



B E N E F I T

Better Effectiveness and Efficiency by Measuring and Modelling Interventional Therapies

DELIVERABLE D1.1.1

State of the art on models for patient risk stratification



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Deliverable review procedure:

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1 Introduction

1.1 Aim of activity

The goal of this document is to provide a state-of-the-art review on **models for patient risk stratification that enable more personalized intervention selection and timing**. It will also survey techniques to **verify the success of an intervention** while the patient is still on the intervention table, so that adaptations to the intervention plan can be made if intervention results are sub-optimal. The objective is to identify how such patient risk and intervention quality control models can be deployed to better triage patients with respect to the **wide range of intervention tools and options**.

The study is based on open literature and the knowledge provided by the clinical partners of the project. Additionally, a *clinical advisory board* with clinical experts will be formed to collect information concerning the current practices and needs in image guided interventions. The clinical advisory board will aid in defining the end-user scenarios and requirements (Task 1.2).

Each of the targeted interventions 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 procedure. The second section describes the existing way of working and the third section reviews the state of the art on risk stratification, intervention selection and procedural success evaluation. The last section provides a list of the clinical experts that were interviewed to collect the information that formed the basis of this document.

1.2 Contributors

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

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2 Executive summary

This document provides the “State of the Art” for the clinical procedures that are targeted by the BENEFIT project. The goal of BENEFIT is to develop technologies that improve efficiency and effectiveness of minimally invasive interventional procedures based on improved quantification and modeling before, during and after these interventions.

In total 5 procedures are addressed:

- Heart valve procedures
- Treatment of (partially) blocked arteries causing ischaemia or infarct of the heart
- Treatment of blocked or ruptured brain arteries
- Treatment of liver tumors
- Treatment of brain tumors

All these procedures are described in a standard way.

From a clinical perspective 2 of these procedures are within the domain of endovascular interventions, 1 in the domain of structural heart disease and 2 in the domain of oncology. As such, the spectrum of selected topics cover a broad range of minimally invasive interventional procedures.

This deliverable D1.1.1 will summarize the state of the art for these procedures on quantification and modeling to enable a more personalized intervention selection and timing.

Next deliverables D1.2.1 and D1.3.1 will give the end user requirements for these procedures and will describe the clinical process flows respectively.



3 Glossary

3DRA	3 Dimensional Rotational Angiography: 3D X-ray imaging of blood vessels
ADC	Apparent Diffusion Coefficient
AR	Aortic regurgitation: back flow of blood from aorta into heart (leakage of aortic valve)
AS	Aortic stenosis: narrowing in aorta
CABG	Coronary Artery Bypass Graft(ing): surgery to place a bypass vessel across an obstructed blood vessel of the heart
CBCT	Cone Beam CT: CT reconstruction made by an interventional X-ray system instead of a dedicated CT scanner
CT	Computer Tomography: method to mathematically reconstruct 3D images from a rotational sequence of 2D X-ray slices
CFR	Coronary Flow Reserve: measure for condition of vessels of the heart
CTA	Computer Tomography Angiography: 3D imaging of blood vessels with CT after injection of a contrast agent into a vessel.
CTO	Chronic Total Occlusion
DSA	Digital Subtraction Angiogram: 2D X-ray imaging of blood vessels after injection of a contrast agent
DWI	Diffusion Weighted Imaging: specific protocol of MRI
FFR	Fractional Flow Reserve: measure for condition of vessels of the heart
Fr	French, a catheter scale: 1 Fr = 0.33 mm
GUI	Graphical User Interface
HMI	Human Machine Interfaces
IGIT	Image Guided Interventional Therapy
IVUS	IntraVascular UltraSound: imaging of a vessel wall from the inside with a US transducer mounted on the tip of a catheter
LGE-MRI	Late Gadolinium Enhancement MRI
LV	Left ventricle
Mediate	patient friendly MEDicAI nTERvention: predecessor ITEA project
MR	Mitral regurgitation: back flow of blood from left ventricle aorta into atrium due to leakage of mitral valve
MRI	Magnetic Resonance Imaging
MR-HIFU	MRI-guided High Intensity Focused Ultrasound
MS	Mitral stenosis: narrowing of miral valve due to calcification
MW	MicroWave
OCT	Optical Coherence Tomography: imaging modality using laser pulses for high resolution imaging of a surface, for instance the vessel wall
OR	Operating Room
PCI	Percutaneous Coronary Intervention: minimally invasive treatment of obstruction in cardiac blood vessel via a catheter
PEI	Percutaneous Ethanol Injection
QCA	Quantitative Coronary Angiography
RF(A)	Radio Frequency (Ablation): removal of tissue by heat
SPECT	Single Photon Emission Computed Tomography: 3D imaging of molecular processes in the body after injection of a radio-isotope
SSS	Symptom Severity Score
TAVI	Transcatheter Aortic Valve Implantation: implantation of artificial heart valve via a catheter (so no open surgery)
TEE	Transesophageal echocardiography: US imaging of the heart with a



TTE transducer mounted on a tube that is inserted in the esophagus
Transthoracic echocardiography: US imaging of the heart with a transducer
on the chest in between of 2 ribs

US UltraSound

VHD Valvular heart disease



4 Bibliography

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5 Clinical Procedures

The clinical use cases on PCI and heart valve treatment in BENEFIT have also been described in the ITEA-2 Mediate project that ended in December 2013. Parts of the clinical introduction for these use cases have been taken from the State of the Art document of Mediate (Aerts, 2011).

5.1 Valvular Assessment and Treatment

Lead authors: FEops & LUMC

5.1.1 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. A stenosed aortic valve may result in a depressed left ventricular ejection fraction and the development of left ventricular hypertrophy due to the higher afterload for the left ventricle. Mitral valve insufficiency on the other hand 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 Europe aortic valve stenosis (33.9%) is the most common form of VHD, followed by mitral regurgitation (24.8%), aortic regurgitation (10.4%) and mitral stenosis (9.5%). Right sided VHD is much less common (1.2%) (Lung, 2003). 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.

5.1.2 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



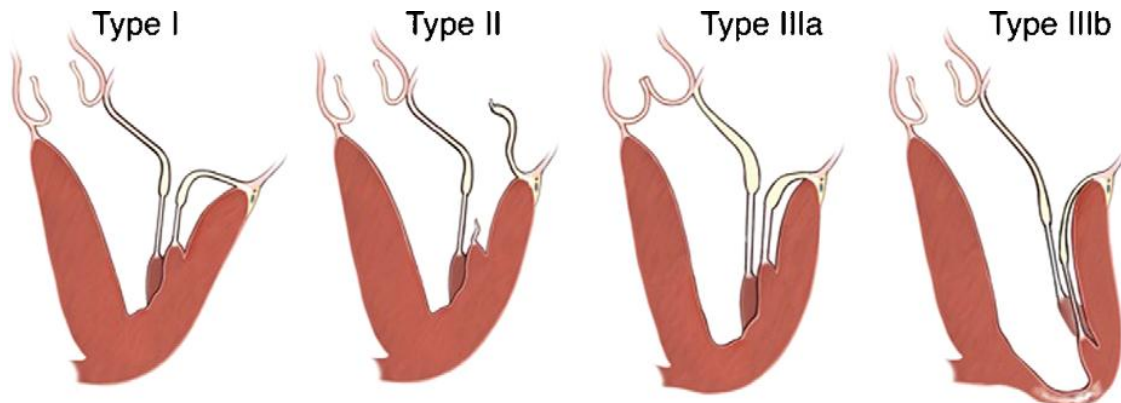
analysis, for accurate study of leaflet morphology/mobility before valvular interventions and for reliable diagnosis in doubtful cases a transesophageal echocardiography (TEE) is commonly performed.

