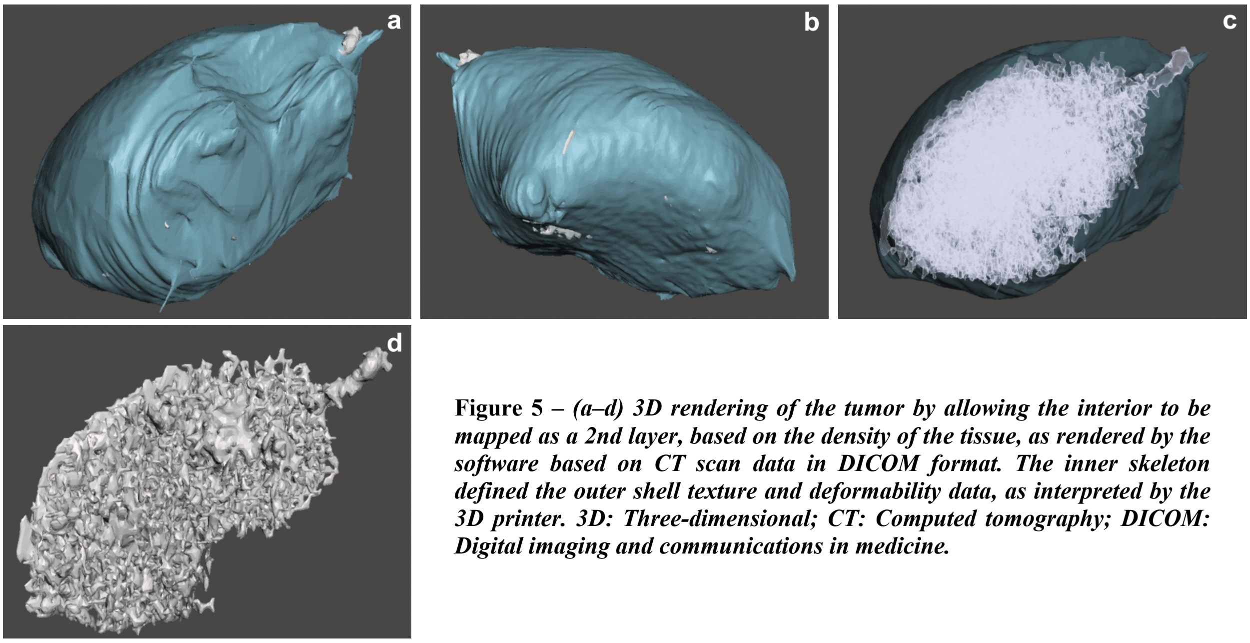



**Figure 5 –** ***(a–d) 3D rendering of the tumor by allowing the interior to be mapped as a 2nd layer, based on the density of the tissue, as rendered by the software based on CT scan data in DICOM format. The inner skeleton defined the outer shell texture and deformability data, as interpreted by the 3D printer. 3D: Three-dimensional; CT: Computed tomography; DICOM: Digital imaging and communications in medicine.***

