

Post Hepatectomy Liver Failure: Risk
Factors and Prediction of Post-Operative
Function using Novel Dynamic MRI

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The candidate confirms that the work submitted is their own, except where work which has formed part of jointly authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

List of included Publications (chapters 3-5)

- I. D Longbotham, A Young, G Nana, R Feltbower, E Hidalgo, G Toogood, JP Lodge, M Attia, KR Prasad (Pre-print) **The impact of age on post-operative liver function following right hepatectomy: a retrospective, single centre experience** *HPB* 2019 Jul 20

I was responsible for study design, data collection, data analysis and writing the manuscript.

The contribution of the other authors was: KR Prasad conceptualised the study, G Nana assisted with data collection. A Young advised on data analysis, R Feltbower advised on the multivariable analysis, all authors advised and contributed to the manuscript.

- II. D Longbotham, S Sourbron, A Guthrie, E Hidalgo, R Prasad **Measuring liver function with gadoteric acid: Is a dual-input model needed in dynamic contrast enhanced liver MRI?** (Oral presentation presented at IHPBA/ASGBI 2015) *HPB* April 16 Volume 18 S2 Page e697

I was responsible for study design, data collection, data analysis and writing the manuscript

The contribution of the other authors was: S Sourbron initiated the study, S Sourbron contributed to study design and assisted with development of the MRI protocol with input from A Guthrie. S Sourbron advised on DGE-MRI analysis, all authors advised and contributed to the manuscript.

- III.** D Longbotham, D Wilson, A Guthrie, I Rowe, M Gilthorpe, E Hidalgo, M Attia, KR Prasad, S Sourbron **Prediction of post-hepatectomy liver function with Dynamic Gadoxetate-Enhanced MRI: A pilot study in patients undergoing Colorectal Liver Metastasis Resection** *In submission (HPB), accepted for presentation at the International Society for Magnetic Resonance imaging in Medicine (ISMRM) annual meeting and exhibition, Sydney, Australia, April 2020*

I was responsible for study design, data collection, data analysis and writing the manuscript

The contribution of the other authors was S Sourbron, A Guthrie, E Hidalgo and KR Prasad initiated the study and advised with study design. D Wilson and S Sourbron developed the MRI protocol with input from A Guthrie. S Sourbron advised on DGE-MRI analysis, I Rowe and M Gilthorpe advised on data analysis and supported interpretation of results. All authors advised and contributed to the manuscript.

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Abstract

Liver surgery is an advancing specialty with improved outcomes in recent years(1). Liver resection is used with curative intent for both primary and metastatic cancer(2)(3)(4). Despite the rapid improvements and increasing range of surgical options, there remains a significant risk of developing Post-Hepatectomy Liver Failure (PHLF) – caused by inadequate remnant liver function after surgery(5)(6). This is a condition with high mortality and morbidity(7) and currently there are no specific treatments for it once it has developed(8). Its pathogenesis is complex and multifactorial(9)(10), and some risk factors, particularly ageing are uncertain as to their contributing significance. This thesis aimed to investigate **risk factors for PHLF development and a imaging based measurement of liver function** after major liver resection. This study identified patients over-75 years have a significantly increased risk of PHLF.

Development of a method to predict post-operative function is needed to aid patient selection and reduce complications for those who undergo resection. Currently, volumetry is performed but this has proven inadequate, with some patients still developing PHLF despite adequate remnant volume(11). Other options such as Indocyanine Green(12) and Technetium-99m labelled Mebrofenin(13) are not readily available. One potential solution is **Dynamic Gadoxetate Enhanced (DGE) MRI of the Liver**, which has been developed to investigate liver function, with promising results for demonstrating liver heterogeneity in patients with parenchymal liver diseases(14). Oncological staging of the liver involves MRI to plan surgical resection, and DGE-MRI can be integrated into the diagnostic protocol easily with no additional burden to the patient. This thesis aimed to demonstrate if **DGE-MRI functional estimates can predict post-operative liver function** after resection of colorectal liver metastases. This study demonstrated that there was good correlation of DGE-MRI-function tests with post-operative hyperbilirubinaemia, a measure of hepatic dysfunction. This could be utilised in surgical planning to improve patient selection and outcomes.

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List of Abbreviations

Abbreviation	Full name	Description/Definition (if required)
AFF	Arterial Flow Fraction	The percentage of arterial blood to total plasma flow
AIF	Arterial Input Function	The point of measurement on the arterial flow into the liver (aorta)
ALPPS	Associating Liver Partition and Portal vein ligation for Staged hepatectomy	A novel surgical approach involving ligation of the portal vein and division of the hemi liver to induce massive rapid hypertrophy for a second staged resection
ALG	Asialoglycoprotein	A liver cell membrane protein found on the sinusoidal surface
ASA Score	American Society of Anaesthesiologist Score	A system of assessing fitness of patients before surgery
CPS	Child-Pugh Score	A prognostic clinical scoring system for patient with cirrhosis
CRLM	Colorectal Liver Metastasis	
CT	Computerised Tomography	A method of imaging using ionising radiation providing cross sectional images
CUSA	Cavitron Ultrasonographic surgical aspirator	A surgical instrument to dissect the liver
DCE-MRI	Dynamic Contrast Enhanced Magnetic Resonance Imaging	Rapidly acquired MRI images with a contrast agent used
DGE-MRI	Dynamic Gadoxetate Enhanced Magnetic Resonance Imaging	DCE-MRI with Gadoxetate as contrast agent
DTPA	Diethylene triamine pentaacetic acid	A ligand for Gadolinium
EHDS	Edinburgh Hepatic Dysfunction Score	A clinical scoring system of PHLF
eGFR	Estimated Glomerular Filtration Rate	An estimate of kidney excretory function calculated using serum creatinine and age
ECV	Extracellular Volume Fraction	The percentage of contrast observed in the extracellular space compared to as a whole
FLASH	Fast low angle shot magnetic resonance imaging	A method developed in the 1980s to allow rapid image acquisition
FNH	Focal Nodular Hyperplasia	A benign liver tumour
G1P	galactose-1-phosphate	A metabolite of Galactose
GA	General Anaesthetic	A method of rendering patients unconscious so they can undergo surgery
Gd EOB-DTPA	Gadoxetic Acid	A liver specific MRI contrast agent
Gd-BOPTA	Gadobenate Dimeglumine	A liver specific contrast agent
Gd-DO3A-butrol	Gadobutrol	A gadolinium-based MRI contrast agent

GECT	Galactose Elimination Capacity Test	A measure of global liver function
GSA	Galactosyl serum albumin scintigraphy	A nuclear medicine method of determining liver function
HCC	Hepatocellular Carcinoma	A type of Primary Liver Cancer
HEF	Hepatic extraction fraction	the amount of contrast retained by the liver at the peak vascular contrast time divided by the peak amount of contrast in the liver
ICG	Indocyanine Green	A measure of global liver function
IHPBA	International Hepato-pancreatobiliary association	An international liver and pancreas surgery society
INR	International Normalised Ratio	The ration of PT of the patient to the normal time for the population
irBF	input relative Blood Flow	measured peak blood flow relative to the input function
ISGLS	The International Study Group for Liver Surgery	A research committee
KDOQI	Kidney Disease Outcomes Quality Initiative	The international group that develop guidelines for kidney disease
k-RAS	Kirsten rat sarcoma viral oncogene homolog	A proto-oncogene
MDT	Multidisciplinary Team	Specialists from various medical and surgical specialties review patients' case for decision making
MELD	Model for End-stage Liver Failure	A prognostic scoring system for patient on the liver transplant waiting list
MRI	Magnetic Resonance Imaging	A mode of imaging
MRP	Multidrug Resistance Protein	An active transporter enzyme on the liver cell surface
MTT	Mean transit time	Area Under Curve of contrast from peak value divided by the irBF
MUST	Malnutrition Universal Screening Tool	A commonly used method of assessing patient's risk of nutritional insufficiency
NAFLD	Non-alcoholic Fatty Liver Disease	An abundance of fat in the liver that could lead to Cirrhosis
NELA	National Emergency Laparotomy Audit	A prospective audit into outcomes of major non-elective abdominal surgery
NET	Neuroendocrine Tumour	A malignant tumour from neuroendocrine cells mostly from gastro-entero-pancreatic and bronchopulmonary origin
OATP	Organic anion transporting polypeptide	An active transporter enzyme on liver cell surface
PBC	Primary Biliary Cirrhosis	An autoimmune disease of the liver where there is progressive destruction of bile ducts
PICO	Population, Intervention, Comparison & Outcome	A method of structuring a research question

PHLF	Post Hepatic Liver Failure	A condition post-surgery where there is inadequate remnant liver for adequate liver function
PSC	Primary Sclerosis Cholangitis	An autoimmune disease of the liver where there is inflammation and fibrosis of bile ducts
PT	Prothrombin time	The time for prothrombin to convert to thrombin in coagulation
PVE	Portal Vein Embolisation	A procedure to block the venous blood flow to a part of the liver to cause atrophy of that part, and hypertrophy of the contralateral part
RF	Radio frequency	A form of electromagnetic energy that is used by MRI scanners to elicit proton excitation
RLE	Relative liver enhancement	percentage of the sum of signal intensity (SI) in the hepatobiliary phase in each liver segment minus the SI pre-contrast. This is then divided by the SI pre-contrast multiplied by 100
ROC	Receiver Operating Characteristic	A graph plotting a tests Sensitivity against 1-specificity (true positive rate vs false positive rate)
ROI	Region of Interest	An area within the liver identified as a point of data acquisition
SI	Signal intensity	The strength of measured contrast within the MRI
SPIO	Superparamagnetic iron oxide	An iron-based MRI contrast agent
T1	Time 1	The time taken for a proton that has been excited to 180° to relax to its resting polarity
T2	Time 2	The time taken for a proton that has been excited to 90° to relax to its resting polarity
TACE	Trans Arterial Chemo-Embolisation	An interventional procedure where direct chemotherapy agents are applied directly to the vasculature of a tumour
TE	Echo time	The time between the application of radiofrequency excitation pulse and the peak of the signal induced in the coil.
TPF	Total Plasma Flow	The total observed blood flowing through the ROI measured in ml/100ml/min
TR	Temporal Resolution	The precision of an MRI measurement with respect to time
TWIST	Time-resolved angiography With Interleaved Stochastic Trajectories	Time-resolved 3D MRA technique with very high temporal (sub-second) and spatial resolution (sub-millimetre) which will allow to capture the multiple arterial, mixed, venous phase images during the passage of a contrast agent through the vascular anatomy.
UF	Uptake Fraction	The percentage of uptake of contrast into the liver within the ROI
UKELD	United Kingdom model of End-stage Liver Failure	A prognostic scoring system for patient on the liver transplant waiting list
VEGF	Vascular endothelial growth factor	A signal protein produced by cells that stimulates angiogenesis
VIF	Venous Input Function	The point of measurement on the venous flow into the liver (portal vein)

Chapter 1 – Introduction, Aims and Hypotheses

Liver surgery is a rapidly advancing specialty with significant improvements in patient outcomes in recent years(1). Liver resection is used with curative intent for both primary and metastatic cancer(2). It is possible for up to 75% of the liver to be resected with improving outcome for the patient, both in terms of cure, and recovery from surgery(3)(4). Despite such improvements, and an increasing range of surgical options, there remains a significant risk of developing a major complication known as post-hepatectomy liver failure (PHLF). This is caused by inadequate remnant liver function after surgery(5)(6). This is a condition with high mortality and morbidity(7) and currently there are no specific treatments for it once it has developed(8). Its pathogenesis is complex and multifactorial(9) and it is essential to understand what increases risk. Current methods of predicting PHLF are inadequate, as such, new approaches are required(10). **Prevention** is critical to PHLF management(8). This thesis aims to investigate **risk factors for PHLF development** after liver surgery and to assess investigations aiming to optimise the patient's pre-operative condition to reduce risk of developing complications.

Development of a method to predict post-operative function is needed to inform patient selection and prevent PHLF for those who undergo resection. Volumetry is currently performed but this has proven inadequate, with some patients still developing PHLF despite adequate remnant volume(11). One potential solution is **Dynamic Gadoxetate Enhanced (DGE-MRI) of the Liver**, which has been developed to investigate liver function, with promising results for demonstrating liver heterogeneity in patients with parenchymal liver diseases(14). Oncological staging involves MRI to plan surgical resection, and DGE-MRI can be integrated into the diagnostic protocol easily with no additional burden to the patient. This thesis tested if DGE-MRI estimates of function can predict post-operative liver function after resection of colorectal liver metastasis, the commonest indication for resection.

1.1 Aims and Hypothesis

Chapter 2 provides a background to current surgical practice, describing the history and development of liver surgery. This retrospective overview current evidence and needs for future developments. It describes the current indications for liver resection, along with current pre-operative assessments of fitness to ensure that patients are suitable for surgery, along with the pitfalls of current practice. The role of MRI in current practice is discussed, and the development of DGE-MRI is described, with a summary of published reports on the measurement of liver function with DGE-MRI that led to the hypothesis that it could be used to assess surgical patients.

Chapter 3 describes a retrospective cohort study designed to investigate known risk factors for PHLF in a population of patients having major liver resection, with age as a primary independent variable, and its impact on PHLF development. The impact of ageing on liver function and surgical outcomes was uncertain prior to this study, and this chapter aimed to investigate outcomes with the following hypothesis that there is an **association between increasing age and the incidence of development of PHLF** in patients undergoing major resection. The population, intervention, comparison & outcome (PICO) study design is described in table 1.

Table 1: PICO for study of PHLF risk factors

Population	Patients undergoing curative right hepatectomy
Intervention	Older patients
Comparison	Younger patients
Outcome	Incidence of PHLF development

Secondary outcome hypotheses were to investigate the extent of association between other known risk factors for PHLF development(6): preoperative eGFR levels <90 (CKD grade 2(15), Pre-operative neo-adjuvant chemotherapy, diabetes status, ASA grade, background liver disease, steatosis if present, operation time (>4h) and intraoperative transfusion.

In addition, a cost-effectiveness analysis between development of PHLF and normal post-operative clinical course was conducted and a discussion of a potential cost-benefit in reducing its PHLF incidence with hypertrophic procedures such as Portal Vein Embolisation (PVE).

This study identified that age is an independent risk factor for PHLF development after right hepatectomy when all other known risk factors are accounted for. Older patients are at risk of PHLF should therefore have their Future Liver Remnant (FLR) pre-operatively assessed and optimised to prevent a poorer outcome in this at-risk population.

Chapter 4 describes a study on the technical aspects of DGE-MRI acquisition. DGE-MRI is a relatively new technological innovation and the best methods of acquisition and how to analyse the data is not yet defined. After an initial analysis of 3 different acquisition models to assess which was the most suitable in a clinically pragmatic manner, a 3D spoiled gradient echo sequence with a temporal resolution of 2.4 seconds was selected as it provided better quality images than other acquisitions and could be analysed easily. Following this, a comparison of different methods of post-processing the results of key perfusion and function parameters was performed to ascertain which model gives the most precise and accurate output values, principally looking at single and dual input models with and without an arterial delay. This demonstrated that the **dual input model with arterial delay** provided results that were in keeping with previously reported literature values and was selected for future analysis of liver function.

Chapter 5 describes a prospective hypothesis-generating study examining if DGE-MRI measurements of function have any role in predicting post-operative function following resection surgery. Patients with Colorectal Liver Metastasis (CRLM) were examined and bilirubin was chosen as the primary dependant variable. Secondary outcomes were correlations of clinical and biochemical risk factors of PHLF and FLR-volume, against post-operative bilirubin and DGE-MRI estimates of function. This was to compare if DGE-

MRI function estimates had any added benefit over other currently used liver function assessment.

Table 2: PICO for DGE-MRI in patients undergoing liver resection study

Population	Patients having major liver resection for CRLM
Intervention	DGE-MRI measured liver function of the FLR
Comparison	Post-operative bilirubin levels
Outcome	Strength of correlation

This study identified that some DGE-MRI estimates of liver function, namely the FLR-cellular uptake of gadoxetate and FLR-clearance of gadoxetate correlate significantly with post-operative bilirubin levels, and thus may have potential to predict post-operative function. Important negatives from this study were the lack of predictive capacity of volumetry and pre-operative clinical markers. This suggests that DGE-MRI estimates have a role beyond current pre-operative assessment standards in predicting post-operative liver function. They have potential to be utilised in surgical planning for how much liver could be resected safely. The secondary outcomes demonstrated patients over 75 and those who required major resection had reduced gadoxetate excretion, suggesting impaired cellular metabolism and function, which has implications in surgical planning for older patients.

Chapter 6 discusses implications of the results of these studies to current practice and future perspectives for ongoing studies. This covers a potential prospective study to improve on clinical outcome for older patients, and a future planned DGE-MRI study HEPARIM aiming to assess DGE-MRI's ability to predict outcomes in patients requiring liver resection for both primary and secondary liver cancers, compared to gold standard measurement of function using indocyanine green (ICG).

Chapter 2 – Background

2.1 Liver Surgery

2.1.1 History of Liver Surgery

To understand progress in the development of liver surgery; it is useful to review the discoveries over the centuries that have led to current practices. The descriptions of the liver's anatomy, physiology, and the subsequent development of surgery and, in particular liver resection techniques has evolved rapidly. Over the last 100 years, understanding of human biology, surgical science and technology have developed significantly, and innovation is ongoing.

2.1.2 Ancient history

Until the 20th century, the liver's function was unclear, but it was always viewed as being important for life. This is exemplified by Prometheus' story of his daily hepatectomy by an Eagle. His liver seems to have been chosen as the organ to be continually devoured as it was considered to be the "seat of the soul and intelligence"(16).

In the 2nd century AD, Galen, conducted research and experiments on various animals and through these he thought the liver itself was the producer of blood. He also felt the liver aided digestion by the heating the stomach:

"why is the stomach surrounded by the liver? Is it in order that the liver may warm it and it turn warm the food? This is indeed the very reason is it closely clasped by the lobes of the liver, as if by fingers"(17)

This was, of course incorrect, but Galen appreciated the liver was a highly important organ, one which without life was not possible.

Surgery on the liver before anaesthesia was exceptionally rare, however as far back as the 4th century BC there have been descriptions of its occurrence. Hippocrates apparently had diagnosed liver abscesses in his patients, and advocated for the incision and drainage of such abscesses by use of "knife or cautery", (18). In the 1st century AD,

Celsus(19) described surgery and debridement of exposed liver in war wounds of soldiers.

2.1.3 Renaissance

No real advances in anatomy or physiology occurred until the 15th century when dissection of executed criminals in Italy was permitted by the catholic church. An early anatomist, Vesalius, demonstrated the gross anatomy of the liver as having 2 lobes, left and right(20).

The French Barber-Surgeon Amboise Paré, the royal surgeon to many French kings in the 16th Century, and otherwise notable for introducing ligation of vessels during limb amputation to stop bleeding(21) – discovered that the liver *in vivo* was extremely vascular. His most sage contribution to liver surgery was with this statement:

"When the liver is wounded, much blood commeth out"(22)¹

William Harvey described the circular motion of blood around the body, and that it was being pumped by the heart, rather than the liver which was previously believed(23). Harvey's student Francis Glisson described both the gross and microscopic vascular supply of the liver by a clever and careful dissection of the liver parenchymal from the vessels in 1654. He found that the liver has **two separate inflows**: one arterial and one venous. He also correctly predicted the microvascular connection between the portal venous and hepatic venous systems (interestingly he did this without using a microscope which didn't become widely used until Robert Hooke published *Micrographia* in 1665(24)). He also described the fibrous capsule around each liver lobule; the small subdivisions of the liver that contain the branch of the portal vein, hepatic arteries, bile canaliculi and the hepatic venules – the eponymously named Glisson's Capsule(25). His

¹ This is often the first thing an aspiring liver surgeon learns, either through a traditional didactic approach, or through very bitter personal experience.

descriptions were lost until rediscovered in the 1890s, but his descriptions remains important(26).

Despite the improved understanding of the liver's structure and vasculature, surgery was confined to extreme situations in war time due to the lack of anaesthesia. Any 'liver surgery' from this period is limited to anecdotal reports of percutaneous debridement and extraction of liver pieces injured by sword wounds or ligating protruding liver from spear injury(27)(28), and as such these descriptions of early surgical adventures are interesting curios, but not really relevant to modern surgery.

2.1.4 Era of anaesthesia

In 1846, Diethyl Ether was found to produce effective anaesthesia when demonstrated successfully by William TG Morton and John Collins Warren, when they excised a tumour from the neck without causing the patient² any distress or pain(29). From this, modern surgical practice could develop in earnest, and a huge array of operations would be described.

The timeline of events for key 19th and early 20th century developments in liver surgery described below were identified by James Foster in History of Liver Surgery(18).

The first case of planned liver surgery was in 1886. Luis reported that he had excised a large pedunculated tumour protruding from the liver of a 67 year old lady, but his attempts to stop the liver bleeding from where he had excised on the liver failed and she ultimately bled to death(30). A more successful attempt was published 2 years later by Langenbuch(31) where a 30 year old lady had a pedunculated tumour hanging off the left liver lobe excised. She also developed a post-operative haemorrhage and required a repeat operation later in the day and had a prolonged and difficult recovery but survived. Patient survival bolstered surgeons, so more extensive operations took place, helped by improved technique and surgical instruments and materials(32).

² or indeed to the captive audience who had come to see the spectacle

The first described resection of part of the liver (as opposed to excision of a tumour hanging outside the liver) has been credited to Tiffany(33). In retrospect this resection from his description seems to be more removal of infected abscess tissue within the liver rather than liver tissue. Others followed with more substantial resections, principally by William Keen(34). Techniques at the time were crude; Keen describes cutting through liver with his thumbnail³.

Morbidity and mortality were very high in these early years. Into the 1960s mortality for liver surgery was reported as being up to 50%(35). Such high risk was dispiriting for both surgeon and potential patients to consider such fraught and risky procedures. Lack of diagnostic imaging, and sole reliance on clinical examination cannot have helped. Blood loss was often uncontrollable and was a major barrier to successful surgery.

2.1.5 Blood loss control

The Pringle manoeuvre (described by J Hogarth Pringle(36)) was a step forward in control of bleeding. It involves compression the hepatoduodenal ligament at the liver hilum (which contains the hepatic artery, portal vein and bile duct). This controls bleeding by reducing blood inflow. Pringle's reported outcomes were unfortunately 100% fatal (all were for trauma patients who were bleeding to death and succumbed to their injury), but the reasoning and the anatomical knowledge behind the manoeuvre was sound, and this technique has persisted to this day. Application reduces bleeding from cut surfaces of the liver. A Pringle manoeuvre has been reported to have been applied to the hilum for up to an hour and the liver survived(37), however is quite an extreme length of time. Local practice is application of Pringle for **no more than 15 minutes** as it can lead to ischaemic damage to the liver, or subsequent reperfusion injury(38).

Ischaemia-reperfusion injury is a complex inflammatory response that involves two stages – the initial ischaemic damage due to lack of available oxygen can lead to hepatocyte death. Reperfusion will lead to massive systemic cytokine release, which in

³ Although 'finger fracture dissection' is still employed at times to this day – it provides a careful surgeon a gentle way of tissue dissection

turn can injure the liver. In addition, bacterial endotoxins re-entering the liver via the bloodstream can also be damaging(39). Back perfusion via the hepatic veins may reduce the extent of injury, and minimising the time applied reduces liver damage whilst reducing intra-operative blood loss(40). In Leeds, back perfusion is utilised throughout Pringle use to reduce risk of ischaemic-reperfusion damage.

Resection along anatomical planes also reduces bleeding. This is called an anatomical resection. This involves ligation of the inflowing vessels to the area of liver to be excised, then subsequent division of the liver along the line of demarcation between the perfused and non-perfused liver. The first anatomical resection was reported by either by Von Harberer, who described ligation the left hepatic artery prior to excision of the left lobe (left hepatectomy)(41), or by Wendel(42)(43)(44)(45). Lorat-Jacob performed what was probably the first extended right hepatectomy(46), although nomenclature for liver resections was variable between reports until the Brisbane convention(47) standardised descriptions.

Segmental anatomy was described by Couinaud in 1954(48) (although it has been suggested that Healey and Schroy(49) may have beaten him to it a year earlier(50)). Couinaud's description based on the branches of the hepatic artery and portal vein into 8 areas remains the anatomical description of choice to this day. This will be discussed later in the section on liver anatomy within this chapter (chapter 2.1.9). Couinaud's work allowed surgeons to understand how to control inflow of blood into each segment, allowing segmental resections. Dissecting in inter-segmental, extra-glissonian planes reduces bleeding(51). This led to improved immediate survival of patients, and refinement of dissection with surgical instruments reduced parenchymal bleeding intraoperatively(52).

Other novel attempts at controlling blood loss have been developed, often first used in trauma where surgeons innovate in desperate situations. Such methods includes hypothermic perfusion to cause vasoconstriction of the liver vessels(53)(54), aortic cross clamping(55), and inferior vena cava (IVC) control(56). Lin (57) described use of surgical

clamps on major vascular pedicles, and such clamps are still in use today(58). The combination of anatomical extra-glissonian dissection and better control of blood inflow and outflow allowed surgery to be performed more safely.

In addition to the technical aspects of surgery, factors such as increased understanding of disease processes; leading to better decision making for who should be a candidate for liver resection. For instance, liver haemangiomas were commonly excised due to uncertain natural history(59). With a better understanding of the pathophysiology of such benign lesions, surgery for haemangioma is now not indicated except in rare circumstances(60).

The introduction of the ultrasonic dissector, of which the Cavitron ultrasound surgical dissector (CUSA) is a commonly used example, allowed more careful dissection of liver parenchyma from vessels due to the difference in mechanical impedance between the two(61). It has been widely adopted(62). The development and use of argon lasers to cause rapid and effective coagulation(63) has also entered routine surgical practice(64)(65)(66). Staplers, harmonic scalpels and hydrodissectors have also been used and are reported as being equally effective as CUSA(67). A randomised trial by Lesurtel and colleagues found that clamp crushing was preferable over other methods for patients with no parenchymal liver disease: quicker, cheaper, had less intra-operative bleeding and fewer transfusion requirements(68). The practice in Leeds at the time of recruitment for the studies described within this thesis was CUSA dissection, based on surgeon preference, familiarity with the technology, and availability.

2.1.6 Modern developments and techniques

The drive to achieve curative resection of what were previously considered non-resectable has led to development of novel and occasionally radical surgeries. One reported technique is to perform a total hepatectomy, perfuse the liver with 'backbench' preparation, excise any tumour and then re-anastomose the livers hepatic artery, portal vein, bile duct and IVC. This was first reported in the late 1980s(69) but with a 33%

mortality, this technique has seldom been employed other than by highly specialised centres with liver transplant expertise.

Tumours that had invaded vessels were once considered unsuitable for resection, however en-bloc liver resection with vascular excision was described in the early 1990s(70). Despite short term technical success and patient survival, vascular invasion carries a worse prognosis for patients; most likely due to the tumour biology with increased recurrence and extrahepatic metastasis(71).

A more frequently used technique is a **staged liver resection** and allowing intra-operative liver hypertrophy. For a patient with tumours in both right and left lobes of the liver, the first operation would involve resection of the tumours in one lobe (ipsilateral resection), leaving the contralateral tumours in situ. Following the first operation, the ipsilateral liver will hypertrophy. A subsequent operation to remove the contralateral liver tumours will take place after a few weeks, and the hypertrophy of the ipsilateral liver will have increased the remnant liver size sufficiently to provide effective function in the post-operative period(72).

Portal vein embolisation (PVE) was developed in Japan in the mid-1980s(73)(74). Occlusion of branches of the portal vein of the part of the liver that is to be resected (ipsilateral liver) is performed by injecting a sclerosing or obstructing agent, originally via a small laparotomy. A substance is injected into the portal vein or another mesenteric vein. It is now more commonly performed via a percutaneous route. Materials used include polyvinyl alcohol, gelatine sponges, n-butyl cyanoacrylate, fibrin glue, ethanol, coils, or vascular plugs(75). This leads to the ipsilateral liver becoming atrophic and stimulates the contralateral liver – the **Future Liver Remnant (FLR)** to hypertrophy⁴. It can induce the size of the FLR by as much as 10%-46%(76)(77)(78). PVE is established as an effective method of improving outcomes, and expanding the number of patients

⁴ Future Liver Remnant or FLR is a hugely important concept in this thesis. It is the predicted part of the liver that will remain after the rest has been excised. Much discussion will follow regarding its potential volume and function

who are suitable for resection with a predicted small FLR(79)(80)(81). One demonstrable risk associated with PVE is sometimes there is an increased growth of tumour size, or even new tumour formation in the FLR in the time following PVE. Such tumour growth may render the liver inoperable. This can lead to a difficult balance between allowing enough time for adequate FLR hypertrophy to ensure safe surgery, and a delay that leads to tumour growth and inoperability(82). Another issue with PVE is that sufficient hypertrophy may not occur between 4%(75) to 37%(81) of the time, preventing surgery to proceed as required. PVE may not technically possible if there is portal vein thrombosis(83), and here has been recent reports of deaths due to complications from percutaneous approaches(84).

One potential solution to the issues related to PVE is a novel surgical technique called “associating liver partition and portal vein ligation in staged hepatectomy” (ALPPS). This operation was discovered accidentally during a patient having hilar cholangiocarcinoma resected when the surgeon felt that should he continue with the original planned surgery the FLR would be too small, so abandoned surgery before completion of the resection(85). This involved the first stage resection as previously described, with ligation of portal vein branch to the ipsilateral liver and a splitting of the liver along Cantlie’s line. This induces rapid hypertrophy in the contralateral liver, and as such avoids the need for prolonged latent periods between first and second stage surgery, which can take place as soon as between 7 and 14 days(86), Initial outcomes reported quite high mortality and morbidity, but this has improved to acceptable rates(86). Laparoscopic first stage ALPPS may allow for patients to recover quicker than open surgery and have fewer complications, improving outcomes(87). Refinement of techniques, such as partial ALPPS, which does not involve such drastic dissection and liver partition shows comparable success in hypertrophy, with fewer complications(88).

Anaesthetic techniques have also been used to achieve successful surgeries. Most of the improvements come from anaesthetic techniques to minimise blood loss, such as creating a low intra-operative central venous pressure (CVP)(89).

One study reported venesection of 0.7% of the patient's weight in blood pre-surgery, to allow reduced CVP and a resultant reduced portal venous flow intraoperatively which led to reduced intra-operative blood loss. This pre-collected blood was then infused back into the patient as an autologous transfusion(90).

2.1.7 Development of Liver Imaging

Liver imaging has allowed clinicians to find out detailed information on the location and extent of tumours. Before imaging, decision making for surgical planning was based solely on clinical examination; you could only detect liver lesions if they were palpable (91). Indications for resections were also ill-defined. It is not possible to know how many patients had undergone a 'diagnostic laparotomy' for palpable masses that were not excised or not reported. As the diagnosis of liver lesions became possible without resorting to surgery, patient care and selection for those who do require surgery has greatly improved.

Ultrasound was developed in the 1940s and used in liver diagnosis since the late 1970s(92). Today liver ultrasound is frequently used to assess both diffuse liver diseases and identify discrete lesions; it is a cheap, safe and reproducible modality. However, it has a lower sensitivity than other imaging methods when used to diagnose liver metastases, it is more useful in excluding lesions. CT and MRI have proven to be more sensitive and specific in metastatic lesion diagnosis(93). Ultrasound is more operator dependant than other modalities which could lead to diagnostic errors, therefore CT and MRI are preferred for cases of cancer(94).

Computerised Tomography (CT) use has led to major diagnostic improvements. CT angioportography was the main mode of imaging of metastases that exploited the fact that the liver parenchyma receives significant blood flow from the portal system, whereas metastasis being non-hepatic in origin do not. When a contrast agent is given the liver parenchyma will enhance during portal phase of contrast and metastasis will not(91). CT has mostly replaced ultrasound as imaging of the liver for discrete lesions although intraoperative ultrasound proved very useful after it was utilised to identify the location of

tumours within the liver that were not visible or palpable (95). Multidetector CT sequences are now available which gain excellent perfusion and dynamic images which improves acquisition speed and has narrower slice thicknesses which can identify smaller lesions. This has improved sensitivity and specificity of diagnosis of liver metastasis(see table 3)(96)(97).

Positron Emission Tomography (PET)/CT is a combination of PET and CT in a single scanner which allows localisation of a radio-labelled tracers, most commonly in the form of glucose ¹⁸Fluorine-fluorodeoxyglucose (FDG) which decays and emits positrons which are detected by the PET. Cells which are termed 'FDG avid', namely those cells that are rapidly dividing and have a high glycolytic metabolism. Cancer cells are usually FDG avid, including most forms of colorectal adenocarcinoma. When the PET image is superimposed over a conventional CT, this can demonstrate very well the location of metastases, with the benefit of showing intra-hepatic and extra-hepatic disease(98).

Magnetic resonance imaging (MRI) will be discussed in more detail below (chapter 2.4). Since it was developed by Sir Peter Mansfield and Peter Lauterbur(99)(100) it has been a major component of diagnosis of discrete liver lesions, and is frequently used in conjunction with CT in planning surgical resections. MRI carries some benefits over CT imaging in that it involves no ionising radiation, and sensitivity and specificity of diagnosis of various discrete liver lesions is improved over other modalities, particularly when liver specific contrast agents are used(101). Many centres, including Leeds, use it for all patients being considered for surgery. It also allows assessment of function with DCE-MRI, which will be investigated in this thesis.

Table 3: Summary of sensitivity and specificity for CRLM(93)(96)

Modality	Sensitivity (per patient) %	Specificity (per patient) %
Ultrasound (93)	63	86.3
Multidetector CT	82	74
PET-CT	74	94
MRI with non-liver specific contrast agent (93)	81.1	86.3
MRI with Liver specific contrast agent	93	87

2.1.8 Liver embryology, anatomy, and physiology

Hepatoblasts form most of the precursor cells of the liver and arise from foregut endoderm in the third week of gestation. Hepatoblasts are bi-potential; capable of turning into hepatocytes, or for those cells next to the portal vein, become biliary epithelial cells (or cholangiocytes); part of the lumen of the future bile duct (102). Stromal cells, stellate cells, Kupffer cells and blood vessels are from mesoderm, and form in tandem with the mesodermal structures invaginating into the hepatoblasts mass. The forming liver bud develops greatly in size between week 9 and 15 and is an important erythropoietic organ for the foetus(103).

These hepatocytes form a structure called the liver bud, which is considered part of the foregut, along with future structures of the gastrointestinal tract from the oesophagus to the second part of the duodenum. As a result, it receives arterial supply from the foregut artery. The liver bud presses into the embryological vitelline veins, surrounding them. The afferent part of the veins fuse to become the portal vein, and the efferent parts of these vitelline veins form the future right hepatic vein and inferior vena cava⁵. The middle and left hepatic veins develop separately from within the left side of the liver bud(104). This explains how the drainage of the left and right liver is functionally different, and a clear division between the two can be seen during surgery.

The ductus venosus connects the left portal vein shunting blood to the IVC shunting 20-30% of the blood flow to bypass the liver in the foetal stage(105)(106). The ductus venosus closes and subsequently fibroses after birth where it is known as the ligamentum venosus (or ligamentus teres⁶) which runs in the border of the peritoneal fold of falciform ligament. The requirement of the left portal vein to allow the shunt gives an

⁵ This is a great oversimplification. They form from various other vessels in addition: a segment of the left vitelline vein, from the termination of the mesenteric vein to the middle inter-vitelline anastomosis; the middle or retro-duodenal inter-vitelline anastomosis; and the segment of the right vitelline vein comprised between the retro-duodenal and the subhepatic anastomoses.

⁶ Teres means 'round' in Latin. There are at least 4 ligamentum teres in the body – the remaining 3 are found: 1. coming from the uterus, 2. attaching the femoral head to the acetabulum, and 3. surrounding the elbow

asymmetry of the left portal vein from the right – an important point to consider in surgery. The ligamentum venosus is an important landmark for a left hepatectomy – it marks the boundary for inflow for the left hemi-liver and thus gives a good guide to the edge of the correct resection margin(107).

2.1.9 Anatomy

The liver is a large intra-abdominal organ, roughly 2.5% (e.g. 1.5kg-2kg) of the total body weight of the individual. It is situated in the right upper quadrant of the abdomen, normally in health hidden beneath the rib cage and generally unpalpable clinically. Inferiorly the gallbladder is adherent to the liver in a recess known as the gallbladder fossa and these structures are separated by a thin fibrous layer.

The gross anatomy of the liver is divided into 4 different lobes. The left and right lobes, which are either side of the falciform ligament make up most of the liver. The quadrate lobe found between the gallbladder fossa on the right and umbilical vein within the falciform ligament on the left, and the caudate lobe is surrounding the inferior vena cava. On the surface there is a visceral peritoneal covering, and deep to this there is a tough fibrous capsule called Glisson's capsule (108). Superiorly, the peritoneum is absent as the liver touches against the diaphragm – the bare area.

The liver receives 3 important structures that enter at the hilum. It receives the portal vein, hepatic artery, and the common hepatic duct. These 3 structures run together in what is known as the hepatoduodenal ligament⁷, also known as the portal triad.

The arterial supply of the liver is from branches of the coeliac trunk – the mature foregut artery, a direct branch off the abdominal aorta. For most individuals, this is in the form of the common hepatic artery. After this artery trifurcates and gives off the gastroduodenal and right gastric arteries and runs towards the liver as the hepatic artery proper. This then bifurcates into right and left hepatic arteries which supply the right and left lobes respectively. Cadaveric studies have shown that there is the occasional (15%) incidence

⁷ The hepatoduodenal ligament is the structure that is compressed during the Pringle Manoeuvre.

of a third artery branch – the median hepatic artery in addition to the right and left. This branch runs to either segment 4 or to 2/3. Between 25-40% of the time the right hepatic artery is a branch of the superior mesenteric artery (the midgut artery). Between 3% and 13% of the time the left hepatic artery is a branch from the left gastric artery itself (109)(110). This is important for both surgery on the liver and for this study for the identification of the arterial input function (AIF) in dynamic MRI imaging.

The portal vein is created from the confluence of the splenic vein and the superior mesenteric vein that run behind the body of the pancreas. These veins (along with the inferior mesenteric which drains into the splenic vein behind the tail of the pancreas) come from the mid and hindgut structures of the abdomen, namely the small and large bowel, with some tributaries from gastric and lower oesophageal veins. The portal vein bifurcates into a left and right portal vein, normally within the liver parenchyma. There are small variations – a third branch, a median vein does come from the portal vein in 15% of the time but there is less variation compared to the arterial system(109)(111).

The common hepatic duct normally is derived from a left and right hepatic duct. There is a lot of variation with the occasional trifurcations and accessory ducts seen. This has less of an impact for functional assessment as there is no need to identify the biliary system in dynamic imaging, but is an important consideration for the surgeon for planning their surgery(111).

The outflow of the liver is via 3 large veins: the left, middle and right hepatic veins. These 3 veins drain into the inferior vena cava superiorly to the liver and here blood re-joins the systemic circulation.

The functional right and left lobes are divided differently from the anatomical lobes. The functional division is the middle hepatic vein and the portal scissura known as Cantlie's line(112). The portal triad structures will divide at or above the hilum giving right and left branches; right and left hepatic arteries, portal veins and hepatic duct.

Before Couinaud's description, the liver's anatomy was subdivided into 4 sectors. The 3 Hepatic veins became the boundaries for this division. As a result, the right lobe was divided into 1) right posterior sector (lateral to the right hepatic vein) and 2) right anterior sector (between right and middle hepatic vein). The left lobe become 3) Left medial sector (between right and middle hepatic vein). The left lobe become 4) left lateral sector (medial to the left hepatic vein)(113).

The descriptions by Couinaud are the most important and clinically useful description of the internal anatomy of the liver. The arrangement and naming of the segments is based on the Arrondissement of Paris, named 1-8, moving from posteriorly, medially, anteriorly and laterally in a clockwise manner(48). These segments are divided according to the arterial supply of the segments: the hepatic artery will divide into a left and right, which then further divide into sectoral arteries, then into the segmental artery. Occlusion of this artery will demarcate the segment itself. The branches of the portal vein run in between the segments, so in the left liver, the division of the segment 2 and 3 is the left portal vein, the division between 5 and 8, and 6 and 7 is the right portal vein(114)

Table 4: Summary of the various descriptions of the liver anatomy

Couinaud Segment	Sector name	Gross Anatomical description
Segment 1	Left medial	Caudate Lobe (aka Spigel lobe)
Segment 2	Left Lateral	Left lobe
Segment 3	Left Lateral	Left Lobe
Segment 4	Left Medial	Quadrangle lobe(115)
Segment 5	Right anterior	Right lobe
Segment 6	Right posterior	Right lobe
Segment 7	Right posterior	Right lobe
Segment 8	Right anterior	Right lobe

Figure 1: A map of Paris, demonstrating the arrangement of the arrondissement

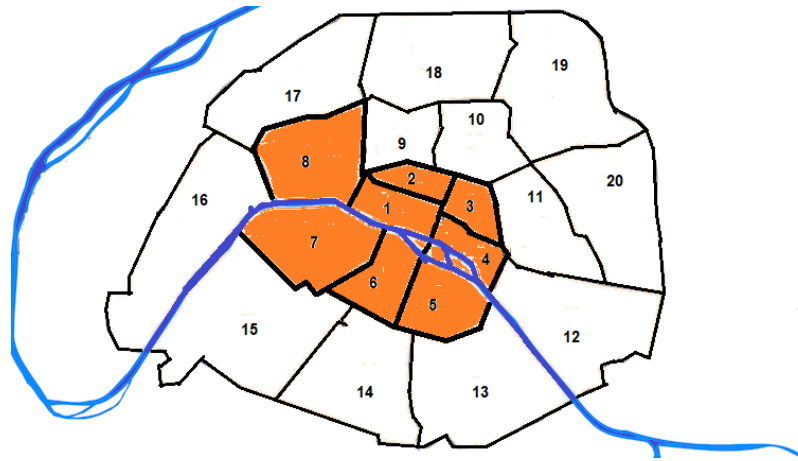
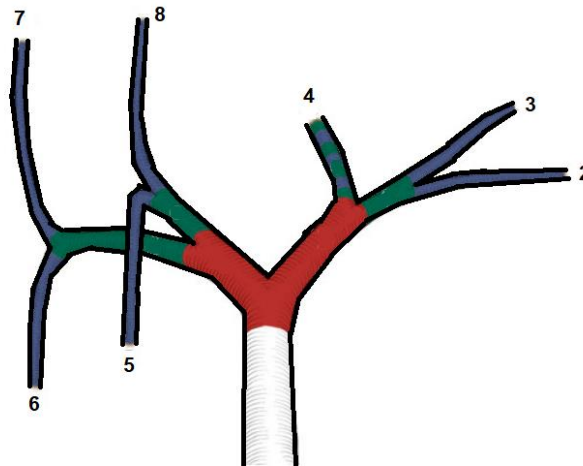


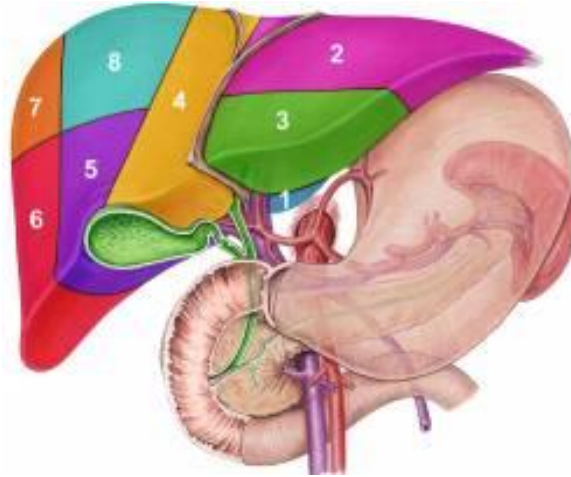
Figure 2 : The internal arterial supply of the liver (numbers corresponding to the segmental artery (adapted from Strasberg (47))



There have been alternative descriptions of the internal liver anatomy. Couinaud himself talked about a 9th segment located in the para-caval liver. He apparently changed his mind about its existence, but some consider it important when reporting on resection in this anatomical area(116)(117). A contemporary view felt the liver had 13 segments(116). Although Couinaud's description has been the most widely adopted, several authors have suggested sub-segmentation of each of these 8 segments into 2,3 or even 4 subsegments based on additional branches observed(118). This has particularly been noted in some of the larger segments like 4 (subtitled 4a and 4b) and 8 (subtitled 8d (for dorsal) and 8v (for ventral) (119)(120). The sub-segmentation if 4 into 4a and 4b is commonly used, however the rest of segments remain simply 1, 2, 3, 5, 6,

7 and 8. The Couinaud description of segments will be used for the remainder of the thesis.

Figure 3: Artistic impression of the liver segments used in Leeds Hospitals NHS Trust for patient information



By compressing the portal triad to each segment (the segmental artery, portal vein and bile duct) the occlusion of the vascular pedicle will de-mark out that segment – so allowing a segmental resection when the parenchyma at the watershed area can be divided(121).

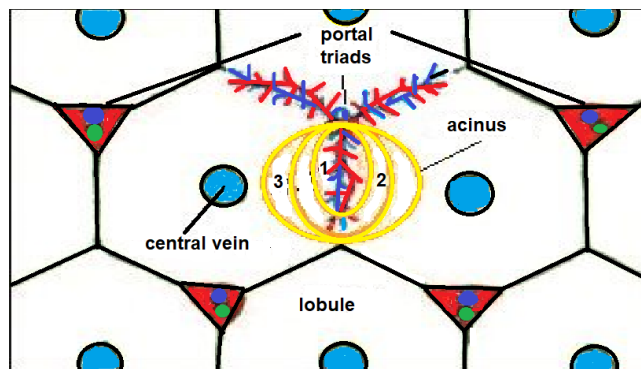
2.1.10 Microscopic Anatomy and Physiology

The liver has multiple functions; metabolic, endocrine, exocrine, and excretory. The liver is a highly vascular structure, receiving around 1.5L/min: around 80% is derived from the portal venous circulation and 20% from the hepatic arterial flow(89). 70% of the mass of the liver is made of hepatocytes.

Microscopically, the functional unit of the liver is the acinus where the portal triads (again the artery, portal vein and bile duct) lie surrounding the draining hepatic venule. These form hexagonal units known as a lobule. The space between the triad and the hepatic venule is described as periportal (zone 1), mid-portal (zone 2), and pericentral (zone 3) of the lobule. This has clinical importance as the pericentral zone is the most prone to necrosis due to its relatively poor oxygenation(105)(122). Sinusoids run from the portal triad to the central vein. Hepatocytes are polygonal and form cords one or two cells thick

within the units separated by sinusoids, with those hepatocytes running with the portal tracks on the edge of the lobule form a limiting plate. Part of the hepatocyte face the sinusoid, part form biliary canaliculi with adjacent cells, so have an interface to allow excretion into the hepatic venous system and the biliary system(123).

Figure 4: Histological structure of the microanatomy of the liver (from Fu(124))



Between the endothelial cells of the sinusoids and the hepatocytes lies the **space of Disse**(125). This space allows exchanges between the circulation and the liver tissue. It contains plasma and connective tissue forming a framework, and hepatic stellate cells (Ito cells). These stellate cells are myo-fibroblastic and allow constriction or relaxation and thus can control blood flow. Lymphatics also form in the space of Disse.

