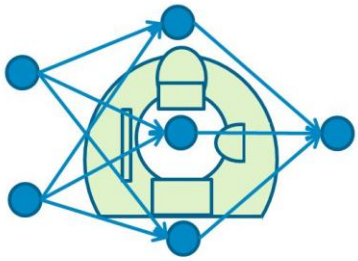

IMPACT

Intelligence based iMprovement of Personalized medicine And Clinical workflow supporT

DELIVERABLE D7.3
Updated State of the Art for clinical areas in IMPACT

Project number:	ITEA 17021
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ITEA Roadmap domains:
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Major: Content & knowledge
Minor: Interaction

HISTORY

Document version #	Date	Remarks
V0.1	June 19, 2021	Starting version, template, definition of ToC
V0.2	Aug 10-26, 2021	Integration of updates for the clinical disease areas
V1.0	Sep 13, 2021	Creation of final version

Deliverable review procedure:

- **2 weeks before due date**: deliverable owner sends deliverable –approved by WP leader– to Project Manager
- **Upfront** PM assigns a co-reviewer from the PMT group to cross check the deliverable
- **1 week before due date**: co-reviewer provides input to deliverable owner
- **Due date:** deliverable owner sends the final version of the deliverable to PM and co-reviewer

TABLE OF CONTENTS

1 Executive summary

This document provides a description of the updated State of the Art for the clinical disease areas addressed in the IMPACT project. The goal of IMPACT is to develop technologies and solutions that optimize diagnosis, treatment planning, treatment execution and overall workflow efficiency in the hospital. Typically, the developed solutions are data driven and heavily rely on Artificial Intelligence as the discriminating factor to deliver improvements in terms of speed and accuracy of diagnosis and better treatment outcome.

Five clinical procedures are addressed so that it is possible to discriminate between common aspects of (in-)efficiencies for these disease areas and specific ones:

- Structural heart diseases
- Treatment of (partially) blocked arteries causing ischaemia or infarct of the heart
- Treatment of liver tumours
- Treatment of lung tumours
- Treatment of brain tumours

This deliverable D7.3 builds further on D1.1 which already provided short descriptions of the abovementioned disease areas and their clinical procedures, summarizing existing workflow steps and bottlenecks. For each disease area a section is added, describing the advancements made in the IMPACT project for that particular area.

2 Glossary

AF	Atrial Fibrillation
AS	Aortic Stenosis
CABG	Coronary Artery Bypass Graft(ing)
CBCT	Cone-Beam CT
CT	Computer Tomography
CFR	Coronary Flow Reserve
CTA	Computed Tomography Angiography
DICOM	Digital Imaging and Communications in Medicine
DWI	Diffusion Weighted Imaging
ECG	Electro Cardio Gram
FFR	Fractional Flow Reserve
GUI	Graphical User Interface
HCC	Hepatocellular carcinoma
IVUS	IntraVascular UltraSound
LAA	Left Atrial Appendage
LAAO	Left Atrial Appendage Occlusion (also called LAAC, where C is closure)
LV	Left Ventricle
MRI	Magnetic Resonance Imaging
MR-HIFU	MRI-guided High Intensity Focused
MS	Mitral Stenosis
MW	MicroWave
OAR	Organ At Risk
OCT	Optical Coherence Tomography
PCI	Percutaneous Coronary Intervention
PEI	Percutaneous Ethanol Injection
PET	Positron Emission Tomography
RECIST	Response Evaluation Criteria in Solid Tumours
RF	RadioFrequent
(non-)STEMI	(Non-) ST Elevation Myocardial Infarction
SPECT	Single Photon Emission Computed Tomography
TACE	Transcatheter Arterial Chemo-Embolization
TAVI	Transcatheter Aortic Valve Implantation
TEE	Transesophageal Echocardiogram
TMVR	Transcatheter Mitral Valve Replacement
TTVR	Transcatheter Tricuspid Valve Replacement
TTE	Transthoracic Echocardiogram
US	UltraSound
VHD	Valvular Heart Disease

3 Introduction

3.1 Aim of activity

The goal of this document is to provide an updated description for the three types of disease areas; Cardiac (data collection and workflow optimization for PCI, data collection and personalized treatment planning for structural heart diseases), Lung and liver oncology (Tumour segmentation and diagnosis, 3D tumour localization, robotized laparoscopy and workflow optimization) and Brain oncology (Tumour segmentation, radiation treatment planning).

Each of the targeted disease areas is described in a standardized way:

- In the first section, a short introduction is given that provides the background & context of the disease and the diagnostic procedures.
- The second section describes the clinical State of the Art for treatment options as captured in deliverable D1.1 in the first year of the project.
- The new third section describes the updated State of the Art realized within the IMPACT project with an emphasis on the clinical aspects.

3.2 Contributors

Several authors contributed to the production of this document. Each of those authors was responsible for one of the targeted disease areas.

#	Section	Authors
1	Cardiac valves and LAA	FEops, Philips
2	Coronary vessels (PCI)	Philips, NewCompliance
3	Liver oncology	LUMC, Philips, UMCU, DEMCON, UT, Barco, NewCompliance
4	Lung oncology	LUMC, Philips
5	Brain oncology	Elekta, Linkoping Univ, Quantib
	Global editor	Philips

4 Clinical disease areas

4.1 Cardiac valves and LAA

4.1.1 Introduction

Valvular heart disease (VHD) is a common public health burden in the developing and industrialized countries. The increasing life expectancy in the western world has resulted in an increasing prevalence of VHD. Diagnosis and treatment of patients with valvular disease is complex as symptoms of the disease may often reveal at a late stage while early treatment is key to optimal prognosis for the patient. Each of the four heart valves may be affected. A valve may be narrowed/hardened (referred to as valvular stenosis) due to fibrosis and calcification, or may be leaking (referred to as valvular regurgitation or insufficiency). In both situations the valve disease may influence cardiac function and remodeling. Mitral valve insufficiency is a disease in 2% of the population that may result in left ventricular and/or left atrial dilatation leading to heart failure, increased risk of cardiac arrhythmias, increased pulmonary resistance and increased end-systolic right ventricular pressure. In patients with (severe) tricuspid valve regurgitation pressure can rise in the right ventricle due to blood flowing backward into the right atrium and less blood flowing forward through the right ventricle and into the lungs. The right ventricle can expand and weaken over time, leading to heart failure. Some people with severe tricuspid valve regurgitation also may have a common heart rhythm disorder called atrial fibrillation. The timing of surgical intervention remains controversial, mostly due to the limited data available and their heterogeneous nature. Surgery should be carried out sufficiently early to avoid irreversible RV dysfunction (Baumgartner, 2017).

Atrial fibrillation is a condition in which the atria beat irregularly and affects 33 million people worldwide. Usually, it is not life-threatening but may lead to blood clots forming in the heart that may circulate to other organs and lead to blocked blood flow (ischemia), including stroke. Therefore, atrial fibrillation needs to be treated to prevent stroke events. In non-valvular AF, over 90% of stroke-causing clots that come from the heart are formed in the LAA. Oral medication (anticoagulant) is not possible for certain patients and therefore a recent treatment alternative is to implant a device that occlude the LAA (BostonScientific, 2019) (Piccini, 2017)

The following sections provide a brief summary on the clinical state of the art related to left sided VHD followed by a description on the state of the art related to the currently available methods and guidelines for risk stratification, treatment planning and success evaluation for clinical management of left sided VHD.

4.1.2 Clinical state of the art

Diagnosis and detailed assessment of the severity of valvular disease includes various examinations. Routine clinical examination may reveal distinctive heart sounds (murmurs) which are used as indicators of VHD. It has been shown however that clinical examination alone is not a reliable guide to diagnosis or severity grading. The gap in the clinical diagnosis of VHD and the late presentation of many patients with severe disease emphasizes the importance of quantitative, high-quality cardiac imaging. Depending on the specific situation a patient may need to undergo several additional tests in order to

obtain an accurate assessment of the severity of the valvular pathology. Currently, cardiac ultrasound (US) is the clinical workhorse for anatomical and functional assessment of the cardiac valves. Transthoracic echocardiography (TTE) is routinely performed during a cardiac examination and is the cornerstone for the diagnosis of valvular heart disease. For more detailed valvular analysis, for accurate study of leaflet morphology/mobility before valvular interventions and for reliable diagnosis in doubtful cases a transesophageal echocardiography (TEE) is commonly performed.

Mitral regurgitation (MR)

MR may be the result of degeneration but also a result of (non-)ischemic left heart disease. Surgical mitral valve repair has become the preferred intervention rather than mitral valve replacement, mainly because it preserves the original heart structure, avoiding abnormal remodeling. As such, imaging techniques are applied to determine whether the patient is a suitable candidate for valve repair and to assess all relevant aspects of the valve pathology, being 1) the disease etiology, 2) the primary valve lesion and 3) the resultant valve leaflet dysfunction. TEE is the preferred imaging modality for this advanced mitral valve assessment due to superior exposition of mitral valve complex compared to TTE, and superior dynamic/functional assessment compared to CT/MRI. In the classification system proposed by Carpentier (Carpentier, 1995) for valve leaflet dysfunction three classes are discerned (Figure 1): normal leaflet motion (Type I), excessive leaflet motion (Type II) and restrictive leaflet motion (Type III). Type III can be further divided into restricted leaflet motion as a consequence of rheumatic valve disease (Type IIIa) and restricted leaflet motion due to papillary muscle displacement as a result of (non-)ischemic ventricular dysfunction and dilatation (Type IIIb).

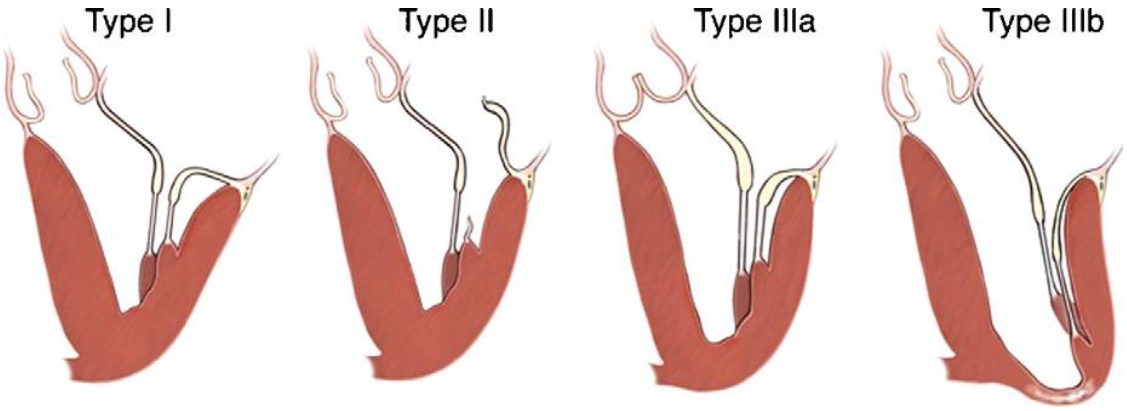


Figure 1 Functional classification of mitral regurgitation according to the classification system of Carpentier. Type I: normal leaflet motion. Type II: increased leaflet motion. Type IIIa: restricted leaflet motion during diastole and systole. Type IIIb: restricted leaflet motion during diastole and systole. Type IIIb: restricted leaflet motion during systole (Chikwe, 2009)

Mitral stenosis (MS)

The prevalence of MS in developed countries is relatively low because rheumatic heart disease is the primary cause of MS. TTE with Doppler velocimetry is the key diagnostic tool. Planimetry based on TTE images of the mitral valve in mid-diastole is used to quantify the valve orifice. The Bernoulli equation is used to calculate the mean pressure

gradient from Doppler velocities, and the pressure half-time method is used to assess the severity of the stenosis from a functional perspective.

Tricuspid regurgitation (TR)

The tricuspid valve has long been described as the "forgotten valve": 1.6 million individuals in US have severe tricuspid regurgitation (associated to high mortality) but only 8,000 patients can undergo surgery. Most patients get drugs, resulting in modest amounts of clinical improvement. Currently, transcatheter tricuspid valve repair and replacement devices are under development and will soon provide a treatment possibility for the many currently untreatable patients. The current transcatheter approaches for treating tricuspid regurgitation include annuloplasty systems, coaptation devices, leaflet devices, caval valve implantation, and tricuspid valve replacement. Imaging tricuspid valve anatomy is more complex compared to mitral valve and aortic valve because its complex structures (three leaflets with largest orifice in the heart, chordae tendineae, usually three papillary muscles) change in shape and size during the cardiac cycle and among different patients. Imaging complexity is going to be the bottleneck for treatment planning and initial human experience has shown high risk of detachment.