Aortic stenosis (AS)

In patients with aortic stenosis (AS), good quality 2D US (TTE) enables assessment of the valve leaflet morphology and mobility and extent of calcification. US based quantification of the functional severity of AS is typically performed by estimating the pressure gradient across the valve. This requires the assessment of the maximal velocity through the stenotic valve using Doppler US and application of the simplified Bernoulli equation. In addition, measurement of the anatomic opening area (planimetry) is performed, and an estimation of the effective valve area is made using the continuity principle. The latter requires measurement of the cross-sectional area of the left ventricular outflow tract for quantification of the left ventricular stroke volume. Due to limitations in the accuracy and image quality of 2D US, in combination with modeling assumptions used in the assessment, the reliability of US based grading of AS severity is sometimes contested. Three-dimensional US has shown to provide more accurate assessment, although this technique has yet to find its place in standard clinical practice. In case of equivocal results from US, invasive pressure gradients obtained during left heart catheterization and the invasive estimation of valve area using the Gorlin formula are commonly used. A non-invasive imaging modality such as cardiac magnetic resonance imaging (CMR) may be used to provide accurate assessment of the aortic valve area and flow across the valve using velocity-encoded CMR. Additionally, cardiac CT (CCT) may be applied to allow quantification of valve calcification and aortic valve area. CCT also provides many relevant anatomical details that are used in planning of percutaneous aortic valve replacement procedures.

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: 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).



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 systole (Chikwe, 2009).

Aortic regurgitation (AR)

The incidence of AR increases with age. AR may result in left ventricular volume overload, but also in increased systolic wall stress which often causes significant eccentric hypertrophy. Patients with severe AR may remain asymptomatic for many years. Patients with AR therefore often require a longer follow-up than those with other forms of VHD. The most important part in patient follow-up is the assessment of LV dimensions and function using standard echocardiography. Several additional imaging modalities may be used such as 3D echocardiography, radionuclide ventriculography or CMR. CMR is particularly useful in AR patients as it allows accurate measurement of LV volumes and function, but also aortic dimensions and calculation of regurgitant volume and fraction.

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.

Echocardiographic indicators of severe valvular heart disease

Valvular lesion	Index	Threshold for severe abnormality
Mitral regurgitation	Color Doppler jet 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 cm ² PAP > 50 mm HG
Aortic stenosis	Peak aortic velocity Aortic valve mean gradient Aortic valve area	> 4 m/s > 40 mmHg < 1 cm ²



	Aortic valve area index Z_{VA}	< 0.6 cm ² /m ² > 5 mmHg/ml/m ²
Aortic regurgitation	CW Doppler half-time Vena contracta with EROA by flow convergence Regurgitant volume Regurgitant fraction Supportive findings	< 200 ms > 6 mm ≥ 30 mm ² ≥ 60 ml ≥ 50 % Pan-diastolic flow reversal proximal descending aorta
<p>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).</p>		

5.1.3 State of the art on risk stratification, intervention selection and success evaluation

The most up to date guidelines regarding the management of patients with VHD are described by the Task Force on Practise Guidelines of the American College of Cardiology and the American Heart Association (Nishimura, 2014).

Depending on the type of VHD several qualitative and quantitative indices are used in patient risk stratification, decision making regarding the proper medical intervention and treatment evaluation. The table above provides a list of the most relevant clinically used echocardiographic indices for evaluation of patients with VHD. The indices listed with its associated threshold values are considered a general guideline. The established threshold values should be used with care as for the individual patient valve disease often is not an isolated pathology but may come in combination with other abnormalities such as coronary artery disease, left ventricular hypertrophy, left ventricular dysfunction or other risk factors.

A complicating factor in assessing the severity of VHD is that valve dysfunction is dependent on various factors including loading conditions. Clinical symptoms may only reveal during exercise, which implies that imaging during stress may be required to reveal the true significance of the valve abnormality. The vena contracta width which is used as index in patients with valvular regurgitation has been shown to be less influenced by hemodynamic variables and has previously been shown to correlate with angiographic estimates of regurgitation severity. However, because of the small values of the width of the vena contracta (usually < 1 cm), small errors in its measurement may lead to a large percent error and misclassification of the severity of regurgitation. It is therefore advised to apply an integrative method combining multiple echocardiographic and clinical parameters when grading valvular heart disease. For instance, in patients with AS it has been shown that the prognosis is poor in case of a peak aortic velocity exceeding 4 m/s. However in patients with depressed LV function and thus low forward flow severe AR may be present with lower peak aortic velocity. In those circumstances it is important to also assess the aortic valve area and stroke volume. Invasive pressure measurements during cardiac catheterization may also be required.

