Master Thesis Report

Development and Evaluation of an Integrated Medical Imaging Workstation for Diagnostic and Surgical Planning Support in Pancreatic Cancer

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Development and Evaluation of an Integrated Medical Imaging Workstation for Diagnostic and Surgical Planning Support in Pancreatic Cancer

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Diederik Willem Marcel Rasenberg

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Preface and Acknowledgements

I can convincingly say that this graduate internship at Philips has been one of the most unique and valuable professional experiences of my life so far. Graduating at Philips allowed me to meet and work with great people, even during these challenging times. Besides, I feel lucky that I have been working trying to improve pancreatic cancer care, which truly fascinated me. This made me enjoy my graduate project every day.

Reflecting on my graduation project, I have got the chance to engage with pancreatic cancer experts from the Catharina Hospital Eindhoven and the Leiden University Medical Centre. Furthermore, I have developed and tested the prototype with usability designers, data designers, clinical scientists, and AI developers. Working closely together with these people in this multidisciplinary context has taught me a great deal in designing, developing, and evaluating medical devices in clinical practice. I think we can be very proud on what we have achieved as a team during the last year and I feel confident that the developed prototype and performed multi-centre study contributed to the e/MTIC project. I strongly believe that this project is revolutionizing how computer-aided detection algorithms can improve the lives of patients diagnosed with the pancreatic cancer, which still is an immensely devastating disease.

Graduating within Philips on this project have made me realize even more that I really get energized from working on medical-, and technology-related innovations. Although I feel a bit sad to leave this project and topic, I am delighted to share that I will start the management traineeship focused on innovation management at Philips. This journey will help me boost my personal and professional development.

I would like to thank all the people I have met during my time at Philips, my members from the e/MTIC team, the members of the strategic design team, the thesis committe members, and all clinicians that have participated in my study. Next, I would like to express my gratitude to a few individuals that joined me during my graduation project.

Thank you, Jenny Dankelman and Frank Willem Jansen, for providing me very insightful and constructive feedback over the complete course of this project. In addition, Frank Willem Jansen has opened his network during this project and introduced me to plenty of valuable people.

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Thank you, Luc Geurts and Vincent Buil, for supervising me on a daily basis during my time at Philips, and giving me the freedom to take responsibility. Besides your relevant experience with design and development of prototypes that you shared with me, you both made my internship a very fun experience!

Thank you, Jon Pluyter and Igor Jacobs, for making me feel an appreciated member of the e/MTIC oncology team, helping me set up this study and iteratively providing me with feedback. I think you will achieve great things with this project!

Thank you, Sven Mieog, Misha Luyer and Mark Ramaekers, for welcoming me multiple times in the operating theatre and sharing your feedback with me. Both Sven and Misha helped me gain a deeper understanding in challenges of treating pancreatic cancer by sharing their expertise.

And lastly, thank you to my awesome family and in particular, my parents Wilco and Susanne Rasenberg, for your unconditional love and support during my years as a student.

Truly excited about what the future will bring!

Diederik Rasenberg

Executive Summary

Introduction Pancreatic cancer is currently the fourth leading cause of cancer death in the United States and has only a 5-year survival rate of 10%. Pancreatoduodenectomy is the cornerstone of curative treatment for patients diagnosed with pancreatic head cancer. Only 20% of the patients are candidate for surgery since many patients present with distant metastases or locally advanced tumours with vascular involvement. Whether tumours are amendable for resection is based on potential vascular involvement with the surrounding vasculature. Assessment of vascular involvement, mainly based on multi-phase computed tomography (CT) scans, requires specific expertise and can be challenging. Computer-aided detection (CAD) and autostereoscopic three-dimensional (3D) patient models might improve accuracy in predicting vascular involvement and improve overall surgical planning. This graduation project aims to assess the added value of autostereoscopic three-dimensional patient models and computer-aided detection for decision support in pancreatic cancer care.

Technical methods An integrated medical imaging workstation was developed based on the clinical needs of clinicians regarding key concepts of the preoperative planning of pancreatoduodenectomy. This workstation is a hardware and software combination that consists of three main components; 1) a medical imaging viewer showing CT scan with basic imaging functionalities, 2) annotations outlining the tumour and anatomical structures (to simulate segmentations generated by CAD algorithms) that are translated to 3D patient models displayed on an autostereoscopic display, and 3) CAD-derived metrics (degrees and length contact) regarding vascular involvement of the tumour.

Clinical methods This integrated medical imaging workstation was evaluated in a multi-centre study including 13 expert hepatopancreatobiliary surgeons and one abdominal radiologist. All participants assessed pancreatic tumours in a simulated setting under 3 different test conditions; assessment using only the regular CT scan (CT-condition), assessment using CT and 3D patient models (3D-condition), assessment using CT, 3D patient models and CAD-derived metrics regarding vascular involvement (CAD-condition). A total of 6 patient cases were evaluated, of which 3 radiologically resectable cases (simple) and 3 radiologically borderline resectable cases (complex) with pancreatic tumours near to major vessels. Perceived fulfilment of clinical needs regarding the preoperative assessment, differences in surgical planning decisions compared to baseline, and confidence in clinical decision-making were evaluated.

Results Clinicians experienced an improved ability to accurately detect pancreatic tumours and determine the degrees and length of tumour-vessel contact under the 3D- and CAD-condition compared to the CT-condition. Additionally, clinicians reported a higher perceived ability to identify, localize and understand anatomical relationships when supported by autostereoscopic 3D models. Lower degrees of tumour-vessel contact were reported under the CAD-condition compared to the CT-condition. Furthermore, clinicians had higher confidence in assessing the need for a vascular resection under the 3D-condition than the CT-condition.

Conclusion CAD and 3D might improve the accuracy of pancreatic tumour detection and reduce the overestimation of degrees of vascular involvement on radiological imaging. The risk of over-trust in CAD mandates thorough evaluation of the accuracy and use of CAD in prospective studies.

Keywords Pancreatic Carcinoma; Pancreatoduodenectomy; Integrated Medical Imaging Workstation; Autostereoscopic Three-Dimensional Patient Models; Computer-aided detection; Preoperative Planning; Vascular Involvement.

List of Abbreviations

2D	Two-dimensional
3D	Three-dimensional
3D-on-2D	Three-dimensional on two-dimensional
ANOVA	Analysis of Variance
AR	Augmented Reality
CA	Celiac Axis
CAD	Computer-Aided Detection and/or Diagnosis
CEA	Carcinoembryonic Antigen
CHA	Common Hepatic Artery
CNN	Convolutional Neural Networks
CP	Current Practice
CSV	Comma Seperatad Values
CT	Computed Tomography
CZE	Catharina Hosptial Eindhoven
DICOM	Digital Imaging and Communication in Medicine
DPCG	Dutch Pancreatic Cancer Group
e/MTIC	Eindhoven MedTech Innovation Centre
ERCP	Endoscopic Retrograde Cholangiopancreatography
EUS	Endoscopic Ultrasound
FBX	Filmbox
GDA	Gastroduodenal Artery
HPB	Hepatopancreatobiliary
ICBE	Internal Committee of Biomedical Experiments
IMA	Inferior Mesenteric Artery
IQR	Interquartile ranges
JSON	JavaScript Object Notation
LPD	Laporasocpic Pancreatoduodenectomy
LUMC	Leiden University Medical Centre
MDCT	Multi-Detector Computed Tomography
METC	Medical Ethical Committee
MPR	Multiplanar Reconstruction
MR	Mixed Reality
MRCP	Magnetic Resonance Cholangiopancreatography
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NET	Neuroendocrine Tumour
NIfTI	Neuroimaging Informatics Technology Initiative
OPD	Open Pancreatoduodenectomy
PD	Pancreatoduodenectomy
PET	Positron Emission Tomography
PV	Portal Vein
PV-SMV	Portal Vein - Superior Mesenteric vein
RAPD	Robot-Assisted Pancreatoduodenectomy
SMA	Superior Mesenteric Artery
SMV	Superior Mesenteric
STL	Stereolithography
TU/e	Technical University Eindhoven
TUD	Delft University of Technology
UI	User-interface
UX/UI	User-experience
VR	Virtual Reality
VTK	Visualization Toolkit

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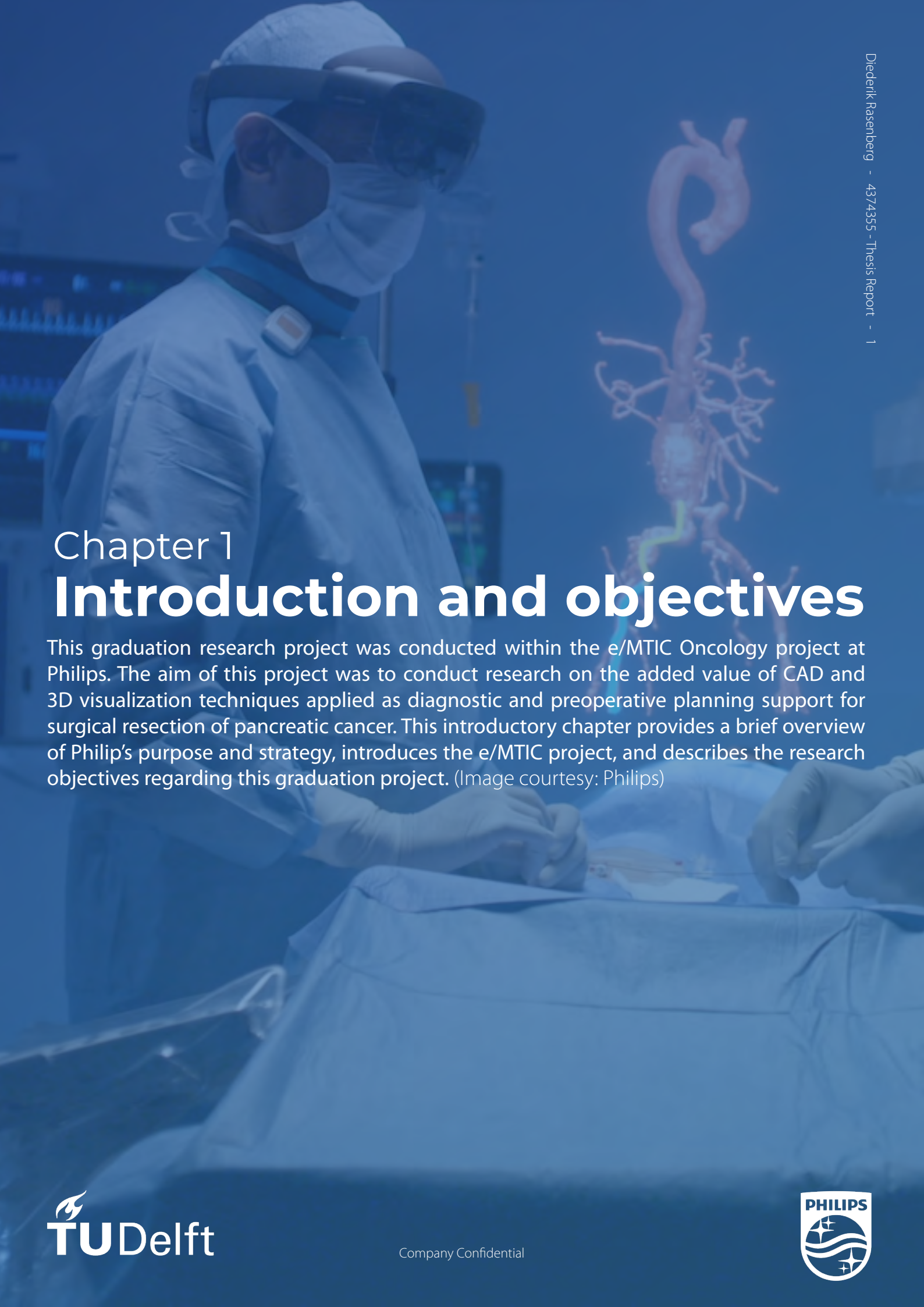

Chapter 1

Introduction and objectives

This graduation research project was conducted within the e/MTIC Oncology project at Philips. The aim of this project was to conduct research on the added value of CAD and 3D visualization techniques applied as diagnostic and preoperative planning support for surgical resection of pancreatic cancer. This introductory chapter provides a brief overview of Philip's purpose and strategy, introduces the e/MTIC project, and describes the research objectives regarding this graduation project. (Image courtesy: Philips)

1.1 About Philips

Philips is a leading health technology company that has the purpose of improving people's health and well-being through meaningful innovation. Philips aims to improve the lives of 2 billion people in a year by 2025, including 300 million people in underserved communities, rising to 2.5 billion and 400 million respectively by 2030(1, 2).

Philips wants to improve those lives by leading the health technology market with innovative solutions combining systems, smart devices, informatics, and services while leveraging big data. To stay ahead of competitors, solutions need to be developed specifically tailored to the needs of the increasingly diverse customers. In developed countries, the healthcare cost has increased to record heights since people live longer and suffer more from diseases during their lifetime. Therefore, solutions should be developed that deliver on the quadruple aim (Figure 1.1).

Delivering on the quadruple aim means solutions will be developed that 1) have better health outcomes, 2) improve the patient experience, 3) improve the (clinical) staff experience, and 4) lower eventually the cost of care. Besides, to develop these solutions, they need to team up with healthcare providers to listen closely to the needsof customers. Philips is increasingly embedding Artificial Intelligence and data science in their propositions to really leverage the value of clinical data in improving the quality and efficiency of healthcare and aiding the clinicians in making diagnosis-, and treatment-related decisions. Philips is focussing on the following healthcare propositions:

Personal health

Focussing on the healthy living of people by providing solutions that will enable healthier lifestyles, personal hygiene and living with chronic diseases.

Diagnosis & Treatment

Focussing on providing innovations that help prevent, diagnose, and treat diseases.

- **Precision diagnosis** – Providing smart, connected, optimized workflows and integrated diagnostic insights, leading to clear care pathways and predictable outcomes.
- **Image-guided therapy** – innovating minimally invasive procedures in a growing number of therapeutic areas, with significantly better outcomes and productivity.

Connected Care

Improving the care management by connecting patients and clinicians from the hospital to the home.

Figure 1.1. Quadruple Aim

1.2 e/MTIC Project

The e/MTIC (Eindhoven MedTech Innovation Center) oncology project is a collaboration between Philips, Catharina Hospital Eindhoven (CZE), and Eindhoven University of Technology (TU/e) (3). This collaboration has the aim to accelerate clinical innovations in oncology care positioned in the precision diagnosis proposition of Philips and bring early research to implementation and commercialization. Since the start of the graduate research internship in September 2020, I have been part of the Philips e/MTIC core team. The Philips core team comprises different expertise (usability designers, data scientists, software developers, clinical scientists) from the Experience Design and Research department.

This team is working together with the clinicians from CZE and data scientists from TU/e on two specific work packages that focus each the application of computer-aided detection and diagnosis (CAD) algorithms on specific clinical use-cases. CAD algorithms are developed to assist clinicians as 'second opinion' in detection and interpretation of suspicious features on medical imaging to improve decision making (4). The popularity of CAD has grown enormously since the 1980s, and its application on medical imaging has become an important research area for cancer (5). CAD algorithms use a wide variety of image processing and artificial intelligence (AI) techniques such as convolutional neural networks (CNNs). CAD can be divided into two main categories, namely computer-aided detection and computer-aided diagnosis. Computer-aided

detection focuses on the localization and detection of lesions and their features.
Computer-aided diagnosis focuses more on classification and differentiating between findings (lesion versus non-lesion or benign versus malignant) (5). Within the e/MTIC Pancreas project, the first work package is focused on CAD for lesion detection and classification in lung nodule assessment. The second work package is focused on the application of CAD and 3D visualization techniques for therapy stratification and evaluation in patients with pancreatic cancer.

This graduation research project was focused on the second work package, which has the aim to bridge between the radiological assessment, therapy decision-making, and surgical planning of pancreatic cancer surgery. CAD classification and segmentation algorithms based on CNNs are being developed and trained based on manually annotated multi-phase CT scans (n=350) of patients (n=200) that were treated in the CZE. The CAD will eventually automatically provide pixel-level segmentations of all relevant anatomical structures. Based on these CAD-generated segmentations, algorithms can derive clinical guideline-based metrics. In addition, 3D patient-specific model can be reconstructed. Eventually, this might improve the detection of pancreatic tumours and accuracy of vascular involvement prediction.

1.3 Graduation scope and objectives

The aim of this project was to assess the added value of autostereoscopic 3D models and CAD applied as diagnostic and preoperative planning support for surgical resection of pancreatic cancer. Therefore, the following objectives were defined:

Objective 1 – Systematic Review

Systematically review the state-of-art literature regarding the application of three-dimensional visualization techniques in surgical oncology to learn more about the clinical relevance of these techniques. *(This literature study was written for the Course BM51010 and is not part of the main thesis. A brief overview of the most important findings is provided in Chapter 2.)*

Objective 2: Understanding the curative treatment of pancreatic cancer

Conduct an additional literature review and a workflow analysis to get a better understanding of the pancreas, cancer development in this organ, and the preoperative planning of surgical resection of pancreatic tumours *(This objective was part of preparatory workf for the main thesis project and is described in Chapter 3).*

Objective 3: Compare the added value of 3D visualization techniques in pancreatic cancer

To compare multiple 3D visualization techniques and gain early feedback on CAD concepts in an explorative and qualitative user study, including clinicians involved in pancreatic cancer care. *(The results analysis was part of preparatory work of the main thesis project. A brief overview of the study is provided in Chapter 4.)*

Objective 4. Iterative design and development of the prototype (main part thesis)

To iteratively design and develop an integrated medical imaging workstation comprising 3D visualization techniques and CAD-derived metrics. The design and features of this prototype are based on the learnings from the literature studies, workflow analysis, and identified clinical and usability needs. *(This objective is described in Chapter 5).*

Objective 5. Evaluation of the integrated medical imaging workstation (main part thesis)

To evaluate the integrated medical imaging workstation, including 3D patient models combined with CAD-derived metrics for diagnostic and preoperative planning support in pancreatic cancer in a multi-centre pilot study including expert surgeons and radiologists. *(This study is provided in Chapter 6.)*

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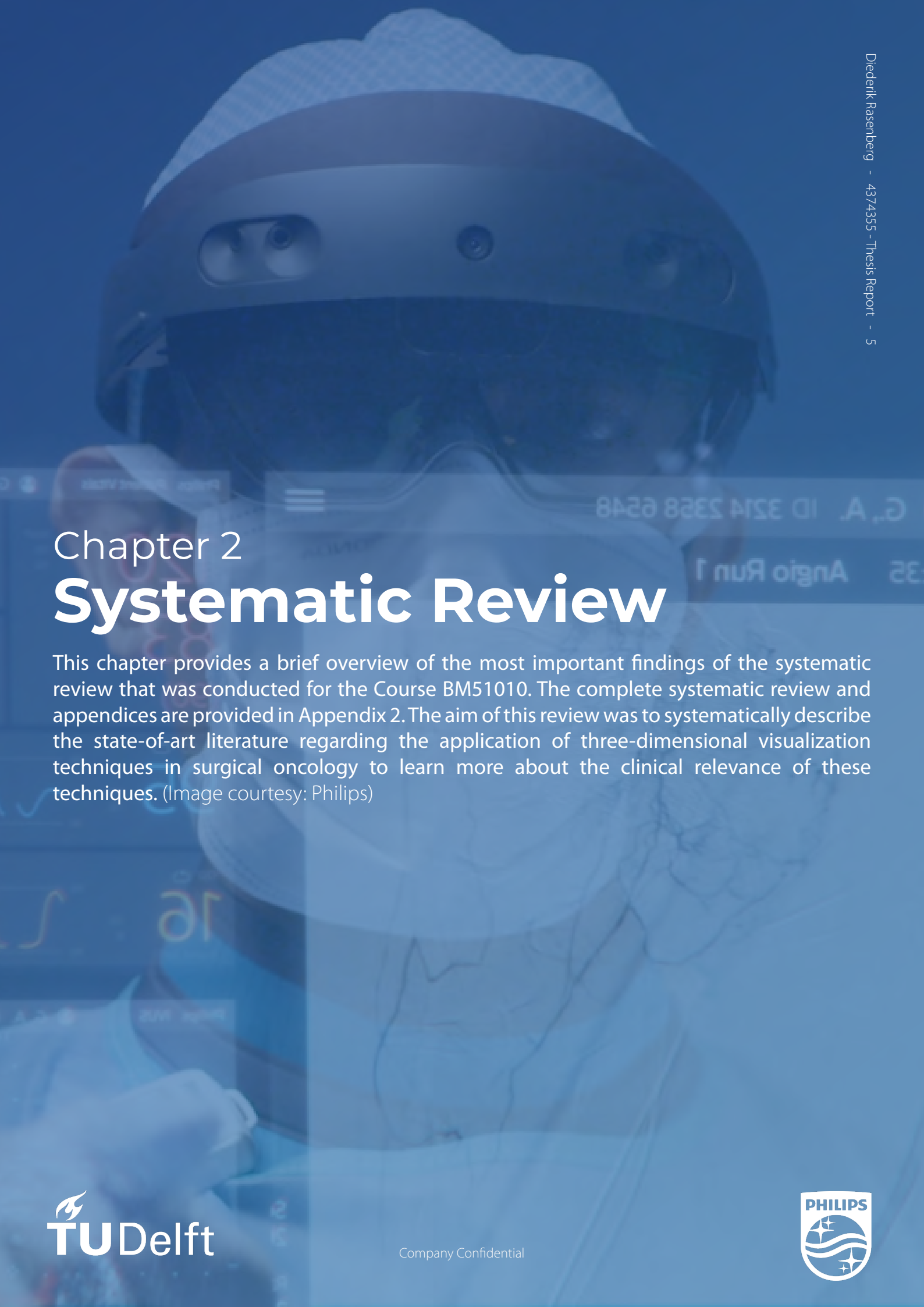

Chapter 2
Systematic Review

This chapter provides a brief overview of the most important findings of the systematic review that was conducted for the Course BM51010. The complete systematic review and appendices are provided in Appendix 2. The aim of this review was to systematically describe the state-of-art literature regarding the application of three-dimensional visualization techniques in surgical oncology to learn more about the clinical relevance of these techniques. (Image courtesy: Philips)

The added value of 3D Visualization Techniques during the Preoperative Planning of Complex Oncological Resection Surgery: A Systematic Review.

Diederik W.M. Rasenberg [1,2], Jon Pluyter, Ph.D.[2], Fokkedien H.M.P. Tummers, M.D.[4], Luc J.F. Geurts, PDEng[2], Frank Willem Jansen, M.D., Ph.D.[1,4], Jenny Dankelman, Ph.D.[1], J. Sven D. Mieog, M.D., Ph.D.[3]

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Keywords

Three-dimensional; virtual reality; mixed reality; three-dimensional printing; holographic display; pre-operative planning; complex surgical oncology.

2.1 Background

In surgical oncology, careful examination of preoperative imaging data aids the surgeon in anticipating the irregular and unpredictable spatial conformation of the patient-specific anatomy and pathology (1). Surgeons currently base their decisions on the information given by conventional two-dimensional (2D) medical imaging scans. However, surgeons need to convert the information provided on the 2D imaging slices into their own mentally constructed three-dimensional (3D) representation of the anatomy. This creates a subjective understanding of the patient anatomy and is not easily shared among the involved clinical personnel (2, 3).

Advancements in image processing techniques have made it possible to translate cross-sectional 2D medical imaging into 3D models. 3D visualization techniques, including three-dimensional printing, virtual reality (VR), mixed reality (MR), and holographic displays (HD), could potentially be of great value for planning complex surgical oncology procedures (Figure 2.1). The aim of this systematic review was to describe the added value of 3D visualization techniques used during the preoperative planning of complex oncological resection surgery.

2.2 Methods

A systematic literature review in accordance with the PRISMA statement was performed by searching Pubmed, Embase, Web of Science, COCHRANE Library, and Emcare from 2010 to October 14th, 2020 (4). The literature search identified 908 articles, of which 20 articles were found eligible for the qualitative analysis. Data regarding study and technology characteristics and outcome measures (compared intra- and postoperative outcomes, questionnaires, and performance assessments) were extracted from the included studies.

2.3 Results

Firstly, five studies reported intra- and postoperative outcomes regarding the operation time, estimated blood loss, clamp time, resection margins, hospital stay, complications, and other procedural relevant outcomes. Multiple studies have reported significantly shorter operating times and significantly decreased estimated blood losses in 3D printing (n=2), MR (n=1), and VR (n=1) groups compared to the non-3D groups (5 - 8).

Secondly, eleven studies conducted questionnaires regarding the utility, experience, usefulness, anatomical understanding, or the surgical strategy used in the preoperative planning. A better understanding of the patient-specific anatomy with 3D printed models than with 3D-on-2D models was reported (6). In addition, the 3D printed models improved communication with the surgical team (6). HD models showed a good interobserver agreement compared to a poor agreement for the non-3D group (2).

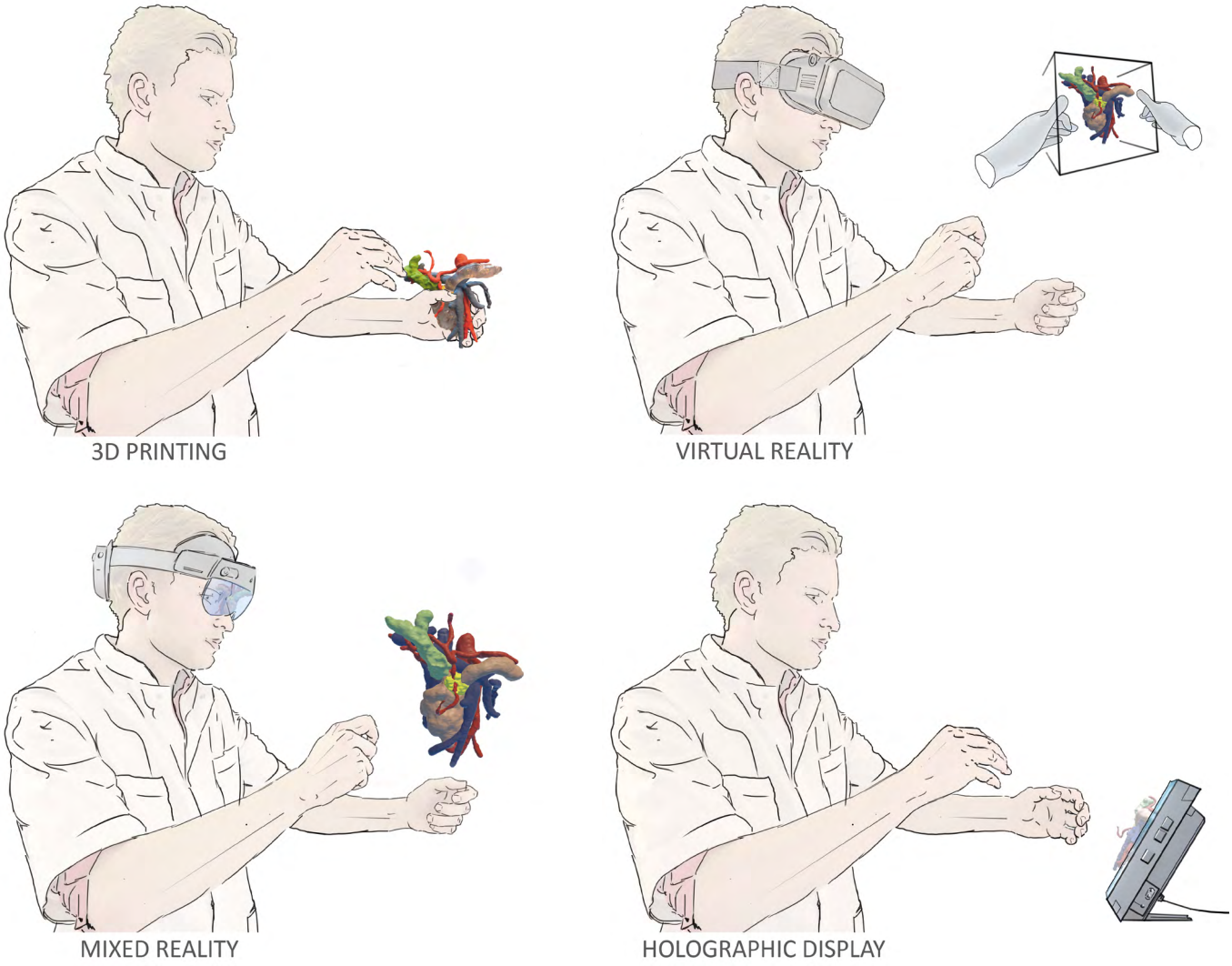

Figure 2.1. Drawings of the technology interaction of the different 3D visualization techniques (3D printing, virtual reality, mixed reality, and the holographic display) with an example 3D reconstructed pancreas cancer patient model. The pancreas cancer patient model has been obtained from a user study within Eindhoven MedTech Innovation Centre (e/MTIC) oncology collaboration (Philips, Eindhoven University of Technology and Catherina Hospital Eindhoven). Illustrations are made by C.H. Broekmeulen and D.W.M. Rasenberg.