Atrial Fibrillation (AF)

Patients with atrial fibrillation are at high risk for stroke, and studies have shown that the majority of the blood clots originate from the left atrial appendage (LAA). The traditional strategy for stroke prevention inthese patients is oral anticoagulant therapy, but this may lead to increased bleeding risk. Therefore, a minimally invasive closure of the LAA has been proposed during which a permanent implant seals the neck of the LAA cavity. The LAA closure (LAAO) market is dominated by two devices, the Watchman (Boston Scientific, CE and FDA approved) and the Amplatzer (Abbott – CE approved). Despite promising clinical results, LAAC remains a complex procedure due to the enormous anatomical variability of the LAA. Device mis-sizing occurs in approximately 10% of cases, which may lead to device embolization or, when detected during the procedure, to device retrieval or repositioning. Several newer generation devices have been withdrawn from the market due to higher than expected clinical complications. Improved pre-operative planning (and guidance) is crucial to avoid mis-sizing, and hence to reduce complications and the complexity of this intervention. Current planning is based on anatomical measurements (CT or echo-based), but due to the anatomical complexity, it is not straightforward to identify the proper location to perform these measurements.

Echocardiographic indicators of severe valvular heart disease

Valvular lesion	***Index***	***Threshold for severe abnormality***
Mitral regurgitation	Color Doppler het area Vena contracta width EROA by flow convergence Regurgitant volume Regurgitant fraction Supportive findings	> 40% LA area > 10cm^2 ≥7 mm ≥ 40mm^{2*} ≥ 60 ml ≥ 50% E Wave velocity >1.2 m/s LA or LV dilatation Pulmonary venous flow reversal
Mitral stenosis	Transmitral gradient Mitral valve area Supportive findings	>10 mmHg <1 cm2 PAP > 50 mm HG
Tricuspid regurgitation**	EROA by flow convergence Regurgitant volume	≥ 40mm^2 ≥ 45 ml

	VC width (mm) PISA radius (mm)	> 7 >9
Each measure should not be taken in isolation but in concert with other signs and imaging parameters to ascertain lesion severity. *An EROA cut-off ≥20 mm2 may have greater sensitivity for severe mitral regurgitation if functional in nature. CW: continuous wave; EROA: effective regurgitant orifice area; LA: left atrial; LV: left ventricular; PAP: pulmonary arterial pressure; Z_{VA}: valvulo-arterial impedance (source Leong 2013). **Arsalan, M, Walther, T, Smith, RL, Grayburn, PA **(2017)**. Tricuspid regurgitation diagnosis and treatment. *Eur. Heart J.*, 38, 9:634-638.		

Electrocardiographic indicators of atrial fibrillation

Atrial fibrillation	no visible P waves and an irregularly irregular QRS complex

During predecessor ITEA project Benefit, FEops has developed a simulation-based technology to predict the outcome and the complications of transcatheter aortic valve replacement starting form routine preoperative imaging.
To virtually treat a patient's heart using TAVIguide, the doctor has to upload the CT image (anonymized DICOM file) through a secured web portal. After 24 hours, the doctor receives the simulation results from FEops on the same portal and can visualize the virtual patient treated using different (possible) procedural options. For each procedure, the 3D model of heart and device can be inspected by rotating / translating and zooming, thanks to the webGL technology. In addition to the 3D models, contour plots and measurements are provided that describe specific physical quantities corresponding to the onset of treatment complications. For the paravalvular leak, blood flow streamlines colored by velocity are shown around the device and the amount of regurgitating flow is reported (fluid flow, in ml/min). Similarly, the risk of conduction abnormality is indicated by contact pressure (distribution and value) exerted by the device onto a region of the heart where the conduction system is located (and can be damaged!). In this way, the doctor can compare the simulated outcome of multiple possible procedural options and is optimally informed to deliver the optimal treatment to the patient.
The clear advantage of TAVIguide is that complications can be evaluated upfront and, therefore, avoided during treatment, potentially increasing the life-expectancy of the patient after TAVI. By complementing the current treatment planning (usually based on anatomical measurements only), engineering simulations have the potential to go beyond TAVI and support multiple emerging structural heart interventions, such as transcatheter closure of left atrial appendage (LAA), repair and replacement of mitral and tricuspid valves and treatment of heart failure.
TAVI has been the main topic in the predecessor ITEA project Benefit, TMVR, TTVR and LAAO simulations will be developed in this project IMPACT and included in a single clinical simulation platform, the FEops HEARTguide.

4.1.3 IMPACT updates

Preoperative planning for Left Atrial Appendage Closure has evolved during IMPACT. A couple of new players entered the field. Besides 3Mensio, also Materialise launched its LAAO planning software (Mimics Enlight) and Circle Cardiovascular Imaging launched TruPlan. These competing products focus on performing measurements on CT images, performing planning for the transseptal puncture (access route) and sometimes providing an overlay of a device on the anatomy. Limitations of these tools:

- The user can not obtain insights regarding the device-anatomy interaction.
- These are traditional software packages installed on a workstation/laptop (not cloud-based).
- These tools require a dedicated desktop, which is available outside the cathlab but is difficult to take into the cathlab.

Within IMPACT, FEops and Philips have aligned with the innovation of the competitors and went significantly beyond that:

- Physicians can now use FEops HEARTguide to better understand the optimal access route (transseptal puncture), as demonstrated in the image below.

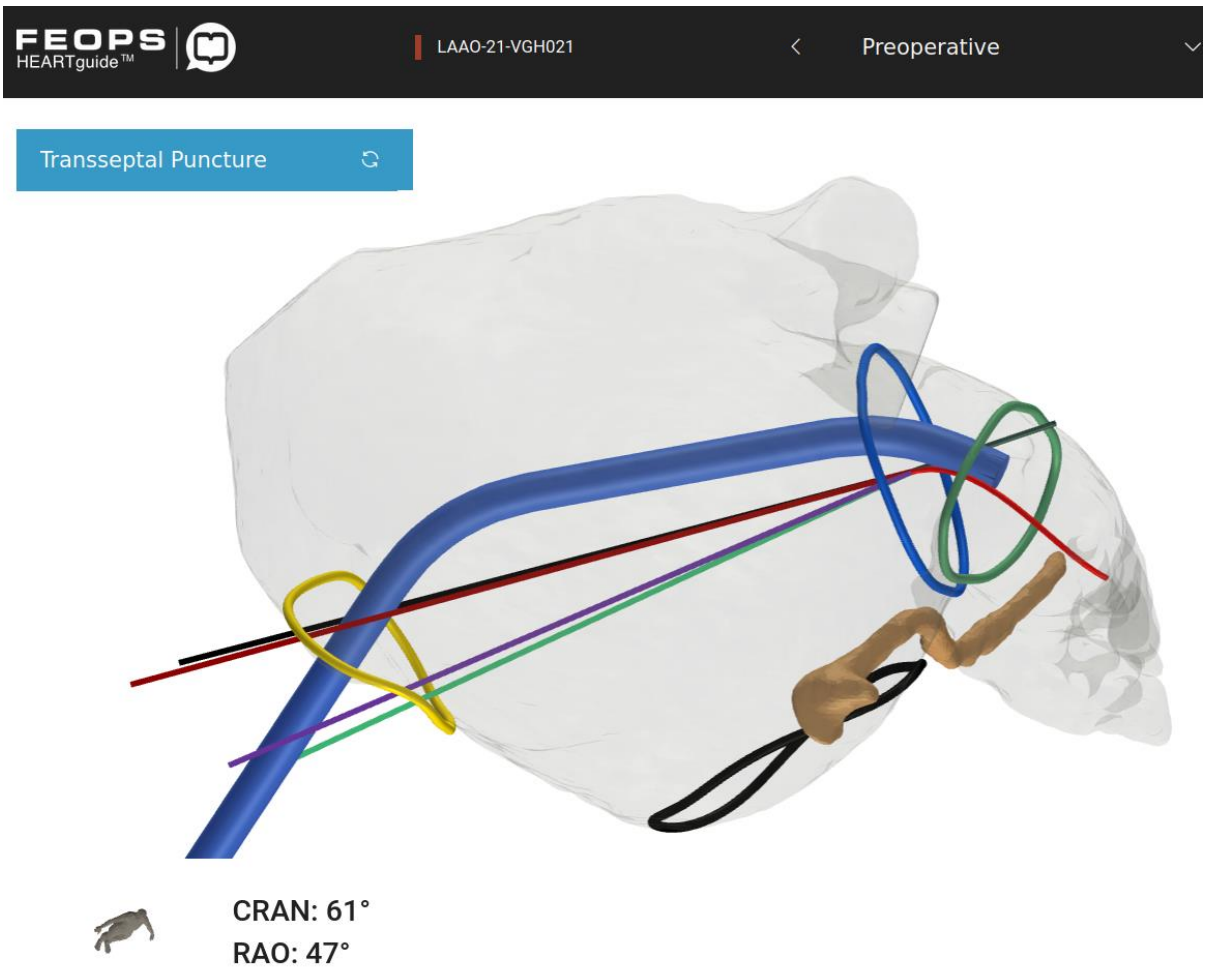
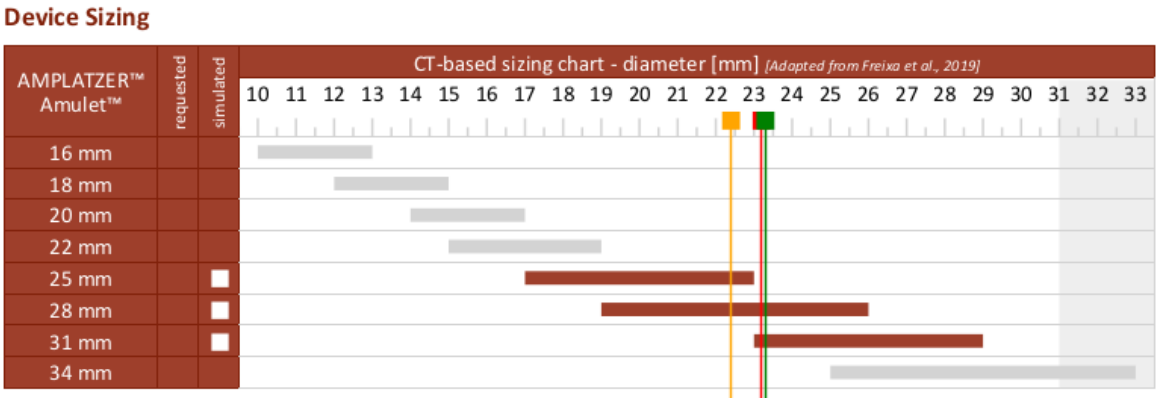


Figure 2 FEops HEARTguide screenshot showing optimal access route

- Starting from the IMPACT project, FEops has developed an AI-supported complete anatomical analysis. It is provided to the customers for both TAVI and LAAO (FEops HEARTguide ALPACA v2.0) and automates segmentation of LAA and aortic root and detection of the annular plane + coronary ostia.
- With FEops HEARTguide release of December 2020 the Watchman FLX device (Boston Scientific) is included. Moreover, simulation runtime for the Amulet device was reduced by a factor 4. Press release: https://www.feops.com/src/Frontend/Files/MediaLibrary/09/fhg-dec-2020-release-press-release-final-2.pdf
- Together with a LAAC device manufacture (Abbott) FEops is in the final phase of enrolling patients for the PREDICT-LAA clinical study with 139 patients of 200 enrolled in May 2021 (https://openheart.bmj.com/content/7/2/e001326). Simulations provide quantitative data to select the optimal device size and implantation position for a specific patient. Most of the times, the sizing chart indicates multiple possible sizes for the same anatomy and an optimal choice can be difficult without simulations, as shown in the Device Sizing (part of FHG-LAA report). Simulations help choosing the best size and position, as shown below in Figure 3 (part of FHG-LAA 3D viewer).