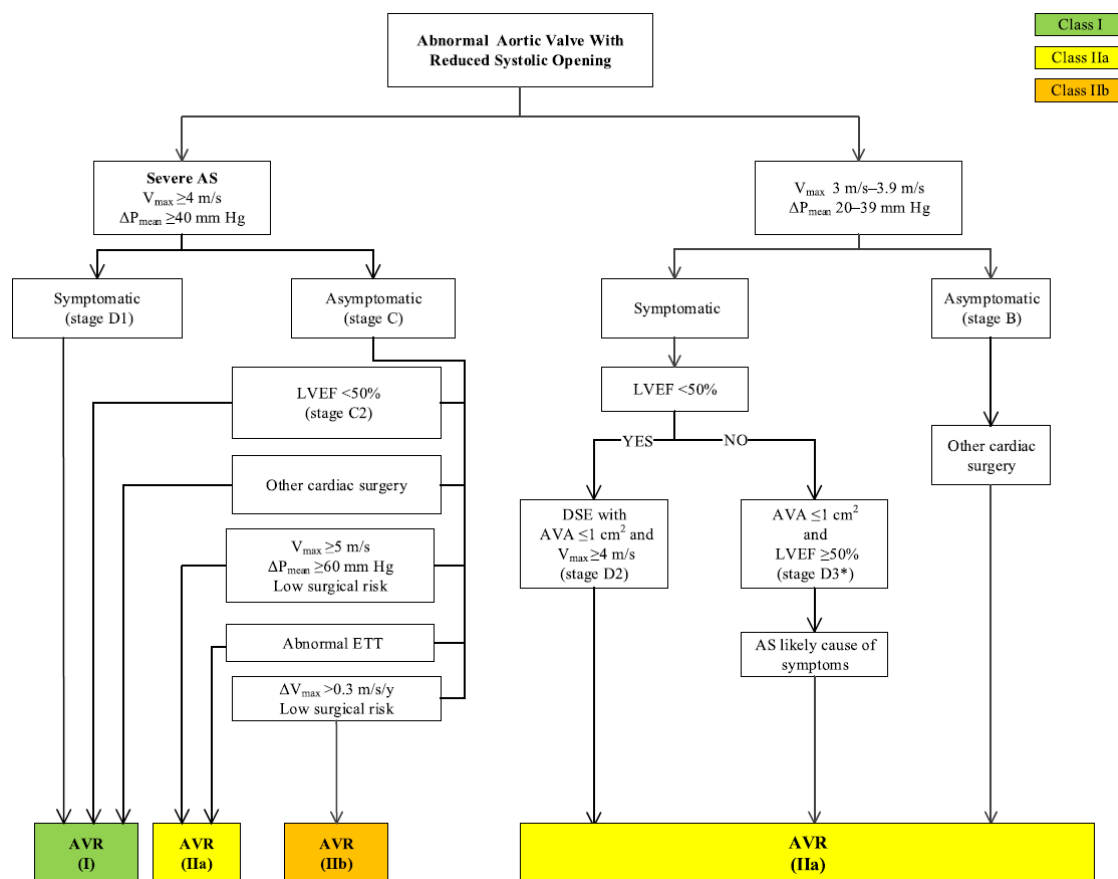


In asymptomatic patients for whom the severity of the VHD does not yet require interventional treatment frequent monitoring is required. Imaging during follow-up visits should include assessment of the hemodynamic severity of the diseased valve, but also assessment of left ventricular and atrial dimensions.

We will describe the treatment options for aortic stenosis and mitral valve regurgitation, as they represent the majority of the cases.

Aortic valve stenosis

The figure below schematically presents the current recommended clinical indications for aortic valve replacement in patients with AS. Evaluation of the success of the interventional treatment is primarily based on assessment of the pressure gradient across the valve based on echocardiography. In patients undergoing TAVI invasive pressure measurements are obtained under X-ray fluoroscopy. Surgical aortic valve replacement has been the standard of care in patients with severe symptomatic aortic stenosis. However, elderly patients can be at high risk for a surgical aortic valve replacement because of frailty and comorbidities. Therefore, next to classical surgical treatments (surgical replacement, minimally invasive surgical replacement, apicoaortic conduit) the transcatheter aortic valve implantation (TAVI) is expanding. TAVI has become a clinical option only less than a decade ago and it is already the standard treatment for inoperable patients. Technological progress is improving the outcome of TAVI, resulting in gradually expanding the target population (Makkar, 2014) (Osnabrugge, 2015).



Indications for aortic valve replacement in patients with aortic stenosis



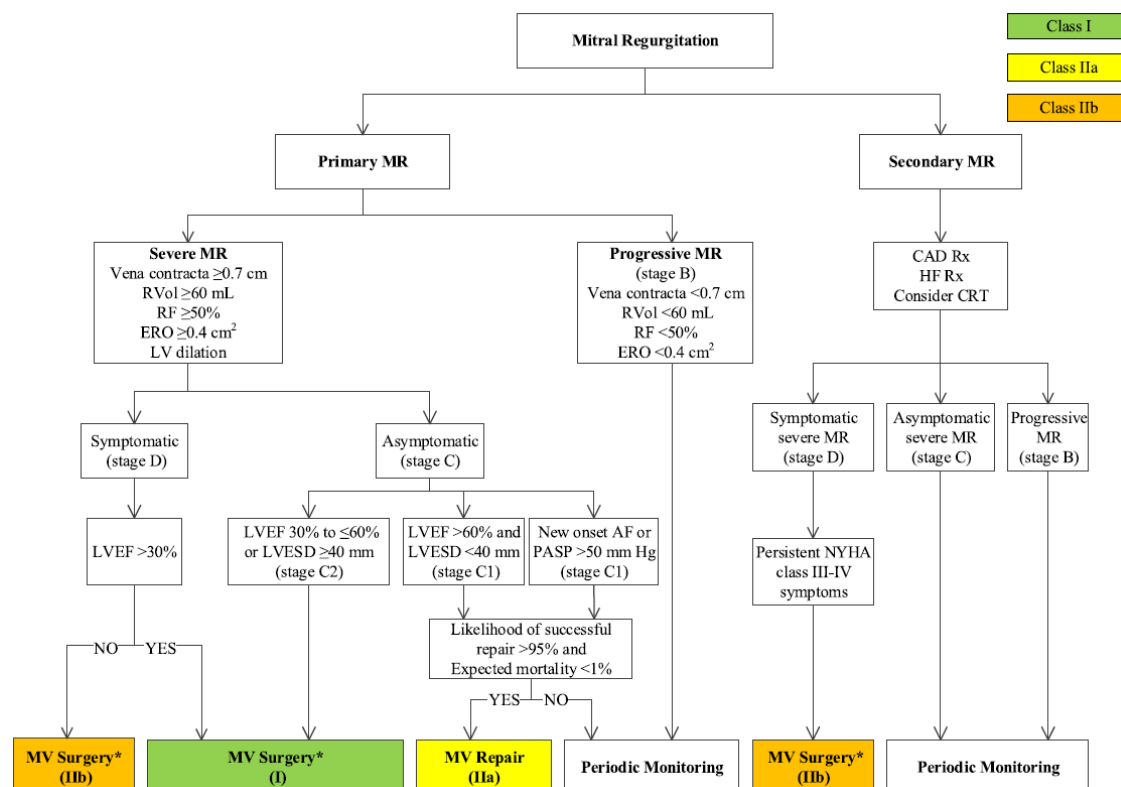
Arrows show the decision pathways that result in a recommendation for AVR. Periodic monitoring is indicated for all patients in whom AVR is not yet indicated, including those with asymptomatic AS (stage D or C) and those with low-gradient AS (stage D2 or D3) who do not meet the criteria for intervention.

*AVR should be considered with stage D3 AS only if valve obstruction is the most likely cause of symptoms, stroke volume index is $<35 \text{ mL/m}^2$, indexed AVA is $\leq 0.6 \text{ cm}^2/\text{m}^2$, and data are recorded when the patient is normotensive (systolic BP $<140 \text{ mm Hg}$).

AS: indicates aortic stenosis; AVA: aortic valve area; AVR: aortic valve replacement by either surgical or transcatheter approach; BP: blood pressure; DSE: dobutamine stress echocardiography; ETT: exercise treadmill test; LVEF: left ventricular ejection fraction; DPmean: mean pressure gradient; Vmax: maximum velocity. (Nishimura, 2014)

Mitral valve regurgitation

When pharmaceutical treatment is not sufficient the mitral valve regurgitation may require an intervention to repair or replace the valve. The figure below schematically presents the current recommended clinical indications for mitral valve repair or replacement. Classical treatment requires invasive surgical intervention: replace the valve with a (bio)-prosthetic device or repair the valve, e.g. by adding a ring (ring annuloplasty) or by stitching the two leaflet edges (edge-to-edge technique or Alfieri stitch). More recently, minimally invasive and even percutaneous trans-catheter interventions are emerging, replicating surgical options. For the moment, there is only one device for transcatheter mitral valve repair recommended for clinical use, being the MitraClip (Glower, 2014). The latter device replicates the edge-to-edge technique using a transcatheter approach. However, other devices are undergoing clinical trials both for repair and replacement. The success of the intervention treatment is primarily based on echocardiography, i.e. by assessment of the residual regurgitation.



