POLITECNICO
MILANO 1863

SCUOLA DI INGEGNERIA INDUSTRIALE
E DELL'INFORMAZIONE

EXECUTIVE SUMMARY OF THE THESIS

Multidisciplinary evaluation of 3D models in hepatobiliary surgery

TESI MAGISTRALE IN BIOMEDICAL ENGINEERING – INGEGNERIA CLINICA

AUTHOR: Serena Bassetto

ADVISOR: Prof. ssa Veronica Cimolin

CO-ADVISOR: Ing. Daniela Motta

Dott. Christian Cotsoglou

ACADEMIC YEAR: 2021-2022

1. Introduction

Three-dimensional reconstructions are one of the developments in medical imaging that support surgeons in performing advanced surgical procedures. 3D models offer great advantages in hepatobiliary surgery due to complex individual liver's anatomy. The assets can be seen during the preoperative planning (to define the best surgical technique that fits patient's needs), during the intraoperative navigation (essential for a complete removal of small tumors with a significant response to chemotherapy), during training of new surgeons and communication with the patient and his family.
This thesis work follows the health technology assessment framework by AGENAS [1] evaluating three-dimensional reconstructions under different points of view (technical, clinical effectiveness, safety, social, economic and organizational). Context data were collected from Electronic Health Records of patients hospitalized in Vimercate Hospital (ASST Brianza, Italy).

2. Health problem and clinical context

The liver is the largest gland of the human body that performs fundamental functions such as bile production for fats digestion, coagulation factors synthetization and deposit of glycogen to balance body metabolism. Its external parenchyma covers a complex vascular structure made of two venous systems (portal and hepatic veins), arteries and bile ducts. For this reason, 3D models can help to have a clearer and broader view of what is inside the liver.
It may be affected by several pathologies that can be roughly divided into 3 different classes: acute

hepatocellular damage, chronic liver disease, biliary tract obstruction. Anyway, the fifth common type of cancer worldwide and the second most common cause of death in cancer patients is primary liver cancer [2]. The only way to definitely remove the cancer is liver transplantation and hepatectomy (a surgical procedure that involves the resection of a liver's portion). Like all invasive procedures, even hepatectomies present perioperative risk due to onset complications and comorbidities. One of them cloud be hepatic failure that occurs when an extended part of the liver is impaired. As a consequence, it's fundamental the calculation of the residual volume through the 3D model, which should not be under 25% otherwise the patient risks liver failure.

3. Description of the technology and its comparators

The generation of 3D rendering is the final output of imaging workflow in computer aided surgery systems. It can be surface-based or voxel-based, whether tissue density information is maintained. The first step is bidimensional images acquisition, typically computerized tomographs (CT) or magnetic resonance images (MRI) in DICOM standards. The quality of 3D models depends on 2D images. A consensus recommendation [3] declare that CT images must be acquired when a contrast medium is administered, scanning the arterial and venous phase during different time intervals. They should be obtained from a 64 or superior slice helical CT scanner with a cross-section thickness of 0.625-1 mm. After an appropriate pre-processing, manually or semi-automatic segmentations are performed. This process means to delineate anatomical structures trough the classification of pixels, voxels, regions, and contours. Pixels can be classified for homogeneity as belonging or not to a specific structure or based on edges that delineates intensity discontinuity. Furthermore, feature extractions can be performed also by machine learning algorithms (e.g., neural networks), able to learn patterns from existing data and applies it to new ones.

In the last years, different 3D reconstruction software has become widespread. However, in this thesis work only those used by surgeons in Vimercate Hospital have been deepened: Hyper Accuracy 3D (Medics3D, Italy), Visible Patient (Johnson&Johnson, France) and Virtual Clone (AIMS Academy, Italy). All of them require surgeon's website submission, from which he can upload 2D images, that have been previously anonymized. The feasibility of DICOM images re-identification was technically tested and then considered a low and acceptable risk. Moreover, Medics 3D and Visible Patient are both certified as medical device with CE marking, because they are able to provide extremely precise and faithful 3D models ready to use with specific surgery simulation. Instead, Virtual Clone can provide the 3D renderings after few minutes running neural networks but it still a work in progress.