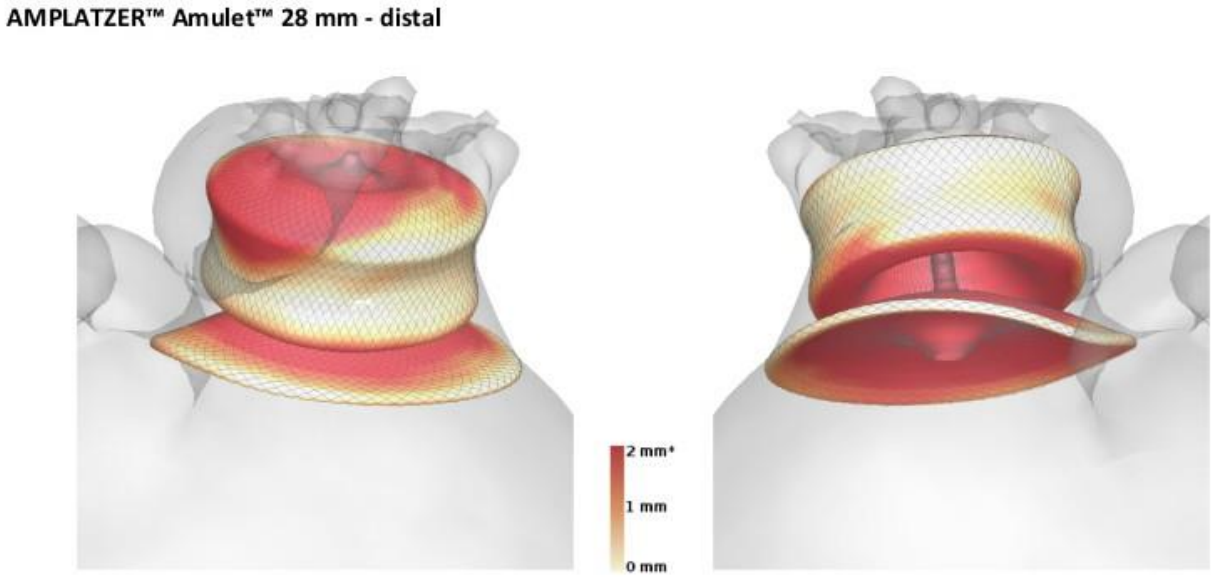


Figure 3 Impression of HEARTguide sizing and positioning suggestions

- While waiting for results of PREDICT-LAA clinical trial, simulations (of?) the LAAC procedure seems to be beneficial for the patient because of less time needed to complete the intervention, less time exposed to radiations (fluoroscopy), less (toxic) contrast to be injected (beneficial for patients with renal impairment), less amount of re-positioning and re-interventions because of better device sizing and selection of target position. To give some numbers, procedure time reduced by 30%, contrast volume reduced by 25%, and fluoroscopy time reduced by 14%. These statistics are based on the comparison of a historical cohort of 70 patients using routine preoperative planning with a cohort of 26 patients using FEops HEARTguide preoperative planning. (Dr Philippe Garot, CSI webinar Oct 30th 2020, "LAA anatomy and imaging")
- Simulation results (are?) provided 24h after CT DICOM file submission. Doctor can review the report the day of the intervention and visualize the 3D model when the patient is on the table, thanks to the integration of Philips'AR and FEops 3D viewer. This allows a side by side evaluation of live imaging (fluoro, echo), preoperative imaging (CT) and simulations (FEops HeartGuide LAAO) and is particularly appreciated when things go wrong and last-minute decisions require to re-evaluate the case based on all source of information.

- When side-by-side visualization is not sufficient, simulations'3D models and living imaging can be fused using FEops HEARTguide in combination with Philips' live imaging (https://www.youtube.com/watch?v=HraYhbfMcuc)

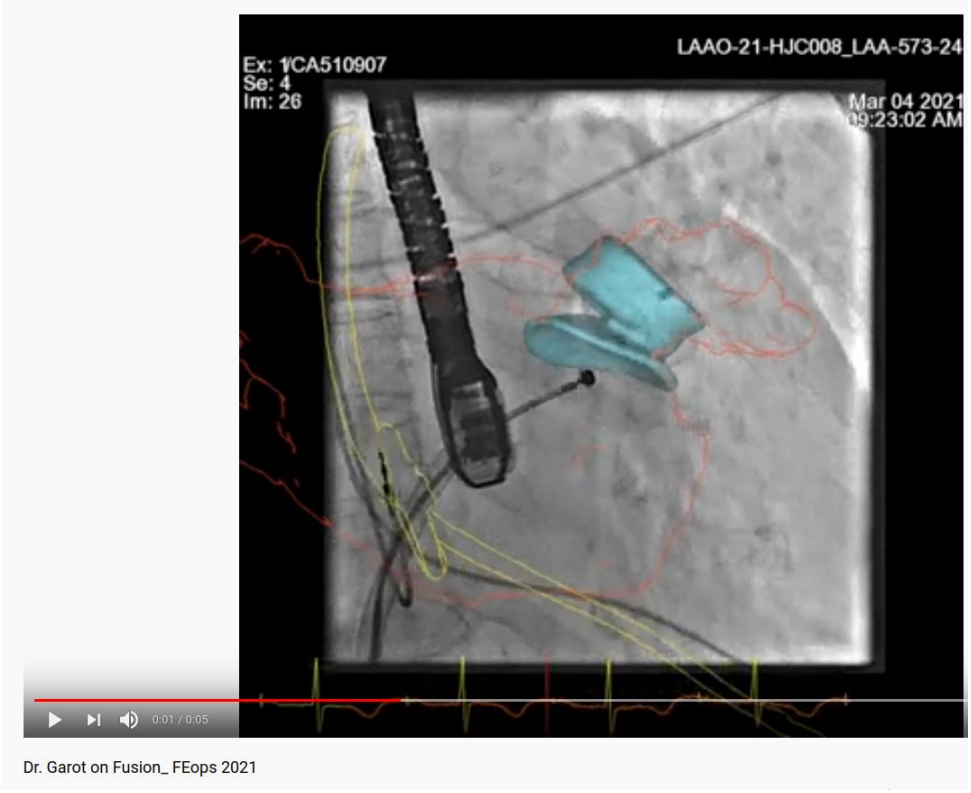


Figure 4 Image 3D simulation and live imaging fusion example

- The Philips' AzurionAR prototype is currently used in 2 hospitals (St. Antonius, Nieuwegein & CCHMC Cincinnati) as an Investigational Device, and we are preparing for 2 additional sites (UMC Utrecht & UMass Worcester).
- The initial clinical results have been shared within Philips through "Voice of the Customer" sessions and will externally at the ECIO conference. Next, the solution will be discussed in detail at the upcoming SIR & CIRSE conferences.

4.2 Coronary vessels

4.2.1 Introduction

Coronary arteries are the blood vessels that take care of the blood supply to the heart muscle. Coronary artery disease is the major cause of death in the Western world (WHO, 2014). The main cause of this disease is atherosclerosis, i.e. a thickening of the coronary artery vessel wall. This process of build-up of fatty deposits in the vessel wall may already start in young adulthood and continue afterwards. The continued build-up of these plaques may eventually lead to a narrowing or occlusion of the coronary lumen, causing ischemia (lack of blood supply) and angina (chest pain) symptoms. Alternatively, a coronary plaque may rupture and release its contents in the artery, causing blood clots and a sudden occlusion, potentially leading to an acute myocardial infarction (heart attack).
There are several risk factors associated with the development of premature ischemic heart disease and acute myocardial infarction, such as smoking, age, diabetes, hypertension and obesity.

Percutaneous coronary intervention (PCI, Figure 5) is one of the treatment options for patients with chronic stable angina (chest pain due to ischemia of the heart muscle). Other options are medication, and coronary artery bypass graft (CABG). Whereas PCI is less invasive than CABG, and thus seems favorable for patients, the preferred treatment depends on various issues, such as patient characteristics and classification of a lesion, and is still subject to investigations and debate. The interventions do not cure the underlying cause of the atherosclerotic disease process but they are carried out to alleviate the symptoms and have a survival benefit for the patients. For acute patients, CABG and PCI are associated with significant short- and long-term mortality benefit.

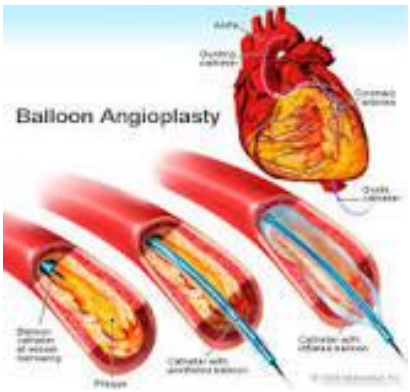


Figure 5 PCI procedure to remove a stenosis with a balloon catheter and stent

Diagnostic preoperative imaging of patients with cardiac problems involves X-ray angiography, which visualizes the lumen of coronary arteries. In this procedure, contrast agent is introduced in the left or right coronary artery, by advancing a catheter via the radial or femoral arteries to the aorta into the coronary ostium. X-ray angiography allows the quantitative assessment of the narrowing of the coronary lumen (stenosis). Coronary X-ray angiography currently is the standard modality for assessing coronary lesions, and a vessel diameter of 50% or less (75% area) is considered a significant lesion. However, the hemodynamic significance of a coronary lesion does not correlate well with stenosis measurements. Therefore, other quantitative measurements and imaging techniques, both before the intervention (SPECT, stress echo, ECG) and during the intervention (FFR, iFR, OCT, IVUS), are used to decide whether an intermediate lesion needs treatment or can be deferred. CTA and intracoronary imaging also provide additional information about the plaque burden and the plaque composition.

4.2.2 Clinical state of the art

The purpose of PCI is to restore the vascularization of the heart muscle by widening stenotic lesions in coronary arteries. To this end, a stent is placed in the coronary artery, possibly after prior dilation with a balloon. The procedure is performed minimally invasively, often via the femoral artery (but also via brachial or radial artery). First a guide catheter is introduced, such that the distal tip of the guide catheter is in coronary artery, to provide a safe access of the guide wires and catheters to the coronary arteries. Subsequently, a guide wire is inserted through this catheter, and advanced beyond the lesion. Optionally, additional intravascular imaging or measurements (IVUS/OCT/CFR/FFR) may be performed to assess the hemodynamic significance of the lesion or the burden and composition of the plaque. In case dilation of the lesion before stent placement is needed, a balloon catheter is advanced over the guide wire, positioned at the lesion in the coronary artery and inflated to dilate the artery. After dilation, a catheter with a balloon-mounted stent is advanced over the guide wire. When the stent is located at the lesion, the balloon is inflated to deploy the stent. After stent deployment, the balloon catheter is removed.

Image guidance during the procedure is performed by mono- or biplane fluoroscopy (see Figure 6), which visualizes the guide wires and catheters (some of which have additional markers for improved visibility). The coronary arteries are visualized by injections of contrast agent, which result in a transient visualization of the vessels. Optionally after the stent placements, the stent deployment is checked by using IVUS or OCT. If struts are not positioned correctly against the lumen wall, a second balloon inflation might be needed to place the struts correctly for a better end result of the procedure.

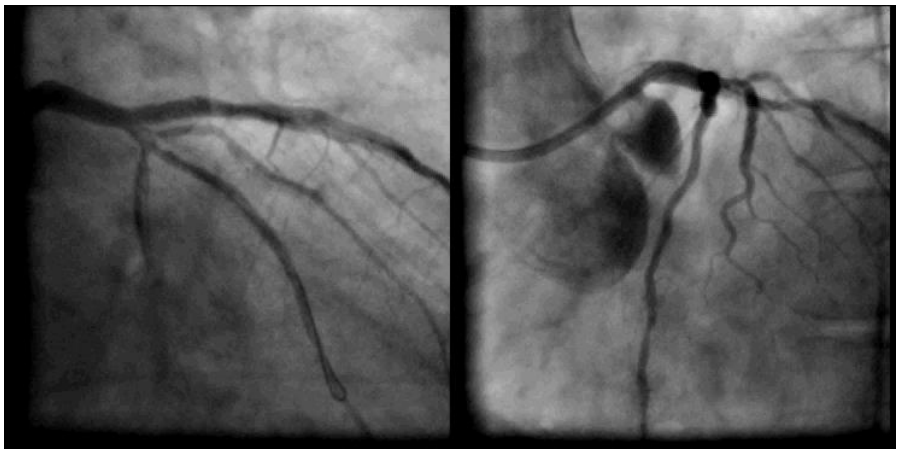


Figure 6 Biplane image of coronary intervention (Image courtesy Erasmus MC)

4.2.3 IMPACT updates

While the clinical practice of PCI has long reached maturity, the operational workflow management around the PCI procedure is far from efficient.
First, there are delays impeding smooth execution of the workflow. In the administrative and nursing activities leading up to the procedure, delays are common. Meanwhile, lacking a real-time overview of the patients' pathway statuses, clinical staff's time is

wasted on checking each other's progress and waiting. This results in suboptimal utilization of staff and Cath-lab resources. Moreover, due to insufficient identification and management of delays, combined with poor communication, procedures frequently overrun, and turnaround time increases, causing overtime and drop in staff satisfaction. Furthermore, data needed to analyze these inefficiencies is unavailable, incomplete, of low quality and/or stored in clinical systems which are not optimized for data analysis targeting measuring and improving operational performance.