Indications for surgery in patients with MR.

AF: atrial fibrillation; CAD: coronary artery disease; CR: cardiac resynchronization therapy; ERO: effective regurgitant orifice; HF: heart failure; LV: left ventricular; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic dimension; MR: mitral regurgitation, MV: mitral valve; MVR: mitral valve replacement; NYHA: New York Heart Association; PASP: pulmonary artery systolic pressure; RF: regurgitant fraction; RVol: regurgitant volume; Rx: therapy. (Nishimura, 2014)

5.1.4 Clinical consultants

<i>Name</i>	<i>Institute</i>
Philippe Bertrand	ZOL, Belgium

5.2 Percutaneous Coronary Interventions

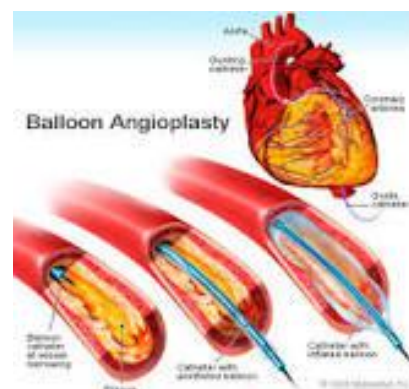
Lead author: LUMC

5.2.1 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) 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.





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 (CTA, SPECT, perfusion MRI, stress echo) and during the intervention (FFR, OCT, IVUS), are nowadays investigated and employed to decide whether a lesion needs treatment. These modalities provide also additional information about the plaque burden and the plaque composition.

5.2.2 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 spot 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 spot, 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 1), 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 1: Biplane image of coronary intervention (Image courtesy Erasmus MC)

5.2.3 State of the art on risk stratification, intervention selection and success evaluation

In case of chronic (not acute) complaints, the following diagnostic means can be used for patient stratification:

- Patient complaints and history, including risk factors such as age, gender, diabetes, blood cholesterol level, smoking habit, blood pressure, medication, previous interventions and family history
- Heart sounds (stethoscope)
- ECG recording during rest and stress in a clinical situation (e.g. the bicycle test) or for a longer time (1 day to 2 weeks) during normal activity with a wearable Holter monitor.
- CT Angiography from which several values can be deduced such as vessel sizes and obstructions, coronary artery calcium score, ejection fraction, TIMI flow and virtual FFR
- Cardiac ultrasound to determine the heart contraction pattern, ejection fraction and blood flow under normal and stress condition
- Cardiac PET scan to determine viability of the heart tissue.

Some of these risk factors have been combined in composite scores, such as the Framingham risk score and the Syntax score (Farooq, 2013). Professional societies have composed guidelines to use risk factors for choice of treatment and follow up, see figure below (Windecker, 2015) which may also partly depend on national or local circumstances (such as availability of equipment and payment by insurance companies)..



Risk models to assess medium- to long-term (≥ 1 year) outcomes

Score	Development cohort	Patient inclusion	Coronary procedures	Number of variables		Outcome	Recommendation		Validation studies	Calculation	Ref ^a
				Clinical	Anatomical		CABG	PCI			
SYNTAX	None, expert opinion	none	-	0	11 (3 general, 8 per lesion)	MACCE	I B	I B	>50	www.syntaxscore.com	30
SYNTAX II	1800 Multicentre	03/2005 – 04/2007	50% CABG, 50% PCI	6	12	4-year mortality	IIa B	IIa B	<5	-	25
ASCERT CABG	174 506 Multicentre	01/2002 – 12/2007	100% (i) CABG	23	2	Mortality >2 years	IIa B		<5	-	27
ASCERT PCI	206 081 Multicentre	2004 – 2007	100% PCI	17	2	Mortality >1 year		IIa B	<5	-	28
Logistic Clinical SYNTAX	6 508 Multicentre	03/2005 – 04-2007	100% PCI	3	11	1-year MACE and mortality		IIa B	<5	-	24

ASCERT: American College of Cardiology Foundation–Society of Thoracic Surgeons Database Collaboration (ACCF–STS) on the comparative effectiveness of revascularization strategies; (i) CABG: (isolated) coronary artery bypass grafting; MACCE: major adverse cardiac and cerebrovascular events; PCI: percutaneous coronary intervention; SYNTAX: synergy between percutaneous coronary intervention with TAXUS and cardiac surgery.

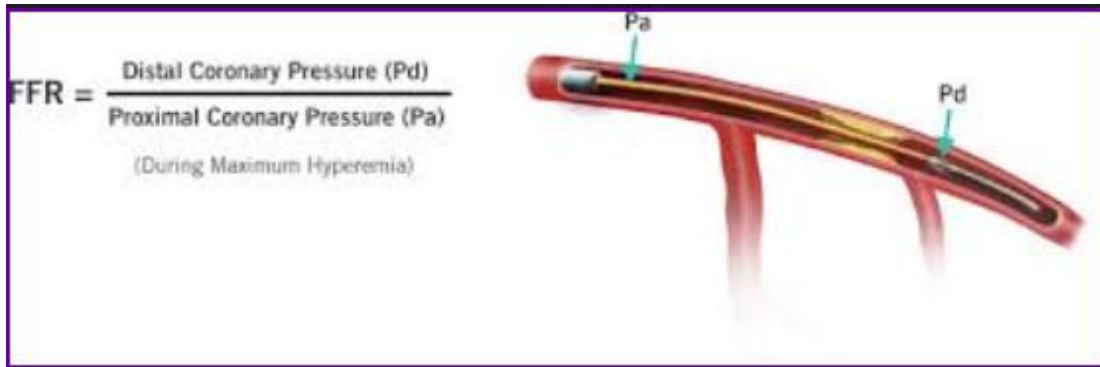
Treatment choices are:

- No direct need for medication or intervention
- Medication only (for instance cholesterol or blood pressure lowering drugs)
- PCI: minimally invasive intervention via a catheter to remove a vessel obstruction
- Coronary Artery Bypass Graft (CABG) surgery: surgical creation of a bypass for the obstructed vessel(s) using a part of a vessel from another part in the body.

Acute patients will mostly be sent directly to the intervention room (with premedication) for coronary angiography to assess the condition of the vessels and heart function and if necessary immediately restore vessel diameter and blood flow to the underperfused parts of the heart.

Several qualitative and quantitative measurements can be made during the intervention:

- Measurement of vessel diameter in ‘normal’ and partly obstructed segments (QCA, Quantitative Coronary Analysis),
- Perfusion of the tissue behind a vessel branch (TIMI flow)
- Fractional Flow Reserve (FFR) or instantaneous wave free ratio (iFR) (Petraco, 2014) indicating the functional severity of a vessel obstruction, using a dedicated pressure wire



- Index of Microcirculatory Resistance with a pressure-temperature wire (Fearon, 2013)
- Intra-arterial imaging with US or OCT to assess the vessel wall condition and to characterize the obstructing tissue (plaque)

Determination of success during and directly after an intervention is mostly based on visual assessment of vessel diameter and blood flow before and after the procedure. Short term success can also be quantified in lumen diameter before and after the intervention, FFR and peri-procedural complications.