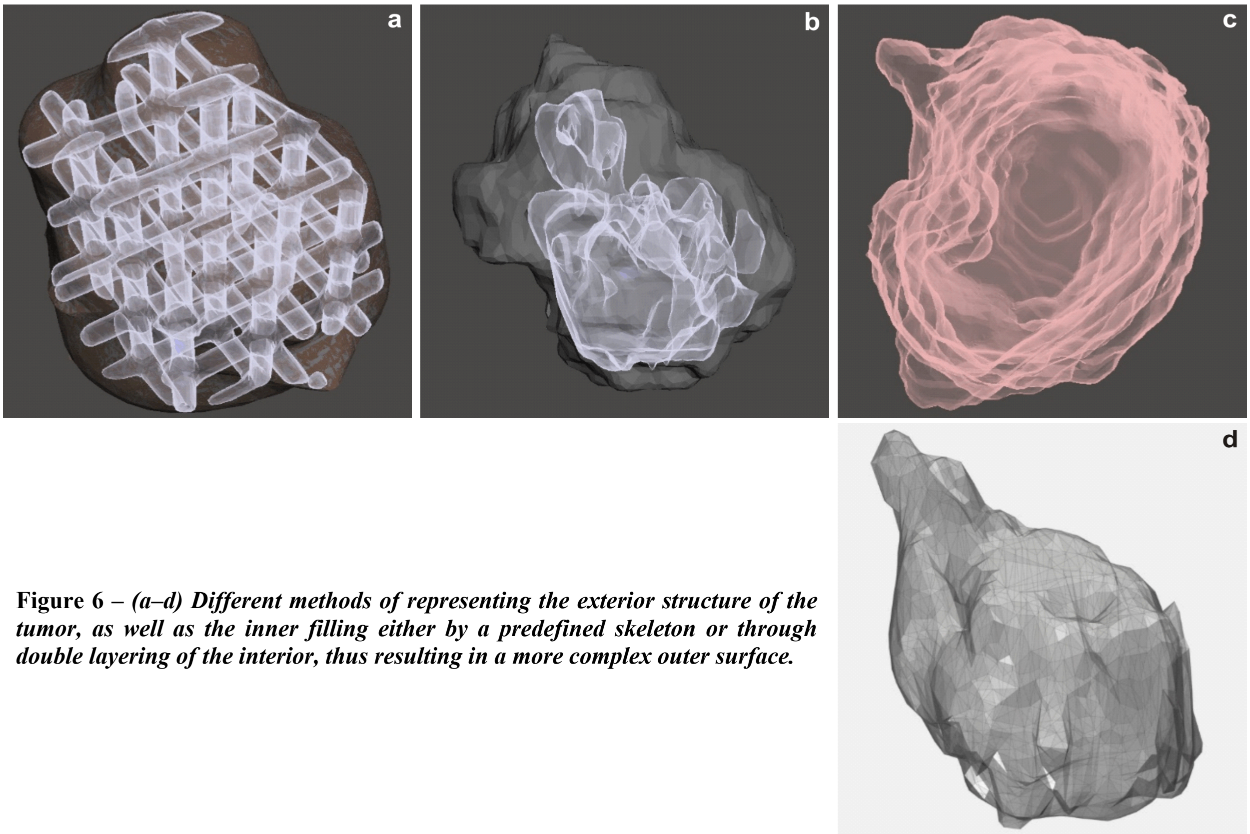



**Figure 6 –** ***(a–d) Different methods of representing the exterior structure of the tumor, as well as the inner filling either by a predefined skeleton or through double layering of the interior, thus resulting in a more complex outer surface.***

**Table 2 –** ***Answers provided by 3rd year medical students to the questionnaire that we administered after interacting with the 3D printed tumors***

| Question | Strongly disagree | Disagree | Partially agree | Agree | Strongly Agree |
|---|---|---|---|---|---|
| *The model is accurate in size* | 0 | 0 | 13 | 25 | 5 |
| *The model is accurate in shape* | 0 | 0 | 17 | 24 | 2 |
| *The weight meets your expectations of a real tumor* | 3 | 5 | 16 | 13 | 6 |
| *The model is easy to maneuver and interact with* | 0 | 0 | 10 | 19 | 14 |
| *The texture of the model feels natural* | 1 | 15 | 20 | 4 | 3 |
| *The models provided useful insight on the tumor characteristics* | 0 | 3 | 10 | 23 | 7 |
| *The models effectively increased your knowledge on the subject* | 0 | 3 | 15 | 22 | 3 |
| *These models will most likely improve management decisions* | 0 | 9 | 0 | 17 | 17 |