In the IMPACT use case for coronary vessels, the following elements are developed to aid this problem.

1. A centralized real-time overview of patient pathway progress is provided by the control tower (Philips Research). It collects and presents workflow data with an at-a-glance view to uncover workflow inefficiencies (**Figure 7**). This helps clinical staff to easily monitor operational workflows. Delays are highlighted to warn the coordinator so that timely responses can be made. Also, the coordination decisions to resolve schedule conflicts, such as room reassignment, are automatically communicated via its connection to the dashboards in individual rooms.

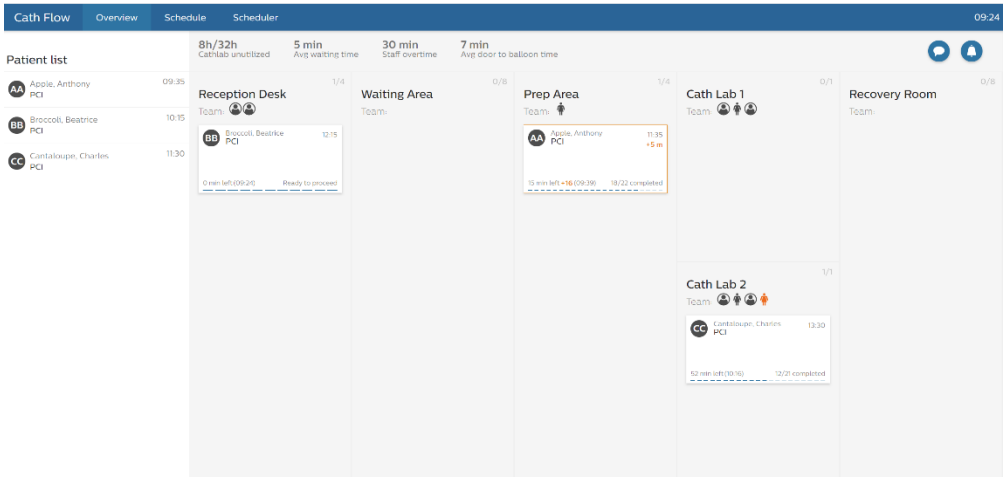


Figure 7. The Cath-lab Control Tower provides an overview of patient flow status and progress (the patients shown here are fictitious). The cards on the board represent the patients, their scheduled procedure time, their progress and delays if applicable.

2. The sensors in Cath-lab rooms (Philips IGT) provide unobtrusive event detecting capability that determines phases of the procedures, allowing the coordinator outside the labs to know the real-time progress via the control tower (**Figure 8**). Similarly, via interaction with NewCompliance dashboard, the staff in Cath-lab rooms can easily communicate their progress and estimation of end time to the control tower (**Figure 9**). These approaches improve the efficiency of communication.

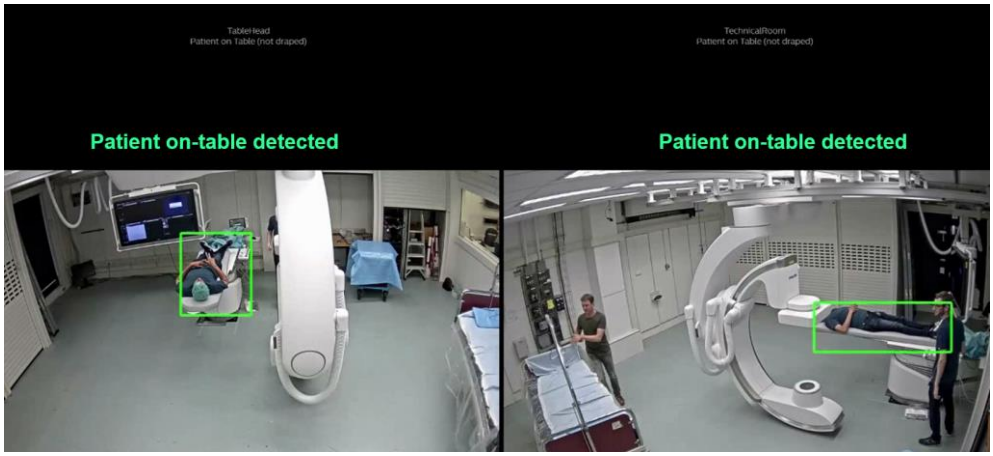


Figure 8. Sensors detect key events in the Cath-lab and communicate the progress to the control tower.

Figure 9. The dashboard in cath-labs communicate progress to the control tower

3. Smart and dynamic checklist (**Figure 10**) prompt users with important safety checks tailored to the current patient context.

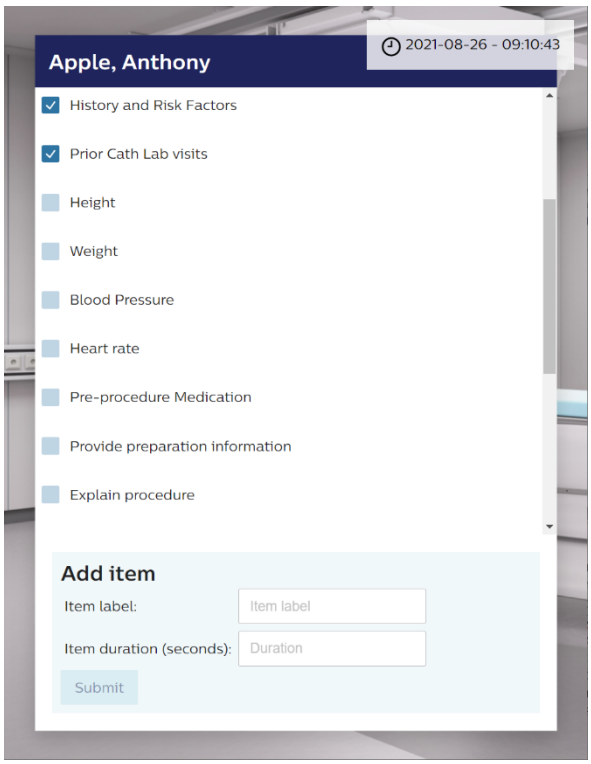


Figure 10. An example of PCI preparation checklist

4. These high-resolution records of workflow execution are analyzed via the performance analysis tool to measure operational performance and analyze performance-improving alternatives.
5. The dashboard in the labs (NewCompliance) also saves prep time and improves quality by providing the most important clinical information about the patient and procedure such as allergies, and risk factors.
6. The day planner ((Philips?) Research) further automates manual scheduling tasks and helps improve scheduling efficiency by automatically detect resource conflicts and generate improved schedules.

4.3 Liver oncology

4.3.1 Introduction

Liver tumours are caused by primary or secondary liver cancer. The most common form of primary liver cancer in adults is hepatocellular carcinoma (HCC). HCC can be caused by a viral infection with Hepatitis B or C or by cirrhosis, a disease that causes chronic liver damage due to non-alcoholic fatty liver disease and abuse. Patients with HCCs often do not show symptoms other than caused by the underlying liver disease, and thus these tumours are detected in a late stage, which gives poor survival rates for patients diagnosed with HCCs (5-year survival of 12%, and median survival ranging from 6 – 20 months). Early detection and adequate treatment options thus are required.
Secondary liver cancer implies liver tumours are metastatic, most commonly from primary colorectal cancer, but also from lung or breast cancer.

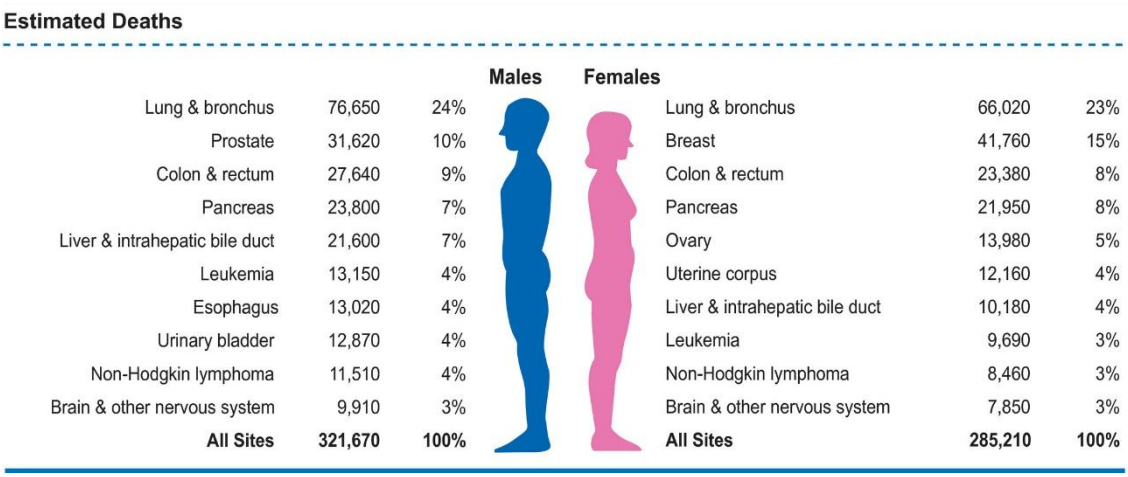


Figure 11 Ten Leading Cancer Types for the Estimated New Cancer Cases and Deaths by Sex, United States, 2019. (Siegel et al. Cancer statistics 2019, Cancer J Clin 2019; 69:7-34)

Figure 11 depicts the most common cancers expected to be diagnosed in men and women in 2019 in the united states. Prostate, lung and bronchus, and colorectal cancers (CRCs) account for 42% of all cases in men, with prostate cancer alone accounting for nearly 1 in 5 new diagnoses. For women, the 3 most common cancers are breast, lung, and colorectum, which collectively represent one-half of all new diagnoses; breast cancer alone accounts for 30% of all new cancer diagnoses in women.

Worldwide, HCC is the third most common cause of cancer-related death. The 2012 GLOBOCAN global analysis estimated a total incidence of 782.000 of primary liver cancer and a mortality of 746.000 worldwide, with 82% of primary liver cancer cases occurring in developing countries. Colorectal cancer showed a worldwide incidence of 1.360.000 and a mortality of 694.000 [globocan.iarc.fr]. Approximately 50% of colon cancer patients will be diagnosed with hepatic metastases [www.cancer.gov].

4.3.2 Clinical state of the art

Based upon an analysis of a patient's medical history and initial physical exams, a doctor can suspect the presence of liver tumours. Imaging is used as a first method for diagnosis. Various imaging techniques are available:

- Ultrasound (US),
- Fluoroscopy,
- Computed tomography (CT),
- Magnetic resonance imaging (MRI).

In addition to such exams a full blood analysis is performed. Also a biopsy may be performed, in which a small portion of suspected liver tissue is removed for accurate pathological examination. A laparoscopy procedure is also sometimes performed as a follow-up to imaging, which involves visual inspection of the liver via a small camera inserted through a minor incision in the abdomen.

The outcomes of the various exams and procedures results into a staging and diagnosis of the disease. Based on the staging, the patient-specific factors, and the available procedures and expertise in the hospital, a treatment plan is composed.
First option is resection of the tumour in the liver (Perini, 2015), or liver transplantation. These are invasive surgical procedures, where the tumour is partly or completely removed by surgery. Not all patients are eligible for these types of surgery, as their health may already be compromised by the underlying liver disease. Varying mortality rates are reported for surgical resection, therefore careful patient selection is thus relevant. Also, survival rates are depending on the stage of the disease, with better survival rates for early stage and single lesions.

Several minimally invasive alternatives for open surgery exist (Li, 2014). Minimally invasive treatments promise benefits over traditional surgery, such as less tissue damage, reduced pain, less scarring, lower risk of complications, shorter or no hospital stays and faster recovery.

One alternative is laparoscopy which is a type of surgical procedure that allows a surgeon to access the inside of the body without having to make large incisions in the skin. Large incisions can be avoided because the surgeon uses an instrument called a laparoscope. This is a small tube that has a light source and a camera, which relays images of the inside of the body to a medical display. A problem in laparoscopic surgery compared to open surgery is the lack of direct sight on the area inside the body (the endoscope has limited flexibility and field of view), lack of haptic feedback by direct palpation and very limited working area inside the patient to maneuver the instruments. This is one reason to investigate the use of robotic support in which the surgeon controls the instruments in the patient via a user interface (a.o. joy sticks) behind a console. It may give more degrees of freedom and accuracy to operate the surgical devices inside the patient. The most well known one is the DaVinci robot by IntuitiveSurgery. This will be explained in more detail in deliverable D4.1.1.