Longer term success is expressed in long term vessel patency and need for revascularization, MACE (Major adverse cardiac event, such as a heart attack) and death.

5.2.4 Clinical consultants

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5.3 Brain vessel interventions

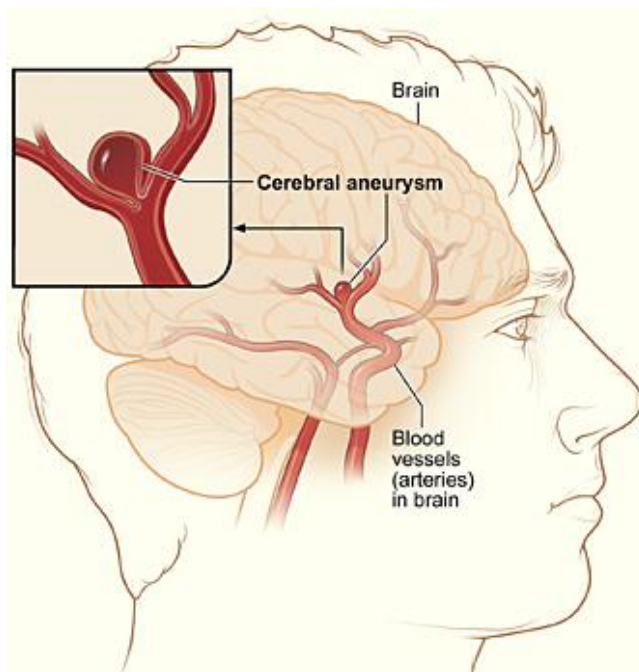
Lead authors: EMC

5.3.1 Introduction

The use case of brain vessel interventions will focus on intracranial aneurysms. An intracranial aneurysm (also called cerebral or brain aneurysm) is a cerebrovascular (related to brain vessels) disorder in which weakness in the wall of a cerebral artery or vein causes a localized dilation or ballooning of the blood vessel. Intracranial aneurysms are quite common, with frequencies report from 0.5 to 9 % (based on imaging and autopsy studies).

The main risk of intracranial aneurysms is a rupture, and a subsequent bleeding (subarachnoid hemorrhage) (Loewenstein, 2012). The majority (~ 80%) of such bleedings in the brain that do not result from trauma, are caused by an aneurysm rupture. These bleedings are associated with 1-month mortality rates ranging from 30% to 50%. Additionally, patients surviving these bleedings may have neurological or functional problems because of the bleeding, or because of rebleeding and insufficient blood supply to the brain. A rupture thus has very serious consequences, and therefore, accurate risk assessment for rupture prediction is of crucial clinical importance.

Cerebral aneurysms are classified both by size and shape. Small aneurysms have a diameter of less than 15mm. Larger aneurysms include those classified as large (15 to 25mm), giant (25 to 50mm), and super giant (over 50mm). A small, unchanging aneurysm will produce few, if any, symptoms. Indeed, many aneurysms are unnoticed, and are discovered incidentally. Also, ruptures can come without clinical symptoms, though before a larger aneurysm ruptures, the individual may experience symptoms as a sudden and unusually severe headache, nausea, vision impairment, vomiting, and loss of consciousness, or the individual may be asymptomatic (i.e., experiencing no symptoms at all).



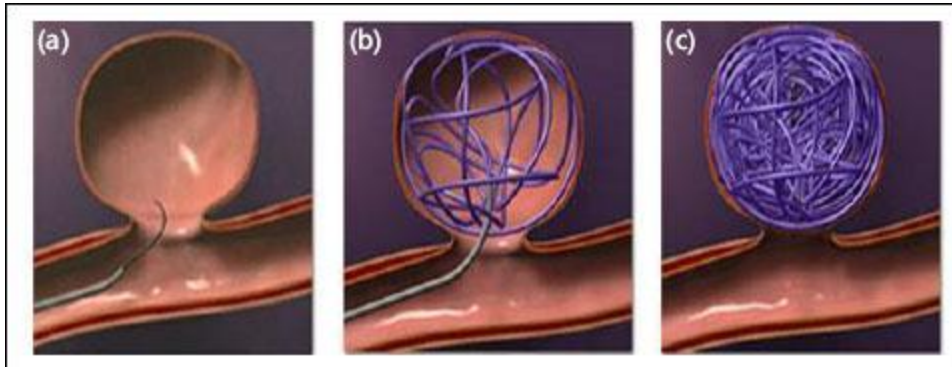
Intracranial Aneurysm (source: Wikipedia)

5.3.2 Clinical State of the Art

When an intervention is deemed necessary (because rupture risk exceeds risks associated with the intervention, or when the aneurysm already ruptured), there are two main types of treatments: neuro-surgical intervention, e.g. clipping of the aneurysm, and endovascular interventions, such as coiling (with or without stent-assistance) and flow diverters. All of the interventions are focused on preventing blood flow into the aneurysm, thus stimulating clot formation, thus reducing the pressure on the aneurysm wall, and reducing rupture risk or rebleeding.

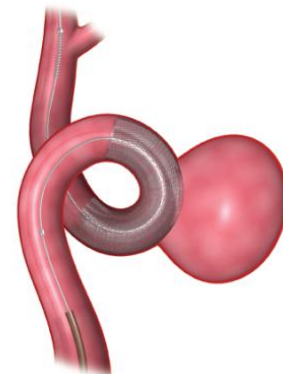
Surgical clipping is the traditional option for treatment of large aneurysms. Clipping was first performed in 1937. In this neuro-surgical procedure, a metal clip, specifically chosen for the aneurysm, is put at the neck of the aneurysm, thus excluding it from blood circulation. This procedure is highly effective, but associated with risks due to the nature of open surgery. It also has been shown that postoperative outcomes depend on the expertise and experience of the neurosurgical team. Neuro-surgical interventions are outside the scope of the project, and will not be discussed further.

Endovascular coiling is a minimally invasive intervention that has been introduced around 20 years ago. In this intervention, catheters are maneuvered to the location of the aneurysm, and subsequently several metal coils are brought into the aneurysm. These coils minimize blood flow and stimulate clot formation.



Challenges in this intervention are to completely coil the aneurysm, while preventing coils entering the feeding vessels. Accurate assessment of aneurysm size and morphology is relevant for these interventions. The main risks associated with clipping are the formation of clots or rebleeding.

Recently, several more advanced approaches have been introduced for the endovascular treatment of intracranial aneurysms, such as stent-assisted techniques and flow diverters. The stent-assisted coil embolization technique has broadened the field for endovascular treatment of intracranial aneurysms to wide-neck aneurysms. The use of neurovascular stents that serve as a scaffold allows for higher coil packing densities with a relatively low chance of coils herniating into parent arteries. Currently, its application is not limited only to giant and fusiform aneurysms but it is also being used for smaller berrylike aneurysms.