Finally, eight studies assessed the performance of surgeons regarding their anatomical understanding, resection time, surgical strategy, and planning time. Three studies reported a significantly reduced planning times in 3DP (n=2) and HD (n=1) groups compared to non-3D groups (2, 9, 10). Another three studies showed a significantly higher performance in anatomical understanding (9-11). One study reported a significantly improved surgical strategy accuracy in the 3D group compared to both the 3D-on-2D group and the non-3D group.

2.4 Conclusion

The systematic review provides an extensive overview on the added values of emerging 3D visualization techniques used during the preoperative planning of complex surgical oncology whilst considering the limitations. First, the application of 3D visualization techniques could reduce the operating time and estimated blood loss in complex surgical procedures. Secondly, 3D visualization techniques enable the surgeons with a better spatial conformation of the patient-specific anatomy and complex tumour-vessel relationships leading to changed surgical strategies. Thirdly, surgeons are more confident in choosing and performing surgical strategies. Even experienced surgeons may benefit from 3D patient models in determining the surgical strategy for patients with a high degree of anatomic complexity.

Lastly, both physical printed and digital stereoscopic models enhance surgeons with new pre-, and intraoperative interaction possibilities. Further technological development needs to be done to facilitate wide clinical implementation of 3D visualization techniques eventually.

2.5 Recommendations

Ultimately, the application of 3D visualization techniques improves the intra- and postoperative clinical outcomes. Four studies reported significantly better clinical outcomes in terms of operating time and estimated blood loss. The outcomes regarding the influence of 3D visualization techniques on the complications rate and positive tumour resection margins were, in contrast to the operating time and estimated blood loss, not supported with any statistically relevant differences.

The contemporary literature still provides limited quantitative data regarding these clinical outcomes. However, the application of 3D visualization techniques is increasingly embraced in clinical practice. This allows for more quantitative follow-up research that could provide more statistical evidence regarding the added value and the clinical relevance of the 3D visualization techniques in complex oncological resection surgery.

Additionally, multiple studies showed that the application of 3D visualization techniques changed the surgical plan. However, it should also be remarked that a changed surgical strategy does not necessarily mean a better surgical strategy. It was not clear in the included studies if the changes in surgical strategy eventually led to improved outcomes of the procedure. Therefore, more research should be done in order to compare the surgical strategies with the real outcome.

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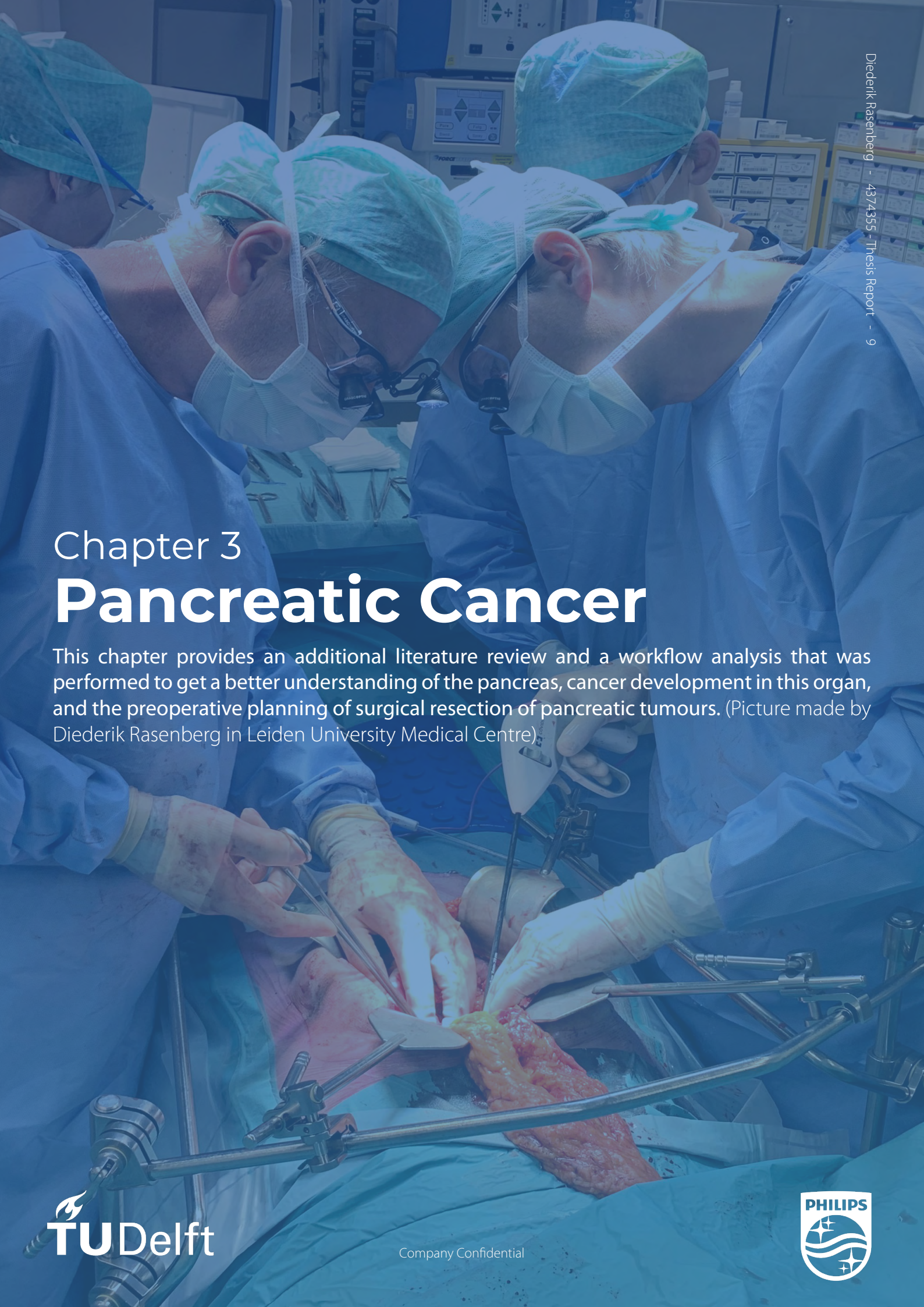

Chapter 3

Pancreatic Cancer

This chapter provides an additional literature review and a workflow analysis that was performed to get a better understanding of the pancreas, cancer development in this organ, and the preoperative planning of surgical resection of pancreatic tumours. (Picture made by Diederik Rasenberg in Leiden University Medical Centre)

3.1 The pancreas

The pancreas is a retroperitoneal organ located in the upper left abdomen and is surrounded by the stomach, gallbladder, liver, spleen, and small intestine (Figure 3.1)(1). It consists of three parts. The wider end, positioned towards the centre of the abdomen, is called the head. The middle part is called the body. The thin end is called the tail and extends to the left side of the body (1). It is surrounded by several major blood vessels that supply this organ and other abdominal organs with blood. The most important vessels are the superior mesenteric artery (SMA), the celiac axis (CA), the common hepatic artery (CHA), the portal vein (PV), and the superior mesenteric vein (SMV).

The pancreas is a gland that has both endocrine and exocrine functions that play a crucial role in the digestive system and regulating the blood sugar level. For 95%, the pancreas contains exocrine gland cells that produce enzymes that play a central role in the digestive system. Enzymes produced by the pancreas help break down proteins (trypsin and chymotrypsin), carbohydrates (amylase), and fats (lipase). The pancreas releases these enzymes after food has entered the stomach and is culminated in the pancreatic duct. The main pancreatic duct joins the common bile duct to form the hepatopancreatic ampulla, also known as the ampulla of Vater. The common bile duct transports bile, another digestive juice, coming from the gallbladder and the liver. The other part of the pancreas consists of the islet cells (islets of Langerhans) that produce and release the main pancreatic hormones, namely insulin and glucagon. Insulin and glucagon are both peptide hormones that are secreted by the Alfa and Beta cells of the islets of Langerhans, respectively, and maintain the correct blood glucose levels (2, 3).

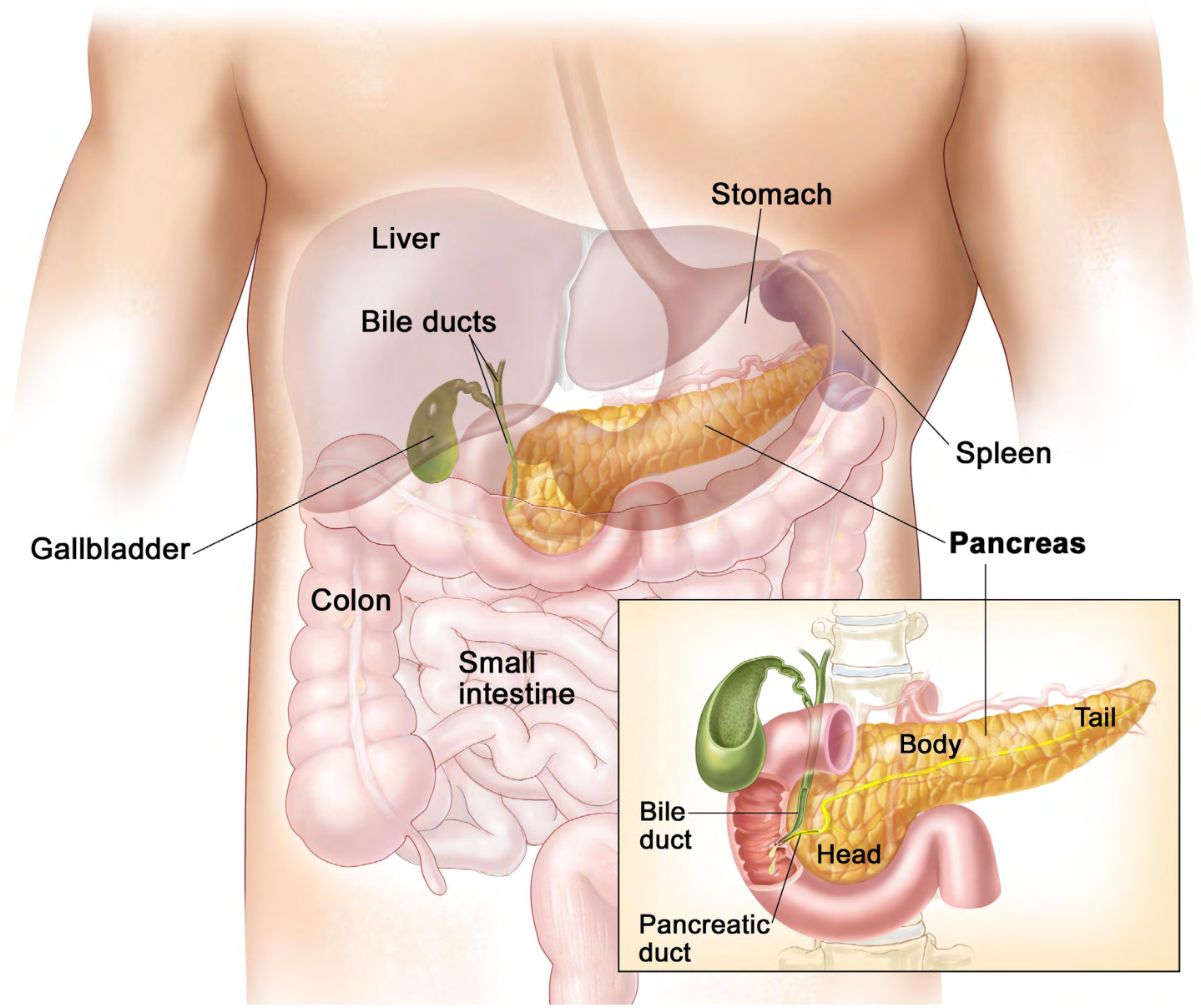

Figure 3.1. Overview of the abdominal anatomy including the pancreas (1) (Image courtesy: Terese Winslow LLC).

3.2 Pancreatic cancer

Pancreatic cancer is a type of cancer where the tumour originates in the pancreas (Figure 3.2) (1). Most patients diagnosed with pancreatic cancer (90%-95%) have exocrine adenocarcinomas that usually start in the ducts of the pancreas. Neuroendocrine tumours (NETs) in the pancreas occur less frequently. In 60%-70% of pancreatic adenocarcinomas cases, the tumour originates in the head of the pancreas, and the remainder originates in the body (15%) and the tail (15%) (4).

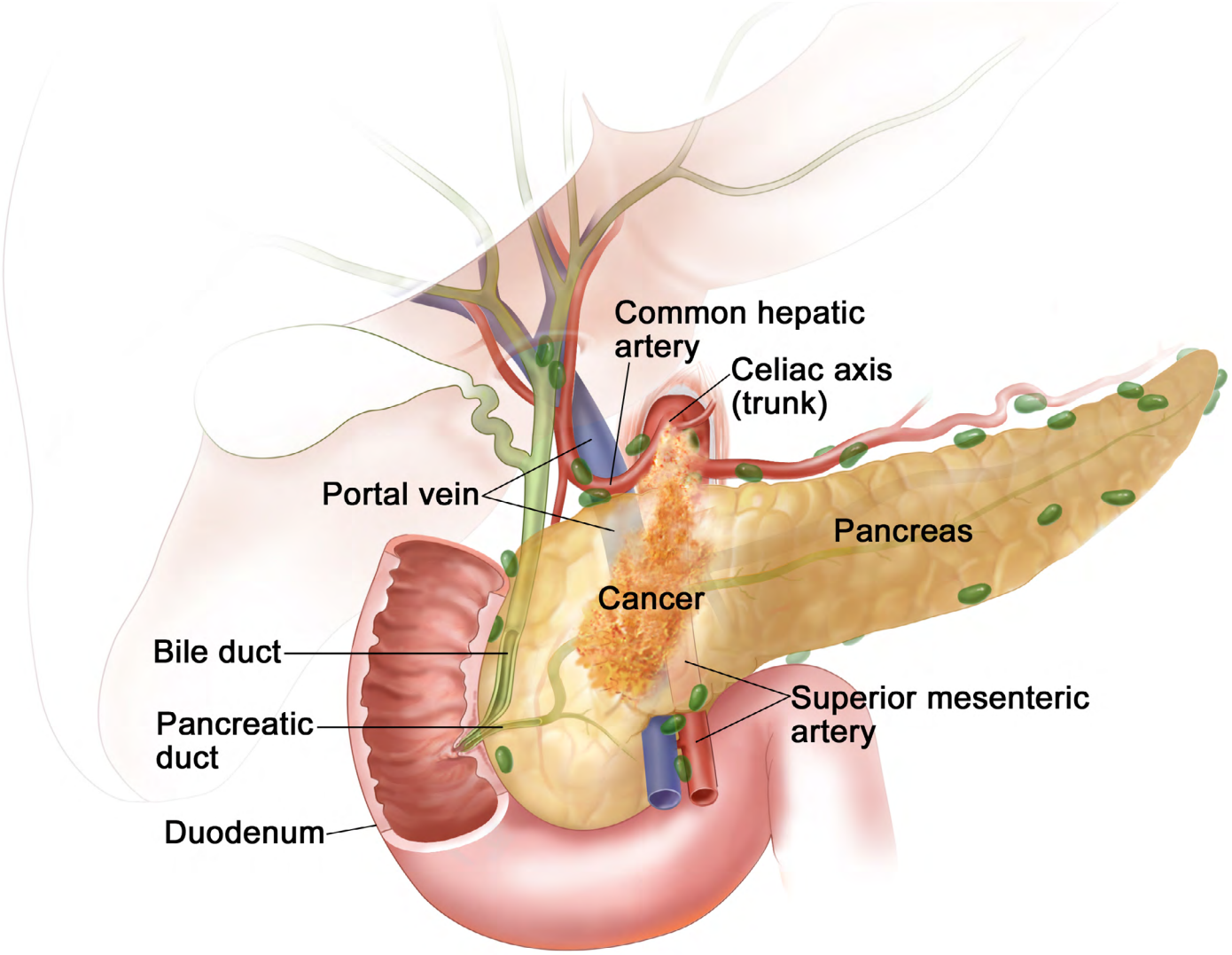

Figure 3.2. Schematic illustration of pancreatic carcinoma (stage III) with surrounding vasculature and organs (1). (Image courtesy: Terese Winslow LLC).

Key statistics of pancreatic cancer

Pancreatic cancer is nowadays still one of the deadliest forms of cancer and is currently the fourth leading cause of cancer death in both men and women in the United States (5). According to the American Cancer Society, 60,430 cases of pancreatic cancer will be diagnosed in the United States of America, and 48,220 patients will die from pancreatic cancer. Patients are usually between 60-80 years old, and males are diagnosed twice as often with pancreatic cancer as females (5-7). The disease accounts for approximately 3% of all cancer cases and for 7% of all cancer deaths. The incidence rate of pancreas carcinomas has increased by approximately 1% per year since 2000, however, its death rate has slightly increased by 0.3% each year. In general, patients with pancreatic cancer have only a 5-year survival rate of 10%. The Dutch integrated cancer centre reported an even lower 5-years survival rate of 5%, excluding NETs in the Netherlands (8). The 5-year survival rates are highly dependent of the specific stage of disease when the cancer is diagnosed and the type of tumour. In case of early cancer detection (only 11% of the people) and successful surgical resection, the 5-year survival rates rise to 39% (9). Pancreatic NETs or islet cell tumours are less common but often have a better 5-years survival rate due to the better prognosis. (9, 10)

Risk factors

Smoking is one of the most important risk factors for pancreatic cancer. Other risk factors for developing pancreatic cancer are age (average age at the time of diagnosis is 70 years old), obesity, type-II diabetes, a family history of pancreatic cancer, chronic pancreatitis, heavy alcohol consumption, Lynch syndrome and genetic syndromes including BRCA1 and BRCA2 (breast cancer type 1 and 2 susceptibility protein) (10, 11).

Signs & symptoms

Pancreatic cancer is challenging to diagnose since patients usually do not present any noticeable signs and symptoms until the cancer is in a more advanced stage. Besides, no validated and specific screening tests are available that could diagnose early-stage pancreatic cancer in patients that do not show any symptoms. Patients that do show symptoms usually have weight loss for no reason, abdominal discomfort in the middle and back, jaundice, loss of appetite, light-coloured stools or dark urine, and fatigue. These symptoms are like signs of many other diseases such as pancreatitis. Some patients also develop type 2 diabetes. Usually, when the cancer is in a more advanced stage, patients show signs like severe abdominal pain, vomiting, and nausea (1, 10).

Diagnosis

If pancreatic cancer is suspected by the physician because a patient shows symptoms, imaging tests will be done to determine in what stage the potential pancreatic tumour is. Imaging modalities that are used for different purposes during the diagnosis phase of pancreatic cancer are Computed Tomography (CT), Magnetic Resonance Imaging (MRI), endoscopic ultrasound (EUS), endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance cholangiopancreatography (MRCP), positron emission tomography (PET) or angiography (11).

The golden standard to diagnose and stage pancreatic cancer is a dedicated pancreatic CT protocol. A multi-detector CT (MDCT) scanner has a faster imaging acquisition and makes scans with thin (preferably sub-millimeter) axial slices. Patients will get an intravenous injection with iodine contrast enhancement to facilitate a multi-phase CT scan. In common practice, images will be acquired in the parenchymal, the portal-venous, and the arterial phase according to this protocol. Different phases are used to improve the opacification of structures. The parenchymal phase (35-45 seconds after contrast injection) is used for better visualization of the tumour. The portal-venous phase (60-70 seconds after contrast injection) improves the visualization of the portal veins, the superior mesenteric vein, the splenic vein, and the pancreas itself (Figure 3.3A and Figure 3.3.B) (12). The arterial phase (10-20 seconds after contrast) enhances the visualization of the celiac axis, superior mesenteric artery, and the peripancreatic arteries (Figure 3.3C and Figure 3.3.D) (12).

Pancreatic tumours are usually difficult to detect on CT scans. No pancreatic abnormalities are seen in 10% of the cases, because the mass is most certainly isoattenuating (5). Often, the detection and localization of the abnormalities are inferred from secondary tumour signs such as the mass effect (abnormal convex contour of the pancreas), obstruction of the pancreatic and common bile duct (double duct sign), and vascular invasion (6, 7, 13). MRI could be used when the suspected tumour is not visible on the CT scan, when contrast enhancement is not feasible in case of severe iodine allergies, or when indeterminate liver lesions are seen on the CT. However, MDCT remains the preferred imaging modality due to the higher cost and the lack of widespread availability of MRI scanners. (14)

Additionally, the physician could use blood tests to help diagnose pancreatic cancer or to help decide which treatment options are desirable. In these blood tests, the function of the liver can be tested, and tumour markers like CA 19-9 or carcinoembryonic antigen (CEA) can sometimes be found in the blood. Although blood tests stand-alone are not accurate enough to diagnose pancreatic cancer, they can be helpful combined with other diagnostic tests (11).

A patient's medical history, the symptoms, and the imaging may strongly suggest pancreatic cancer. To confirm this diagnosis, the physicians often decide to perform a biopsy. These could be done by inserting a thin and hollow needle percutaneously, inserting a small needle into the tumour during EUS, placing a brush in the pancreatic, or bile duct during ERCP or by taking samples during laparoscopic surgery (1, 11).

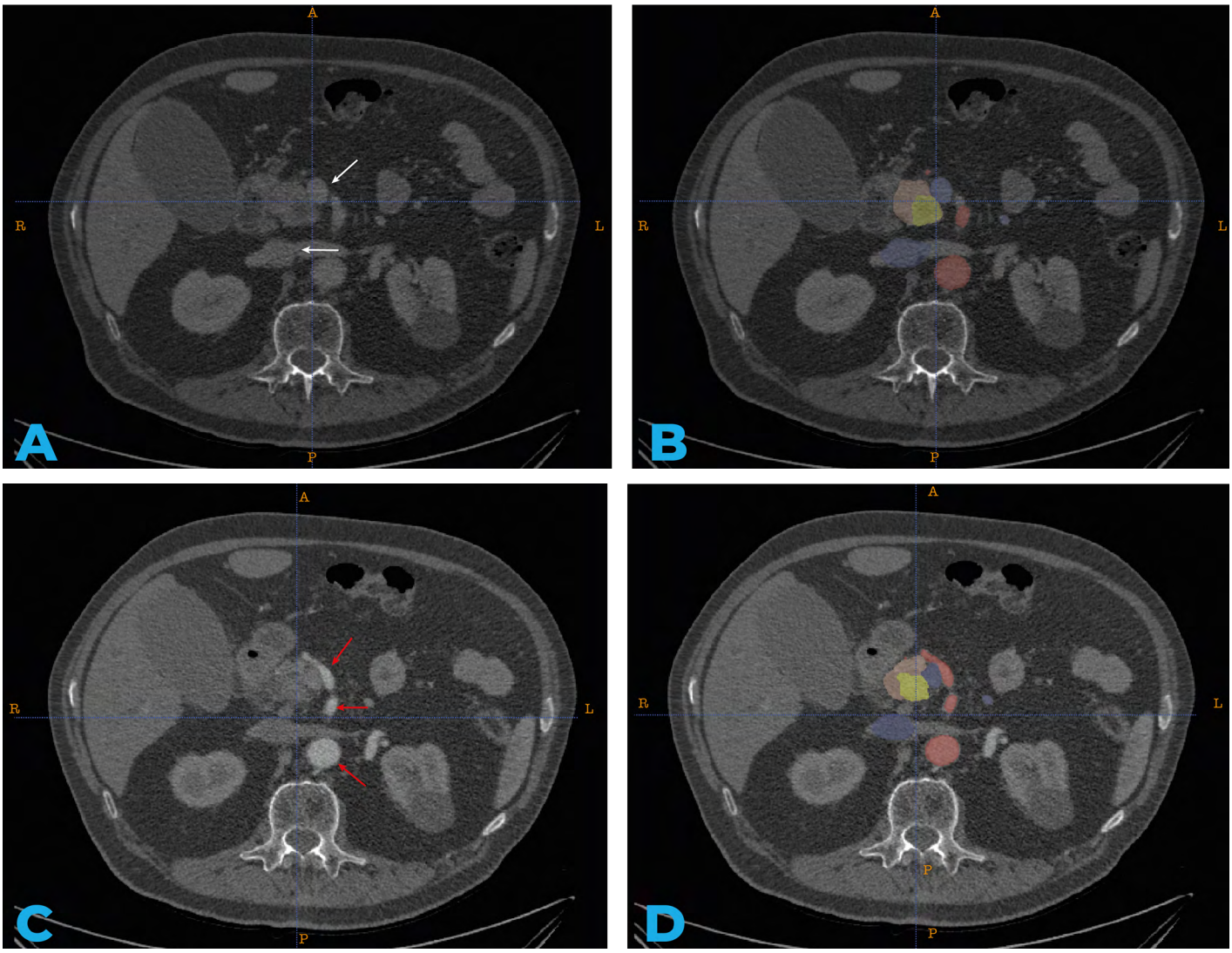

Figure 3.3. CT scan with contrast-enhancement from a patient with pancreas cancer treated in Catharina Hospital Eindhoven. (A) Portal-venous phase scan without annotations, white arrow indicating the veins. (B) Portal-venous phase scan with annotations yellow = tumour, red = arteries, blue = veins, light brown = pancreas. (C) Arterial phase scan without annotations, red arrow indicating the arteries. (D) Arterial phase scan with annotations, yellow = tumour, red = arteries, blue = veins, light brown = pancreas.

3.3 Pancreatoduodenectomy

Surgical resection of pancreas carcinoma, pancreatoduodenectomy (PD), is the only curative treatment option for patients with evidence of no metastasis at diagnosis and can yield the 5-year survival rates to 24% (15). Pancreatoduodenectomy, better known as the Whipple procedure, is considered one of the most complex procedures in gastrointestinal surgery (16-18). In this type of procedure that was popularized by Allen O. Whipple in 1935, hepatopancreatobiliary (HPB) surgeons are focused on the resection of abnormalities, especially cancerous tumours, located in the pancreas (19-21).

Workflow analysis

A workflow analysis was performed to better understand the challenges that the surgical are facing during pancreaticoduodenectomies. Two expert HPB surgeons (dr. Misha Luyer and dr. Sven Mieog) and one expert radiologist (dr. Joost Nederend) have been interviewed in several semi-structured interviews to understand their tasks and the challenges they are facing in their daily work.