Among the minimally invasive alternatives are also needle-based approaches, where a needle is brought in through the skin (percutaneously), such that the needle tip is in the tumour. These approaches are often image-guided, using ultrasound or CT to visualize the target anatomy. Examples of these approaches are radiofrequency ablation (RFA),

microwave ablation (MWA), cryoablation, and percutaneous ethanol injection (PEI). In the first two approaches, radiofrequency is used to locally heat the tumour, whereas in cryoablation, cooling is used to destroy the tumour, and in PEI, ethanol is injected to kill the tumour. The latter intervention may need multiple sessions. A recently novel approach is irreversible electroporation (IRE), where high voltages are used to damage the tumour cells.

To improve accurate and fast needle placement robotic support tools guided by 3D imaging have been developed (Arnolli, 2017). However, these are not yet part of standard clinical workflow.
Because the liver is moving due to breathing during needle insertion, compensation is needed to prevent inaccurate targeting of a tumour. Models have been developed to follow the lesion position in real time based on internal or external markers (Fahmi, Simonis, & Abayazid, 2018, 14:e1940.).

The complication rate after resection is almost ten times higher than after ablation and the hospital stay more than twice as long. Yet, hepatic resection yields better results regarding local recurrence compared to ablation. For the different minimally invasive methods, it remains difficult to judge whether the entire tumour has been treated since there is no pathological feedback like during resection. Therefore, surgical resection remains the treatment of choice for most patients, despite higher morbidity and mortality rates.

Transarterial approaches are another class of minimally invasive interventions. In these interventions, instruments are navigated to the tumour via the arterial system. Often, an incision in the groin is made to access the femoral artery, and then via the aorta and the hepatic artery, catheters are brought to the tumour for local treatment. There are several versions of these approaches, such as transarterial embolization (TAE), transarterial chemo-embolizations (TACE) and transarterial radio-embolization. In all cases, embolization is meant to stop the blood supply to the tumour. In case of chemo-embolization, chemotherapy is applied together with the embolization, and in case of radio-embolization, radiotherapy (radioactive isotopes) is combined with embolization. These approaches are generally used for patients for whom resection and the ablation approaches (too many, too diffuse, too large tumours) are not applicable. Transarterial approaches are performed under X-ray and fluoroscopy image guidance. In case of radioembolization additional nuclear imaging is required to ensure no leakage or shunting of the embolizing particles to other critical organs exist. In recent years image acquisition and analysis tools have been developed to support radiologists to navigate the catheter to the tumour sites (Miyayama, 2016).

Owing to improvements in the understanding of the biological principles of tumour initiation and progression, a wide variety of novel targeted therapies have been developed. Developments in biomedical imaging, however, have not kept pace with these improvements and are still mainly designed to determine lesion size alone, as reflected in the Response Evaluation Criteria in Solid Tumours (RECIST) and may fail to detect successful responses to these novel agents Various imaging approaches targeting a single dedicated tumour feature have been successful in preclinical

investigations, and some have been evaluated in pilot clinical trials. However, these approaches have largely not been implemented in clinical practice (Gerwing, 2019).

Stereotactic radiotherapy is an alternative approach. However, the liver is a very radiosensitive organ, which is a major drawback of this approach. Additionally, localization of the tumour during treatment is a challenge. To counter this an MRI-linac system has been developed (for instance the Elekta Unity system) in which the MRI system tracks the motion of the tumour in real time and the linac adapts its radiation treatment beam to follow the tumour.

Another relatively novel approach is high intensity focussed ultrasound (HIFU). In this approach, high intensity ultrasound waves are focussed at the tumour location, and in that way the tumour is heated and destroyed. HIFU can be performed under MR or US image guidance. Challenges in these approaches are shadowing caused by the ribs (the beam should be send between the ribs), and tumour motion caused by breathing.

Additionally, combinations of aforementioned approaches have been proposed, e.g. using a minimally invasive approach before surgery, or combining stereotactic radiotherapy with other minimally invasive approaches.

4.3.3 IMPACT updates

Important bottlenecks, which have been addressed in the IMPACT project for the liver oncology, are the time consuming and subjective resection plane planning and ablation margin assessment for both CT and MRI datasets. The resection plane planning results are also presented during laparoscopic/robotic surgery to handle the bottleneck of the lack of overview. The 3D model provides additional information to the operator. Finally, the availability of information during the procedures is improved by using a real-time dashboard in the operating room.

For both the resection plane planning and ablation application, the liver vascular trees are now detected automatically as shown in Figure 12. The venous and portal trees in the liver are segmented by the manual placement of seed points on the contrast-filled vessels. Next, the arterial tree is added using the registration parameters from the registration procedure that is applied on the pre-procedural venous and arterial scan. Then the trees are automatically converted into three-dimensional models in which each tree is depicted in a different color.

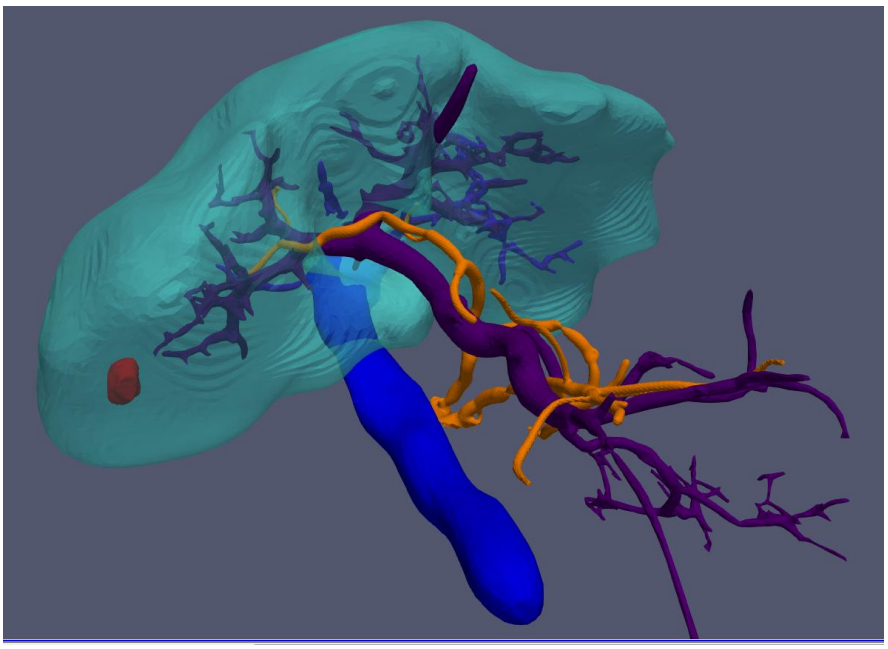


Figure 12 3D model of the liver (blue) and the different blood vessels (orange, purple, dark blue)

For the ablation application, the registration of pre-procedural and post-procedural images is as automatic as possible. This is realized by performing the next steps: First, the segmentation of the liver is now fully automated using deep learning. The data sets is feed into the DL network. At the moment, the deep learning algorithm is integrated in a Docker container, which gets a CT or MR image as input and provides the segmentation as output. Next, the liver segmentations are used as region of interest to initialize the registration between the datasets. The image registration is performed by using Elastix (https://elastix.lumc.nl) which also allows adding manual correction points if necessary to aid and steer the registration. The resulting registration transformation is used to align the 3D segmentation masks. In these regions, the tumors are segmented automatically in the pre-procedural stage using deep learning. An example from such a segmentation is shown in Figure 13. The tumor regions are superimposed on the 3D model. Next, the ablation zone is segmented using similar deep learning methods from the post-procedural images and these results are also superimposed on the 3D model.
Based on the surfaces of the ablation zone and the tumor zone, the margin (distance tumor to ablation zone) is determined in 3D. For this the minimal distance, the area below a certain distance to the ablation zone and the volume of the tumor below a certain distance to the ablation zone is determined. In Figure 14, this is shown as a color indication of the distance between the tumor and the ablation zone.
The final goal is to have this software available during the ablation procedure, to check whether the ablation resulted in big enough margin, or the ablation should be continued.

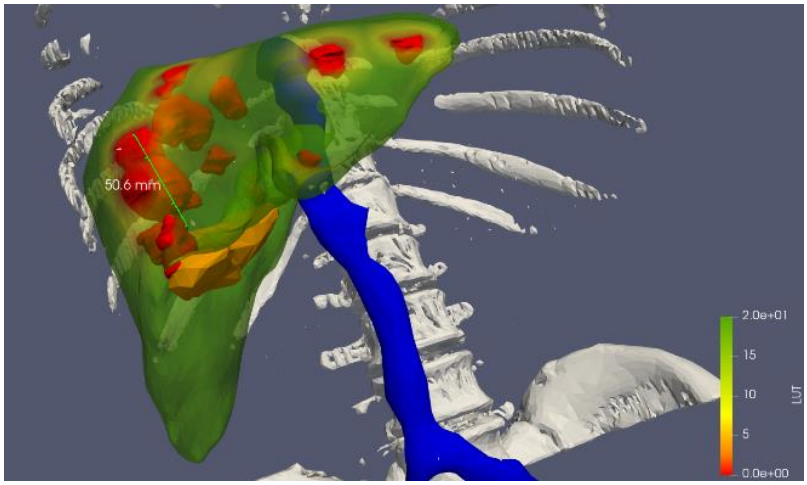


Figure 13 3D model of the liver (green) with different tumor regions (red).

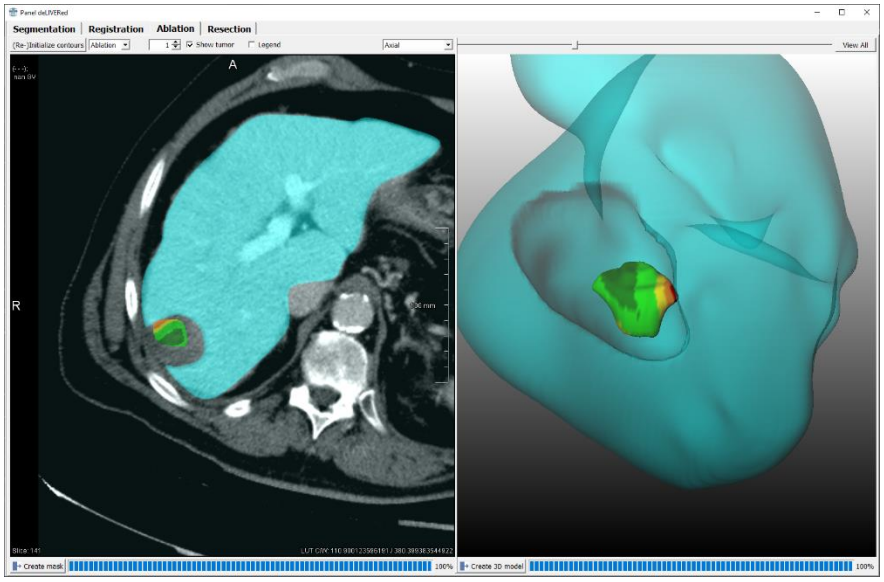


Figure 14 3D model of the liver (blue), ablation zone (darker blue) and tumor (green). The color-coding on the tumor indicates distance to the tumor margin. Red means the distance is too small according to current clinical practice.

The same software tools as developed for the ablation are used to determine the optimal resection planes for surgery. Having the liver, tumor and blood vessels segmented for the pre-procedure stage, it is determined which cutting planes do remove the tumors but do not cut through the main blood vessels as shown in Figure 15. The resection margin can also be a wedge to spare more tissue.

The results of the resection plane planning are shown in the surgical cockpit is shown in Figure 16.