4. Current use of the technology in the National Health System

For what regard the diffusion of 3D technology in Italian hospitals, Medics in 2020 had already reached over 40 hospitals in Italy, covering most of the Italian territory. However, the potential reference market is much larger, and it is estimated to grow worldwide. A further development that is catching on is 3D laboratory inside hospitals for managing 3D printers directly at health facilities even in emergency situations. It consists of a 3D workstation able to guarantee fluidity during the post-processing of radiological images and printers for physical object production. This process is strengthened by a multidisciplinary collaboration between radiologists, engineers, and technicians. Indeed, to benefit from 3D renderings human interventions remains crucial for small vessels and anatomical details.

5. Clinical effectiveness

Clinical effectiveness was analyzed through an ad hoc survey and the analysis of the difference between intra-operative and post-operative outcomes of patients whose surgical planning was done on 3D (intervention group) and on 2D (control group).

5.1 Survey

The primary aim of the survey was to determine whether 3D reconstruction improves the understanding of the relationship of the tumor with neighboring vascular structures with respect to the standard 2D CT scan imaging. Firstly, the

feasibility and the potential of the full-scale project, were tested through promising results of the pilot study. Furthermore, for the sample size and statistical power calculations, it was assumed as null hypothesis that the accuracy is the same between the two methods. Moreover, the inter-surgeon agreement is assumed to be good enough, while the trial is expected to involve a total of minimum 10 highly experienced HPB Surgeons from different tertiary centers (multicentric survey). Under this assumption, 11 independent patients were required to achieve at least 80% power to reject the null hypothesis. However, in Vimercate Hospital only five 3D renderings could have been used within the survey, hence six more patients with a particularly complex liver anatomy were retrospectively selected and their 3D rendering was made using Virtual Clone Platform. Nevertheless, these six 3D renderings need to be manually post-processed. This phase was made through a free, open-source software, called 3D Slicer, that allows the user to edit manually the segmentation.
Once all 3D models were ready, for each included patient, the surgeon answered to a standardize questionnaire about vascular invasion of 16 different structures previously looking at the bidimensional images and then they answered to the same questions looking to the respective 3D model. The score of each question has been calculated equal to 1 if the answer was equal to the operative response, while it has been calculated equal to 0 if the operative response was different from the given answer. For each combination surgeon j and patient i, the number of correct assessments made with the 2D method ($\Sigma 2Dji$ and the 3D method ($\Sigma 3Dji$) was added together, and the difference $\delta ji = \Sigma 3Dji - \Sigma 2Dji$ was computed. Finally, the average difference Δ of all surgeons was calculated as the arithmetic mean of δi. An average difference Δ greater than zero means that 3D accuracy is better than 2D.
After seventeen completed questionnaires, the overall mean was 1,72 with a p-value less than 0.001. Hence, it has been demonstrated, with statistically significant results, that using 3D renderings the accuracy in the comprehension of the relationship between the tumor and the closer vascular structures is higher than the accuracy achieved using traditionally bidimensional images.

5.2 Comparative analysis of intraoperative and post-operative outcomes.

Clinical effectiveness was also evaluated comparing retrospectively intraoperative and post-operative outcomes of operations planned with 3D reconstructions (intervention group) against surgery with 2D images (control group).
Thanks to the full integration and interoperability of different software in Vimercate Hospital, several outcomes were retrieved. The choice of which outcomes were interesting in such evaluation was made based on what was already highlighted in literature and which outcomes were actually reported [4]. Firstly, preoperative clinical data were analyzed to identify if the two groups shared similarities, because if only people with a clinical status already compromised were considered, intraoperative and postoperative outcomes could have been affected. This preliminary analysis shows a high similarity between the intervention and control group especially in those parameters that classify the general state of the patient. The only differences were related to those parameters not available for each patient, so it was difficult to compute an average within the group.
For what regard intraoperative outcomes, in the intervention group, blood loss was found to be lower even though the procedure and surgical technique do not differ particularly between the two groups. As a result, the surgery planned with 3D reconstructions has demonstrated to be more accurate. Moreover, operations performed with 3D pre-operative planning have a slightly shorter duration.
The advantages of the postoperative course are evident especially in terms of the length of the hospitalization and tumor recurrence. Indeed, if the surgery has been planned with the use of 3D, the surgeon has a more precise idea of the tumor location, and he manages to remove it completely. In addition, a surgery planned precisely according to the anatomy of the patient also leads to a shorter and more regular course of hospitalization. Thus, it was noted that cases with a higher number of complications were found mainly in the control group. However, there was not much difference between the two groups as to the variability of the type of post-operative complications: pleural effusion was the most common complication in both groups. The results of post-operative

laboratory tests made after 5 and 10 days after surgery differ considerably between the two groups. Nevertheless, in the control group the number of patients who risk liver failure was higher. This is an important result that highlight the importance of volume liver calculation.
It can be concluded that the major benefits of 3D rendering in preoperative planning led to less blood loss during surgery, less hospitalization time, and more precise surgical margins (non-tumorous tissue around a tumor that has been surgically removed).