Bile canaliculi form between hepatocytes polygonal edges and form tortuous routes within the lobule, and form into structures known as the canals of Hering, which drain bile ductules, and then into a terminal duct(126).

The hepatocyte membrane allows bilirubin uptake into hepatic tissue from the bloodstream via transporter enzymes called organic anion transporting polypeptide (OATP) 1-B1 and B3(14). There, it is excreted into the biliary sinusoids via an active transporter multidrug resistant protein 2 (MRP2)(127). These transporters are key for the pharmacodynamics of the contrast agent Gadoteric Acid (or Gadoterate) as this utilises the same receptors for a large part of its excretion pathway(128).

2.1.11 Liver regeneration

The liver's capacity to regenerate and grow after partial resection had been noticed as early as 1879 when Tilmann noted enlargement of the remnant liver in animals after he excised part of the liver and subsequently carried out post mortems on these animals after their demise(129).

Normal healthy liver has an ability to restore its architecture, size, and function to a remarkable degree. It is a very complex process that is not fully understood. During normal regeneration, bile acids are rapidly upregulated, and up to 100 serum factors rapidly induce regeneration in the liver(130). IL-6 seems to be the most important, at least in rodent models(130). During regeneration, non-parenchymal cells; macrophages, hepatic stellate cells and liver sinusoidal endothelial cells signal to hepatocytes to enter mitosis. There are no fibrotic changes in these instances. What leads to arrest of the regeneration again is complex, but involves upregulation of suppressors of cytokine signalling, which act in a negative feedback loop, blocks IL-6 and initiates the termination of growth(130).

In **abnormal regeneration**, hepatocytes are increasingly senescent and unable to divide efficiently, the hepatic stellate cells are activated to myofibroblasts and excessive scar tissue inhibits regeneration. Excessive cellular debris inhibits efficient liver regeneration (131). Animal models do offer some explanation of mechanism, however clinical human studies of liver regeneration often have participants exposed to multiple liver injuries which does make translational research more challenging(132).

For healthy patients the liver will, after resection, regenerate to a volume comparable to the pre-operative liver, and functions can recover significantly(132). However, despite this regeneration, there are multiple factors that may impede regeneration in many individuals. Age(133) and various co-morbidities(6) may have significant impacts. This will be discussed further in the section on PHLF (chapter 2.2).

2.1.12 Current indications for Liver Resection Surgery

Liver resection is most commonly performed for malignant liver tumours; primary cancers such as hepatocellular carcinoma, cholangiocarcinoma and neuroendocrine tumours (NET), or secondaries from colorectal, breast, gastric, melanoma and extra-hepatic primary NET(134). There is an indication for palliative debulking of NET metastasis with improved symptoms and survival(135). Surgery for benign lesions is also performed(136). Often patients with benign liver lesions are younger and fitter than those with malignancy so will have better outcomes, and surgery is considered safe(137). Recently there has been an increase in the number of benign lesions undergoing surgery, which may be due to the availability of laparoscopic and minimally invasive surgery(82)(138).

The argument for resection of malignant disease is much more compelling as malignant liver tumours lead to significant morbidity and shortened lifespan, for HCC, untreated prognosis is ~20% 3 year survival(139)(140) and cholangiocarcinoma has a ~15% 5 year survival(141). The prognosis for patients with metastatic liver tumours does depend on the underlying aetiology, stage, and grade. Survival for patients with unresected/unresectable metastatic liver cancer is dismal at ~5% at 5 years(142). Well differentiated NET have much better prognosis with a 10 year survival of around 18%(143).

For benign disease it more controversial if to operate at all. Decision making is guided by the symptoms of the patient, weighed against the benefits and risks from surgery. Indications for surgery are taken on a case by case basis(136).

Table 5: Current indications for hepatic resection

Benign indications(137)				Malignant indications(43)	
Risk of Malignant transformation	Uncertain diagnosis	Symptomatic	Transplantation	Primary Cancers	Metastatic Cancer
Adenoma	Haemangioma	Cysts	Live liver donation(144)	Hepatocellular Carcinoma	Colorectal
Cystadenoma	Focal nodular hyperplasia			Intrahepatic Cholangio-carcinoma	Stromal
	Cysts			Sarcoma	Neuroendocrine
		Clear Cell carcinoma	Cell carcinoma	Breast	
Melanoma					
Locally advanced colonic					
Hilar Cholangio-carcinoma					
				Gallbladder	
				Adrenal	

2.1.13 Pathogenesis of Colorectal Liver Metastasis

Colorectal cancer is the fourth most common cancer and the second most lethal(145). Up to 50% of patients with colorectal cancer will develop colorectal liver metastasis (CRLM). Liver resection of CRLM is the most common indication for liver resection in the UK, accounting for 60-70% of liver resections in Western Countries(146). For this reason, it has been chosen as the main population for study in this thesis due to the significant burden of work, the recruitment timetable, and relative ease at modification of DGE-MRI protocols for patients with CRLM.

Colorectal cancer develops from an adenoma to carcinoma sequence in the vast majority of cases(147). The process for this formation is complex, but in simple terms involves the '*multi-hit hypothesis*': corruption of cellular mechanisms to promote cell immortality and turning off the apoptosis controls, the downregulation of tumour suppressor genes (such as adenomatous polyposis coli – APC and p53) and the activation of oncogenes such as Kirsten rat sarcoma viral oncogene homolog (K-Ras)(147).

The liver itself is a frequent site of metastatic disease and seems to be susceptible for metastases to establish themselves, particularly from colorectal adenocarcinoma.

The mechanism of metastasis is a multiple step process, in which a neoplastic cell or cells must invade into either lymphatic or capillaries, embolise systemically to reach the

site of metastasis, become adherent within the tissue, extravasate into the metastatic site and proliferate(148).

Specifically for colorectal cancer, the liver is a 'target organ' and often the sole location of metastasis(149). The anatomy of the portal venous system allows metastatic cells from the colon to enter the portal venous system's blood stream, spreading into the microvasculature of the liver. Sinusoids appear to allow rapid movement of metastatic cells from the intravascular space to beyond the basement membranes with alarming speed (<6h in experimental models) compared to movement of metastatic cells in other organs (followed next in speed by lung tissue at ~11h – the second most common site of metastasis of colorectal cancer)(150). Indeed the microstructure of the liver seems to 'help' the metastasis enter tissue(151); as the liver's basement membrane is less well defined as other organs; it seems to disintegrate upon exposure and this disintegration leads to proliferation of endothelial cells, and endothelialisation of tumour cells – promoting early angiogenesis and hence metastatic spread.

The developing metastases may not be apparent at the time of diagnosis of the primary colorectal cancer, the phenomenon of metachronous (those developing at a later date) metastasis is frequently observed(152) and for this reason a 5-year surveillance follow up with CT of the thorax, abdomen and pelvis (CT TAP), tumour markers (commonly carcinoembryonic antigen - CEA) and clinical review for symptoms is recommended(153).

2.1.14 Current pre-operative investigations for Liver Metastasis resection

The decision to operate on CRLM comes down to achieving a curative resection, preferably with clear resection margins (R0). Around 30% of patients with CRLM will have resectable and curative liver metastases(154). There are options available to widen the scope and increase number of patients who have resectable disease such as neoadjuvant chemotherapy with the aim to reduce tumour bulk and volume(155).

Adjuvant chemotherapy after R1⁸ resection conveys no survival benefit and therefore is not indicated(156). The recurrence rate remains present for a significant period of time, and patients will need to be followed up years after their surgery to detect late recurrence(157). In Leeds, current practice is for a 10-year follow up, due to cases of very late recurrent metastasis identified up to this time.

Detailed guidelines exist for the multi-disciplinary approach to patient selection for surgery, chemotherapy guides and imaging strategies(142).

For CRLM to be considered operable, they must fulfil certain criteria. These are summarised in the table below based on technical and the underlying biology of the cancer (table 6).

Table 6: Technical contraindications to liver resection for CRLM(158)

	Technical	Oncological
Absolute	Absolute Impossibility of R0 resection with $\geq 30\%$ liver remnant	Concomitant extrahepatic disease (unresectable)
	Presence of unresectable extrahepatic disease	
Relative	R0 resection possible only with complex procedure (portal vein embolisation, two-stage hepatectomy, hepatectomy combined with ablation)	Number of lesions ≥ 5
	R1 resection	Tumour progression

After the technical aspects of the surgery have been considered, patients' fitness for surgery is assessed. Even if a patient has resectable liver disease they would need to withstand the burden and risk of the anaesthetic, blood loss and physiological derangements that are unavoidable in surgery. This could be done by clinical review and decision from a senior surgeon, however different scoring systems have been developed and are utilised to try and form a more objective and translatable method of patient selection.

⁸ This is macroscopically cleared tumour margins but microscopic involvement

2.1.15 Patient factors and fitness for surgery

Performance Status

Performance status is a widely adopted method of a patient's fitness assessment and has a prognostic impact. It is simple and helpful in screening for fitness for both surgery and for chemotherapy or radiotherapy use(159). It is a subjective assessment that can lead to interobserver bias(160). In current practice, a patient would only be deemed fit enough for elective cancer resection surgery if their performance status is 0 or 1, as any lower performance would reflect reduced physiological reserve.

Table 7: Performance Status(161)

Grade	Explanation of activity
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead ⁹

ASA

American Society of Anaesthesiology's grading system (ASA)(162) gives a good overall view of a patient's physiological reserve and is proven to have a correlation between increased score and increasing morbidity and mortality(163)(164). It is entirely subjective and there will inevitably be interobserver variability as with performance status. It is a useful screening tool that is quick, easily understood and implemented(165). Most candidates for surgery would be ASA 2 (or less commonly ASA 3) as the cancer itself counts towards their systemic disease, and when above 2 the patients physiology may be sufficiently impaired to prohibit major surgery.

⁹ Very unlikely to be used

Table 8: ASA

ASA	Description
1	A normal healthy patient
2	A patient with mild systemic disease
3	A patient with severe systemic disease
4	A patient with severe systemic disease that is a constant threat to life
5	A moribund patient who is not expected to survive

Frailty scoring

Frailty scoring is a more recent introduction. Robinson and colleagues combined seven measures that have been used independently in terms of frailty by Care of the Elderly physicians. They defined frailty as non-frail (0-1), pre-frail (2-3) and frail (≥ 4). They found the higher the patient's frailty, the more complications they developed(164). It does not seem to have yet been applied to liver resection surgery but includes major intra-abdominal and cardiac operations which both have a significant physiological insult as liver surgery. As a result they could theoretically be applied to liver surgical patients in the future(166). At present is not commonly currently used in patient selection in Leeds.

Table 9: Robinson's frailty scoring(166)

Test	Method	Abnormal result
Timed 'Up-and Go'(166)	The time needed to stand up from a chair, walk 10 feet, return to the chair, and sit	≥ 15 seconds.
Katz Score (167)	independence of activities of daily living (bathing, dressing, transferring, walking, toileting, and feeding)	dependence in one or more activity of daily living.
Mini-Cog (168)	paired three-item recall and clock draw task	score ≤ 3 .
Charlson Index (169)	19 categories of co-morbidities weighted on their risk of one-year mortality	score ≥ 3 .
Anaemia of chronic disease (170)		Haematocrit $< 35\%$.
Poor nutrition (171)		serum albumin level below 3.4 g/dL.
Geriatric syndrome of falls(172)	Number of falls in prior six-months	≥ 1 fall in the six-months prior

CPEX

Cardio-Pulmonary Exercise Testing (CPEX) has been employed pre-operatively for many major surgeries; cardiac, lung and intra-abdominal surgeries(173).

This involves the patient using an exercise bicycle. They have a spirometry test during a 3-min rest period, followed by 3 min of freewheeling and then pedalling against a ramped resistance/workload to determine the patient's anaerobic threshold (VO_2 ml/kg/min) by measuring expired CO_2 . It has been used for risk stratification for patients undergoing anaesthetic for major surgery. Specifically when investigated in liver surgery patients, Kasivisvanathan and colleagues determined a cut-off of <10.2 ml/kg/min as having an increased risk of morbidity development post-operatively(174). It has yet to become established practice in patients considered for liver resection in Leeds, unless there is a specific concern or indication raised by the anaesthetic team, and so no patients included in this thesis routinely underwent this test.

Physiology scoring systems

Other physiology scores such as APACHE III (175) and P-POSSUM(176) are detailed scoring systems which are more commonly used for emergency general abdominal surgery(177) but neither have an established role. P-POSSUM is not effective for predicting morbidity or mortality(176) and APACHE III is calculated post-operatively and so cannot be used for pre-operative risk stratification(176).

The combination of patient fitness and technical and oncologically resectable disease all need to be satisfied for a patient to be deemed suitable for surgery. At the time of recruitment for the studies included in this thesis, preassessment modalities utilised were ASA and performance status. CPEX was rarely performed and frailty assessment took place in an outpatient clinic review rather than formal frailty scoring.

Such pre-operative assessments cannot effectively exclude all patients at risk from surgery, which indicates that alternative risk stratification methods are required in liver surgery to maximise patient safety.

2.1.16 Liver resection technique and hemihepatectomy

To resect a segment of liver, the parenchyma needs to be divided with excision or occlusion of the vascular inflow and outflow as much as possible to minimise blood loss.

A major liver resection is defined as excision of 3 or more segments in a single operation(47). Most liver resections are currently performed via an open/laparotomy technique with an incision in the right upper quadrant and a midline extension – often termed a ‘reverse L’. More recently, laparoscopy is utilised(121), which has some promising improvements in early patient recovery(178) A currently ongoing randomised trial, ORANGE II PLUS, is comparing outcomes of laparoscopic versus open right and left hepatectomy is expected to report in early 2020(179). At the time of this study, all major liver resections were done via laparotomy in Leeds.

Figure 5: Intra-operative picture of a right hepatectomy in progress



For a right hepatectomy, one commonly used method involves an incision (called a hepatotomy) into segment 4 in the gallbladder fossa, then a second hepatotomy made inferior to the main right portal branch near the caudate lobe. A blunt clamp is then passed superior from the hepatotomy in segment 4 through liver parenchyma and then exiting via the inferior hepatotomy – surrounding the right portal triad, staying outside the Glissonian capsule as previously described by Launois(180)(181). A vascular clamp is

used to compress this tissue and right portal pedicle allowing for demarcation of the right lobe. Once this is confirmed, the pedicle can be ligated or stapled.

For a left hepatectomy, the hilar plate is elevated, and the left portal pedicle is identified in the umbilical fissure. A hepatotomy is made at the level of lowering the hilar plate and a second hepatotomy in the back of segment II. The same clamp should be used to come around this pedicle with subsequent vascular clamping to check for demarcation and then a vascular stapler to transect the left portal pedicle(114)(182).

For segmental liver resection (excision of isolated segments) the inflowing portal triad can be found within the liver parenchyma, carefully clamped to allow demarcation and subsequent dissection via the preferred technique (in Leeds it is the CUSA) to minimise bleeding and the segments triad is ligated or stapled to complete the segmental resection(183)(184).

2.2 Complications of Surgery

All surgery carries a risk of complications. Surgical complications traditionally were classified in terms of if they were local to the site of surgery, or systemic, and related to their time, immediate, early, or late. Historical descriptions were subjective and variable – one surgeon’s complication could be another’s variation on normal. Since the early 1990s Clavien and colleagues have worked to create a unifying scheme of the description of complications, first for cholecystectomy(185), then liver transplants, before applying their method to all surgery – the Clavien-Dindo classification(186). This has been widely adopted in reporting across multiple surgical subspecialties and is currently considered the most robust reporting method and the current gold standard for reporting complications(187)(188)(189).

Table 10: Clavien-Dindo Classification of Surgical Complications(186)

Grade	Definition
I	Deviation from normal postoperative course without need for intervention (including antiemetics, antipyretics, analgesics, diuretics, IV fluid, Physio, local wound management)
II	Pharmacological intervention
III	Surgical/Endoscopic/Radiological intervention
a	No GA
b	GA
IV	Life-threatening complications needing ICU management
a	Single organ dysfunction
b	Multiorgan dysfunction
V	Death
Suffix d	Prolonged disability after discharge (e.g. cardiac insufficiency post MI, faecal incontinence post injury of nerves, stroke etc.

2.2.1 Complications of Liver Surgery and Post Hepatectomy Liver Failure

Other than the general risks of surgery as discussed above, the resection of liver leads to a reduction of functional liver mass. If extreme, this can lead to the development of **Post Hepatectomy Liver Failure (PHLF)**. This has been recognised phenomena for many decades. The two most commonly recognised risk factors first identified were background liver disease, and extent of resection.

2.2.2 Background liver disease and PHLF

PHLF leads to an increased complication rate and mortality in patients undergoing surgery for HCC who have a background of cirrhosis or chronic cholestasis. This population had higher morbidity and mortality compared to the same degree of resection on patients with no liver disease(190)(191). Jaundice due to other pathology at the time of surgery was found to have a poor outcome(146)(192). The underlying pathology of malignant disease over benign disease was felt to increase risk of both morbidity or mortality(191). Cirrhosis itself increases the risk of infection, due to impaired endotoxin clearance and increased TNF α release(193). The Kupffer cells act as gatekeepers for haematogenous bacterial infection(194) and the dysfunction of the reticuloendothelial system seen in cirrhosis combine to impair immunity(195).

2.2.3 Future Liver Remnant

The FLR is the predicted volume of the remaining liver after surgical resection. It can be described either in terms of remnant segments, or % of remnant volume.

For example, a patient having a right hepatectomy will have segments 5, 6, 7 and 8 resected. The FLR will be segments 1, 2, 3, and 4. If you calculate the volume of the whole liver, and then subtract the volume of the resected segments it will give a percentage which is the FLR %. Segments vary in size from person to person, so the number of segments in the FLR does not always correspond to the volume, and more commonly FLR is described as a percentage rather than number of remnant segments. If the FLR is deemed too small after surgery the term **small for size** is used, like the problem encountered in liver transplantation when the graft size is inadequate(3).

2.2.4 Extent of resection and PHLF

Major resection surgery is known to be associated with increased incidence of complications, which increases with a smaller FLR(196). Early resection surgeons adopted a dogmatic approach to leave at least one third of the liver as the FLR – although this size was not scientifically determined. It was based on the experience of other

surgeons' reported outcomes. Studies from the late 1990s described the critical remnant size of the FLR as the volume at around 20-30% in non-cirrhotic livers(197)(198). Schindl and colleagues determined a critical threshold of FLR determined by CT volumetry in patients with normal pre-operative liver tests of 26.6% for patients to avoid development of PHLF(4).

For those patients with cirrhosis, the FLR is always considered to be much higher, a minimum of 40% FLR has been advocated by some authors(199)(200) however such estimations are complex. A patient-centred approach assessing fitness, understanding potential prognosis for their disease and a detailed multi-disciplinary input is always required.

2.2.5 PHLF in CRLM resection

Liver failure has been reported in patients who had major resection for CRLM since the 1990s(201). In their study, Laurent and colleagues(202) reported PHLF after CRLM resections was seen worsen the short term outcome for morbidity and mortality. Such patients also had a reduced 5-year survival rate; which the authors suggested could be due to the increased regeneration response allowing neoplastic promotion and increased recurrence(203).

2.2.6 Different definitions of PHLF

At least 56 descriptions and definitions of PHLF have been described, as collated in the ISGLS consensus summary(5). In the interest of brevity, only selected definitions will be discussed which have been commonly used in published reports. Most use the same biochemical markers in their definitions, with some extra clinical parameters added. The shifting definitions are due to progress and evolution of criteria, with multiple incremental changes as understanding of the underlying pathophysiology has improved over time.

Early studies use clinical biochemical markers of synthetic function with coagulation factors (often as a prothrombin time (PT) or international normalised ratio (INR)) and excretory function of serum bilirubin(197). Factors such as albumin levels which can be

affected by many factors have been demonstrated to have poor correlation with outcomes and as a result are not often used in the context of surgical outcomes(204). Transaminases such as Alanine Transferase (ALT) and Aspartate Transferase (AST) are used as markers of hepatocellular damage and are released on cellular injury into the circulation. Despite this, they seem to have poor correlation with outcome post-operatively and are considered by many to have no prognostic value(204)(205). A report by Olthof and colleagues seems to contradict the received wisdom and does find raised transaminases in the first 24h to have a correlation with a worse outcome, particularly with perihilar cholangiocarcinoma patients(206). However, no scoring system of PHLF utilises them and overall, they are not used in this thesis in post-operative assessment.

Hemming and colleagues described one of the earliest definitions of PHLF in 2003 which they defined as: '*development of encephalopathy, ascites requiring sustained diuretics or paracentesis, or coagulopathy unresponsive to vitamin K requiring FFP after the first 24 hours postresection*'(207). Although this clearly does represent a non-functioning liver, it is quite a serious condition for a patient, and would correspond to a Child's C status patient. It would eliminate patients with less severe, but definite liver dysfunction. Also, the time of 24 hours was selected arbitrarily and may be too short a period of time to fully establish the clinical picture in terms of liver function. The same authors later revised their definition to include a bilirubin greater than 10 mg/dL or refractory ascites that persisted longer than 10 days post resection(208). This was further modified by Vauthey into the more precise: '*Bilirubin >10 mg/dL (unrelated to biliary obstruction or leak) and/or INR >2 more than 2 days after resection and/or clinically significant ascites/hepatic encephalopathy*'(208)¹⁰. They used the term 'hepatic insufficiency' – a synonym of PHLF that is often used. Presence of ascites post-operatively, was

¹⁰ It is worth noting there is a difference in how biochemical values are reported in US and European studies. Most American studies use the mg/dL, whereas the rest use the SI units $\mu\text{mol/l}$. For conversion, mg/dL needs to be multiplied by 17.1 (e.g. 10mg/dL = 171 $\mu\text{mol/L}$) or alternatively to convert from $\mu\text{mol/L}$ it should be multiplied by 0.059(208).

subsequently shown not to be associated with degree of failure, or morbidity or mortality and was not used in following definitions(209).

Schindl and colleagues, in the same paper as that which determined a critical FLR volume, devised a scoring system based on their study of 104 patients(4). This was based on the association of elevated bilirubin, prolonged PT, evidence of ischaemia (measured by lactate) and encephalopathy observed in PHLF patients(79)(146)(209). Lactate is often used as a marker of tissue ischaemia(210). The authors reported a good correlation between their liver dysfunction scores and % volume of FLR. This seems to be the first study to consider liver dysfunction as a spectrum and divided their results ordinally rather than a nominally as in the previous literature.

Table 11: Schindl's PHLF score

Score	0	1	2
Bilirubin (mmol/L)	<20	21-60	>60
PT (seconds above normal)	<4	4-6	>6
Lactate	<1.5	1.6-3.5	>3.5
Encephalopathy	0	1-2	3-4
Severity (the four domains above are added together to give a sum value – this then stratifies patients into 4 groups range is 0 to 8)			
None	Mild	Moderate	Severe
0	1-2	3-4	>4

Balzen and colleagues described the '50-50' criteria. This was the most commonly and robust method used for 6-7 years(211) until the current ISGLS definition was adopted. It used bilirubin and PT as previous studies had done and defined PHLF as:

$$PHLF = \text{Prothrombin Time} > 50\% \text{ of baseline and Serum Bilirubin} \\ > 50\mu\text{mol/L on Day 5 post operatively.}$$

This was devised based on the observation on the trend of the kinetics of both bilirubin and PT over the first week of surgery. The authors did select their cut-off values arbitrarily but were based on the reported values in Child Pugh Scoring (CPS) as measures of

impaired excretory function with bilirubin, and impaired synthetic function with PT. They didn't use CPS in this study as they felt it would be biased in the post-operative period. As they investigated the trend over time of these two parameters, elevated bilirubin on day 5 had a 15% mortality, and elevated PT had a 33% mortality. With persistent elevation of both bilirubin and PT on day 5 had a 59% mortality, whereas both elevated on day one had a 14% mortality. They conclude that early rises in bilirubin and PT particularly between day 1 and 3 are representative of a normal physiological response. It would be in this phase that massive regeneration of the liver is starting its process, and enough regeneration has occurred by day 5. Those patients with inadequate regeneration by this would seem to be those who will not regenerate sufficiently in time, and by consequence have persistent liver dysfunction and PHLF.

Mullen and colleagues determined a critical post-operative value in their series of over 1000 resections of bilirubin alone $>7\text{mg/dL}$ ($\sim 120\mu\text{mol/L}$) as a defined PHLF (they used the term 'insufficiency') and reported strong correlation with adverse outcome. This value had high sensitivity and specificity of 93% and 94% respectively. This was indeed stronger than prolonged PT (they used $\text{INR} >2$) independently or even in combination – sensitivities and specificities around 70-75%; and was better than the '50-50 criteria', at least in their population(1). Although this is a robust study demonstrating an important threshold, it again only represents the extreme of patients who develop PHLF – severe cases who die or are affected with complications, and such a value could not be used for the mild or moderate cases that will be more commonly observed.

Rahman and colleagues examined post-resection C-reactive protein (CRP) as a biomarker for PHLF. The authors reported that a CRP of less than 32g/dL on day one post-operatively was associated with PHLF and increased mortality. They concluded CRP concentration reflected the synthetic capacity of the remnant liver and low levels represented both a reduced synthetic function, and also an impaired metabolic role for regeneration(212).

Many of these studies detected major biochemical parameter changes and the ones associated with poor outcome, every publication used their own system. As an answer to this, the International Study Group of Liver Surgery (ISGLS) performed a systematic review of the literature and highlighted papers with the most robust results (which were those discussed above) and determined a consensus definition, and classification of severity.

“A postoperatively acquired deterioration in the ability of the liver (in patients with normal and abnormal liver function) to maintain its synthetic, excretory, and detoxifying functions, characterized by an increased INR (or need of clotting factors to maintain normal INR) and hyperbilirubinemia (according to the normal cut-off levels defined by the local laboratory) on or after postoperative day 5. If INR or serum bilirubin concentration is increased preoperatively, PHLF is defined by an increasing INR (decreasing prothrombin time) and increasing serum bilirubin concentration on or after postoperative day 5 (compared with the values of the previous day). Other obvious causes for the observed biochemical and clinical alterations such as biliary obstruction should be ruled out”(5).

Table 12: ISGLS definition of PHLF

Grade A	PHLF resulting in abnormal laboratory parameters but requiring no change in the clinical management of the patient.
Grade B	PHLF resulting in a deviation from the regular clinical management but manageable without invasive treatment.
Grade C	PHLF resulting in a deviation from the regular clinical management and requiring invasive treatment.

This definition has, as a result become the most frequently reported description of PHLF since 2011 in subsequent publications (6) (10) (83) (213) (214) (215) (216) (217). It will therefore be the definition that is used throughout the rest of this thesis.

2.2.7 Risk factors for PHLF

Risks for PHLF are multifactorial and there is not a complete understanding of which are the most important, or how much they contribute a risk to PHLF development. Most identified risk factors have been identified as a secondary objective as part of large retrospective analyses based on either large databases or single centre studies. There is often a large variation of resection size and therefore subsequent FLR size that could be confounding results. Although each of the factors discussed below seem plausible to be contributing to PHLF development, and would satisfy Bradford-Hill's criteria for association and causation¹¹(218), there is a requirement for more evidence to understand the true impact of contributing factors on the pathogenesis of PHLF. A large number of risk factors were identified in Tzeng's large retrospective database study involving 894 elderly patients; their findings are discussed below(219).

2.2.8 Pre-operative risk

Diabetes

Diabetes is a common endocrine disease that leads to hyperglycaemia, reduced cellular metabolism of glucose, and can lead to organ dysfunction via multiple mechanisms. It seems to be a risk factor for increased mortality and morbidity in patients undergoing liver resection. Diabetic patients have increased risk of non-alcoholic fatty liver disease (NALFD)(220). Patients requiring insulin have been reported to have higher operative times, transfusion rates and prolonged ventilation requirements after liver surgery – all which are independent risks for complications. Tablet controlled diabetes, however do not seem to have any particular risk of these factors, which Gedaly and colleagues believe is due to tablet controlled diabetic patients having better glycaemic control, and their diabetes less severe than those requiring insulin(221). Wiggins and colleagues found that diabetic patients had three times increased 90-day mortality and doubled increased risk of developing acute kidney injury (AKI). They did not comment on any

¹¹ Bradford-Hill's criteria to show association is due to causation were strong strength of association, consistency between studies, specific exposure leading to outcome, correct time association, evidence of a exposure/response biological gradient, and plausibility of explanation.

association between diabetes and PHLF specifically, but given its association with increased mortality, it can be considered as contributing to a PHLF syndrome – as death would count as PHLF in its severest form(222).

Renal insufficiency

Wiggins and colleagues also reported development of renal insufficiency increases 90-day mortality from 2.7% in patients with no immediate complications to 10%; as risky as PHLF itself. When AKI and PHLF are both present, mortality leaped from 10% to 45%(222). Regarding chronic kidney disease (CKD), there doesn't seem to be any prior clear studies into its effect on liver surgery specifically, but it is mentioned as a risk factor for PHLF in some publications(146). CKD and AKI are felt to be highly intertwined with each other, and each is a risk factor for the others development(223). It seems plausible given the associated outcomes that CKD should be viewed with concern for PHLF, even if no study until present had examined this independently.

Obesity

Obesity is the pandemic of our times, with over a third of the population in Western countries, such as the USA, being obese(224). There have been conflicting results regarding obesity and surgery; with evidence that complications such as wound infections are more common in obese patients(225) however there is compelling evidence that obesity itself does not increase risks of general surgical operations(226). Liver surgery, however does present a different case; as obese patients are more likely to have steatosis of the liver(227) and steatosis seems to have a deleterious outcome on liver surgery(228) it can be extrapolated that obesity is a risk factor. Certainly, obese patients undergoing liver resection have longer operations, more transfusions and longer hospital admission than non-obese patients(221).

Chemotherapy

Pre-operative use of chemotherapy is commonly used in metastatic disease and for CRLM. It can be used for regression and reduction of tumour burden in the liver(142)(155). Many commonly used agents for CRLM are associated with liver injury

and chemotherapy induced liver injury (CILI) (see table 13 below). Development CILI is a risk factor for PHLF due to the chemotherapy agent's injury to liver parenchyma, sinusoidal dilatation (termed sinusoidal obstructive syndrome or SOS), atrophy of hepatocytes, and/or hepatocytic necrosis. This leads to impaired function both in the short term, and potential development of chronic liver disease(229)(230)(231). If liver injury is seen, reflected in elevated bilirubin beyond normal reference ranges (over 20µmol/L), it will lead to a delay in operation until any recover is seen, or even render the patient inoperable, or reduce the extent of resection possible(232)(233)(234). Most centres including Leeds will always delay surgery for at least 6 weeks following chemotherapy administration to hopefully allow time for the liver to recover from any actual or potential CILI.

Table 13 - Commonly used chemotherapy agents in CRLM(142)

Chemotherapy agent	Associated with CILI
5-Fluorouracil (5-FU)	Yes(142)
Capecitabine	no(232)
Irinotecan	yes(231)
Oxaliplatin	yes(231) – associated with SOS
Trifluridine and Tipiracil	no(233)

Hepatitis, fibrosis, and cirrhosis

A significant amount of resection is for primary cancers, particularly in East Asian countries. This is often related to the development of cirrhosis due to viral hepatitis. In particular Hepatitis B(235)(236) and C(237)(238) are strongly associated with cirrhosis and the subsequent development of HCC requiring a liver resection(239). As cirrhosis is defined by the development of liver dysfunction in both synthetic or excretory roles, it is evident that its presence would have increased risk of PHLF as such patients are already in a clinical state of liver dysfunction, its risks have been well documented(1)(3)(240). These patients will have impaired excretion and may be jaundiced, and have impaired synthesis, and may be coagulopathic. Pre-operative hyperbilirubinaemia in itself (either in absence or presence of cirrhosis) was found to have six-fold increased risk of death after liver resection(241). As a result, any obstructive biliopathy (such as tumour

associated bile duct obstruction) is generally relieved prior to surgery because of this increased risk.

It is possible for patients with cirrhosis to develop CRLM and all patients are screened for it prior to surgery(242). Consumptive thrombocytopenia due to the associated splenomegaly seen in cirrhosis (due to portal hypertension and venous engorgement of the spleen)(229) and coagulopathy before surgery is associated with an increased relative risk of death of 2.7 times(219).¹²

The risk of surgery on patients with fibrotic liver disease, which is a precursor to cirrhosis development, can increase risk of PHLF development due to fibrosis reducing the rate of liver regeneration(190)(228)(243)(244).

Malnutrition

Malnutrition can refer to either undernutrition which leads to wasting and micronutrient deficiency, or overnutrition – obesity which has been discussed above. In this section, the focus is on undernutrition: weight loss >10% was associated with a 3 times increased mortality risk (5% vs 15%) in the elderly(219). In the UK, the malnutrition universal screening tool (MUST) score has been adapted in almost every hospital as is regarded as the current gold standard for nutrition screening(245). High MUST scores are associated with poorer outcomes in the national emergency laparotomy audit (NELA) data on emergency surgery(177). It is worth noting there is a proposed study upcoming – the NURIMAS study that is to investigate malnutrition and liver surgical candidates prospectively(246).

Lung disease

Formally diagnosed chronic obstructive pulmonary disease (COPD) increases risk to 3 times that of non-COPD patients (219). Undiagnosed lung disease (evidence of dyspnoea on minimal exertion) and smoking is associated with 1.7 times increased risk

¹² This does not include patients who are deliberately anticoagulated

of mortality(241). This association ties into the results of CPEX testing discussed in the section on pre-operative risk stratification(174).

Age

Age is a contentious risk factor for surgery in general and also in liver surgery. Historically patients of advancing age, termed 'geriatric' patients, were excluded from being considered for surgery, a form of ageist discrimination. This has improved recently, but no doubt still exists to some degree(247). In the UK, the NHS has mandated there is no age discrimination in their charter(248). There is limited evidence on ageing and surgery, due to elderly patients being excluded from high quality research studies and only reported in anecdotal or limited series(249).

It is known that our population is getting older as people are living longer. Following efforts to tackle age discrimination and investigate outcomes of elderly patients, multiple studies investigated age and outcomes, and there is evidence on both sides of the argument, some saying the risk is much higher than the younger population, some stating risk is acceptable for oncological surgery and as beneficial as for the younger population. Others say risk remains significantly high and as a result careful patient selection is required. A summary of such publications is found in table 14.

The overall number of patients who are elderly and have surgery is now higher than ever. Several of the later published studies below rely on large national databases of disease outcomes, morbidity, and mortality. Such databases are highly useful and important for understanding outcomes when there are relatively few cases of procedures done in limited centres, but do have their drawbacks, namely the possibility of missing values, incorrectly entered data, curse of dimensionality, and lack of bias control. Such databases cannot test causality, resulting from residual confounding and reverse causation effects, and so such studies should be interpreted carefully with vigilance(250).

One issue with many reports is the use of arbitrary cut-off ages. Over 65, over 70 and over 75 are frequently given as the nominal binary representation between 'old' and

young' which muddies the ability to compare different studies. Study heterogeneity leads to difficulty in translation, with 20-year variation in the various studies' definition of elderly. If age is to be investigated as a risk factor, a more quantitative continuous approach, rather than discrete analysis is required to understand its impact.

Table 14: Comparison of the effect of age on surgical outcome

	Type of Surgery	Elderly definition (age)	Number of participants	Reported Morbidity %	Reported mortality %
Authors conclusion of acceptable risk of ageing					
Dunlop(251)	All	>65	8,899	8.3	4.1
Leung(252)	Non-cardiac	>70	544	11.2	3.7
Adam(253)	Oesophageal	>80	31	22.5	16
Patel (Meta-analysis) (254)	Colorectal	65-74	11,625	19	1.8x ¹³
		75-84	9,232	23	3.2x
		>85	2,735	25	6.2x
Stroumbakis(255)	Urology	>80	44	51	4.5
Susini(256)	Gynaecology	>70	213	17	2.8
Djokavic(257)	All	80	500	Not reported	6.2
Authors consider increased risk					
Liu(258)	All	80	367	25	4.6
Massarweh(259)	Intra-abdominal	65-69	29,705	14.6	2.5
		70-74	27,094	16.1	3.8
		75-79	21,032	18.8	6
		80-84	13,855	19.9	8.1
		85-89	6,851	22.6	12.6
		>90	2,781	22.7	16.7
Marusch(260)	Colorectal	>80	2,932	43.5	8

Due to the findings of such studies, surgery in the older population is considered acceptable, but with increased risks of morbidity and mortality and patients will need to be counselled carefully so they can make an informed decision if they wish to undergo surgery. The use of the previously discussed adjuncts of pre-operative assessment are highly important to be able to appropriately convey risk.

Liver surgery represents a separate issue. Tzeng and colleagues reported that older patients have reduced physiological reserve and thus a reduced speed of hypertrophy. They reported that older patients had increased morbidity (23.9% vs. 18.4%); more than

¹³ This study did not report the actual mortality, just the increased relative risk the <65-year-old group

double the mortality (4.8% vs. 2%), and for patients who developed a complication they were twice as likely to die than younger patients (20% vs 10%)(219).

From a physiological point of view, it has been demonstrated previously that older people have a slower rate of liver regeneration(133). Older patients have a higher baseline bilirubin level than younger people, which may reflect a global reduction of excretory function(261). Cieslak and colleagues demonstrated impaired function in older patients using their Technetium-99m-mebrofenin study(262). Age can be considered a **risk factor** for surgical complications. However, many studies have reported safe outcomes in elderly patients (see table 28), and so increasing numbers of patients are being considered for surgery. The difficulty arises due to knowing the extent of liver resection. A patient who has a small metastatectomy with a couple of millimetres of liver parenchyma surrounding and a FLR of >95% will not have to endure the physiological insult of a right hepatectomy where the FLR is ~40%. Many of the studies reported include all sizes of resection, minor and major. This makes conclusions much more difficult to translate to major resections in the elderly, as a major resection and a minor resection may well behave very differently in the post-operative period.

The uncertainty of the true impact of ageing, and of other risk factors on the outcomes of liver surgery leads to the study to address these highlighted issues, described in chapter 3, which investigates age as a primary risk factor. This included only major resections and examines age to determine if there is any increased risk of PHLF, and if so, at which age could be considered a threshold point, and to ascertain the outcomes related to older patients and development of PHLF.

2.2.9 Intraoperative risks

Blood loss and transfusion

Intraoperative transfusion rates in patients who have liver resection is a marker of operative complexity – certainly it is seen more in major resections due to large vessel ligation and the extent of parenchymal division and injury. Transfusion is used when

there is clear blood loss, which will lead to intra-operative hypotension. Menon and colleagues found a hazard ratio of 2.4x risk to life when >3 units were transfused(263). Tranchart found patients with intra-operative transfusion during liver surgery had a post-operative complication rate of 33% vs 2% for patients not requiring transfusion (264).

Hypotension in surgery can lead to organ ischaemia which can adversely impact on the liver's regenerative ability(130). It may induce an effect like 'hepatic shock' or ischaemic hepatitis, whereby prolonged hypoperfusion causes ischaemic hepatocyte necrosis in the pericentral area (zone 3) - centrilobular hepatic necrosis. Interestingly this leads to marked transaminase increases initially rather than raised bilirubin, so cannot solely explain the features of PHLF, but certainly hypoperfusion is best avoided in surgery(265)(266).

Massive transfusion reactions have only recently been examined for their physiological effects, but it is now known than multiple transfusions can in themselves make a patient coagulopathic, acidotic, hypocalcaemic, hyperkalaemic and hypothermic(267) – all that, if uncorrected leads to continual blood loss unless reversed. This is essentially the 'triad of death' that has been observed in major trauma patients(268). Jin and colleagues felt that the metabolic effects of transfusion were deleterious in liver surgery, especially that the liver itself has its own role in coagulation and thermoregulation and the two combined could lead to PHLF(213).

2.2.10 Post-operative risk

Post-operative bleeding

As with intra-operative blood loss and transfusion use, the main risk of post-operative bleeding is hypotension and subsequent organ ischaemia. Jarnagin and colleagues found an increased relative risk of 1.35 of complications when patients had a bleed post operatively(146). The best way to avoid this is careful intra-operative haemostasis, and monitoring and correction of coagulation and electrolyte disturbance post-operatively.

Post-operative infection

There is a risk of infection following abdominal surgery. Common sites are chest, (due to reduced inspiration caused by pain), surgical site infection, urinary (from catheterisation of patients) and intra-abdominal collection/abscess¹⁴. Tzeng and colleagues reported intra-abdominal infection was found to have an increased PHLF risk, associated with prolonged hospital stay after liver surgery (219).

It is established that the liver is liable to be injured in sepsis. The liver has a role in bacterial clearance in bloodborne infections and sets off a pro-inflammatory response(269) but pathogens, toxins, or inflammatory mediators can also cause liver injury and cellular necrosis. Counterintuitively, the liver can respond to bacteraemia associated with infection with an immunosuppressive effect; a function believed to be related to the balance of commensal gut bacteria – to prevent destruction of this important ecosystem if bacteria translocate haematologically(270). Either over expression of the pro-inflammatory response with subsequent ‘cytokine storm’ and liver injury or excessive immunosuppression release can exacerbate liver injury(271). Add into the mix that the liver size and function is reduced, it can potentially lead to either promotion of infection, or an infection causing liver injury and PHLF. Increased infection rates in patients with small FLR have been observed, and the authors in those studies felt this was due to the overall reduction in Kupffer cells and their role in innate immunity(272) and reduction of cellular signal production, particularly IL-6(273).

¹⁴ Remembered by medical students as ‘winds, waters and wounds’

Table 15: Risk factors associated with development of PHLF (from Kauffman(6))

Patient related	Surgery related	Post-operative management
Diabetes mellitus	Blood Loss >1,200 mL	Post-operative haemorrhage
Obesity	Intra-operative transfusions	Intra-abdominal infection
Chemotherapy-associated steatohepatitis	Need for vascular resection	
Hepatitis B, C	>50% liver volume resected	
Malnutrition	Major hepatectomy including right lobectomy	
Renal insufficiency	Skeletonisation of hepatoduodenal ligament	
Hyperbilirubinemia	<25% of liver volume remaining	
Thrombocytopenia		
Lung disease		
Cirrhosis		
Age >65 years		

All risk factors described above are now considered when planning surgery. If at all possible, these are either corrected or accounted for during surgical planning. However, despite correction, PHLF still occurs; indeed, sometimes patients with few or no risks may develop it, and others with multiple did not. A study into the extent of risk factors in development of PHLF in major liver resection patients was required. This is the rationale for the study described in chapter 3.

2.3 Current and alternative methods of determining liver function

Liver function is a complex, involving **synthetic, excretory, and detoxifying functions** and as such it is difficult to state one simple process of stating how the liver is actually working(5). As a result, many different methods have been described, each with its strengths and drawbacks, and these will be discussed below in sections 2.3.1-2.3.4. DGE-MRI is a novel imaging-based assessment of liver function which could provide a solution to the drawbacks of currently available methods. It has yet to be investigated whether it has any benefits over current function assessments in a surgical population. Chapters 4 and 5 describe the results of studies assessing the utility of DGE-MRI in patients undergoing liver resection.

2.3.1 Global measures

Indocyanine Green (ICG)

This is commonly used in other countries such as Japan(12)(274), but isn't currently licenced in the United Kingdom for hepatic assessment. ICG is a dye that binds to albumin in the plasma and subsequently is exclusively taken up by hepatocytes via organic-anion-transporting polypeptide (OATP) 1B3 and sodium-taurocholate co-transporting polypeptide 15. It is excreted unchanged into the bile by the multidrug resistant protein (MRP) 2. These are the same receptors involved in bilirubin metabolism and excretion. It is not reabsorbed via the entero-hepatic circulation, therefore follows simple pharmacodynamics (12)(275).

Following injection, an interval sample is taken (at 15 minutes post injection) to determine the retention fraction – the amount of ICG remaining in the blood that hasn't been excreted(276). It has been shown that a high ICG retention fraction is associated with an increase in mortality for patients having liver resection for HCC(277). This test is non-toxic in the administered doses of 2mg/kg (lethal dose in 50% (LD50) is 50-80mg/kg)(12) and provides an excellent measure of global liver function. It has mostly been used to assess patients with parenchymal liver disease. It can only be used as a discriminator for patients with already severe liver dysfunction as to whether to even attempt surgery.

In isolation with a patient with supposed normal functioning liver it would be difficult for ICG to be able to help in risk stratification.

Galactose Elimination Capacity Test (GECT)

This test is performed in a similar fashion to the ICG test; a substrate is injected intravenously, in this case galactose. It differs from ICG by the measurement of galactose's breakdown products rather than the substrate itself. Galactose is phosphorylated intracellularly by galactokinase to galactose-1-phosphate, which in turn is converted to glucose-1-phosphate (G1P) within the liver. G1P is then measured directly(278). An interval blood test is taken at around 20-50 minutes and the G1P levels are determined(279). In states of fasting or where there is concurrent liver regeneration there is a high false positive result(280). As with ICG, this would only give a global liver function and has the same limitations. It cannot not be used to determine the extent of surgery, only if there is enough function to even consider surgery(281).

LiMAx test

This method, available since 2008, uses radioactively labelled ^{13}C -methacetin – a prodrug for paracetamol that is metabolised throughout the liver by cytochrome P450 1A2 enzyme with the release of the labelled ^{13}C . This is excreted as $^{13}\text{CO}_2$, which can be measured in the patient's respiratory expiration.

The lower the expired value seems to indicate reduced liver metabolism and function, and as such has proven useful in being able to exclude patient from surgery or lead to altered surgical planning given the degree of the LiMAx result(282).

It can be used in two ways: initially it can be used to risk stratify patients into:

- low risk (LiMAx $>315\mu\text{g}/\text{kg}/\text{h}$) \rightarrow suitable for surgery
- moderate risk ($140\text{-}315\mu\text{g}/\text{kg}/\text{h}$) \rightarrow risk stratification via combined assessment with CT volumetry
- high risk ($<140\mu\text{g}/\text{kg}/\text{h}$) \rightarrow unsuitable for surgery

Should a patient fall into the moderate risk group a comparison of a CT measured FLR volume compared to the LiMAx for the FLR can be used to allow a risk stratification:

- <80 µg/kg/h – unsuitable for surgery
- 80-100 µg/kg/h - critical resection (parenchymal preserving)
- 100-150 µg/kg/h – feasible resection
- >150 µg/kg/h – regular resection

The utility of LiMAx has been demonstrated by Jara and colleagues who reported that following their implementation of LiMAx testing by the above method they reduced their incidence of PHLF and mortality – they attribute this to the LiMAx allowing improved patient selection for resections(283).

LiMAx does provide an excellent stratification of risk for surgical candidates and it is much more commonly being used for this purpose. At the time that the present study was designed and recruited its participants it was not being used in Leeds either in patient selection or in conjunction for study, and therefore its relationship to the findings of DGE-MRI in chapter 5 cannot be compared.

2.3.2 Anatomical assessment

These methods use imaging providing a more detailed assessment of the liver and involve radiological imaging as part of the investigation. These methods are the most comparable in principle to our proposed mode of investigation DGE-MRI, although they rely on other modalities of imaging, from nuclear medicine studies to CT.