Additionally, three pancreaticoduodenectomies including the planning of these procedures were observed in the Leiden University Medical Centre and Catharina Hospital Eindhoven (Figure 3.6, 3.7, 3.8). Based on these interviews and the National Comprehensive Cancer Network Guidelines for Pancreatic Adenocarcinoma, an extensive workflow analysis was developed and can be found in Appendix 4.1 (14).

Surgical technique

The procedure used to belong only to the field of traditional open surgery called open pancreatoduodenectomy (OPD) (Figure 3.6). With the aim to reduce high perioperative morbidity rates, Gagner and Pomp were the first who performed laparoscopic pancreatoduodenectomy (LPD) (22). Due to difficulties in the retroperitoneal pancreas location, its relationships with essential vasculature, and the challenge of reconstructing three anastomoses, LPD has not been widelyadopted (23). With the implementation of the Da Vinci robotic platform (Intuitive Surgical, CA, USA), the popularity and adoption of minimally invasive pancreatic surgery have changed drastically. Robot-assisted pancreatoduodenectomy (RAPD) has solved many of the minimally invasive challenges and offers, in contrast to LPD, a stereoscopic three-dimensional view of the surgical situation and restores the hand-eye coordination with its instrumentation (23) (Figure 3.7 and Figure 3.8). Studies reported superior RAPD outcomes in terms of time to recovery compared to OPD and rate of conversion compared to LPD (24). PD procedures, in general, remain highly challenging and require careful preoperative examination of the medical imaging. This should aid the surgeon in anticipating on tumour interactions with the relevant vasculature and irregular and unpredictable spatial conformation of potential anatomical variations (25).

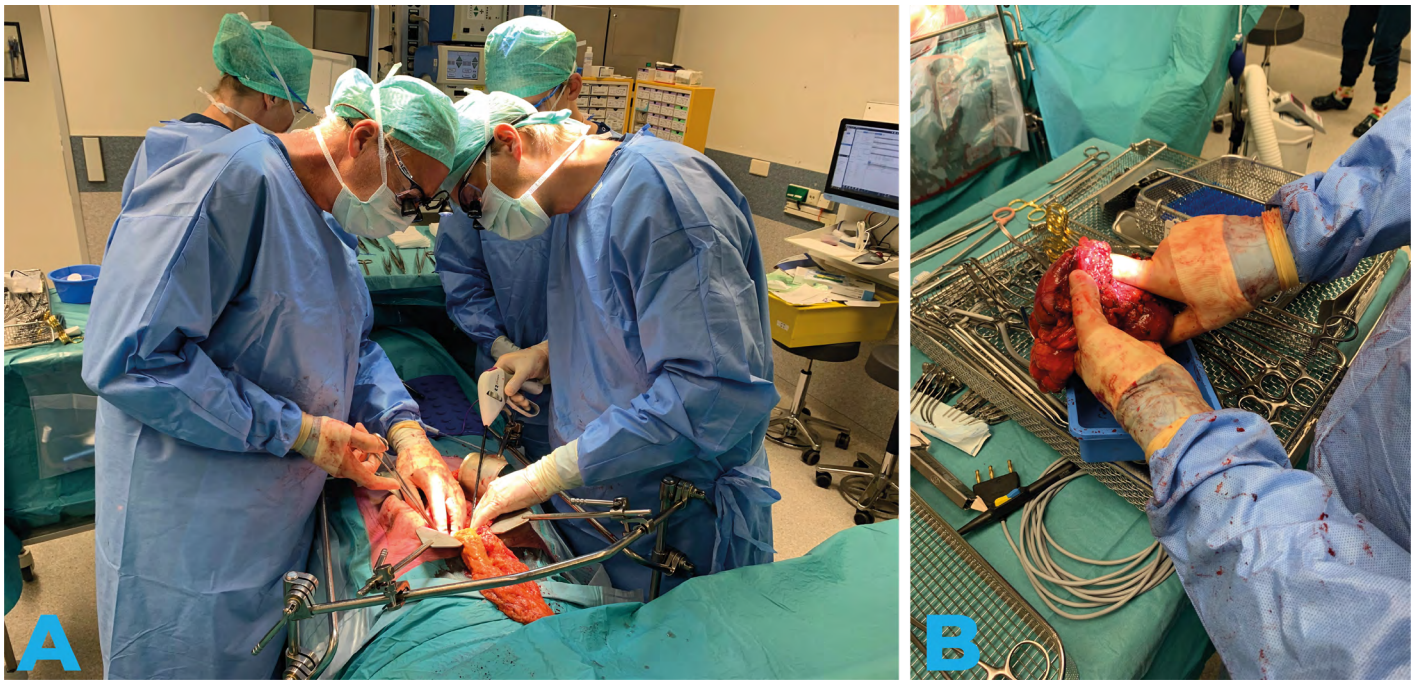

Figure 3.6. Pictures made during open pancreatoduodenectomy (OPD) (A) Overview of the surgical situation. (B) Surgeon demonstrating the anatomical relationship between the tumour, the pancreas and the PV-SMV.

Tumour resectability

Whether patients are eligible for surgical resection and, if yes, what type of surgical procedure is based on the resectability of the tumour and the performance status (PS) of the patients. The performance status scores the ability of patients diagnosed with cancer to perform activities of daily living without the help of others (26). Whether the patient is eligible for surgical resection depends on the preoperative radiological assessment of potential vascular involvement with the superior mesenteric artery (SMA), the common hepatic artery (CHA), the celiac axis (CA) and the portal vein-superior mesenteric vein (PV-SMV) (Figure 3.2).

To assess resectability, HPB surgeons and abdominal radiologists use resectability criteria defined by multiple (international) cancer associations, among others the Dutch Pancreatic Cancer Group (DPCG) and the National Comprehensive Cancer Network (NCCN) (14, 27). Based on these criteria, tumours can be classified as resectable, borderline resectable, and irresectable (Table 3.1). The National Comprehensive Cancer Network uses different cut-off points regarding the degrees of vascular involvement (14). However, the DPCG criteria were taken into consideration in this thesis.

Resectable tumours do not have arterial and/or <90° degrees venous tumour involvement. In case of no vascular involvement, resectable tumours are usually resected in RAPD according to the Miami International Evidence-based Guidelines on Minimally Invasive Pancreas Resection (28).

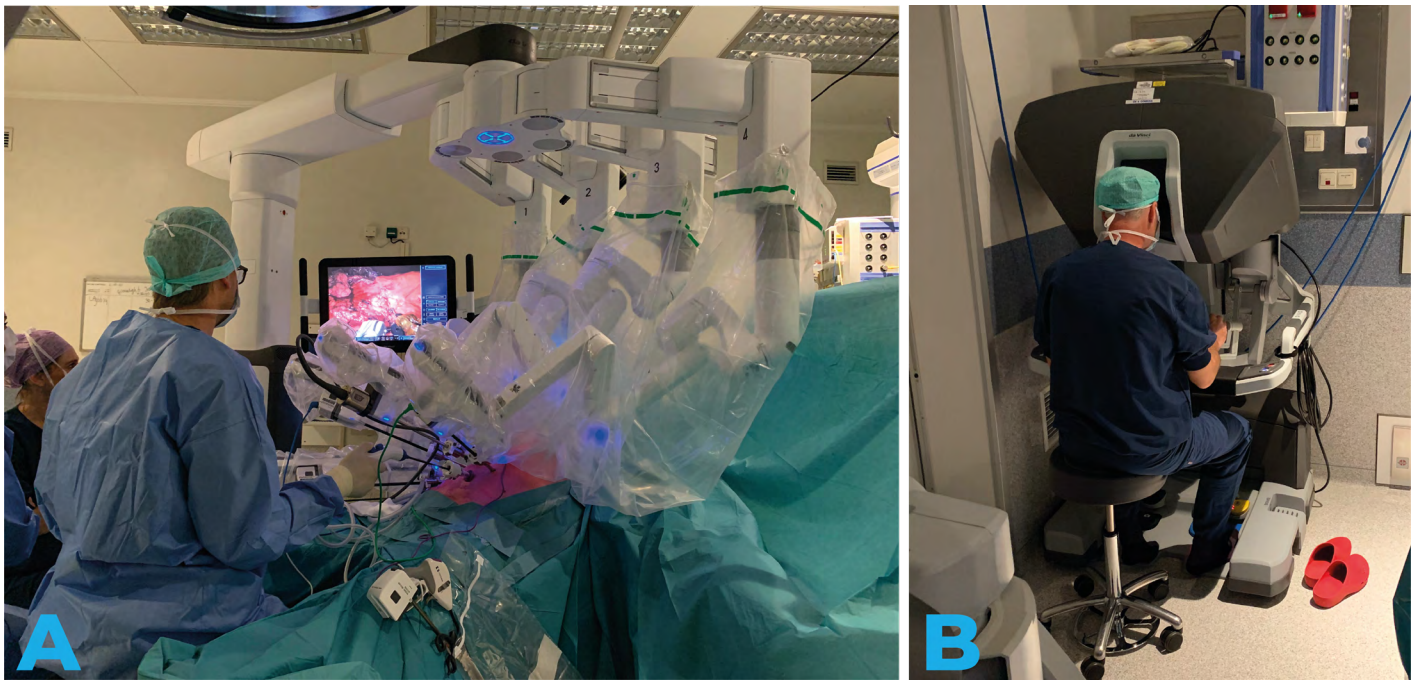

Figure 3.7. Pictures made during robot-assisted pancreatoduodenectomy (RAPD) at the Leiden University Medical Centre. (A) Overview of the surgical situation showing one of the surgeons assisting laparoscopically during the procedure. (B) Surgeon controlling the Da Vinci robot during pancreatoduodenectomy).

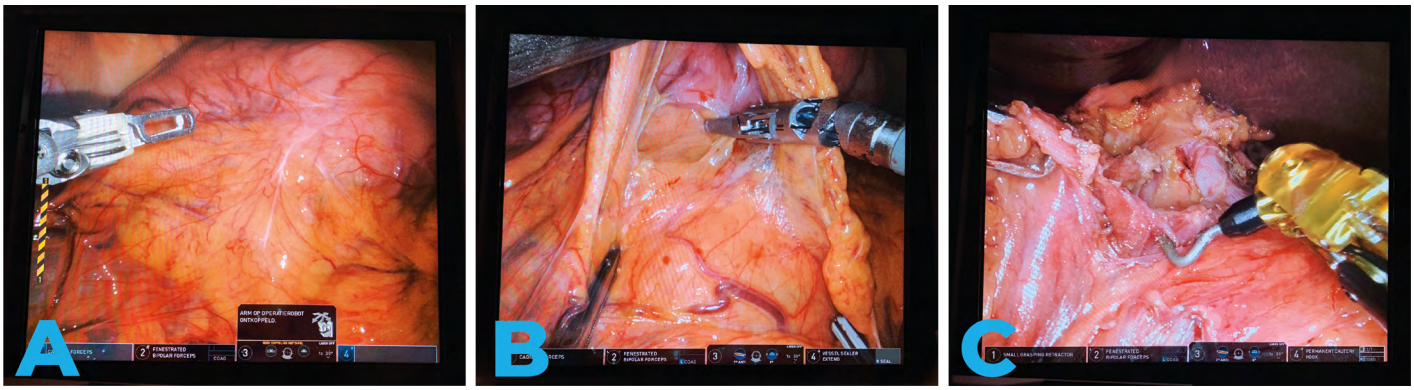

Figure 3.8. Pictures made of the display of the Da Vinci robot during robot-assisted pancreatoduodenectomy (RAPD) at the Leiden University Medical Centre. (A) Starting surgical situation. (B) Preparing organs for resection of the tumour. (C) Resecting the pancreas including the tumour.

Borderline resectable tumours have <90° degrees arterial or 90° - <270° degrees venous tumour involvement. According to the current guidelines, patients who present borderline resectable tumours undergo OPD after receiving neoadjuvant (chemoradio)therapy if the PS and the patient's wish allows for such a complex and invasive procedure (29). Neoadjuvant therapy usually consists of chemotherapy with or without radiation therapy before resection (1). If tumours have, after neoadjuvant therapy, >90° degrees arterial or >270° degrees venous tumour involvement or metastases, the tumour is classified as irresectable. Adjuvant systemic therapy (e.g. chemoradiation) as a palliative treatment option will be considered to improve quality of life and extend lifetime.

After patients undergo pancreatoduodenectomy, pathological examination of the resection status is essential in determining the right follow-up treatment and has been shown as an important prognostic factor (30). Three different resection margins are defined. An R0 resection margin means microscopic tumour clearance, which suggests that all the cancer is removed. An R1 resection margin means that all visible tumour tissue was removed during surgery. However, the pathologist suspect that small areas of cancer are still present based on the lab tests of the removed tissue. Lastly, an R2 resection margin means that the surgeon could not remove visible tumour tissue during the procedure (10).

Table 3.1. Dutch Pancreatic Cancer Group resectability criteria of pancreatic tumours (27).

	Superior Mesenteric Artery	Celiac Axis	Common Hepatic Artery	Portal Vein - Superior Mesenteric Vein
Resectable (all four required)	No contact	No contact	No contact	≤ 90° contact
Borderline Resectable (minimally one required)	≤ 90° contact	≤ 90° contact	≤ 90° contact	90°-270° contact and vessel occlusion
Irresectable (minimally one required)	contact > 90°	contact > 90°	contact > 90°	contact > 270° or occlusion

3.4 Preoperative planning

Careful evaluation of the available medical imaging should provide the surgical team with a comprehensive preoperative understanding to make appropriate decisions regarding the surgical technique, approach, personnel, and materials. Vascular involvement prediction is mainly based on the information provided by the multi-phase MDCT scans. Furthermore, to avoid the chance of vessel-related complications (e.g., damaging a blood vessel), the surgeon needs to identify variations in vascular anatomy and assess if the SMA and CA are accessible.

Resectability assessment

The DPCG has set clear cut-off points regarding the resectability based on the degrees of involvement and vessel occlusion (27). Discriminating between tumour, inflammatory, fibrotic, and healthy tissue after neoadjuvant therapy and predicting vascular involvement utilizing the imaging is experienced as highly challenging. This makes it in clinical practice difficult to determine, especially after neoadjuvant chemoradiotherapy, whether tumours are, for example borderline resectable or irresectable (Figure 3.9). Cassinotto et al. showed that the sensitivity of MDCT predicting vascular involvement is only 80% and drops to 50% after neoadjuvant treatment (31). Low sensitivities in preoperative radiological vascular involvement could result in performing surgical procedures in patients that were not eligible for PD.

Besides assessing the degrees of tumour-vessel contact, the length of the invasion (especially in the case of PV-SMV involvement) is significant for the prognosis of the patient. Patients who underwent surgery for resection of tumours involved in the PV-SMV have better long-term survival when the length of venous invasion was less than 3 cm (32). Surgeons need to determine more objectively and accurately the tumour-vessel contact trajectory.

Decision-making during preoperative planning

Decisions regarding neoadjuvant (chemoradio)therapy, the surgical technique, and whether vascular resection is needed are based on the vascular involvement prediction. In the case of vascular involvement, en bloc resection is seen as the golden standard in the high-volume centres. However, it occurs only in 20-40% of the cases that were preoperatively classified as vascular involved (16, 33). This indicates that the incidence of vascular resection is highly dependent on the pre-, and intraoperative judgement of the surgeon (34).

Unfortunately, limited comparative data regarding vascular resections performed with RAPD versus OPD exist. Consequently, evidence-based Miami Guidelines regarding minimally invasive pancreas resections prescribe that only highly experienced surgeons in high-volume centres perform vascular resections robotically (28). Beane et al. reported that a group of surgeons, which performed over 80 RAPDs before vascular resection, achieved comparable postoperative outcomes of RAPD with and without vascular resection (24, 35).

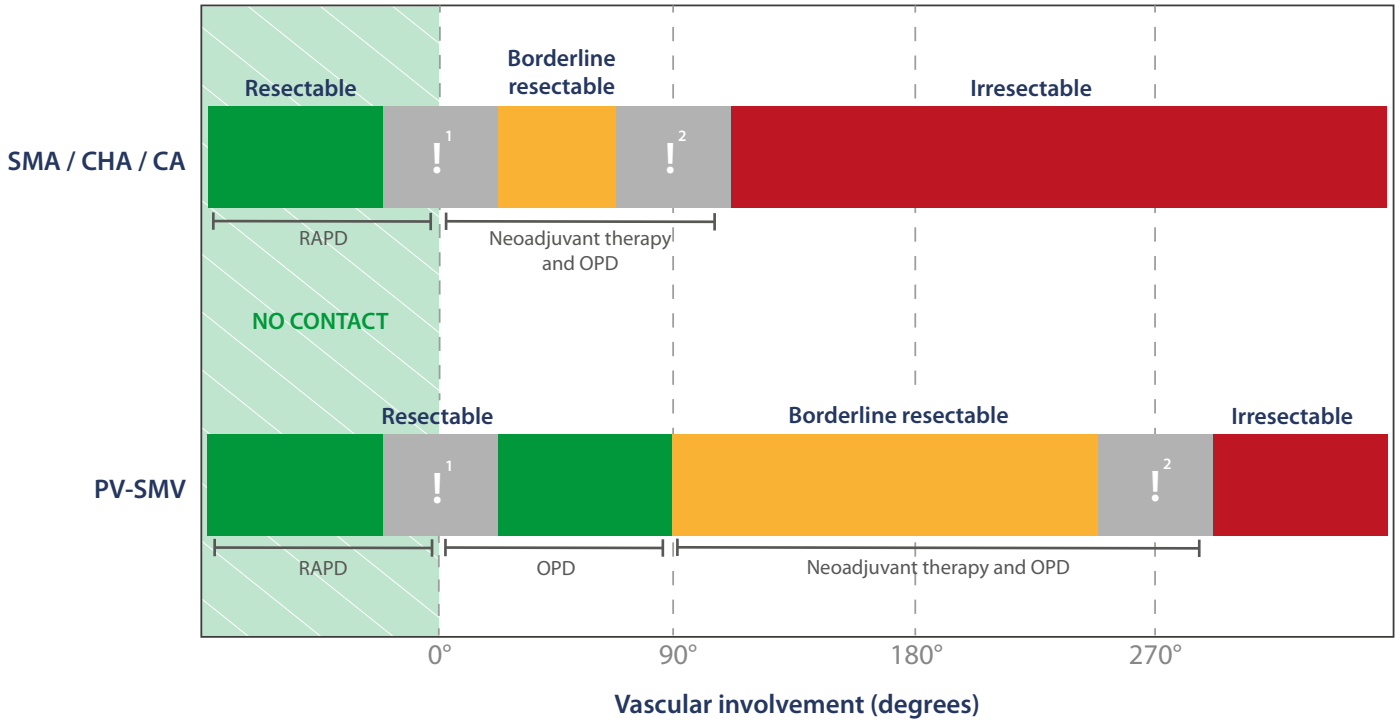

Figure 3.9. Resectability pancreatic carcinomas based on the criteria formulated by the Dutch Pancreatic Cancer Group (Table 3.1).
SMA = superior mesenteric artery; CHA = common hepatic artery; CA = celiac axis; PV-SMV = portal vein – superior mesenteric vein.
[1] Difficulties assessing whether tumours are resectable or borderline resectable and thus if patients are eligible for RAPD.
[2] Difficulties assessing whether tumours are borderline resectable or irresectable and thus if patients are eligible for OPD after neoadjuvant therapy.

However, the study did show an increased estimated blood loss (EBL), operating time (OT) and conversion rate (RAPD to OPD). According to the Miami Guidelines vascular resections are not a strong contraindication. Although, Dutch HPB surgeons generally agreed that vascular resections should not be performed robotically before a surgeon has performed over 100 RAPDs. To improve resectability assessment, reduce the chance of irradical resection, and stratify patients for the right surgical technique surgeons need to determine more accurately and confidently the extend of vascular involvement.

Anatomical understanding

A comprehensive anatomical understanding of the vascular system is required to reduce vessel-related complications. Even though many patients present typical vascular anatomy, arterial anomalies in the pancreatic region (e.g., aberrant right hepatic artery) and variations in the PV-SMV anatomy are commonly observed (32). Identifying these variations is considered crucial in the planning of these procedures.

Furthermore, in the case of chronic occlusion of the SMA and/or CA caused by atherosclerosis or median arcuate ligament compression, the mesenteric blood flow is maintained by collateral circulation between the gastroduodenal artery (GDA) and inferior mesenteric artery (IMA). The GDA is commonly fully encased by pancreatic head tumours and will be sacrificed fied in such cases. When mainly the GDA takes care of the mesenteric blood supply, concerns regarding potential intestinal ischemia arise if this artery is sacrificed. Therefore, the accessibility of CA and SMA should be carefully assessed to decide whether preoperative stenting or a bypass is needed before performing PDs (36).

3.5 References

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Chapter 4

User study comparing 3D visualization techniques

This chapter briefly describes the explorative and qualitative user study, including clinicians from CZE performed by the Philips team working on the pancreas work package. Multiple 3D visualization techniques and CAD concepts were compared to identify which technique would potentially add the most value and learn how the prototypes could be improved. Additionally, clinical stakholders' needs during diagnosis, surgical planning, and treatment phase have been identified. This need analysis was part of the preparatory work of the main thesis project. (Picture made during the user study at Philips)

4.1 Introduction

Whether patients are eligible for surgical resection of pancreatic cancer is based on the resectability, defined by multiple (international) cancer associations, among others the Dutch Pancreatic Cancer Group (DPCG) (1). Predicting vascular involvement using imaging is experienced as highly challenging. This makes it in clinical practice difficult to determine whether tumours are, for example, borderline resectable or irresectable.

Besides determining resectability, surgeons also need carefully evaluate the preoperative imaging to prepare for irregular and unpredictable spatial conformation of the patient-specific anatomy (2). Currently, surgeons need to mentally translate the two-dimensional (2D) imaging into the three-dimensional (3D) surgical situation, which create a subjective understanding of the patient anatomy (3, 4). This often results the fact that surgeons can only understand the patient-specific anatomy to a certain extent before surgery and need to evaluate the situation again intraoperatively, which could result in unexpected situations.

Computer-aided detection and diagnosis (CAD) classification and segmentation algorithms based on artificial intelligence techniques like Convolutional Neural Networks (CNNs) that provide pixel-level annotations of the tumour, and surrounding structures could potentially help improve resectability assessment (5). In addition, 3D patient models displayed on 3D visualization techniques like on a 2D display (3D-on-2D), virtual reality (VR), 3D printing (3DP) and 3D display) could potentially aid the surgeon in preoperatively planning complex resection surgeries. The aim of this user study was to explore and gain qualitative feedback on the value of anatomical annotations (to simulate CAD-generated segmentations) integrated into 3D patient models displayed on various 3D visualization for the diagnosis and treatment planning of pancreatic cancer.

4.2 Methods

Participants

Eight healthcare professionals that are part of the pancreatic oncology multidisciplinary team (two expert surgeons, three surgical residents, one expert radiologist, one radiology resident, and one gastroenterologist) from the Catharina Hospital Eindhoven (CZE) were included in this user study.

Data

The data of one patient that was diagnosed with a borderline resectable pancreatic tumour that underwent surgery in the CZE was used in this study. The CT scans and annotations of the relevant structures (pancreas, arteries, veins, gall bladder, tumour) were received from the CZE. The annotations were converted to 3D patient models. The anatomical structures were annotated by a surgical resident from CZE and were supervised by an expert radiologist. The annotations were not generated by artificial intelligence.

Prototyping

Multiple (3D) prototypes based on the anatomical annotations were developed to compare in this user study. Firstly, an open-source medical imaging viewer, ITK-SNAP, was used to present the CT scans and annotations (6). Secondly, a 3D model was reconstructed in Unity (Unity Technologies, San Francisco, CA, USA) and displayed by different visualization techniques (Figure 4.1)(7). The 3D patient model was displayed as 3D model on a regular 2D screen (3D-on-2D), in VR on an Oculus Quest (Oculus VR, United States of America, SF, California, Irvine), on the Looking Glass as an autostereoscopic 3D display based on lenticular lenses (Looking Glass Factory, United States of America, NY, Brooklyn) and was reconstructed physically as 3D printed model (3D Systems, United States of America, SC, Rock Hill) (8-10). Lastly, a CAD mood board including was created to mimic outcomes regarding resectability assessment that CAD could potentially generate based on automatically generated annotations (Figure 4.2).

Study design

The patient was introduced by a fictional case description, including age, comorbidities, and symptoms. In this study, participants had to determine the tumour resectability and formulate the surgical strategy. First, participants started to evaluate the CT scan of the patient on the ITK-SNAP imaging viewer, which was followed by evaluation CT scan by adding the annotations.

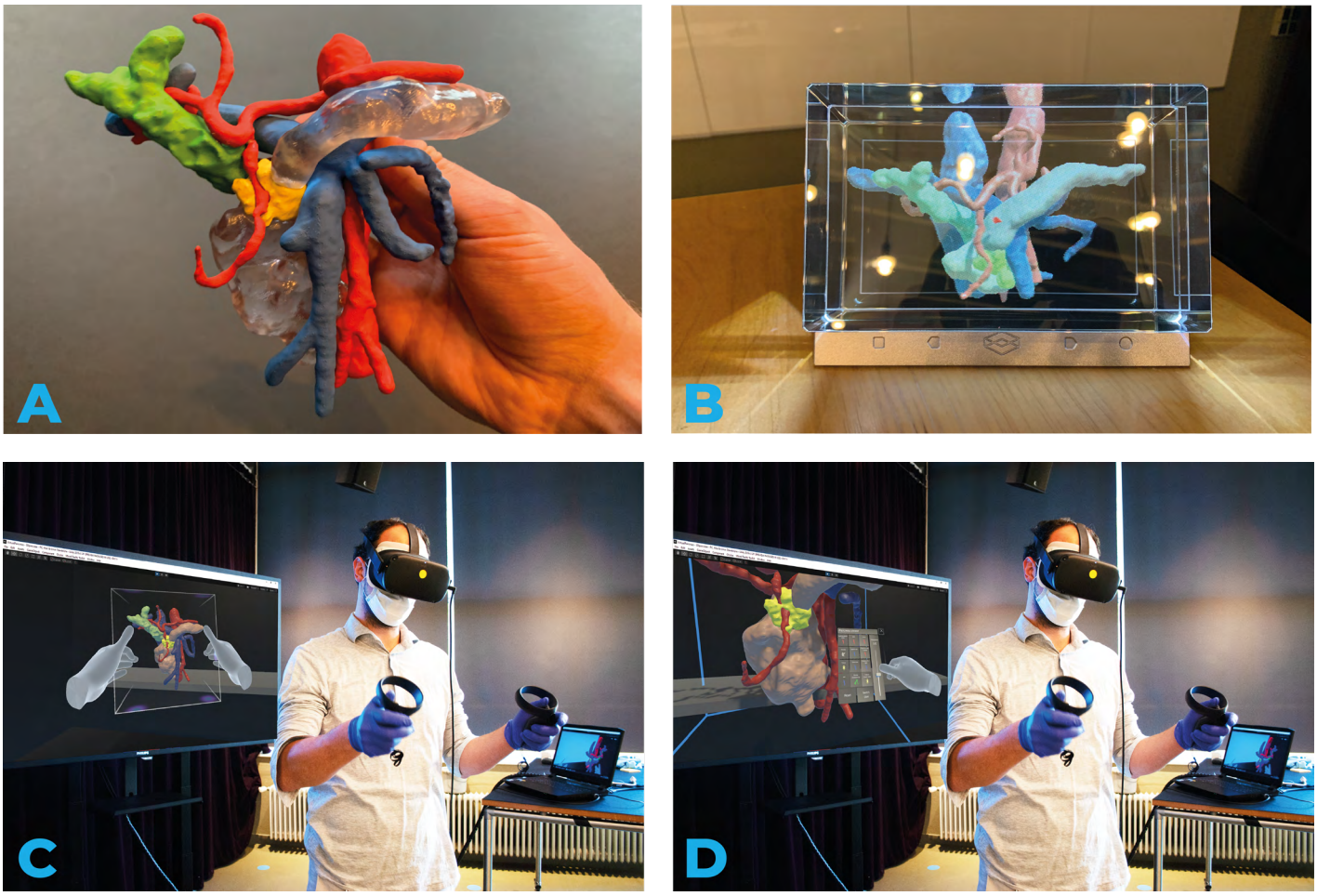

Figure 4.1. Pictures showing different prototypes used in the user study conducted in December 2020. (A) Physical 3D printed patient model. (B) 3D patient model displayed on the Looking Glass. (C) Edited picture illustrating a participant interacting with the 3D model in virtual reality. (D) Edited picture illustrating a participant interacting with the 3D model zoomed in in virtual reality via the user-interface.