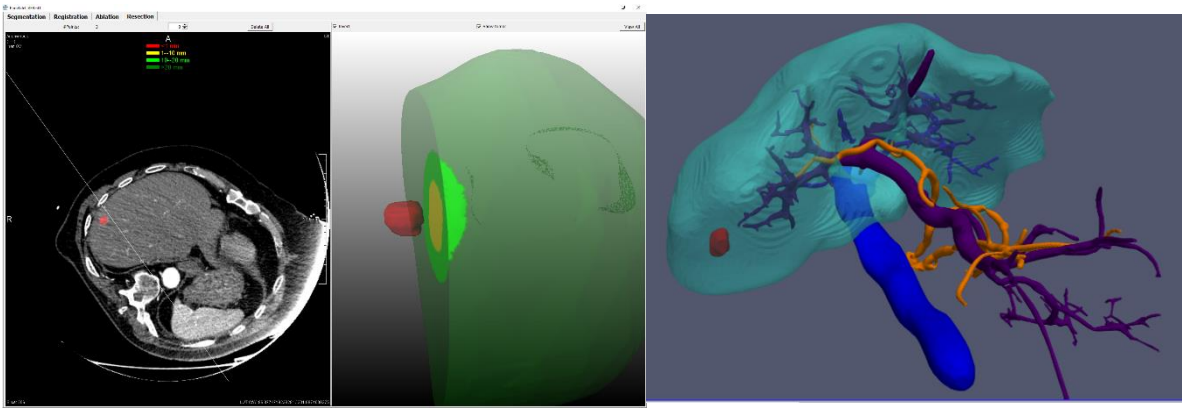


Figure 15 3D of liver (Blue), liver tumor (red) and resection plane (yellow).

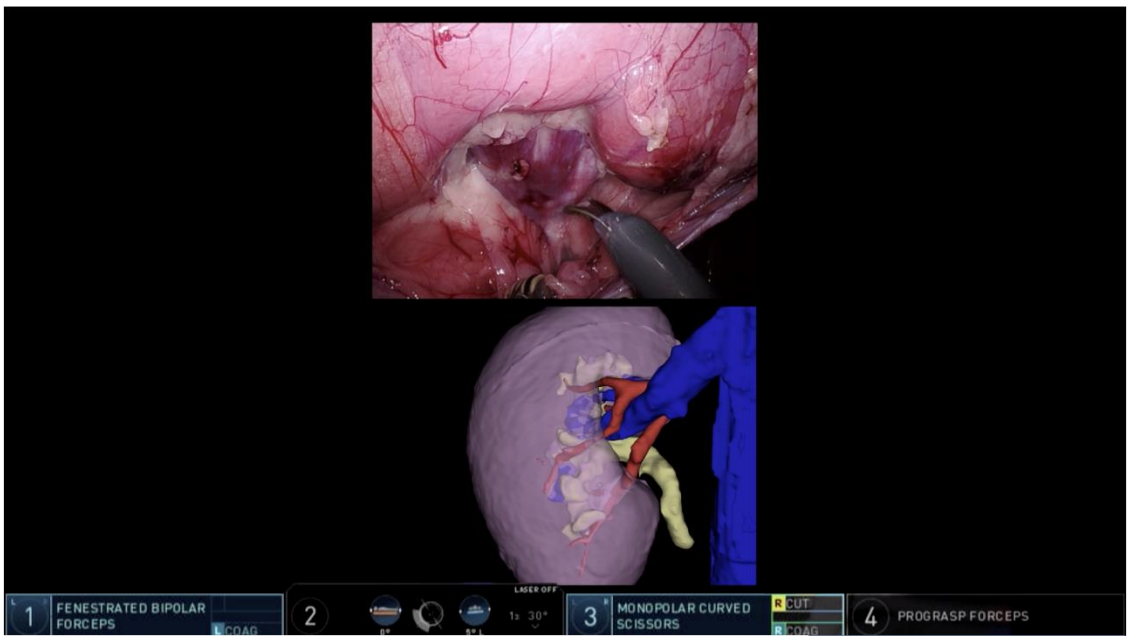


Figure 16 View in the surgical cockpit.

To provide the OR Team members with intelligent alerts, checklists and workflow guidance, a dashboard for liver oncology has been designed and implemented. This allows the staff to make pro-active decisions and not forget important items including tasks, patient specific risks etc. Figure 17show an example of the layout of the dashboard.

Figure 17 Surgical dashboard for liver oncology.

4.4 Lung oncology

4.4.1 Introduction

Despite advances in diagnostic modalities, supportive care and novel treatment options, the prognosis of lung cancer patients remains bleak (See fig 1 in 4.3.1: lung cancer deadliest type of cancer).
When diagnosed with non-small cell lung cancer, the 5-year survival rate for patients with all stages of the disease combined is 23%. Even when the tumour is staged as local disease, without lymph node or distant metastases, despite curative intended treatment, 5-year survival rate is only 60%.
To improve the prognosis of lung cancer patients, all facets of diagnosis and treatment are currently being studied. Recent literature demonstrates the benefit of lung cancer screening in high risk patient groups. This leads to earlier diagnosis of the disease, at a lower stage, increasing the possibility of curative intended treatment. Surgical treatment of smaller tumours can be challenging, as exact tumour localization can be difficult. Especially in the light of minimally invasive, lung parenchyma sparing resections, there is a clinical need for intra-operative tumour identification tools. Tumour-targeted imaging using near-infrared fluorescence has the potential to identify tumours in real-time during surgery.

Various treatment modalities are available for lung cancer treatment. In the past, curative treatment consisted of major surgery, and treatment in a palliative setting included chemotherapy and/or radiotherapy. In recent decades, stereotactic ablative radiotherapy (SABR) has been added as a curative intended treatment option. However, long-term results in comparison to surgery are still unclear. Furthermore, in recent years targeted therapies have entered the field. These include therapies targeting a driver mutation, such as anaplastic lymphoma kinase (ALK) inhibitors and endothelial growth factor receptor (EGFR) inhibitors, and immunotherapy, including immune checkpoint inhibitors targeting the programmable death receptor 1 (PD-1) and its ligand (PDL-1).(2) Although these therapies were initially studied in palliative patients with metastasized disease, the extraordinary outcomes have resulted in new clinical trials studying these therapies in patient with lower stages of lung cancer. However, despite all these options, surgery remains the cornerstone of curative treatment in lung cancer. All these trials will add knowledge to the vast amount of treatment and outcome data currently available and have the potential to greatly increase the prognosis of lung cancer.

4.4.2 Clinical state of the art

Ongoing clinical trials provide positive data on lung cancer screening. Lung cancer screening programs are being implemented across U.S.A. and expected in Europe. Due to increased screening and quality of diagnostic tools, more patients are diagnosed with a small, early stage lung tumour. Current literature suggests that a parenchyma sparing, sublobar resection (i.e. anatomic segmentectomy), has similar oncologic outcomes in comparison to conventional lobectomy. Intraoperative identification of these smaller lesions and the anatomical relation to hilar structures such as segmental pulmonary

arteries and segmental bronchi can be challenging. In recent years, intraoperative imaging using near-infrared fluorescence has been used in clinical studies for tumour localization in other cancer types, such as ovarian cancer and colorectal cancer.

The optimal molecular targets for visualizing the various subtypes of non-small cell lung cancer, have yet to be determined. Using artificial intelligence to integrate data from available protein and cell databases, potential molecular candidates have been identified, which are currently being investigated in vitro.

Preoperative planning of a resection using the currently available imaging modalities (contrast enhanced CT scan and PET/CT) and 3D anatomical models based on available imaging data can be challenging. Intraoperative access to these models in combination with intraoperative, tumour-targeted near-infrared fluorescence imaging, may support the treating physicians in performing the least invasive, most optimal treatment for each patient.
Alternatively tumours can be marked by radiopaque fiducials under guidance of Cone Beam CT imaging and surgically removed in the same session in a hybrid X-ray – surgery room (Schroeder, 2018)

Apart from surgical resection tumours can be biopsied and removed by ablation via a needle or catheter. Tumours close to the big airways (bronchi) can be approached via a catheter. Using 2D and 3D image guidance (US, X-ray fluoroscopy and Cone Beam CT, CT), overlay of preinterventional images and/or electromagnetic navigation of the catheter (Pritchett, 2017) the physician can target the tumour to take biopsies or destroy it by heat or freezing it. Recently the FDA has approved a robotic system to navigate a steerable catheter through the bronchi to a lung tumour (Intuitive Surgical, 2019)
Tumours in the periphery of the lung can be approached from the outside by needle puncturing through the skin. In this case the same tools are applicable as mentioned in section 4.3.2 to improve accuracy of needle targeting and to compensate for breathing motion.

4.4.3 IMPACT updates

An Important bottleneck, which has been addressed in the IMPACT project for the lung oncology, is the resection plane planning in CT. The segmentation of the different vascular structures is time consuming and should be automated. Accurate resection plane planning saves healthy lung tissues and reduces the risk of re-occurrence the lung tumor. The bottleneck with respect to the lack of information during the procedure can use the same type of surgical dashboard as for the liver oncology. During the design, this has been taken into account.

It should be stated that the software as described could not be tested further due to the COVID-19 situation. There was no access to the labs and the clinical lung experts were too busy with COVID. This also hampered the next step to define the optimal resection planes due to the lack of ground truth data. This also hampered the implementation of the lung oncology surgical dashboard.

For the resection plane planning, the segmentation of lung arterial, venous and bronchus trees was made automatic. The segmentation consists of the following steps. First, a mask of the region of interest is created. For whole lungs, this is done automatically using atlas based registration. For user-defined regions, this is indicated through manual delineation. Next different properties such as vesselness and CT intensity values are combined and a graph-cut algorithm is used to segment the lung vessels. After the vessels are segmented, their centerlines are automatically extracted and combined into a graph. Finally, a deep-learning network is used on 3D local patches along the centerlines to do the final segmentation of the lung veins and artery. If needed manual correction can be performed after each step. Figure 18 shows the skeletonized segmented vessels and Figure 19 shows the artery/vein volume.

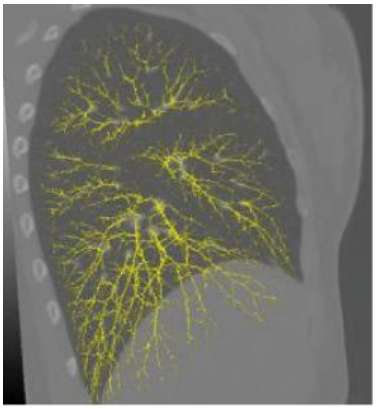


Figure 18 Skeletonized segmented vessels.

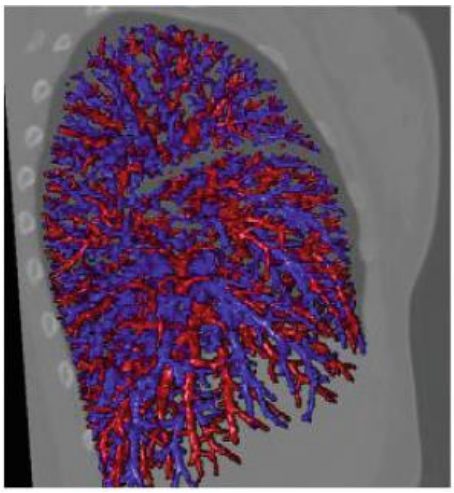


Figure 19 Artery/Vein volume.

4.5 Brain oncology

4.5.1 Introduction

A brain tumour occurs when abnormal cells form within the brain. There are two main types of tumours: cancerous (malignant) tumours and benign tumours. Cancerous tumours can be divided into primary tumours, which start within the brain, and secondary tumours, which have spread from elsewhere, known as brain metastases.
Primary brain tumours occur in around 250,000 people a year globally, making up less than 2% of cancers. Secondary, or metastatic, brain tumours are about four times more common, with about half of metastases coming from lung cancer.
Both cancerous and benign brain tumours occupy precious space in the brain and may cause serious symptoms (e.g., vision or hearing loss) and complications (e.g., stroke). All cancerous brain tumours are life threatening (malignant) because they have an aggressive and invasive nature. A noncancerous primary brain tumour is life threatening when it compromises vital structures (e.g., the brainstem).
Tests for brain cancer involve a history, physical exam, and usually a CT or MRI scan; sometimes a brain tissue biopsy is done. Treatments typically include surgery, radiotherapy, radiosurgery, or chemotherapy, often in combination. Depending on the brain cancer type and overall health status of the patient, brain cancer frequently has only a fair to poor prognosis; children have a somewhat better prognosis. Side effects of treatments range from mild to severe.
Primary brain cancer can arise from many different types of brain cells, which affects its characteristics. Based on the microscopic cell appearance, the tumour's aggressiveness is graded on a scale from one to four, where four is the most aggressive.
After a brain tumour has been diagnosed, a multidisciplinary team typically assesses the treatment options. Various types of treatment are available depending on tumour type and location and may be combined to give the best chances of survival. Survival rates depend on the type of tumour, age, functional status of the patient, the extent of surgical tumour removal and other factors specific to each case. This underlines the importance of accurate characterization of each tumour for a personalized treatment plan. In IMPACT we will address this topic by fusion of information from different MRI acquisition protocols and deep learning.