Galactosyl Serum Albumin Scintigraphy (GSA)

This is a nuclear medicine technique, in which 99m-technetium (99mTc) labelled GSA is injected intravenously. GSA is an analogue ligand of the Asialoglycoprotein (ALG) that binds to ALG receptors expressed on hepatocytes cell membranes on the sinusoidal surface facing the space of Disse. ALG receptor expression is decreased in chronic liver disease; therefore, uptake of GSA into the liver (given as a ratio of hepatic uptake compared to that observed in the circulation) is reduced in this case after 15mins(284).

It has been investigated in chronic liver diseases(285). Despite combinations with CT scans to provide increased anatomical information (286) this has proved inadequate and method can only distinguish vague regional liver function, therefore it is unable to provide the level of anatomical and region function that is required(274). In addition, it is only approved for use in Japan and is unavailable in the UK at present, and therefore cannot be studied locally(280).

Techneium-99m Mebrofenin Hepatobiliary Scintigraphy

Radioactively labelled Mebrofenin is an albumin-bound substrate taken into hepatocytes by OATP1B1 and B3 and excreted by MRP2, (again like bilirubin, ICG and Gadoteric Acid (287)). This has been shown to provide some anatomical difference in function, and has demonstrated a correlation between predicted function remnant liver preoperatively and postoperatively, as well as biliary excretion assessment(288). The images this method produces tend to be low resolution and the quality in detailed anatomy required to differentiate segments is difficult. Analysis is limited to demonstrating heterogeneity between left and right lobes only, which could be useful for left and right hepatectomy patients. Studies by Cieslak and colleagues(13) have demonstrated combination with CT scans increases accuracy of regional liver function (274), and subsequent the ability to predict post-operative outcomes(289). The combination with single photon emission Computed Tomography (SPECT) and CT minimises patient exposure to ionising radiation(286), Alternative methods such as DGE-MRI have potential benefits over Mebrofenin scintigraphy if it can demonstrate the same predictive capacity without radiation exposure.

CT Volumetry

This is the most utilised method locally in Leeds and within the UK. It cannot measure function per se; but relies on the concept that the liver's volume and function can be correlated. This is the most common radiological assessment for surgical planning(11). This involves calculation of the volume of the liver, and the volume of the FLR. Freehand drawing of total liver volume (termed standardised liver volume or SLV) and predicted

FLR(290). A percentage of FLR can be calculated, and operative decision making to allow sufficient FLR volume and avoid small for size liver remnant. Automated computer modelling is available and is equivalent to freehand methods; automation is much quicker and can be used to assess many patients in a timely manner(291).

There have been studies that demonstrate CT volumetry's benefit; when the FLR value is low, it has been associated with PHLF and complications. Schindl and colleagues showed a threshold of 26.6% for FLR volume was associated with poor patient outcome(4) and Kishi and colleagues showed 20% as their critical FLR for PHLF development(292). It assesses the volume of the liver in millilitres (or cm^3) and can predict the amount of volume that is to remain after resection. It can also be used to measure the degree of liver hypertrophy after PVE, with decisions about whether new growth has been adequate based on the volumetry of the new FLR post-embolisation (e.g. volume of segments 2 and 3 if an extended right hepatectomy is required).

One potential drawback with this method is it assumes that liver volume and liver function are equivalent, and function is **homogenously distributed**. Ribero and colleagues compared the outcome of patients with a measured FLR volume (called the mFLR) compared to an estimated FLR based on their weight and body surface area (BSA) with the following calculation:

$$eTLV (\text{cm}^3) = -794.41 + 1267.28 \times BSA$$

BSA was calculated using weight and height according to the Mosteller formula(293):

$$BSA = [\text{weight (kg)} \times \text{height (cm)} \div 3600]^{1/2}$$

They found that 11% of patients who had an adequate mFLR developed some degree of PHLF, and these would have been detected by using the eFLR method, which suggests measured volumetry isn't as robust as it needs to be, that even when patient's measure FLR volume was expected to be enough, it wasn't. This fact becomes particularly important around the threshold values for accepted FLR; those with a measure FLR volume 20-30%(10). It is plausible that such patients may have enough remnant volume, but that volume is not functioning adequately or, if that liver's regenerative capacity is diminished for some reason.

Another issue with CT is the significant ionising radiation burden which is a proven carcinogen(294). CT imaging in patients who already have a diagnosis of cancer is often the desired modality. In these patients the benefits of CT for diagnosis outweighs the small associated risk of the radiation, particularly as the 'lead time' from exposure to malignant transformation can be decades(295), but certainly for younger patients (such as those in their 30s or 40s) who undergo treatment with a curative intent for CRLM then it is worth considering this increased risk in their surveillance strategies. Other modalities that do not require ionising radiation doses should be considered(296), for which MRI could be a suitable alternative.

2.3.3 Concept of liver inhomogeneity

There was an assumption that liver function was homogeneous throughout, giving a rationale for volumetry(297). Global measures have been useful in predicting hepatic reserve, as a result the amount of liver to leave as the FLR was one that was calculated by algebra – if a person required a certain critical threshold FLR, then the volume that could be removed would be calculated by subtracting the FLR-volume from the total liver volume(297). Shoup and colleagues reported <25% FLR is associated with PHLF¹⁵ however 2 patients out of their series of 126 had less than <25 and were clinically fine, and conversely 20 patients with >25% FLR developed PHLF(197). There is no clear answer why some will be fine post-operatively despite being small of size, and the others with 'acceptable' FLR developed dysfunction. One possible explanation is that rather than uniform distribution of function, there is inhomogeneity of function – certain parts or segments of the liver work better than others, known as a **Functional Bias**. This is where a patient's liver per unit of volume is either over- or under-functioning relative to its volume.

¹⁵ Albeit a different definition for PHLF, defined by the authors as prothrombin time greater than 18 seconds or serum bilirubin level greater than 3 mg/dl. This definition was discussed in more detail in the section describing 56 various methods reviewed by ISGLS

In studies examining perfusion and functional uptake of contrast agents in cirrhotic liver diseases such as in Nilsson and colleagues studies on primary sclerosing cholangitis(298), primary biliary cirrhosis(299), alcohol or viral induced cirrhosis(300) there was differences between areas affected by the disease having inhomogeneous perfusion and uptake of contrast. It has been suggested in a simulated study of left hepatectomy, those with inhomogeneity in their FLR would have a lower measured function(301). These studies involve patients with established liver disease with impaired clinical and biochemical dysfunction. It is much less clear if those patients with either normal livers or patients with CRLM who appear to have normal liver have any inhomogeneity. The fact that some patients who have resection of CRLM develop PHLF despite pre-operative planning does lead to some credence that some factor is leading to this(215); a patient which adequate FLR volume who still develops PHLF is difficult to explain, unless the FLR volume is **under-functioning** – a functional bias in favour of function < volume. This idea that function is inhomogeneously spread – where the volume is adequate there has to be a ‘**small function for size**’ concept.

Figure 6: Uptake in a healthy volunteer showing homogeneous uptake (images from S Sourbron, University of Leeds, data from H Nilsson, Karolina Institute, Stockholm)

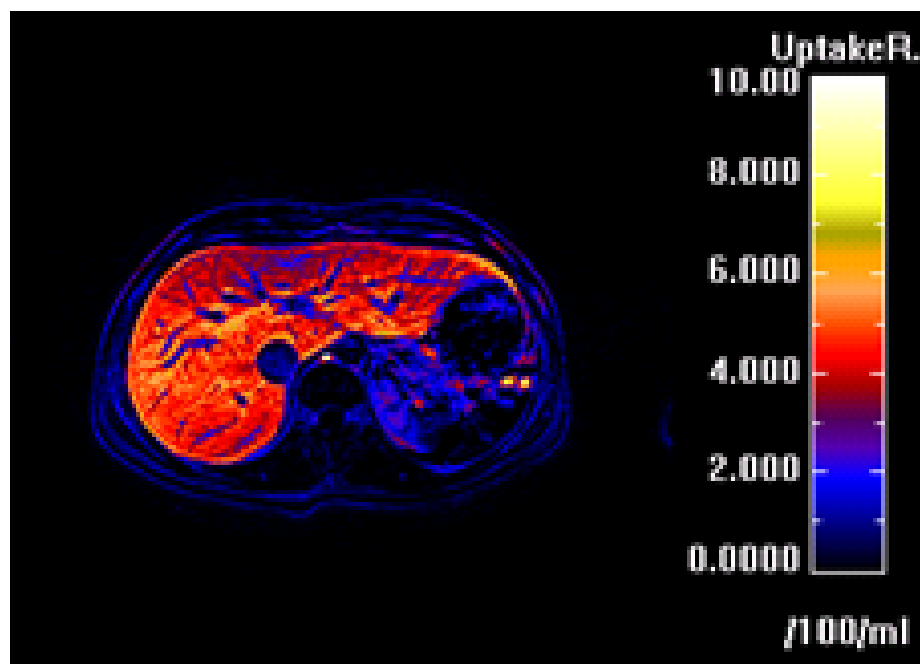
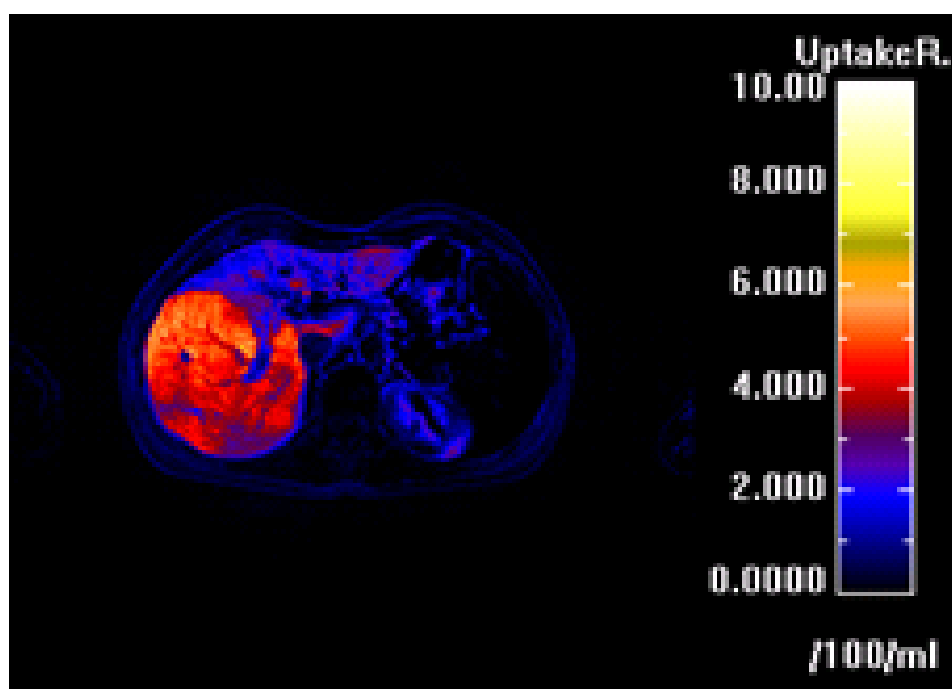


Figure 7: Uptake in a patient with PSC showing inhomogeneous uptake, with under-functioning left hemi liver (images from S Sourbron, University of Leeds, data from H Nilsson of the Karolima Institute, Stockholm)



2.3.4 Dysfunction Scoring models

Risk stratification based upon clinical parameters are easily determined and have been extensively evaluated for their benefits in patients with established liver disease. They are proven to have important prognostic roles in such patients, but they cannot be utilised in patients with apparently normal or sub-clinical liver problems.

Child Pugh Score (CPS)

This scoring system was originated in 1963(302) and was modified to include coagulation parameters in 1973(303). It has been used and is known to predict mortality in patients with chronic liver disease from multiple aetiologies. It is simple to calculate, using objective data routinely measured in patients (tables 16-18). The original cohort of patients were surgical, however they were not undergoing liver surgery itself, instead they were having other operations and had liver disease as a comorbidity.

Table 16: Child Pugh Score

	Score		
	1	2	3
Hepatic encephalopathy grade	None	1-2	3-4
Serum bilirubin ($\mu\text{mol/l}$)	<35	35–50	>50
Serum albumin (g/l)	>35	35–28	<28
Prothrombin time prolongation (s)	<4	4–6	>6
International normalized ratio	<1.7	1.7–2.3	>2–3
Ascites	Absent	Mild–moderate	Severe

Table 17: CPS and predicted mortality¹⁶

Child-Pugh grade	% Survival		
	1 year	5 years	10 years
A (5-6)	84	44	27
B (7-9)	62	20	10
C (10-15)	42	21	0

Table 18: West Haven Criteria for Hepatic Encephalopathy

West Haven Criteria for Hepatic Encephalopathy (209)		
Grade	Features	Asterixis
0	No abnormality detected	Absent
1	Impaired higher function	Usually absent
2	Lethargy, personality change, inappropriate behaviour, and disorientation	Usually present
3	Confusion and gross disorientation, increased somnolence	Present
4	Coma	Absent

This method, although simple and validated, can only be used for patients with established liver disease. For patients who are otherwise well with presumed normal liver (apart from their metastatic burden), it cannot be used. Any patient with evidence of pre-surgery liver dysfunction was excluded from the analysis in the forthcoming chapters and so CPS scores in those cohorts would be not applicable.

MELD/UKELD

The Model for End-stage Liver Disease was developed to assess prognosis following trans-jugular intrahepatic portosystemic shunt (TIPS) for portal hypertension(304), and

¹⁶ This table's risk of death is not related to surgery specifically, it is all cause mortality.

then applied to patients with cirrhosis on the liver transplant waiting list for prognostic purposes(305).

$$MELD = 3.8 * \ln(\text{bilirubin}[\text{mg/dL}]) + 11.2 * \ln(\text{INR}) + 9.6 * \ln(\text{creatinine}[\text{mg/dL}]) \\ + 6.4 * (\text{aetiology: } 0 \text{ if cholestatic or alcoholic, } 1 \text{ otherwise})$$

The UKELD is a later modification that includes the serum sodium level, specifically for transplant waiting list mortality(306):

$$UKELD = [(5.395 * \ln(\text{INR})) + (1.485 * \ln(\text{creatinine})) + (3.13 * \ln(\text{bilirubin})) \\ - (81.565 * \ln(\text{sodium}))] + 435$$

As with CPS, this has proven useful for established cirrhotic disease, and as such is frequently used by transplant teams during allocation and for risk assessment of patients with a scarcity of liver donors. It has little role in those with no known liver disease. As a result, they are of limited use in patients who have no evidence of liver dysfunction, such as patients with resectable colorectal liver metastasis.

Despite the availability of these methods, none can be applied to population of patients who require liver resection for CRLM; this is a population who normally have biochemical markers in the normal reference range. CPS, MELD and UKELD are global measures that can only lead to a risk stratification of suitability to undergo surgery for patients with established liver disease, and the alternative measures of liver volumes and function are either not able to give good anatomical assessment of segments or rely on the concept that volume and function are equal throughout the liver, which may not be the case. One potential solution to these issues is the development of MRI imaging with dynamic contrast enhancement (DGE-MRI).

2.4 Magnetic Resonance Imaging

MRI is a widely available modality with excellent diagnostic sensitivity and specificity (table 3). The scientific principles of MRI are described in below in chapter 2.4.1. Recently developed liver-specific contrast agents such as Gadoxetate have improved the quality of liver MRI and it is seen as essential for liver cancer staging(96). The mechanism of action of contrast agents and why gadoxetate is effective for function assessment is discussed in chapter 2.4.3.

Acquisition sequences can be readily modified to obtain dynamic imaging which can be used to assess function per segment, without compromising high quality diagnostic imaging. It may offer a more robust pre-operative assessment of function, with the development of DCE-MRI and quantitative functional assessments. The development of DGE-MRI acquisition is described in chapter 2.4.5.

2.4.1 How MRI Works

A hydrogen atom (H^1) consists of a single proton nucleus, so has a positive charge. It will demonstrate a phenomenon known as 'spin' when an external magnetic field is applied. Application of a magnetic field of sufficient strength to the proton will align the spin and the atom will move much like a gyroscope – a so called “precession of spinning magnetic dipolar structure with a magnetic vector”(307). This speed of precession, also called the Larmor frequency, is proportional to the strength of the external magnetic field, and is calculated by the following Larmor equation:

$$\omega = -\gamma B$$

- ω = angular frequency (MHz)
- γ = gyromagnetic ratio (MHz/tesla)
- B = magnitude of the applied magnetic field (tesla)

If the energy of magnetic pulse (delivered by an external Radiofrequency (RF) coil such as one contained in an MRI scanner) has the same frequency as the Larmor frequency

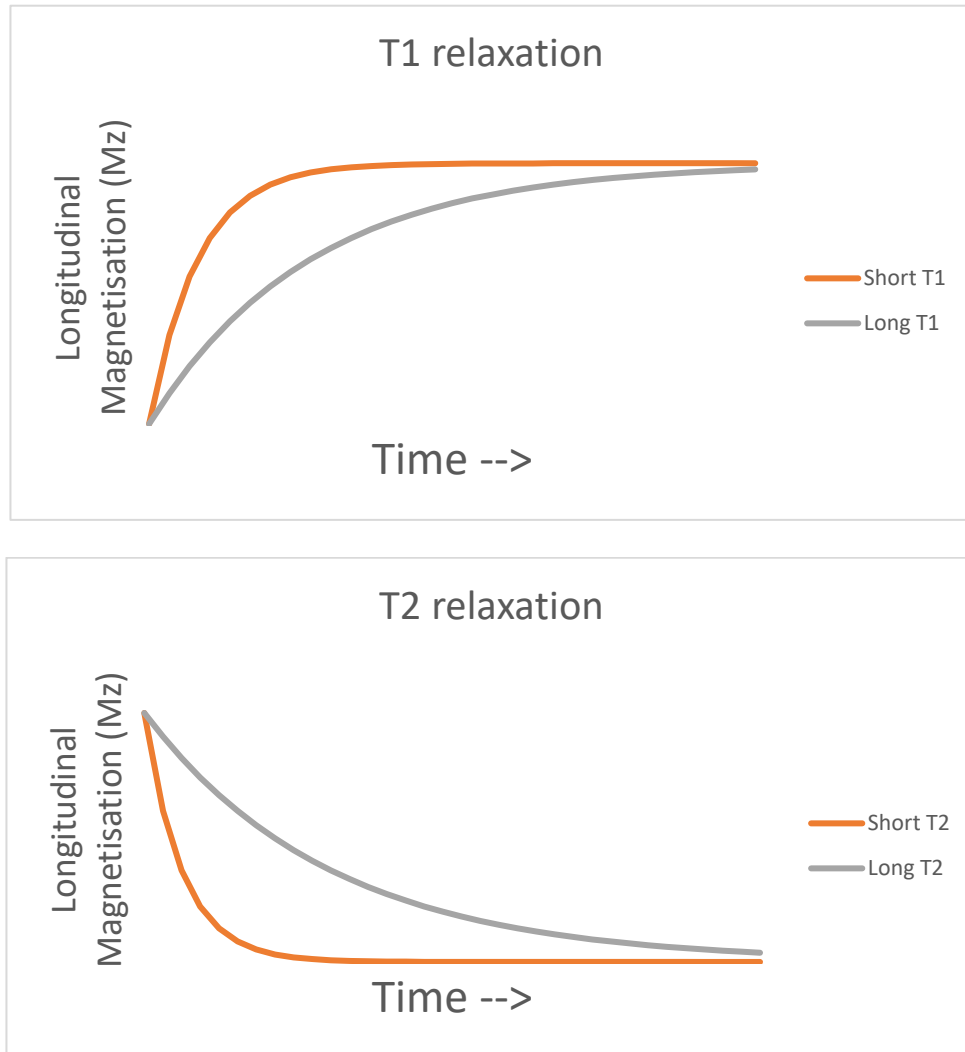
then hydrogen protons will align and precess (rotate) in-phase, in a state called **longitudinal magnetisation**. If the RF pulse is longer and stronger it will cause the magnetization vector to flip to 90° and the atom's precession moves sideways, which is called **transversal magnetisation**. When the RF pulse stops, the spin will 'relax' and return to its resting state and release a small amount of energy which can be measured, hence an MRI scanner is able to detect this energy signal. Any molecules containing hydrogen, such as water (H₂O) are strongly affected by magnetism; and as the human body is abundant with water it allows use of MRI to delineate tissues, based on the extent of water content contained within them.

Those atoms that have been spinning longitudinally will return to their relaxed state (regaining their magnetic vector) on cessation of RF, and the time it takes for the magnetic vector to return to 63% of its original strength is known as the longitudinal relaxation time or T1 relaxation.

Those atoms precessing in-phase will lose this on cessation of RF and revert to their normal position, losing their transverse magnetisation. When they have lost 37% of the maximal magnetism, this is called 'transverse relaxation' or T2 relaxation(307).

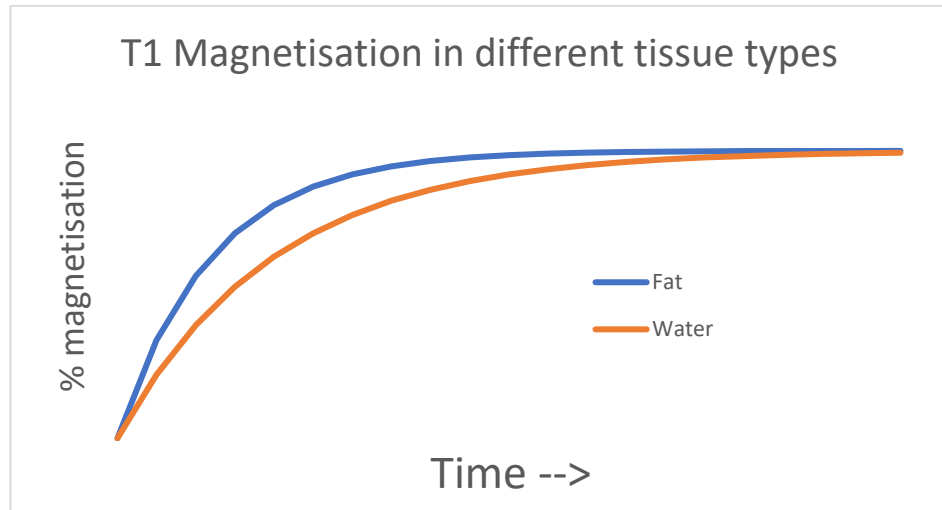
Different tissues contained within humans will relax at different times based on their individual content— this fact allows differentiation of different tissues by the MRI depending on the time of the relaxation.

Figure 8a and b: Strength of magnetisation for T1 and T2 relaxation in different tissues



T1 is longer than T2 in most tissues. Generally T2 times are longer in liquids than in fat, which in turn is longer than muscle or liver which is important when imaging different tissues(308). Tissue that has more liquid contained within will have a longer T2 time and so can be distinguished from the surrounding liquid-less structures and will appear differently. The classical teaching to surgeons (who are not trained beyond the basics in MR theory) is that T1-weighted imaging provides better anatomical delineation, and T2-weighted imaging demonstrates pathology due to the increased enhancement of fluid that is seen in inflammatory disease processes and oedematous tissue. DGE-MRI typically uses T1-weighted images as the basis for analysis(218)

Figure 9 – The difference in T1 relaxation time in fat vs. water



2.4.2 MRI and Liver Imaging

MRI and diagnostic liver imaging has been reported as far back as 1988(309) and has become a mainstay of liver disease diagnosis. It is often for staging for metastatic disease, and is highly useful in distinguishing equivocal lesion seen on CT to know if they are benign or malignant (310). See table 3 for sensitivity and specificity for CRLM diagnosis.

Given the complex anatomy and physiology of the liver; the dual inflow, the metabolic and excretory functions, and structure it is widely accepted that order to obtain diagnostic images, the MRI is used in conjunction with a contrast agent(14). Contrast agents are adjuncts to enhancing and defining the nature of the liver parenchyma and generally can be divided into two types: 'unspecific extracellular fluid space agents' and 'targeted and organ-specific agents'.

2.4.3 Contrast Agents

MR contrast agents are used to enhance the visibility of tissues by the MRI scanner, and are either Gadolinium-based or Iron-Based. Gadolinium is a metal that exhibits paramagnetic properties; when a magnetic field is applied, a magnetic effect is observed but does not retain magnetism unlike iron(311). Although unbound gadolinium is toxic,

when it is chelated it is generally safe for human use(312). The ligands which chelate the gadolinium determine its biological behaviour within the body.

Gadolinium based agents shorten the T1 time of protons, which produces a higher signal intensity and therefore 'enhances' the contrast between the tissue that the gadolinium is within compared to surrounding tissue.

Iron-based agents, known as superparamagnetic particles of Iron-Oxide (SPIO) are taken up by Kupffer cells in the liver. They are useful for distinguishing liver tissue from non-liver tissue such as metastases. As metastases are not liver tissue, they will not contain any Kupffer cells. However, they cannot determine significant discrete lesions of liver origin such as FNH, and they do not provide any information of hepatocytes, and therefore cannot be used in studies that relate to function, metabolism and excretion of hepatocytes(313). SPIO therefore cannot be used assess function.

Use of liver specific gadolinium-based contrast agents are most beneficial in assessing the metabolism of the liver, and in lesion characterisation. Gadoxetic acid (Gd-EOB-DTPA) and Gd-BOPTA are the two currently available commercially.

Gadoxetic acid enters hepatocytes through the organic anion transporting polypeptides OATP1B1 and OATP1B3 and exits through the ATP-dependent canalicular membrane multidrug resistance protein MRP2, MRP3 and MRP4 – the same receptors and transporter proteins that bilirubin¹⁷ is metabolised and excreted through. Around 50% of Gadoxetic acid is excreted this way, which compared to 3-5% of Gd-BOPTA, the other available liver-specific agent(128)(314). Based on the pharmacodynamics of Gadoxetic acid, it is the most suitable contrast agent to assess hepatocyte uptake – which is highly important for DGE-MRI assessments of cellular function. This increased hepatic enhancement allows much better assessment of liver parenchyma, and the rate of its

¹⁷ And ICG for that matter

diffusion from the extracellular to the intracellular space can reflect hepatocyte membrane function – which can be extrapolated to inform us of the cellular function.

Figure 10: Chemical structure of Gadoteric Acid

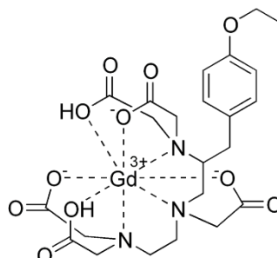


Table 19: Non-specific and liver-specific MRI agents (Adapted from Sommer(14))

Non-specific contrast agents	Liver Specific contrast agents
Gadopentetate dimeglumine	Ferumoxide
Gadodiamide	Ferucarbotran
Gadoterate meglumine	Mangafodipir trisodium (Mn-DPDP) – no longer commercially available
Gadoteridol	Gadobenate dimeglumine (Gd-BOPTA)
Gadobutrol	Gadoxetic acid (Gd-EOB-DTPA)
Gadobenate dimeglumine	

2.4.4 Breathing and MRI

An important consideration for liver MRI is that the liver moves on breathing. Imaging with free breathing (i.e. normal respiration) may degrade image quality and artefact formation. Multiple MRI techniques such as diffusion weighted imaging (DWI) will exhibit artefacts, increased signal-to-noise and contrast-to-noise problems(315). One solution is 'breath-hold' sequences, where the patient holds their breath during the period of acquisition. However, this method, although it reduces artefacts can restrict image quality due to reduced scan duration (typically no more than 20 seconds is feasible), problems of the quality of breath-hold, and some patients will simply not be able to hold their breath for enough time to be able to image. Another solution is 'triggered' or 'gated' imaging, where acquisition is programmed to occur in a timely manner, such as a phase of respiration, or after a period of time. This again can lead to problems due to breathing

position drifts and changes in breathing patterns may lead to sequences getting out sync(316). The ideal liver MRI would not require breath holding.

2.4.5 Liver DCE-MRI

Radiological investigations produce either a static image at one moment in time, such as a chest radiograph or can produce dynamic images where imaging occurs over time, such as ultrasonography. Most conventional liver MRI imaging is static, allowing a single image to be created during a certain time, either during contrast introduction, when contrast is in the arterial phase, in the venous phase or delayed after uptake and diffusion of contrast agents.

DCE-MRI is a form of dynamic imaging that has been recently developed to assess liver function and perfusion. Multiple studies have reported being 'dynamic' and 'dynamic contrast enhanced' even as far back as 1986(317), however these studies are very different in methodology; due to technical limitations and focus on lesion identification and bear no impact on current contexts.

Sommer and colleagues define the aims of DCE-MRI as being the ability to:

“determine perfusion parameters and quantify the microcirculatory status of liver parenchyma and focal liver lesions” by “quantification and comparison of important parameters of tissue perfusion and tissue characteristics like blood (or plasma) flow, arterial blood flow fraction, extracellular volume or mean transit time”(14).

DCE-MRI as reported today is a more robust, reproducible, and quantitative rigorous study, was first used in a Rabbit model in 2004 by Ryeom and colleagues, wherein they scanned rabbits using Gadoteric Acid in a DCE-MRI sequence¹⁸, followed by the induction of liver injury by giving the rabbits carbon tetrachloride. Following a repeat MRI

¹⁸ AIF in the aorta, ROI in the liver, FLASH, TR/TE = 11/4.2 milliseconds, flip angle = 15, acquisition time 1 second, slice thickness = 5 mm, matrix = 128×128, field of view = 120 mm) sequence with 1.5 sec time intervals

by the same sequence, the authors calculated the hepatic extraction fraction (HEF). After this, the rabbits were euthanised for histological examination of their liver to correlate between degree of liver injury and their HEF. They found that HEF dropped from 100% (defined as the baseline pre-injury level) to ~77%.

An important methodological improvement described in this paper is the introduction of mathematical modelling. Using deconvolutional analysis based on Brown and colleagues method(318) to calculate a HEF, this introduced a more objective, quantitative assessment of the change in function(319). This methodology was implemented in a human study by Nilsson and colleagues shortly after, which showed DCE-MRI was viable and able to calculate HEF reproducibly(320). Both studies used a **single input, single compartment** model due to measurement of combined contrast intensity within the liver and no differentiation between arterial or venous inflow.

Nilsson and colleagues have used this model in investigation of different functions seen in primary sclerosing cholangitis (PSC)(298), primary biliary cirrhosis (PBC)(299), cirrhosis(300) and described inhomogeneous functional distribution within the liver(301). One drawback for these studies is the acquisition method. These involved participants having to perform 41 breath-holds of 12 seconds each, which is a significant burden on the participant. A healthy volunteer may do this, but it will become more challenging for patients with any respiratory or cardiovascular disease, as their ability to hold breath is diminished. Use of this protocol in clinical practice is unfeasible for the majority of patients who actually need liver imaging without significant alterations to the acquisition methodology.

This single input, single compartment model is an improvement on previous DCE-MRI studies that used 'semi-quantitative' measures such as maximal signal intensity (S_{MAX}), the time to reach S_{MAX} (T_{MAX}), the half-life ($T_{1/2}$) and the area under the curve(321). Semi-quantitative measures are easily calculated but they are not reproducible between studies. Values vary between different contrast agent doses, different body sizes of patients (the 'dilution effect'), different sequence parameters and imaging sequence, and

variation in physiological state lead these to be unfit for quantitative function assessment(14).

Ryeom and Nilsson's studies were important steps in creating a viable, reproducible and precise method of quantitative function assessment. The model they described is adequate for an organ like the kidney that has only an arterial inflow (322), the liver has **2 inputs** rather than the one, and as such cannot fully reflect the liver physiology, and can only provide limited perfusion information.

Materne and colleagues had described a **dual input, single compartment** model in a study using Gadoteric acid (Gd-DOTA), a non-specific liver agent. This model measured both arterial and venous inflows and allowed for a physiological delay time (arterial delay) to expand the number of perfusion measurements. It assumed continuous and impedance-free movement between the capillary bed and the extracellular space of Disse which, in normal healthy tissue seems to be the case(323). Gadoxetic acid does seem to behave in the extracellular space in the same way as the non-specific agents(324). However, in either diseased liver; fibrosis or cirrhosis, or in presence of tumour, there may not be such free movement. As a result, Sourbron and colleagues enhanced the model to have a **dual input, two compartment** model(218). The two compartments in question are the extracellular compartment (comprising of intravascular and extracellular – the space of Disse) and an intracellular compartment (in this case the hepatocytes). Another key improvement of this study was the pragmatic use of free-breathing throughout the DCE-MRI over a 5-minute period using a T1 time-resolved angiography with interleaved stochastic trajectories (TWIST) sequence which was well tolerated by participants¹⁹. An arterial delay is added to separate out the arterial and venous signals derived by interpolation(218).

The dual input, two compartment model has the benefit over the previously described models, in that it not only allows direct measurement of both arterial and venous inflow

¹⁹ The authors used a sequence with a temporal resolution of 2.2 s, 3D T1-weighted spoiled gradient-echo sequence TWIST

and perfusion, but the use of 2 compartments in modelling can determine function of the liver. It allows a pragmatic and tolerable sequence to be obtained and is readily reproducible. This model had yet to be examined in patients due to undergo liver resection, and it was not clear if it can detect more subtle functional differences, as it has so far only been applied to patients with diseased livers. It has been reported there is correlation with ICG and GSA(274) – well established measurements of hepatic function. It may be able to measure function pre-operatively with added benefit of detailed segmental assessment. Chapter 4 includes the results of differing models and the effect on function and perfusion estimates.

Figure 11: Example of the dual input two compartment model data curve

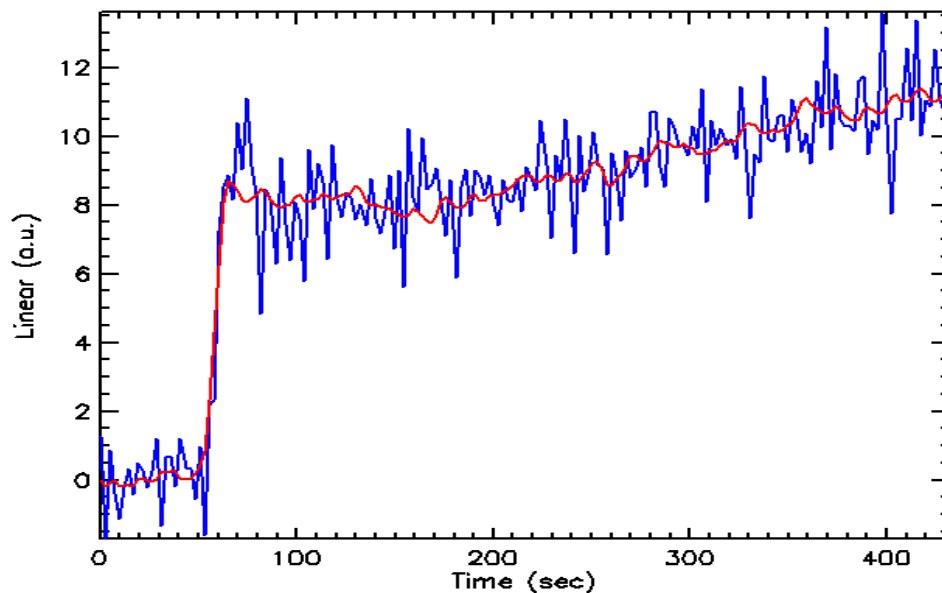
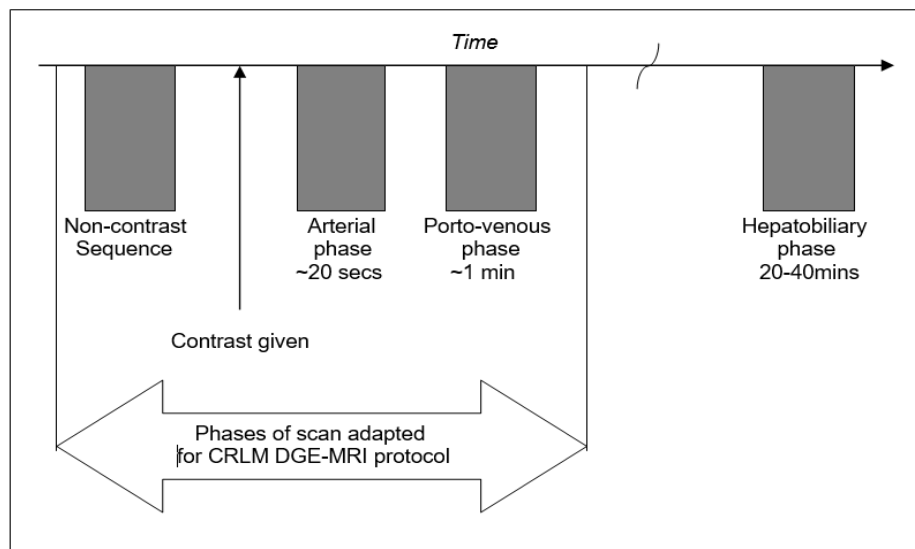


Figure 12: Representation of the alteration to MRI acquisition to include DGE data



DCE-MRI enhanced with Gadoteric acid (DGE-MRI) could be used to assess function in each segment. By using this segmental assessment and a pre-operative FLR-function can be estimated and could be used to predict post-operative function. Chapter 5 describes a study aimed to investigate this hypothesis.

Figure 13 – Summary of the various input models used in DCE-MRI Liver (from Sommer and colleagues(14))

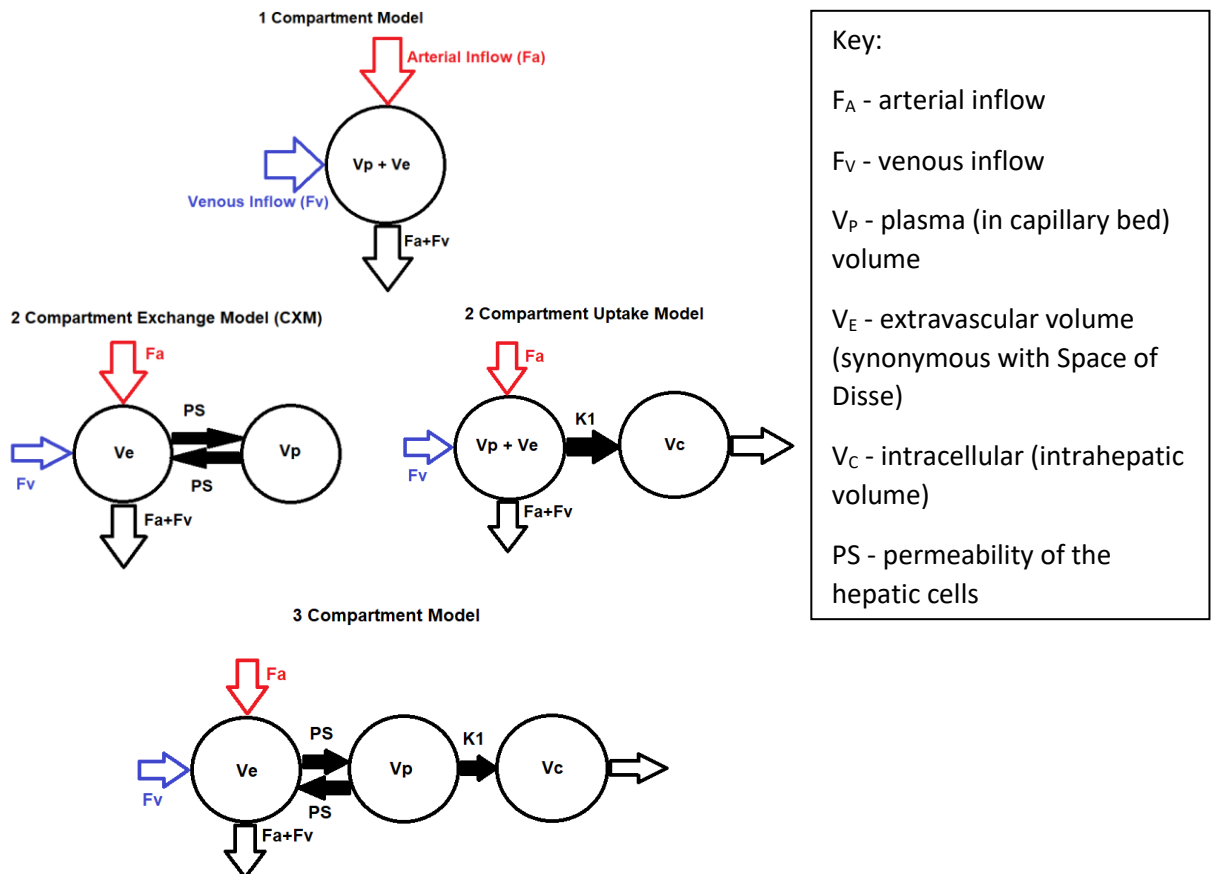


Table 20: terms used in DCE-MRI

HEF	The amount of contrast agent removed from the extracellular space by the liver over time
S_{MAX}	Maximum signal intensity
T_{MAX}	Time taken to reach maximum intensity
$T_{1/2}$	Time until the signal has decayed to half the maximum strength
AUC	The area under curve

2.4.6 Current role of DGE-MRI and future developments

DGE-MRI continues to develop with improving acquisition methods, and the use of gadoxetate has proven to be the most effective liver-specific contrast agent for function

assessment due to its high hepatic excretion rates. There remain questions on some technical aspects of acquisition, and uncertainty for its utility in clinical surgical practice.

A **dual input, two compartment** model appears to be the most robust available to determine both perfusion and function of the liver, however this has yet to be examined in detail whether a model of this complexity is necessary or beneficial. There is uncertainty in what is the best method of acquisition of DGE-MRI; particularly around the required rate of image acquisition (temporal resolution) and spatial resolution to give optimal quality. These questions are addressed in chapter 4 which reports on a study comparing acquisition sequences and a comparison of the effect of different input and compartment models has on perfusion and function parameters.

DGE-MRI reporting has focussed on patients with established liver disease where there is inhomogeneous function(298)(299)(300). At present, no study has reported on patients undergoing surgery if DGE-MRI estimates of function have a role in surgical planning. Chapter 5 describes a pilot study examining the predictive capacity of DGE-MRI estimates of liver function and clinical outcomes post liver resection.

Chapter 3 – The impact of age on post-operative liver function following right hepatectomy

This study has been published in HPB:

D Longbotham, A Young, G Nana, R Feltbower, E Hidalgo, G Toogood, JP Lodge, M Attia, KR Prasad (Pre-print) **The impact of age on post-operative liver function following right hepatectomy: a retrospective, single centre experience** *HPB* 2019 Jul 20

Due to the retrospective nature of the study ethical approval for this study was not required. Patients consenting for surgery in Leeds Teaching Hospital consent for the use of anonymised patient clinical and biochemical data being used for audit and research. The design and publication were approved by the Department of Hepatobiliary and Transplant Surgery at St James's University Hospital, Leeds.

3.1 Abstract

Background

An increasing number of patients undergoing liver resection are of advancing age. The impact of ageing on liver regeneration and post-operative outcomes following a major resection are uncertain. We aimed to investigate risk factors for patients who developed Post Hepatectomy Liver Failure (PHLF) following right hepatectomy with age as the primary risk-factor.

Method

Patients undergoing right hepatectomy between July 2004-July 2018 in a single-centre were included. Receiver operating characteristic analysis (ROC) was performed to identify at which age PHLF development-risk increased. Secondary endpoints were length of stay (LOS), post-operative complications, and cost.

Results

332-patients met inclusion criteria. ROC demonstrated a cut-off age of 75-years in which PHLF risk increased. >75 there was an increased risk of PHLF (35% >75yrs vs. 7% ≤75yrs (p=<0.001), OR=8.8 (95% CI=3.6-21)). There was no difference between the age groups for any other PHLF risk factor. Patients >75yrs had longer LOS (11-days vs. 7-days (p=0.04). Patients who developed PHLF had increased hospital costs: £10,987.50(£6,175-£46,050) vs. £2,575(£900-£46,050 p=0.01).

Conclusions

Patients >75yrs have increased risk of developing PHLF after right hepatectomy, contributing to increased mortality and economic burden. Pre-operatively identifying patients at risk of PHLF is important to consider liver volume optimization strategies and improve outcomes.

3.2 Introduction

Major liver resection surgery is increasingly being considered for both benign and malignant disease with improving outcomes(5)(325)(326) Despite such advances there remains a significant risk of developing Post Hepatectomy Liver Failure (PHLF); reported in up to 12% of liver resections(5). PHLF is associated with increased morbidity and mortality(6).

The cause of PHLF is multifactorial and patient selection for major resection is important to minimise this risk.

There are conflicting accounts of the impact of age as an independent risk factor for PHLF. Many studies report no increased risk for over 70-year olds developing PHLF(214)(219)(235)(327)(328)(329), despite increased mortality, and others demonstrated no risk for long term outcome(149)(330) on liver cancer resection, ascribing their reduced patient survival to co-morbidities in older populations. These studies did not solely consider patients having major liver resection, but also included minor resections.

Patients who are older have a higher prevalence of fatty liver disease(331). Older people may have reduced liver function due to age-related physiological changes(332). There seems to be an association between ageing and a higher background bilirubin(261), suggesting possible reduction in function in ageing populations. Such patients may be at risk of PHLF when subjected to major liver resection. In addition, a recently published large population-cohort study showed patients >75 had higher mortality after liver surgery for Colorectal Liver Metastasis (CRLM), which in part may be due to PHLF(333). As such, the data on advancing age, PHLF and outcomes following major liver resection is conflicting.

Given the uncertainty of the effect of ageing on patient's postoperative liver function when undergoing a major resection, we analysed the effect of ageing on right hepatectomy with a primary outcome of PHLF development.

3.3 Methods

3.3.1 Patients

A prospectively maintained liver resection database for St James's Hospital, England, UK was scrutinised for patients undergoing right hepatectomy for both cancer and benign disease. Right hepatectomy (segments 5, 6, 7 and 8 as defined by the Brisbane 2000 nomenclature of liver resections)(47) was chosen for study as it is a commonly performed, standardised major liver resection with anticipated adequate future liver remnant (FLR) (79). Confirmation of the surgery was performed by review of histopathology results, operation notes and clinical correspondence.

All patients undergoing right hepatectomy between July 2004 and July 2018 were examined and the following exclusion criteria applied: concurrent metastasectomy, re-do resection, second staged resection, benign liver cyst (due to the likely small volume of liver parenchyma resected), pre-operative portal vein embolisation (PVE), and liver dysfunction pre-operatively (defined as bilirubin $>50\mu\text{mol/L}$ or International Normalised Ratio (INR) >1.5 in absence of anti-coagulation).

All right hepatectomies were performed using a similar open surgical technique by 5 surgeons in our centre; an extra-glissonian approach to the porta, liver dissection using Cavitron Ultrasonic Surgical Aspirator (CUSA) and intermittent Pringle (a maximum of 15-minutes on and at least 5-minutes off) as required.

We applied the International Study Group for Liver Surgery (ISGLS) grading system for PHLF(1). We performed a ROC analysis to determine if age itself carried a risk for PHLF, and subsequently determined a cut-off value for study, comparing those above and below this age-point. The following demographic, clinical and histopathological data were analysed:

- Pre-operative risk factors: sex, estimated Glomerular Filtration Rate (eGFR) <90 (Chronic Kidney Disease grade 2(15), neo-adjuvant chemotherapy, diabetes, American Society of Anaesthesiologist's Physical Status (ASA) grade,

background liver disease (on resection histology), elevated Charlson Index (with malignancy excluded from the index score)(334) and degree of steatosis (<33%=mild, 34-66%=moderate and >66%=severe) based on the pathologist's report.