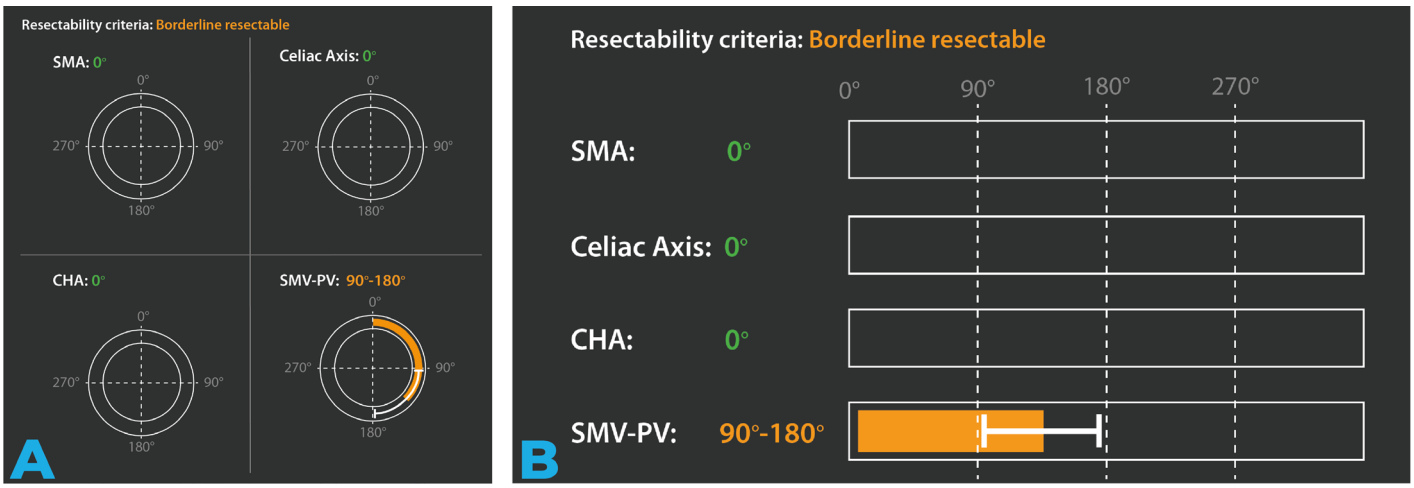

Figure 4.2. CAD concepts communicating the degrees (90° - 180°)of vascular involvement with the portal vein – superior mesenteric vein. (A) Pie chart. (B) Bar chart.

Secondly, the 3D models were evaluated, starting with the 3D-on-2D, followed by the 3D printed model, the VR model, and the 3D model on the 3D display. Finally, the CAD mood board was presented to the participants. After experiencing the prototypes, the participants were asked if and how the prototype changed the decision regarding the treatment plan.

While interacting with the prototypes, the participants were asked to think aloud and open and semi-structured interview questions to gather qualitative feedback were asked. These questions were focused on the expected added value of these techniques, how it would potentially fit within their workflow, and the user experience.

Data collection and analysis

All data collected during the user study including audio recordings, video recordings, screen recordings, pictures, and written notes were gathered and combined in preparation for analysis. Video and audio recordings will be transcribed in Microsoft Excel. After transcribing, clinical and usability needs were identified based on their quotes. Needs were categorized in themes, the level of need fulfilment was determined (unmet, partially met, met, not needed), and it was reported to which prototype the need belongs.

4.3 Results

After transcribing and analysing >10 hours of video and audio material, 16 clinical needs regarding pancreatic cancer-related tasks were identified and mapped against the specific phases in the workflow of the clinicians (Figure 4.3). Additionally, after evaluating the different 3D visualization techniques and the CAD mood board, 28 usability needs regarding the prototypes were identified (Figure 4.4). The most important qualitative findings mentioned by the participants regarding the value of the prototypes are described below.

Annotations

The annotations were perceived as helpful in detecting and localizing tumours. Annotations made the size of the tumour more apparent and clearly showed the interaction of the tumour with the relevant vessels. It would help communicate the CT scan findings to other (less experienced) clinicians and help non-expert hospital increase their sensitivity in tumour detection and potentially decrease the number of missed tumours.

3D printed models

3D printed models provided a natural depth perception and were perceived as practical, especially during the multidisciplinary team (MDT) meetings since everyone would be able to see and touch the model. However, the 3D printed model could not be taken apart to get a better view of the tumour-vessel interaction. Furthermore, the models need to be reconstructed and printed, which currently lasts a couple of days. Besides the printing time, it also brings additional costs per printed model, which would make the use of 3D models more expensive.

Virtual Reality

Participants mentioned that VR patient models would not fit well into the clinical workflow. It must be set up before every use, which makes it a hassle to quickly look again to the 3D patient model. Additionally, participants mentioned that they were completely disconnected from the 'real' world making it less feasible for discussions (e.g., MDT meetings). Lastly, the interactions were experienced as difficult and required a learning curve, making VR less user-friendly and easy to use.

Looking Glass

Participants perceived the 3D model interactions (with mouse and keyboard) on the 3D display as relatively easy and were experienced as user-friendly and intuitive. Next, they mentioned that the 3D display could be easily integrated into the workflow of surgeons. According to the feedback, the 3D display provided them with a good depth perception close to reality. Lastly, participants mentioned that the 3D display enables them to easily switch between the medical imaging viewer and the 3D display.

CAD Moodboard

The mocked-up CAD outcomes regarding the degrees of vascular involvement, visualized in bar or pie charts, were perceived as helpful. Participants mentioned that combining CAD outcomes with the 3D models gave them a complete overview of the resectability situation. However, participants mentioned that it is essential to communicate the (statistical) validation of the outcomes in the future and to explain (as much as possible) the working principle of the algorithm.

4.4 Discussion

It can be concluded from this user study that 3D patient models displayed on 3D visualization techniques and the mocked-up CAD outcomes could potentially improve the surgical planning for treating pancreatic cancer. The models could be applied for diagnosis, preparation of the surgery, intraoperative use, team communication, and patient communication purposes.

Compared to 3D printed and VR models, the 3D display provides clinicians with the benefits of 3D depth perception and intuitive digital interactions (changing transparency and manipulating the model) while being easy to integrate in the workflow. 3D displays can be set up in the outpatient clinic, the expert's personal desk, in the OR , making it widely applicable for the complete course of the workflow.

Determining the degrees of vascular involvement is still done by the human eye. Especially discriminating between tumour, inflammatory, fibrotic, and healthy tissue after neoadjuvant therapy and predicting vascular involvement and resectability using the currently available imaging is experienced as highly challenging. Therefore, it would be helpful for radiologists and surgeons to quantify the vascular involvement based on the automatically generated annotations after neoadjuvant therapy. This might make the resectability assessment more accurate while providing surgeons and radiologists more confidence in their decision.

Combining autostereoscopic 3D models with CAD outcomes could provide a complete overview of the patient-specific anatomy, improving the resectability assessment of pancreatic tumours and the surgical planning quality. In the next iteration, an integrated platform that comprises the CT viewer, the 3D models and CAD suggestions should be developed to meet the needs identified in this study. By means of such platform, further research should be done to perform more quantitative research regarding the added value of these techniques.

4.5 References

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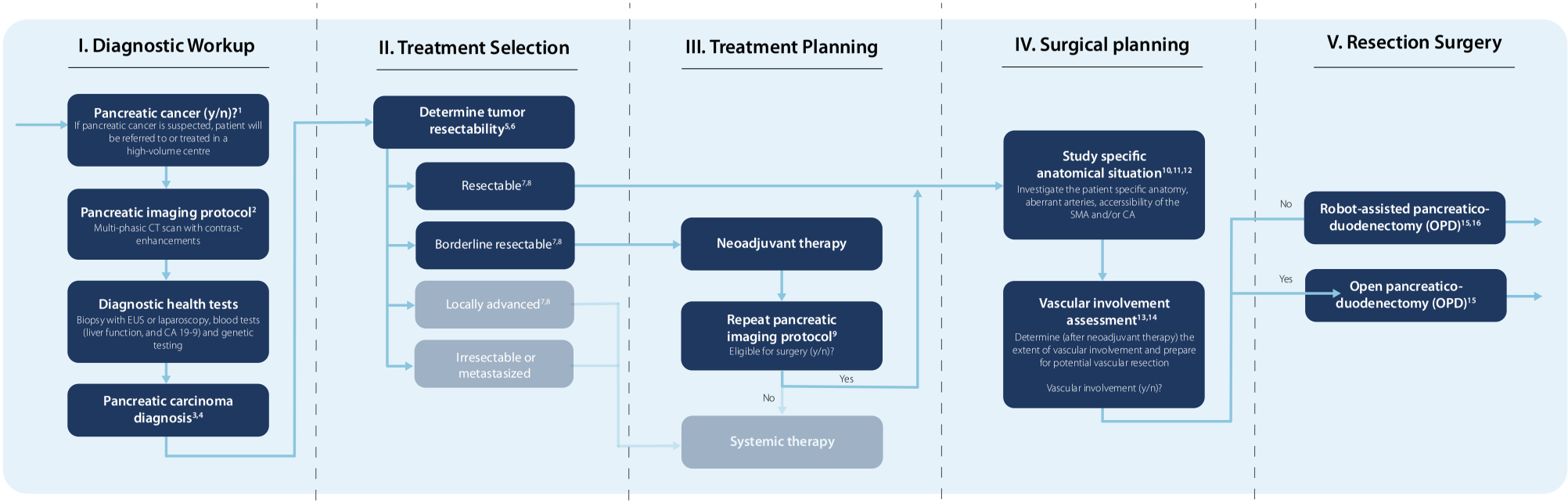


1. **Patient referral**
I NEED non-expert hospitals to improve pancreatic tumor detection/localization SO THAT patient referral to expert hospitals is improved.

2. **Tumor detection**
I NEED to identify primary (e.g. hypoattenuation) and secondary signs (e.g. pancreatic duct cut-off, dilatation of the pancreatic duct or common bile duct) of pancreatic cancer on (contrast-enhanced) medical imaging SO THAT I improve detection/localization of the tumor.

3. **Tumor detection**
I NEED to improve discrimination between types of abnormalities (carcinoma, benign tumor, pancreatitis) SO THAT I increase my diagnostic certainty.

4. **Metastases detection**
I NEED improved detection of metastases (in liver, lymph node, and other organs) TO improve treatment stratification (prior to surgery).

5. **Tumor classification**
I NEED better discrimination between tumor, inflammatory, fibrotic, treated and healthy tissue TO improve the assessment of resectability and reduce the chance of irradical resection.

6. **Vascular involvement (ingrowth)**
I NEED TO determine the extent of vascular ingrowth TO improve patient stratification for resection, determine surgical strategy and reduce chance of irradical resection.

7. **Vascular involvement (degrees)**
I NEED TO determine the degrees of contact between the tumor and vascular structures TO improve patient stratification for resection, determine surgical strategy and reduce the chance of irradical resection.

8. **Vascular involvement (length)**
I NEED TO determine more objectively the length of the tumor-vessel contact trajectory TO improve patient stratification for resection, determine surgical strategy and reduce chance of irradical resection.

9. **Tumor classification**
I NEED better discrimination between tumor, inflammatory, fibrotic, treated and healthy tissue TO improve the assessment of resectability (after neoadjuvant therapy) and reduce the chance of irradical resection.

10. **Understanding patient specific anatomy**
I NEED get a peroperative view of the anatomical structures (e.g. bifurcation of jejunal branch) SO THAT I can better understand the spatial conformation of the patient specific anatomy.

11. **Understanding varying vascular anatomy**
I NEED to identify and understand the spatial conformation of the anatomical variations (e.g. aberrant arteries) SO THAT I can reduce the risk of complications during (minimally invasive) surgery (e.g. chance of damaging blood vessel) and the chance of irradical resection.

12. **Understanding patient specific anatomy**
I NEED recognizable (patient specific) anatomical waypoints/landmarks that affirm my surgical approach SO THAT I can better prepare for (vascular) resection.

13. **Prepare vascular resection**
I NEED TO assess if and how I can do a vascular resection SO THAT I can better prepare the surgical procedure (e.g., prepare myself, consult a vascular surgeon in the planning, plan a vascular surgeon to join the surgery) or decide not to operate.

14. **Prepare vascular resection**
I NEED TO know the length of the tumor-vessel contact trajectory SO THAT I can judge if I can reconstruct veins with sufficient blood outflow.

15. **Intraoperative communication**
I NEED the surgical team to have a common understanding of the patient specific anatomy and the surgical plan SO THAT I can optimally execute the surgical procedure.

16. **Intraoperative navigation**
I NEED have an improved view of the tumor and the surrounding anatomical structures during (minimally invasive, i.e. laparoscopic or robotic) surgery SO THAT I can better navigate during my procedures and reduce the chance of complications (e.g. chance of damaging blood vessel) or irradical resection.

Figure 4.3. Clinical needs, extracted from the qualitative analysis of the e/MTIC user study with CZE, mapped against the simplified workflow analysis.

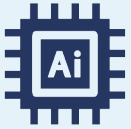
Medical imaging viewing application

1. **Imaging quality**
   I NEED a high quality CT scan (thin section and proper contrast administration) SO THAT I can accurately identify tumor location and assess resectabilityrounding structures.
2. **Imaging settings**
   I NEED TO (easily) have the right image viewing settings SO THAT I have the best view on patient anatomy.
3. **Patient identification**
   I NEED to be sure that I am not looking at an outdated image SO THAT I am confident that the tumor did not progress before surgery.
4. **Workflow fit**
   I NEED different solutions (AI and/or 3D) for different pain points accross the carepath.
5. **Workflow fit**
   I NEED the 3D model and AI suggestions to be instantly available at the points of care SO THAT it is easy to access.
6. **Annotations**
   I NEED annotations of the tumor and relevant structures SO THAT I as a non-expert in reading CT scans, improve my ability to localize and delineate abnormalities in relation to surrounding structures.
7. **Annotation validation**
   I NEED TO validate the annotations with the conventional imaging SO THAT I am more confident that what I saw on the segmentations model is correct.

Three-dimensional visualization techniques

8. **Level of realism**
   I NEED to have stereoscopic visualizations SO THAT I get a realistic depth perception of the 3D model.
9. **3D model interaction**
   I NEED TO rotate the model to look at structures from different angles.
10. **3D model interaction**
    I NEED an easy way to know the (keyboard) controls to manipulate the 3D Model.
11. **3D model interaction**
    I NEED a model that is intuitive to handle.
12. **Predefined viewpoints**
    I NEED TO select in one click the tumor and vasculature in the model SO THAT I can quickly focus on the relevant structures.
13. **Visibility of surrounding structures**
    I NEED to turn structures (e.g. tumor) on/off SO THAT I have better visibility of the relation with surrounding structures.
14. **Visibility of surrounding structures**
    I NEED to adjust the transparancy of structures (e.g. tumor) SO THAT I have better visibility of the relation with surrounding structures.
15. **Vascular involvement emphasis**
    I NEED a footprint where the tumor interacts with other relevant structures.
16. **Vascular involvement assessment**
    I NEED to be able to have insight or measure metrics related tovascular involvement and simulate a proposed surgical plan SO THAT I can anticipate on the possible outcome.
17. **Vascular involvement assessment**
    I NEED TO view the important vasculature from the inside SO THAT I can assess the extend of vascular ingrowth.
18. **Real-time registration**
    I NEED a real-time connection between the echoscopy location and 3D model (i.e. marker) SO THAT I improve biopsy guidance.
19. **Multi-user aspect**
    I DO NOT WANT to be disconnected from my environment during the multiple phases of the workflow SO THAT I can still communicate with people around me when studying the model.
20. **Communication**
    I MIGHT NEED to record the preoperative surgical plan SO THAT I can better perpare venous reconstruction and use it to brief the OR team.

Artifical Intelligence Suggestions



21. **AI output validity**
    I NEED to know what the AI output is based on (e.g. ground truth) and affected by (e.g. scan quality) SO THAT I improve interpretability of confidence levels and cut-off levels.
22. **Vascular involvement assessment**
    I NEED the AI to communicate what tumor, inflammatory, fibrotic, treated and healthy tissue is SO THAT I can improve the resectability assessment and the planning of venous reconstruction.
23. **Vascular involvement quantification**
    I NEED the AI output to communicate the degrees of tumor contact and the uncertainty of the degree prediction SO THAT I improve the resectability assessment.
24. **Vascular involvement quantification**
    I NEED the AI output to communicate the length of the tumor-vessel trajectory and the uncertainty of the trajectory prediction SO THAT I improve the assessment resectability.
25. **AI output explainability**
    I NEED TO instantly understand in which orientation the AI based output regarding the degrees of vascular involvement (with respect to the patients body) SO THAT I do not get confused.
26. **AI output validity**
    I NEED freedom in the interaction flow of reviewing AI findings and medical images of different dates and type, SUCH THAT I can switch to the information that I need for decision-making.
27. **AI output validity**
    I NEED to validate what I see (e.g. length of tumor vessle contact) in the 3D model on the CT image SO THAT I am more confident that what I saw in the 3D model is correct.
28. **Vascular involvement emphasis**
    I NEED to assess the (emphasized) vascular involvement in multiple dimensions at once SO THAT I can see in one view what the contact looks like.

Figure 4.4. Usability needs, extracted from the qualitative analysis of the e/MTIC user study with CZE, mapped for the medical imaging platform, three-dimensional visualization techniques and artificial intelligence suggestion.

Chapter 5
The Design and Development of an Integrated Medical Imaging Workstation

This chapter describes the design process and technical details regarding the development of the integrated medical imaging workstation comprising 3D visualization techniques and CAD suggestions. The final set-up is a hard- and software combination that consist of four major parts: 1) a CT imaging viewer 2) interactive autostereoscopic 3D patient models displayed on a 3D display 3) CAD-derived metrics regarding tumour-vessel involvement, and 4) a user-interface functioning as layout that visualizes the CAD outcomes, the CT views, and the 3D models. (Picture made by Diederik Rasenberg at Philips).

5.1 Introduction

Decisions in the surgical planning of pancreatic tumours are mainly based on the vascular involvement prediction. However, discriminating between tumour, inflammatory, fibrotic, and healthy tissue predicting vascular involvement, especially after neoadjuvant therapy using regular radiological imaging is experienced as highly challenging. Clinical guideline-based metrics derived on the CAD-generated segmentations (e.g., degrees of tumour-vessel contact) could provide surgeons and radiologists with more accurate information regarding the extent of vascular involvement. Besides, 3D patient-specific models of the tumour, pancreas, and surrounding vascular structures could be generated from these CAD-generated segmentations. Displaying these 3D models on autostereoscopic techniques with a realistic depth perception provides clinicians with a better spatial understanding of the complex anatomical conformation and relationships (2). The aim of this objective was to design and develop a prototype (hardware and software combination) that integrates an integrated platform (hard- and software combination) autostereoscopic 3D patient models and CAD suggestions regarding vascular involvement. By means of such platform, further research should be done to perform more quantitative research regarding the added value of these techniques.

5.2 Prototype requirements

The prototype was developed by the project members Luc Geurts, Bin Yu and Diederik Rasenberg (lead). Based on the findings of the systematic review (Chapter 2), additional desk research and the workflow analysis (Chapter 3), and the user study findings (Chapter 4), prototype requirements were defined in agreement with the e/MTIC Oncology project team (Table 5.1). The prototype requirements were structured according to MoSCoW guidelines to describe the relative importance of each requirement (3). This technique helps to understand and manage priorities regarding prototype development. The letters in the word MoSCoW stand for: 'Must have', 'Should have', 'Could have', and 'Won't have this time'. All development steps are further described in this chapter.

5.3 Data acquisition and processing

Data acquisition

The data of retrospectively collected and de-identified patient cases have been provided by CZE. The data consisted of the baseline patient data and medical imaging data. This medical imaging data consisted of two parts, namely the digital imaging and communication in medicine (DICOM) files of the multi-phasic CT scan and the visualization tool kit (VTK) and stereolithography (STL) annotation files. The following structures were annotated: tumour, pancreas, aorta, superior mesenteric artery, celiac axis, common hepatic artery, splenic artery, gastroduodenal artery, vena cava, vena porta, superior mesenteric vein, inferior mesenteric vein, splenic vein, aberrant arteries.

Data processing

The flowchart provided in Figure 5.1 visualizes all data that is implemented in the prototyping platform. Baseline patient data from the electronic health records (EHR), medical imaging data, and pixel-level were acquired from the Catharina Hospital Eindhoven (CZE)(4). After receiving the data from the CZE, the multi-phasic CT scans were uploaded to the Orthanc Server (the University of Liège, Department of Medical Physics, Liège, Belgium), which is an open-source and lightweight DICOM server for medical imaging (5). This server was installed locally on a Philips workstation and was not connected to the internet. The Orthanc Server sends the DICOM data towards the integrated medical imaging viewer. The pixel-level annotations have been created in IntelliSpace Portal (ISP) based on the multi-phasic CT scans (4). Annotations were received by the CZE as VTK files and needed to be converted to NIfTI files (Neuroimaging Informatics Technology Initiative) for further processing in Python (Python Software Foundation, Wilmington, Delaware, USA) (6). Degrees of vascular involvement and the length of tumour-vessel trajectory has been quantified in Matlab (MathWorks, Natick, MA, USA) (7). Next, the quantification data were imported and processed as comma-separated values (CSV) files into the workstation. The processed annotations, NIfTI files, including the footprint data have been converted towards JSON files (JavaScript Object Notation) were then imported into the workstation.

Table 5.1. Prototype requirements

Category	Priority	Description
Data acquisition and processing		
Case collection	M	Acquire all patient data consisting of baseline data, CT imaging data and annotation files from CZE needed for the prototype.
Data structuring	M	Structure all relevant patient (medical imaging) data and corresponding 3D models and quantification data on a safe storage.
Data conversion	M	Convert annotation files to appropriate file structures for further processing.
Medical imaging workstation		
Upload CT data	M	Upload CT data of included patient cases on Orthanc server.
UX/UI design	M	Design the user-experience and -interface (UX/UI) according to the pancreatic cancer workflow and guidelines.
Medical Image Viewer	M	Developed web-based medical imaging viewer with basic medical imaging functionalities
Annotations	M	Functionality that creates the colour-coded anatomical annotations as overlay outline on the medical imaging.
Multi-planar reconstruction	S	Implement functionality that reconstructs two-dimensional orthogonal axial slices (z-axis) into coronal slices (x-axis) and sagittal slices (y-axis).
Crosshair interaction	S	Implement crosshair interaction on three viewports that indicates the location in each direction based on the 3D coordinate system (x, y, z) of the CT scan.
Vascular involvement quantification algorithm		
Quantification algorithm	S	Develop algorithm that quantifies the number of degrees and length of the tumor-vessel trajectory of vascular involvement
Footprint calculation	S	Develop algorithm that calculates the tumor footprint of the involved vessel and exports this footprint as annotation file.
Three-dimensional visualization of anatomical patient models		
Develop 3D models	M	Create for every included patient case based on the anatomical annotations the 3D models
Connection medical imaging viewer and 3D display	S	Develop a server that communicate predefined viewpoints from the medical imaging viewer towards the 3D model.
Transparency functionality	S	Develop functionally that allows the user to change the transparency of anatomical structures of interests in the 3D model by using the computer mouse.
Integrate 3D footprint	S	Convert tumor footprint calculation to 3D structure and integrate this artificially generated structure in the 3D patient-specific models.
Predefined viewpoints	S	Define and develop predefined viewpoints in the 3D model
Bigger 3D display	C	Arrange bigger and/or better 3D display.
3D crosshair	W	Implement crosshair in the 3D model that indicates the location of the volumetric CT model in each direction based on the 3D coordinate system (x, y, z) of the CT scan.

M = must have; S = Should have; C = Could have; W = Will not have.

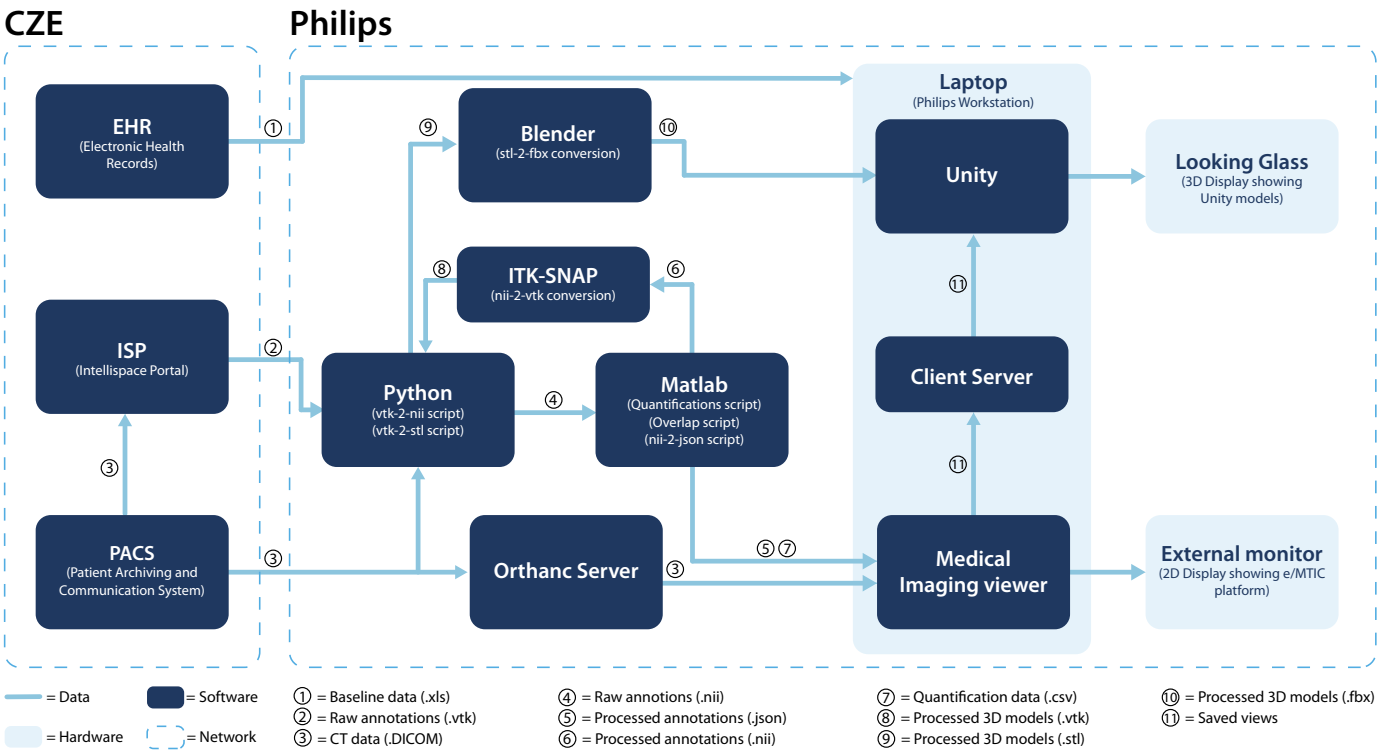


Figure 5.1. Flowchart of all data used in the integrated medical imaging workstation created by Diederik Rasenberg.