6. Safety analysis

Safety depends on the quality of the 3D: if the rendering is not accurate enough, the surgical planning will not be adequate to the needs of the patient due to a distortion of reality. The quality of a surface rendering depends on how two-dimensional images were captured and how they were interpreted. For 3D models, both the CT scan and the MRI scan can be used, both acquired with contrast medium and in an adequate way to have the maximum of the spatial resolution. Nevertheless, the best method is the fusion of images, but it still little adopted due to the difficulty of integration in the software development phase. In addition, there must be a good interpretation of the image, also determined by the accuracy of the clinical question about surgery simulation. Anyway, the most important part in building a 3D rendering is segmentation, closely related to the interpretation of the image: the 3D model represents how the two-dimensional image was interpreted by the operator who performed the reconstruction. While in literature a consensus recommendation [3] defines a 3D visualization quality score referring to preoperative surgical simulation, intraoperative 3D surgical navigation and postoperative 3D reconstruction, Medics 3D and Visible Patient follows the standard ISO 13485. It addresses the development, implementation, and maintenance of a quality management system for manufacturers and suppliers of medical devices. It concerns safety and performance requirements of devices throughout their life cycle, stressing the need to assess the 'usability' of medical devices. Indeed, Sternini et al. evaluate the usability of a new medical device intended to assist the intraoperative planning with the visualization of 3D patient-specific organ models [5]. The high-level usability was confirmed both during the formative and summative evaluation. The former was iterated until a satisfactory quality level was reached in the early stage of development, while the summative evaluation, during the last phase, confirmed the usability of the medical device.

7. Analysis of the patient's point of view

Another advantage of using 3D models is the most immediate communication with the patient. 3D rendering, especially when printed, allows to give clearer and understandable explanations to the patient and his family, who do not have particular clinical skills. In this way, the patient also has a clearer and broader idea of the risks associated with a certain complex surgical procedure.
As a result, patient perceptron was tested in literature [6] trough a questionnaire about patients' overall satisfaction of a 3D printed model during case discussion. The results highlight that also patients can benefit from the introduction of personalized physical 3D models because they facilitate mutual understanding between patient and physician. Moreover, quality of life (QoL) was measured in patients of Vimercate hospital whose preoperative planning was based on 3D (intervention group) and 2D (control group). These patients are the same previously selected for clinical effectiveness evaluation (paragraph 5). QoL (1: perfect health, 0: worst health) was measured assessing a level of severity to five different dimensions: mobility, self-care, usual activities, pain, discomfort and anxiety and depression. This method, called EQ-5D-3L, tries to find the coefficients of the regression analysis that translate the five dimensions after surgery into the QoL. The average quality of life after 4 months from the planned surgery with 3D rendering was 0.70, while the average QoL of patients in the control group was 0.33. This difference is mainly because many patients in the control group, 4 months after surgery, still carried out drainage and chemotherapy due to the recurrence of the tumor or a re-hospitalization.
Thus, it was demonstrated that an adequate and personalized surgical planning leads to better results already during the follow up.

8. Analysis of organizational and economical aspects

The organizational procedure of different 3D software is very similar. The surgeon must subscribe on the portal cloud based. In his private section, the doctor can open a new case, upload the relevant DICOM images, enter the details of the case and his own specific requests.
The company can accept or reject the case through specific segmentation protocols that must be executed to allow 3D reconstruction.
Within 72 hours of the opening of the case, the anatomical reconstruction is ready, in a viewable and transferable form.
From an economic point of view, decision makers in healthcare must be informed about resources needed for each alternative trough different types of economic evaluations. Cost-effectiveness analysis was carried out based on 3D costs and quality of life gained. As already mentioned, the difference between the intervention group and the control group in QoL was 0.37, while the hospital must spend at least 1000 euros for each 3D reconstruction. Hence, the cost-effectiveness ratio shows that 27 euros are needed for an increase in quality of life.
Furthermore, the clinical effectiveness analysis demonstrates a statistically significant difference in the length of hospitalization. In Italy, the economic value of each treatment can be quantified by the DRG system. The economic weight associated with each DRG therefore express the number of resources to be used to treat the pathology in the standard case of the standard patient. However, treatment of patients with particular clinical conditions leading to exceptionally long inpatient stays (outliers) may result in a significant deviation in resource consumption compared to the average of their category. Hence, it emerged that the average cost of inpatient stays operated using 2D was higher than the cost of inpatient stays whose preoperative planning was based on 3D, despite the additional cost of rendering. This is because, as previously demonstrated, the use of the 3D causes a decrease in the duration of hospitalization and therefore a lesser use of resources.
In addition, the rate of extra days is lower than the average cost of the single day of stay in an ordinary hospital. This increases the costs that the hospital faces if the length of stay increases, as the total use of resources is not fully reimbursed. Therefore, if the use of 3D models decreases the duration of hospitalization, consequently it decreases the costs that the hospital needs to face.