- Intra-operative risk factors: operation time, intra-operative blood transfusion.
- Post-operative factors: bilirubin, INR, PHLF grade, length of stay (LOS), surgical complications, medical complications, peak serum C-reactive protein (CRP), R1 resection, vascular invasion status of the tumour, 30- and 90-day mortality(6).

3.3.2 Volume measurement

Retrospective Computed Tomography (CT)-volumetry using PMI was performed on the pre-operative staging CT of those patients over-75, performed less than 8-weeks before surgery, to assess if there were differences in FLR for both those who developed PHLF and those who did not.

The clinical outcome was blinded to the author who performed this (DL) at the time of analysis. This allowed calculation of the total liver volume and FLR (based on the identification of the middle hepatic vein) with tumour volume subtracted

3.3.3 Cost Analysis

The cost of inpatient stay was obtained from the Trust's coding and finance departments, and checked against tariffs for the Department of Health's coding guides and the Intensive Care Society figures(335). The total cost for LOS was calculated based on itemised cost of £1700/day (~\$2550) on ICU, £1000/day (~\$1500) on HDU and £225/day (~\$337.50) on a surgical ward.

3.3.4 Statistical Analysis

Univariable analysis was performed using Chi-Squared, and Mann Whitney test for LOS and CRP. Multivariable logistic regression analysis was carried out to identify variables that were independently predictive for PHLF grade B / C, with the latter defined as the dependent variable. We included known risk factors for PHLF in the model to assess the

size and level of association: pre-operative chemotherapy, background liver disease, diabetes, ASA ≥ 3 , male sex, elevated Charlson Index, intraoperative transfusion, surgery over 4 hours and intraoperative Pringle use. A separate multivariable logistic regression analysis was additionally performed on a subgroup of those with steatosis and replacing background liver disease with a variable for moderate and severe steatosis.

A significance level of 0.05 was assumed. All statistical analysis was performed using SPSS v22 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp).

3.4 Results

3.4.1 Patients

2989 patients underwent liver resection during the study period. 390 patients had a right hepatectomy, and 332 patients were included for analysis after rigorous checks for the defined exclusion criteria. 17 patients were excluded due to pre-operative hepatic dysfunction, 25 for pre-operative PVE, and 16 for benign liver cysts.

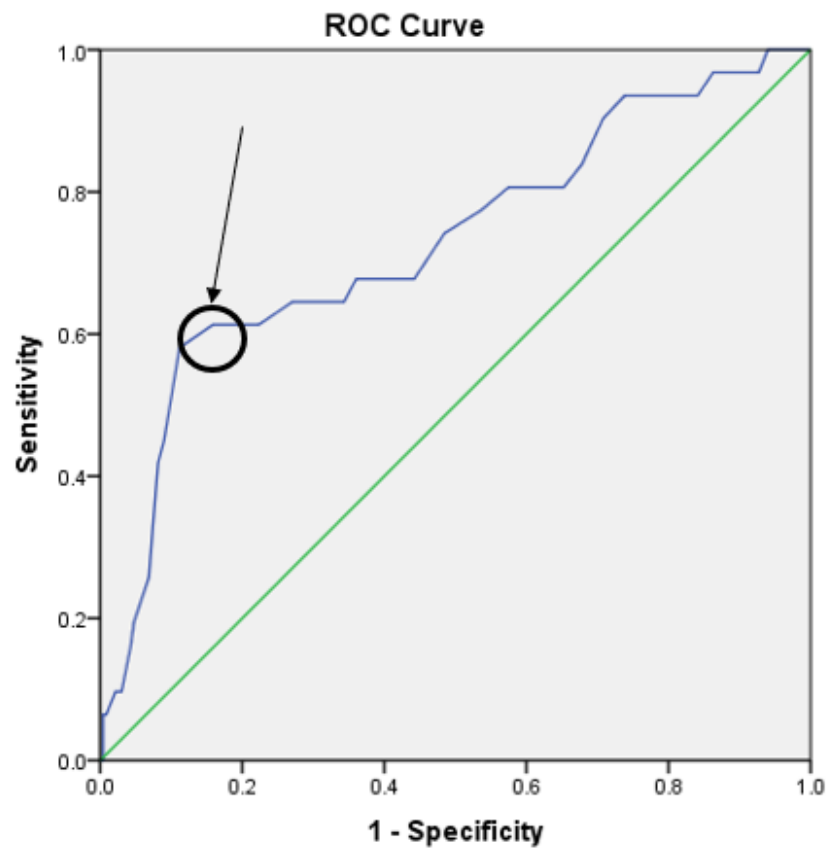
Median follow-up was 991 days (90-4439). Indications for resection are listed in table 23.

Table 21: Indication for right hepatectomy

Indication for resection	Number of cases
Malignant n=307	
Colorectal Liver Metastasis	237
HCC	36
Associated hepatitis B infection	1
Intrahepatic Cholangiocarcinoma	18
Neuroendocrine Metastasis	6
Breast Liver Metastasis	4
Anal Squamous Cell Carcinoma Metastasis	1
Tongue Squamous Cell Carcinoma Metastasis	1
Renal Clear Cell Carcinoma Metastasis	1
Ampullary Cancer Metastasis	1
Fallopian Tube Cancer Metastasis	1
Gallbladder Squamous Cell Carcinoma Metastasis	1
Benign n=25	
Focal Nodular Hyperplasia	9
Live Liver Donation	4
Haemangioma	5
Caroli's disease	3
Pseudotumour	1
Adenoma	1
Post Cholecystectomy complication	2

A ROC analysis was undertaken and a cut-off value of 74.5 years old was identified for increased risk of PHLF with an area under the curve (AUC)=0.73 (CI:0.58-0.78; p=0.001). Patients were subsequently stratified by age group: under-75yrs (n=283) vs over-75yrs (n= 49) for analysis.

Figure 14: ROC Analysis of age compared to incidence of PHLF. A cut-off was identified at 74.5 years old. (AUC = 0.73)



Risk factors

There was no significant difference between the two age groups for sex, neo-adjuvant chemotherapy, diabetes, ASA, background liver disease, degree of steatosis, elevated Charlson Index, operation time >4hours, intraoperative transfusion, surgical complications, medical complications, CRP level, R1 resection, or vascular invasion status of the tumour (table 22).

Table 22: Univariable analysis of age < 75 vs. > 75

	Under 75 n= (%) (n=283)	Over 75 (%) (n=49)	χ^2 test
Median Age	62 (19-74)	78 (75-83)	
Pre-operative factors			
Male Sex	155 (55)	20 (40)	0.56
Pre-Operative Chemotherapy	124 (44)	17 (35)	0.23
Background Liver Disease	124 (44)	20 (45)	0.8
No steatosis	189 (67)	30 (61)	0.42
Mild Steatosis	80 (28)	17 (34)	0.42
Moderate Steatosis	11 (4)	2 (5)	0.9
Severe Steatosis	3 (1)	0 (0)	1
Pre-op GFR <90	75 (27)	35 (71)	<0.001
Diabetic patients	24 (8)	8 (16)	0.086
ASA 3 or 4	28 (9)	3 (6)	0.4
Charlson Index >1 (with malignant status excluded)	90 (32)	17 (35)	0.69
Intraoperative factors			
Pringle Use	192 (68)	33 (68)	0.96
Intraoperative transfusion	18 (6)	3 (6)	0.95
Surgery over 4 hours	25 (9)	6 (12)	0.45
PHLF			
ISGLS grade A (Bilirubin >50)	39 (14)	19 (40)	<0.001
PHLF ISGLS grade B/C definition)	21 (7)	20 (41)	<0.001
Post-operative outcomes			
Surgical complication (e.g. bile leak, intraabdominal collection)	31 (11)	2 (4)	0.081
Medical complications (e.g. pneumonia, myocardial infarction, Stroke)	34 (12)	8 (16)	0.4
Reoperation	6 (2)	1 (2)	0.86
30-day mortality	3 (1)	1 (2)	0.42
90-day mortality	8 (3)	4 (8)	0.12
Median Length of stay (range)	7 (3-66)	11 (3-580)	Mann Whitney test = <0.001
Median Peak post-operative CRP (range)	67 (8-292)	77 (45-146)	Mann Whitney test = 0.4
Cancer patients only	N=251	N=41	
R1 resection	40 (16)	5 (12)	0.74
Disease recurrence (in either primary, liver or other metastasis)	100 (40)	18 (44)	0.3
Vascular invasion of tumour	85 (34)	9 (22)	0.09

There was a significantly higher level of pre-operative Chronic Kidney Disease (CKD) in patients >75yrs (71% vs 27%, $p < 0.001$) however CKD was not associated with PHLF development when this was examined separately in a multivariable model (table 23).

There was no significant difference between pathology (metastatic, primary, or benign) and any risk factor. There was a higher incidence of diabetes in primary cancer patients. Primary cancer patients also had higher disease recurrence rates (table 24).

Table 23: Multivariable model of Risk Factors for development of PHLF

	No PHLF % (n=291)	PHLF B/C % (n=41)	Odds ratio (95% CI)	P-value
Known risk factors for PHLF				
Age >75 vs age<75	10	49	8.8 (3.6-21)	<0.001
Male sex vs Female	53	73	0.44 (0.2-0.98)	0.05
Chemotherapy use vs None	43	41	1.3 (0.58-2.7)	0.98
Diabetes vs none	8	20	1.8 (0.5-2.7)	0.35
None/mild steatosis vs moderate/severe	34	32	1.6 (0.44-6)	0.47
Any Background liver disease (including steatosis, fibrosis etc.) vs none	45	37	0.48 (0.13-1.7)	0.26
eGFR <90 pre-operatively vs >90	30.5	51	1 (0.4-2.4)	0.99
ASA ≥3 vs <3	10	7	0.6 (0.12-2.7)	0.5
Charlson Index >1 (with malignant status excluded)	31	41	1.4 (0.5-3.8)	0.5
Intraoperative risk factors for PHLF				
Intraoperative transfusion	13	10	2.2 (0.5-9.1)	0.26
Surgery over 4 hours	10	2	0.2 (0.02-1.5)	0.13
Pringle use	64	63	0.89 (0.326-3)	0.85

Table 24: Comparison of patients with CRLM and other metastatic cancers, primary liver cancer and benign disease

	Metastatic% (n=253)	Primary cancer % (n=54)	Benign disease % (n=25)	P value
Pre-operative factors				
Age over 75	37	12	0	0.23
Male Sex	53	53	84	0.17
Diabetes	8	19	0	0.04
Background liver disease	42	46	60	0.67
ASA grade 3 or 4	10	11	0	0.99
eGFR <90	31	46	24	0.09
Chemotherapy	40	46	0	0.8
Charlson	29	43	40	0.75
Intra-operative factors				
Pringle				
Surgery >4h	9	9	8	0.64
Intra-operative transfusion	6	8	0	0.26
PHLF				
ISGLS A	15	26	4	0.26
ISGLS B/C	12	13	12	0.72
Post-operative factors				
Surgical complications	12	5	8	0.11
Reoperation	2	2	4	0.88
Medical complication	13	17	4	0.2
30-day mortality	1	2	0	0.74
90-day mortality	4	2	0	0.56
Cancer patients only				
R1 resection	14	29	n/a	0.46
Vascular invasion	25	45	n/a	0.14
Disease recurrence	16	85	n/a	<0.001

Due to the complex aetiology of PHLF it is important to assess each known variable, although it is unknown which factors will contribute most strongly. We were unable to discriminate by excluding any risk factor from the analysis.

If only hepatotoxic factors were included a multivariable model; chemotherapy use, background liver disease and intra-operative transfusion, then there is still find a significant result; indeed, the OR increases to 9.1 (see table 25).

Table 25: Alternative multivariable model of hepatotoxic factors

	Odds Ratio (95% CI)	P value
Age >75 (1)	9.1 (4.4-19)	< 0.001
Chemotherapy given	1.3 (0.6-2.7)	0.5
Background Liver Disease	0.6 (0.3-1.3)	0.2
Intra-operative transfusion	1.9 (0.6-6.9)	0.3

3.4.2 Post Hepatectomy Liver Failure

41 patients (12%) in total developed PHLF grade B/C as defined by ISGLS: 21 patients under-75 (7%) and 20 over-75 (49%). The odds ratio was significant for those over-75 developing PHLF (OR=8.8 (3.6-21), $p < 0.001$) Additionally, there were more patients over-75 with ISGLS grade A PHLF (elevated bilirubin on day 5) (40% vs 14%, $p < 0.001$). There was no difference in Pringle Manoeuvre times: for those who developed PHLF grade B, median total time = 29 minutes (4-81minutes) vs. 28 minutes (5-70minutes), $p = 0.82$; hepatic ischaemia therefore did not contribute.

There was no difference in 30- or 90-day mortality observed between the age groups. There was a significant increased 30 and 90-day mortality seen in those patients who developed PHLF. (30-day: no PHLF 0.5% vs PHLF 13% $p < 0.001$, 90-day: no PHLF 2% vs 13% $p = 0.01$), but no increase in complications. A summary of complications and reasons for return to theatre is found in table 26. Of the patients who developed bile leak, 1 had reoperation, all other cases were managed radiologically or endoscopically.

Table 26: Post-operative complications

Complication	Number of cases (%) (n=332)
Chest Infection	29 (9)
Wound Infection	12 (4)
Bile Leak	9 (3)
Encephalopathy	5 (1.5)
Acute Kidney Injury requiring Renal Replacement Therapy	5 (1.5)
Intra-abdominal Collection	5 (1.5)
Post-operative Haemorrhage (requiring reoperation)	3 (1)
Myocardial Infarction	2 (0.6)
Small bowel obstruction	1 (0.3)
Gastroparesis	1 (0.3)
Dehiscence	1 (0.3)
Biliary Stricture	1 (0.3)
Aspiration	1 (0.3)
Reoperations	7 (2)
Indication for reoperation (n=7)	
Bleeding	3
Intraabdominal Abscess	1
Bile Leak	1
Wound dehiscence	1
Biliary Stricture	1

3.4.3 Steatosis

There was no difference between the degree of steatosis in those over-75 and those under-75 (table 22). Furthermore, there was no association with PHLF development in a separately performed multivariable model that excluded other background liver pathologies (e.g. fibrosis) (table 23). Age remained an independent risk factor in this model. There were 5 patients (all under-75) with HCC and fibrosis but no cirrhosis. Three patients had severe steatosis, all in their 50s, none developed PHLF.

Table 27: A separate multivariable analysis of patients with moderate or severe steatosis, excluding liver disease of other causes

	No PHLF % (n=280)	PHLF B/C % (n=36)	Odds ratio (95% CI)	P-value
Known risk factors for PHLF				
Age >75 vs age<75	11	38	6.3 (1.1-14)	0.03
Male sex vs Female	54	69	1.5 (0.7-4)	0.4
Chemotherapy use vs None	16	31	1.2 (0.45-3.6)	0.69
Diabetes vs none	6	19	2.2 (0.48-9.5)	0.3
None/mild steatosis vs moderate/severe	49	38	0.8 (0.1-0.97)	0.9
None/mild/moderate vs severe	87	0	-	-
eGFR <90 pre-operatively vs >90	27	46	1.1 (0.3-3.4)	0.98
ASA ≥3 vs <3	11	4	0.2 (0.02-1.8)	0.16
Intraoperative risk factors for PHLF				
Intraoperative transfusion	7	8	2.5 (0.3-14.5)	0.3
Surgery over 4 hours	11	0	-	-
Pringle use	62	62	1 (0.6-4.2)	0.89

3.4.4 CT Volumetry

Volumetric analysis was retrospectively performed on all patients with PHLF where images were obtained (40 out of 49). All 40 patients were in the over-75 years age group. The median volume of liver with tumour volume subtracted was 1204ml (666ml-2302ml) and the FLR was 486ml (306ml-1166ml). The FLR for those over-75 measured a median of 42.5% (range 25%-72%) for those who developed PHLF grade B and 47.4% (32%-51%) for those who did not (p=0.925). None were below 25% volume.

3.4.5 Cost analysis

Patients who developed PHLF had a longer median total hospital stay (11 days vs 7 days, p=0.04), and longer ICU stay: 6 days (3-16) vs 0 (0-18) p<0.001). There was no difference in HDU stay. The calculated cost demonstrated that the bed stay for PHLF was higher: £10,987.50 (£6,175-£46,050) vs £2,575 (£900-£46,050 p=0.01). (USD=\$16,481.25 (\$9,262.5-\$69,075) vs. \$3,862.50 (\$1,350-\$69,075)).

3.5 Discussion

This is a large series, all with a comparable FLR due to a standardised right hepatectomy. Patients had a similar co-morbidity profile with comparable ASA (no cases with ASA 4 underwent right hepatectomy), eGFR and Charlson Indices – suggesting patients were fit-for-surgery and would not be expected to be at increased risk of PHLF. Our results show that when the cut-off identified by ROC-AUC, patients over-75 are at a higher risk of developing PHLF and have longer LOS and greater inpatient cost.

There were no significant differences between other known risk factors for PHLF when analysed in the multivariable model as these will have been corrected through patient selection. Patients who develop PHLF have a reported mortality of 12%(5) The mortality in our series is comparable with a 13% 90-day mortality.

3.5.1 Previous studies

Allard and colleagues quoted a risk ratio of 5.6 for PHLF in the over-70 age group in their major liver resection study of 277 patients(214), but no risk on their multivariable analysis. Other studies had no difference in rates of liver failure or mortality(235)(328)(329). Unlike the present study, none of these series accounted for variation in the extent of resection.

All patients in this study had an anatomical resection of segments 5,6,7 and 8, the majority having <50% FLR. Older patients may be at no increased risk from smaller resections or metastatectomies, but major resections present a massive physiological stress to patients, and factors like sub-clinical reduced synthetic/excretory function may explain our findings of increased PHLF development.

Vallance and colleagues(333) recently published a population study of 6081 CRLM resection patients and found an increased Hazard Ratio for death of 1.47 for those over 75, in line with the age cut-off identified by this series. Although they did not look specifically at outcomes of PHLF, our findings of increased risk are consistent, and as such those over-75yrs should be managed with this risk in mind.

Tzeng and colleagues(219) considered the fact that older patients have reduced physiological reserve and thus a reduced speed of hypertrophy. It has been previously demonstrated that older people have a slower rate of liver regeneration(133) and certainly this would be in keeping with the results of higher PHLF for the older cohort; these patients did not ‘catch up’ to provide adequate function.

We summarise previous studies investigating liver resection in the elderly in Table 28. Unlike the present series, most patients included in those studies were minor resections, or specific outcomes of PHLF were not discussed. Our study differs from the negative findings of previously published studies (Table 7) as it eliminates confounding differences in resection extent, and analyses specifically for PHLF by the updated definition of “*a post-operatively acquired deterioration in the ability of the liver to maintain its synthetic, excretory, and detoxifying functions, which are characterized by an increased INR and concomitant hyperbilirubinemia on or after postoperative day 5*”. By using this definition, we eliminate those patients with post-operative hyperbilirubinaemia due to such causes as bile leak, as these patients would not have impaired coagulation.

Table 28: Comparison of other studies examining outcome of older patients

	Number of patients	% Older patients	% Major resections	Difference in Complication Rate Older vs. Younger Patients (Relative Risk)	% PHLF in Older	% PHLF in Younger patients
Fong et al(330)	128	100	34	n/a	5	2
Caratozzola et al (336)	392	13	32	1.7	n/a	n/a
Hanazaki et al (337)	483	31	24	1.05	0.6	1.5
Bockhorn (338)	59	100	27	n/a	3.3	n/a
Mann (339)	191	25	66	1.5	2	3
Menon(263)	517	25	100	0.93	n/a	n/a
Present series	332	15	100	8.8 (OR)	49	10

Our results in terms of mortality itself are comparable, although not significant, but death in those who develop PHLF was 13%. Complications for those who did and did not develop PHLF were comparable, and we cannot say whether any complications that

developed led to impaired liver regeneration, or vice-versa, again in line with Vallance and colleagues' findings(333).

3.5.2 Other Risk factors

There were no other known risk factors found to be associated with PHLF development. This may be due to careful patient selection to exclude clearly at-risk patients from major resection. As such, known risk factors such as Diabetes (222)(239), where patients requiring insulin have been reported to have higher operative times and transfusion rates after liver surgery(221) were not found to have significantly increased risk. For a similar rationale, we conclude this to be the reason for comparable Charlson Indices (169)(334); the well-recognised measure of categorising co-morbidities. Pre-operative assessment for higher risk candidates/higher modified (excluding malignancy) Charlson Index patients were excluded prior to coming to surgery.

Similarly, although neo-adjuvant chemotherapy is associated with liver injury and steatohepatitis(229)(230)(231), any patient who developed these would have been excluded from this series; hence why no risk was demonstrated here. Our protocol was to wait 6-weeks between chemotherapy cessation and surgery, ensuring there was no preoperative evidence of hepatic dysfunction.

During the length of the study period, chemotherapy regimens and treatment protocols changed in response to new evidence. Most commonly in management of colorectal liver metastases (CRLM), 5-fluorouracil and Oxaliplatin were introduced while capecitabine and Irinotecan were used in other cases. As such, it was not possible to perform reliable analysis of varied chemotherapies utilised and their effect on PHLF.

There was no evidence of background liver disease contributing to failure. Just over half of patients had background liver disease, however it was mainly mild steatosis (there were 3 cases of severe steatosis, all in younger patients in their 50s) with minimal fibrosis. There were 3 patients with confirmed autoimmune hepatitis, 2 with primary sclerosis cholangitis, 1 with hemochromatosis and 1 patient with HBV – all aged under

55, and no other viral hepatitis cases. Our study population did not include patients with cirrhosis; such patients would have had a more parenchymal-sparing surgery or PVE.

Pre-operative renal insufficiency and liver resection has rarely been discussed in the literature, more often it is featured in studies examining the development of renal dysfunction or acute kidney injury (AKI) postoperatively(146)(222)(326). Our results show that the over-75 age group have a higher prevalence of CKD stage 2 or above(15) but in itself CKD did not place a significant increased risk of PHLF in this series. No patient with eGFR <40 was included and so the effect of more advanced renal dysfunction cannot be assessed here. The retrospective nature of this analysis means we cannot say how many patients were planned for right hepatectomy but then an intra-operative decision was made that the liver was not of sufficient quality to safely proceed which could have led to selection bias.

Overall our results show that despite careful preoperative patient selection for major resection older patients remain at higher risk. In addition, our analysis shows that the inpatient LOS for a patient that develops PHLF would cost on average £8,412 more than a patient without.

3.5.3 FLR

Most centres would consider 25% to be their threshold for the limit of resection in otherwise normal liver tissue(3)(4) without requiring procedures to induce pre-operative hypertrophy. All the patients included for Volumetry analysis had a volume greater than this threshold, with the median volume for those with PHLF 42.5%. The right hepatectomy was chosen for investigation for this study, as we would expect the remnant volume to be well above the threshold and therefore have low level of PHLF, which is demonstrated. So, despite adequate FLR-volumes, our older cohort still developed PHLF more frequently, suggesting that measurement of FLR-volume alone in this age group may not be enough to ensure adequate post-operative function. Factors such as increased fat fraction, differences in vascularisation and bilious drainage of remnant liver could be more prevalent in the older population(340).

There was no difference in R1 resections or vascular invasion between the ages or those who developed PHLF. This reflects that the degree of resection did not significantly differ between the two groups. An extended right or trisectionectomy may have achieved a higher R0 resection rate, but would have carried an inherent increased risk of PHLF(2).

3.5.4 Potential solutions for improving outcomes for older patients

One potential solution to improve outcomes for patients over-75 could be PVE. Despite our cohort's FLR being above the accepted 25% threshold, PHLF developed nearly half the time; one explanation is that patients over-75s require a larger FLR, similar to those patients with parenchymal liver disease. Older patients who require resection of ≥ 4 segment could be considered.

One influential randomised controlled trial by Farges and colleagues(79) showed there was no benefit for patients to undergo PVE before right hepatectomy, however the age group of this cohort was much younger, with the mean age being 53 for those without PVE and 58 for those undergoing PVE. Our cohort is much older, and we feel that this older group should be considered differently due to different physiology in older patients. PVE costs approximately £5,000 per procedure. If performing PVE on those over-75 years could prevent PHLF then it would be cost-effective, notwithstanding the potential for improved clinical outcomes.

However, a dedicated prospective study to investigate this hypothesis should take place as, although PVE does increase FLR(81)(75), it may induce some tumour growth in the contralateral liver in patients, which could render disease inoperable(341), in addition to the risk of complications from PVE itself such as abscess, cholangitis or thrombosis(75).

3.5.5 Limitations

Certain known risk factors such as BMI and malnutrition status, estimated blood loss couldn't be included in analysis as this data was not consistently documented in the notes or patient database.; a recognised weakness given the retrospective nature of data review. The practice at the unit was to screen and manage all malnourished patients with

dietitian input and enteral support. All patients were subject to enhanced recovery protocols post-operatively. We have used surrogate markers of blood loss (e.g. transfusion) which may not reflect directly blood loss to overcome this limitation. It is impossible to know if patients who would otherwise have been considered for a right hepatectomy underwent more limited parenchymal-preserving surgery at their planning stage or were denied their operation based on anaesthetic assessment, or significant co-morbidity altered their operative plan. This could have led to some degree of selection bias as our patient selection strategy may not be the same as other units' individual patient selection policies.

Using our defined age of 75 years old we find there is a sensitivity of 50%, specificity of 90%, PPV of 41% And NPV of 93% for PHLF. As such, age is a low-sensitivity, high-specificity test. As such we could not advocate age solely as an indication or contra-indication for surgery, as we appreciate certain older patients may have robust physiology sufficient to cope with the stress of major hepatectomy. This can be difficult to assess, however. Our findings demonstrate age allows a good risk stratification, enough to consider older patients at risk.

The consequences of development of PHLF is severe, we wish to promote to colleagues the importance of a potential increased risk this age group, and assessment in a holistic manner to maximise the chance of good outcome, with careful patient assessment and pre-operative work-up which may mean either hypertrophic procedures or a more limited resection. A prospective study in a multi-institutional setting may provide a definitive answer.

We feel our study's main strength: a large series with homogeneous resection population, identifies a significant risk for over-75s to develop PHLF. This contributes to our understanding of how best to manage this at-risk population of elderly patients who are considered for life-saving liver surgery, allowing better patient selection criteria to improve outcomes and reduce cost.

Chapter 4 – DGE-MRI acquisition and analysis methods

Prior to embarking on a clinical DGE-MRI study (chapter 5), a pilot study was performed to identify an appropriate acquisition and analysis method. See Appendix B for detailed recruitment strategy. This chapter presents the results of this pilot, part of which (describing the comparison of different post-processing models) was presented at the International Hepato-Pancreatobiliary Association meeting (IHBPA) and Association of Surgeons of Great Britain and Ireland meeting (ASGBI) in Manchester 2015 and published in *HPB April 16 Volume 18 S2 Page e697*.

4.1 Abstract

Aims

DGE-MRI of the liver provides perfusion and functional estimates which have potential clinical applications for liver disease assessment. There are methodological issues regarding appropriate acquisition method and analysis modelling. Data can be analysed with a dual-input uptake model, but it is unknown this is necessary. Visual assessment of image quality and time curves is a simple way to assess suitability of an acquisition protocol. This study aimed to assess suitability of 3 different acquisitions sequences, and compare accuracy of DGE-MRI perfusion and function parameters generated by a dual-input model, and simplified models.

Methods

3 acquisition protocols previously reported were performed on 5 patients each. Protocol 1: spoiled gradient 3D sequence, temporal resolution (TR) =2.4 seconds, protocol 2: TWIST 3D Sequence, TR = 1 second, Protocol 3: 2D multiplanar imaging, all post-injection of 10 ml of Gadoxetate for 7 minutes. Visual examination of each led to selection of the most suitable for further study. 5 more patients were subsequent recruited and imaged using the selected protocol. Their dynamic images were analysed the following models: dual input with, and without arterial delay, arterial input function (AIF) only and venous input function (VIF) only. Region of interests (ROI) were identified within each

segment in normal-appearing liver. Mean values for all ROIs were calculated using each model. Mean perfusion measurements (total plasma flow (TPF), arterial flow fraction (AFF) and extracellular volume (ECV)) and function measurements (uptake fraction (UF)) were compared using T test (Microsoft Excel 2015).

Results

Protocol 1 was selected as most suitable to evaluate different post-processing models. There was a significantly lower TPF with AIF-only model (dual-input with delay 152ml/100ml/min vs. AIF-only 70ml/100ml/min $p=0.003$) and a significantly higher UF observed (dual-input 9.4% vs AIF-only 16% $p = 0.001$). Removing arterial delay reduced AFF from 30% to 11% ($p=0.01$). The dual input model with arterial delay provided results similar to previous published reports. There was no difference in ECV fraction in any model (38% vs 37%).

Conclusions

An AIF-only analysis is only suitable for the measurement of ECV, which has been identified as a potentially useful parameter in the evaluation of fibrosis. Accurate TPF and UF are needed to fully assess function, so a dual-input model is required.

4.2 Introduction

DGE-MRI has emerged as an imaging-based modality to measure partial liver function with promising results(14). DGE-MRI is a relatively recent innovation, with multiple reported methods of data acquisition(218)(274). Two technical issues need to be addressed to allow a standardisation of DGE-MRI methodology:

- a) it has not been established which of the many available acquisition methods would give optimal quality image data without compromising on temporal or spatial resolution,
- b) it remains uncertain if is any improvement in data precision and accuracy by applying complex dual input modelling following acquisition.

There are many available acquisition sequences that give variable temporal and spatial resolutions(218)(274)(300)(322)(342), and increasingly complex analysis that can be applied in post-processing to dynamic MRI data. The introduction of mathematical modelling that can separate AIF, VIF and intracellular and extracellular spaces has led to the option of a dual-input, two compartment model (see chapter 2.4.5)(218) but it is unknown such a model is necessary or beneficial to obtain accurate measurements of perfusion and function. The lack of standardised methodology could mean comparison between different published reports is not possible.

4.2.1 Acquisition optimisation

Recently published studies utilised a spoiled-gradient 3D acquisition which has proven effective, but has potential flaws due to a relatively long temporal resolution and lower spatial resolution than other available techniques(218)(274). An acquisition using time-resolved angiography with interleaved stochastic trajectories (TWIST) could lead to a shorter temporal resolution by interpolation of measurements. This could potentially produce more accurate perfusion measurements, due the shorter interval between images during the arterial and venous contrast phases(218)(300).

Another approach is the use of multiplanar 2D sequences which are free from intra-frame artefacts and have been used in DCE-MRI of the kidneys(322)(342). Such a technique

could provide improved spatial resolution and image quality making identification of ROI, AIF and VIF more robust. Conversely, displacements between neighbouring slices due to breathing motion could render proper motion correction and segmentation difficult.

4.2.2 Application of dual input model

Data can be analysed with a dual-input two-compartment uptake model that accounts for arterial delay(218) (343)(344). The role of adding an arterial delay into the model is thought to be required due to the unique dual inflow anatomy of the liver; having predominantly venous inflow of ~80% and ~20% arterial inflow. Contrast will enter the liver at different times in the cardiac cycle. Automated measurements by linear regression modelling are thought to improve measurement parameters to improve precision and accuracy, but often the time delay generated will be non-physiological, often in the range of 8-12 seconds, whereas in reality this delay would be less than 1 second. It is uncertain why this non-physiological delay occurs(345).

Identification of the VIF can be difficult on some sequences due to reduced spatial resolution and movement artefact. If comparable perfusion or functional values exist without the need for VIF measurements, it would be both technically easier and quicker for analysis.

4.2.3 Aims

Given the variety of methods for image acquisition and post-processing that are available, before embarking on a study assessing the utility of DGE-MRI in a clinical setting, this pilot study aimed clarify on these two technical issues:

- a) identification of a suitable acquisition method by image quality assessment of 3 DGE-MRI acquisition methods: 3D spoiled gradient, 3D TWIST and 2D multiplanar imaging by visual examination to select the most suitable for further study
- b) assessment of the most suitable model for analysis by comparison of the effect on key perfusion and functional parameters when analysed with a dual input model with and without arterial delay, compared to simplified models.

This study was approved by submission to the REC committee South Central - Hampshire A and the application is included in Appendix B for detailed recruitment strategy (page 226-246).

4.3 Methods

Patients with histologically confirmed CRLM (selected as the most common indication of liver surgery and staging liver MRI) were recruited consecutively after they had been selected for curative liver resection in the hepatobiliary multidisciplinary team meeting based on preoperative CT findings. A DGE-MRI protocol was added into their planned diagnostic MRI. The study was performed in 2 phases, the first assessing acquisition optimisation, the second comparing analysis methods.

4.3.1 Acquisition optimisation

The following 3 free-breathing protocols were visually compared. 5 patients were recruited to each of 3 protocols: 15 patients were included in total.

1. Standard 3D Sequence obtaining images every 2 seconds: 3D spoiled gradient echo sequence with a temporal resolution of 2.4 seconds over a 8-min acquisition (3D fast low angle shot MRI (FLASH), temporal resolution (TR)/Echo Time (TE)=2.45/0.76ms, Flip Angle=24°, acquisition matrix=128x77, 61 phase encoding steps, reconstructed matrix 128x128, Field of view (FOV)=400x400 mm, slice thickness 10mm, 30 slices, reconstructed pixel size 3.125mm.
2. TWIST 3D Sequence obtaining images every second: 3D TWIST sequence (TR/TE = 2.8/1.1 ms, FOV = 400 mm, matrix = 128, flip angle=25°) with a interpolated temporal resolution of 1 second.
3. Pre-bolus 2D slice sequence with a multi-slice 2D sequence every 6 seconds (TR/TE = 1/1.1 ms, FOV = 400 mm, matrix = 128, flip angle=24°) .

For protocols 1 & 2, a dose of 10ml Gadoxetate (Primovist, Bayer) was delivered at 1ml/sec. Protocol 3 also received a dose of 10ml Gadoxetate (Primovist, Bayer) but an

initial pre-bolus of 1ml was given prior to acquisition, followed by the remaining 9ml delivered at 1ml/sec.

In addition to the DGE-MRI acquisition, a full diagnostic MRI was obtained for each patient: pre-contrast sequences included coronal and transversal T2-weighted imaging, axial T1-weighted Dixon imaging, axial fat-saturated T1-weighted imaging. The DGE-MRI sequence was followed by Echo Planar Imaging (EPI) diffusion imaging with b-values and repeat of the axial fat-saturated T1-weighted imaging at 20 minutes post contrast injection (hepatobiliary phase).

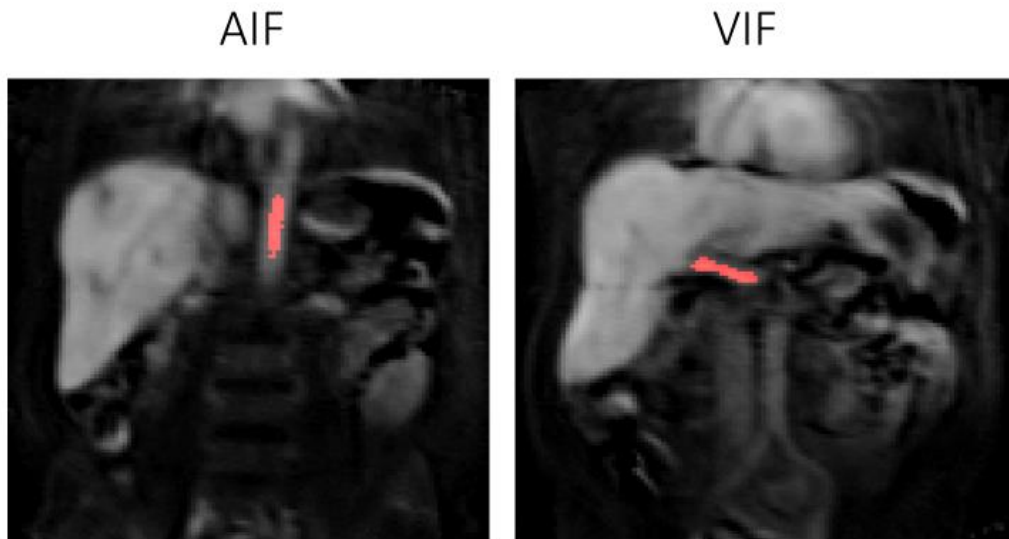
Each patient's DGE-MRI data was examined visually to assess image dynamics, maximum intensity maps, VIF time curves and delineation, image artefacts, and continuity of time curves using in-house software PMI 0.4 (sites.google.com/site/plaresmedima). The most appropriate acquisition sequence was decided prior to application of post-processing modelling.

Following the decision of the most suitable acquisition, 5 more patients were examined, 10 patients in total, using the selected sequence and analysed in PMI for comparison of different post-processing models.

4.3.2 Post processing modelling

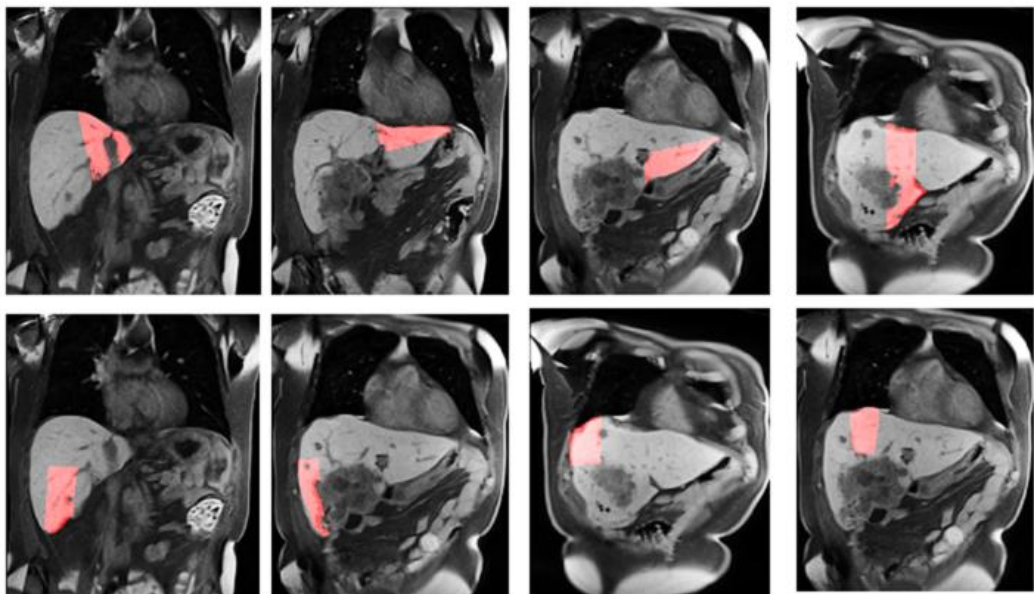
The maximum signal change over time was calculated and an AIF and VIF were defined on this map by drawing a small ROI in the abdominal aorta and portal vein (figures 15).

Figure 15: Identification of the AIF in the Aorta and VIF in the Portal Vein



An ROI was identified within each liver segment in normal-appearing liver tissue, avoiding any visible metastasis and benign discrete lesions, with no motion correction. A total of 8 ROI curves per patient were identified and mean values for all ROIs (a total of 80 separate analyses were performed, 8 from each patient included – figure 16) and patients were calculated by fitting signal-enhancement time courses to a dual-input two-compartment uptake model with arterial delay as described by Sourbron and colleagues(218) and described previously in Chapter 2.4.5.

Figure 16: Identification of ROI in Segments I-VIII



The fit was then repeated with three simplified models: (1) no delay fitted (i.e. arterial delay fixed to zero), (2) AIF only, (3) VIF only. The effect of the model simplification on the mean values of perfusion parameters (total plasma flow (TPF), arterial flow fraction (AFF) and extracellular volume (ECV)), and function parameters (uptake fraction (UF)) were tested by comparing the means with Student T test.

Data analysis was performed by two authors (David Longbotham and Steven Sourbron) using PMI 0.4. Statistical significance was defined at $p < 0.05$ and performed using Microsoft Excel (2019).

4.4 Results

4.4.1 Selection of Acquisition Protocol

Protocol 1 yielded an image quality that was relatively free of artefact, allowing segmental ROI delineation, AIF and VIF identification in all 5 patients, with appearances of time curves consistent with previous studies (see figure 11).

Image quality for participants undergoing Protocol 2 suffered from significant artefacts. The image quality was inferior to those obtained by protocol 1, and it did not appear that the improvement in temporal resolution had any difference on the appearance of time curves, therefore was rejected for further study as VIF identification could be more difficult.

Protocol 3 imaging could not be analysed in the PMI software. Due to nature of 2D multiplanar sequences and the free breathing acquisition, each slice was taken during a different part of the breathing cycle, making motion correction difficult without additional data. Measurement of the liver volume was compromised, with a mismatch of the true liver and segmental volumes. This yielded an unsuitable acquisition method, therefore was rejected for any further study.

Protocol 1 (described in 4.3.1) was therefore chosen as the most appropriate acquisition method. 5 extra patients with CRLM underwent data acquisition using this protocol.

4.4.2 Application of post-processing modelling

TPF was significantly lower with the AIF-only model (dual-input 152ml/100ml/min vs. AIF-only 70ml/100ml/min $p=0.003$) and there was a significantly higher uptake fraction (dual-input 9.4% vs AIF-only 16% $p = 0.001$). There was no difference in ECV (38% vs 37%); suggesting ECV to be robust parameter that is independent of the details of the model. Models that excluded VIF had a significantly reduced measurement of plasma flow and uptake fraction but ignoring the arterial input did not affect the mean values. The functional parameter uptake fraction is not sensitive to the use of an arterial delay. The

arterial delay caused a significant reduction in measured AFF but did not affect the TPF (table 29).

Table 29: Results comparing use of the full model (left) and three simplified versions

	Dual-inlet model with arterial delay	No delay (Mean (SD))	AIF only (Mean (SD))	VIF only (Mean (SD))
Total Plasma Flow (ml/100ml/min)	152 (66)	158 (35)	70 (31)*	192 (28)
Arterial Flow Fraction %	30 (13)	11 (6.7)*	N/A	N/A
Extracellular Volume Fraction %	38 (7.6)	42 (12)	31 (3.6)	45 (18)
Uptake Fraction %	9.4 (5.2)	8.8 (5.6)	16 (7.6)*	7.5 (4.9)
Arterial Delay (secs)	9 (5.9)	N/A	10 (2.1)	N/A

*p<0.05 T test

All values above are given as Mean (SD)

4.5 Discussion

4.5.1 Dual input compared to single input models

If a measurement of the AFF is required in order to derive functional parameters, then a dual-input model is needed. The choice of fitting an arterial delay parameter has a significant effect on the mean value of the AFF, but not on the other measured parameters. In particular the measurements of function are not affected by the choice of the arterial delay strategy. As no gold-standard is available this study cannot identify whether fitting an arterial delay produces more accurate results, but AFF values fitted with a delay are more consistent with literature values(346). On the other hand, the fitted delay values are higher than expected for a transit from aorta to liver. This is similar to those reported in studies by Chouhan and colleagues(345), however given the potential for a multitude of DGE-MRI models and acquisition sequences it can be difficult to extrapolate data between inter-departmental studies – something which requires development to standardise within the literature.

If perfusion parameters are not required, there is no need to include the AIF in the analysis, as a single inlet model with VIF alone does not affect the mean parameter values of the uptake fraction. In such a case this step in the analysis protocol can be eliminated, and a simpler and faster model fit can be performed. This may have

significant implications for the practicality of the method and robustness of single-pixel results.

A single-input model with an AIF alone is most attractive from a practical point of view as the AIF is more easily identified than the portal vein. Given the significant different measurements of TPF between the models, and the need for plasma flow in function analysis then both AIF and VIF need to be included as they may affect the accuracy of function measurement, and all further analysis will need both input functions to be measured. These results suggest that an AIF-only analysis is only suitable for the measurement of ECV, which has been identified as a potentially useful parameter in the evaluation of fibrosis due to the increased water content of fibrotic tissues(299). No patient included in the study had any evidence of fibrosis, or significant parenchymal liver disease so this could not be tested further. The results are consistent with the relatively low contribution of arterial perfusion in healthy liver.

Table 30: Summary of models and which data is obtained

Model used	Data obtained
Dual-input model with arterial delay	Liver Function and Perfusion
Dual-input model with no delay	Liver Function and Perfusion (less accurate)
AIF only	Extracellular volume (fibrosis measurement)
VIF only	Liver function only

4.5.2 Limitations

The small cohort size analysed may impact on the validity of the results leading to a type 1 error. The lack of defined gold-standard values of any DGE-MRI parameters remain challenging to address what should be the 'correct' range of measurements, we concluded that previously published results were in line of what was expected. With the technology being in the early development stages with no large population studies to validate reference ranges, caution is always required regarding validity of results. Along the same lines this study cannot identify whether fitting an arterial delay produces more accurate results.

The lack any quantitative assessment for the selection of protocol 1 over the other examined acquisitions reduces the validity of the conclusions of protocols 1's perceived benefits. It was decided, given the extensive artefacts on protocol 2 that it would make the VIF more difficult to identify. It was not possible to analyse protocol 3 at all, and it was felt further data collection was unnecessary. By rejecting these 2 acquisition protocols, 10 patients were recruited for study and no data was included in the clinical study, as described in chapter 5. Given the tight recruitment timetable and paucity of available patients, in retrospect, it was unnecessary to obtain so many scans to select the acquisition protocol and the decision could have been made at an earlier stage in patient recruitment. Those 10 patients underwent their diagnostic imaging in addition to the DGE-MRI sequences, so their care was not compromised, with completed liver staging MRI reporting by a liver radiologist and appropriate surgical intervention as per their disease state.

4.5.3 Conclusions

The 3D spoiled gradient DGE-MRI sequence with a TR of 2.4 seconds was thought to be the most suitable acquisition. A dual-input model is required to separate arterial and venous perfusion. All other parameters can be measured using a single-input model with a venous input. Accurate TPF and uptake fractions are needed to fully assess function, so a dual model is required for any future analysis of DGE-MRI estimates of liver function, but options of simplified models exist for fibrosis assessment. Parameter values suggest that an arterial delay must be included when a dual-input model is used, but a question remains why the values for the arterial delay appear non-physiological. A future simulation study may help to provide a more conclusive answer.

Chapter 5 - Prediction of post-hepatectomy liver function with Dynamic Gadoxetate-Enhanced MRI

This study was approved by the REC committee Wales 6. For the detailed recruitment strategy see Appendix C. Chapter 5 has been prepared with the intention to submit to HPB for consideration of publication. It has been accepted for presentation at the 28th International Society for Magnetic Resonance Imaging in Medicine (ISMRM) annual meeting and exhibition in Sydney, Australia, April 2020.

This chapter describes the results of a study assessing DGE-MRI estimates of function compared with post-hepatectomy clinical outcomes. The primary outcome was correlation of FLR-function estimates with post-operative bilirubin. Secondary outcomes were assessment of DGE-MRI function estimates with volumetry, and risk factors for PHLF development.

5.1 Abstract

Aims

Risk assessment for major hepatectomy relies on predictions of FLR volume, but this is a poor surrogate of FLR function in the presence of liver disease. We hypothesize that FLR-function as estimated by DGE-MRI provides a more reliable and widely available assessment of surgical risk. The aim of this study is to identify DGE-MRI biomarkers that can predict post-hepatectomy liver function.