**Aneurysm treatment by
flow diverter**

5.3.3 State of the art on risk stratification, intervention selection and success evaluation

Rupture risk prediction, as stated before, is crucial for clinical decision making in the case of unruptured intracranial aneurysms. However, despite many studies investigating rupture risks, a clear decision model is still lacking.

Intracranial aneurysms may result from diseases acquired during life, or from genetic conditions. Lifestyle diseases including hypertension, smoking, excess alcohol consumption, and obesity are associated with the development of aneurysms. Other acquired associations with intracranial aneurysms include head trauma and infections. Several studies have looked at other identifying factors for rupture risk. Size of the aneurysm has been shown to be a significant predictor for rupture. However, a clear cut-off threshold above which aneurysms have a (much) greater risk is not known, nor is the exact relation between aneurysm size and rupture risk



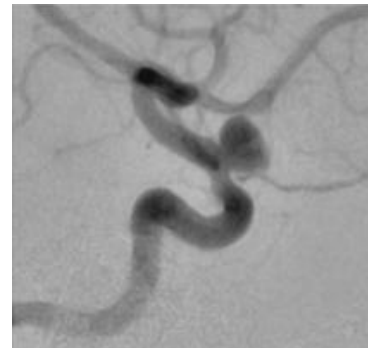
Aneurysm growth also is also hypothesized to be a predictor for rupture risk. Additionally, aneurysm growth leads to larger aneurysms, which in themselves also are associated with larger rupture risks.

Aneurysms in the posterior circulation (basilar, vertebral and posterior communicating arteries) also have a higher risk of rupture. Basilar artery aneurysms represent only 3%-5% of all intracranial aneurysms but are the most common aneurysms in the posterior circulation.

The relation between rupture risk and aneurysm morphology has also been investigated. Aneurysm-to-vessel size ratio, and aneurysm angle have strong correlation with rupture risk. Other parameters that have been demonstrated to correlate with rupture risk are the deviation of the shape from a sphere and the number of concave regions on the aneurysm surface.

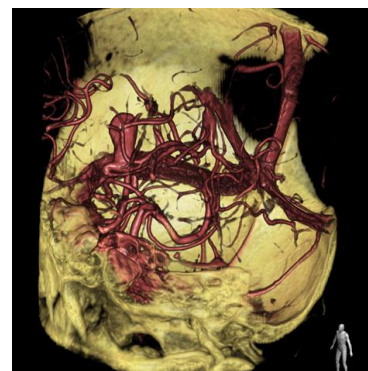
Despite all these studies, there are no hard criteria on which a decision on treatment can be based. The current guidelines (Steiner, 2013) still suggest that the decision should be based on a multidisciplinary discussion of the individual case, taking into account all above-mentioned factors. This is also the case for a definite decision whether to clip or to coil.

Because of the potential risk of aneurysm regrowth and of in-stent stenosis with the use of neurovascular stents, careful patient monitoring after endovascular treatment is essential. Patient follow-up is conventionally performed by catheter-based DSA because it provides a high spatial and temporal resolution. However, a disadvantage of this technique is that it only provides 2D information of the vascular anatomy, and the relationship of the vascular anatomy to the stent and coil mass may not be fully appreciated.



Digital subtraction angiogram of an intracranial aneurysm

The latest generation of angiographic C-arm systems equipped with flat panel technology not only provide conventional 2D fluoroscopy but enable in situ 3D conebeam CT (CBCT) that can be used for peri-interventional evaluation. Recently, the development and application of high-resolution contrast-enhanced conebeam CT (VasoCT; Philips, Best, the Netherlands) with the use of an angiographic flat-panel C-arm system has been reported. This technique enables detailed 3D visualization of neurovascular stents and host arteries that allows for a more complete determination of stent-wall apposition and in-stent stenosis. (Bom, 2013.)

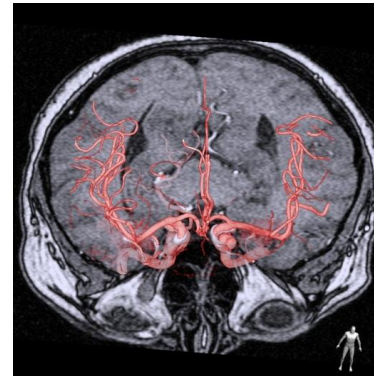


3D CBCT reconstruction of an intracranial aneurysm

In the domain of interventional x-ray imaging, digital subtraction angiography (DSA) and three-dimensional rotational angiography (3DRA) are the gold standard for imaging vascular lesions. Though these provide valuable information regarding the vascular morphology, it is still difficult to extract functional information from DSA. The recent advancements in minimally invasive treatment of vascular lesions, however,



could considerably benefit from the availability of quantitative functional measurements during the course of the interventional procedure. For example, the flow pattern inside aneurysms is considered to be one of the parameters that can be used to predict rupture and clotting. Also in stenosis grading, arterio-venous malformations, and post-interventional hyperperfusion flow measurements can be valuable. (Bonnefous, 2012).



Fused 3DRA and MR

5.3.4 Clinical consultants

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5.4 Liver tumor treatment

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5.4.1 Introduction

Liver tumors 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. Patients with HCCs often do not show symptoms other than caused by the underlying liver disease, and thus these tumors 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 tumors are metastatic, most commonly from primary colorectal cancer, but also from lung or breast cancer.

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].

5.4.2 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 tumors. 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 bloodwork analysis is performed. 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 lead to a diagnosis and staging of the disease. Based on the staging, patient-specific factors, and available procedures in the hospital a treatment plan is composed.

First option is resection of the tumor in the liver (Perini, 2015), or liver transplantation. These are invasive surgical procedures, where the tumor is completely removed by surgery. Not all patients are eligible for these types of surgery, as their health may already be comprised by the underlying liver disease. Varying mortality rates are reported for surgical resection, 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.

Among the minimally invasive alternatives are needle-based approaches, where a needle is brought in through the skin (percutaneously), such that the needle tip is in the tumor. 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 tumor, whereas in cryoablation, cooling is used to destroy the tumor, and in PEI, ethanol is injected to kill the tumor. The latter intervention may need multiple sessions. A recently novel approach is irreversible electroporation (IRE), where high voltages are used to damage the tumor cells. All these needle-based approaches are generally associated with low complications rates, but are also considered less effective than surgical resection, and thus are the option of choice if the patient is not able to undergo the surgical procedure.

Transarterial approaches are another class of minimally invasive interventions. In these interventions, instruments are navigated to the tumor 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 tumor 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 tumor. 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 (see for example Figure 3). These approaches are generally used for patients for whom resection and the ablation approaches (too many, too diffuse, too large tumors) 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 embolizing particles to other critical organs exist.

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 tumor during treatment is a challenge.