Regarding 3D model reconstruction, the processed annotations were first imported in ITK-SNAP, which is an open-source medical imaging viewer, for conversion to VTK files (8). Secondly, these VTK files were converted to STL files in Python (6). Thirdly, the STL files of the 3D reconstructions were imported in Blender, which is open-source 3D modeling software, for conversion to FBX (Film box) files (9). The processed annotations, JSON files, were then imported into the e/MTIC platform. The processed 3D Models were imported and processed into Unity (Unity Technologies, San Francisco, CA, USA) (10). Using Unity, the 3D patient models were displayed on the Looking Glass (1).

5.4 Medical imaging workstation

Prototype design

The UX/UI of the prototype was designed and developed by Diederik Rasenberg in Adobe XD (Adobe Inc. United States of America, California, San Jose) (11). The design was focused on integrating the medical imaging viewer, the 3D display, and the CAD suggestions. The final design is shown in Figure 5.2 and Figure 5.3.

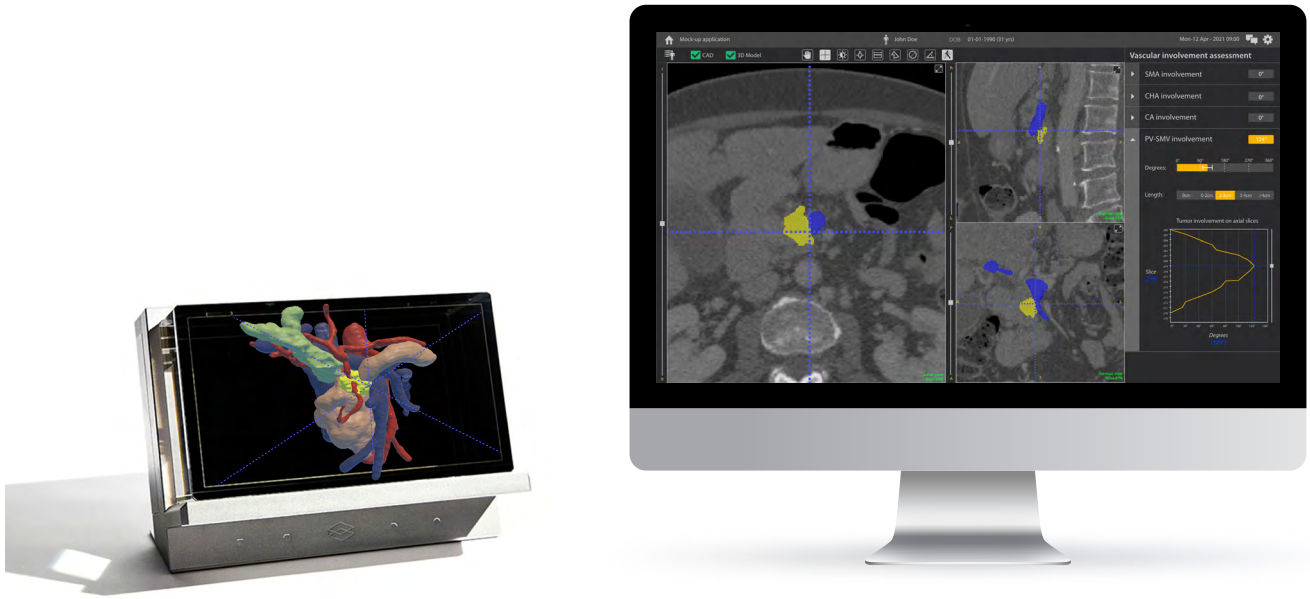


Figure 5.2. Final design UX/UI of the integrated medical imaging workstation

First, the design comprises three different viewports to present the CT scan in different anatomical directions (axial, coronal, and sagittal). Multiple functionalities, shown as icons on the top menu bar, are integrated into the design to manipulate the CT scan by zooming, panning, windowing (grey-value mapping), and magnifying.

Next, the design of the CAD-panel communicates the guideline-driven vascular involvement metrics. The panel is designed to have two layers. The first layer communicates a range of degrees of tumour-vessel contact (according to resectability criteria) for the relevant vessels (12). The second layer provides a more detailed overview of the quantifications regarding vascular involvement for a specific vessel. In this layer, an interactive chart shows the degrees of contact calculated per CT slice. In addition, the length of the trajectory will be calculated.

Thirdly, the 3D patient-specific model will be displayed on a 3D display that is synchronized with the medical imaging viewer and the CAD panel. When the user clicks on one of the quantified vascular involvements, a crosshair in the 3D model, the medical imaging viewer and the interactive chart in the CAD panel will navigate, based on the coordinate system of the volumetric image, to automatically generated viewpoints where the involvement is detected. These viewpoints should provide the clinician with the most optimal view of the 3D model or slice of the CT scan to assess the vascular involvement.

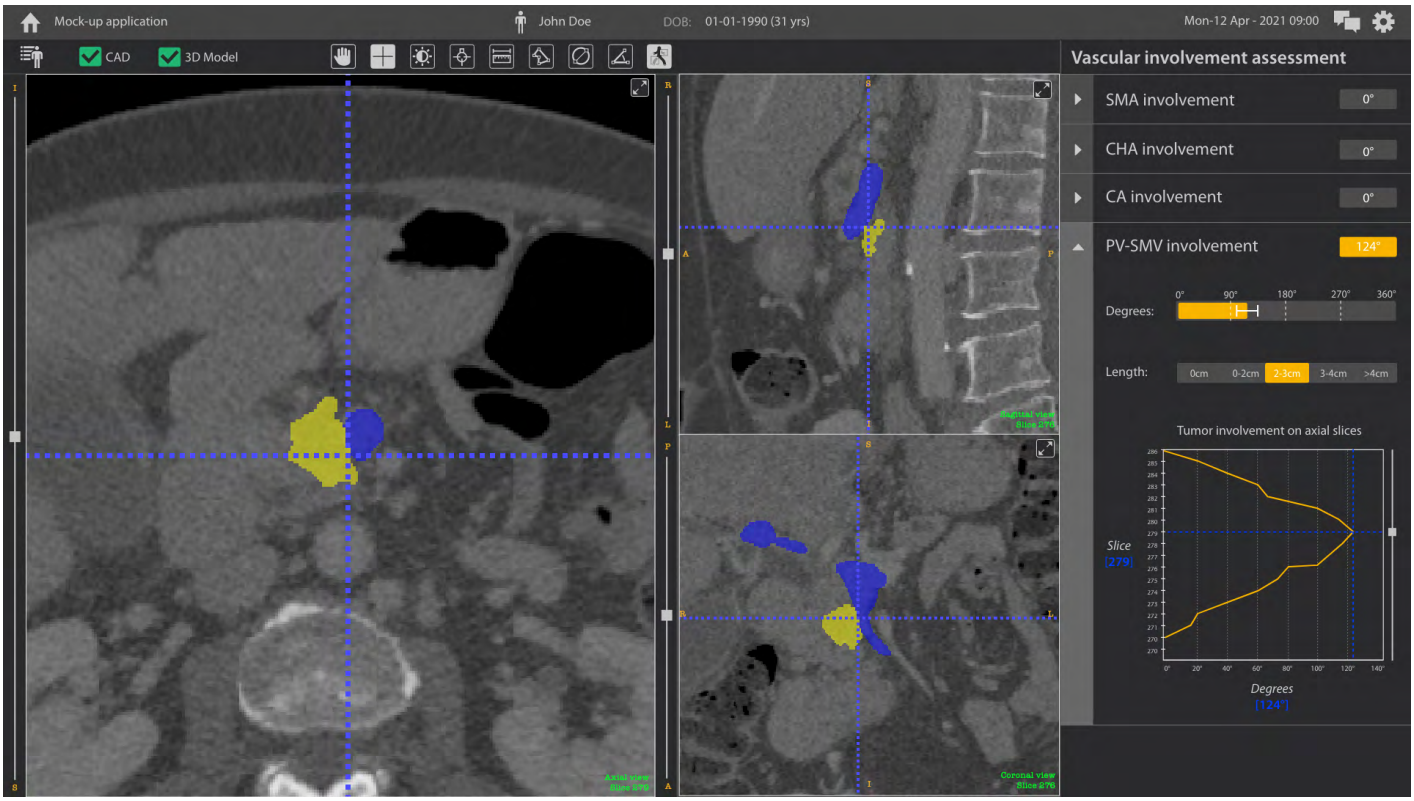


Figure 5.3. Screenshot of the final UX/UI design of the integrated medical imaging workstation.

Medical imaging viewer

A web-based medical imaging viewer, programmed in JavaScript based on the Cornerstone.js library, developed by Bin Yu, was used in the development of our workstation (Figure 5.4)(13). This Cornerstone.js library was used to build the application that can perform rendering and medical imaging manipulation functionalities (13). The DICOM imaging data is extracted from the Orthanc Server and rendered in this medical imaging viewer. The next iteration of this imaging viewer for the pancreas work package was developed by Bin Yu, Luc Geurts, and Diederik Rasenberg. First, the multi-planar reconstruction (MPR) functionality, including a reference line, was implemented in the prototype to allow users evaluating imaging in different anatomical directions (axial, coronal and sagittal). Secondly, the pixel-based annotations were converted to annotation outlines in Matlab. The annotation outline of each relevant anatomical structure was plotted in different colors and aligned to the corresponding CT slices. Arteries were coloured red, veins were coloured blue, the pancreas was coloured light brown, and the tumour was coloured yellow. Thirdly, imaging manipulation functionalities (zooming, panning, windowing en magnifying) were integrated to allow users for appropriate CT slice analysis. Lastly, the user interface, including the CAD-panel, was developed based on the design of the prototype.

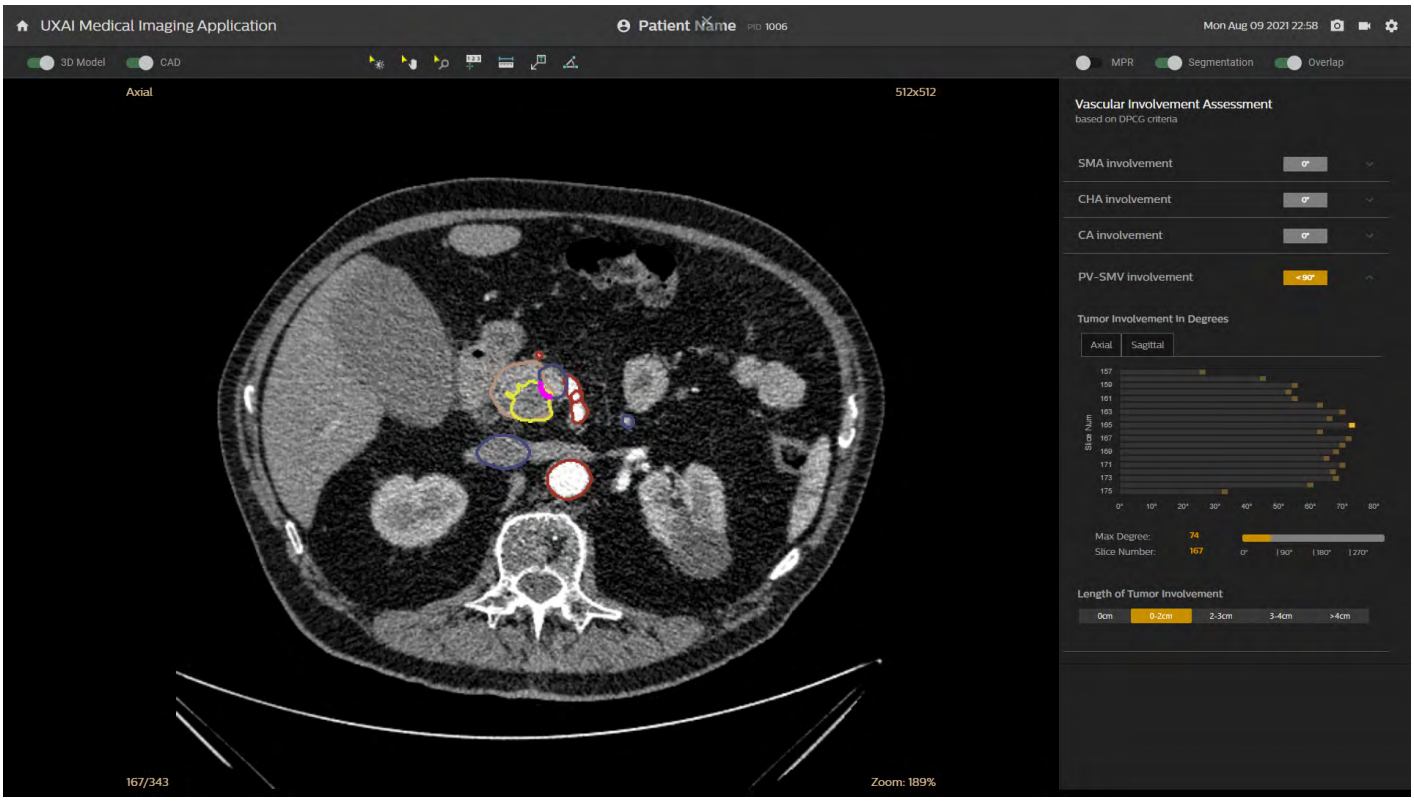


Figure 5.4. Screenshot user-interface of the medical imaging viewer and CAD panel

5.5 Vascular involvement quantification algorithm

The quantification algorithm was developed in Matlab by Diederik Rasenberg and John van der Ven. The algorithm can determine based on the CT scans and the pixel-level annotations if a) a tumour is vascular involved with one of the four vessels (superior mesenteric artery (SMA), common hepatic artery (CHA), celiac axis (CA), portal vein-superior mesenteric vein (PV-SMV) and b) if the tumour is involved, quantify the degrees per slice and calculate the length of the tumour-vessel trajectory in the axial direction. Subsequently, a footprint of the tumour-vessel interaction that is converted into a 3D structure will be created if vascular involvement is detected.

Technical steps of the algorithm

The following steps were taken to quantify the degrees and length of the tumour-vessel trajectory in Matlab:

1. Import the CT (DICOM), 3D volumetric annotation (NIfTI) files separated per anatomical structure and corresponding annotation labels into Matlab. The slice thickness was extracted from the DICOM file information.
2. Extract both the tumour and involved vessel annotations and determine per slice the outline of these annotations.

The following steps (steps 3 to13) are taken per slice:

3. Grow the tumour outline annotation by 1 pixel by applying a morphological dilatation step. In binary images, a morphological dilation a pixel value will be set to 1 if any neighbouring pixels have the value 1 (14)
4. Apply a logical 'AND' operation to the dilated tumour outline annotations and the vessel outline annotation. This step will yield the pixels where the dilated tumour outline contacts the vessel outline.
5. Save the contact pixels found in step 4 in a three-dimensional matrix (this matrix is needed to create a volumetric pixel-level annotation file of the tumour-vessel footprint).
6. Determine the 2D coordinates of the contact pixels found in step 4.
7. Determine the 2D coordinates of the centroid of the vessel annotation by calculating the means of all x and y pixels of the pixel-level annotation.
8. Calculate, using the 2-argument arctan, all angles between the coordinates of the centroid (step 7) of the vessel and the coordinates of the contact pixels (step 4).
9. Convert the angles that were calculated in step 7 to a range of 0° and 360° by adding 360 to all negative angles.
10. Find the minimum and maximum angle from the angles found in steps 7 and 8.
11. Subtract the minimum angle from the maximum angle to get the angle of vascular involvement on that slice.

12. Calculate the mean of the angles found in steps 7 and 8.
13. If the mean angle of this step is less than the minimum angle or more than the maximum angle found in step 9, it means that the vascular involvement contact area starts at the contact pixel with the maximum angle and ends at the contact pixel with the minimum angle. In that case, the angle found in step 10 is the inverse of the actual vascular involvement angle. Therefore, 360° should be subtracted to get the correct angle.

    Repeat steps 3 to 13 for every axial and sagittal slice to get all angles in axial and sagittal direction.

14. Calculate the length of vascular involvement by multiplying the amount axial and sagittal slices by the slice thickness.
15. Export the (maximum) vascular involvement angle(s) with corresponding slice number(s) and the calculated length of tumour-vessel trajectory in a CSV file.
16. Export all pixel-level annotations, including overlap annotation, as a NIfTI file.

Degrees and length quantifications of patient cases

Six pancreatic cancer cases were processed by following the steps of the quantification algorithm. The data included three simple cases with resectable tumours away from all vascular structures and three complex cases in near contact with the vascular structures with vascular involvement with the PV-SMV. By processing the simple cases, the algorithm detected no vascular involvement and thus, the degrees and length of the trajectory were considered as 0° degrees and 0 mm respectively. By processing the complex cases, the algorithm detected vascular involvement with the PV-SMV.

For patient case 4, the maximum degrees in axial and sagittal direction was detected on slice 248 and slice 264 and was 84° and 58°, respectively. The total length of the tumour-vessel trajectory was calculated as 20.8 mm in both directions combined. The visualization of the quantification of the maximum degrees in both axial and sagittal direction is provided in Figure 5.5.

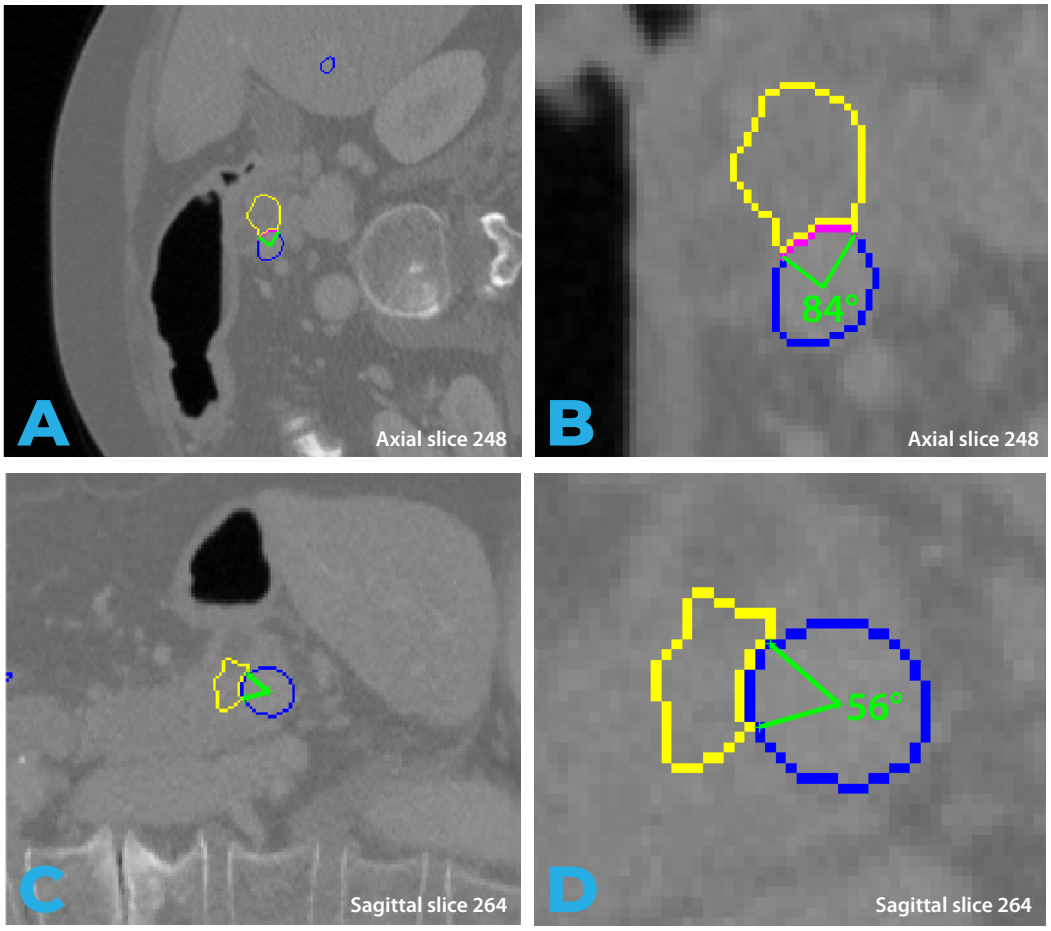


Figure 5.5. Quantification visualization of maximum degrees in axial direction (slice 248) and sagittal direction (slice 265) of patient case 4. (A) Axial outline tumour and vessel annotation zoomed out. (B) Axial outline tumour and vessel annotation zoomed in with angle calculation. (C) Sagittal outline tumour and vessel annotation zoomed out. (D) Sagittal outline of tumour and vessel annotation zoomed in with angle calculation. Yellow = tumour; Blue = PV-SMV; Pink = calculated contact area in axial direction; Green = maximum angle.

For patient case 5, the maximum degrees in axial and sagittal direction was detected on slice 407 and slice 205 and was 54° and 63° respectively. The total length of the tumour-vessel trajectory was calculated as 30.3 mm in both directions combined. The visualization of the maximum degrees quantification in both axial and sagittal direction is provided in Figure 5.6.

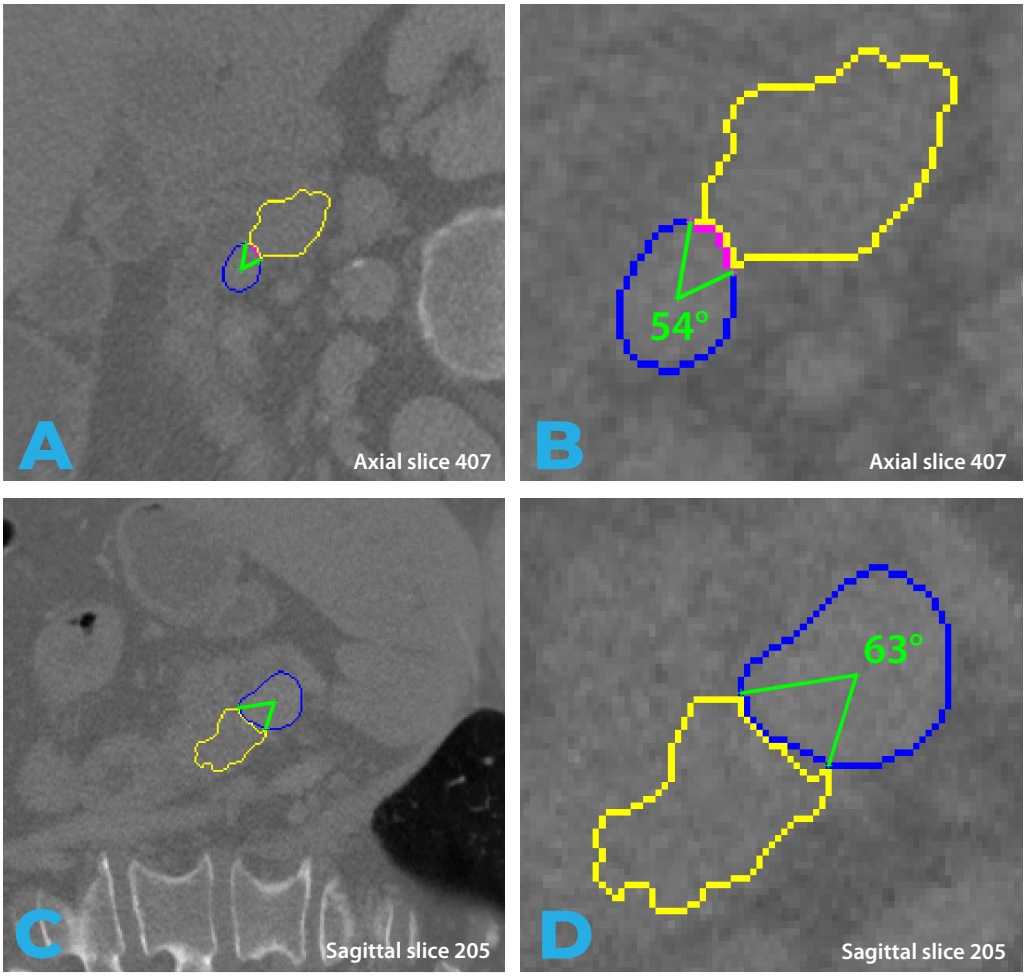


Figure 5.6. Quantification visualization of maximum degrees in axial direction (slice 407) and sagittal direction (slice 205) of patient case 5. (A) Axial outline tumour and vessel annotation zoomed out. (B) Axial outline tumour and vessel annotation zoomed in with angle calculation. (C) Sagittal outline tumour and vessel annotation zoomed out. (D) Sagittal outline of tumour and vessel annotation zoomed in with angle calculation. Yellow = tumour; Blue = PV-SMV; Pink = calculated contact area in axial direction; Green = maximum angle.

For patient case 6, the maximum degrees in axial direction was detected on slice 167 and was 74°. Vascular involvement in sagittal direction was detected, however this not seen as circumferential contact with the vessel and was therefore considered as 0°. The axial length of the tumour-vessel trajectory was calculated as 13.3 mm. The visualization of the maximum degrees quantification in axial direction is provided in Figure 5.7.

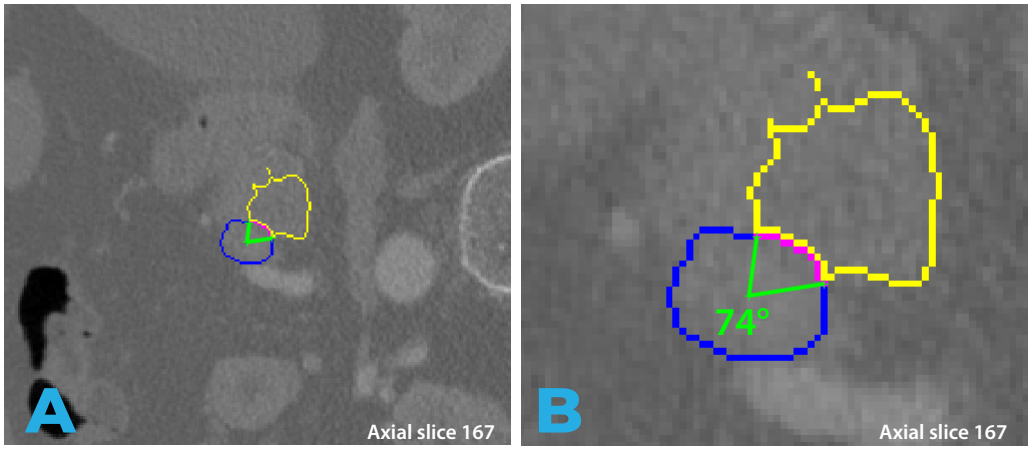


Figure 5.7. Quantification visualization of maximum degrees quantification in axial direction (slice 167) of patient case 6. (A) Outline tumour and vessel annotation zoomed out. (B) Outline tumour and vessel annotation zoomed in with angle calculation. Yellow = tumour; Blue = PV-SMV; Pink = calculated contact area in axial direction; Green = maximum angle.