**Table 3 –** ***Answers provided by resident gastroenterologists and surgeons, to the questionnaire that we administered after interacting with the 3D printed tumors***

| Question | Strongly disagree | Disagree | Partially agree | Agree | Strongly Agree |
|---|---|---|---|---|---|
| *The model is accurate in size* | 0 | 0 | 0 | 5 | 7 |
| *The model is accurate in shape* | 0 | 0 | 0 | 10 | 2 |
| *The weight meets your expectations of a real tumor* | 0 | 2 | 1 | 9 | 0 |
| *The model is easy to maneuver and interact with* | 0 | 0 | 1 | 2 | 9 |
| *The texture of the model feels natural* | 1 | 9 | 1 | 2 | 0 |
| *The models provided useful insight on the tumor characteristics* | 0 | 0 | 2 | 6 | 4 |
| *The models effectively increased your knowledge on the subject* | 0 | 0 | 1 | 9 | 2 |
| *These models will most likely improve management decisions* | 0 | 0 | 1 | 5 | 6 |

## Discussions

We presented here a cheap and reproducible solution for 3D printing of liver tumors with data extracted from contrast-enhanced sectional imaging, with added stiffness data and accurate morphology. Its applications are in both student training, as well as pre-operative planning of liver surgery for HCC training, or in other therapeutic protocols.

The correctness of anatomical interpretation of a patient and the disease changes are very important in choosing the right therapeutic method [31]. A better understanding of the relationships between the anatomical structures will allow the physician to have a better picture thus choosing the optimal procedure. Our proposed model has a high fidelity, when compared to imaging data. The reconstructed virtual model underwent basically no alteration before printing, with only the interior mesh being recreated through several methods, in order to simulate different stiffness levels.

3D printing is an innovative tool that brings many benefits to the surgical education because it can be personalized from patient to patient in a relatively short time, allowing a preoperative plan to be performed as efficiently as possible [26, 27, 30]. This method may be adopted in certain situations where choosing the correct strategy occupies an important plan in the preoperative process allow a more efficient therapy. Also, printing 3D models with rendered images gives additional clues to surgeons who can preoperatively identify or manipulate the tumors and adjacent anatomical structures [31, 32]. The results from this study reveal that the quality of the preoperative plan is greatly improved when physicians have been able to inspect 3D print models.

The superiority of using the 3D print model is based on at least two key factors. Firstly, the 3D rendering of the organ offers only the possibility of viewing the anatomy on a monitor, while at the printed model there is the possibility of physical touching the target organ to appreciate its texture and shape, which gives it a major advantage. Thus, surgeons have the ability to improve the mental anatomy of the organ of each patient, thus developing eye-hand coordination to better mimic interactions in the operating room [33, 34].

Secondly, the performance of a surgeon specializing in liver surgery is directly proportional to the understanding of several types of anatomies of different patients. Traditionally, anatomy and exercise on animals do not bring obvious benefits to forming a proper preoperative plan. The emergence of technology that allows 3D printing of patient-specific models has greatly helped to understand and educate the simulated environment. In addition, the variety of materials has contributed to a better teaching process, with the texture of patterns allowing for better adaptation to specific needs [31–34].

This method may also represent a landmark for students and trainees in the learning process of both anatomy as well as the new available therapeutic methods from tumor consistency to therapeutic methods such as vascular access or surgical options. Enhancing the spectrum of comprehension may allow young physicians to explore new different approaches and enhance their process of evaluation. This may establish a foundation with new opportunities than the ones existing so far.

The ultimate goal of using printed designs would be to create a model that accurately matches the tissue of an internal organ. This would bring a great benefit to the trainee surgeons who could practice the surgery in a safe environment. This will also allow patients to have a better understanding of their disease and additionally to acquire more knowledge on the treatment that they were going to go through.

## Conclusions

Evidence-based medicine is a continuous evolving field that requires a rigorous assessment before a method may be standardized. 3D printing may bridge the gap between complex surgical techniques and the preoperative planning by creating a new generation of physicians with new opportunities in performing surgery more rapidly and more efficient. Our model may provide help in both academic settings, aiding medical students with their curricula, as well as in normal HCC medical management, providing additional detail to both gastroenterologists and surgeons.

**Conflict of interests**

The authors declare that they have no conflict of interests.

**Authors' contribution**

Costin Teodor Streba and Sorin Popescu have contributed equally to this paper and thus share main authorship.

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