9. Conclusion and future developments

3D reconstruction allows individualized visualization of the tumor spatial relationship with nearby vascular structures for a more accurate and personalized pre-operative planning and intraoperative navigation, that brings such simulation into the field of operation to guide surgeons during tumor resection. This technology facilitates and increases the effectiveness of surgery, but evidence of its effect on operating results remains limited in the literature.
The aim of this thesis is to perform a multidisciplinary HTA-style evaluation of three-dimensional reconstructions in the preoperative and intraoperative phase, to determine a more appropriate customized therapeutic strategy in hepatobiliary surgery.
The most substantial part of this thesis concerns the clinical effectiveness. Such evaluation highlights that 3D reconstructions improve the understanding of the patient's liver anatomy with respect to the standard 2D CT scan imaging and the use of 3D leads to better preoperative and post-operative outcomes (less blood loss during surgery, shorter hospitalization, and less cancer recurrence). Other benefits demonstrated are related to an improvement in quality of life during the follow up and a decrease of hospital's resources consumption despite the cost of each rendering.
In conclusion, it has been demonstrated that 3D visualization has many advantages over standard practice from different points of view. However, this study is limited by the number of participants involved. For this reason, a future development of this analysis can be an evaluation, based on HTA framework, about different 3D techniques applied to a larger number of patients in hepatobiliary surgery.

Indeed, more and more advanced technologies will spread in hepatobiliary surgery in which visualization of the 3D model is only one part of a complex and innovative system.
Sometimes the visualization is not enough, and the 3D model will be printed, to obtain a concrete manipulation. As a matter of fact, in most of the cases 3D printed models were used when vascular

reconstruction was performed. They help to reduce bleeding and post-operative complication, facilitating intraoperative detection of small and deeply locate tumors. Indeed, printed models are fundamental in case of vanishing lesions: removal of small tumors invisible by both preoperative and intraoperative ultrasonography [7].

Aside from 3D print, augmented and mixed reality applications provide the preoperative data in the operating room during liver surgery. The virtual environment allows the transparency of the structure to be altered and scaled according to the users' preferences, to make the preoperative planning more flexible. Augmented reality (AR) shows great potential to enhance both laparoscopic and laparotomy surgery. The setting consists of screens with augmented and not augmented image. In these cases, the fundamental step is calibration, performed following instruments with a passive optical tracking system.

Furthermore, different navigation modes are available: the first one is the overview mode that permits to augment the 3D image with the complete preoperative reconstructed information; the second modality is the one used during resections where the 3D image is displayed in a circular area, the center of which is determined by the surgical instrument and the radius can be selected by the operator [8]. Furthermore, the surgeon can have a 3D visualization of tool position and orientation relative to the available patient-specific preoperative virtual model and 2D augmentation of US images with co-registered preoperative image data in order to correctly display anatomical features that were visible in the preoperative image data but not by intraoperative US (vanishing lesions) [9]. Image guidance is essential to reduce the overall surgical invasiveness, potentially pushing forward the limits of current surgical oncological treatment strategies. Moreover, a further technological development in surgery is the use of mixed reality (MR), a new digital holographic imaging technology that enables real-world and virtual 3D images to be displayed in the same visual space.

Hence, in literature it is already increasing the number of case reports where technologies that go beyond the visualization of 3D reconstructions have been analyzed, which will catch on more and more in the medicine of future. However, the visualization of 3D models has already many advantages over standard practice from different points of view. It represents the surgical and dynamic perception of the anatomy of a specific patient, a tool that does not replace traditional two-dimensional images, but that makes preoperative planning more immediate and 'surgical like'.

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