5.6 Three-dimensional visualization of patient models

3D model reconstruction

The 3D patient models were developed by Luc Geurts and Diederik Rasenberg in Unity, which is a development platform for creating and operating among other things 3D applications (9). Following the data processing steps described earlier, the pre-processed 3D models, including the calculated tumour footprint in case of vascular involvement, were imported in Unity. The anatomical structures were given a colour that was based on illustrations in the book Essential Clinical Anatomy (15). Arteries were coloured red, veins were coloured blue, the pancreas was coloured light brown, and the tumour was coloured yellow. The footprint, which was only present in complex tumours (patient cases 4, 5 and 6) was given a bright pink colour to make clear that the footprint was an artificially generated structure. The final 3D reconstructed patient models are provided in Figure 5.8 (default views) and Figure 5.9 (tumour footprint views).

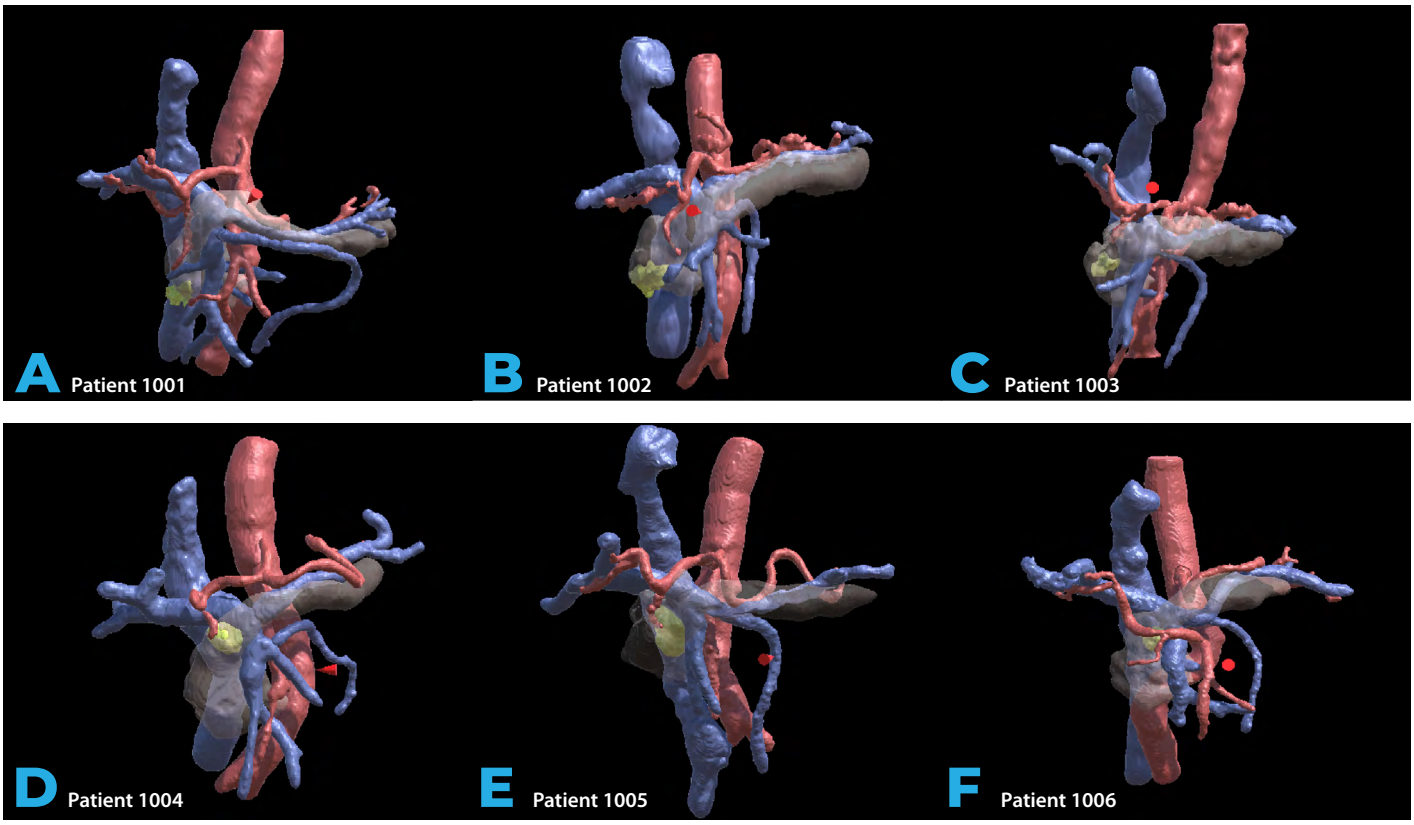


Figure 5.8. Three-dimensional reconstructed patient-specific models. (A) Patient case 1; (B) Patient case 2; (C) Patient case 3. (D) Patient case 4; (E) Patient case 5; (F) Patient case 6.

3D model interaction

An interaction system was developed in C# by Luc Geurts in collaboration with Diederik Rasenberg for interacting with the structures in the 3D model. In the analysis of the usability of previous developed prototypes, clinicians highlighted that the 3D model should have the following functionalities: rotate the model, turn separate structures on and off, change the transparency, zoom in and out, and go back to default settings. Furthermore, it became clear from this analysis that the mouse and keyboard were the most appropriate devices for controlling the 3D model. Gesture control was considered. Although gesture control is seen as an intuitive way of interaction, it comes with a learning curve. Besides using mouse and keyboard for 3D model manipulation as well, users do not need to switch interaction when moving from the CT viewer to the 3D display resulting in less cognitive load and improved overall ease of use. By mouse, participants were able to rotate (click and drag left mouse button), zoom in and out (scrolling wheel), pan (click and drag scrolling wheel), focus on structure (double click left mouse button) and change the transparency of structures (click and drag right mouse button). In Figure 5.8 the tumour was made transparent to improve the visual inspection of the tumour footprints. By keyboard, participants were able to turn structures on and off (T-key), turn the footprint on and off (F-key) and reset the model to the default view (R-key).

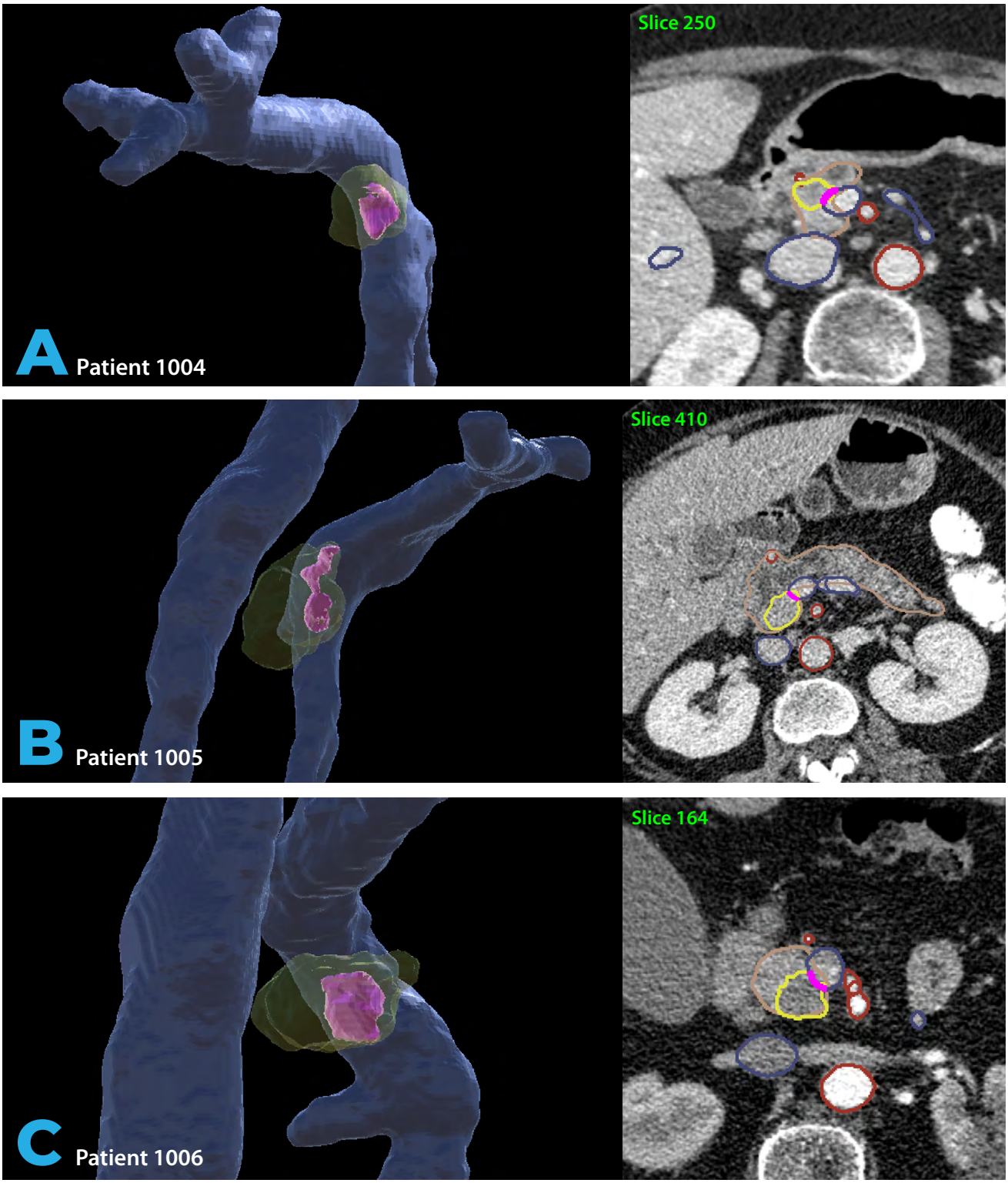
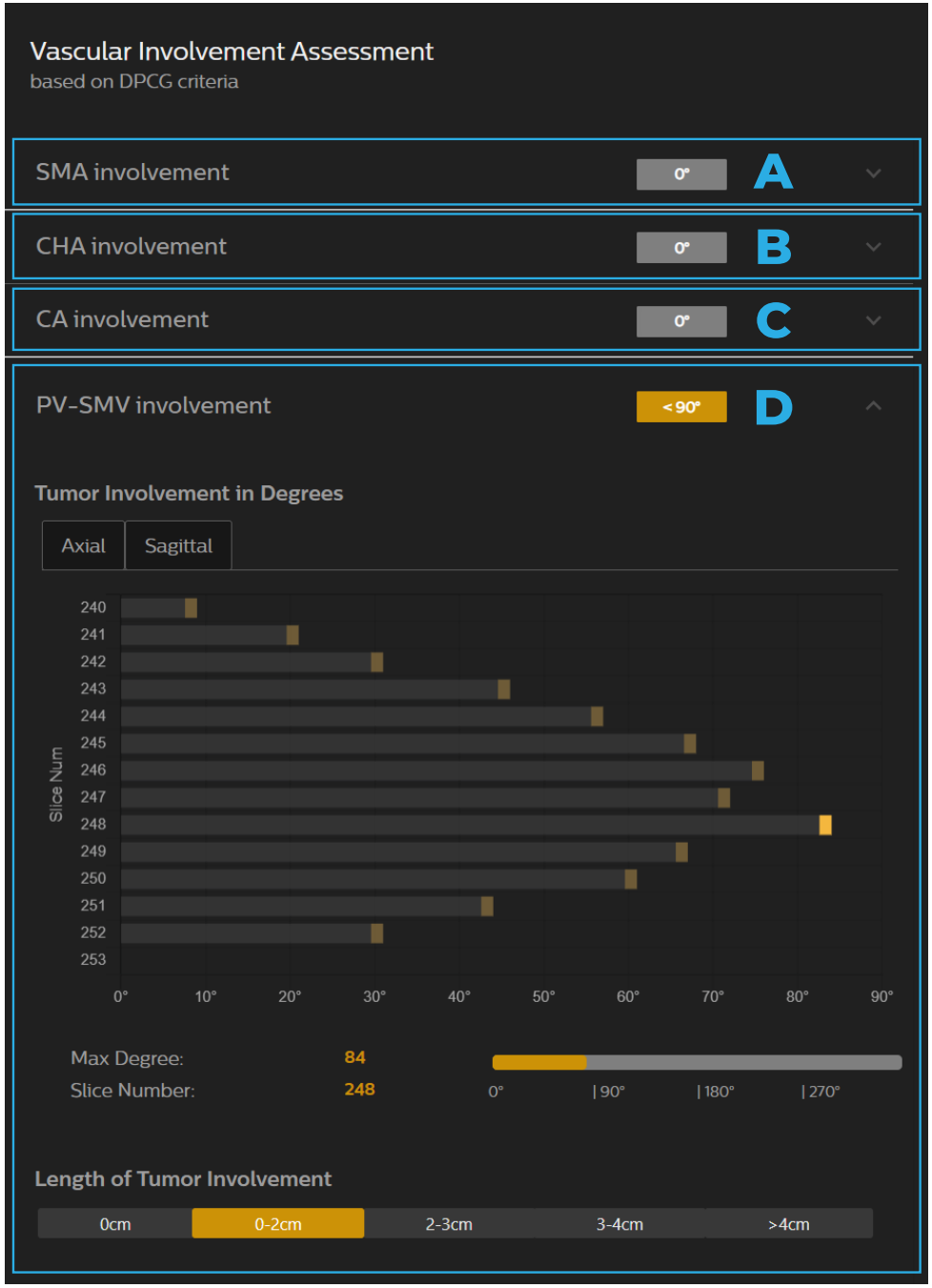


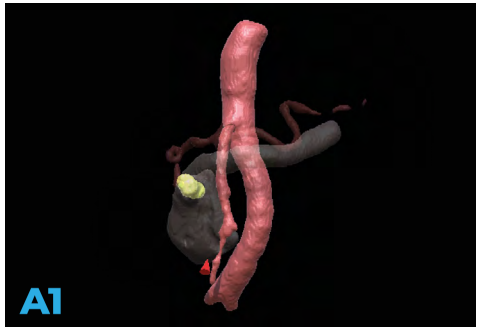
Figure 5.9. Tumour footprints highlighted on three-dimensional reconstructed portal vein – superior mesenteric vein and the corresponding CT slice. (A) Patient case 4; (B) Patient case 5; (C) Patient case 6. Blue = veins; red = arteries; yellow = tumour; pink = tumour footprint; light brown = pancreas.

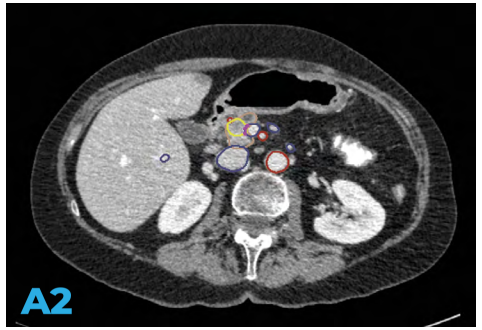
Pre-defined viewpoints

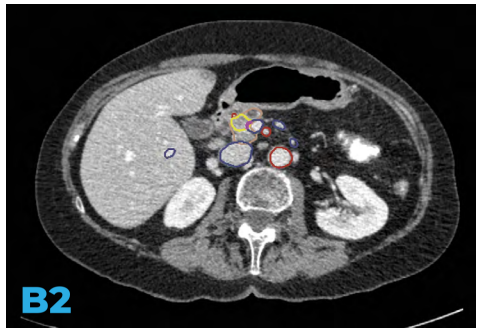
Viewpoints were defined that should show the most optimal view in 3D and CT focusing on the relationship of the tumour and a vessel (Figure 5.10). After choosing a pre-defined viewpoint by clicking on one of the buttons (A, B, C, D), clinicians can interact with the model and scan. After evaluating, the clinician can switch easily to other viewpoints or back to the default model (all structures turned on). The following steps were taken to create the views in 3D:

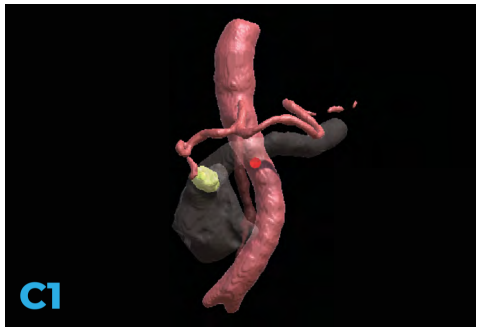
1. All non-relevant structures are turned off in the 3D model (e.g., vessel that lies further away and has no connection to the vessel of interest).
2. The pancreas is made transparent to have a clear view of the tumour and vessel.
3. A viewpoint is chosen that shows the most optimal angle to evaluate the relationship.
4. The footprint can be made visible to clarify the contact trajectory between tumour and vessel.

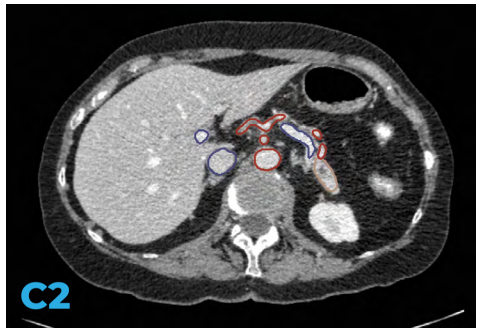


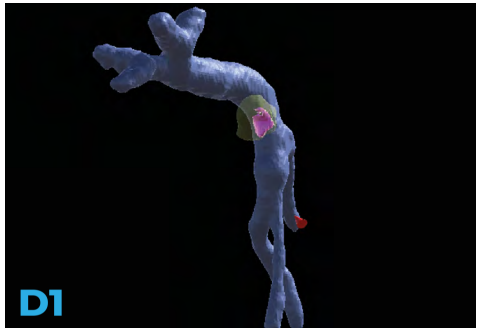












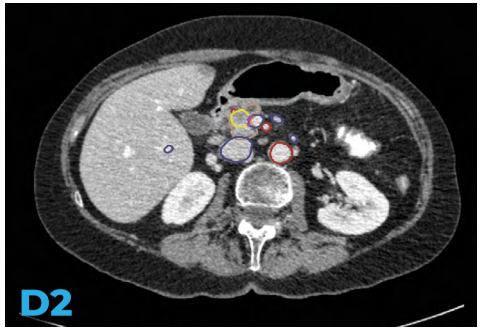


Figure 5.10. Vascular involvement panel with CAD suggestions (A-B) with corresponding predefined 3D views (A1-D1) and CT slices (A2-D2). (A, A1, A2) SMA assessment; (B, B1, B2) CHA assessment; (C, C1, C2) CA assessment; (D, D1, D2) PV-SMV assessment showing the CAD suggestion regarding the tumour involvement. The bar chart provides the calculated degrees per axial slice.

5.7 Visualization technique

Based on the results coming from the first user study (Chapter 4), the project had decided to focus on 3D displays rather than 3D printing and Virtual Reality (VR). Compared to 3D printed and VR models, the 3D display provides clinicians with the benefits of 3D depth perception and intuitive digital manipulating model interactions while being easy to integrate in the workflow.

Hardware choice

The final 3D reconstructed patient models were displayed on the autostereoscopic Looking Glass 8.9" landscape model (Looking Glass Factory, United States of America, NY, Brooklyn) (Figure 5.11)(16, 17). The Looking Glass is a multiview display technique presenting 45 different views of the 3D models in a viewing cone of 50°. The input resolution of the looking glass is 355 x 256 pixels per view resulting in a total input resolution of 2560 x 1600 pixels (18). The device needs to be connected via HDMI and USB-C input to the computer. No additional power supply is needed.

This display was chosen for multiple reasons. First, this autostereoscopic display enables to evaluated 3D models from different angles and perspectives without the need for additional hardware. Thirdly, no discomfort or nausea will be caused be looking at the display. Fourthly, in contrast to many other stereoscopic techniques, the looking glass allows multiple users to evaluate 3D models at the same time. Lastly, compared to other autostereoscopic techniques, the looking glass is relatively affordable and turned out to fit well in the workflow.

Besides the Looking Glass, the Dimenco Simulate Reality prototype laptop (Dimenco, Veldhoven, Noord-Brabant, The Netherlands) was considered as well (19, 20). This laptop comprises a system with a bigger display (15.6" compared to 8.9") and a higher resolution than the Looking Glass. The resolution of the Dimenco laptop was 3840 x 2160 pixels compared to 2560x1600 pixels for the Looking Glass. Nevertheless, this laptop was still a prototype and could not meet the internal IT requirements of Philips. If a laptop cannot meet IT requirements, it is not allowed to store and display any patient and confidential data. Therefore, it was decided to continue developing with the Looking Glass.

Figure 5.11. Looking Glass displaying 3D anatomical model

Autostereoscopic display technology

Stereo parallax (seeing a different image with each eye) and movement parallax (seeing different images when we move our head) are missing perceptual cues when humans are reconstructing 3D structures from 2D projection (21). Stereoscopic 3D technologies could provide users with stereo parallax. Autostereoscopic technologies provide the user with this 3D experience created by stereo parallax without additional headwear (22). Multiview and/or head-tracked autostereoscopic technologies trick the visual perception system with both stereo and movement parallax without additional headwear (1, 21, 22).

The Looking Glass is a multiview autostereoscopic technique displaying 45 different views from different angles, presenting different views to each eye. Additionally, moving your head around the Looking Glass will change the user's aspects of the 3D model. Users perceive 3D when both eyes are anywhere in the multiview zone. Multiple people can use the Looking Glass at the same time, each user seeing the 3D model from his/her perspective (21). The interactive diagram in Figure 5.12 demonstrates the working principle of the Looking Glass. The left image shows 45 views simultaneously which is called a quilt. The moving red box in the image indicates which image of the quilt is displayed. On the right image you can see the 2D projections of the views one by one of all 45 views in the quilt. Each eye sees multiple views from the quilt in varying intensities at the same time.

Displaying 3D models on Looking Glass

To facilitate displaying Unity developed models on this device, HoloPlay Service (Looking Glass Factory, United States of America, NY, Brooklyn) was used (23). HoloPlay Service is responsible for converting 3D objects in Unity into a quilt of 45 images as shown in Figure 5.12.

5.8 Final integrated medical imaging workstation

The set-up of the final integrated medical imaging workstation is shown in Figure 5.13 The design of the user interface and user experience was developed by Diederik Rasenberg supported. The software components of the demonstrator were developed by Bin Yu, Luc Geurts and Diederik Rasenberg. Three invention disclosures were written on three new technical or UI principles to protect intellectual property.

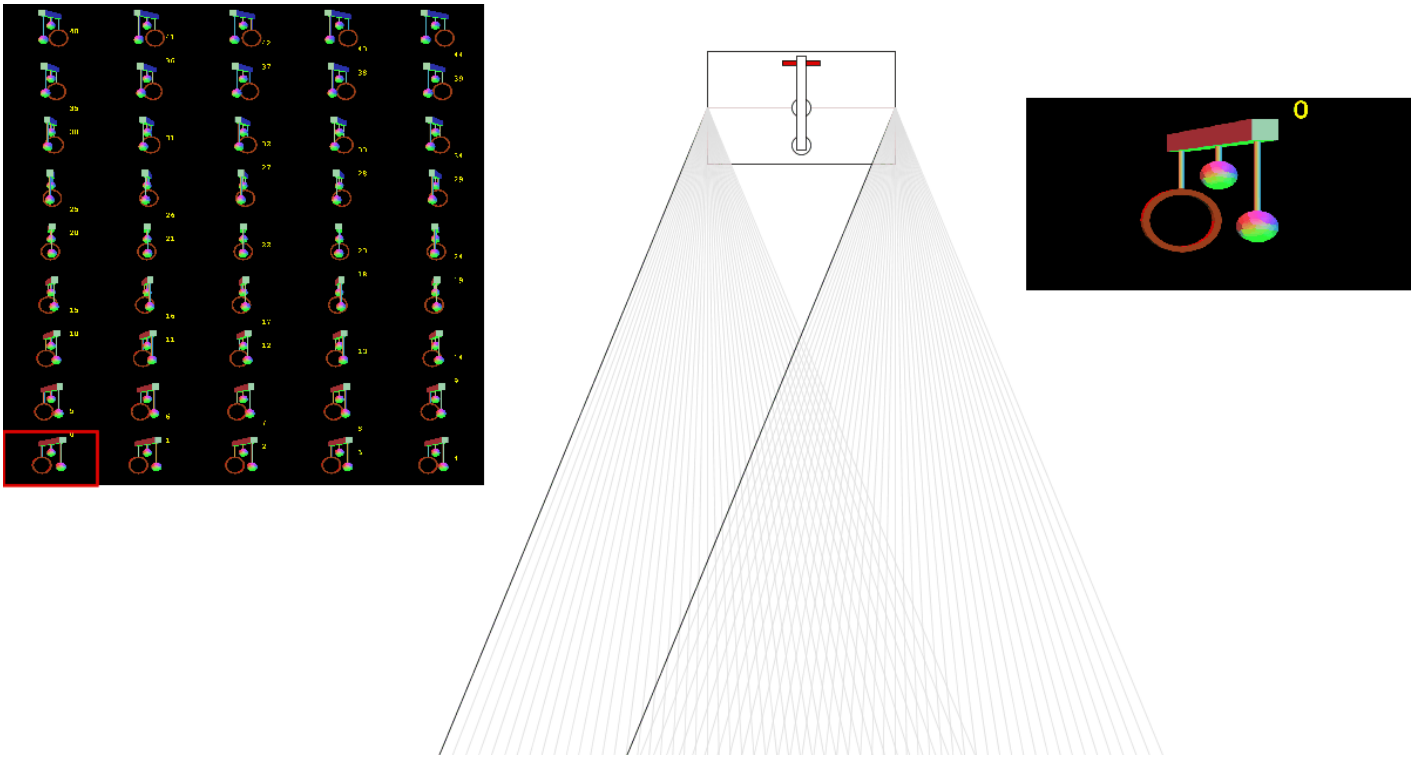


Figure 5.12. Diagram that demonstrates the working principle of the Looking Glass (1). Image Courtesy: Looking Glass Factory. (A) Top left image where 45 views are shown simultaneously called a quilt. The moving red box indicates which subsection of the quilt is seen for each viewing perspective. (B) Centre image shows the bird's eye view of the Looking Glass. The dark lines indicate the viewing perspective. (C) Top right image shows the 2D images that correspond to each viewing perspective.

Figure 5.13. Picture of the final integrated medical imaging workstation.

The final workstation integrates the following components and features:

1. **CT imaging viewer -** DICOM viewer showing volumetric CT imaging data and corresponding annotation outlines.
    a. Basic image manipulation functionalities – users can scroll through the CT slices, change the windowing level (grey-value mapping) of CT scan, zoom in and out, magnify a frame of the CT scan, and reconstruct the other orthogonal views, sagittal and coronal, based on the axial scan called a multiplanar reconstruction (MPR) (Appendix 5.2.B).
    b. Annotation outlines – users can visualize the outlines of anatomical structures by turning the annotations of the tumour, arteries, veins, and pancreas on and off.

2. **Autostereoscopic 3D visualizations –** interactive autostereoscopic 3D patient models displayed on the Looking Glass.
    a. Interactive 3D patient models - pixel-level anatomical annotations converted to 3D patient models developed in Unity.
    b. Specific visualizations - tumour footprint (projection of contact area of tumour on the vessel) visualized as 3D structure in the model.
    c. Looking Glass - technique that can present 3D models autostereoscopically on an external 8.9" display.

3. **CAD suggestions –** Clinical guideline-driven metrics regarding tumour-vessel involvement
    a. Vascular involvement quantification - degrees and length of tumour-vessel contact quantified based on the pixel-level anatomical annotations.
    b. Tumour footprint – contact area between tumour and vessel exported as annotation and 3D structure.

4. **User interfaces -** functioning as layout, rendering and interaction manager that is build according to the workflow for oncological interventions. The layout of the user interfaces for different prototype conditions are provided in Appendix 5.2.
    a. CAD panel - assess vascular involvement with interactive UI panel that could present the quantified vascular involvement data and can navigate to specific predefined viewpoints.
    b. Predefined viewpoints – viewpoints in 3D and CT focussing on the relationship between the tumour and relevant vessels and highlighting vascular involvement with the tumour footprint.