4.5.2 Clinical state of the art

After a brain tumour has been diagnosed, a multidisciplinary team typically assesses the treatment options. For benign tumours, neurosurgeons typically observe the evolution of the tumour before proposing a management plan. For malignant tumours the treatment is initiated as soon as possible. Various types of treatment, detailed below, are available depending on tumour type, size and location and may be combined to give the best chances of survival. Survival rates depend on the type of tumour, age, functional status of the patient, the extent of surgical tumour removal and other factors specific to each case.

Surgery

The primary and most desired course of action described in medical literature is surgical removal (resection) via craniotomy. Minimally invasive techniques are becoming the dominant trend in neurosurgical oncology (Spetzler, 2012). The prime remediating

objective of surgery is to remove as many tumour cells as possible, with complete removal being the best outcome and cytoreduction (partial removal that enhances the effectiveness of radiotherapy or chemotherapy) of the tumour otherwise. In some cases, access to the tumour is impossible and impedes or prohibits surgery.

Several current research studies aim to improve the surgical removal of brain tumours by fluorescent labeling of tumour cells (Moiyadi, 2014). Postoperative radiotherapy and chemotherapy are integral parts of the therapeutic standard for malignant tumours. Radiotherapy may also be administered in cases of "low-grade" tumours, when a significant tumour burden reduction could not be achieved surgically. Single session radiosurgery has an increasing role in the management of such tumours, particularly in the recurrent setting.

Radiotherapy

The goal of radiation therapy is to kill tumour cells while leaving normal brain tissue unharmed. In standard external beam radiation therapy, multiple treatments of standard-dose "fractions" of radiation are applied to the brain. This additional treatment provides some patients with improved outcomes and longer survival rates.

Radiosurgery is a treatment method where a small number (often one) of high dose fractions of radiation, is delivered stereotactically, i.e. guided by a three-dimensional coordinate system, to a region of interest while minimizing the radiation dose to the surrounding tissue. Radiosurgery may be an adjunct to other treatments, or it may represent the primary treatment technique for some tumours. It can be performed using machines such as the Leksell Gamma Knife.

Proton therapy is another form of high-energy, external radiation therapy that uses streams of protons instead of photons. It may be used to treat brain cancers, but is a relatively new therapy that is usually reserved for rare types of tumours. This means that, compared to other forms of radiotherapy, there is little evidence about its effectiveness and long-term side-effects.

Chemotherapy

Patients undergoing chemotherapy are administered drugs designed to kill tumour cells. Although chemotherapy may improve overall survival in patients with the most malignant primary brain tumours, it does so in only about 20 percent of patients. Chemotherapy is often used in young children instead of radiation, as radiation may have negative effects on the developing brain. The decision to prescribe this treatment is based on a patient’s overall health, type of tumour, and extent of the cancer. The toxicity and many side effects of the drugs, and the uncertain outcome of chemotherapy in brain tumours puts this treatment further down the line of treatment options with surgery and radiation therapy preferred.

Recent advances

In BENEFIT, the treatment planning in Elekta’s software Leksell GammaPlan was improved by introducing important brain areas as organs at risk (OAR) during the treatment planning (to reduce the radiation dose in these areas). Specifically, as shown in the left Figure 5 below, image segmentation was used to obtain volumes of the brain stem (blue), the optical nerve (orange), hippocampus (green), chiasma (green), as well as lenses and retina (red). Furthermore, diffusion weighted images were used to generate

volumes of certain nerve fiber tracts as additional OARs , see the right Figure below, as damaging nerve fibers can lead to severe consequences for the patient. All these OARs should receive as little radiation as possible

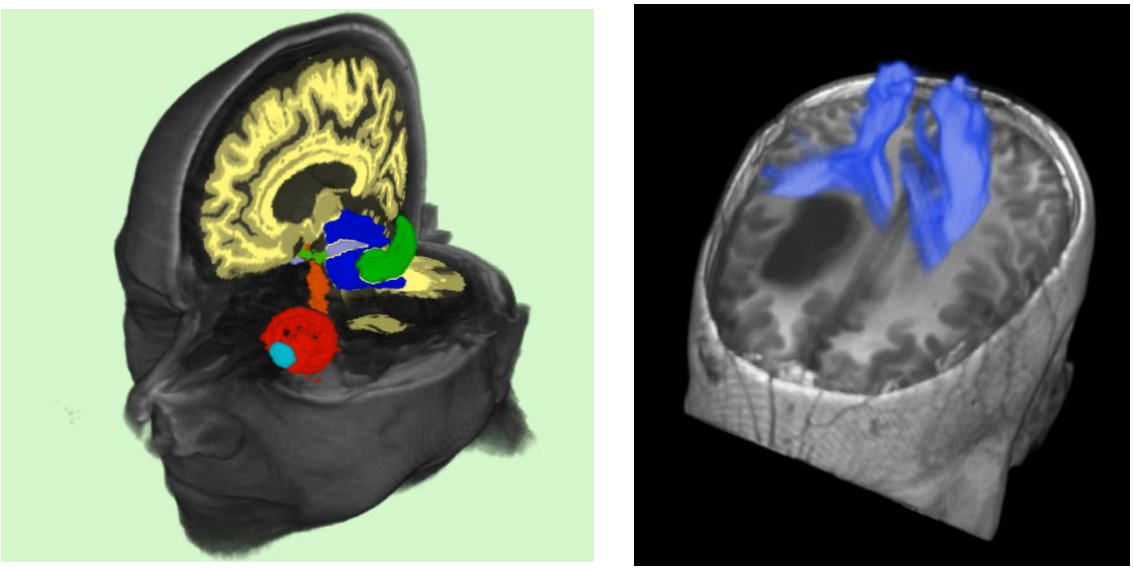


Figure 20 Segmentation of different parts of the brain (left) and nerve fiber tracts (right), to be used as organs at risk during the treatment planning, to reduce the radiation in these areas.

Figure 5. Segmentation of different parts of the brain (left) and nerve fiber tracts (right), to be used as organs at risk during the treatment planning, to reduce the radiation in these areas.

Finally, the automatically segmented brain tumour and the OARs were used to create two treatment plans, one manual (created by an experienced user of GammaPlan, Figure 21) and one automatic (created by solving an optimization problem, Figure 22), see one example in the Figures below. The manual plan took 45 – 60 minutes to generate, while the automatic plan took only 10 – 15 minutes. The mean radiation dose in the organs at risk is similar or lower for the automatic plan. The procedure was repeated for four different subjects and the manual and automatic treatment plans were compared with similar results in all four cases.

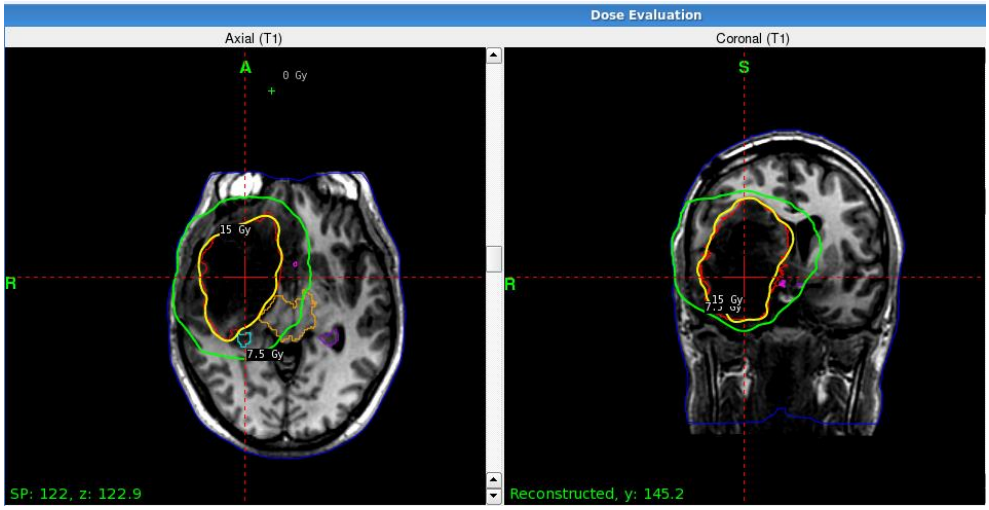


Figure 21 A manually created treatment plan. Target border in red, 15 Gray isoline in yellow, brainstem in light brown, chiasma in purple, hippocampus in cyan

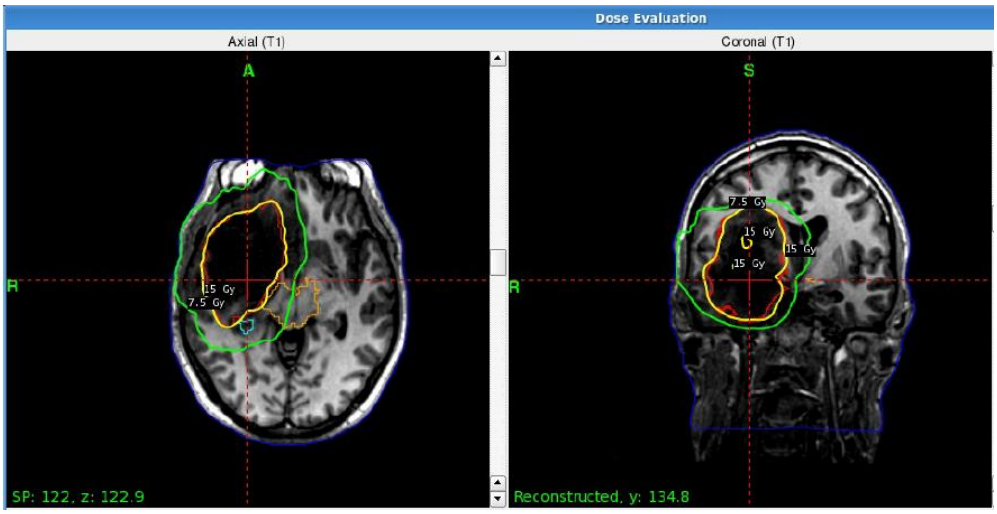


Figure 22 An automatically created treatment plan. Target border in red, 15 Gray isoline in yellow, brainstem in light brown, chiasma in purple, hippocampus in cyan.

4.5.3 IMPACT updates

Radiotherapy planning can take considerable time, as it is necessary to collect MR images, perform segmentation of tumor(s) or metastases (to know their location and size), perform segmentation of risk organs (which should be damaged as little as possible), and generate an efficient treatment plan. In IMPACT, the partners have worked together to save time in all these steps.

Regarding collecting MR images, SyntheticMR has in IMPACT reduced the time in the MR scanner from 60 to 6 minutes, for a 1 mm isotropic quantitative MRI (qMRI) sequence, see Figure 23. Compared to conventional anatomical images, qMRI provides quantitative measurements of T1 relaxation time, T2 relaxation time and proton density, which are invariant to the MR scanner used (e.g. Philips, Siemens, GE).