Material and Methods

29 patients with normal liver function requiring resection for CRLM were recruited. DGE-MRI was added to their pre-surgery staging MRI. Imaging biomarkers were derived, characterizing whole liver and FLR-volume, perfusion and function. Primary outcome was post-operative bilirubin. DGE-MRI and biochemical biomarkers were correlated individually against the primary outcome to identify those with predictive potential using linear regression models. Secondary outcomes tested FLR-function with FLR-volume,

and association of function parameters (principally gadoxetate uptake rate (UR), fraction (UFR) and function (UFu) with PHLF risk factors development using T test and Mann-Whitney test. Significance was defined as $p < 0.05$.

Results

Four DGE-MRI biomarkers of FLR-function were predictive of hyperbilirubinaemia, including FLR-uptake rate ($r = -0.57$, $p = 0.007$) and FLR-clearance ($r = -0.53$, $p = 0.014$). Notably neither FLR-volume, or pre-operative biochemistry were correlated with post-operative bilirubin. Secondary outcomes showed there was strong correlation between FLR-volume and FLR-function ($R_2 = 0.977$ $p < 0.001$). Older patients had reduced function: a lower UR (6.1ml/100ml/min vs 14.6ml/100ml/min $p = 0.02$), UFu (78.6ml/min vs 211ml/min $p = 0.01$) and UFR (5.7% vs 10% $p = 0.009$). Patients who underwent major resection compared to limited resection had a significantly lower UFu (181ml/min vs 294ml/min $p = 0.047$) and UFR (7.6% vs 12.6% $p = 0.047$).

Conclusions

DGE-MRI estimates of function show potential to inform patient selection and surgery planning, relevant in patients with liver disease where volumetry isn't reliable. Older patients and patients with higher metastatic burden had reduced uptake and metabolism of contrast; suggesting such patients have impaired liver excretory physiology. Future studies should aim to confirm this hypothesis using direct post-operative function measurements with ICG.

5.2 Introduction

Determining liver function is increasingly required for patients who require major liver resection for CRLM; the commonest indication for surgery(3)(157)(347). It is important to have a robust pre-operative method of determining liver function to reduce risk of complications caused by inadequate functioning liver, such as PHLF; a condition with high morbidity and mortality(5)(6).

Methods such as ICG(12), GECT(278), and LiMAX(282)(283) are effective in assessing global liver function, however such methods are inadequate for surgical planning if there is heterogeneity of liver tissue or the FLR volume is expected to be marginal or potentially insufficient (as discussed in chapter 2.3).

CT volumetry is most commonly used for pre-operative planning, however it does come with some limitations(199)(348). In particular there is uncertainty around the correlation of CT volumetry with liver function and postoperative outcome(349). Even an estimated FLR based on patient weight has been demonstrated to be superior to measured FLR for prediction of PHLF (see chapter 3.4.4)(10).

FLR-volume may not reflect FLR-function when there is underlying parenchymal disease or hepatic comorbidity such as fibrosis, CILI(350), cirrhosis, or steatosis leading to inhomogeneous liver function(351). A functional bias may be observed. However, if function is homogenous then volume and function will be equivalent. For patients with CRLM and no other liver disease this may be the case. Scintigraphy has demonstrated that there is a role in segmental function assessment of the liver in patients undergoing major hepatectomy which is more robust than volumetry alone(13). Unfortunately, hepatobiliary scintigraphy is underused.

More recently, Gadoxetate-enhanced MRI has emerged as a more widely available alternative imaging-based method to measure liver partial function(14) (chapter 2.4.3). Static Gadoxetate-enhanced imaging has diagnostic benefit(352) for lesion characterization in the hepatobiliary/delayed phases; for benign(353), malignant(354)

and cirrhotic liver disease(355). It is commonly used in pre-operative staging of CRLM. Signal enhancement indices correlate with reference measurements of global liver function: ICG and GSA in animal(356) and human models(357).

Segmental liver function and perfusion can be quantified by DGE-MRI, which involves rapid dynamic imaging in the minutes after injection of the agent and data interpretation by pharmacokinetic analysis (218) (358). Since function can be measured at a segmental level, DGE-MRI can potentially provide a direct prediction of post-operative liver function in absolute units (mL) blood cleared of Gadoxetate per min and per kg body weight) by defining the FLR-function accurately based on expected extent of resection.

There is currently limited data on the added value of DGE-MRI functional assessments for patients undergoing liver resection as compared to current pre-operative assessments such as biochemical tests and FLR-volumetry. Reports by Nilsson and colleagues showed DGE-MRI can accurately predict function in patients with expected liver segmental function heterogeneity such as PBC(299), PSC(298) and alcohol-related and viral-induced Cirrhosis(300). One study demonstrated potential utility in liver surgery planning, by simulating a left hemihepatectomy (segments 2, 3 and 4) in patients with cirrhosis and control studies(301). However, there are so far no studies correlating pre-operative DGE-MRI measurements of liver function directly with post-operative outcomes. The optimal management of PHLF is to accurately predict when it will develop and use this prediction to tailor an operative plan to optimise the FLR. It is postulated DGE-MRI could have a role in the prediction of liver dysfunction, most pertinently predicting PHLF.

PHLF risk factors are numerable and it is unclear what is the exact mechanism for their contribution to the PHLF syndrome (discussed in chapter 2.2 and 3). If the causative reason that factors such as age increase PHLF risk is because of a pre-operative impaired liver function that was not clinically detected, it would be important to identify this prior to subjecting patients to major surgery. DGE-MRI could have a role in identifying such impaired physiology(218)(Chapter 5.4.2).

Study objectives

The primary aim of this study is to determine if any pre-operative DGE-MRI biomarkers of liver function and perfusion can predict post-operative outcomes. The question was addressed by measuring correlations between pre-operative DGE-MRI biomarkers with post-operative liver function, using bilirubin as the primary outcome and surrogate marker for function.

Secondary outcomes aimed to assess the correlation of functional estimates with volumetry to demonstrate if DGE-MRI can demonstrate if liver function is homogeneous in patients with CRLM, and whether DGE-MRI estimates of function can predict PHLF itself, or if any known PHLF risk factor is associated with liver dysfunction(6).

5.3 Materials and methods

5.3.1 Subjects

This was a single centre, prospective non-randomised observational study approved by the local research ethics committee. 29 patients with confirmed CRLM were recruited consecutively after they had been selected for curative major liver resection in the hepatobiliary multidisciplinary team meeting based on their preoperative CT. Additional inclusion criteria were: >18 years old, histologically confirmed colorectal carcinoma: either resected or expected resectable primary disease with radiological evidence of resectable metastatic disease. Exclusions were pregnancy, allergy/intolerance to Gadolinium-based contrast agents, and inability to undergo MRI. Their histology specimen was used to determine evidence of parenchymal liver steatosis based on the pathologist's report.

5.3.2 MR scanning

All participants underwent a pre-operative staging MRI on a Siemens Aera scanner (1.5T) as part of their routine pre-surgical assessment. For this study, the routine protocol was modified by including a DGE-MRI sequence. DGE-MRI data were not shared with the clinical care team to avoid an influence on operative management decision making.

DGE-MRI was performed with a free-breathing protocol using a 3D spoiled gradient echo sequence describe in detail in chapter 4.3.1 (protocol 1), briefly, this was a spoiled gradient 3D sequence with a temporal resolution of 2.4s and 8-min acquisition. A 10ml dose Gadoxetate was delivered at 1ml/sec. Diagnostic imaging included pre-contrast sequences included coronal and transversal T2-weighted imaging, axial T1-weighted Dixon imaging, axial fat-saturated T1-weighted imaging. The DGE-MRI sequence was followed by EPI diffusion imaging with b-values and repeat of the axial fat-saturated T1-weighted imaging at 20min post contrast injection (hepatobiliary phase).

5.3.3 Surgery

Patients underwent liver resection appropriate to their oncological and radiological staging based on their MRI and CT reports, and 'fitness for surgery' assessment.

Hepatectomies were performed using a similar open surgical technique by 5 different surgeons; an extra-glissonian approach to the porta hepatis, liver dissection using CUSA and intermittent Pringle as required. Intra-operative ultrasound was occasionally applied for lesion identification. The descriptions of segments resected and the naming of the operations were based on the Brisbane Classification(47) and are described as such throughout (see chapter 2.1.9).

5.3.4 Post-operative care

All patients were admitted to a High Dependency Unit following resection for a minimum of 24 hours, as part of an enhanced recovery program. Their biochemical and clinical progress was observed, and the patient was discharged home when medically fit.

5.3.5 DGE-MRI post-processing

The post-processing analysis of the DGE-MRI was performed by two of the authors (DL and SS); blinded to the clinical outcome of any of the patients at the time of analysis. Images were post-processed using PMI 0.4 (218). Five independent parameters were produced for each segment: TPF (ml/min/100ml), arterial delay (sec), AFF (%), ECV (%), hepatocellular UR (ml/min/100ml).

The details of the image processing have been described previously (218). Briefly, AIF and VIF were defined semi-automatically on a maximum signal-enhancement map, using an interactively defined threshold to select pixels with high enhancement values inside the aorta and portal vein, respectively. Tissue ROIs were drawn semi-automatically to cover each liver segment on a map of the area under the enhancement curve. First, threshold was set interactively to identify liver tissue in 3D and exclude metastases and discrete benign lesions. Second, segments were delineated manually on these thresholded ROIs using IHPBA's segment definition(47) and Dodd's radiological description(359) using as landmarks the inferior vena cava, the right hepatic vein, middle hepatic vein and the falciform ligament. Concentration-time curves for each segmental ROI, AIF and VIF were calculated by assuming linear signal-relationship by subtracting the baseline signal. The dual-input two-compartment uptake model was then fitted to these data on a segment-per-segment basis. Figures 15 and 16 (chapter 4.3.2) demonstrate the drawn ROI defining the AIF, VIF and segments.

5.3.6 FLR volume and function measurement

The segmental volumes (V , ml) were determined for each segment by following the same segmentation approach as for the DGE-MRI but applied to the late-phase post-contrast breath hold T1-weighted imaging.

A segmental uptake function (UF, ml/min) was determined by multiplying segmental UR and V ($UF = UR \cdot V$). Absolute FLR function (ml/min) and absolute FLR volume (ml) were calculated by adding up UF and V , respectively, for all the segments in the FLR. Whole liver function and -volume were determined in the same way by adding up UF and V , respectively, for all segments. To arrive at directly comparable quantities and align with surgical convention, a *relative* FLR function (%) and *relative* FLR volume (%) were calculated by dividing absolute FLR function and -volume by the corresponding whole liver quantities.

A segmental plasma flow (PF, ml/min) was determined by multiplying segmental tissue plasma flow and V . FLR plasma flow was calculated by adding up PF for all the segments

in the FLR, and whole liver plasma flow was calculated by adding up PF for all the segments.

A complete measure of liver function needs to account for the blood flow to the liver as well as hepatocellular function and should be considered relative to patient size to allow comparisons between subjects. The most direct measure of function is therefore the liver clearance (CL) of an indicator in units of mL/min/kg (mL blood plasma cleared of the indicator per min and per kg body weight). CL for the FLR and the whole liver are calculated using a known formula as $UF * PF / (UF + PF)$, and subsequently divided by body weight.

Total liver function and -volume were determined in the same way by adding up UF and V, respectively, for all segments. To arrive at directly comparable quantities and align with surgical convention to express cut-offs on FLR volumes as a percentage of total liver volume, we calculated *relative* FLR function (%) and *relative* FLR volume (%) by dividing absolute FLR function and -volume by the corresponding total liver quantities.

5.3.7 Data Analysis

Post-operative bilirubin measured on day 5 was chosen as the primary outcome biomarker due to sharing the same cellular excretion as Gadoxetate, and its common use as surrogate for liver function and a marker of post-surgery dysfunction(215)(360).

The primary objective was assessed with a linear regression model and Pearson's test to measure strength of correlation between FLR-based biomarkers with post-operative bilirubin levels. We also tested predictive value of whole liver biomarkers to determine whether there is an added benefit in measuring the FLR separately. In order to determine whether DGE-MRI has added value over cheaper and readily available clinical markers, we also correlated common clinical risk factors for hepatic dysfunction(6) and biochemical measures against post-operative bilirubin levels. Available pre-operative clinical factors were weight (kg), age, diabetes status, BMI >30, pre-operative chemotherapy use (defined as receiving one or more cycle), renal insufficiency (defined

as eGFR <90), presence of background liver steatosis, and predicted number of segments removed. Available pre-operative biochemical markers were bilirubin, ALT, Alkaline Phosphatase, Albumin, INR, Prothrombin time, Lactate.

5.3.8 Secondary outcomes

Secondary analyses tested the strength of correlation between FLR-volume and FLR-function using Pearson correlation to determine if liver function was homogeneous in the studied population.

Any difference between the main risk factors for PHLF(6) and DGE-MRI estimates of function and perfusion was tested with T-test and Mann-Whitney test. The dependant variables were:

- Perfusion Parameters: Total Plasma Flow, Arterial and Venous Flow Fraction, Extracellular Volume, and Mean Transit Time.
- Function Parameters: Uptake Rate, Uptake Fraction and Uptake Function.
- Volume
- Functional bias

The Functional bias, a measure of the discrepancy between volume and function was calculated:

$$\text{Functional Bias} = \text{FLR Volume \%} - \text{FLR Function \%}$$

The independent variables were known risk factors for liver dysfunction:

- Pre-operative factors: chemotherapy, background liver steatosis, diabetes, BMI >30, renal dysfunction (eGFR <90), pre-operative liver dysfunction (bilirubin >20)
- Intra-operative factors: major vs. minor resection
- Post-operative factors: post-operative infection

A ROC analysis was performed for each variable to assess the effectiveness of the DGE-MRI parameters as a diagnostic test.

A significance level of 0.05 was assumed. All statistics were performed using SPSS v22 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp).

5.4 Results

5.4.1 Patient Demographics

29 patients were recruited, and 28 patients were included. 1 was excluded due to incomplete dynamic data collection. The median age was 63 years (Range 41-83). 18 were male. 23 patients underwent liver resection: 15 patients had major liver resection; 8 patients underwent a more parenchyma-preserving limited resection. 6 patients were deemed inoperable, either due to findings on their staging MRI of more extensive liver metastasis or extra-hepatic disease, or subsequent clinical reasons for being unfit for surgery, and hence excluded from analysis of FLR prediction. Patients who received chemotherapy underwent a minimum of 3 cycles of either oxaliplatin plus fluorouracil and leucovorin (FOLFOX) or single agent Capecitabine. No patient had hyperbilirubinaemia prior to surgery. All cases of histologically confirmed steatosis were mild only (<5% total liver volume). Demographics are included in table 31. A detailed description of each patient's results included in Appendix A.

Table 31: Patient demographics

	Major Liver resection (n=15)	Minor Liver Resection (n=8)	No liver resection (n=6)
Age	63 (41-83)	63 (47-78)	63 (49-69)
Patients aged Over 75 %	27	12.5	0
Median Number of segments resected	3 (3-5)	2 (1-2)	0
Median Remnant Liver Volume (%)	55 (27-60)	73 (67-90)	n/a
Median Remnant Liver Function (%)	53 (24-62)	74 (65-91)	n/a
Pre-operative chemotherapy use (%)	73	37.5	100
Evidence of background liver steatosis (%)	53	75	n/a
Pre-operative bilirubin	18 (5-20)	8 (5-26)	
Pre-operative ALT	20 (11-96)	21 (9-56)	
Pre-operative ALP	231 (155-555)	231 (150-336)	
Pre-operative Albumin	45 (41-50)	44 (41-48)	
Pre-operative INR	1 (0.9-1.1)	1 (0.9-1)	
Pre-operative PT	11 (10-12)	11 (10-11)	
Pre-operative Lactate	1 (0.9-1.3)	1 (0.9-1)	

5.4.2 DGE-MRI function estimates and post-operative function

Three parameters measuring FLR function were negatively correlated with post-operative bilirubin (Table 32, Figure 17 and 18): FLR-UR ($r = -0.57$, $p = 0.007$), FLR-CL ($r = -0.53$, $p = 0.014$), FLR-UF ($r = -0.45$, $p = 0.04$). In particular FLR volume, either in absolute or relative units, was *not* predictive of post-operative function. Equally, FLR perfusion and related parameters such as the arterial fraction were *not* predictive of outcome. One whole liver parameter (WL-UR) was significantly correlated ($r = -0.43$, $p = 0.04$), but not as strongly as the equivalent parameter for the FLR.

Figure 17: Comparison of post-operative bilirubin with FLR-GC ($r=-0.53$, $p=0.014$)

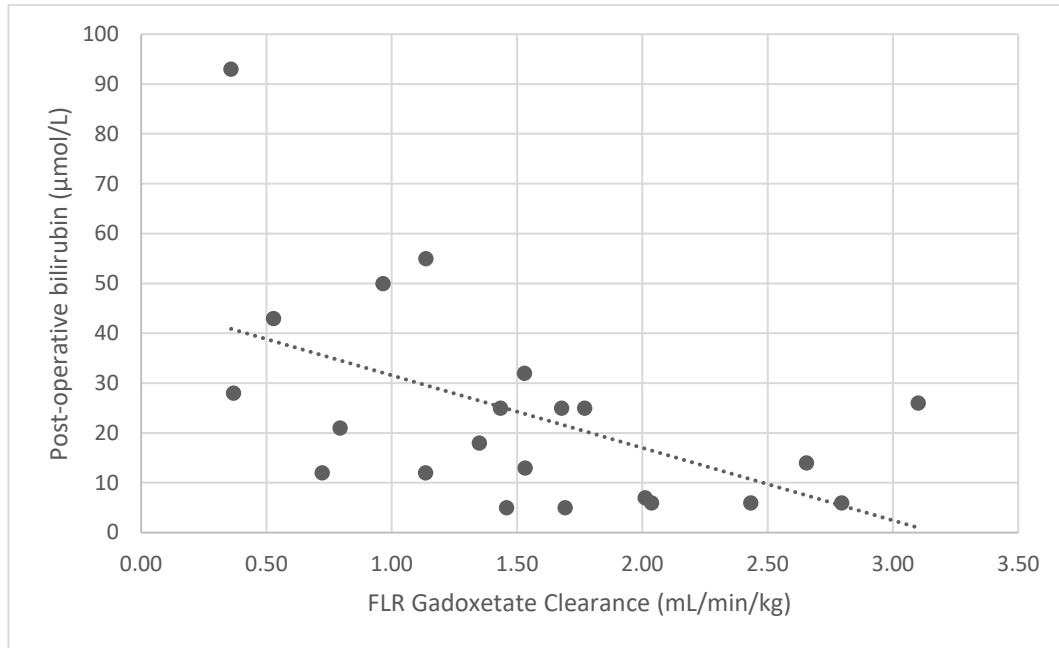
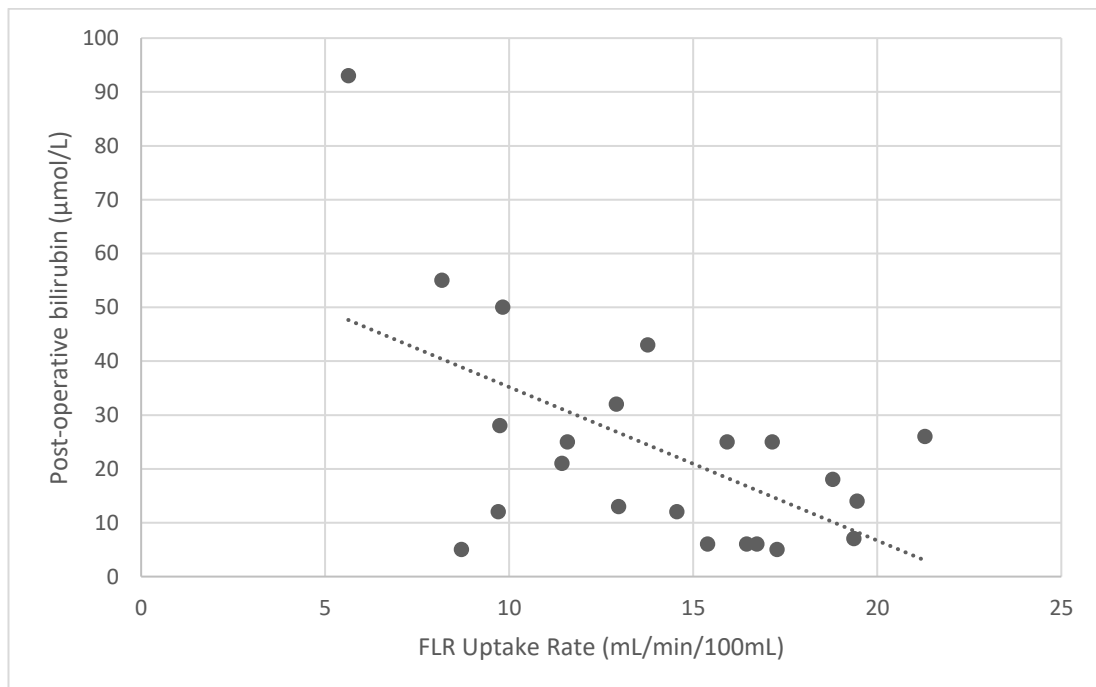


Figure 18: Comparison of post-operative bilirubin with uptake rate ($r=-0.57$, $p=0.007$)



5.4.3 Clinical markers

There was no correlation of FLR-volume with post-operative bilirubin (table 32). As mentioned, volumetry is considered an important assessment to ensure adequate FLR to avoid post-operative dysfunction, so this result is important in context of this study as the predictive value of function assessment has increased utility over volume.

5.4.4 Pre-operative biochemical biomarkers

There was correlation with an elevated pre-operative bilirubin, and the presence of background liver steatosis as per the pathology report ($R=0.43$ $p=0.04$), and although there was no association of patients' weight, when corrected into BMI there was an association with post-operative bilirubin ($R=0.46$ $p=0.03$). It is known that obese patients have a higher incidence of NAFLD, and this may explain this finding. No other risk factor examined was predictive of post-operative function (table 32).

Table 32: Correlation of DGE-MRI estimates with post-operative bilirubin

	Correlation with post-operative bilirubin (umol/L)	P-value
Whole Liver estimates		
Liver Volume (ml)	0.1	0.65
Total Plasma Flow (ml/100ml/min)	-0.17	0.44
Arterial Flow Fraction (%)	0.23	0.35
Extra Cellular Volume (ml/100ml)	-0.17	0.45
Uptake Rate (ml/100ml/min)	-0.43	0.04
Arterial Plasma Flow (ml/100ml/min)	0.36	0.13
Venous Plasma Flow (ml/100ml/min)	-0.18	0.46
MTT (secs)	0.01	0.95
Uptake Fraction (%)	-0.2	0.36
Uptake Function (ml/min)	-0.34	0.12
Plasma Flow (mL/min)	-0.097	0.67
Normalised clearance (mL/min/kg)	-0.4	0.056
FLR estimates		
Volume (ml)	-0.34	0.13
Total Plasma Flow (ml/100ml/min)	-0.14	0.54
Arterial Flow Fraction (%)	0.08	0.74
Extracellular Volume (ml/100ml)	-0.16	0.48
Uptake Rate (ml/100ml/min)	-0.57	0.007
Arterial Plasma Flow (ml/100ml/min)	0.36	0.15
Venous Plasma Flow (ml/100ml/min)	-0.03	0.91
MTT (secs)	0.04	0.86
Uptake Fraction (%)	-0.27	0.24
Uptake Function (ml/min)	-0.45	0.04
Plasma Flow (mL/min)	-0.27	0.24
Normalised clearance (mL/min/kg)	-0.53	0.014
Volume %	-0.34	0.09
Function %	-0.41	0.07

Table 33: Correlations of patient factors and pre-operative biochemical tests

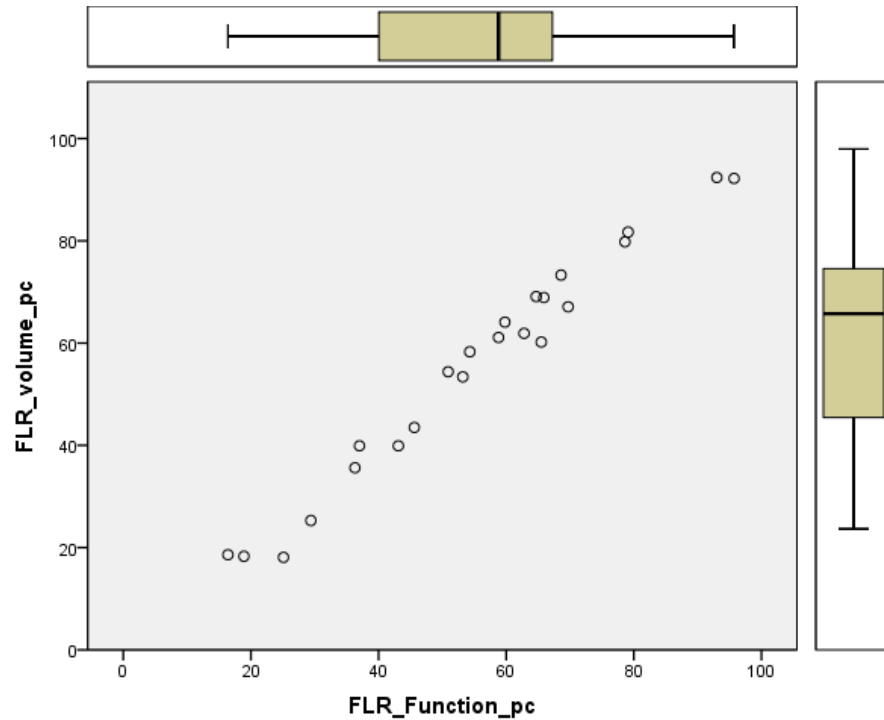
	Correlation with post-operative bilirubin ($\mu\text{mol/L}$)	P-value
Pre-operative patient factors		
Weight (kg)	0.13	0.56
Age	0.39	0.07
Diabetes status (present vs not)	0.03	0.98
BMI >30 vs <30	0.46	0.03
Chemotherapy vs no chemotherapy	0.32	0.14
Renal Insufficiency (eGFR <90) vs eGFR >90	-0.05	0.83
Liver steatosis vs normal liver	0.11	0.628
Pre-operative biochemical tests		
Bilirubin ($\mu\text{mol/L}$)	0.28	0.21
ALT (U/L)	0.13	0.58
Alkaline Phosphatase (U/L)	0.1	0.67
Albumin ($\mu\text{mol/L}$)	0.07	0.76
INR	-0.3	0.18
Prothrombin time (s)	-0.2	0.33
Lactate (mmol/L)	0.14	0.54
Number of segments	0.29	0.2

5.4.5 Secondary outcomes

5.4.6 Association of FLR volume and function

There was a strong correlation between the normalised FLR-volume and FLR-function %, Pearson correlation = 0.989, $R_2 = 0.977$ and a B value = 1.024 ($p < 0.001$). This demonstrates that in our population FLR-volume and -function are equivalent and FLR-function testing robust; and would suggest that liver function in this population is homogeneous. FLR-function could therefore be considered for assessment of the FLR in this population in place of volumetry if reduction of ionising radiation exposure is desirable.

Figure 19: FLR volume and FLR function



5.4.7 Association of PHLF risk factors with DGE-MRI estimates

When all risks were examined, there were significant differences for 3 subsets of patients for functional parameters: age, steatosis, and extent of resection. All other tested variables had non-significant results.

5.4.8 Function parameters

Age

There was a significantly reduced uptake of contrast for the measures of function: uptake rate, uptake fraction and uptake function in patients over 75, indicating that older patient's livers may have impaired uptake ability and excretory function. This was seen in both assessment of the uptake of the whole liver and the FLR, which suggests that there is global impairment of the older patients' liver. ROC Analysis showed significant AUC values of over 0.75 for each functional parameter, demonstrating each function estimate could have a role as a diagnostic test (see table 34).

Table 34: Age compared to the Whole Liver functional parameters

	Age <75 (Mean SD) n=10	≥75 (Mean SD) n=5	P value (T test)	<75 Median (Range)	≥75 Median	P value (Mann Whitney test)	AUROC	P value
Whole Liver Function								
Uptake Rate ml/100ml/min	14 (3.9)	8 (4.4)	0.03	14.6 (2-21)	6.1 (4-13)	0.019	0.84	0.02
Uptake Fraction %	12 (6)	6 (1.2)	0.002	10 (5-28)	5.7 (5-8)	0.009	0.88	0.01
Gadoxetate clearance ml/min	225 (73)	107 (69)	0.013	211 (98-324)	78.6 (45-200)	0.012	0.87	0.01
FLR Function								
Uptake Rate ml/100ml/min	14 (4)	8 (4)	0.05	15 (8-21)	5.9 (4-13)	0.012	0.87	0.01
Uptake Fraction %	11.5 (6)	6 (1.4)	0.004	9.8 (4-29)	6 (5-8)	0.03	0.82	0.03
Gadoxetate clearance ml/min	127 (74)	67 (59)	0.09	113 (35-297)	43 (11-158)	0.09	0.76	0.08

Figures 20 and 21 show case examples for a younger vs older patient. demonstrating differences in uptake parameters.

Figure 20: A patient in their 40s undergoing right hepatectomy (T1 axial & coronal)

Younger patient

41-year-old female who underwent right hemihepatectomy.

She had a 7.2cm solitary liver metastasis in segment 7/8 compromising the right hepatic vein and interfacing with the IVC.

She received pre-operative neoadjuvant chemotherapy.

She had an eGFR of >90.

Background histology demonstrated <1% steatosis

Whole liver

- UR = 12.5ml/100ml/min
- Ufr = 7.3%
- Ufu = 166ml/min

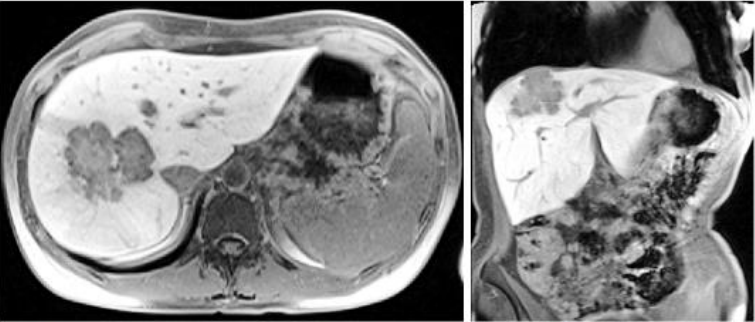
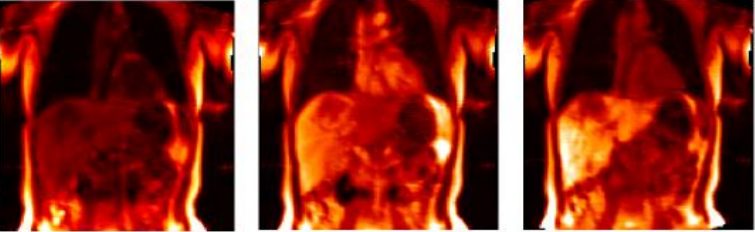
FLR

- UR 14.5ml/100ml/min
- Ufr 9.9%
- Ufu = 49ml/min

FLR volume = 25.9%

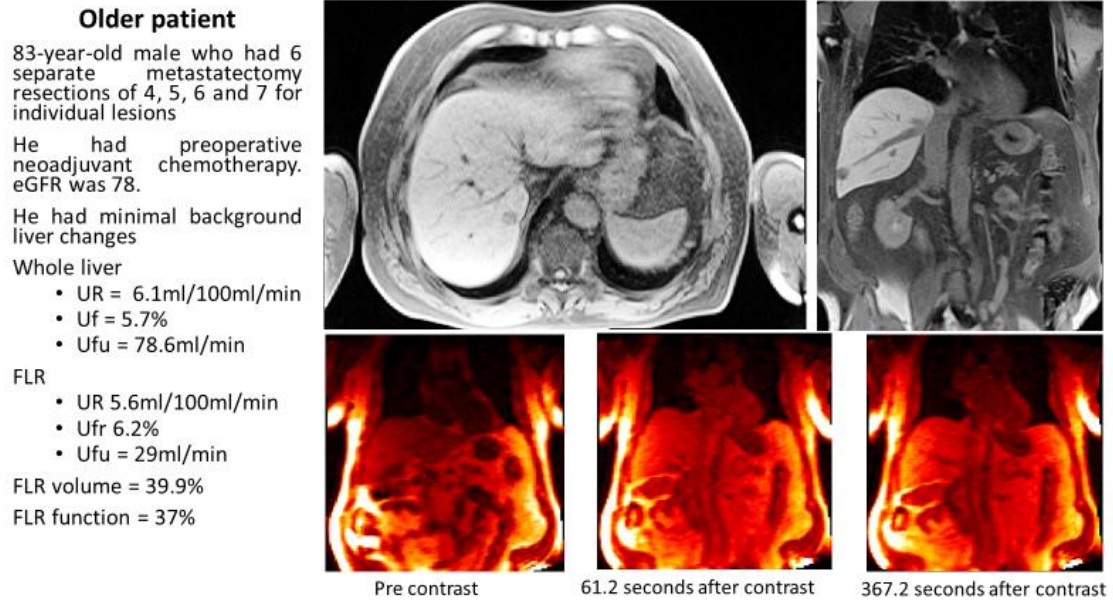
FLR function = 29.4%

resect003

Pre contrast 61.2 seconds after contrast 367.2seconds after contrast

Figure 21: A patient in their 80s undergoing multiple metastatectomy



Background liver steatosis

The uptake fraction was significantly lower for patients with normal liver parenchyma when the whole liver segment was analysed, however although the trend in other uptake operators showed lower values, the other functional parameters were non-significant in either whole liver or FLR ROIs. It is not clear if this has any meaningful reason for its effect. In addition, the extent of steatosis was not confirmed with objective immunohistochemical testing, rather based on the reporting pathologist report, therefore there is risk of type 1 error due to potential misdiagnosis of extent of steatosis(361).

Table 35: Background liver and whole liver functional assessment

	Normal liver mean n=10	BG Liver Steatosis mean n=13	P value (T test)	Normal Liver median	Background liver median	P value (Mann Whitney test)	AUROC	P value
Uptake Rate ml/100ml/min	11.5 (4.4)	13.9 (4.9)	0.24	11.3 (4-18)	13.3 (4-21)	0.2	0.67	0.18
Uptake Fraction %	8 (2.5)	12.6 (6.7)	0.04	7.2 (5-13)	10.8 (5-28)	0.04	0.75	0.04
Gadoxetate clearance ml/min	165 (84)	226 (80)	0.09	163 (45-309)	184 (45-324)	0.67	0.73	0.06

Extent of resection

Patients who required major liver resection for multiple or centrally based tumours had significantly lower UF and UR than those who had parenchymal minor liver resection,

which was observed, in both whole liver and FLR models. This indicates that patients who have larger resection – which indicates either increased cancer burden with increased metastasis or larger tumours – seem to have a reduced Gadoxetate uptake than those with fewer/smaller metastasis, possibly indicating different cellular function.

Table 36: Type of resection and functional parameters

	Minor resection mean n=8	Major resection mean n=15	P value (T test)	Minor resection median	Major resection median	P value (Mann Whitney test)	AUROC	P value
Whole Liver								
Uptake Rate ml/100ml/min	15 (5.8)	12 (3.8)	0.09	16.4 (4-21)	12 (4-18)	0.08	0.73	0.07
Uptake Fraction %	14	8.5	0.016	12.6 (5-28)	7.6 (5-14)	0.047	0.75	0.049
Gadoxetate clearance ml/min	246 (98)	174 (70)	0.05	294 (55-324)	181 (45-299)	0.047	0.76	0.045
FLR Function								
Uptake rate ml/100ml/min	15 (5.7)	12 (3.8)	0.2	16.6 (4-21)	12 (26-46)	0.11	0.71	0.1
Uptake fraction %	14 (8)	8.5 (3.3)	0.03	12 (5-29)	185 (43-297)	0.05	0.75	0.05
Gadoxetate clearance ml/min	174 (80)	82.5 (48)	0.003	185 (43-297)	75 (11-179)	0.008	0.83	0.01

61% of patients under 75 had a major resection and 80% over 75s had major resection; there was no significant association between those patients age >75 and major resection (χ^2 p=0.41). Both groups can therefore be considered independent of each other, and as such there is no evidence of confounding between age and extent of resection. Figures 22 and 23 show examples for a major resection vs a more limited resection.

Figure 22: A patient having an extended right hepatectomy

Major resection

64-year-old female had an Extended right hemihepatectomy and segment 3 metastatectomy.

She received no pre-operative neoadjuvant chemotherapy. eGFR was 72.

Background histology showed mild steatosis

Whole liver

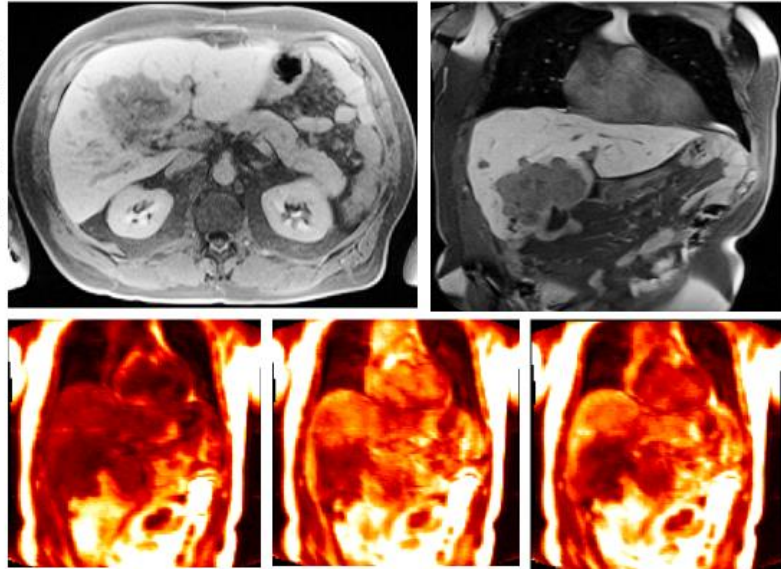
- UR = 11.1ml/100ml/min
- Ufr = 7.6%
- Ufu = 236.6ml/min

FLR

- UR 9.7ml/100ml/min
- Ufr 4.6%
- Ufu = 39ml/min

FLR volume = 28.6%

FLR function = 26.4%



Pilot001

Pre contrast

61.2 seconds after contrast

367.2 seconds after contrast

Figure 23: A patient having a two-segment resection

Minor resection

A 54-year-old male who had a segment 6 and 7 resections for a 2.1cm segment 6 metastasis and a resolved segment 7 lesion.

He had preoperative neoadjuvant chemotherapy. eGFR was >90.

He had mild steatosis and portal inflammation.

The segment 6 lesion was an R1 resection.

Whole liver

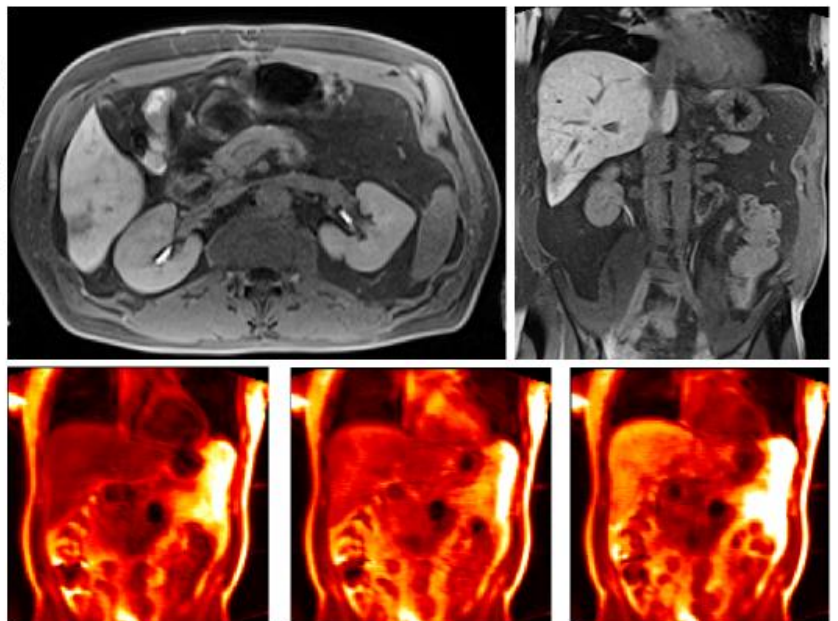
- UR = 16ml/100ml/min
- Ufr = 15.8%
- Ufu = 284.4ml/min

FLR

- UR 15.9ml/100ml/min
- Ufr 14.6%
- Ufu = 151ml/min

FLR volume = 69%

FLR function = 71%



Resect008

Pre contrast

61.2 seconds after contrast

367.2 seconds after contrast

PHLF and functional bias

No perfusion or function parameter was predictive for PHLF when tested and as such no individual parameter could be used for this purpose (table 37).

Table 37: Key DGE-MRI function parameters with & without PHLF development

	No PHLF Mean (SD)	PHLF Mean (SD)	P value (T Test)
Whole Liver			
Uptake Function (ml/min)	231.6 (86.9)	188.8 (73.8)	0.22
Uptake Fraction (%)	11.3 (6.3)	10.2 (5.1)	0.6
Clearance (mL/min)	203.2 (74)	166.9 (57.1)	0.2
Normalised clearance (mL/min/kg)	2.6 (0.8)	2.2 (0.6)	0.11
FLR			
Uptake Function (ml/min)	159.6 (54.1)	99.8 (78.3)	0.06
Uptake Fraction (%)	11.7 (6.9)	9.8 (5.0)	0.46
Clearance (mL/min)	139.5(46.1)	88.0 (65.3)	0.055
Normalised clearance (mL/min/kg)	1.8 (0.6)	1.2 (0.8)	0.06

When the functional bias was tested, there was no difference between the median value of no=PHLF compared with cases of PHLF (PHLF=+1 vs no PHLF =+0.2 p=0.74). Overall the number of observed cases of clinically significant PHLF (B or C) was low at 4 cases of PHLF B, therefore too few cases were observed to be able to adequately assess for significance of any predictive ability of our method, although FLR clearance was found to be near significance(5).

5.4.9 Perfusion parameters

There was no significant difference seen in any of the perfusion parameters (plasma flow, arterial plasma flow, venous plasma flow, or MTT) with any pre-operative or post-operative risk factor, suggesting that liver perfusion in isolation cannot detect any clinically significant differences. Plasma flow parameters are required to calculate uptake fraction % and gadoxetate clearance in our estimates of liver function and therefore are still required.

5.5 Discussion

These results demonstrate that DGE-MRI estimates of FLR-function are predictive of post-operative function as measured by hyperbilirubinaemia. No currently utilised modality such as biochemical biomarkers, clinical parameters or volumetry were predictive. This indicates that DGE-MRI could have utility in operative planning in combination with currently available investigations.

The DGE-MRI study was designed to have a pragmatic acquisition methodology which could be adapted into a clinically acceptable protocol to both patient and the busy MRI department; one with free breathing and requiring no additional acquisition time or additional scanning. By adding the DGE-MRI sequence into diagnostic imaging this allows flexibility and ease of use in pre-operative planning and could supersede CT volumetry when critical FLR values are required; particularly useful to reduce the burden of additional scanning to patients.

5.5.1 Utility of pre-operative FLR-function and post-operative function

Elevated bilirubin levels are known to be associated with impaired liver function, predominantly in parenchymal liver disease(362). When elevated in the post-operative period it is an indicator of inadequate liver tissue to handle adequate excretion and it is an independent measure of risk of PHLF and mortality(1). It is established that very high post-operative bilirubin levels (over 7mg/dL) have high sensitivity and specificity for mortality or morbidity(1), both of which are associated with a smaller FLR of <25%(6).

If it is possible to predict pre-operatively which patients may be at more risk for inadequate liver function when FLR is close to 25% (or 0.5% of the total body weight(363)), or to be used in the assessment of patients with parenchymal liver disease, such as those with hepatocellular carcinomas with background fibrotic or cirrhotic liver, it would be beneficial to either offer a more limited, parenchymal resection, or offer a hypertrophic liver procedure such as portal vein embolisation or ligation. Such measures improves outcome for patients with marginal threshold for FLR(76)(86)(364), or indeed

allow patients who would have otherwise been deemed unsuitable to have major surgery.

There was a predictive value of using FLR-function estimates for post-operative hyperbilirubinaemia. The only clinical risk factor predictive of functional outcome was increased BMI. None of the biochemical markers were predictive of post-operative function (table 33).

Bilirubin was chosen as the primary outcome measure over liver transaminases in the post-operative period. Bilirubin and Gadoxetate share a common excretion pathway. Impaired hepatocellular excretion would reduce both bilirubin clearance and Gadoxetate clearance. FLR-uptake and clearance could prove useful in assessing patients who are to undergo major resection (with predicted marginal FLR) to estimate the likelihood of post-operative dysfunction.

Transaminases are commonly used measures of hepatic dysfunction, predominantly in parenchymal liver diseases(365), however in a large prospective study of 651 liver resections, Boleslawski and colleagues found there was no association with post-operative transaminases and function(205). As such they have not been investigated here.

5.5.2 Negative results

DGE-MRI perfusion measurements did not have any predictive capacity, but this expected considering no patients enrolled in this study had significant parenchymal, macrovascular or microvascular pathology which would impair hepatic perfusion. There were no reported cases of CILI. Perfusion is useful when there is parenchymal liver pathology and, in this context, its true role requires elucidation. A separate issue that may play a role is that perfusion parameters are generally less precisely measurable. To some extent that may also reduce the correlations with other markers.

It is also interesting that FLR volume was not predictive of outcome. CT volumetry is commonly used in pre-operative assessment and MRI volumetry has been shown to be

equivalent(297)(366). However, volumetry is traditionally only used to assess whether resection would reach a critical cut-off point (e.g. FLR < 20% in healthy liver), but not as a direct predictor of post-operative function.

BMI was the only clinical/biochemical marker predictive of outcome though the correlations were weaker than for FLR-UR. It is known that patients with increased BMI have higher incidence of steatosis and NAFLD(367), and could explain why there was alteration in liver function measured; although steatosis itself did not demonstrate correlation. Only 4 patients had a BMI of >30 and steatosis and BMI did not correlate when tested separately (some patients with normal BMI had steatosis and visa versa). Whether BMI is true predictive factor for post-operative function future higher-powered study would be required to determine the true relationship.

Other markers such as pre-operative bilirubin were not predictive of post-operative bilirubin, but this may be due to the fact that the population was selected to have healthy liver and therefore all bilirubin levels were in or close to the normal range – any patients with hyperbilirubinaemia would have been excluded from analysis.

5.5.3 Benefits of DGE-MRI over other modalities

Global measures such as ICG (12), have proved useful as a screening tool to risk-stratify patients for liver surgery. This test does provide an excellent measure of global liver function, mostly used in patients with liver disease as a discriminator for patients with already severe liver dysfunction as to whether to even attempt surgery(12)(274). As a result, in isolation with a patient with supposed normal functioning liver it would be difficult for this to be able to help in risk stratification. DGE-MRI's strengths until now have been for patients with heterogeneous liver function, but these results suggest DGE-MRI could prove a more useful function biomarker for patients with homogeneous function distribution, and has added benefit as different FLR-ROI can be constructed to assess for differences between major or minor resection (for instance the difference in FLR-function between a 4-segment right hepatectomy or 2-segment right posterior sectionectomy). This could help with surgical planning strategies.