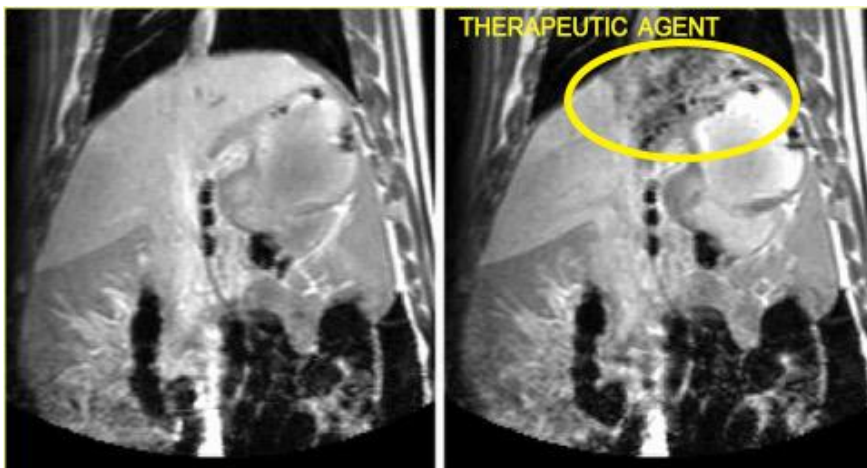


Figure 3 Local drug delivery in the liver. Left: before treatment. Right: after treatment, the therapeutic agent is visible in the top right part of the liver.

Another relatively novel approach is high intensity focussed ultrasound (HIFU). In this approach, high intensity ultrasound waves are focussed at the tumor location, and in that way the tumor 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 tumor 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.

5.4.3 State of the art on risk stratification, intervention selection and success evaluation

There are different staging systems for liver cancer in use:

- The TNM system as defined by the American Joint Committee on Cancer
- The Barcelona Clinic Liver Cancer (BCLC) system
- The Cancer of the Liver Italian Program (CLIP) system
- The Okuda system
- The Hong Kong Liver Cancer Staging System.

No comparative analysis/research has been performed with respect to these systems. Currently all four systems are in use in certain parts of the system, with some being more used than others. An example is given in Figure 4.

Risk stratification differs per treatment. Fong's method includes five criteria for hepatic resection for metastatic colorectal cancer based on 1001 consecutive patients: two imaging factors (number and size of metastases) and three oncological parameters (disease-free interval, carcinoembryonic antigen level and node-positive primary tumor) (Fong, 1999). Stang et al. determined four relevant criteria for RFA of colorectal liver metastases based on a study of 88 consecutive patients: response to systemic therapy, number and size of metastases and carcinoembryonic antigen level (Stang, 2014).

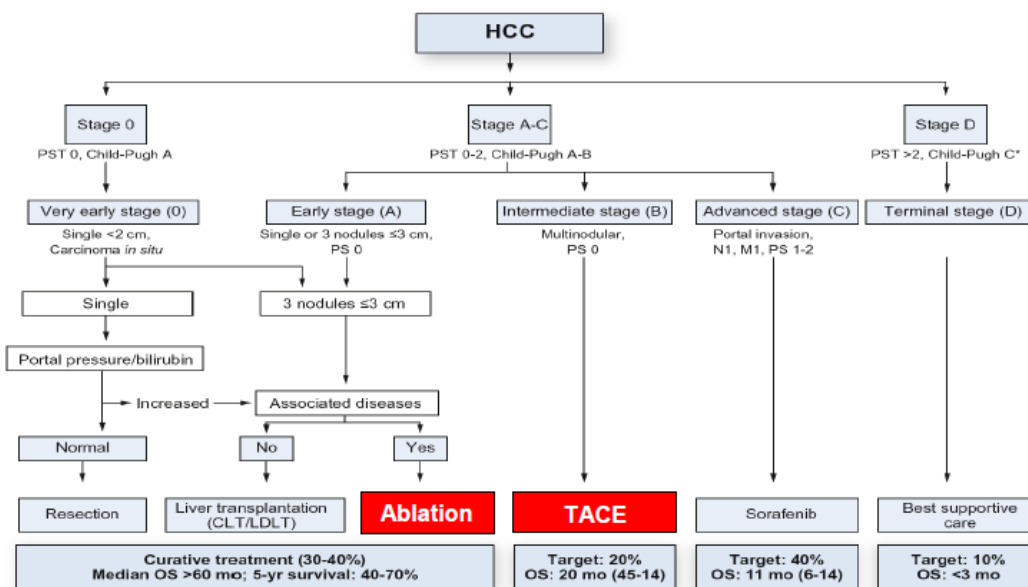


Figure 4 BCLC staging system for liver cancer therapy

In general, there is consensus that surgical resection is associated with the best prognosis for early stage disease, whereas the minimally invasive approaches are used for advanced stages or patients in a bad condition. Resection is however not always safely possible, for example due to a tumor's location close to the main arteries, veins and bile duct and/or comorbidities. Systematic therapy of colorectal liver metastases such as chemotherapy can be used palliatively, but long term overall survival is uncommon. Ablation techniques were initially developed for palliative treatment of unresectable liver tumors. Its success is now leading to an increased number of physicians suggesting the use of RFA in the treatment of both primary and metastatic liver tumors. This extended application of ablation techniques has been increasing in the past years, but prospective studies are required to compare its effectiveness to the gold standard (Higgins, 2006).

The Child-Pugh score is used to assess liver function after (partial) hepatectomy, in combination with various laboratory data and imaging techniques. For RFA and other ablation therapies, initial evaluation is based on imaging and can be performed 24 hours after treatment to confirm the ablation zone and identify any residual tumor tissue. Follow-up imaging is performed weeks to months later.



5.4.4 Clinical consultants

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5.5 Brain tumors

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5.5.1 Introduction

Primary brain tumors occur in around 250,000 people a year globally, making up less than 2% of cancers (World Health Organization, 2014). Although primary brain tumors can be either cancerous or noncancerous, both types take up space in the brain and may cause serious symptoms (e.g., vision or hearing loss) and complications (e.g., stroke). All cancerous brain tumors are life threatening (malignant) because they have an aggressive and invasive nature. A noncancerous primary brain tumor 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 tumor's aggressiveness is graded on a scale from one to four, where four is the most aggressive.

Among adults, the most common types of brain tumors are:

- **Astrocytoma:** The tumor arises from star-shaped glial cells called astrocytes. In adults, an astrocytoma most often arises in the cerebrum. Based on the tumor grade, astrocytomas are further categorized as follows:
 - Grade I or II astrocytoma: also referred to as a low-grade glioma.
 - Grade III astrocytoma: also referred to as a high-grade, or an anaplastic, astrocytoma.
 - Grade IV astrocytoma: also referred to as a glioblastoma or malignant astrocytic glioma.
- **Meningioma:** The tumor arises in the meninges. It can be grade I, II, or III. It is usually benign (grade I) and grows slowly.
- **Oligodendroglioma:** The tumor arises from cells that make the fatty substance that covers and protects nerves. It usually occurs in the cerebrum. It is most common in middle-aged adults and can be grade II or III.