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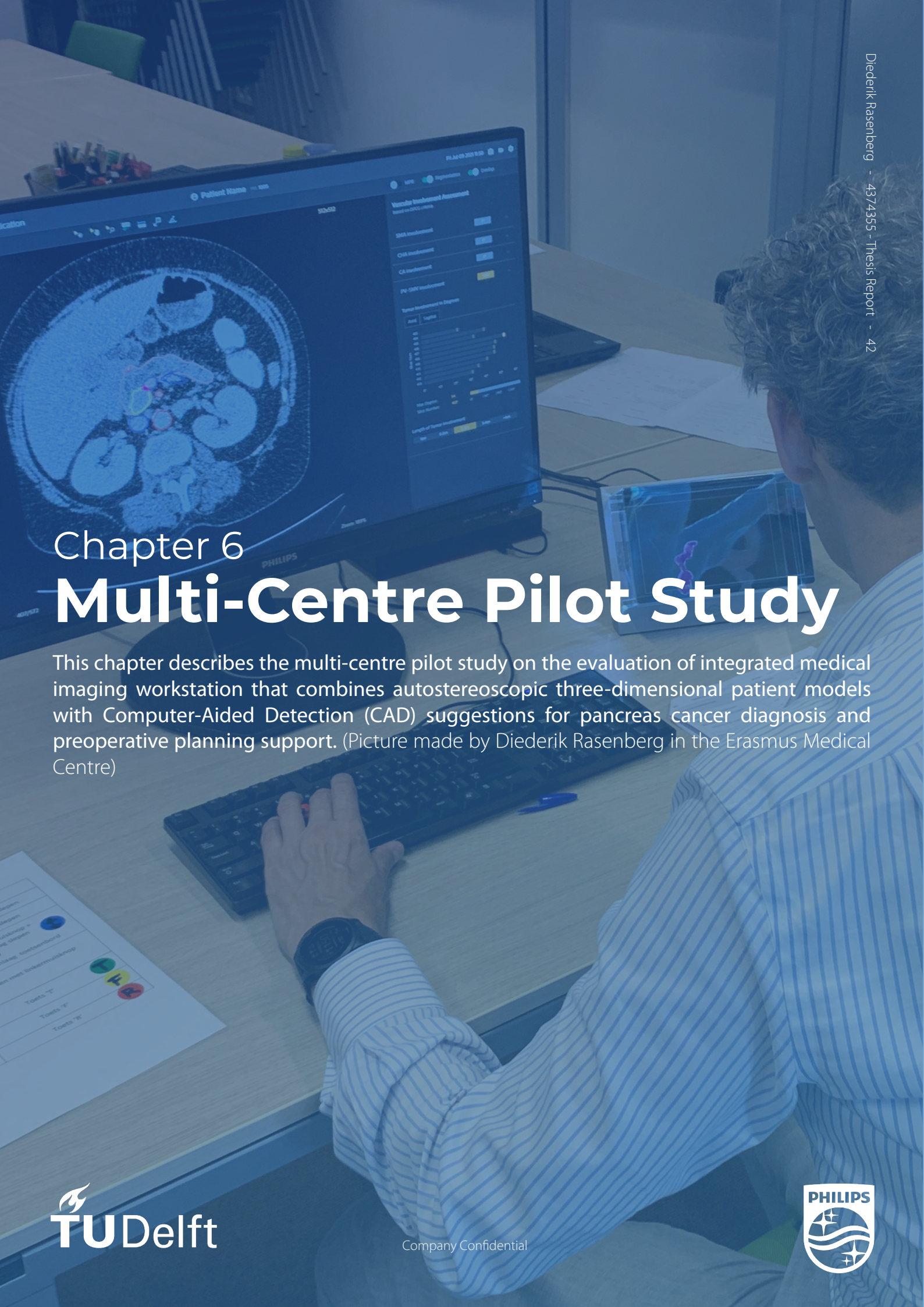

Chapter 6

Multi-Centre Pilot Study

This chapter describes the multi-centre pilot study on the evaluation of integrated medical imaging workstation that combines autostereoscopic three-dimensional patient models with Computer-Aided Detection (CAD) suggestions for pancreas cancer diagnosis and preoperative planning support. (Picture made by Diederik Rasenberg in the Erasmus Medical Centre)

TU Delft

PHILIPS

Evaluation of autostereoscopic 3D patient models and Computer-Aided Decision Support in Pancreatic Cancer: A Multi-Centre Pilot Study.

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6.1 Abstract

Objective. To assess the added value autostereoscopic three-dimensional patient models and computer-aided detection (CAD) derived metrics of vascular involvement for decision support in pancreatic cancer care.

Background. Pancreatoduodenectomy is the cornerstone of curative treatment for patients diagnosed with pancreatic head cancer. Only 20% of the patients are candidate for surgery since many patients present with distant metastases or locally advanced tumours with vascular involvement. Assessment of vascular involvement, which is mainly based on multi-phase CT scans, requires specific expertise and can be challenging. CAD and autostereoscopic three-dimensional patient models might improve accuracy in predicting vascular involvement and improve overall surgical planning.

Methods. This is a multi-centre study, including 13 expert hepatopancreatobiliary surgeons and one expert radiologist. All participants assessed pancreatic tumours in a simulated setting under 3 different test conditions; assessment using only the regular CT scan (CT-condition), assessment using CT and 3D patient models (3D-condition), assessment using CT, 3D patient models and CAD-derived metrics regarding vascular involvement (CAD-condition). A total of 6 patient cases were evaluated, of which 3 radiologically resectable cases (simple) and 3 radiologically borderline resectable cases (complex) with pancreatic tumours near to major vessels. Perceived fulfilment of clinical needs regarding the preoperative assessment, differences in surgical planning decisions compared to baseline, and confidence in clinical decision-making were evaluated.

Results. Clinicians experienced an improved ability to accurately detect pancreatic tumours and determine the degrees and length of tumour-vessel contact under the 3D- and CAD-condition compared to the CT-condition. Additionally, clinicians reported higher perceived ability to identify, localize and understand anatomical relationships when supported by autostereoscopic 3D models. Lower degrees of tumour-vessel contact were reported under the CAD-condition compared to the CT-condition. Furthermore, clinicians had a higher confidence in assessing the need for a vascular resection under the 3D-condition compared to the CT-condition.

Conclusion. CAD and 3D might improve the accuracy of pancreatic tumour detection and reduce the overestimation of degrees of vascular involvement on radiological imaging. The risk of over-trust in CAD mandates thorough evaluation of the accuracy and use of CAD in prospective studies.

Keywords

Pancreatic Carcinoma; Pancreatoduodenectomy; Integrated Medical Imaging Workstation; Autostereoscopic Three-Dimensional Patient Models; Computer-aided detection; Preoperative Planning; Vascular Involvement.

6.2 Introduction

Pancreatic cancer is currently the fourth leading cause of cancer death in the United States (1). People diagnosed with pancreatic cancer only have a 5-year survival rate of 10% (2). Surgical tumour resection, pancreatoduodenectomy (PD), is the cornerstone for curative treatment in patients without metastases at diagnosis with a postoperative 5-year survival rate of 20% (3). Pancreatoduodenectomy, better known as the Whipple procedure, is considered one of the most complex procedures in gastrointestinal surgery (4-6). This procedure is traditionally performed via open surgery. However, over the past decades, minimal invasive surgery, including robot-assisted surgery, is increasingly performed (7). However, less than 20% of the patients present surgically resectable tumours at the time of diagnosis of pancreatic cancer and most patients have distant metastases or tumours that are locally

advanced involving surrounding vascular structures (8). Dedicated pancreatic imaging consisting of a multi-phase (arterial and portal-venous) contrast-enhanced multi-detector computed tomography (MDCT) is the golden standard in evaluating potential pancreatic carcinomas and assessment of resectability (1, 9). The degrees of circumferential contact between tumour and important vessels are considered a critical factor predicting of tumour resectability and survival (10, 11). Additionally, the length of the tumour-vessel trajectory is important in predicting resectability since patients with the portal vein and/or superior mesenteric vein (PV-SMV) involvement with a length of less than 3 cm have better long-term survival (12). Standardized resectability criteria have been developed by various institutions, including the Dutch Pancreatic Cancer Group (DPCG) (13). Tumours can be classified as radiologically resectable, borderline resectable, or irresectable, based on the extent of vascular involvement.

Resectable tumours are increasingly being resected through a minimal invasive approach (14). Neoadjuvant therapy is increasingly used to improve pancreatic cancer care (15, 16). A subset of patients that present borderline resectable tumours undergo surgery after they have received neoadjuvant (chemoradio)therapy to increase R0 resection rates (16, 17). A meta-analysis of 38 studies and 3843 patients with resectable and borderline pancreatic tumours reported higher R0 resection rates (87% vs. 67%) after neoadjuvant therapy than upfront surgical resection (18). Patients with distant metastases or locally advanced tumours with vascular involvement are not eligible for resection. Adjuvant systemic therapy to extend lifetime will be considered in patients with irresectable pancreatic tumours. In some cases, patient respond very well to adjuvant treatment and may be candidates for surgery after all (16).

Decisions regarding resectability, neoadjuvant therapy, the surgical technique (open or robotic) and whether vascular resection is needed are based on the extent of vascular involvement. In case of vascular involvement, en bloc resection is seen as the golden standard. However, en bloc resection occurs in approximately 20-40% of the cases that were preoperatively classified as venous involved with the ability to achieve R0 resection (4, 19, 20). This indicates that preoperative radiological assessment of vascular involvement is typically overestimated compared to intraoperative judgement of the surgeon.

Computer-aided detection (CAD) segmentation algorithms based on artificial intelligence techniques like Convolutional Neural Networks (CNNs) can provide pixel-level segmentations of the pancreatic tumour and surrounding structures. Automatically segmented tumours can potentially improve pancreatic cancer detection and localization (21). Secondly, metrics regarding vascular involvement in terms of degrees and length of the tumour-vessel contact could be automatically derived from CAD output to provide surgeons and radiologists with more accurate information on the extent of vascular involvement. Lastly, 3D patient models can be reconstructed from the anatomical segmentations. Autostereoscopic techniques can display these 3D patient models with a realistic depth perception without the use of additional headwear (22). This might provide surgeons with a better spatial understanding of complex anatomy and tumour-vessel relationships (23). The combination of 3D patient models and CAD-derived metrics can provide decision-support and visual guidance to surgeons in preoperative assessment of tumour resectability leading to an improved surgical strategy. This multi-centre pilot study aims to evaluate the added value of autostereoscopic 3D patient models and CAD-derived vascular involvement metrics for decision-support in pancreatic cancer care.

6.3 Methods

In this study, participants individually performed preoperative planning for pancreatoduodenectomy in a simulated setting under different study conditions, using the integrated medical imaging workstation. The study was approved by the Internal Committee of Biomedical Experiments (ICBE) of Philips and the Medical Ethics Committee of Catharina Hospital Eindhoven (CZE). Informed consent was obtained from each surgeon or radiologist before participation (Appendix 6.1).

Data collection

Data of retrospectively collected and de-identified patient cases have been acquired from the Catharina Hospital Eindhoven (CZE), Eindhoven, The Netherlands. The data consisted of medical imaging data and relevant clinical information. The clinical information comprised all pre-, intra-, and postoperative information regarding tumour characteristics, vascular involvement, anatomical conformation, and surgical approach coming from the radiology-, pathology-, and surgery reports. Six patient cases with adenocarcinoma in the head of the pancreas that underwent pancreatoduodenectomy in CZE between 2014 and 2018 were included. Three cases were classified as resectable and three were classified as borderline resectable based on radiological assessment, according to DPCG criteria (13). The cases that were radiologically classified as resectable were considered simple cases, and the cases that were radiologically classified as borderline resectable were seen as complex cases.

Segmentation of tumour and vasculature

An arterial and/or a portal-venous phase CT scan was acquired for each patient. To mimic CAD generated segmentations, relevant anatomical structures (tumour, pancreas, aorta, superior mesenteric artery, celiac axis, common hepatic artery, splenic artery, gastroduodenal

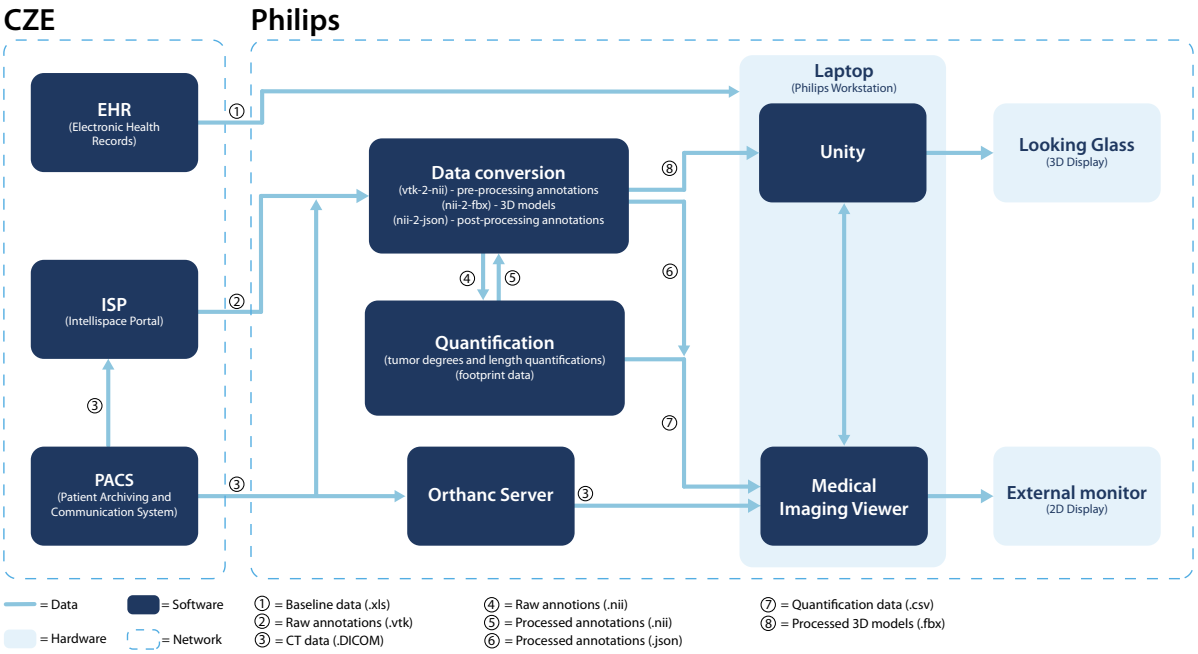


Figure 6.1. Flowchart of all data used in the integrated medical imaging viewer.

artery, vena cava, vena porta, superior mesenteric vein, inferior mesenteric vein, splenic vein, aberrant arteries) were annotated separately by a surgical resident and supervised by an abdominal radiologist from CZE using IntelliSpace Portal (Philips, The Netherlands, Eindhoven) (24). The pixel-level segmentations were exported for 3D model reconstruction as visualization tool kit (VTK) files.

Medical image post-processing

The flowchart in Figure 6.1 visualizes the data integrated in the medical imaging workstation. First, the CT scans were uploaded as digital imaging and communication in medicine (DICOM) files to the Orthanc Server. This is an open-source DICOM server for medical imaging and sends the DICOM files to the workstation (25). The annotation VTK files were converted to NifTI files (Neuro Informatics Technology Initiative). Secondly, the degrees of involvement and length of tumour-vessel trajectories were quantified in Matlab (MathWorks, Natick, MA, USA)(26). Subsequently, the vascular involvement quantifications and the processed annotation outlines were sent to the workstation. The CAD-derived metrics suggested <90° tumour-PV-SMV involvement for all complex cases. Lastly, the annotations, including a tumour footprint, were reconstructed as a three-dimensional model in a Unity (Unity Technologies, San Francisco, CA, USA) interactive visualization and displayed on the Looking Glass (Looking Glass Factory, Brooklyn, NY, United States of America) (27-29).

Integrated medical imaging workstation

The integrated medical imaging workstation is a hardware and software combination that consists of three major components (Figure 6.2). The first component is the medical

Figure 6.2. The integrated medical imaging workstation including the autostereoscopic 3D display.

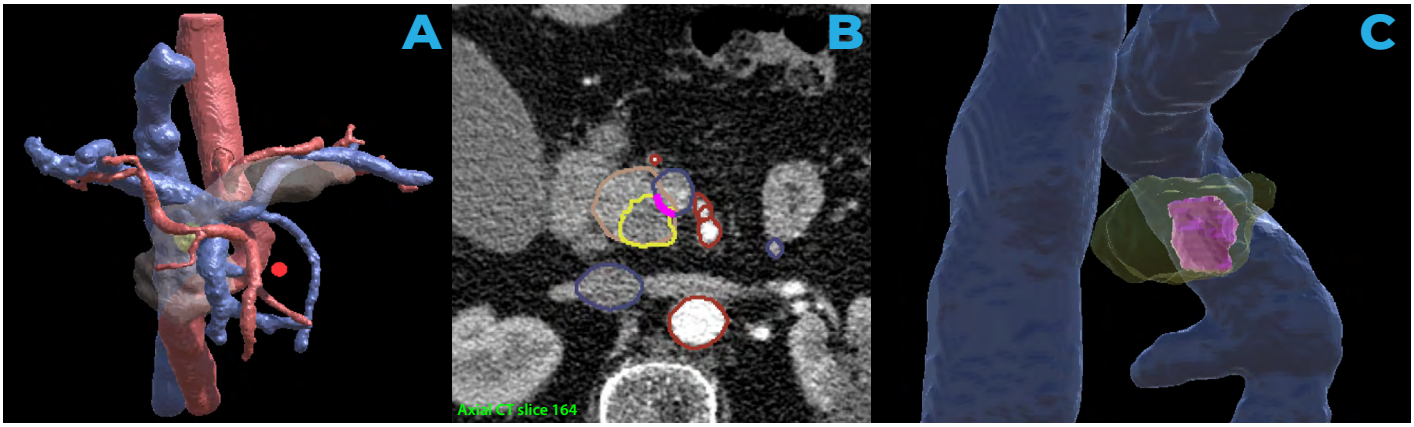


Figure 6.3. (A) 3D reconstructed patient model; (B) Segmentations outlining the anatomical structures; (C) Viewpoint showing the tumour and PV-SMV relationship including the tumour footprint. Blue = veins; red = arteries; yellow = tumour; pink = tumour footprint; light brown = pancreas.

imaging viewer showing three-dimensional CT scans with basic imaging manipulation functionalities (windowing, scrolling, zooming, multiplanar reconstruction). The second component consists of the segmentations (to simulate segmentations generated by CAD algorithms) outlining anatomical structures (Figure 6.3B). In addition, this component also contains the segmentations translated to autostereoscopic 3D patient models (Figure 6.3A) displayed on the looking glass (on the right on Figure 6.2). The third component consists of the CAD-derived metrics regarding vascular involvement, including the degrees of tumour-vessel contact, the length of the tumour-vessel trajectory, the tumour footprint (the contact area where the tumour touches a vessel), and automatically generated viewpoints in the 3D model to investigate the tumour-vessel relationships (Figure 6.3C).

Study design

The simulated surgical planning sessions were conducted with 13 expert hepatopancreatobiliary (HPB) surgeons and 1 abdominal radiologist from multiple Dutch high-volume pancreatic cancer centers. The sessions consisted of three phases, starting with the pre-test questionnaire, followed by the simulated surgical planning, and ending with a post-test questionnaire (Figure 6.4).

The pre-test questionnaire captured information regarding surgical experience and the perceived fulfilment of clinical needs (Likert scale) in current practice. The needs were divided into five categories, namely tumour detection/localization, preoperative tumour assessment, preoperative vascular involvement assessment, preoperative anatomical understanding, and intraoperative understanding (Appendix 6.3).

Subsequently, participants performed the simulated surgical planning on six cases, one simple and one complex case for each study condition. The study conditions were defined as follows:

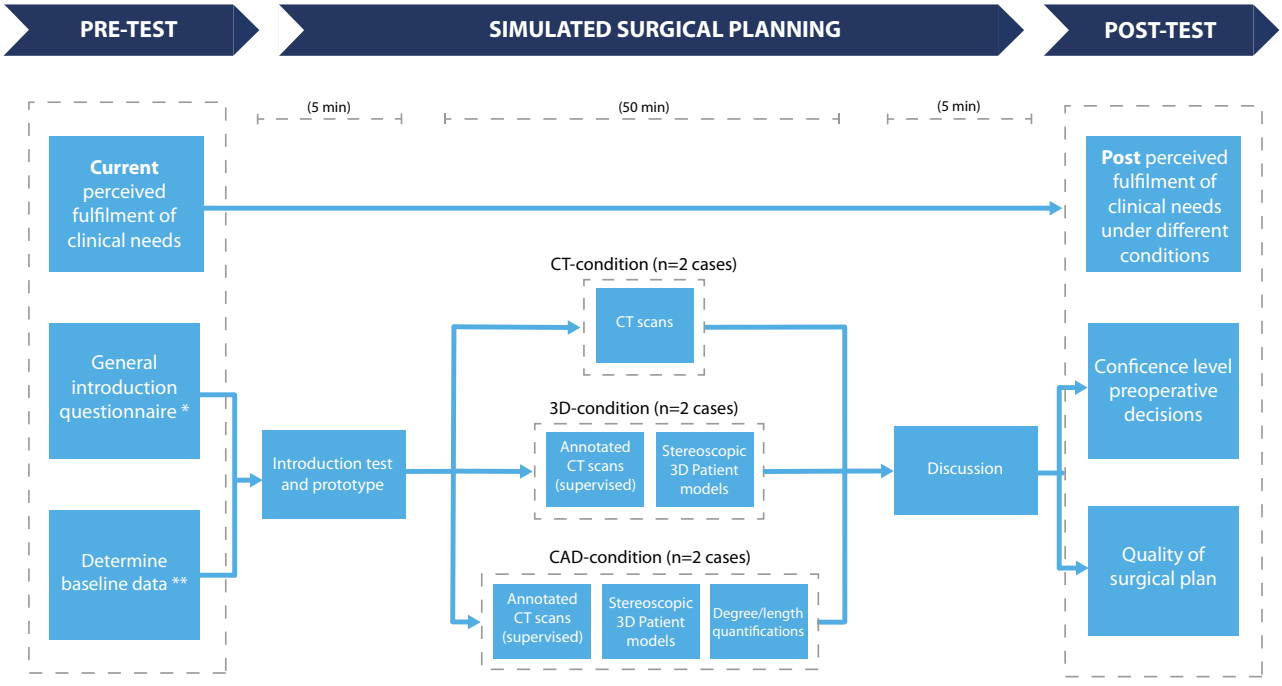


Figure 6.4. The complete design of the study including all pre-, during and post-test components.
* General introduction questionnaire consisting of questions regarding the expertise and experience of the study participants.
** Baseline information extracted from the radiology-, pathology-, and surgery reports.

1. **CT-condition:** assessment using only a regular CT image viewer with basic image manipulation functionalities (zooming, panning, windowing, multi-planar reconstruction).

2. **3D-condition:** assessment using the CT image viewer, segmentations (to simulate CAD output) outlining anatomical structures, and autostereoscopic 3D patient models.

3. **CAD-condition:** assessment using the CT image viewer, segmentations outlining anatomical structures, autostereoscopic 3D patient models (including tumour footprint), and CAD-derived metrics regarding vascular involvement.

Participants started with the CT-condition, followed by the 3D-condition and finally the CAD-condition (Figure 6.4). This order was chosen to reduce the cognitive load associated with learning the prototype functionalities in the study conditions. Participants were divided into three groups, each group planning two different patient cases in each test condition compared to the other groups (Appendix 6.4). For each patient case, participants had to fill in a surgical planning form capturing their surgical planning decisions (Appendix 6.5). More specifically, it was asked to determine the degrees of tumour-vessel contact, predict tumour resectability, predict whether vascular resection was needed, and identify potential vascular variations. Additionally, the confidence regarding the resectability decision and vascular resection prediction was captured (30).

Lastly, participants filled in a post-test questionnaire that captured the perceived fulfilment of identified clinical needs per condition and how participants experienced working with CAD (Appendix 6.6).

Outcome measures

The primary outcomes of this study were the perceived fulfilment of clinical needs around key aspects of the surgical planning before and after the study, the degrees of tumour contact with the PV-SMV for complex cases, the accuracy of the resectability and vascular resection prediction, and the confidence regarding vascular involvement decisions.

Perceived fulfilment of clinical needs: expressed on a Likert scale (1 = strongly disagree, 5 = strongly agree) for the current practice (CP-condition) and each study conditions.

The degrees of tumour contact: expressed as ordinal variables (no contact, <90° contact with PV-SMV, between 90°–180° contact with PV-SMV, >180° contact with PV-SMV, cannot determine) for each study condition.

The prediction accuracy: (number of correct predictions) / (total number of predictions) x 100%. Predictions were considered correct if the answer that is given by the participant corresponded to the actual ground truth based on the pathology- and surgical report. Prediction accuracy was defined for the following three decisions 1) the resectability (resectable, borderline resectable, irresectable), 2) whether vascular resection was needed (yes, no, cannot determine), and 3) anatomical variation (yes or no). The ground truth regarding resectability was defined as follows: Resectable: tumours that were resected without vascular resection with an R0 resection status. Borderline resectable: tumours that were resected with vascular resection with an R1 resection status were considered borderline resectable.

Confidence in decisions: expressed on a 1-10 scale (1=low, 10=high) for each study condition related to the prediction of resectability and the prediction of whether a vascular resection was needed.

Data processing and (statistical) analysis

Data regarding perceived fulfilment of clinical needs, the degrees of tumour contact, the level of confidence were imported in Matlab (MathWorks, Natick, MA, USA) for statistical analysis (26). The ANOVA Kruskal-Wallis test was performed to analyse the perceived fulfilment of clinical needs, the degrees of tumour contact decisions, and confidence levels. This statistical test is used since the sample sizes are relatively small and the outcomes did not have a normal distribution (31). The confidence and need fulfilment were expressed as the median and the interquartile ranges (IQR). Multiple comparison tests were performed using the Kruskal-Wallis results to determine whether the mean ranks of the conditions are significantly different. A p-value of <.05 was considered statistically significant, and p-values were rounded to two decimal places.

6.4 Results

Demographics, surgical experience, and pre-test confidence in surgical planning

The study was conducted with thirteen experienced hepatopancreatobiliary surgeons and one experienced radiologist from multiple high-volume pancreatic cancer centers in the Netherlands. All participants were males between 36 – 65 years old. Their (surgical) experience is reported in Table 6.1. 21% of the participants had between 6 - 10 years of experience, 71% had 11 years or more experience as a specialist. Every included surgeon had performed over 100 open pancreaticoduodenectomies (OPDs), and 64% of the surgeons had performed over 200 OPDs. 39% of the surgeons had no experience in performing robot-assisted pancreatoduodenectomies (RAPDs), 39% had performed over 50 RAPDs, and one had performed more than 100 RAPDs.

Participants scored via a Likert scale their confidence in

resectability and vascular involvement assessment in current practice (Appendix 6.7). Six participants reported lower confidence in <20% of the cases, four participants reported lower confidence in 20% - < 40% of the cases, two participants reported between 40% - 60% of the cases, and another two participants were in >60% - 80% of the cases not confident about their decision. The main factor contributing to lower confidence was the poor visibility and distinguishability of tumour, fibrosis, pancreatitis tissue after neoadjuvant therapy, which results in a challenging vascular involvement assessment, reported by 71.4% of the participants. Participants had little to no experience with (auto)stereoscopic 3D visualization techniques and CAD (Appendix 6.7).