LiMAx has been demonstrated in a large series by Jara and colleagues that following their implementation of LiMAx testing by the above method they reduced their incidence of PHLF and mortality – they attribute this to the LiMAx allowing improved patient selection for resections(283). LiMAx does provide an excellent stratification of risk for surgical candidates and it is much more commonly being used for this purpose. However, its role is limited as with the ICG when there is expected to be close to the threshold of FLR or in inhomogeneous liver and DGE-MRI will give added benefit of true FLR assessment.

Scintigraphic techniques using radio-labelled Mebrofenin as an albumin bound substrate have been developed as predictors of function(288). The drawback with such methods is images tend to be low resolution and the quality in detailed anatomy required to differentiate segments is difficult. They require combination with CT to obtain a high enough resolution for accurate FLR assessment(13).

CT Volumetry is considered the gold standard for pre-operative planning, however it does come with some limitations; variation in tumour size, presence of multiple lesions, and atrophic or hypertrophic liver, make CT volumetry an error-sensitive imaging technique(348)(199). It involves ionising radiation exposure. This study identified DGE-MRI as demonstrating good estimates of FLR- function, and it being as efficacious as volumetry measurements in a homogeneous liver (chapter 5.4.5). It could be considered as an alternative imaging modality over CT. All patients received MRI with Gadoxetate as part of their oncological staging, and the DGE-MRI protocol adapted in this study does not require an additional examination or hospital visit. It allows diagnostic and function assessment in a clinically acceptable timeframe in one scan, avoiding ionizing radiation and potentially offering effective assessment.

DGE-MRI may offer additional benefit when there is inhomogeneous function, such as patients with underlying parenchyma disease or hepatic comorbidity. However, this study could not examine if this is possible, as this cohort of patients had at most mild steatosis

and most had no liver parenchymal disease at all. Further study may be able to fully assess DGE-MRI's utility

Volumetry was performed on MRI rather than CT, however this should not be an issue as CT and MRI volumetry have been shown to be equivocal(297)(366).

5.5.4 Secondary outcomes

Age and patients requiring major resection that may have impaired liver cellular function for other reasons than fibrotic/cirrhotic diseases.

5.5.5 Age and function assessment

The age of 75 was used as a cut-off value to discriminate between younger and older patients. This is the age which risk of liver surgery increases(329). This was also the determined age cut-off determined in chapter 3.

Patients in this study who were older tended to have reduced Gadoxetate uptake rate, function and fraction observed which may be explained by current understanding of the physiology of ageing; essentially older patients may have reduced liver function due to age-related physiological changes(332). There seems to be an association between ageing and a higher background bilirubin(261), signifying a reduction in liver function, and the uptake and excretion of bilirubin in ageing populations, which would follow given the shared excretory pathway of both bilirubin and Gadoxetate. Such results to marry up with mebrofenin scintigraphy studies by Cieslak and colleagues which demonstrate declining uptake as patients age(262), Vallance and colleagues findings of worsening outcome with age(333) and the right hepatectomy study found in chapter 3. All this suggests **older patients have impaired function** and this should be taken into consideration when planning surgery.

5.5.6 Background liver steatosis and function assessment

Uptake function % values were significantly lower in patients with normal liver compared to steatotic liver, however this difference was not observed with other functional parameters. In fact, from a biological perspective, the expected reduced uptake would

be expected to be seen in the reverse situation; that steatotic liver will not uptake contrast as well as non-fatty liver. In addition, the degree of steatosis seen in the histological resection was very small, always reported as less than 5%, and it is therefore unlikely to have such a major effect on the function of the liver itself. As a result, this finding should be interpreted with caution as to if it signifies any true biological explanation or is a type 1 error. A Bonferroni correction (multiplication of the observed p-value by the number of performed statistical analyses)(368) would render this value non-significant ($p=0.12$)

5.5.7 Extent of resection and function assessment

These results suggest that patients who needed major resection, viz. those with increased tumour burden have reduced functional parameters – the uptake of the contrast is diminished and the transfer from molecules from the extra-hepatic space to intra-hepatic space is slower.

The liver is a 'target organ' of metastasis(149). Metastatic cells from the colon that enter the venous system via haematogenous spread, and so would drain via the portal system into the microvascular structure of the liver. Sinusoids allow rapid movement of metastatic cells from the intravascular space to beyond the basement membranes(150). The microstructure of the liver seems to 'help' the metastasis enter tissue(151); as the liver's basement membrane is less well defined as other organs; it seems to disintegrate upon exposure and this disintegration leads proliferation of endothelial cells, and endothelialisation of tumour – promoting early angiogenesis and hence metastasis growth.

Whether our results reflect something different about such patients' liver metabolism that predisposes patients to increased metastatic disease burden – impaired function leads to failure to either destroy metastases or allow implantation into the liver raises a very interesting hypothesis about the pathogenesis of CRLM that should be evaluated with a larger study.

5.5.8 PHLF

Part of this study aimed to assess if there was any association between DGE-MRI parameters, or FLR-function and the development of PHLF. Due to the few cases of PHLF observed – no severe, 4 moderate and 8 minor it could not demonstrate any parameter was predictive. Indeed, the number recruited was based on a pre-recruitment power calculation of 30 major resections based on what was deemed appropriate to test the hypothesis of prediction, led to the study being underpowered.

Our population seldom was close to the critical threshold of 25% at which the risk becomes unacceptably high(3), and the total number of **major resections** was only 15, which is only half the number required to achieve adequate power to test this hypothesis. Due to the practicalities of the recruitment process and a finite window of one year only to recruit study participants, it was not possible to fulfil this obligation, despite the best efforts of the authors and the MRI department at St James's Hospital, Leeds.

As a result there would not be the expectation of the development of PHLF in this population, especially as patients are carefully assessed and any patients felt to be at undue risk of PHLF will either be deemed inoperable, have a small parenchymal resection or undergo a hypertrophic procedure to reduce PHLF risk, so perhaps this population examined was not ever likely to show PHLF, and as such studies on patients having major resection with a higher number will have the power to demonstrate if a difference exists.

5.5.9 Limitations

Background liver disease assessment was assessed by a pathologist with a special interest in liver disease, but no immunohistochemical analysis was available which may have improved assessment of the extent of steatosis or CILI(361). This could have led to confounding results.

Liver function is multifactorial, and bilirubin may only represent excretory function, and no synthetic or metabolic elements. ICG is a test that does measure liver function directly, and future studies should use ICG as primary outcome measure after surgery.

Our population had homogeneous liver function and generally had resections that maintained patients had adequate FLR; the numbers of cases who ultimately underwent major liver resection was less than anticipated. Although the intent was to recruit patients who required a major liver resection, unforeseen clinical findings led some patients to either being inoperable or ultimately undergoing a more minor, parenchymal preserving surgery, due to the surgeon's concern of subjecting patients to undue risk once clinical assessment and staging was complete. This means this study was unable to make any assessment of patients with established liver disease such as fibrosis or cirrhosis and assessing for PHLF risk was not able to be determined in our population.

Given the nature of this pilot study design and analysis, it is possible there could be a familywise type 1 error which could not be controlled. Application of a Bonferroni correction (368), would mean many results in this study become non-significant, with only comparisons between UF% and age ($p=0.006$) and both UF% and GC and extent of resection (whole liver UF% $p=0.048$, FLR CG $p=0.009$) remaining significant. Bonferroni correction can reduce type 1 errors, but often overestimates type 2 errors. It is most effective if proof of equivalency is required and a type 1 error has to be excluded for critical patient treatment decisions. In the case of hypothesis generation studies where a large number of tests are carried out, such as this study, it could potentially exclude interesting findings from further investigation erroneously(368). This research is preliminary and hypothesis generating, and future study such as HEPARIM should provide more definitive results.

5.5.10 Conclusions

The data confirm the hypothesis that DGE-MRI based predictions of post-operative liver function show potential as a means of informing patient selection and surgery planning. This could be particularly relevant in patients with underlying liver disease where volumetric estimates are not reliable.

DGE-MRI function assessment appears to be as effective as volumetry for assessing patient's FLR when undergoing liver resection for CRLM. Older patients and patients who underwent major resections had reduced functional parameters measured by our model suggesting possible reduced physiological function in such patients.

A follow-up study (HEPARIM) informed by these data is currently recruiting and will aim to confirm this hypothesis in a less selective population, using a more direct measurements of post-operative liver function with ICG.

Chapter 6 – Discussions and Future projections

6.1 Inference from studies

The primary objective of the study described in chapter 3 was to examine the risk of increased age on patients having a major resection. It identified being over 75 was an independent risk factor for PHLF development. Such new knowledge allows patients being considered for major hepatectomy to be risk-assessed for fitness of their resection. This may lead to a parenchyma-preserving operation that increases risk of incomplete or R1 resection, or for hypertrophic procedures such as PVE, or even ALPPS to be used.

The study described in Chapter 5 demonstrated there is a significant correlation of FLR-function and post-operative bilirubin levels, which was improved over FLR-volume measurement and biochemical and clinical risk factors.

The original intent and design of the DGE-MRI study to assess if PHLF could be predicted pre-operatively however due to the limited number of patients who actually developed a significant degree of PHLF was too low and as such it could not demonstrate any difference. However, it did detect a significant difference in age; namely older patients had reduced liver function. The findings from both studies do marry up logically and do add credence to the idea that age related deterioration of the liver leads to reduced function in that sub-group and when exposed to a major physiological insult, older patients are therefore more at risk of PHLF development.

This leads us to question the most appropriate way of optimising older patients do require surgery. As discussed, the role of hypertrophic procedures does improve the FLR volume and presumed FLR function and can be considered when patients are on the borderline of having too small a liver remnant.

The results show of the role of DGE-MRI derived FLR-function could be useful in patients with CRLM, however in patients with parenchymal liver disease who require surgery this could prove pivotal in pre-operative assessment of the liver when there may be a significant mismatch of volume and function.

6.2 Future studies

6.2.1 Pre-operative PVE study

The Chapter 3 study raised interesting perspectives for future study. The influential study by Farges and colleagues(79) showed there was no benefit for patients to undergo PVE before right hepatectomy, however our results suggest that as older patients have increased risk of PHLF, so some kind of intervention is required. Farges' patient cohort was much younger, with the mean age being 53 for those without PVE and 58 for those undergoing PVE. Older patients should be considered to be a different patient population, and their function may well be impaired, with a mismatch of volume and function. The DGE-MRI study does show there may be a difference between the FLR-volume (which was not correlated with post-operative bilirubin levels) and FLR-function (which uptake rate and clearance were correlated with post-operative bilirubin).

Current cost for PVE is approximately £5,000 per procedure. This analysis shows that just on LOS cost that a patient who develops PHLF would cost on average £8,412 more than a patient without. If performing PVE on those over-75 years could eliminate PHLF then simply performing this on 2 patients could lead to this being cost effective, notwithstanding the potential for improved clinical outcomes. There is evidence that PVE does induce hypertrophy and therefore increases future liver remnant volume(81)(75). It may induce some tumour growth in the contralateral liver in patients, which could render disease inoperable(341). As such for this a dedicated prospective randomised controlled study should take place to be able to assess both the clinical and the cost-effectiveness of PVE in the older population. This study is yet to be fully designed or implemented.

Table 38: Hypothesis for potential future study

Population	Older Patients undergoing major hepatectomy (4 or more segments)
Intervention	PVE of the contralateral liver prior to surgery
Comparison	Surgery without hypertrophic procedure
Outcome	Incidence of PHLF development

6.2.2 HEPARIM study

DGE-MRI is a potentially useful clinical biomarker for hepatic function, with multiple applications beyond the surgical perspective of estimating post-operative function.

The original intent of this study was to assess if DGE-MRI could have a role in the prediction of clinical outcomes, principally the prediction of PHLF. As previously discussed, no patients enrolled in the study ultimately really were the patients who would run the risk of PHLF; either too minor a resection, or those who had major resection were young, with no other comorbid risk factor, and with sufficient FLR remaining that there was no predictive capacity. Time and resource limitations limited the opportunity. There was only a limited recruitment window and due to the lack of additional funding limited to recruitment to no more than 1 patient a week, therefore too few major resections were recruited. However the promising results of this pilot study have led to the 'hepatectomy risk-prediction with functional Magnetic Resonance Imaging' (HEPARIM) study being initiated, and recruitment beginning.

The aims of further study such as HEPARIM should focus on both technical improvements and refinement of methods, plus an expanded population base and the addition of the comparison of ICG as an improved measure of liver function, over bilirubin or clinical scoring systems.

There was variation in results in many key components for both function and perfusion parameters seen depending on complexity of models that was described in chapter 4. It is not currently clear what the values should be, or the expected range of data, across both a control and disease group of patients, and particularly if more complex models are needed to have clinically efficacious results, and a larger population may help define the normal range of values.

DGE-MRI scan methods have undergone significant improvement since the data for this study were collected. In particular free-breathing radial imaging sequences have become available since these data were collected that promise rapid scanning with high

diagnostic quality. This will likely have a major positive impact on the accuracy of DGE-MRI measurements. It can be expected that this will lead to improved correlations compared to this study, which uses scanning sequences that suffer from significant motion artefacts and low spatial resolution. Refinement of methodology should improve predictive capacity by increased precision and accuracy of data. The methods used in this study of analysis were time consuming and potentially error prone, particularly with VIF identification – as many patients had poorly imaged or small portal vein that made it difficult to identify and draw a consistent ROI that was not overly affected with movement artefact - any individual scan could take several hours to draw ROI even with extruding ROI in multiple planes, and as such may deter clinical use initially. If improved ROI drawing for FLR can be optimised, or even automated, to improve analysis time then it would be a more attractive solution to define FLR function.

Until recently, most studies have assessed patients with liver disease which this study did not assess. It was designed pragmatically to fit in with the busy diagnostic scheduling of the MRI department, and no additional scans were able to be performed due to time and lack of funding for research scans. Patients with parenchymal liver disease have clear disparity between functional healthy liver and dysfunction diseased liver. Assessment of FLR for such patients that are undergoing resection for primary liver cancers would be paramount to ensure lack of complications. DGE-MRI could prove most fruitful in this subset of patients, which is planned for future studies.

ICG is widely recognised for its role in direct measurement of liver function and is considered the gold standard measurement. Any future study will require concordance with ICG parameters to be truly representative of measurement of liver function as this is currently recognised as the gold standard. ICG has seldom been available in the UK for use in liver function assessment, despite its common applications routinely in Japan and South Korea(319). Approval for concurrent use has been achieved for HEPARIM and the utilisation of this with patient having DGE-MRI imaging will hopefully prove fruitful in improving assessment of liver diseases and patients requiring liver surgery.

HEPARIM's primary outcome is to compare DGE-MRI functional measurements against the results of ICG, which is more robust than using bilirubin as a measurement, which levels can vary due to other post-operative factors such as bile leak. ICG is considered the gold standard measurement of liver function - to determine if preoperative function of the FLR as measured by Gadoxetate Clearance in DGE-MRI is an accurate prediction of post-hepatectomy liver function.

Table 39: Primary outcome of HEPARIM

Population	Patients requiring major hepatectomy for any malignant tumour
Intervention	DGE-MRI prediction of FLR function
Comparison	Change in ICG measurement of liver function from pre- to post-op
Outcome	Strength of correlation

HEPARIM requires around 120 participants to achieve a power of 80% and is currently ongoing in recruitment at the University of Leeds and St James's University Hospital.

Secondary outcomes of HEPARIM develop on some of the ideas that the study in chapter 5, that ultimately required more participants to study. They are to:

1. determine the measurement uncertainty in DGE-MRI measurements of liver function – by refinement of DGE-MRI methodology
2. determine if preoperative measurement of FLR function can predict severe post-hepatectomy liver failure, whether FLR function improves the prediction of long-term outcome compared to a risk assessment that only uses currently available predictor variables – to assess fully the impact that the study described in chapter 5b aimed to address
3. to assess if functional measures can play a role in the selection of a suitable time point after PVE/ALPPS to perform the hepatectomy – Hypertrophic procedures are being considered more readily to increase the extent of resection, and timing after such procedures as to when surgery can be considered

Essentially, as previously discussed, there was not significant number recruited to be able to test some of the original hypotheses related to development of a method to predict PHLF, although there is some interesting results that were described in chapter 5, and HEPARIM will aim to fully explore the role of DGE-MRI in assessing surgical patients.

6.3 Conclusions

The aims of this thesis were to explore risk factors after liver surgery, particularly PHLF, and design a novel approach for prediction of surgical outcome using DGE-MRI. A large retrospective cohort study found ageing to be an independent risk factor for PHLF, and as such patients require careful management and pre-operative optimisation. Utilisation of DGE-MRI can estimate post-operative function to a greater extent than volumetry or clinical predictions, and as such shows significant promise for pre-operative liver assessment; further study is planned for assessing the true role of DGE-MRI in the surgical patient across the spectrum of liver resection surgery.

References

1. Mullen JT, Ribero D, Reddy SK, Donadon M, Zorzi D, Gautam S, et al. Hepatic Insufficiency and Mortality in 1,059 Noncirrhotic Patients Undergoing Major Hepatectomy. *J Am Coll Surg*. 2007;204(5):854–62.
2. Halazun KJ, Al-mukhtar A, Aldouri A, Malik HZ, Attia MS, Prasad KR, et al. Right Hepatic Trisectionectomy for Hepatobiliary Diseases. *Ann Surg*. 2007;246(6):1065–74.
3. Clavien PA, Oberkofler CE, Raptis DA, Lehmann K, Rickenbacher A, El-Badry AM. What is critical for liver surgery and partial liver transplantation: Size or quality? *Hepatology*. 2010;52(2):715–29.
4. Schindl MJ, Redhead DN, Fearon KCH, Garden OJ, Wigmore SJ. The value of residual liver volume as a predictor of hepatic dysfunction and infection after major liver resection. *Gut*. 2005;54(2):289–96.
5. Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R, et al. Posthepatectomy liver failure: A definition and grading by the International Study Group of Liver Surgery (ISGLS). *Surgery*. 2011;149(5):713–24.
6. Kauffmann R, Fong Y. Post-hepatectomy liver failure. *Hepatobiliary Surg Nutr*. 2014;3(5):238–46.
7. Helling TS. Liver failure following partial hepatectomy. *HPB* 2006;8(3):165–74.
8. Hammond JS, Guha IN, Beckingham IJ, Lobo DN. Prediction, prevention and management of postresection liver. *Br J Surg*. 2011;1188–200.
9. Lafaro K, Buettner S, Maqsood H, Wagner D, et al. Defining Post Hepatectomy Liver Insufficiency: Where do We stand? *J Gastrointest Surg* 2015 ;19(11):2079–92.
10. Ribero D, Amisano M, Bertuzzo F, Langella S, Lo Tesoriere R, Ferrero A, et al. Measured versus estimated total liver volume to preoperatively assess the adequacy of the future liver remnant: which method should we use? *Ann Surg* 2013;258(5):801–6;
11. Lim MC, Tan CH, Cai J, Zheng J, Kow AWC. CT volumetry of the liver: Where does it stand in clinical practice? *Clin Radiol* 2014;69(9):887–95.

12. Reinhart MB, Huntington CR, Blair LJ, Heniford BT, Augenstein VA. Indocyanine Green: Historical Context, Current Applications, and Future Considerations. *Surg Innov* 2016;23(2):166–75.
13. Cieslak KP, Bennink RJ, de Graaf W, van Lienden KP, Besselink MG, Busch ORC, et al. Measurement of liver function using hepatobiliary scintigraphy improves risk assessment in patients undergoing major liver resection. *HPB* 2016;18(9):773–80.
14. Sommer WH, Sourbron S, Huppertz A, Ingrisich M, Reiser MF, Zech CJ. Contrast agents as a biological marker in magnetic resonance imaging of the liver: Conventional and new approaches. *Abdom Imaging*. 2012;37(2):164–79.
15. Stevens PE, Levin A. Guideline Evaluation and Management of Chronic Kidney Disease : Synopsis of the Kidney Disease : Improving Global Outcomes 2012 Clinical. *Ann Intern Med* 2014;158(11):825–31.
16. Chen TS, Chen PS. The myth of Prometheus and the liver. *J R Soc Med* 1994;87(12):754–5.
17. Galen (transl. Margaret Tallmadge). *Galen on the Usefulness of the Parts of the Body*. Cornell University Press, Ithaca, N. Y 1968.
18. Foster JH. History of liver surgery. *Arch Surg* 1991;126(3):381–7.
19. Richet C. An Address On Ancient Humorism And Modern Humorism: Delivered at the International Congress of Physiology held in Vienna, *Br Med J* 1910;2(2596):921–6.
20. Versalius A. *De humani corporis fabrica libri septum*. Wellcome Collection CC 1543.
21. Hernigou P. Ambroise Pare II: Pare’s contributions to amputation and ligature. *Int Orthop*. 2013;37(4):769–72.
22. Pare A. The Apologie and Treatise of Ambroise Pare. *Calif Med*. 1970; 112(2): 95;19-68
23. Besterman EMM. William Harvey and his discovery of the circulation of the blood. *West Indian Med J*. 2004;53(6):425–6.
24. Hooke R. *Micrographia: or, Some physiological descriptions of minute bodies made by magnifying glasses*. Qontro Classic Books, 1665 (published 2010).

25. Glisson F. *Anatomia Hepatis. Typis DuGardianis* 1654.
26. Cantlie J. On new arrangement of right and left lobes of liver. In: *Proceedings of the Anatomical Society of Great Britain and Ireland, J Anat Physiol.* 1897;32(1–24):4–6.
27. MacPherson J. Cited by: Mikeskey WE, Howard JM DM. Injuries of the liver in 300 consecutive patients. *Int Abstr Surg.* 1956;103:323–37.
28. Berta G. Cited by: Fagarasanu I, Ionescu-Bujor C, Aloman D AE. *Surgery of the Liver and Intrahepatic Ducts.* St Louis, Mo: WH Green; 1972. 412–430.
29. Daniel H. Robinson & Alexander H. Toledo. *Historical Development of Modern Anesthesia.* *J Investig Surg.* 2012;25(3).
30. Lius A. *Di un Adenoma del Fegato.* *Gazz delle Clin.* 1886;23.
31. Langenbuch C. Ein Fall von Resection eines linksseitigen Schnurlappens der Leber. *Heilung Klin Wochenschr.* 1888;25:37.
32. Kousnetzoff, M; Pensky J. Etudes cliniques et experimental essur la chirurgie du foie sur la re section partielle du foie. *Rev Chir.* 1896;16:954.
33. Tiffany L. Removal of solid tumor from the liver by laparotomy. *Md Med J.* 1890;23:531.
34. Keen W. Report of a case of resection of the liver for the removal of a neoplasm with a table of seventy-six cases of resection of the liver for hepatic tumors. *Ann Surg.* 1899;30:267.
35. Brunshwig A. Hepatic lobectomy for metastatic cancer. *Cancer.* 1963;16:277–82.
36. Pringle J. Notes on the arrest of hepatic hemorrhage due to trauma. *Ann Surg.* 1908;48:541.
37. Huguet, C; Nordlinger, B; Galopin, JJ; Bloch, P; Gallot D. Normothermic hepatic vascular exclusion for extensive hepatectomy. *Surg Gynecol Obs.* 1978;147:689–93.
38. Smyrniotis V, Kostopanagiotou G, Lolis E, Theodoraki K, Farantos C, Andreadou I, et al. Effects of hepatovenous back flow on ischemic- reperfusion injuries in liver resections with the pringle maneuver. *J Am Coll Surg* 2003 1;197(6):949–54.
39. Zhai Y, Petrowsky H, Hong JC, Busuttil RW, Kupiec-Weglinski JW. Ischaemia-

- reperfusion injury in liver transplantation-from bench to bedside. *Nat Rev Gastroenterol Hepatol.* 2013;10(2):79–89.
40. Wei X, Zheng W, Yang Z, Liu H, Tang T, Li X, et al. Effect of the intermittent Pringle maneuver on liver damage after hepatectomy: a retrospective cohort study. *World J Surg Oncol.* 2019;17(1):1–9.
 41. Von Haberer H. Zur Frage der nicht parasitären Leberzysten. *Wien Klin Wochenschr.* 1909;22:1788.
 42. Wendel W. Ueber Leberlappenresektion. *Arch Klin Chir.* 1920;114:982–1000.
 43. Parks RW, Garden OJ. Liver resection for cancer. *World J Gastroenterol.* 2001;7(6):766–71.
 44. Meyer-May; Tung T. *Bull Mem Acad Chir Paris.* 1939;65:1208.
 45. Donovan, EJ; Santulli T. Resection of the left lobe of the liver for mesenchymoma. *Ann Surg* 1946;124:90.
 46. Lortat-Jacob, JL; Robert H. Hepatectomie droite reglee. *Press Med.* 1952;60:549.
 47. Strasberg SM, Phillips C. Use and dissemination of the brisbane 2000 nomenclature of liver anatomy and resections. *Ann Surg* 2013;257(3):377–82.
 48. Couinaud C. Lobes de segments hépatiques: notes sur architecture anatomique et chirurgicale du foie. *Press Med.* 1954;62:709.
 49. Healey, John E; Schroy PC. Anatomy of the Biliary Ducts Within the Human Liver. *Arch Surg.* 1952;599–616.
 50. Fasel, Jean H. D; Schenk A. Concepts for Liver Segment Classification: Neither Old Ones nor New Ones, but a Comprehensive One. *J Clin Imaging Sci.* 2013;3:48.
 51. Lin TY, Chen KM LT. Total right hepatic lobectomy for primary hepatoma. *Surgery,* 1960;48:1048–60.
 52. Quattlebaum J. Massive resection of the liver. *Ann Surg.* 1953;137:787–96.
 53. Fortner JG, Shiu MH, Howland WS, Gaston JP, et al. A new concept for hepatic lobectomy. Experimental studies and clinical application. *Arch Surg* 1971;102(4):312–5.

54. Bernhard, W; McMurrey, JD; Curtis G. Feasibility of partial hepatic resection under hypothermia.. N Engl J Med. 1955;253:159.
55. Heaney, JP; Stanton, WR; Halbert, DS; Seide, I J; Vice T. An improved technic for vascular isolation of the liver. Ann Surg. 1966;(163):237–44.
56. Schrock, T; Blaisdell, FW; Mathewson C. Management of blunt trauma to the liver and hepatic veins. Arch Surg. 1968;(96):698–704.
57. Lin TY. Results in 107 hepatic lobectomies with a preliminary report on the use of a clamp to reduce blood loss. Ann Surg. 1973;177:413–21.
58. Li AKC, Mok SD. Simplified Hepatectomy: the Tourniquet Method. Aust N Z J Surg. 1989;59(2):161–3.
59. Trastek VF, van Heerden JA, Sheedy PF, Adson MA. Cavernous hemangiomas of the liver: Resect or observe? Am J Surg. 1983;145(1):49–53.
60. Erdogan D, Busch ORC, Van Delden OM, Bennink RJ, Ten Kate FJW, Gouma DJ, et al. Management of liver hemangiomas according to size and symptoms. J Gastroenterol Hepatol. 2007;22(11):1953–8.
61. Hodgson WJB, DelGuercio LRM. Preliminary experience in liver surgery using the ultrasonic scalpel. Vol. 95, Surgery. 1984. 230–234 p.
62. Savlid M, Strand AH, Jansson A, Agustsson T, Söderdahl G, Lundell L, et al. Transection of the liver parenchyma with an ultrasound dissector or a stapler device: Results of a randomized clinical study. World J Surg. 2013;37(4):799–805.
63. Go, P; Goodman, G; Bruhn Ehj. The Argon Beam Coagulator Provides Rapid Hemostasis of Experimental Hepatic and Splenic Hemorrhage in Anticoagulated Dogs. J Trauma. 1991;31(9):1294–300.
64. Papadimitriou JD, Fotopoulos AC, Prahalias AA, Vassiliou JG, Papadimitriou LJ. The impact of new technology on hepatic resection for malignancy. Arch Surg 2001;136(11):1307–13.
65. Wolf RF, Xie H, Petty J, Teach JS, Prah SA. Argon ion beam hemostasis with albumin after liver resection. Am J Surg. 2002;183(5):584–7.

66. Mueller GR, Wolf RF, Hansen PD, Gregory KW, Prahla SA. Hemostasis after Liver Resection Improves after Single Application of Albumin and Argon Beam Coagulation. *J Gastrointest Surg.* 2010;14(11):1764–9.
67. Hammond JS, Muirhead W, Zaitoun AM, Cameron IC, Lobo DN. Comparison of liver parenchymal ablation and tissue necrosis in a cadaveric bovine model using the Harmonic Scalpel™, the LigaSure™, the Cavitron Ultrasonic Surgical Aspirator® and the Aquamantys® devices. *HPB.* 2012;14(12):828–32.
68. Lesurtel M, Selzner M, Petrowsky H, McCormack L, et al. How should transection of the liver be performed? A prospective randomized study in 100 consecutive patients: Comparing four different transection strategies. *Ann Surg.* 2005;242(6):814–23.
69. Pichlmayr, R; Grosse, H; Hauss, J; Gubernatis, G; Lamesch, P Bretschneider H. Technique and preliminary results of extracorporeal liver surgery (bench procedure) and of surgery on the in situ perfused liver. *Br J Surg.* 1990;77:21–6.
70. Kumada K, Ozawa K, Okamoto R, Takayasu T, Yamaguchi M, Yamamoto Y, et al. Hepatic resection for advanced hepatocellular carcinoma with removal of portal vein tumor thrombi. *Surgery.* 1990 ;108(5):821–7.
71. Kurosaki I, Hatakeyama K, Minagawa M, Sato D. Portal vein resection in surgery for cancer of biliary tract and pancreas: Special reference to the relationship between the surgical outcome and site of primary tumor. *J Gastrointest Surg.* 2008;12(5):907–18.
72. Adam R, Laurent A, Azoulay D, Castaing D, Bismuth H. Two-stage hepatectomy: A planned strategy to treat irresectable liver tumors. *Ann Surg* 2000;232(6):777–85.
73. Makuuchi M, Thai BL, Takayasu K, Takayama T, Kosuge T, Gunven P, et al. Preoperative portal embolization to increase safety of major hepatectomy for hilar bile duct carcinoma: a preliminary report. *Surgery.* 1990 ;107(5):521–7.
74. Kinoshita H, Sakai K, Hirohashi K, Igawa S, Yamasaki O, Kubo S. Preoperative portal vein embolization for hepatocellular carcinoma. *World J Surg.* 1986;10(5):803–8.
75. Van Lienden KP, Van Den Esschert JW, De Graaf W, Bipat S, Lameris JS, Van Gulik TM, et al. Portal vein embolization before liver resection: A systematic review.

- Cardiovasc Intervent Radiol. 2013;36(1):25–34.
76. Abulkhir A, Limongelli P, Healey AJ, Damrah O, Tait P, Jackson J, et al. Preoperative portal vein embolization for major liver resection: a meta-analysis. *Ann Surg.* 2008;247(1):49–57.
77. Liu H, Zhu S. Present status and future perspectives of preoperative portal vein embolization. *Am J Surg* 2009;197(5):686–90. Available from: <http://dx.doi.org/10.1016/j.amjsurg.2008.04.022>
78. Wicherts DA, de Haas RJ, Andreani P, Sotirov D, Salloum C, Castaing D, et al. Impact of portal vein embolization on long-term survival of patients with primarily unresectable colorectal liver metastases. *Br J Surg.* 2010;97(2):240–50.
79. Farges O, Belghiti J, Kianmanesh R, Regimbeau JM, Santoro R, Vilgrain V, et al. Portal vein embolization before right hepatectomy: prospective clinical trial. *Ann Surg.* 2003;237(2):208–17.
80. Nagino M, Kamiya J, Nishio H, Ebata T, Arai T, Nimura Y. Two hundred forty consecutive portal vein embolizations before extended hepatectomy for biliary cancer: surgical outcome and long-term follow-up. *Ann Surg.* 2006;243(3):364–72.
81. Shindoh J, Tzeng CWD, Aloia TA, Curley SA, Zimmitti G, Wei SH, et al. Portal vein embolization improves rate of resection of extensive colorectal liver metastases without worsening survival. *Br J Surg.* 2013;100(13):1777–83.
82. Hoekstra LT, van Lienden KP, Doets A, Busch ORC, Gouma DJ, van Gulik TM. Tumor Progression After Preoperative Portal Vein Embolization. *Ann Surg.* 2012;256(5):812–8.
83. Vennarecci G, Laurenzi A, Santoro R, Colasanti M, Lepiane P, Ettorre GM. The ALPPS procedure: A surgical option for hepatocellular carcinoma with major vascular invasion. *World J Surg.* 2014;38(6):1498–503.
84. Lee EC, Park SJ, Han SS, Park HM, Lee SD, Kim SH, et al. Mortality after portal vein embolization: Two case reports. *Medicine.* 2017;96(6):2–6.
85. De Santibañes E, Clavien PA. Playing play-doh to prevent postoperative liver failure: The “aLPPS” approach. *Ann Surg.* 2012;255(3):415–7.

86. Lodge JPA. ALPPS: The argument for. *Eur J Surg Oncol*. 2017;43(2):246–8.
87. Levi Sandri GB, Colace L, Vennarecci G, Santoro R, Lepiane P, Colasanti M, et al. Laparoscopic first step approach in the two stage hepatectomy. *Hepatobiliary Surg Nutr*. 2015;4(5):345–7.
88. Kumar N, Duncan T, O'Reilly D, Káposztás Z, Parry C, Rees J, et al. Partial ALPPS with a longer wait between procedures is safe and yields adequate future liver remnant hypertrophy. *Ann Hepato-Biliary-Pancreatic Surg*. 2019;23(1):13.
89. Hartog A, Mills G. Anaesthesia for hepatic resection surgery. *Contin Educ Anaesthesia, Crit Care Pain*. 2009;9(1):1–5.
90. Hashimoto T, Kokudo N, Orii R, Seyama Y, Sano K, Imamura H, et al. Intraoperative Blood Salvage During Liver Resection. *Ann Surg* 2007;245(5):686–91.
91. Tanabe KK. The Past 60 Years in Liver Surgery. *Cancer*. 2008;(9):1888–96.
92. Gosink BB. Evaluation of hepatic neoplasms. *Am J Roentgenol* 1980 Mar 1;134(3):621.
93. Floriani I, Torri V, Rulli E, Garavaglia D, Compagnoni A, Salvolini L, et al. Performance of imaging modalities in diagnosis of liver metastases from colorectal cancer: A systematic review and meta-analysis. *J Magn Reson Imaging*. 2010;31(1):19–31.
94. Pinto A, Pinto F, Faggian A, Rubini G, Caranci F, Macarini L, et al. Sources of error in emergency ultrasonography. *Crit Ultrasound J* 2013;5
95. Makuuchi M, Hasegawa H, Yamazaki S. Intraoperative ultrasonic examination for hepatectomy. *Ultrasound Med Biol*. 1983;Suppl 2:493–7.
96. Choi SH, Kim SY, Park SH, Kim KW, Lee JY, Lee SS, et al. Diagnostic performance of CT, gadoxetate disodium-enhanced MRI, and PET/CT for the diagnosis of colorectal liver metastasis: Systematic review and meta-analysis. *J Magn Reson Imaging*. 2018;47(5):1237–50.
97. Oğul H, Kantarci M, Genç B, Pirimoğlu B, Çullu N, Kizrak Y, et al. Perfusion CT imaging of the liver: Review of clinical applications. *Diagnostic Interv Radiol*. 2014;20(5):379–89.
98. Sacks A, Peller PJ, Surasi DS, Chatburn L, Mercier G, Subramaniam RM. Value of

- PET/CT in the management of liver metastases, part 1. *Am J Roentgenol.* 2011;197(2):256–9.
99. Mansfield P, Pykett IL. Biological and medical imaging by NMR. *J Magn Reson.* 1978;29(2):355–73.
100. Lauterbur PC. Image formation by induced local interactions. Examples employing nuclear magnetic resonance. *Nature.* 1973;242:190–1.
101. Braga L, Guller U, Semelka RC. Modern hepatic imaging. *Surg Clin North Am.* 2004;84(2):375–400.
102. Lemaigre FP. Development of the biliary tract. *Mech Dev.* 2003;120:81–87.
103. Zorn. Liver Development. *StemBook* 2008;1–26.
104. Collardeau-Frachon S, Scoazec J-Y. Vascular Development and Differentiation During Human Liver Organogenesis. *Anat Rec Adv Integr Anat Evol Biol* 2008;291(6):614–27.
105. Krishna M. Microscopic anatomy of the liver. *Clin Liver Dis.* 2013;2(Suppl. 1):4–7.
106. Kiserud T, Acharya G. The fetal circulation. *Prenat Diagn.* 2004;24(13):1049–59.
107. Kim JH. Usefulness of the Ligamentum Venosum as an Anatomical Landmark for Safe Laparoscopic Left Hepatectomy (How I Do It). *J Gastrointest Surg.* 2018;22(8):1464–9.
108. Juza RM, Pauli EM. Clinical and surgical anatomy of the liver: A review for clinicians. *Clin Anat.* 2014;27(5):764–9.
109. Chaib E, Bertevello P, Saad WA, Pinotti HW, Gama-Rodrigues J. The main hepatic anatomic variations for the purpose of split-liver transplantation. *Hepatogastroenterology.* 2007;54(75):688–92.
110. Pérez-Saborido B, Pacheco-Sánchez D, Barrera Rebollo A, Pinto Fuentes P, Asensio, et al. Incidence of hepatic artery variations in liver transplantation: Does it really influence short- and long-term results? *Transplant Proc* 2012;44(9):2606–8.
111. Kishi Y, Imamura H, Sugawara Y, Sano K, Kaneko J, Kokudo N, et al. Evaluation of donor vasculobiliary anatomic variations in liver graft procurements. *Surgery* 2010;147(1):30–9.

112. Van Gulik TM, Van Den Esschert JW. James Cantlie's early messages for hepatic surgeons: How the concept of pre-operative portal vein occlusion was defined. *HPB*. 2010;12(2):81–3.
113. Bismuth H. Surgical anatomy and anatomical surgery of the liver. *World J Surg*. 1982;6(1):3–9.
114. Aragon RJ, Solomon NL. Techniques of hepatic resection. *J Gastrointest Oncol*. 2012;3(1):28–40.
115. Lafortune M, Matricardi L, Denys A, Favret M, Déry R P-LG. Segment 4 (the quadrate lobe): a barometer of cirrhotic liver disease at US. *Radiology*. 1998;206(1):157–60.
116. C. Couinaud. Dorsal sector of the liver. *Chirurgie*. 1998;123(1):8–15.
117. López-Andújar R, Montalvá E, Bruna M, Jiménez-Fuertes M, Moya A, Pareja E, et al. Step-by-step isolated resection of segment 1 of the liver using the hanging maneuver. *Am J Surg* 2009;198(3):e42–8.
118. Lee JH, Jin GY, Jin ZW, Yu HC, Cho BH. Ramification of Glisson's sheath peripheral branches and clinical implications in the era of local ablation therapy. *Surg Radiol Anat* 2010;32(10):911–7.
119. Cho A, Okazumi S, Takayama W, Takeda A, Iwasaki K, Sasagawa S, et al. Anatomy of the Right Anterosuperior Area (Segment 8) of the Liver: Evaluation with Helical CT during Arterial Portography. *Radiology*. 2000 1;214(2):491–5.
120. Minh T Van, Galizia G. [Segmentation of the liver and anatomical variants of the portal system]. *Ann Chir*. 1990;44(7):561–9.
121. Poon RTP. Current techniques of liver transection. *HPB*. 2007;9(3):166–73.
122. Young, Barbara; O'Dowd, Geraldine; Woodford P. *Wheater's functional histology : a text and colour atlas*. 6th ed. Edinburgh ; New York: Churchill Livingstone; 2013.
123. Crawford a R, Lin XZ, Crawford JM. The normal adult human liver biopsy: a quantitative reference standard. *Hepatology*. 1998;28(2):323–31.
124. Fu X, Sluka J, Clendenon S, W. Dunn K, Wang Z, Klaunig J, et al. Modeling of

- xenobiotic transport and metabolism in virtual hepatic lobule models. *PLoS One*. 2018;13:e0198060.
125. Saxena R, Theise ND, Crawford JM. Microanatomy of the human liver-exploring the hidden interfaces. *Hepatology*. 1999;30(6):1339–46.
 126. Saxena R. Canals of Hering: Recent Insights and Current Knowledge. *Semin Liver Dis*. 2004;24(1):43–8.
 127. Trauner M, Boyer JL. Bile Salt Transporters : Molecular Characterization , Function , and Regulation Transport. 2003;633–71.
 128. Van Beers BE, Pastor CM, Hussain HK. Primovist, eovist: What to expect? *J Hepatol* 2012;57(2):421–9.
 129. Tillmans H. Experimentelle und anatomische Untersuchungen ober wonden der Leber und Niere. *Virchows Arch*. 78:437.
 130. Mao C a, Glorioso J, Scott N. Liver Regeneration. *Transl Res*. 2015;163(4):352–62.
 131. Forbes SJ, Newsome PN. Liver regeneration-mechanisms and models to clinical application. *Nat Rev Gastroenterol Hepatol*. 2016;13(8):473–85.
 132. Kele PG, De Boer M, Van Der Jagt EJ, Lisman T, Porte RJ. Early hepatic regeneration index and completeness of regeneration at 6 months after partial hepatectomy. *Br J Surg*. 2012;99(8):1113–9.
 133. Shimada M, Matsumata T, Maeda T, Itasaka H, Suehiro T, Sugimachi K. Hepatic regeneration following right lobectomy: estimation of regenerative capacity. *Surg Today* 1994;24(1):44–8.
 134. Healy A., Tracey J., Habib N.A. JLR. Indications for Liver Resection. In: *Liver and Biliary Tract Surgery*. 2006. p. 357–62.
 135. Maxwell JE, Sherman SK, O'Dorisio TM, Bellizzi AM, Howe JR. Liver-directed surgery of neuroendocrine metastases: What is the optimal strategy? *Surgery* 2016;159(1):320–35.
 136. Ibrahim S, Chen CL, Wang SH, Lin CC, Yang CH, Yong CC, et al. Liver resection for benign liver tumors: indications and outcome. *Am J Surg*. 2007;193(1):5–9.

137. Newhook TE, Lapar DJ, Lindberg JM, Bauer TW, Adams RB, Zaydfudim VM. Morbidity and mortality of hepatectomy for benign liver tumors. *Am J Surg* 2016;211(1):102–8.
138. Kim Y, Amini N, He J, Margonis GA, Weiss M, et al. National trends in the use of surgery for benign hepatic tumors in the United States. *Surg* 2015;157(6):1055–64.
139. El-Serag HB, Rudolph KL. Hepatocellular Carcinoma: Epidemiology and Molecular Carcinogenesis. *Gastroenterology*. 2007;132(7):2557–76.
140. Greten TF, Papendorf F, Bleck JS, Kirchhoff T, Wohlberedt T, Kubicka S, et al. Survival rate in patients with hepatocellular carcinoma: A retrospective analysis of 389 patients. *Br J Cancer*. 2005;92(10):1862–8.
141. Anderson, CD. Wright Pinson, C. Berlin C. Diagnosis and Treatment of Cholangiocarcinoma. *Oncologist*. 2004;9:43–57.
142. Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol*. 2016;27(8):1386–422.
143. Man D, Wu J, Shen Z, Zhu X. Cancer Management and Research Dovepress Prognosis of patients with neuroendocrine tumor: a SEER database analysis. *Cancer Manag Res* 2018;13(10):5629–38.
144. Pamecha V, Mahansaria SS, Bharathy KGS, Kumar S, Sasturkar SV, Sinha PK, et al. Selection and outcome of the potential live liver donor. *Hepatol Int*. 2016;10(4):657–64.
145. Misiakos EP, Karidis NP, Kouraklis G. Current treatment for colorectal liver metastases. *World J Gastroenterol*. 2011;17(36):4067–75.
146. Jarnagin WR, Gonen M, Fong Y, DeMatteo RP, Ben-Porat L, Little S, et al. Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. *Ann Surg* 2002;236(4):397–406
147. Goel A, Boland CR. Recent insights into the pathogenesis of colorectal cancer. *Curr Opin Gastroenterol*. 2010;26(1):47–52.
148. Fidler IJ. Critical factors in the biology of human cancer metastasis. *Cancer Res*. 1990;50:6130–8.

149. Kanas GP, Taylor A, Primrose JN, Langeberg WJ, Kelsh MA, Mowat FS, et al. Survival after liver resection in metastatic colorectal cancer: Review and meta-analysis of prognostic factors. *Clin Epidemiol.* 2012;4(1):283–301.
150. Paku S, Döme B, Tóth R, Timár J. Organ-specificity of the extravasation process: An ultrastructural study. *Clin Exp Metastasis.* 2000;18(6):481–92.
151. Paku S, Lapis K. Morphological aspects of angiogenesis in experimental liver metastases. *Am J Pathol.* 1993;143(3):926–36.
152. Riihimaki M, Hemminki A, Sundquist J, Hemminki K. Patterns of metastasis in colon and rectal cancer. *Sci Rep* 2016;6:1–9.
153. Li Destri G, Di Cataldo A, Puleo S. Colorectal cancer follow-up: Useful or useless? *Surg Oncol.* 2006;15(1):1–12.
154. Konopke R, Roth J, Volk A, Pistorius S, Folprecht G, Zöphel K, et al. Colorectal liver metastases: an update on palliative treatment options. *J Gastrointestin Liver Dis* 2012;21(1):83–91.
155. Khan K, Wale A, Brown G, Chau I. Colorectal cancer with liver metastases: Neoadjuvant chemotherapy, surgical resection first or palliation alone? *World J Gastroenterol.* 2014;20(35):12391–406.
156. De Haas RJ, Wicherts DA, Flores E, Azoulay D, Castaing D, Adam R. R1 resection by necessity for colorectal liver metastases: Is it still a contraindication to surgery? *Ann Surg.* 2008;248(4):626–36.
157. Tomlinson JS, Jarnagin WR, DeMatteo RP, Fong Y, Kornprat P, Gonen M, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. *J Clin Oncol.* 2007;25(29):4575–80.
158. Adam R, De Gramont A, Figueras J, Guthrie A, Kokudo N, Kunstlinger F, et al. The oncosurgery approach to managing liver metastases from colorectal cancer: a multidisciplinary international consensus. *Oncologist.* 2012;17(10):1225–39.
159. Young J, Badgery-Parker T, Dobbins T, Jorgensen M, Gibbs P, Faragher I, et al. Comparison of ECOG/WHO performance status and ASA score as a measure of

- functional status. *J Pain Symptom Manage* 2015;49(2):258–64.
160. Kelly CM, Shahrokni A. Moving beyond Karnofsky and ECOG Performance Status Assessments with New Technologies. *J Oncol*. 2016;2016.
161. West HJ, Jin JO. Performance Status in Patients With Cancer. *JAMA Oncol* 2015;1(312):2015.
162. Saklad Meyer MD. Grading of patients for surgical procedures. *J Am Soc Anesthesiol*. 1941;2(3):281–4.
163. Yurtlu DA, Aksun M, Ayvat P, Karahan N, Koroglu L, Aran GÖ. Comparison of Risk Scoring Systems to Predict the Outcome in ASA-PS V Patients Undergoing Surgery: A Retrospective Cohort Study. *Medicine*. 2016;95(13):e3238.
164. Fitz-Henry J. The ASA classification and peri-operative risk. *Ann R Coll Surg Engl*. 2011;93(3):185–7.
165. Owens WDMD. American Society of Anesthesiologists Physical Status Classification System Is Not a Risk Classification System. *Anesthesiology*. 2001;94(2):378.
166. Robinson TN, Wu DS, Pointer L, Christina L. Simple frailty score predicts post-operative complications across surgical specialities. *Am J Surg*. 2013;206(4):544–50.
167. Katz S, Downs TD, Cash HR, Grotz RC. Progress in Development of the Index of ADL. *Gerontologist* 1970;10:20–30.
168. Borson S, Scanlan JM, Chen P, Ganguli M. The Mini-Cog as a screen for dementia: Validation in a population-based sample. *J Am Geriatr Soc*. 2003;51(10):1451–4.
169. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis*. 1987;40(5):373–83.
170. Clevenger B, Richards T. Pre-operative anaemia. *Anaesthesia*. 2015;70(3):71–4.
171. Senesse P, Assenat E, Schneider S, Chargari C, Magné N, Azria D, et al. Nutritional support during oncologic treatment of patients with gastrointestinal cancer: Who could benefit? *Cancer Treat Rev*. 2008;34(6):568–75.