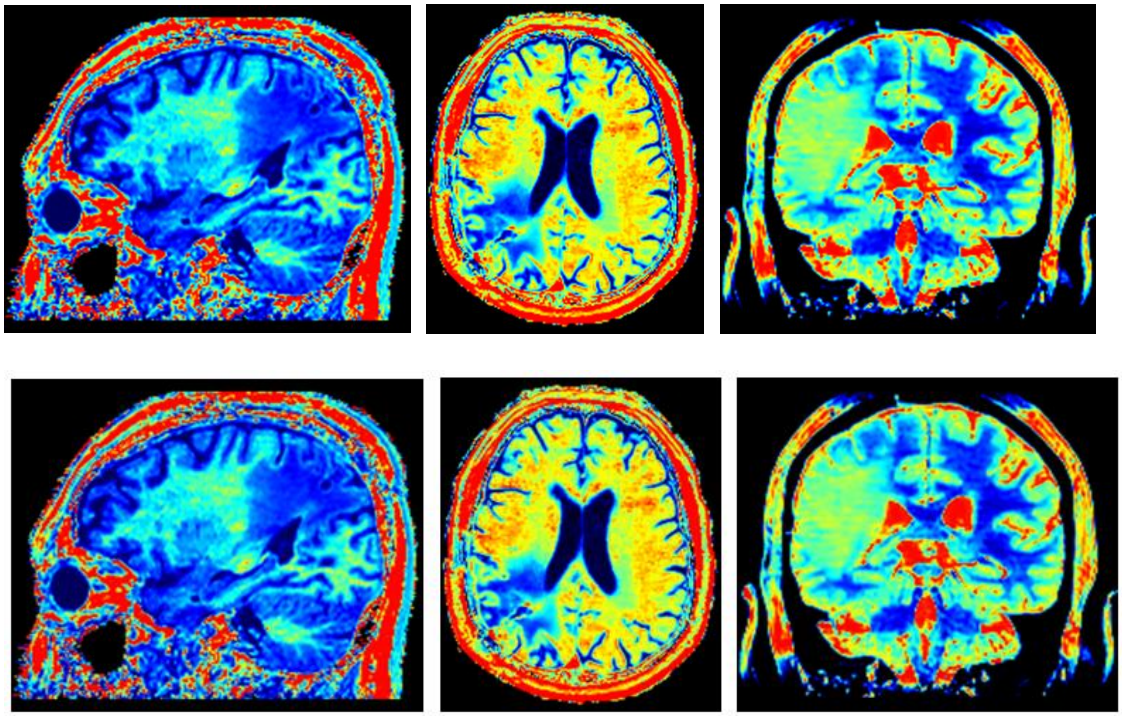


Figure 23 SyntheticMR has developed an MRI sequence that in 6 minutes can provide a 1 mm isotropic volume of R1 relaxation rate (left), R2 relaxation rate (middle) and proton density (right). This is about 10 times faster compared to state of the art before IMPACT. R1 relaxation rate = 1 / T1 relaxation time, R2 relaxation rate = 1 / T2 relaxation time. These quantitative measurements can be used to, for example, better define the tumor border

Linköping University has together with Inovia and Quantib developed deep learning based automatic segmentation of brain tumors, which reduces the time per patient from some 3 – 20 minutes (manual segmentation) to about 20 seconds. The segmentation network can use only conventional MR images, or a combination of conventional MR images and qMRI (from SyntheticMR) to further improve segmentation accuracy (about 10%), see Figure 24. The segmentation can be started from Elekta's Leksell GammaPlan software, runs in Inovia's medical data lake, and the resulting segmentation is then sent back to GammaPlan.

Linköping University also developed a constrained estimation method for q-space trajectory imaging (an advanced form of diffusion MRI, used to for example study brain connectivity), called QTI+. The method provides significant improvements in the accuracy as well as precision of the estimates of the parameters indicative of the tissue microstructure. The improvement is more pronounced for acquisition protocols involving a small number of volumes (i.e. a short scan time), boosting the clinical applicability of the method. Figure 25 illustrates the histograms of the errors for simulations derived from a diffusion MRI scan of the human brain for three such parameters.

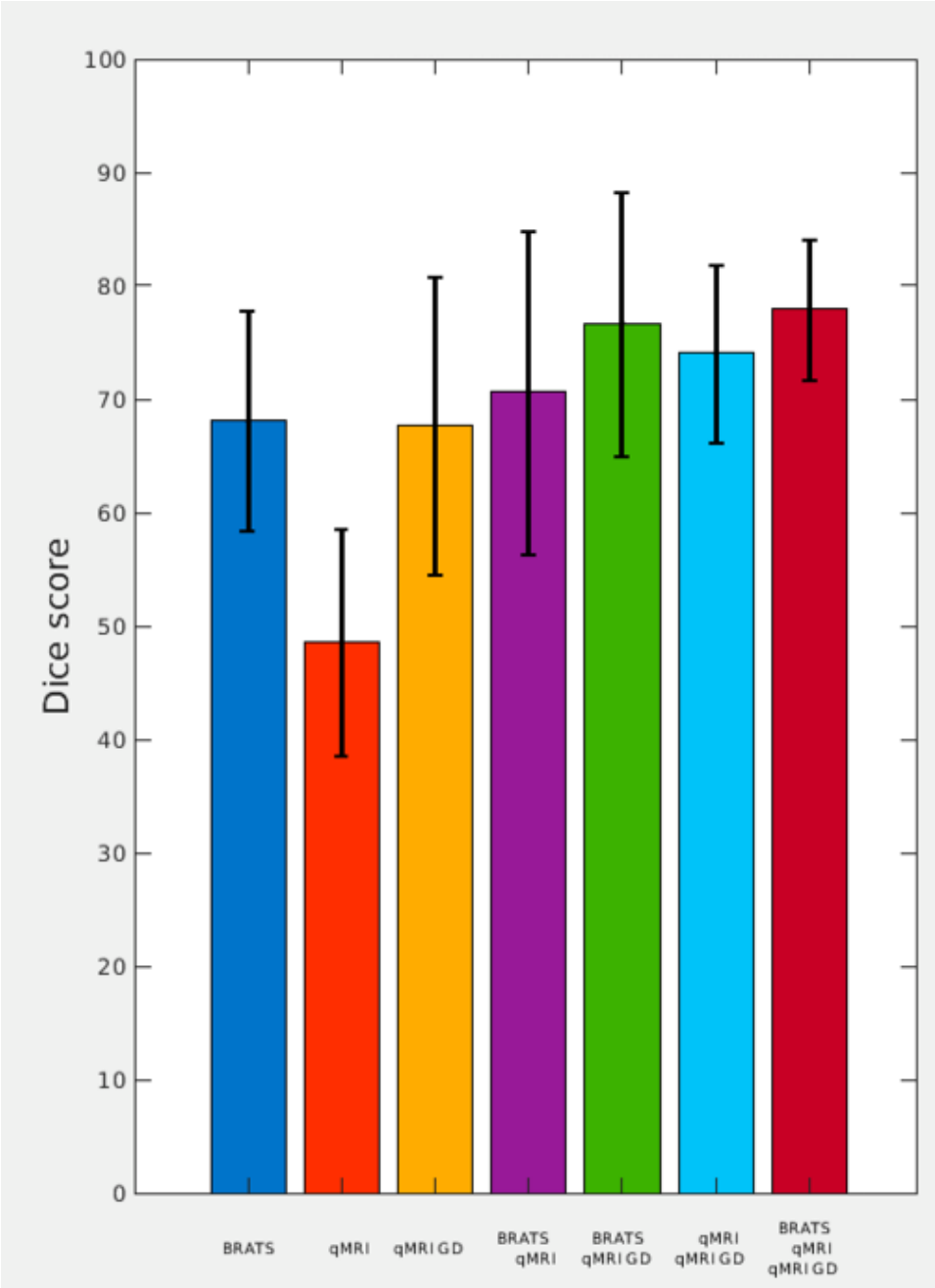


Figure 24 Segmentation accuracy (Dice score) for brain tumor segmentation using only conventional anatomical images (BRATS), or a combination of conventional images and qMRI (with and without gadolinium (GD) contrast). Adding qMRI improves the segmentation accuracy

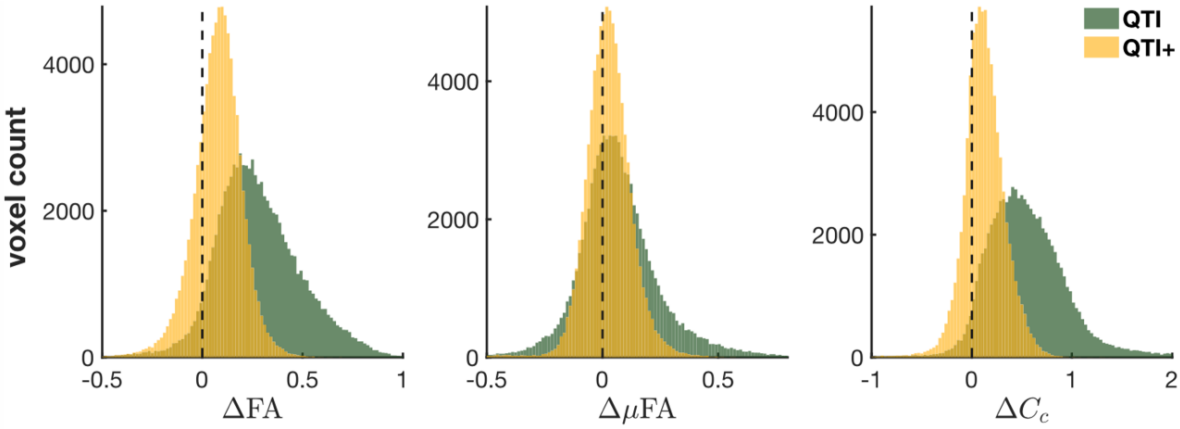


Figure 25 Histograms of errors in fractional anisotropy (FA), microscopic FA (μFA), and coherence (CC) maps. The improvement obtained through the QTI+ method (green) is evident for all three measures. This can in turn be used to reduce the MR scan time, without increasing errors.

Elekta has developed deep learning based automatic segmentation of brain metastases (which are much smaller compared to glioma), and the trained network can process a brain volume in about 1 minute regardless of the number of metastases. This will save considerable time for patients with many small metastases.

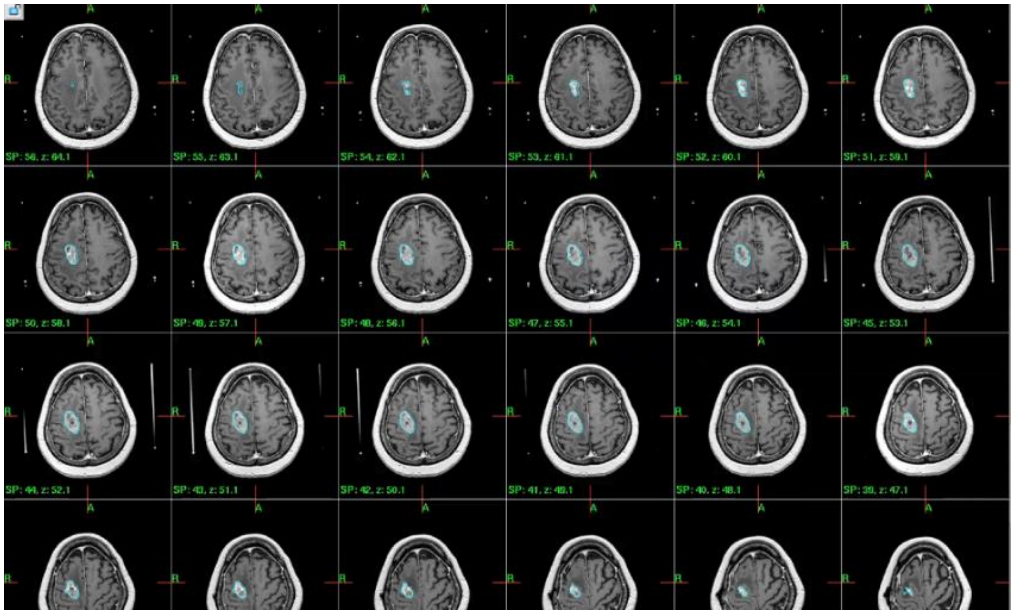


Figure 26 Automatic segmentation of brain metastases integrated into Elekta's brain tumor treatment planning software Leksell GammaPlan. This automatic segmentation will save time for the clinician who plans the tumor treatment, compared to manual segmentation (especially if a patient has many metastases).

Elekta has also further improved the inverse planner in Leksell GammaPlan. It now supports multiple targets (tumors or metastases) and multiple risk organs, and usually runs in 1 - 2 minutes. This is substantially faster compared to the 10 - 15 minutes obtained in BENEFIT. The previous inverse planner was a non-convex optimizer and dose planning was done per target. Now with the new inverse planner, which uses a linear

programming approach, multiple targets and organs-at-risk are taken into account at once.

Together, the mentioned improvements can save some 90 – 120 minutes per patient, which may have a rather large impact since some 80,000 patients are treated using radiotherapy every year.

5 Conclusions

This document gives an overview of the clinical disease areas addressed in the IMPACT project and describes the updated State of the Art for the clinical procedures targeting these diseases. Generally, complexity in diagnosis and treatment steps is recognized as a common challenge and has been addressed in the project in all use cases. Apart from the commonalities also differences remain. For instance, in brain oncology the focus is on the optimal treatment planning for each and every patient, which strongly depends on accurate detection of all metastases and their sizing and staging. So the focus is here on improved imaging protocols and the workflow efficiency for analysis of diagnostic data and treatment dose planning. The radiation treatment itself involves less staff members and can be planned in advance.
On the contrary in cardiac procedures the focus is less on the pre-interventional imaging modalities but more on simulations to prepare optimal device selection and on the workflow during treatment, in which emergency patients with a heart attack may override the preplanned work schedule.

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