Table 6.1. (Surgical) experience participants.

Characteristic	Range	% Participants (n)
Experience as surgeon or radiologist	6-10 yr	29% (n=4)
	11-15 yr	29% (n=4)
	16 - 20 yr	29% (n=4)
	> 20 yr	14% (n=2)
No. of OPD performed (Surgeons only)	n = 101 - 200	31% (n=4)
	n = 201 - 300	23% (n=3)
	n = 301 - 400	23% (n=3)
	n = 401 - 500	15% (n=2)
	n > 500	8% (n=1)
No. of RAPD performed (n) (Surgeons only)	n = 0	39% (n=5)
	n = 1-25	15% (n=2)
	n = 26 - 50	8% (n=1)
	n = 51 - 75	23% (n=3)
	n = 76 – 100	8% (n=1)
	n > 100	8% (n=1)

OPD = open pancreatoduodenectomy; RAPD = robot-assisted pancreatoduodenectomy.

Perceived fulfilment of clinical needs

The perceived fulfilment of clinical needs showed no significant differences between the current practice (CP) and CT-condition (Figure 6.5). This indicates that the CT-condition reflects the current clinical practice situation well (32). Multiple significant differences between the CP-condition or CT-condition and the 3D- or CAD-condition were seen. First, participants felt that evaluating cases under the 3D- and CAD-condition, they would be able to detect and localize pancreatic tumours more accurately compared to the CP-condition (p=.048 and p=.038, respectively) (Figure 6.5A). Secondly, participants expected that non-expert hospitals would detect and localize pancreatic tumours more accurately and therefore refer patients in time to expert hospitals under the 3D-condition (p=.0027) and CAD-condition (p<.001) compared with current practice (Figurer 6.5B). Thirdly, participants felt that CAD-derived metrics regarding vascular involvement (CAD-condition) would help determine degrees of contact more accurately than only using the regular CT scan in the CP- and CT-condition (p=.018 and p=.022, respectively) (Figure 6.5C). Additionally, participants felt that this would also help them determine the length of the tumour-vessel contact more accurately compared to the CP- and CT-condition (p=.0021 and p=.0030 respectively) (Figure 6.5D). Lastly, participants felt that the autostereoscopic 3D patient models in the 3D-condition (p=.011) and CAD-condition (p=.024) would help them better identifying, localizing, and understanding the spatial conformation of the anatomy compared to the CP-condition (Figure 6.5E). The perceived fulfilment of other clinical needs can be found in Appendix 6.8.

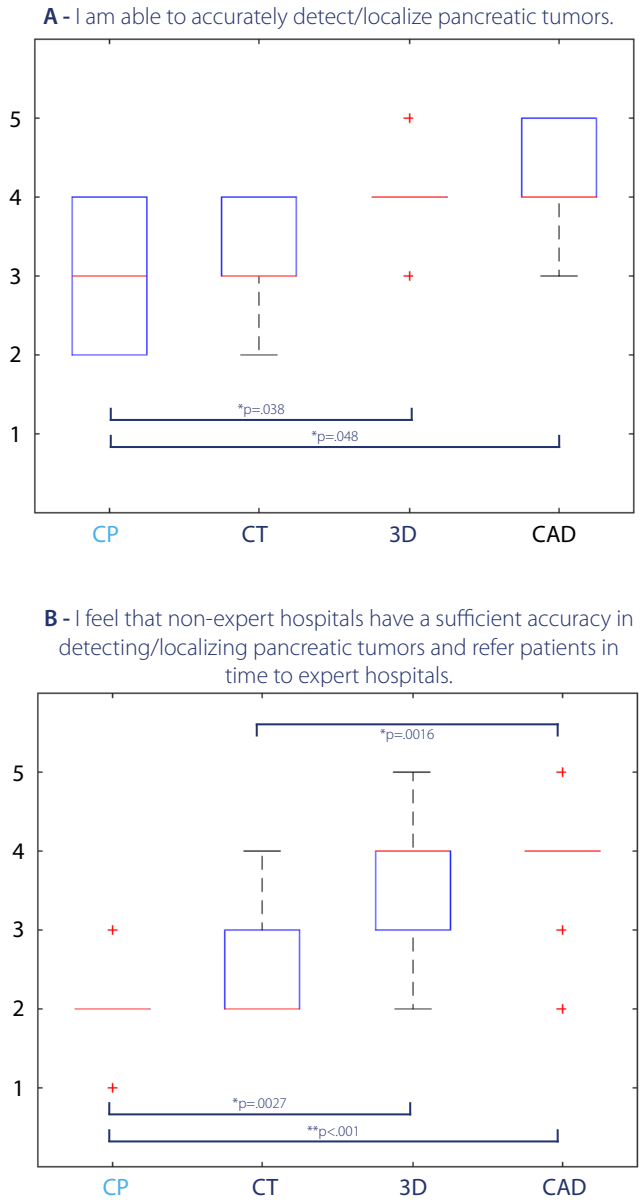
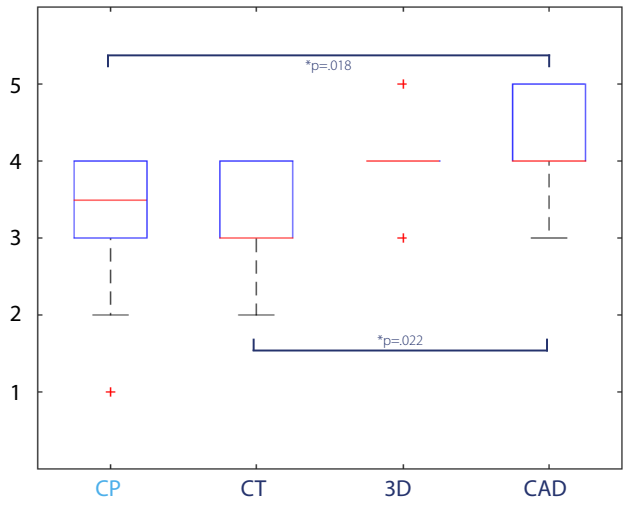
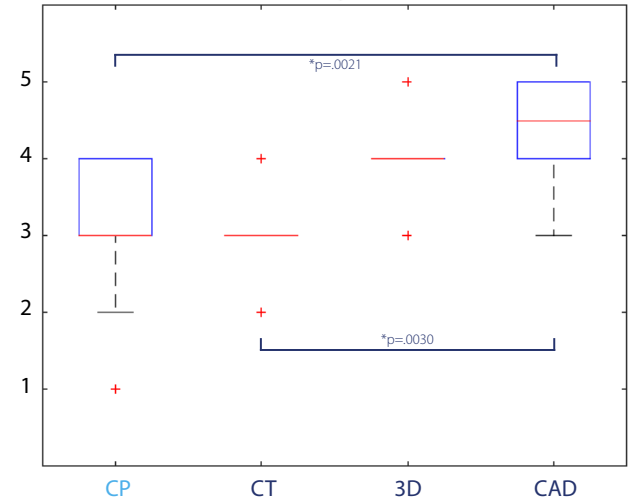


Figure 6.5.1. Box plots perceived fulfilment of clinical needs (A, B). CP = current practice (pre-test); CT, 3D, and CAD = study conditions (post-test). Scored on a Likert Scale (1=completely disagree, 5=completely agree). Red lines = medians; blue boxes = 25th and 75th percentile; red crosses = outlier values; dotted black line = range of values. *p-value < .05; **p-value<.001.

C - I am able to accurately determine the degrees of contact between the tumor and vascular structures.



D - I am able to accurately determine the length of the tumor-vessel contact trajectory.



E - I am able to accurately identify/localize and understand the spatial conformation of the anatomy (e.g. bifurcation of jejunal branch).

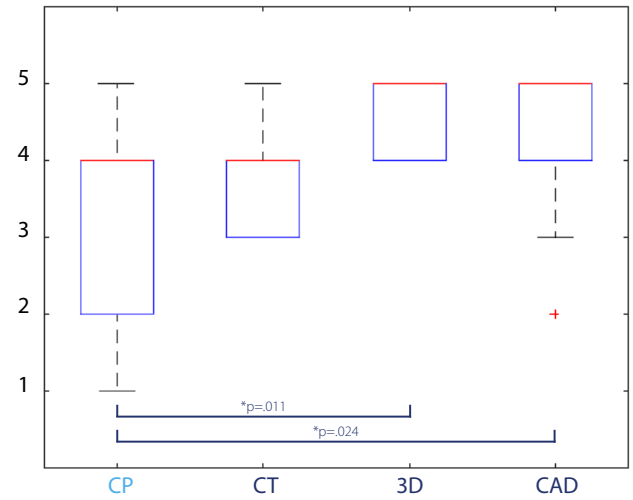


Figure 6.5.2. Box plots perceived fulfilment of clinical needs (C, D, E). CP = current practice (pre-test); CT, 3D, and CAD = study conditions (post-test). Scored on a Likert Scale (1=completely disagree, 5=completely agree). Red lines = medians; blue boxes = 25th and 75th percentile; red crosses = outlier values; dotted black line = range of values. *p < .05; **p<.001.

Comparison of simulated surgical planning with historical data

Historical patient data

Three (simple) cases with radiologically resectable tumours located distant from all vascular structures were included, and three (complex) cases with radiologically resectable tumours in near contact with the vascular structures were included (Table 6.2). No vascular involvement or contact was seen during surgery and radical tumour resection (R0) was achieved in all simple cases. All three borderline resectable cases had between 90°–180° PV-SMV according to the radiological assessment. No ground truth data regarding degrees of tumour-vessel contact was available in the pathology report. Based on the surgical report, the tumours of patients 4 and 6 were classified as resectable since no vascular resection was needed and an R0 resection status was achieved. The tumour of patient 5 was classified as borderline resectable since venous resection, and an R1 resection margin was reported in the pathology report. The length of the tumour-vessel contact was not available. No patient has been treated with neoadjuvant therapy, and each tumour was resected in open pancreatoduodenectomy.

Degrees of tumour contact with PV-SMV

Table 6.3 points out that 64% of the participants reported a vascular involvement between 90°–180° in the CT-condition compared to 27% in the CAD-condition. Additionally, only 14% of the participants reported <90° of vascular involvement in the CT-condition compared to 73% in the CAD-condition. Participants determined lower degrees of tumour-vessel contact for complex cases in assessment supported by 3D models and CAD-derived metrics than regular radiological assessment (p=.037) (Figure 6.6).

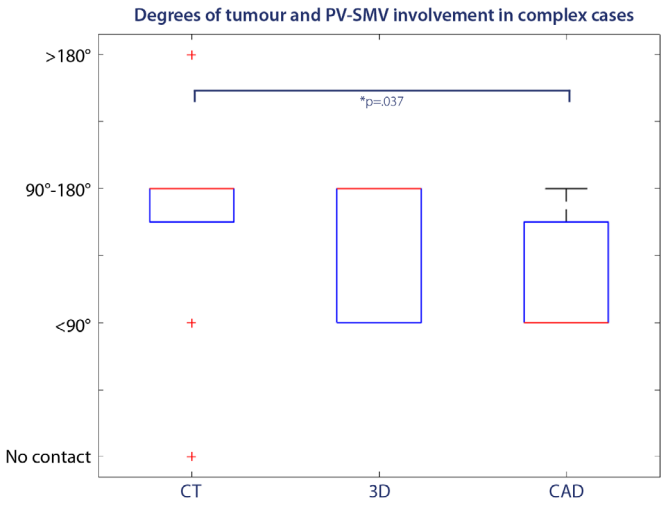


Figure 6.6. Box plot regarding degrees of tumour and PV-SMV involvement in complex cases. Red lines = medians; blue boxes = 25th and 75th percentile; red crosses = outlier values; dotted black line = range of values. *p-value < .05.

Table 6.2. Baseline patient data received from CZE.

Category	Patient cases					
	1 (simple)	2 (simple)	3 (simple)	4 (complex)	5 (complex)	6 (complex)
Vascular involvement						
Vessels involved [RR, SR]	None	None	None	**PV-SMV**	**PV-SVM**	**PV-SMV**
Degrees of vascular involvement [RR]	0	0	0	**90°-180°**	**90°-180°**	**90°-180°**
Vascular resection [SR]	No	No	No	No	**Yes**	No
Resection margin [PR]	R0	R0	R0	R0	**R1**	R0
Anatomical information						
Anatomical variation [RR, SR]	**Yes**	**Yes**	**Yes**	No	No	**Yes**
Decision-making						
Resectability [SR, PR]	Resectable	Resectable	Resectable	Resectable	Borderline resectable	Resectable

[RR] Extracted from radiology report; [SR] Extracted from surgical report; [PR] Extracted from pathology report. PV-SMV = Portal Vein – Superior Mesenteric Vein. See appendix 6.2 for a more elaborate overview.

Table 6.3. Degrees of tumour involvement in complex cases

Category	CT-condition		3D-condition		CAD-condition	
	Obs. (n) / total obs. (n) - %*		Obs. (n) / total obs. (n) - %		Obs. (n) / total obs. (n) - %	
No contact	1/14	7%	-	-	-	-
<90°	2/14	14%	5/13	38%	11/15	73%
90°–180°	9/14	64%	7/13	54%	4/15	27%
>180°	1/14	7%	-	-	-	-
Cannot determine	1/14	7%	1/13	8%	-	-

* Percentages may not total 100% because of rounding. Obs. = observations. See appendix 6.9 for a more elaborate overview.

Table 6.4. Prediction accuracy of vascular involvement assessment.

Category	CT-condition		3D-condition		CAD-condition	
	Correct (n)/total (n) - PA (%)		Correct (n)/total (n) - PA (%)		Correct (n)/total (n) - PA (%)	
Resectability						
All cases combined	18/27	67%	22/28	79%	22/29	76%
Simple cases	13/13	100%	15/15	100%	14/14	100%
Complex cases	5/14	36%	7/13	54%	8/15	53%
Vascular resection						
All cases combined	19/27	70%	19/28	68%	18/29	62%
Simple cases	12/13[1]	92%	14/15[1]	93%	13/14[1]	93%
Complex cases	7/14[6]	50%	5/13[2]	38%	5/15[3]	33%

Prediction accuracy was calculated by the formula: (number of correct predictions) / (total number of predictions) x 100%; Correct (n) = correct predictions; Total (n) = total number of predictions. The superscript reports the number of times a participant could not determine whether vascular resection was needed. See appendix 6.9 for a more elaborate overview.

Table 6.5. Prediction accuracy of determining an anatomical variation

Category	CT-condition		3D-group		CAD-group	
	Correct (n)/total (n) - (%)		Correct (n)/total (n) - (%)		Correct (n)/total (n) - (%)	
All cases combined	22/27	81%	25/28	89%	26/29	90%
Cases with arterial variation	14/18	78%	17/19	89%	16/19	84%
Cases without arterial variation	8/9	89%	8/9	89%	10/10	100%

Prediction accuracy was calculated by the formula: (number of correct predictions) / (total number of predictions) x 100%; Correct (n) = correct predictions; Total (n) = total number of predictions. See appendix 6.9 for a more elaborate overview.

Accuracy of resectability and vascular resection prediction

Participants correctly predicted that all simple cases were resectable with no difference between the study conditions (Table 6.3). Additionally, almost all participants correctly predict whether vascular resection was needed in the simple cases in all study conditions.

For the complex cases, 54% (CAD-condition) and 53% (3D-condition) of the participants correctly predicted the tumour resectability according to the DPCG criteria compared to 36% in the CT-condition. Remarkably, two participants, evaluating patient 6, reported an irresectable tumour while, in fact, the tumour was resectable according to the surgical report and an R0 resection margin was achieved. No participants reported irresectable tumours in the 3D-condition or CAD-condition for all cases. Furthermore, 50% of the participants correctly predicted whether a vascular resection was needed under the CT-condition compared to 38% and 33% in the 3D-condition and CAD-condition, respectively. However, six participants felt that they were not able to determine if a vascular resection was needed in the CT-condition, two participants in the 3D-condition and three participants in the CAD-condition.

For all cases combined, 90% (CAD-condition), 89% (3D-condition), and 81% (CT-condition) of the participants correctly predicted the presence of an arterial variation (Table 6.4). Focusing only on the patients with varying arteries, 4 arterial variations were missed in the CT-condition, 2 in the 3D-condition and 3 in the CT-condition. The arterial phase CT scan was only available for patient case 6, the other five patients were evaluated with a portal-venous phase. Patient case 6 had an arterial variation according to the surgical report. However, 2/5 participants evaluating the patient under the CT condition did not identify this variation while planning with the arterial phase CT scan.

Level of confidence regarding vascular involvement assessment

Significantly lower confidence levels were seen for the resectability decision and the decision to perform vascular resection for complex cases compared to simple patient cases under all conditions (Appendix 6.10)(32). This indicates that the case complexity (simple or complex) corresponded to how confident participants were regarding the vascular involvement assessment. Significantly higher confidence was seen in predicting whether a vascular resection was needed under the 3D-condition compared to the CT-condition (p=.033) for all cases combined (Table 6.6). No significantly differences were seen in the confidence regarding the resectability prediction under all conditions (Table 6.6).

6.5 Discussion

In this study, surgical planning of pancreatoduodenectomy under different study conditions was simulated with expert clinicians. The aim was to evaluate the added value of autostereoscopic 3D patient models and CAD-derived vascular involvement metrics for decision-support in pancreatic cancer care. This study demonstrates that 3D patient models combined with CAD-derived metrics might aid expert clinicians to determine the extent of vascular ingrowth more accurately than current radiological assessment which can to improved resectability prediction. Furthermore, displaying 3D patient models with autostereoscopic techniques provide clinicians with a quicker, more realistic, and more thorough spatial understanding of the tumour-vessel relationships and potential vessel variations.

Vascular involvement prediction is typically overestimated based on radiological assessment compared to the intraoperative situation (16, 20). In this study, participants consistently reported less vascular involvement in complex cases when supported by the 3D models and CAD-derived metrics compared with radiological assessment only. This indicates that expert clinicians tend to follow the judgement of the CAD. Unfortunately, the CAD-derived metrics could not be compared to actual ground truth data. Assuming that the CAD-derived metrics and tumour footprint accurately predicted the degrees of tumour-vessel contact, it means that the prediction of vascular involvement based on radiological assessment in this study was indeed overestimated.

Discriminating between tumour, inflammatory, fibrotic, and healthy tissue after neoadjuvant therapy is experienced as highly challenging, even for experienced HPB surgeons and abdominal radiologists. Cassinotto et al. showed that the sensitivity of MDCT in predicting vascular involvement is only 80% and drops to 50% after neoadjuvant treatment (33). Additionally, the IMPALA study demonstrates the

Table 6.6. Level of confidence regarding vascular involvment assessment

Category	CT- condition *Median [25th and 75th percentile]*	3D-condition *Median [25th and 75th percentile]*	CAD-condition *Median [25th and 75th percentile]*	CT vs 3D *p-value*	CT vs CAD *p-value*	3D vs CAD *p-value*
All cases combined						
Resectability	8 [6.25 - 9]	8 [8 - 10]	8 [7.75 – 9]	.17	.29	.94
Vascular resection	7 [6 - 8]	9 [7 - 9]	8 [6.75 - 9]	**.033***	.26	.59

Median, 25th and 75th percentiles were calculated with the Kruskal-Wallis statistical tests. P-values for comparing different conditions were calculated by performing multi-comparison testing. *p-value < .05; **p-value<.001. See appendix 6.10 for a more elaborate overview.

complexity of resectability assessment on imaging after treatment with neoadjuvant chemotherapy. Only 39% of the patients that were surgically explored after neoadjuvant chemoradiotherapy eventually received surgical resection (16). Moreover, patients diagnosed with pancreatic cancer are increasingly receiving neoadjuvant therapy. Therefore, improved vascular involvement prediction in borderline resectable and locally advanced tumours after neoadjuvant therapy is desperately needed. CAD algorithms that can distinguish the tumour from other surrounding tissue types and derive the extent of vascular involvement after neoadjuvant therapy would add significant value in resectability assessment.

Nonetheless, not everyone blindly followed the CAD suggestions due to under trust in the tumour segmentations. Participants mentioned they need to understand on what data the algorithm is trained and validated before they trust the output. Important to understand is that the accuracy of 3D models and CAD-derived metrics entirely depends on the accuracy of segmentations. To substantially improve the sensitivity of the vascular involvement prediction, especially after neoadjuvant therapy, CAD algorithms should be highly accurate in segmenting the critical structures. Nevertheless, CAD segmentation algorithms are not 100% correct. Trusting the output on moments that the algorithm is mistaking could result in wrongly judgements. Therefore, clinicians should use the 3D model and CAD-derived metrics as a 'second opinion'. Ideally, clinicians have the right amount of trust in the CAD, called the appropriate trust concept, which leads to optimal use of the algorithms (34). Besides providing transparency on which data the algorithm is trained and validated, communicating the uncertainty of the CAD in the segmentations and 3D models might be a solution that leads to appropriate trust (35).

Unexpectedly, 3D patient models and CAD-derived metrics did not result in higher confidence regarding the resectability prediction. Case complexity and the distinguishability of the tumour on CT, which was similar under all study conditions, were the main reason for a certain level of confidence according to the participants. This might explain comparable confidence levels. Nevertheless, the 3D patient models provide clinicians with more confidence in predicting whether a vascular resection was needed to achieve an R0 resection margin. Interestingly, 3D patient models combined with CAD-derived metrics did not result in a more accurate prediction regarding the need for vascular resection. The segmentations and the tumour footprint might have wrongly suggested vascular ingrowth of the tumour resulting in a lower prediction accuracy.

In current clinical practice, arterial variations are detected by evaluating the arterial phase CT scan. In this study, the arterial phase CT scan was only available in one patient case. It was expected that fewer variations would have been missed if the arterial phase scan was also available for the other patient cases. Nevertheless, a highly rare variation where the CHA arises from the SMA was missed twice with radiological assessment on an arterial phase CT scan (36). Besides, 3D patient models enable clinicians to understand the relevant vasculature quickly, these models might improve accuracy in identifying arterial variations. This can result in fewer vessel related complications during surgery.

This study has several limitations. First, some participants mentioned a relatively low CT resolution. This could make tumour detection less reliable and might have influenced their confidence in decisions. Secondly, this study was an individual simulation of surgical planning. In clinical practice, clinicians have more information available (patient characteristics, tumour details, additional imaging, biopsy results, and blood test results) that may aid adequate assessment of resectability (8). Furthermore, the prototype included only one contrast phase (arterial or portal-venous) CT scan, while in clinical practice, clinicians use typically three phases to assess the patient. The arterial phase is especially crucial for the determination of anatomical variations. Similarly, the portal-venous phase is required to evaluate thoroughly potential venous involvement, which was unavailable in one case. Decisions and the confidence levels might have been influenced by the absence of the arterial or portal-venous phase. However, the relevance of two phases CT scan became less crucial when 3D models and CAD-derived metrics supported the planning. Thirdly, segmentations were annotated manually to simulate CAD output. Although realistically simulated, this could have influenced the trust and confidence of participants in the segmentations. Lastly, this study was only a pilot study exploring the potential added value of 3D imaging and CAD in pancreatic cancer. It included a relatively low number of participants and patient cases, making it challenging to statistically analyse simulated planning outcomes. Besides, the study was sensitive to selection and tendency bias (31).

6.6 Conclusion

In conclusion, experts perceived a higher fulfilment of their needs regarding key concepts of preoperatively planning pancreatic cancer surgery. Besides, current findings indicate that CAD-derived metrics can potentially aid in reducing the overestimation of the extent of vascular involvement on current radiological imaging. In combination with CAD segmentation algorithms that can discriminate tissue types after neoadjuvant therapy, this could eventually lead to an increase in the number of patients eligible for curative treatment. The risk of over-trust in CAD mandates thorough evaluation of the accuracy and use of CAD in prospective research to provide a more definite answer.

6.8 References

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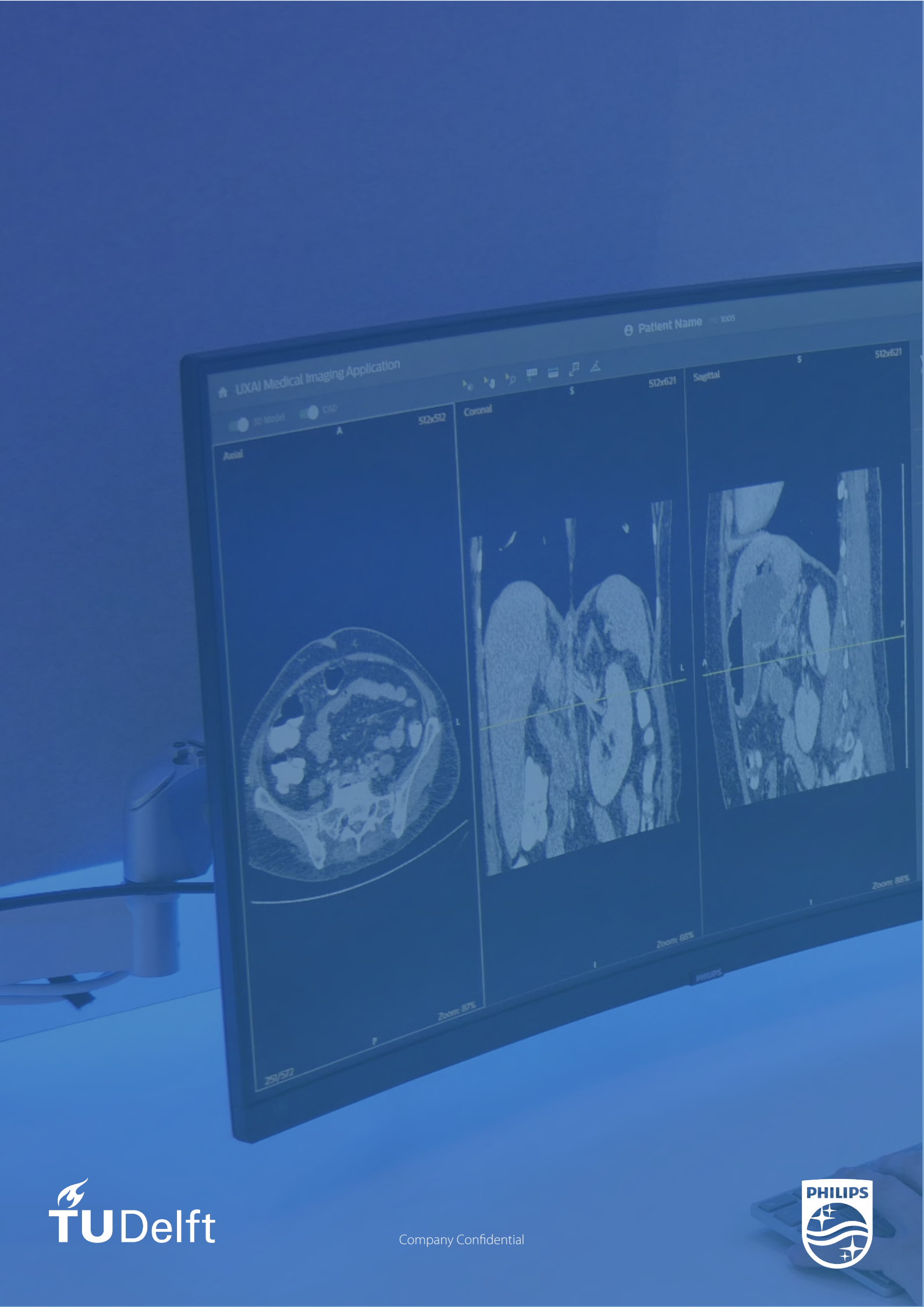

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