172. Inouye SK, Studenski S, Tinetti ME, Kuchel GA. Geriatric syndromes: Clinical, research, and policy implications of a core geriatric concept. *J Am Geriatr Soc.* 2007;55(5):780–91.
173. Weisman IM, Weisman IM, Marciniuk D, Martinez FJ, Scirba F, Sue D, et al. ATS/ACCP Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med.* 2003;167(2):211–77.
174. Kasivisvanathan R, Abbassi-Ghadi N, McLeod ADM, Oliver A, Rao Baikady R, Jhanji S, et al. Cardiopulmonary exercise testing for predicting postoperative morbidity in patients undergoing hepatic resection surgery. *HPB.* 2015;17(7):637–43.
175. Sirio, Knaus A, Draper A, Wagner P, Zimmerman E, Bastos G, et al. The APACHE III Prognostic System Risk Prediction III Hospitalized of Hospital Mortality Adults for Critically Ill Hospitalized Adults. *Chest.* 1991;100:1619–36.
176. Chen T, Wang H, Wang H, Song Y, Li X, Wang J. POSSUM and P-POSSUM as predictors of postoperative morbidity and mortality in patients undergoing hepato-biliary-pancreatic surgery: A meta-analysis. *Ann Surg Oncol.* 2013;20(8):2501–10.
177. NELA Project Team. Third patient report of the National Emergency Laparotomy Audit. RCoA London 11;2016
178. Jiang B, Yan XF, Zhang JH. Meta-analysis of laparoscopic versus open liver resection for hepatocellular carcinoma. *Hepatol Res.* 2018;48(8):635–63.
179. van Dam RM, Wong-Lun-Hing EM, van Breukelen GJP, Stoot JHMB, van der Vorst JR, Bemelmans MHA, et al. Open versus laparoscopic left lateral hepatic sectionectomy within an enhanced recovery ERAS® programme (ORANGE II - Trial): Study protocol for a randomised controlled trial. *Trials.* 2012;13:1–11.
180. Launois B, Tay KH, Meunier B. The posterior intrahepatic approach to liver resection. *HPB.* 1999;1(4):209–14.
181. Giordano M, Lopez-Ben S, Codina-Barreras A, Pardina B, Falgueras L, Torres-Bahi S, et al. Extra-Glissonian approach in liver resection. *HPB.* 2010;12(2):94–100.
182. Blumgart LBJ. *Surgery of the liver, biliary tract, and pancreas.* 4th ed. Philadelphia, PA: Saunders Elsevier; 2007.

183. Jarnagin WR. Blumgart's Surgery of the Liver, Biliary Tract and Pancreas. 5th Editio. Saunders Elsevier; 2012.
184. Hamady ZZR, Kotru A, Nishio H, Lodge JPA. Current techniques and results of liver resection for colorectal liver metastases. *Br Med Bull.* 2004;70(3):87–104.
185. Clavien PA, Sanabria JR, Strasberg SM. Proposed classification of complications of surgery with examples of utility in cholecystectomy. *Surgery.* 1992;111(5):518–26.
186. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg.* 2004;240(2):205–13.
187. Mentula PJ, Leppäniemi AK. Applicability of the Clavien-Dindo classification to emergency surgical procedures: A retrospective cohort study on 444 consecutive patients. *Patient Saf Surg.* 2014;8(1):1–7.
188. Mitropoulos D, Artibani W, Biyani CS, Bjerggaard Jensen J, Rouprêt M, Truss M. Validation of the Clavien-Dindo Grading System in Urology by the European Association of Urology Guidelines Ad Hoc Panel. *Eur Urol Focus.* 2017;
189. Seely AJE, Ivanovic J, Threader J, Al-Hussaini A, Al-Shehab D, Ramsay T, et al. Systematic classification of morbidity and mortality after thoracic surgery. *Ann Thorac Surg* 2010;90(3):936–42.
190. Farges O, Malassagne B, Flejou JF, Balzan S, Sauvanet A, Belghiti J. Risk of major liver resection in patients with underlying chronic liver disease: a reappraisal. *Ann Surg* 1999;229(2):210–5.
191. Belghiti J, Hiramatsu K, Benoist S, Massault PP, Sauvanet A, Farges O. Seven hundred forty-seven hepatectomies in the 1990s: An update to evaluate the actual risk of liver resection. *J Am Coll Surg.* 2000;191(1):38–46.
192. Kanai M, Nimura Y, Kamiya J, Kondo S, Nagino M, Miyachi M, et al. Preoperative intrahepatic segmental cholangitis in patients with advanced carcinoma involving the hepatic hilus. *Surgery.* 1996;119(5):498–504.
193. Nakatani Y, Fukui H, Kitano H, Nagamoto I, Tsujimoto T, Kuriyama S, et al. Endotoxin

- clearance and its relation to hepatic and renal disturbances in rats with liver cirrhosis. *Liver*. 2001;21(1):64–70.
194. Navasa M. Bacterial infections in patients with cirrhosis: reasons, comments and suggestions. *Dig Liver Dis* 2001;33(1):9–12.
195. Bolognesi M, Merkel C, Bianco S, Angeli P, Sacerdoti D, Amodio P, et al. Clinical significance of the evaluation of hepatic reticuloendothelial removal capacity in patients with cirrhosis. *Hepatology*. 1994;19(3):628–34.
196. Poon RT, Fan ST, Lo CM, Liu CL, Lam CM, Yuen WK, et al. Improving perioperative outcome expands the role of hepatectomy in management of benign and malignant hepatobiliary diseases: Analysis of 1222 consecutive patients from a prospective database. *Ann Surg*. 2004;240(4):698–710.
197. Shoup M. Volumetric Analysis Predicts Hepatic Dysfunction in Patients Undergoing Major Liver Resection. *J Gastrointest Surg* 2003;7(3):325–30.
198. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg*. 1999;230(3):309–18;
199. Vauthey JN, Chaoui A, Do KA, Bilimoria MM, Fenstermacher MJ, Charnsangavej C, et al. Standardized measurement of the future liver remnant prior to extended liver resection: Methodology and clinical associations. *Surgery*. 2000;127(5):512–9.
200. Hackl C, Schlitt HJ, Renner P, Lang SA. Liver surgery in cirrhosis and portal hypertension. *World J Gastroenterol*. 2016;22(9):2725–35.
201. Doci R, Gennari L, Bignami P, Montalto F, Morabito A, Bozzetti F, et al. Morbidity and mortality after hepatic resection of metastases from colorectal cancer. *Br J Surg* 1995;82(3):377–81.
202. Laurent C, Sa Cunha A, Couderc P, Rullier E, Saric J. Influence of postoperative morbidity on long-term survival following liver resection for colorectal metastases. *Br J Surg*. 2003;90(9):1131–6.
203. Slooter GD, Marquet RL, Jeekel J, Ijzermans JN. Tumour growth stimulation after partial

- hepatectomy can be reduced by treatment with tumour necrosis factor alpha. *Br J Surg* 1995;82(1):129–32.
204. Fan, Sheung Tat; Lo, Chung-Mau, Lai; Edward CS, Chu; Kent-Mau, Liu; Chi-Leung W. Perioperative Nutritional Support in Patients undergoing Hepatectomy for Hepatocellular Carcinoma. *N Engl J Med.* 1994;331(23):1547–52.
205. Boleslawski E, Vibert E, Pruvot FR, Le Treut YP, Scatton O, Laurent C, et al. Relevance of postoperative peak transaminase after elective hepatectomy. *Ann Surg.* 2014;260(5):815–21.
206. Olthof PB, Huiskens J, Schulte NR, Wicherts DA, Besselink MG, Busch OR, et al. Postoperative peak transaminases correlate with morbidity and mortality after liver resection. *HPB* 2016;18(11):915–21.
207. Hemming AW, Reed AI, Howard RJ, Fujita S, Hochwald SN, Caridi JG, et al. Preoperative Portal Vein Embolization for Extended Hepatectomy. *Ann Surg.* 2003;237(5):686–93.
208. Hemming MSc AWMD, Reed AIMD, Langham MRJMD, Fujita PhD SMD, Howard PhD RJMD. Combined Resection of the Liver and Inferior Vena Cava for Hepatic Malignancy. *Annals* 2004;239(5):115–24.
209. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy - Definition, nomenclature, diagnosis, and quantification: Final report of the Working Party at the 11th World Congresses of Gastroenterology, Vienna, 1998. *Hepatology.* 2002;35(3):716–21.
210. Andersen, LW; Mackenhauer, Roberts, J; Berg, KM; Cocchi, MN; Donnino M. Etiology and therapeutic approach to elevated lactate. *Mayo Clin Proc.* 2013;88(10):1127–40.
211. Balzan S, Belghiti J, Farges O, Ogata S, Sauvanet A, Delefosse D, et al. The “50-50 criteria” on postoperative day 5: an accurate predictor of liver failure and death after hepatectomy. *Ann Surg.* 2005;242(6):824–8
212. Rahman SH, Evans J, Toogood GJ, Lodge PA, Prasad KR. Prognostic utility of postoperative C-reactive protein for posthepatectomy liver failure. *Arch Surg.*

- 2008;143(3):247–53.
213. Jin S, Fu Q, Wuyun G, Wuyun T. Management of post-hepatectomy complications. *World J Gastroenterol*. 2013;19(44):7983–91.
214. Allard M-A, Adam R, Bucur P-O, Termos S, Cunha AS, Bismuth H, et al. Posthepatectomy portal vein pressure predicts liver failure and mortality after major liver resection on noncirrhotic liver. *Ann Surg* 2013;258(5):822–9;
215. Narita M, Oussoultzoglou E, Bachellier P, Jaeck D, Uemoto S. Post-hepatectomy liver failure in patients with colorectal liver metastases. *Surg Today* [Internet]. 2015;45(10):1218–26. Available from: <http://dx.doi.org/10.1007/s00595-015-1113-7>
216. Lafaro K, Buettner S, Maqsood H, Wagner D, Bagante F, Spolverato G, et al. Defining Post Hepatectomy Liver Insufficiency: Where do We stand? *J Gastrointest Surg*. 2015;19(11):2079–92.
217. Cammann S, Oldhafer F, Ringe KI, Ramackers W, et al. Use of the liver maximum function capacity test (LiMAx) for the management of liver resection in cirrhosis – A case of hypopharyngeal cancer liver metastasis. *Int J Surg Case Rep* 2017;39:140–4.
218. Sourbron S, Sommer WH, Reiser MF, Zech CJ. Combined Quantification of Liver Perfusion and Function with Dynamic Gadoteric Acid-enhanced MR Imaging. *Radiology*. 2012;263(3):874–83.
219. Tzeng CWD, Cooper AB, Vauthey JN, Curley SA, Aloia TA. Predictors of morbidity and mortality after hepatectomy in elderly patients: Analysis of 7621 NSQIP patients. *HPB*. 2014;16(5):459–68.
220. Hazlehurst JM, Woods C, Marjot T, Cobbold JF, Tomlinson JW. Non-alcoholic fatty liver disease and diabetes. *Metabolism* 2016;65(8):1096–108.
221. Gedaly R, McHugh PP, Johnston TD, Jeon H, Ranjan D, Davenport DL. Obesity, diabetes, and smoking are important determinants of resource utilization in liver resection: a multicenter analysis of 1029 patients. *Ann Surg* 2009;249(3):414–9.
222. Wiggins MG, Shahtahmassebi G, Bowles MJ, Aroori S, Stell DA. Renal dysfunction is an independent risk factor for mortality after liver resection and the main determinant of

- outcome in posthepatectomy liver failure. *HPB Surg.* 2013;2013.
223. Chawla LS, Eggers PW, Star RA, Kimmel PL. Acute Kidney Injury and Chronic Kidney Disease as Interconnected Syndromes. *N Engl J Med* 2014;371(1):58–66.
224. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and Trends in Obesity Among US Adults, 1999-2008. *J Am Med Assoc.* 2010;303(3):235–41.
225. Amri R, Bordeianou LG, Sylla P, Berger DL. Obesity, outcomes and quality of care: Body mass index increases the risk of wound-related complications in colon cancer surgery. *Am J Surg* 2014;207(1):17–23.
226. Dindo D, Muller MK, Weber M, Clavien PA. Obesity in general elective surgery. *Lancet.* 2003;361(9374):2032–5.
227. Fabbrini ESS ;Klein. Obesity and Nonalcoholic Fatty Liver Disease: Biochemical, Metabolic and Clinical Implications NIH Public Access. *Hepatology.* 2010;51(2):679–89.
228. Veteläinen R, van Vliet A, Gouma DJ, van Gulik TM. Steatosis as a risk factor in liver surgery. *Ann Surg* 2007;245(1):20–30.
229. Fong Y, Bentrem DJ. CASH (Chemotherapy-Associated Steatohepatitis) Costs. *Ann Surg* 2006;243(1):8–9.
230. Karoui M, Penna C, Amin-Hashem M, Mitry E, Benoist S, Franc B, et al. Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases. *Ann Surg* 2006;243(1):1–7.
231. Fernandez FG, Ritter J, Goodwin JW, Linehan DC, Hawkins WG, Strasberg SM. Effect of steatohepatitis associated with irinotecan or oxaliplatin pretreatment on resectability of hepatic colorectal metastases. *J Am Coll Surg.* 2005;200(6):845–53.
232. Luo HY, Li YH, Wang W, Wang ZQ, Yuan X, Ma D, et al. Single-agent capecitabine as maintenance therapy after induction of XELOX (or FOLFOX) in first-line treatment of metastatic colorectal cancer: Randomized clinical trial of efficacy and safety. *Ann Oncol.* 2016;27(6):1074–81.
233. Nam SJ, Cho JY, Lee HS, Choe G, Jang JJ, Yoon YS, et al. Chemotherapy-associated hepatopathy in Korean colorectal cancer liver metastasis patients: Oxaliplatin-based

- chemotherapy and sinusoidal injury. *Korean J Pathol.* 2012;46(1):22–9.
234. Maor Y, Malnick S. Liver injury induced by anticancer chemotherapy and radiation therapy. *Int J Hepatol* 2013;2013:815105.
235. Wang H, Yang J, Zhang X, Yan L, Yang J. Liver resection in hepatitis B-related hepatocellular carcinoma: Clinical outcomes and safety in overweight and obese patients. *PLoS One.* 2014;9(6):6620–5.
236. Hino O, Shows TB, Rogler CE. Hepatitis B virus integration site in hepatocellular carcinoma at chromosome 17;18 translocation. *Proc Natl Acad Sci U S A.* 1986;83(21):8338–42.
237. Toshikuni N, Arisawa T, Tsutsumi M. Hepatitis C-related liver cirrhosis - strategies for the prevention of hepatic decompensation, hepatocarcinogenesis, and mortality. *World J Gastroenterol.* 2014;20(11):2876–87.
238. McGivern DR, Lemon SM. Virus-specific Mechanisms of Carcinogenesis in Hepatitis C Virus Associated Liver Cancer. *Oncogene.* 2011;30(17):1969–83.
239. Eguchi H, Umeshita K, Sakon M, Nagano H, Ito Y, Kishimoto SI, et al. Presence of active hepatitis associated with liver cirrhosis is a risk factor for mortality caused by posthepatectomy liver failure. *Dig Dis Sci* 2000;45(7):1383–8.
240. Tu R, Xia LP, Yu A Le, Wu L. Assessment of hepatic functional reserve by cirrhosis grading and liver volume measurement using CT. *World J Gastroenterol.* 2007;13(29):3956–61.
241. Aloia TA, Fahy BN, Fischer CP, Jones SL, Duchini A, Galati J, et al. Predicting poor outcome following hepatectomy: Analysis of 2313 hepatectomies in the NSQIP database. *HPB.* 2009;11(6):510–5.
242. Chiou W-Y, Chang C-M, Tseng K-C, Hung S-K, Lin H-Y, Chen Y-C, et al. Effect of liver cirrhosis on metastasis in colorectal cancer patients: a nationwide population-based cohort study. *Jpn J Clin Oncol* 2015;45(2):160–8.
243. Suk KT, Kim DJ. Staging of liver fibrosis or cirrhosis: The role of hepatic venous pressure gradient measurement. *World J Hepatol.* 2015;7(3):607–15.

244. Hong H, Li J, Jin Y, Li Q, Li W, Wu J, et al. Performance of real-time elastography for the staging of hepatic fibrosis: A meta-analysis. *PLoS One*. 2014;9(12):1–15.
245. Bapen. Malnutrition Universal Screening Tool. *Malnutrition Advis Gr*. 2011;1–6.
246. Probst P, Fuchs J, Schoen MR, Polychronidis G, Forster T, Mehrabi A, et al. Nutritional risk in major abdominal surgery: NURIMAS Liver (DRKS00010923) – protocol of a prospective observational trial to evaluate the prognostic value of different nutritional scores in hepatic surgery. *Int J Surg Protoc* 2017;6:5–10.
247. Gottlieb G. Is the NHS ageist? *RCS Bull*. 2015;10–1.
248. Department of Health. NHS Constitution for England. *NHS Const Establ Princ values NHS Engl*. 2015;(7):1.
249. Preston SD, Southall ARD, Nel M, Das SK. Geriatric surgery is about disease, not age. *J R Soc Med*. 2008;101(8):409–15.
250. Lee CH, Yoon H-J. Medical big data: promise and challenges. *Kidney Res Clin Pract* 2017;36(1):3–11.
251. Dunlop WE, Rosenblood L, Lawrason L, Birdsall L, Rusnak CH. Effects of age and severity of illness on outcome and length of stay in geriatric surgical patients. *Am J Surg*. 1993;165(5):577–80.
252. Leung JM, Dzankic S. Relative importance of preoperative health status versus intraoperative factors in predicting postoperative adverse outcomes in geriatric surgical patients. *J Am Geriatr Soc*. 2001;49(8):1080–5.
253. Adam DJ, Craig SR, Sang CTM, Cameron EWJ, Walker WS. Esophagectomy for carcinoma in the octogenarian. *Ann Thorac Surg*. 1996;61(1):190–4.
254. Patel SA, Zenilman ME. Outcomes in Older People Undergoing Operative Intervention for Colorectal Cancer. *J Am Geriatr Soc* 2001;49(11):1561–4.
255. Stroumbakis, Nicholas; Herr, Harry W.; Cookson, Michael S.; Fair WR. Radical Cystectomy In The Octogenarian. *J Urol*. 1997;158(6):2113–7.
256. Susini T, Scambia G, Margariti PA, Giannice R, Signorile P, Benedetti Panici P, et al.

- Gynecologic oncologic surgery in the elderly: A retrospective analysis of 213 patients. *Gynecol Oncol.* 1999;75(3):437–43.
257. Djokovic JL, Hedley-Whyte J. Prediction of outcome of surgery and anesthesia in patients over 80. *Jama.* 1979;242(21):2301–6.
258. L.L. L, J.M. L. Predicting adverse postoperative outcomes in patients aged 80 years or older. *J Am Geriatr Soc* 2000;48(4):405–12.
259. Massarweh NN, Legner VJ, Symons RG, McCormick WC, Flum DR. Impact of advancing age on abdominal surgical outcomes. *Arch Surg.* 2009;144(12):1108–14.
260. Marusch F, Koch A, Schmidt U, Steinert R, Ueberrueck T, Bittner R, et al. The impact of the risk factor “age” on the early postoperative results of surgery for colorectal carcinoma and its significance for perioperative management. *World J Surg.* 2005;29(8):1013–21.
261. Boland BS, Dong MH, Bettencourt R, Barrett-Connor E, Loomba R. Association of serum bilirubin with aging and mortality. *J Clin Exp Hepatol* 2014;4(1):1–7.
262. Cieslak KP, Baur O, Verheij J, Bennink RJ, van Gulik TM. Liver function declines with increased age. *HPB* 2016;18(8):691–6.
263. Menon K V., Al-Mukhtar A, Aldouri A, Prasad RK, Lodge PA, Toogood GJ. Outcomes after Major Hepatectomy in Elderly Patients. *J Am Coll Surg.* 2006;203(5):677–83.
264. Tranchart H, Gaillard M, Chirica M, Ferretti S, Perlemuter G, Naveau S, et al. Multivariate analysis of risk factors for postoperative complications after laparoscopic liver resection. *Surg Endosc* 2014;(11):2538–44.
265. Soleimanpour H, Safari S, Rahmani F, Nejabatian A, Alavian SM. Hepatic Shock Differential Diagnosis and Risk Factors: A Review Article. *Hepat Mon* 2015;15(10):1–6.
266. Lightsey JM, Rockey DC. Current concepts in ischemic hepatitis. *Curr Opin Gastroenterol.* 2017;33(3):158–63.
267. Grant J. Complications of Blood Transfusion. *Practitioner.* 1965;195(2):179–86.
268. Mitra B, Tullio F, Cameron PA, Fitzgerald M. Trauma patients with the “triad of death.” *Emerg Med J.* 2012;29(8):622–5.

269. Protzer U, Maini MK, Knolle PA. Living in the liver: Hepatic infections. *Nat Rev Immunol*. 2012;12(3):201–13.
270. Li F, Tian Z. The liver works as a school to educate regulatory immune cells. *Cell Mol Immunol* 2013;10(4):292–302.
271. Yan, J; Song, Li; Li S. The Role of the Liver in Sepsis. *Int Rev Immunol*. 2014;33(6):498–510.
272. Wiezer MJ, Meijer C, Wallast-Groenewoud HP, Tool AT, Prins HA, Houdijk AP, et al. Impaired leukocyte phagocytosis in patients undergoing hemihepatectomy for liver metastases. *Liver Transplant Surg* 1999;5(3):238–45.
273. Lan AKM, Luk HN, Goto S, Chen SMS, Eng HL, Chen Y Sen, et al. Stress response to hepatectomy in patients with a healthy or a diseased liver. *World J Surg*. 2003;27(7):761–4.
274. Saito K, Ledsam J, Sourbron S, Hashimoto T, Araki Y, Akata S, et al. Measuring hepatic functional reserve using low temporal resolution Gd-EOB-DTPA dynamic contrast-enhanced MRI: A preliminary study comparing galactosyl human serum albumin scintigraphy with indocyanine green retention. *Eur Radiol*. 2014;24(1):112–9.
275. Reinhart MB, Huntington CR, Blair LJ, Heniford BT, Augenstein VA. Indocyanine Green. *Surg Innov* 2016;23(2):166–75.
276. Faybik P, Hetz H. Plasma Disappearance Rate of Indocyanine Green in Liver Dysfunction. *Transplant Proc*. 2006;801–2.
277. Lau H, Man K, Fan S-T, Yu W-C, Lo C-M, Wong J. Evaluation of preoperative hepatic function in patients with hepatocellular carcinoma undergoing hepatectomy. *Br J Surg* 1997;84(9):1255–9.
278. Redaelli CA, Dufour J-F, Wagner M, Schilling M, Hüsler J, Krähenbühl L, et al. Preoperative galactose elimination capacity predicts complications and survival after hepatic resection. *Ann Surg* 2002;235(1):77–85.
279. Ranek L, Andreasen PB, Tygstrup N. Galactose elimination capacity as a prognostic index in patients with fulminant liver failure. *Gut*. 1976;(7):959–64.

280. Hoekstra LT, de Graaf W, Nibourg G a. a., Heger M, Bennink RJ, Stieger B, et al. Physiological and Biochemical Basis of Clinical Liver Function Tests. *Ann Surg*. 2012;257(1):1.
281. Reichen, Jürg; Widmer, Thomas; Cotting J. Accurate Prediction of Death by Serial Determination of Galactose Elimination Capacity. *Hepatology*. 1991;14(9):504–10.
282. Stockmann M, Lock JF, Malinowski M, Niehues SM, Seehofer D, Neuhaus P. The LiMAx test: A new liver function test for predicting postoperative outcome in liver surgery. *HPB*. 2010;12(2):139–46.
283. Jara M, Reese T, Malinowski M, Valle E, Seehofer D, Puhl G, et al. Reductions in post-hepatectomy liver failure and related mortality after implementation of the LiMAx algorithm in preoperative work-up: A single-centre analysis of 1170 hepatectomies of one or more segments. *HPB*. 2015;17(7):651–8.
284. Kokudo N, Vera DR, Makuuchi M. Clinical application of TcGSA. *Nucl Med Biol*. 2003;30(8):845–9.
285. Onodera Y, Takahashi K, Togashi T, Sugai Y, Tamaki N, Miyasaka K. Clinical assessment of hepatic functional reserve using 99mTc DTPA galactosyl human serum albumin SPECT to prognosticate chronic hepatic diseases--validation of the use of SPECT and a new indicator. *Ann Nucl Med* 2003;17(3):181–8.
286. Kwon A, Matsui Y, Ha-kawa SK, Kamiyama Y. Functional Hepatic Volume Measured by Technetium-99m-Galactosyl-Human Serum Albumin Liver Scintigraphy : Comparison Between Hepatocyte Volume and Liver Volume by Computed Tomography. *Am J Gastroenterol*. 2001;96(2):541–6.
287. Graaf W De, Häusler S, Heger M, Ginhoven TM Van, Cappellen G Van, Bennink RJ, et al. Transporters involved in the hepatic uptake of 99mTc-mebrofenin and indocyanine green. *J Hepatol* 2011;54(4):738–45.
288. de Graaf W, van Lienden KP, van Gulik TM, Bennink RJ. 99mTc-Mebrofenin Hepatobiliary Scintigraphy with SPECT for the Assessment of Hepatic Function and Liver Functional Volume Before Partial Hepatectomy. *J Nucl Med* 2010;51(2):229–36.

289. Cieslak K. Scintigraphic assessment of liver function in patients requiring liver surgery. (PhD Thesis), 2017, University of Amsterdam, The Netherlands
290. Perandini S, Faccioli N, Inama M, Mucelli RP. Freehand liver volumetry by using an electromagnetic pen tablet: Accuracy, precision, and rapidity. *J Digit Imaging*. 2011;24(2):360–5.
291. Suzuki K, Epstein ML, Kohlbrenner R, Garg S, Hori M, Oto A, et al. Quantitative radiology: Automated CT liver volumetry compared with interactive volumetry and manual volumetry. *Am J Roentgenol*. 2011;197(4):706–12.
292. Kishi Y, Abdalla EK, Chun YS, Zorzi D, Madoff DC, Wallace MJ, et al. Three hundred and one consecutive extended right hepatectomies: evaluation of outcome based on systematic liver volumetry. *Ann Surg*. 2009;250(4):540–8.
293. Mosteller R. Simplified Calculation of Body-Surface Area. *N Engl J Med*. 1987;317:1098.
294. Bernier MO, Journy N, Baysson H, Jacob S, Laurier D. Potential cancer risk associated with CT scans: Review of epidemiological studies and ongoing studies. *Prog Nucl Energy*. 2015;84:116–9.
295. Amis ES Jr, Butler PF, Applegate KE, Birnbaum SB, Brateman LF, Hevezi JM, Mettler FA, Morin RL, Pentecost MJ, Smith GG, Strauss KJ ZR. American College of Radiology white paper on radiation dose in medicine. *J Am Coll Radiol*. 2007;4:272–84.
296. Schmidt CW. CT scans: balancing health risks and medical benefits. *Environ Health Perspect*. 2012;120(3):118–21.
297. D'Onofrio M, De Robertis R, Demozzi E, Crosara S, Canestrini S, Pozzi Mucelli R. Liver volumetry: Is imaging reliable? Personal experience and review of the literature. *World J Radiol* 2014;6(4):62–71.
298. Nilsson H, Blomqvist L, Douglas L, Nordell A, Jacobsson H, Hagen K, et al. Dynamic gadoxetate-enhanced MRI for the assessment of total and segmental liver function and volume in primary sclerosing cholangitis. *J Magn Reson Imaging*. 2014;39(4):879–86.
299. Nilsson H, Blomqvist L, Douglas L, Nordell A, Jonas E. Assessment of liver function in primary biliary cirrhosis using Gd-EOB-DTPA-enhanced liver MRI. *HPB*

- 2010;12(8):567–76.
300. Nilsson H, Blomqvist L, Douglas L, Nordell A, Janczewska I, Näslund E, et al. Gd-EOB-DTPA-enhanced MRI for the assessment of liver function and volume in liver cirrhosis. *Br J Radiol* 2013;86(1026):20120653.
301. Nilsson H, Karlgren S, Blomqvist L, Jonas E. The inhomogeneous distribution of liver function: Possible impact on the prediction of post-operative remnant liver function. *HPB*. 2015;17(3):272–7.
302. Child CG, Turcotte JG. Surgery and portal hypertension. *Major Probl Clin Surg*. 1964;1:1–85.
303. Pugh, RNH; Murray-Lyon, IM; Dawson, JL; Pietroni, MC; Williams R. Transection of the Oesophagus for Bleeding Oesophageal Varices. *Br J Surg*. 1973;60(8):1971–4.
304. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg P. A Model to Predict Poor Survival in Patients Undergoing Transjugular Intrahepatic Portosystemic Shunts. *Hepatology*. 2000;(31):864–71.
305. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. *Hepatology*. 2001;33(2):464–70.
306. Barber, KM; Pioli, SE; Blackwell, JE; Collett, D; Neuberger, JM; Gimson A. Development Of A UK Score For Patients With End-Stage Liver Disease. *Hepatology*. 2007;46(4):431–531.
307. Weishaupt DVDKBM. How does MRI work? : an introduction to the physics and function of magnetic resonance. 2nd ed. Springer-Verlag Berlin Heidelberg 2006
308. Nilsson H. Magnetic Resonance Imaging for the Assessment of Liver Function. PhD Thesis 2011 Karolinska Institutet, Stockholm, Sweden.
309. Chezmar JL, Rumancik WM, Megibow AJ, Hulnick DH, Nelson RC, Bernardino ME. Liver and abdominal screening in patients with cancer: CT versus MR imaging. *Radiology* 1988;168(1):43–7.
310. Kang S II, Kim DW, Cho JY, Park J, Lee KH, Son IT, et al. Is MRI of the Liver Needed

- during Routine Preoperative Workup for Colorectal Cancer? *Dis Colon Rectum*. 2017;60(9):936–44.
311. John R. Rumble; David R. Lide TJB, editor. *CRC handbook of chemistry and physics : a ready-reference book of chemical and physical data*. 98th ed. Boca Raton: CRC Press; 2017.
312. Rogosnitzky M, Branch S. Gadolinium-based contrast agent toxicity: a review of known and proposed mechanisms. *BioMetals*. 2016;29(3):365–76.
313. Namkung S, Zech CJ, Helmberger T, Reiser MF, Schoenberg SO. Superparamagnetic iron oxide (SPIO)-enhanced liver MRI with ferucarbotran: Efficacy for characterization of focal liver lesions. *J Magn Reson Imaging*. 2007;25(4):755–65.
314. Seale MK, Catalano OA, Saini S, Hahn PF, Sahani D V. Hepatobiliary-specific MR Contrast Agents: Role in Imaging the Liver and Biliary Tree. *RadioGraphics* 2009;29(6):1725–48.
315. Choi JS, Kim MJ, Chung YE, Kim KA, Choi JY, Lim JS, et al. Comparison of breathhold, navigator-triggered, and free-breathing diffusion-weighted MRI for focal hepatic lesions. *J Magn Reson Imaging*. 2013;38(1):109–18.
316. Maxim Zaitsev, Julian. Maclaren MH. Motion Artefacts in MRI: a Complex Problem with Many Partial Solutions. *J Magn Reson Imaging*. 2015;42(4):88–901.
317. Ohtomo K, Yoshikawa K, Itai Y, Kokubo T, Yashiro N, Iio M. Dynamic MRI of hepatic tumors using gadolinium-DTPA--preliminary results. *Radiat Med*. 1986;4(2):51–3.
318. Brown PH, Juni JE, Lieberman D a, Krishnamurthy GT. Hepatocyte versus biliary disease: a distinction by deconvolutional analysis of technetium-99m IDA time-activity curves. *J Nucl Med* 1988;29(5):623–30.
319. Ryeom H-K, Kim S-H, Kim J-Y, Kim H-J, Lee J-M, Chang Y-M, et al. Quantitative evaluation of liver function with MRI Using Gd-EOB-DTPA. *Korean J Radiol* 2004;5(4):231–9.
320. Nilsson H, Nordell A, Vargas R, Douglas L, Jonas E, Blomqvist L. Assessment of hepatic extraction fraction and input relative blood flow using dynamic hepatocyte-specific

- contrast-enhanced MRI. *J Magn Reson Imaging*. 2009;29(6):1323–31.
321. Jarnagin WR, Schwartz LH, Gultekin DH, Gönen M, Haviland D, Shia J, et al. Regional chemotherapy for unresectable primary liver cancer: Results of a phase II clinical trial and assessment of DCE-MRI as a biomarker of survival. *Ann Oncol*. 2009;20(9):1589–95.
322. Attenberger U, Sourbron, Sp; Michaely, H; Reiser M, Schoenberg So. Retrospective respiratory triggering renal perfusion MRI. *Acta radiol*. 2010;(16):1163–71.
323. Materne R, Smith AM, Peeters F, Dehoux JP, Keyeux A, Horsmans Y, et al. Assessment of hepatic perfusion parameters with dynamic MRI. *Magn Reson Med*. 2002;47(1):135–42.
324. Huppertz A, Haraida S, Kraus A, Zech CJ, et al. Enhancement of Focal Liver Lesions at Gadoteric Acid-enhanced MR Imaging: Correlation with Histopathologic Findings and Spiral CT—Initial Observations. *Radiology* 2005 1;234(2):468–78.
325. Khatri VP, Petrelli NJ, Belghiti J. Extending the frontiers of surgical therapy for hepatic colorectal metastases: Is there a limit? *J Clin Oncol*. 2005;23(33):8490–9.
326. Tanaka K, Matsuyama R, Takeda K, Matsuo K, Nagano Y, Endo I. Aggressive liver resection including major-vessel resection for colorectal liver metastases. *World J Hepatol* 2009;1(1):79–89.
327. Orcutt ST, Artinyan A, Li LT, Silberfein EJ, Berger DH, Albo D, et al. Postoperative mortality and need for transitional care following liver resection for metastatic disease in elderly patients: A population-level analysis of 4026 patients. *HPB*. 2012;14(12):863–70.
328. de Liguori Carino N, van Leeuwen BL, Ghaneh P, Wu A, Audisio RA, Poston GJ. Liver resection for colorectal liver metastases in older patients. *Crit Rev Oncol Hematol*. 2008;67(3):273–8.
329. Motoyama H, Kobayashi A, Yokoyama T, Shimizu A, Sakai H, Furusawa N, et al. Impact of advanced age on the short- and long-term outcomes in patients undergoing hepatectomy for hepatocellular carcinoma: A single-center analysis over a 20-year period. *Am J Surg* 2015;209(4):733–41.

330. Fong Y, Blumgart LH, Fortner JG, Brennan MF. Pancreatic or liver resection for malignancy is safe and effective for the elderly. *Ann Surg* 1995;222(4):426–34;
331. Wang Z, Xu M, Peng J, Jiang L, Hu Z, Wang H, et al. Prevalence and associated metabolic factors of fatty liver disease in the elderly. *Exp Gerontol* 2013;48(8):705–9.
332. Fox M, Fox J, Davies M. Diagnosis and management of chronic liver disease in older people. *Rev Clin Gerontol*. 2011;21(01):1–15.
333. Vallance AE, Young AL, Kuryba A, Braun M, et al. The impact of advancing age on incidence of hepatectomy and post-operative outcomes in patients with colorectal cancer liver metastases: a population-based cohort study. *HPB* 2018 7;1-8
334. Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, et al. Updating and validating the charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. 2011;173(6):676–82.
335. Summaries HRGC. Reference Costs Group. Department of Health 4;2014.
336. Caratozzolo E, Massani M, Recordare A, Bonariol L, Baldessin M, Bassi N. Liver resection in elderly : comparative study between younger and older than 70 years patients. *Out*. 2007;28:419–24.
337. Hanazaki K, D P, Kajikawa S, D P, Shimozawa N, Shimada K. Hepatic resection for hepatocellular carcinoma in the elderly. *J Surg Oncol* 2009;99(3):154–60.
338. Bockhorn M, Sotiropoulos GC, Sgourakis G, Neuhaus JP, Molmenti EP, Lang H, et al. Major liver resections in the elderly - Is an aggressive approach justified? *Int J Colorectal Dis*. 2009;24(1):83–6.
339. Mann CD, Neal CP, Pattenden CJ, Metcalfe MS, Garcea G, Dennison AR, et al. Major resection of hepatic colorectal liver metastases in elderly patients - An aggressive approach is justified. *Eur J Surg Oncol*. 2008;34(4):428–32.
340. Young AL, Wilson D, Ward J, Biglands J, Guthrie JA, Prasad KR, et al. Role of quantification of hepatic steatosis and future remnant volume in predicting hepatic dysfunction and complications after liver resection for colorectal metastases: A pilot study. *HPB*. 2012;14(3):194–200.

341. Simoneau E, Aljiffry M, Salman A, Abualhassan N, Cabrera T, Valenti D, et al. Portal vein embolization stimulates tumour growth in patients with colorectal cancer liver metastases. *HPB* 2012;14(7):461–8.
342. Khalifa F, El-ghar MA, Abdollahi B. A comprehensive non-invasive framework for automated evaluation of acute renal transplant rejection using DCE-MRI. *NMR Biomed.* 2013;(S9):1460–70.
343. Chandarana H, Block TK, Ream J, Mikheev A, Sigal SH, Otazo R, et al. Estimating Liver Perfusion From Free – Breathing Continuously Acquired Dynamic Gadolinium-Ethoxybenzyl-Diethylenetriamine Pentaacetic Acid – Enhanced Acquisition With Compressed Sensing Reconstruction. *Invest Radiol.* 2015;50(2).
344. Gill AB, Black RT, Bowden DJ. An investigation into the effects of temporal resolution on hepatic dynamic contrast-enhanced MRI in volunteers and in patients with hepatocellular carcinoma An investigation into the effects of temporal resolution on hepatic dynamic contrast-enhanced MRI. *Phys Med Biol.* 2014;(59):3187.
345. Chouhan MD, Bainbridge A, Atkinson D, Punwani S, Mookerjee RP, Lythgoe MF, et al. Estimation of contrast agent bolus arrival delays for improved reproducibility of liver DCE MRI. *Phys Med Biol* 2016;61(19):6905–18.
346. Vollmar B, Menger MD. The Hepatic Microcirculation : Mechanistic Contributions and Therapeutic Targets in Liver Injury and Repair. *Physiol Rev.* 2009;(89):1269–339.
347. Simmonds PC, Primrose JN, Colquitt JL, Garden OJ, Poston GJ, Rees M. Surgical resection of hepatic metastases from colorectal cancer: A systematic review of published studies. *Br J Cancer* 2006;94(7):982–99.
348. Marsman HA, Van Der Pool AE, Verheij J, Padmos J, Ten Kate FJW, Dwarkasing RS, et al. Hepatic steatosis assessment with CT or MRI in patients with colorectal liver metastases after neoadjuvant chemotherapy. *J Surg Oncol.* 2011;104(1):10–6.
349. Dinant S, de Graaf W, Verwer BJ, Bennink RJ, van Lienden KP, Gouma DJ, et al. Risk Assessment of Posthepatectomy Liver Failure Using Hepatobiliary Scintigraphy and CT Volumetry. *J Nucl Med* 2007;48(5):685–92.

350. Zorzi D, Laurent A, Pawlik TM, Lauwers GY, Vauthey JN, Abdalla EK. Chemotherapy-associated hepatotoxicity and surgery for colorectal liver metastases. *Br J Surg*. 2007;94(3):274–86.
351. Ratziu V, Bugianesi E, Dixon J, Fassio E, Ekstedt M, Charlotte F, et al. Histological progression of non-alcoholic fatty liver disease: A critical reassessment based on liver sampling variability. *Aliment Pharmacol Ther*. 2007;26(6):821–30.
352. Tamada T, Ito K, Sone T, Yamamoto A, Yamashita T. Dynamic Contrast-Enhanced Magnetic Resonance Imaging of Abdominal Solid Organ and Major Vessel : Comparison of Enhancement Effect between Gd-EOB-DTPA and Gd-DTPA. *J Magn Reson Imaging*. 2009;640:636–40.
353. Stern, W; F .Schick, A.F.Kopp, P.Reimer, K.Shamsi . Dynamic Mr Imaging Of Liver Metastases With Gd-EOB-DTPA. *Acta radiol*. 2000;41:255–62.
354. Zech CJ, Grazioli L, Breuer J, Reiser MF. Diagnostic Performance and Description of Morphological Features of Focal Nodular Hyperplasia in Gd-EOB-DTPA-Enhanced Liver Magnetic Resonance Imaging : Results of a Multicenter Trial. *Invest Radiol*. 2008;43(7):504–11.
355. Tschirch FTC, Petrowsky H. Contrast-enhanced MR cholangiography with Gd-EOB-DTPA in patients with liver cirrhosis: visualization of the biliary ducts in comparison with patients with normal liver parenchyma. *Eur Radiol*. 2008;18:1577–86.
356. Kim S, Kim J, Kim H, Lee J. Quantitative Evaluation of Liver Function with MRI Using. *Korean J Radiol*. 2004;5(12):231–9.
357. Motosugi U, Ichikawa T, Sou H. Liver Parenchymal Enhancement of Hepatocyte- Phase Images in Gd-EOB-DTPA-Enhanced MR Imaging : Which Biological Markers of the Liver Function Affect the Enhancement ? *J Magn Reson Imaging*. 2009;1046:1042–6.
358. Karageorgis A, Lenhard SC, Yerby B, Forsgren MF, Liachenko S, Johansson E, et al. A multi-center preclinical study of gadoxetate DCE-MRI in rats as a biomarker of drug induced inhibition of liver transporter function. *PLoS One*. 2018;13(5):1–18.
359. Dodd D. An American's guide to Couinaud's numbering system. *Radiology*.

- 1993;(161):574–5.
360. Shindoh J et al. Optimal Future Liver Remnant in Patients Treated with Extensive Preoperative Chemotherapy for Colorectal Liver Metastases. *Ann Surg Oncol*. 2013;20(8):1–15.
361. Takahashi Y, Fukusato T. Histopathology of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. *World J Gastroenterol*. 2014;20(42):15539–48.
362. López-Velázquez JA, Chávez-Tapia NC, Ponciano-Rodríguez G, Sánchez-Valle V, Caldwell SH, Uribe M, et al. Bilirubin alone as a biomarker for short-term mortality in acute-on-chronic liver failure: An important prognostic indicator. *Ann Hepatol*. 2014;13(1):98–104.
363. Truant S, Oberlin O, Sergent G, Lebuffe G, Gambiez L, Ernst O, et al. Remnant Liver Volume to Body Weight Ratio $\geq 0.5\%$: A New Cut-Off to Estimate Postoperative Risks after Extended Resection in Noncirrhotic Liver. *J Am Coll Surg*. 2007;204(1):22–33.
364. May BJ, Madoff DC. Portal vein embolization: Rationale, technique, and current application. *Semin Intervent Radiol*. 2012;29(2):81–9.
365. Limdi J, Hyde G. Evaluation of abnormal liver function tests. *Postgr Med J*. 2003;79:307–12.
366. Lee J, Kim KW on, Kim SY eon, Kim B, Lee SJ ung, Kim HJ ung, et al. Feasibility of semiautomated MR volumetry using gadoxetic acid-enhanced MRI at hepatobiliary phase for living liver donors. *Magn Reson Med*. 2014;72(3):640–5.
367. Fan R, Wang J, Du J. Association between body mass index and fatty liver risk: A dose-response analysis. *Sci Rep* 2018;8(1):15273.
368. Armstrong RA. When to use the Bonferroni correction. *Ophthalmic Physiol Opt*. 2014;34(5):502–8.

Appendix A – Supplemental Clinical Information

Summary of participants clinical course

For each of the 29 patients included in the DGE-MRI study below is the following:

- A brief clinical overview of their pre-operative and post-operative results
- The MRI report provided for the clinical team, all reported by either a Consultant Radiologist or by a Radiology Registrar/Trainee with review and approval by a Consultant Radiologist
- The final pathology report following liver resection, all reported by Consultant Pathologists with a special interest in Liver pathology, or by a trainee with Consultant review and approval

Pilot001

A 64-year-old female who underwent an extended right hepatectomy and segment 3 metastatectomy (segments 4, 5, 6, 7, 8). She had a 2.6 cm metastasis within segments 7/8, a 2.6 cm metastasis in the 8/4, a 7-mm metastasis in segment 7, a 1.4 cm metastasis segment 6 and a 6-mm metastasis in segment 3. eGFR was 72. She received no pre-operative neoadjuvant chemotherapy. Background histology showed mild steatosis. Day 5 post-operative bilirubin was 28, INR 1.4, Lactate 1.7, indicating mild PHLF. She had post-operative pain management issues and was discharged on day 7.

MRI report

There is a 2.6 cm metastasis the subcapsular occasion within segments 7/8, a 2.6 cm metastasis in the interface between segments eight and four, there is a 7 mm lesion posteriorly within segment seven close to the interface with segment six and a 1.4 cm metastasis within segment six immediately beneath this. Immediately deep to the anterior capsular surface of segment three there is a 6 mm metastasis. The major vascular structures are patent and uncompromised. No upper abdominal lymphadenopathy.

Pathology report

Macroscopic Description:

Right liver- Specimen weighs 1097g and 20 x 11 x 9cm. Slicing shows four metastatic deposits as follows:

- Lesion one, segment VII/VIII, 30mm diameter, subcapsular (block B1).

- Lesion two, segment VI, 10mm diameter (block B2).
- Lesion three, segment IV/VIII, 28mm diameter (blocks B3 and B4).
- Lesion four, segment VI, 15mm diameter (block B5).

All the deposits are well away from the resection margin, the closest being the lesion in segment IV/VIII (lesion three) and this is 20mm from the margin.

C: Segment III Mets- 25 x 20 x 16mm wedge of liver. Slicing shows a central 12mm lesion, which is 5mm from the resection margin.

Microscopic Description:

A: Sections show normal gall bladder mucosa and wall with no inflammation or neoplasia.

B & C: Right liver and segment III Mets:

Summary:

- Number of tumour(s) present - Five (right liver and segment III)
- Maximum diameter - 30mm
- Tumour grade - Moderate
- Minimum distance from margin- 5mm (segment III lesion) (assessed macro)
- Vascular invasion - Yes
- Response to neoadjuvant therapy - Not known
- Lymph nodes - None submitted
- Background liver - Mild steatosis

Comment:

It is not known if this patient had pre-op treatment, but there is marked necrosis in the metastasis in the right liver while the segment III lesion shows haemorrhagic changes.