Among children, the most common types are:



- **Medulloblastoma:** The tumor usually arises in the cerebellum. Sometimes called a primitive neuroectodermal tumor, it is grade IV.
- **Grade I or II astrocytoma:** In children, this low-grade tumor occurs anywhere in the brain. The most common astrocytoma among children is juvenile pilocytic astrocytoma, which is grade I.
- **Ependymoma:** The tumor arises from cells that line the ventricles or the central canal of the spinal cord. It's most commonly found in children and young adults. It can be grade I, II, or III.
- **Brain stem glioma:** The tumor occurs in the lowest part of the brain. It can be a low-grade or high-grade tumor. The most common type is diffuse intrinsic pontine glioma.

5.5.2 Clinical State of the Art

After a brain tumor has been diagnosed, a multidisciplinary team typically assesses the treatment options. Neurosurgeons typically observe the evolution of the tumor before proposing a management plan. This is only true if benign. For malignant they will want to treat asap. Various types of treatment, detailed below, are available depending on tumor type and location and may be combined to give the best chances of survival. Survival rates depend on the type of tumor, age, functional status of the patient, the extent of surgical tumor 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 tumor cells as possible, with complete removal being the best outcome and cytoreduction (partial removal that enhances the effectiveness of radiotherapy or chemotherapy) of the tumor otherwise. In some cases access to the tumor is impossible and impedes or prohibits surgery.

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

Radiotherapy

The goal of radiation therapy is to kill tumor 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 single high dose fraction of radiation, is delivered stereotactically (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 tumors. It can be performed using machines such as the Leksell Gamma Knife.

Proton therapy is another form of radiation therapy,

Chemotherapy

Patients undergoing chemotherapy are administered drugs designed to kill tumor cells. Although chemotherapy may improve overall survival in patients with the most malignant primary brain tumors, 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 tumor, and extent of the cancer. The toxicity and many side effects of the drugs, and the uncertain outcome of chemotherapy in brain tumors puts this treatment further down the line of treatment options with surgery and radiation therapy preferred.

5.5.3 State of the art on risk stratification, intervention selection and success evaluation

For brain tumors, it can be difficult to determine response to therapy and tumor progression in an accurate and reproducible manner. Current response criteria vary depending on the pathology and have several limitations. Until recently, the most widely used criteria for gliomas were the "Macdonald criteria" (Macdonald, 1990), based on two-dimensional tumor measurements on computed tomography (CT) or magnetic resonance imaging (MRI), in conjunction with clinical assessment and corticosteroid dose. However, the Response Assessment in Neuro-Oncology (RANO) Working Group has published new recommendations in high-grade gliomas (Wen, 2010) and diffuse low-grade gliomas and is working on recommendations for other nervous system tumors. The new recommendations are still based on two-dimensional tumor measurements, although the RANO working group acknowledges its limitations and shows a clear interest in volumetric anatomic assessment. Nevertheless, they did not believe that there was sufficient standardization and availability to recommend adoption of volumetric assessment of tumor volume at the time of the report (2010). Moreover, it was noted that emerging data suggested that advanced MRI techniques such as perfusion imaging (dynamic susceptibility MRI), permeability imaging (dynamic contrast-enhanced MRI), diffusion imaging, magnetic resonance spectroscopy, and [¹⁸F]-fluorothymidine and amino acid positron emission tomography may predict tumor response or allow the differentiation of nonenhancing tumor from other causes of increased FLAIR signal.

The evaluation of treatment in high-grade gliomas currently relies either on the duration of patient survival or, more commonly in patients with recurrent disease, the radiographic response rate or progression-free survival. Cognitive evaluations and quality-of-life measurements are increasingly recognized as important end points in clinical trials (Bent, 2011), which is even more true for patients with low-grade gliomas that often present with seizures only. The slow growth pattern of most low-grade gliomas, and the rare radiological true responses despite a favorable clinical response to treatment, interferes with the use of progression-free survival as the primary endpoint in trials.



In current clinical routine, MRI images are evaluated using qualitative (e.g. presence of hyper-intense tissue in an MRI image) or basic quantitative measures such as the maximum tumor diameter measured on axial image slices. Image processing can replace these basic assessments with accurate and reproducible measurements of the relevant tumor and its substructures. Fully automatic image processing routines and also semi-automatic methods have an enormous potential for improving and speeding up diagnosis, treatment planning and follow-up of individual patients. The number of clinical studies involving brain tumor quantification based on medical images has increased significantly. About a quarter of these studies rely on fully automatic methods. In semi-automatic brain tumor segmentation, user interaction is often used to initialize the method, to provide the possibility of steering the segmentation process, to inspect the accuracy of the segmentation, and to correct the segmentation result. In fully automatic methods, the computer determines the segmentation of tumor without any human interaction.

Developing automatic brain tumor segmentation techniques is technically challenging. Lesions are defined through intensity changes that are relative to the surrounding normal tissue. Partial volume effect and bias field artefacts increase the complexity of the task. Furthermore, tumor structures vary considerably across patients in terms of size, extension, appearance and localization. When growing, lesions can displace normal brain tissues while resection cavities appear after treatment. Finally, in different clinics a large variety of MRI acquisition protocol and sequences are used to image the tumor or tumor-induced tissue changes. This lack of standardization makes it more difficult to develop a general image processing algorithm.

Automatic methods for brain tumor segmentation generally start with preprocessing of the individual images by applying noise filtering, inhomogeneity correction to correct for MRI bias field artefacts and image normalization. In case multiple MRI images are acquired from one subject, automatic image registration is used to align the images to each other on voxel level. Next, image-derived features and prior information are used as input for either generative probabilistic models or discriminative approaches resulting in a tumor segmentation. A generative model combines explicit models of the anatomy and appearance of the tumor region to obtain a segmentation. In this way domain-specific prior knowledge can be incorporated in the segmentation process. However, since the location and appearance of a tumor is hard to predict, encoding prior knowledge is difficult and often the tumor is modeled as an outlier. In addition, if the anatomical model relies on registration of accurately aligned images, problems occur in presence of large lesions or resection cavities. A discriminative approach, often based on pattern recognition techniques, directly learns the relationship between image-derived features and segmentation labels based on example segmentations. In order to be robust, a substantial amount of training data is required. Another drawback is that discriminative approaches explicitly depend on the value of image intensities limiting the application only to images acquired with the same protocol as used for the training images. To overcome the above limitations, joint generative-discriminative methods were developed. These techniques use a generative method in a preprocessing step to create a reliable input for a subsequent discriminative model that can be trained to predict the class labels of the voxels.

An overview of state of the art image processing methods is presented in review articles by Gordillo (Gordillo, 2013) and Menze (Menze, 2014). In the second article,



the Multimodal Brain Tumor Segmentation (BRATS) benchmark is presented which allows the comparison of different segmentation methods on a standardized set of data. This set consisted of 65 multi-contrast MR scans of low- and high-grade glioma patients which were manually annotated by up to four raters. Analysis of the inter-rater results showed Dice overlap scores of 74-85% illustrating the difficulty of the task. Automatic methods achieved overlap scores close to the inter-rater variability. The best results were obtained by methods which employed both a generative probabilistic model and a discriminative approach. Future directions are to include the local certainty, accuracy of the segmentation result, and to evaluate the performance of automatic methods in longitudinal setting as change in tumor structures is often of primary relevance.

5.5.4 Clinical consultants

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