DIAGNOSIS:

Right liver and segment III resection - Metastatic colorectal adenocarcinoma x 5; all excised.

Pilot003

A 41-year-old female who underwent right hepatectomy. She had a 7.2cm solitary liver metastasis in segment 7/8 compromising the right hepatic vein and interfacing with the IVC. She received pre-operative neoadjuvant chemotherapy. She had an eGFR of >90. Background histology demonstrated <1% steatosis. She had FLR-volume of 44%, and FLR-function of 41%. Day 5

postoperative bilirubin was 26, INR 1.5, Lactate 1.6, indicating moderate PHLF. She developed a post-operative wound infection requiring antibiotics. She was discharged on day 7.

MRI report

There is a solitary liver metastasis which involves segments seven and eight. The maximal diameter is 7.2 cm. The lesion compromises the right hepatic vein with intrahepatic collaterals from segments five and six draining into the middle hepatic vein. The tumour reaches the cava with an interface of less than 90 degrees. There is a simple cyst within the right lobe, but no other metastases are identified.

Pathology report

Right hemihepatectomy - 70g, 16 x 10 x 8cm. On slicing, the metastasis is seen with an irregular outline, 8.5cm maximum diameter, less than 1mm from the surgical margin.

Microscopic Description:

A. Representative histology from the gall bladder shows mucosa and gall bladder wall within normal limits. No evidence of chronic cholecystitis, dysplasia or malignancy.

B. Histology from the metastases shows moderately differentiated adenocarcinoma with a pattern consistent with a primary site in the large bowel. It surrounds the hepatic vein branch, which is narrowed by intimal fibrosis but not infiltrated. It is a minimum of 1.5mm from the surgical margin.

Background liver tissue shows no evidence of chronic liver disease and less than 1% of hepatocyte cholestasis.

Summary:

- Number of tumour(s) present 1
- Maximum diameter - 72mm
- Tumour grade - Moderate
- Minimum distance from margin 1.5mm (assessed macro/micro combined)
- Vascular invasion - Not identified
- Response to neoadjuvant therapy - Not identified
- Lymph nodes - None received
- Background liver - Normal

Right hepatectomy - Metastatic colorectal adenocarcinoma, one lesion, 1.5mm from margin

Pilot005

An 81-year-old female who underwent a right hepatectomy and segment 3 metastatectomy. She had 4 metastases; 4 mm metastasis in segment eight, an 8-mm segment 8 close to the right hepatic vein, 1.3cm in segment 6, and 4 mm in segment 4/3. She underwent preoperative neoadjuvant chemotherapy, and preoperative portal vein embolisation. eGFR was 63. Background histology showed effects of the PVE. She had a FLR-volume of 40% and FLR-function of 45.5%. Day 5 postoperative bilirubin was 11, INR 1.1, Lactate 1.4, with no evidence of PHLF. She had a routine postoperative course and was discharged on day 6.

MRI report

- Lesion 1 - 4 mm segment eight towards the vertex 4 mm (there is a simple cyst close to this lesion).
- Lesion 2 - segments eight centrally located 8 mm in maximal diameter close to the right hepatic vein.
- Lesion 3 - segment six -1.3 cm in diameter
- Lesion 4 - segment three 4 mm in diameter close the capsular surface of the inferior aspect of the left lobe.

On the pre-treatment examination there was a further subcapsular lesion high within segment two, I cannot identify that on the current examination.

All lesions are smaller than on the baseline imaging indicating a positive response to chemotherapy. There is however abnormality of the signal of the liver parenchyma in keeping with chemotherapy related liver injury.

Pathology report

Macroscopic Description:

B: Right hemihepatectomy-

Piece of liver 120 x 100 x 60mm. The capsular surface has been sliced through and there appears to be a subcapsular tumour. Specimen sliced horizontally from superior to inferior. Three definite lesions seen; tumour in segment VI has been sampled for research prior to receipt. A further 3mm suspicious lesion is seen in the centre of segment VIII (B5). Background liver also sampled (B6). Lesion one, upper part segment VIII, subcapsular, 6mm maximum, 20mm from resection margin (B1).

Lesion two, centre segment VIII, 12mm maximum, abutting the margin (B2 and B3).

Lesion three, segment VI, subcapsular, 12mm maximum, 40mm from margin (B4).

C: Liver segment III- Triangular piece of tissue 18 x 11 x 10mm. On slicing, there is an 8mm lesion, 2mm from closest margin.

D: Liver segment II- Piece of tissue 12 x 12 x 10mm. On slicing, there is an 8mm lesion, which appears to abut the margin.

Microscopic Description:

A: The gallbladder mucosa is near normal with minimal chronic inflammatory infiltrate, and there is no fibrosis of the wall to suggest previous chronic cholecystitis. Within the serosa there are multiple foci of foreign body granulomatous reaction to intravascular material - presumably related to the previous right portal vein embolisation. This is not associated with any mucosal ulceration nor inflammation/fibrosis in the gall bladder wall.

B-D: All the sampled lesions (three in right lobe, also one each in segments II and III) are deposits of metastatic moderately differentiated adenocarcinoma of a pattern in keeping with primary origin in the large bowel. All show some central fibrosis/inflammation, consistent with partial response to chemotherapy. The minimum margin is 0.5mm for lesion 2 in the right lobe and 0.3mm for lesion segment II part D. There is no vascular invasion identified.

Background liver in part B shows portal vein embolisation, and some atrophy of parenchyma with apposition of portal areas and congestion. There is no steatosis or evidence of other chronic liver disease.

Summary:

- Number of tumour(s) present - 5
- Maximum diameter - 12mm, 12mm, 8mm, 8mm.
- Tumour grade - Moderate and poorly differentiated
- Minimum distance from margin - 0.3mm (assessed macro/micro combined)
- Vascular invasion - Not identified
- Response to neoadjuvant therapy - Yes incomplete
- Lymph nodes - None received
- Background liver - Effects of portal vein embolisation in right liver

DIAGNOSIS:

Liver (right hemihepatectomy, metastatectomy segments II and III) - 5 x metastatic colorectal adenocarcinoma, minimum margin 0.3mm.

Pilot008

A 71-year-old male who underwent a resection of segment 5 and 6 of a solitary 1.3cm metastasis in 5/6. He had undergone preoperative neoadjuvant chemotherapy. eGFR >90. Background liver histology showed mild steatosis and an R1 resection. He had a FLR-volume of 67% and FLR-function of 65%. Day 5 bilirubin was 25, INR 1.1 Lactate 1.9, indicating mild PHLF. He developed a chest infection requiring antibiotics and was discharged on day 13.

MRI report

Findings: A solitary 1.3cm lesion is seen peripherally in segment V, best appreciated on delayed post contrast imaging. Appearances consistent with metastasis. No further lesions demonstrated in the liver.

Comment: Solitary 1.3cm metastasis in segment V.

Pathology report

Macroscopic Description:

A. Segment 5 metastasis - A wedge of liver 44g, measures 6 x 3.5 x 3cm. On slicing, there is a single tumour 1.6cm maximum, which extends to one of the lateral resection margins. It is subcapsular. Background liver appears normal.

Microscopic Description:

A. The tumour is a moderately differentiated adenocarcinoma with morphology characteristic of metastatic colorectal cancer. There are areas of haemorrhagic necrosis within the centre of the tumour. The advancing edge of the tumour has a multinodular configuration and extends focally to the tumour margin. This is in keeping with the macroscopic description (A1). There is no convincing vascular invasion seen (A1 and A2). The histology of the background liver (A3) shows mild steatosis and focally mild portal inflammation without fibrosis.

Special stains have not been performed.

Summary:

- Number of tumour(s) present - 1
- Maximum diameter - 16mm
- Tumour grade - moderate
- Distance from nearest hepatic resection margin - Tumour cells at margin - (R1)
- Vascular invasion - Not identified
- Response to neoadjuvant therapy - n/a

- Lymph nodes - none received
- Background liver - mild Steatosis

DIAGNOSIS:

Liver segment 5 - Metastatic adenocarcinoma consistent with colorectal carcinoma. Tumour cells at margin (R1).

Resect001

A 62-year-old male who underwent a left hepatectomy for a 1.4 cm lesion just above the bifurcation of the left portal vein causing obstruction of the segment 2/3 bile ducts. He had pre-operative bilirubin of 20. eGFR was >90. Background liver histology demonstrated obstructive changes. He had an FLR-volume of 57% and a FLR-function of 53%. He had a day 5 bilirubin of 55, INR 1, Lactate of 1.9, indicating mild PHLF. He had a normal post-operative course and was discharged home day 5.

MRI report

Appearances within the liver have not significantly changed since the MRI with a 1.4 cm lesion just above the bifurcation of the left portal vein causing obstruction of the segment 2/3 bile ducts. The degree of dilatation has not changed and there are no newly dilated ducts elsewhere in the liver or new liver lesions. Stable appearances of the remaining solid organs. Small stable left inguinal lymph nodes. Stable appearances of the thick fibrosis in the presacral space and resolution of a previous fluid collection within it. Ileostomy in the right iliac fossa. A few small stable retroperitoneal lymph nodes. The lungs are clear. No destructive bony lesion.

Comment: Stable appearances in the liver. No new sites of disease identified.

Solitary 1.3cm lesion with characteristics of metastasis

immediately above left main branch of the portal vein, obstructing segment II and III bile radicals.

Pathology report

Macroscopic Description:

371g measuring 11cm transversely, 11cm in height and 5cm antero-posteriorly. Specimen sliced horizontally into 15 slices. The lesion is present in slices 4-6. It is a white lesion with an irregular outline, 2cm maximum diameter, which encircles structures entering the liver and has a component within the main portal tract in continuity with an intrahepatic component, which is about 1cm deep. Specimen photographed slices 4-7. The left portal vein is distended by blood. Other than this, the liver is macroscopically normal.

Microscopic Description:

A: Representative histology from the gall bladder shows marked cholesterosis and minimal features of inactive chronic cholecystitis. No dysplasia or malignancy.

B: Histology confirms this is moderately differentiated adenocarcinoma, with a histological pattern of central necrosis consistent with a primary site in the large bowel. There is quite extensive vascular invasion, including the blood vessels in the connective tissue at the extrahepatic part of the left main ducts and vessels. The main portal vein is not thrombosed. There is also extension of the tumour as polypoid growth within the left hepatic duct. There is perineural infiltration. Tumour within blood vessels at the porta hepatis is less than 1mm from the surgical margin.

Immunohistochemistry confirms this is metastatic colorectal adenocarcinoma, being positive for CK20 and negative for CK7.

Representative histology from the background liver shows prominent changes of large bile duct obstruction, with atrophy of hepatic parenchyma and apposition of portal areas. There is no evidence of other background chronic liver disease.

Summary:

- Number of tumour(s) present - One
- Maximum diameter - 20mm
- Tumour grade - Moderate
- Minimum distance from margin - 0.8mm from porta hepatis resection margin (assessed macro/micro combined)
- Vascular invasion - Yes
- Response to neoadjuvant therapy - Not identified
- Lymph nodes - None received
- Background liver - Large bile duct obstruction

DIAGNOSIS:

Left liver resection - Metastatic colorectal adenocarcinoma, one lesion, 0.8mm from margin.

PILOT013

A 69-year-old male who was found to be inoperable when MRI showed liver is studded with metastases throughout every segment.

MRI report

Findings: liver is studded with metastases throughout every segment. The largest lesion in the segment 2/3 measures 4.6 cm, these range down to tiny sub-centimetre lesions.

Resect002

A 64-year-old male who underwent a segment 7 metastatectomy for a solitary metastasis. He had preoperative neoadjuvant chemotherapy. He had a BMI >30. eGFR was >90. Background liver histology demonstrated mild sinusoidal obstructive syndrome (SOS) and macro-vesicular steatosis. He had an FLR-volume of 88.5% and FLR-function of 86%. He had a day 5 bilirubin of 36, INR 1.1, Lactate 1.8, indicating mild PHF. He had a normal post-operative course and was discharged on day 5.

MRI report

Findings: In the interim since the baseline CT scan from November 2013 the liver metastases have responded well to chemotherapy. The smaller lesion on the posterior surface of segment 7 is no longer clearly demonstrated although there is some chemotherapy induced SOS around this area. The larger lesion on the anterior surface of segment 4 has reduced in size from 3.0 cm to 1.1 cm. No other metastases demonstrated. There are a few small benign cystic lesions elsewhere within the liver. No other significant abnormality demonstrated.

Conclusion: Residual 11 mm metastasis on the surface of segment 4. The prior segment 7 metastasis is no longer demonstrable. Minor SOS within the liver.

Pathology report

Macroscopic Description:

Received is a wedge of liver weighing 17.3g and measuring 56 x 38 x 18mm. The capsular surface contains a linear defect measuring 22mm. The specimen has been serially sliced to reveal a subcapsular tumour measuring up to 15mm in maximum dimension with areas of yellow necrosis. The linear defect continues into the tumour and very close to the deep resection margin. The tumour appears to abut the resection margin focally.

Block 1 = tumour closest to resection margin; 2 = small nodule of possible tumour within a vessel/duct in the adjacent slice; 3 = background liver.

Microscopic Description:

The tumour is a moderately differentiated adenocarcinoma with intraluminal necrosis consistent with metastatic colorectal carcinoma. The tumour extends to the surgical margin. The subcapsular

part of the tumour shows evidence of regression following chemotherapy. There is no evidence of capsular invasion or vascular invasion. A small Von Meyenburg complex is noted within the tumour.

The background liver shows a mild degree of macrovesicular steatosis. There is no evidence of chronic liver disease.

Summary:

- Site of tumour - Segment IV.
- Number of tumour(s) present - One.
- Maximum diameter - 15mm.
- Tumour type - Adenocarcinoma.
- Tumour grade - Moderately differentiated.
- Minimum distance from margin - At margin. (assessed macro/micro combined)
- Vascular invasion - Not identified.
- Response to neoadjuvant therapy - present
- Lymph nodes - None submitted.
- Background liver - Macrovesicular steatosis.

DIAGNOSIS:

Liver segment IV - Metastatic colorectal carcinoma, extends to margin.

Resect003

A 73-year-old female who had an extended right hepatectomy for 6 metastases in segments 4, 5, 6, 7 and 8. She had type 2 diabetes. eGFR was 88. She had preoperative neoadjuvant chemotherapy. Background liver showed mild steatosis and SOS. She had an FLR-volume of 25% and FLR-function of 25%. Day 5 bilirubin was 43, INR 1.1, Lactate 1.8, indicating mild PHLF. She had a normal post-operative course and was discharged day 5.

MRI report

As previously documented, there are multiple metastases within the right lobe segments involving segment 8 (2 lesions), segment 7 (2 lesions) and segment 6 (1 lesion) (see Key Images on PACS). There is a further sub-centimetre metastasis superiorly within segment 4. Unchanged benign cystic lesions are present within the inferior aspect of segment 4 and the left lateral section. No other focal liver lesions. There is a large benign cyst within the left kidney. No measurable extra-hepatic disease within the volume scanned.

Conclusion: 6 metastases within the liver - segments 4, 6, 7 and 8 (see Key Images on PACS).

Segments 1-3 are clear.

Pathology report

Macroscopic Description:

B: Right lobe of liver- 792g portion of liver measuring 135mm medio-lateral, 180mm supero-inferior and 68mm antero-posterior. The specimen is sliced into 24 slices from superior to inferior.

On sectioning, the specimen contains 5 tumours. Segment VIII contains 2 tumours; segment VII contains 1 tumour and segment VI contains one. These four tumours match those described in the MRI report. A piece of tissue has been previously removed from segment VII and taken for research. No obvious residual tumour seen at this site. The background liver appears normal (block B6)

Tumour one, segment VIII, slices 1 -2, 7mm maximum, more than 30mm from the margin (block B1).

Tumour two, segment VIII, slices 6-9, 28mm maximum, 30mm from the margin (block B2).

Tumour three, segment VII, slices 1-4, 25mm maximum, 40mm from the margin (block B3).

Tumour four, segment VI, slice 9 and 10, 12mm maximum, 50mm from the margin. (block B5).

Block 4 = site of previous removal of ? tumour. Block 6 - background liver.

Microscopic Description:

A: Sections from the gallbladder show features of mild chronic cholecystitis.

B: All the four tumours in the right hepatectomy show features of moderately differentiated metastatic colorectal adenocarcinoma. The second lesion in segment VII was taken for research (block four described in macroscopic description) and no residual tumour identified at this site macroscopically or microscopically.

The background liver shows mild steatosis and a microscopic focus of metastatic adenocarcinoma measuring 0.4mm. There are features of sinusoidal obstruction syndrome which is likely chemotherapy effect. There is no evidence of chronic liver disease. All the tumours are more than 30mm from the resection margin.

Summary:

- Number of tumour(s) present - 4
- Maximum diameter - 28mm
- Tumour grade - Moderately differentiated

- Minimum distance from margin - 30mm (Assessed macro)
- Vascular invasion - Absent
- Response to neoadjuvant therapy - Not known
- Lymph nodes - Not submitted
- Background liver - Mild steatosis, Sinusoidal obstruction syndrome.

DIAGNOSIS:

Right lobe of liver: Metastatic colorectal adenocarcinoma x 4

Resect004

A 68-year-old male who had a large central (4/8) metastasis, and metastasis in the left lobe. He was deemed unsuitable for surgery due to extrahepatic disease and lymphadenopathy in the right para-cardiac and posterior mediastinal regions.

MRI report

Unfortunately, several of the sequences are degraded by breathing artefact which significantly reduces the quality of the study. The large central metastasis seen on the recent CT involving segments four and eight has increased in size and now measures at least 10.2 cm in longest axis (previously 8 cm in May 2015). This abuts the portal bifurcation and contacts the proximal left portal vein and more extensive contact with the right portal vein and its anterior branch. There is a peripheral metastasis within segment two of the liver measuring approximately 4.1 cm diameter. In addition, there are small foci of tumour within the medial aspect of segment two abutting the falciform ligament which are in close proximity with the central metastasis and likely to represent further tumour foci. In addition, there are enlarged right para-cardiac lymph nodes and a further node in the posterior mediastinum on the right which show restricted diffusion and these raise concern for extra-hepatic disease (see Key Images on PACS).

Conclusion: Poor quality study due to difficulty with breath holding. Interim enlargement of the large central metastasis which abuts the portal bifurcation. Smaller volume metastatic disease within the left lateral segment. Probable nodal disease in the right para-cardiac and posterior mediastinal regions.

Resect005

A 49-year-old Male who was deemed inoperable after MRI demonstrated multiple bilobar liver Metastases, and widespread residual small volume metastases which were scattered throughout every segment within the liver.

MRI report

MRI Diffusion weighted: There has been a good partial response to chemotherapy within the multiple bilobar liver metastases demonstrated on previous imaging. Unfortunately, there are however widespread residual small volume metastases which are scattered throughout every segment within the liver apart from the caudate lobe (see Key Images on PACS). These include a number of small awkwardly placed lesions deep within segments 4 and 8. There is background fatty infiltration within the liver which is likely to be related to chemotherapy. No other significant abnormality demonstrated.

Conclusion: Partial response to chemotherapy but residual widespread small volume liver metastases throughout the liver (see Key Images on PACS).

Resect006

A 49-year-old female underwent a bisegmentectomy 5 and 6, metastatectomy of 7 and segment 1 for 2 metastases in segment 5 and 6 and what proved to be peribiliary gland hamartomas in 6 and 1. She had preoperative neoadjuvant chemotherapy. eGFR was >90. Background liver appeared normal. FLR-volume was 57%, FLR-function 60%. Day 5 bilirubin was 5, INR 1, lactate 1.2, so no evidence of PHLF. She had no postoperative complication and was discharged home day 5.

MRI report

Findings: There are 2 lesions in segment 5 - one 8 mm and one 4 mm - these have not changed significantly in size since the initial CT from 8/11/14 and whilst the imaging characteristics are more in keeping with metastases, the stability is surprising and introduces an element of doubt. There is a questionable tiny lesion involving the tip of the caudate lobe.

(If a watch and wait strategy is adopted Gadolinium rather than Primovist may be of value).

Pathology report

Macroscopic Description:

A: Segment V/VI- 5g, capsular surface 27 x 20mm with underlying tissue 20mm. On slicing there is one lesion 10mm in diameter at the deep resection margin.

B: Segment V- 2g, capsular surface 17 x 15mm with underlying tissue 17mm. There is an indistinct 3mm lesion seen at the deepest aspect, adjacent to the resection margin.

C: Segment VII- 0.3g, 10 x 9 x 7mm, sliced and all embedded. There is 2mm subcapsular lesion.

D: Segment II- 0.1g, 10 x 6 x 4mm, sliced and all embedded. 2mm lesion seen.

E: Segment I- 0.2g, 11 x 9 x 7mm irregular liver tissue. 2mm subcapsular lesion. All embedded.

Microscopic Description:

A: This is a small focus of metastatic adenocarcinoma, moderately differentiated with a pattern consistent with a primary site in the large bowel. The tumour is about 7mm in diameter and is surrounded by a capsule of fibrosis and inflammatory tissue. There is about 0.2mm of fibrosis separating the adenocarcinoma from the deep surgical resection margin.

Tissue from the background liver shows a normal architecture with no fatty change or evidence of chronic liver disease. There are very minor equivocal features that may represent sinusoidal obstruction syndrome, but insufficient for a confident diagnosis.

B: The second segment V lesion is a focus of adenocarcinoma at the deep resection margin. This is again surrounded by dense fibrosis and the adenocarcinoma measures about 3mm in diameter. It is separated from the deep resection margin by about 0.4mm of fibrous capsule.

C-E: All three lesions from segments VII, II and I are peribiliary gland hamartomas and there is no evidence of metastatic carcinoma in any of these specimens.

Summary:

- Number of tumour(s) present - Two
- Maximum diameter - 10mm, 3mm
- Tumour grade - Moderate
- Minimum distance from margin - 0.2mm (assessed macro/micro combined)
- Vascular invasion - Not identified
- Response to neoadjuvant therapy - Not identified
- Lymph nodes - None received
- Background liver - Normal

DIAGNOSIS:

Liver metastatectomy specimens - 2 x metastatic carcinoma in segment V - 3 x peribiliary gland hamartomas.

Resect007

A 79-year-old female underwent a right posterior segmentectomy (6/7) and segment 3 resections for a 4-cm lesion in segment seven, a 3-cm lesion at the interface between segments six/seven. a 2.1 cm segment metastasis. eGFR was >90. She had preoperative neoadjuvant chemotherapy. The background liver was unremarkable. Her FLR-volume was 60%, FLR-function was 63%. Day

5 bilirubin was 25, INR 1.1, Lactate 1.6, so no evidence of PHLF. She developed a postoperative chest infection requiring antibiotics and was discharged day 8.

MRI report

Findings: Three lesions with characteristics of liver metastases demonstrated, all well way from major vascular structures: -

1. there is a 4 cm lesion in segment seven,
2. a 3 cm lesion at the interface between segments six/seven
3. a 2.1 cm metastasis inferiorly within segment three.

No additional lesions demonstrated.

Pathology report

Macroscopic Description:

A: Segment III liver - Specimen measures 65 x 65 x 30mm. It weighs 75g. Slicing reveals a tumour measuring 20 x 22 x 15mm. It abuts the capsular surface and lies 14mm from the resection margin.

B: Segment VI/VII liver - Specimen measures 70 x 65 x 10 mm. It weighs 265g. Slicing reveals two lesions, the first in segment VI measuring 35 x 22 x 22mm. It lies 24mm from the resection margin. The 2nd lesion is in segment VII and measures 45 x 40 x 33mm. It lies 13mm from the resection margin. The background liver is unremarkable.

Blocks B1 and B2 = first lesion; B3 and B4 = second lesion.

Microscopic Description:

A&B) All three lesions show features of metastatic moderately differentiated adenocarcinoma with areas of dirty necrosis, mucin lakes and fibrosis. The appearances are consistent with colorectal origin. All the lesions are excised.

Summary:

- Number of tumour(s) present - Three.
- Maximum diameter - 22, 35, 45 mm.
- Tumour grade - Moderately differentiated.
- Minimum distance from margin - 5,10,12mm. (assessed combined)
- Vascular invasion - yes.
- Response to neoadjuvant therapy - Unknown.
- Lymph nodes - None submitted.

- Background liver - Unremarkable.

DIAGNOSIS:

A) Liver resection, segment III - Metastatic colorectal adenocarcinoma x 1.

B) Liver resection, segment VI/VII - Metastatic colorectal adenocarcinoma x 2.

Resect008

A 54-year-old male who had a segment 7 and 8 resections for a 2.1 cm segment 7 metastasis and a resolved segment 8 lesion. He had preoperative neoadjuvant chemotherapy. eGFR was >90. He had mild steatosis and portal inflammation. The segment 8 lesion was an R1 resection. His FLR-volume was 69% and FLR-function was 71%. Day 5 bilirubin was 9, INR 1, Lactate 1.3, indicating no evidence of PHLF. He had no postoperative complications and was discharged day 5.

MRI report

Previously demonstrated segment VI metastasis has decreased in size and now measures 21 mm (previously 44 mm). Previously demonstrated smaller 8mm lesion in segment 8 is not appreciable in today's examination it was peripheral - see previous SJUH MR index lesion. No new focal liver lesions.

There is evidence of chemotherapy related liver injury (mild- in the right lobe).

Pathology report

Macroscopic Description:

A: Segment VIII- Liver tissue measuring 19 x 14 x 16mm. Resection margin inked black. Specimen serially sliced. On slicing a white ill-defined nodule is identified 9mm maximum, which appears to abut the resection margin in one of the sections. All embedded in 3 blocks.

B: Segment VII- Segment of liver measuring 90 x 63 x 45mm. Two sections have been cut out of the capsular surface. At the edge of where one of these sections has been taken, there appears to be a tumour abutting the capsular margin. The section that has been taken of tumour appears to be 19 x 28 x 22mm and the section of background liver taken measures 12 x 26 x 19mm. Prior to slicing the maximum dimension of the tumour visible appears to be 29mm. The resection margin is inked black. Segment sliced into 18 slices and tumour is seen within slices 7-16. On slicing, the maximum tumour dimension seems to be 38mm however this is difficult to estimate due to the previous tissue taken. The tumour is clear of the resection margin by 13mm.

Microscopic Description:

A: Segment VIII-

This specimen comprises liver infiltrated by atypical epithelial cells forming glandular structures with central necrosis. The appearance is consistent with a metastatic colorectal adenocarcinoma.

The tumour reaches the resection margin. There is no evidence of regression effect.

Summary:

- Number of tumour(s) present - 1
- Maximum diameter - 9mm
- Tumour grade - moderately-differentiated
- Minimum distance from margin - reaches resection margin (assessed macro/micro combined)
- Vascular invasion - Yes
- Response to neoadjuvant therapy - No
- Lymph nodes - None submitted
- Background liver - Mild steatosis

B: Segment VII- This comprises liver infiltrated by metastatic adenocarcinoma with areas of necrosis. It shows the same morphology as specimen A. The tumour lies 10mm from the resection margin. There is fibrosis and dystrophic calcification suggesting regression effect. Background liver shows mild steatosis and mild portal tract inflammation.

Summary:

- Number of tumour(s) present - 1
- Maximum diameter - 38mm
- Tumour grade - moderately-differentiated
- Minimum distance from margin - 10mm (assessed macro/micro combined)
- Vascular invasion - no
- Response to neoadjuvant therapy - Yes
- Lymph nodes - None submitted
- Background liver - Mild portal inflammation

DIAGNOSIS:

Liver Segment VIII: Metastatic Colorectal Adenocarcinoma, involved resection margin

Liver Segment VII: Metastatic Colorectal Adenocarcinoma, fully excised

Resect009

A 65-year-old female who had segment 6 resection and segment 2 metastatectomy for a 3cm metastasis in 6 and an indeterminate lesion in segment 2, that was FNH. She had no preoperative chemotherapy. eGFR was >90. Her background liver was normal and had an R1 resection, Her FLR-volume was 69% and FLR-function was 71%. Day 5 bilirubin was 5, INR 1 Lactate 1, and so showed no evidence of PHLF. Her post-operative course was uneventful and was discharged day 3.

MRI report

As previously there are multiple benign cystic lesions in both lobes of the liver.

The concerning lesion segment 5/6 at the inferior tip of the liver measures 30mm which demonstrate signal characteristics of metastatic deposit. This has increased in size from previous study (17mm previously). Further 7mm lesion in segment 2, this is irregular in contour and does not have the high signal of a simple cyst and is more intermediate in signal intensity, this appears unchanged in size and character compared to the MRI dated 04/02/15, it is indeterminate in character, I think it more likely to represent benign malformation than a metastasis. If left in situ it will need to be followed. A subcapsular haemangioma is noted in segment seven. The lesions are away from the major vascular structures.

Pathology report

Macroscopic Description:

Metastatectomy specimen 65g and measures 85 x 55 x 35mm. Specimen received disrupted, previously incised - no description of tumour sampling. This incision goes into the surgical margin. Sliced at right angles to plane of resection, there is a single solid yellowish tumour with macroscopic characteristics of metastatic colorectal carcinoma, 35mm maximum diameter and generally greater than 10mm from the surgical plane, although previous incision makes this difficult to assess.

Microscopic Description:

Histology confirms this is metastatic adenocarcinoma, which is moderately differentiated and with a pattern characteristic of metastatic colorectal adenocarcinoma. The specimen has split on the resection margin, but elsewhere adjacent to this, the adenocarcinoma is seen at a minimum of 0.3mm from the surgical margin. No vascular invasion is identified.

The background liver shows no steatosis and no evidence of chronic liver disease. It does show "glycogenic islands" - a physiological change in hepatocyte cytoplasm, which is not of pathological significance.

Summary:

- Number of tumour(s) present - One
- Maximum diameter - 35mm
- Tumour grade - Moderate
- Minimum distance from margin - 0.3mm (R1) (assessed macro/micro combined)
- Vascular invasion - Not identified
- Response to neoadjuvant therapy - Not identified
- Lymph nodes - None received
- Background liver - Normal

DIAGNOSIS:

Liver (segment VI resection) - Metastatic colorectal adenocarcinoma, extends to 0.3mm from margin.

Resect010

A 59-year-old Male who had a bisegmental resection of 5 and 6 for a solitary metastasis in 5/6. He did not receive any preoperative chemotherapy. eGFR was >90. He had normal background liver. His FLR-volume was 71% and FLR was 73%. Day 5 bilirubin was 6, INR 1, Lactate 1.1, and so showed no evidence of PHLF. His postoperative was uneventful and was discharged on day 3.

MRI report

As demonstrated on previous MRI scan dated 17/04/2015, there is a solitary metastasis in the segment V/ VI which has increased in size and now measures 29 mm (18 mm previously). This lesion is well from the major vascular structures although there is a local perfusion effect. No further new concerning lesions are demonstrated in the rest of the liver.

The periportal lymph nodes are a little enlarged.

Pathology report

Macroscopic Description:

Specimen weighs 311g and measures 13 x 9 x 7cm. Slicing shows a single tumour deposit 25mm in maximum diameter and it is 10mm from the margin.

Microscopic Description:

Summary:

- Number of tumour(s) present - One
- Maximum diameter - 24mm
- Tumour grade - Poorly differentiated
- Minimum distance from margin - 10mm (assessed macro)
- Vascular invasion - Yes
- Response to neoadjuvant therapy - Not known
- Lymph nodes - None submitted
- Background liver - Unremarkable

DIAGNOSIS:

Liver segments V and VI - Metastatic poorly differentiated colorectal adenocarcinoma. - Excised.

Resect011

A 63-year-old female who was found to be inoperable due to Liver metastases within segment two and eight and probable new metastasis within the right adrenal gland.

MRI report

MRI Diffusion weighted: As demonstrated on the recent CT there is a central metastasis within segment eight which measures 2.8 cm in dimension and abuts the right portal and hepatic veins. There is a further small metastasis measuring 9 mm within the superior aspect of segment two. In addition, there is a nodule arising from the body of the right adrenal gland which has developed since the baseline CT in March 2015 and shows diffusion restriction which is concerning for a further site of metastatic disease. There are unchanged part calcified nodules within the right lower lobe which may be benign. No other new features demonstrated.

Conclusion: Liver metastases within segment two and eight and probable new metastasis within the right adrenal gland.

Resect012

A 60-year-old male underwent a left lateral resection and segment 6 resections. He received pre-operative chemotherapy He had a 2.7cm metastasis in the left lateral tip and a 9mm segment 2 metastases. He also had a metastasis on the right lateral margin in segment 6. eGFR was >90. FLR-volume was 61% and FLR-function 56%. This was for a moderately differentiated adenocarcinoma. Background liver showed mild stenosis with no other evidence of chronic liver

disease. Day 5 bilirubin was 6 and INR was 1.2, and so had no evidence of PHF. He developed a post-operative chest infection and was discharged after 7 days.

MRI report

Findings: there are multiple benign lesions of varying sizes throughout the remnant liver and artefact from the surgical clips. Three metastases are demonstrated, a 2.7 cm metastasis at the left lateral tip, a 9 mm lesion within segment two abutting the anterior capsular surface, and within the right lateral margin of what I take to be residual segment four there is 2.9 cm metastasis. The lesions well way from major vascular structures. No upper abdominal lymphadenopathy of pathological dimensions.

Pathology report

Macroscopic Description:

A: Segment IV tumour-

31g capsular surface 65 x 45mm with underlying tissue up to 27mm deep. Wedge shaped portions of tumour and background liver previously taken. The capsular surface is covered by adhesions.

On slicing, there is a residual tumour about

25mm diameter, which is 5mm from the surgical margin.

Block A1 = tumour; A2 = background liver.

B: Segment III lesion-

9.5g capsular surface 30 x 22mm covered by adhesions, underlying tissue 25mm deep. There is a subcapsular tumour 11mm in diameter, 2mm from the nearest resection margin.

C: Segment II lesion-

30g tissue with capsule over two surfaces and associated adhesions. The specimen is 55 x 40 x 29mm. On slicing, there is a single subcapsular tumour 29mm maximum diameter, 10mm from the surgical margin.

Microscopic Description:

A-C: Histology from all three tumours confirms these are metastatic moderately differentiated adenocarcinomas, with a morphology consistent with a primary site in the large bowel. The lesion in part A extends into the surgical resection margin. The lesion in part B is suggestive of invasion through the capsule into adherent connective tissue, although does not breach the margin of this. The lesion in part C is also subcapsular, but the capsule is not invaded.

Representative histology of background liver in part A shows normal architecture, mild steatosis and no evidence of other chronic liver disease.

Summary:

- Number of tumour(s) present - Three
- Maximum diameter - 29mm, 25mm and 11mm
- Tumour grade - Moderate
- Minimum distance from margin - Tumour cells at margin (segment IV tumour) (assessed macro/micro combined)
- Vascular invasion - Not identified
- Response to neoadjuvant therapy - Not identified
- Lymph nodes - None received
- Background liver - Mild steatosis

DIAGNOSIS:

Liver metastatectomy x 3 (segments IV, III and II) - Metastatic adenocarcinoma x 3, margin positive in segment IV lesion.

Resect013

A 47-year-old female underwent a segment 3 resections for a metastasis. 2 other lesions in segment 6 and 7 appeared benign. She didn't receive any chemotherapy. eGFR was >90. She had mild steatosis in her liver. Her FLR-volume was 90% and FLR-function was 91%. Day 5 bilirubin was 6, INR 1, Lactate 1.1 and so showed no evidence of PHLF. She had a normal post-operative course and was discharged day 3.

MRI report

Two well defined lesions are identified.

Lesion 1: 9mm lesion in segment 3 (mild high T2, restricted diffusion and does not concentrate Primovist) - Metastatic

deposit. This is well away from the major vascular structures.

Lesion 2: 6mm lesion in segment 7 (high T2 with shine through and does not concentrate Primovist) – Benign lesion.

A wedge-shaped area in segment 6 which extends from the subcapsular surface with reduced uptake on Primovist on delayed phase imaging and has altered diffusion on DWI. No sinister lesion identified in relation to this, it is likely to represent a perfusion effect.

Pathology report

Macroscopic Description:

Wedge of liver measuring 65 x 50 x 25mm. The excision margin measures 60 x 25mm. An area of puckering is identified on both anterior and posterior capsular surfaces measuring 10 x 10mm. On slicing, a well circumscribed lesion is identified, which appears fibrotic at the periphery and necrotic in the centre. This measures 7mm in maximum dimension and lies at 16mm from the resection margin.

Microscopic Description:

Sections of the tumour show a moderately differentiated adenocarcinoma with morphology in keeping with colonic primary. The lesion contains a fibrotic and necrotic centre together with marked indrawing of the capsule, indicating there has been significant partial response to chemotherapy.

The background liver shows atrophic changes beyond the tumour. Elsewhere there is very mild steatosis. There is no sinusoidal obstruction syndrome or evidence of chronic liver disease.

Summary:

- Number of tumour(s) present - 1
- Maximum diameter - 7mm
- Tumour grade - Moderately differentiated
- Minimum distance from margin - 16mm (assessed macro/micro combined)
- Vascular invasion - Not present
- Response to neoadjuvant therapy - Yes. Incomplete.
- Lymph nodes - N/A
- Background liver - Mild steatosis

DIAGNOSIS:

Liver segment III - Moderately differentiated metastatic colorectal adenocarcinoma. Excised. Mild steatosis.

Resect014

A 60-year-old male who was deemed inoperable for liver disease progression involving all segments apart from segment 1

MRI report

Comparison is made with serial examinations dating back to the CT of the 24/11/2014. Unfortunately the majority of the lesions within the liver have increased in size, for example the lesion in segment four close to the interface with segment two measures 11 mm compared to 9 mm on the prior study of 16/3/15 and the lesion within the medial aspect of segment 5/6 measures 1.5 cm compared to 1.1 cm. The implication being that they are metastases. The lesions are widespread involving all segments apart from segment one.

Resect015

A 68-year-old male who underwent a segment 8 resections for a 2.7cm lesion in segment 8. He didn't receive any preoperative chemotherapy. He had mild background liver steatosis. eGFR was 83. His FLR-volume was 91% and FLR-function was 92%. Day 5 bilirubin was 7, INR 1, Lactate 1.7 so had no evidence of PHLF. He had an uneventful postoperative course and was discharged day 3.

MRI report

A solitary metastatic deposit is demonstrated in segment eight of the liver measuring 27 mm which is marginally larger than the previous examination (25 mm previously). This lesion is well away from the major vascular structures. Small lesions with benign characteristics are present in segment 1 and 5. No other concerning lesions demonstrated rest of the liver.

Pathology report

Macroscopic Description: 134g of liver measuring 80 x 70 x 35mm. Slicing shows a subcapsular tumour deposit, maximum 36mm diameter and it is 20mm from the resection margin.

Microscopic Description:

Summary:

- Number of tumour(s) present - One
- Maximum diameter - 36mm
- Tumour grade - Moderately differentiated
- Minimum distance from margin - 20mm (assessed macro)
- Vascular invasion - Yes
- Response to neoadjuvant therapy - Pre-op treatment not stated
- Lymph nodes - None submitted
- Background liver - Steatosis

DIAGNOSIS:

Liver segment VIII - Metastatic colorectal adenocarcinoma; excised.

Resect016

A 57-year-old female who had resection of segments 5, 6 and 7 for a metastasis in each. She had preoperative neoadjuvant chemotherapy. eGFR was >90. She had mild background steatosis and had an R1 resection. Her FLR-volume was 59% and FLR-function was 57%. Day 5 bilirubin was 50, INR 1, Lactate 1.7 indicating mild PHLF. She developed a postoperative chest infection requiring antibiotics and was discharged day 8.

MRI report

As previously demonstrated, two discrete lesions in segment VII which have signal characteristics of metastatic deposits.

Lesion 1: The larger lesion measures 19mm and is marginally smaller (21mm previously).

Lesion 2: Subcapsular lesion measures 12mm and is unchanged.

Both these lesions are well away from the major vascular structures. No new concerning lesions in the rest of the liver.

Pathology report

A: Mesenteric lymph node.

B: Segment VI liver metastatectomy.

C: Segment V lesion.

Macroscopic Description:

A: Mesenteric lymph node-

Fibrofatty tissue 11 x 7 x 3mm. Possible lymph node 5mm maximum identified. All embedded.

B: Segment VI liver metastatectomy- Portion of liver weighing 125g and measuring 75 x 65 x 30mm. There is an ill-defined whitish area protruding on the capsular surface measuring 10 x 8mm. The specimen has been serially sliced into 9 slices. On slicing two lesions are revealed. The larger measures 19 x 22 x 20mm and appears to abut the deep margin. The smaller lesion measures 10 x 10 x 10mm and lies at about 22mm from the deep and 11mm from the peripheral margin. The background parenchyma appears unremarkable.

C: Segment V lesion- Fragment of liver weighing 1.2g and measuring 17 x 14 x 8mm. This is covered in part by capsule. There is a well circumscribed whitish area identified on the capsular surface measuring 4mm in maximum dimension. The specimen was serially sliced into 6 slices.

On slicing an ill-defined white lesion is identified, corresponding to the area noted on the capsular surface. This measures 6mm in maximum dimension and appears to be excised at a clearance of 2mm at the deep margin and at least 3mm at the peripheral margin.

Microscopic Description:

A. Histology reveals fibrofatty tissue with a central area of fat necrosis and associated inflammation. There is no evidence of lymphoid tissue. There is no evidence of neoplasia.

B. Sections from both lesions reveal moderately differentiated colorectal adenocarcinomas, the smaller of which is mucin producing. The larger lesion extends to <1mm from the deep resection margin.

C. Sections reveal a small subcapsular deposit of moderately differentiated metastatic colorectal adenocarcinoma, which shows no signs of regression. The tumour appears to be excised at a clearance of 1.8mm.

The background parenchyma shows mild steatosis without features of steatohepatitis. The portal tracts are normal. There is no fibrosis or inflammation. The bile ducts are unremarkable and in appropriate numbers.

Summary:

- Number of tumour(s) present - 3
- Maximum diameter - 22mm, 10mm, 6mm
- Tumour grade - Moderately differentiated
- Minimum distance from margin - R1 (largest lesion, segment VI <1mm from margin), (assessed macro/micro combined)
- Vascular invasion - not identified
- Response to neoadjuvant therapy - not identified
- Lymph nodes - N/A
- Background liver - Steatosis

DIAGNOSIS:

A. Mesenteric lymph node - Fat necrosis. No evidence of lymphoid tissue.

B. Segment VI liver metastatectomy - Metastatic, moderately differentiated colorectal adenocarcinomas X 2. The largest at the resection margin

C. Segment V liver lesion - Metastatic moderately differentiated colorectal adenocarcinoma. Excised.

Resect017

An 83-year-old male who had 6 separate metastatectomy resections of 4, 5, 6 and 7 for individual lesions. He had preoperative neoadjuvant chemotherapy. eGFR was 78. He had minimal background liver changes. FLR-volume was 45% and FLR-function was 42%. Day 5 bilirubin was 93, INR 1, Lactate 2. This indicated moderate PHLF. He developed a post-operative wound infection requiring antibiotics. He was discharged on day 9.

MRI report

Findings: there are two lesions with characteristics of metastases demonstrated in segment 7, one 5 mm in diameter of the other 1 cm. There is a subcapsular lesion high within segment four 4 mm in diameter, a subcapsular metastasis in segment five 1.6 cm in diameter. A more equivocal lesion which is likely to represent metastasis is present adjacent to the gallbladder at the interface between segments five and four. No other lesions identified. The lesions are well way from major vascular structures. The background liver parenchyma appears normal.

Pathology report

Subcapsular lesion high within segment 4, 4mm in diameter, subcapsular metastasis segment 5, 1.6cm. More equivocal lesion likely to represent metastasis is present adjacent to the gallbladder at the interface between segments 5 and 4.

Macroscopic Description:

B: Liver, segment 7 A disc shaped sample of liver (30 x 20 x 20mm, weight 7.5g) with capsule on one side and resection margin on the other three.

On sectioning there is a yellow coloured tumour, maximum 18mm which is free of the resection margin by 2mm grossly. Sampled in one cassette (B1).

C: Liver, segment 4 A disc of liver (10 x 10 x 5mm) with capsule on one side and resection margin on the others. On serial sectioning there is an indistinct yellow-white tumour approximately 6mm in maximum dimension. All embedded in one cassette (C1).

D: Liver, segment 4/5 A specimen of liver (30 x 20 x 15mm weight 5.8g). The specimen has a groove on the inferior surface consistent with the lobulation between segments 4/5. On sectioning there is a single yellow-white tumour approximately 8mm in maximum dimension which is free of the resection margin by 2mm grossly. Sampled in one cassette (D1).

E: Liver, segment 6. A wedge of liver tissue (40 x 40 x 20mm, weight 20.1g) with capsule on two sides and resection margin on the other. The capsule is wrinkled and roughened, and a bosselated tumour is seen on the surface. On serial slicing there is a single whitish tumour (maximum dimension 20mm) which is free of the resection margin by 8mm.

F: Liver, segment 7: A wedge of liver tissue (22 x 15 x 10mm) with capsule on one side and resection margin on the others. On serial slicing there is a single small yellowish tumour 6mm in maximum dimension which is 3mm from the resection margin. Sampled in one cassette (F1).

G: Liver, segment 6: A wedge of liver (20 x 20 x 14mm). On slicing there is a single yellowish tumour 9mm in maximum size which is free of the resection margin by 7mm. Sampled in one cassette (G1).

Microscopic Description:

B.-G. Liver, multiple metastatectomies, see macroscopy

Within these 6 metastatectomy specimens, 5 of the lesions found grossly show similar histological features. They comprise mostly necrotic lobulated lesions with focal calcification. They are surrounded by fibrosis and evidence of old haemorrhage. There is focal foreign body giant cell reaction, and non-specific chronic inflammation. They show no viable carcinoma. Only the lesion in specimen G shows evidence of residual viable adenocarcinoma, with one area approximately 6 mm in size.

Otherwise the background liver shows mild non-specific portal inflammation and minimal degree of macro vesicular steatosis.

These histological appearances are of one viable metastasis, in keeping with colorectal carcinoma (specimen G), and 5 necrotic lesions in keeping with a complete response to therapy.

Summary:

- Number of tumour(s) present 1
- Maximum diameter - 6mm (microscopically)
- Tumour grade - Moderate
- Minimum distance from margin - 7mm (grossly) (assessed macro/micro combined)
- Vascular invasion - No

- Response to neoadjuvant therapy - Significant, see above
- Lymph nodes - None
- Background liver - Minimal changes

DIAGNOSIS:

B.-G. Liver, multiple metastasectomies, see macroscopy a single viable metastasis, 5 showing complete response to therapy/regression, see above

Resect018

A 60-year-old male who had a left hepatectomy and segment 6/7 metastasectomy for multiple metastasis: 11 mm metastasis within segment two, a 1.4 cm and 4 mm metastasis in segment three, a 2.1 cm and a 2.6cm metastasis in segment 7, a 3.5 cm metastasis just above the left main branch of the portal vein in segment four extending into segment two, a 2.3 cm metastasis in segment 1 abutting the IVC. He had no preoperative chemotherapy. eGFR was >90. His background liver was unremarkable. FLR-volume was 40% and FLR-function 41%. Day 5 bilirubin was 25 INR 1.5, lactate 1.7. This indicated moderate PHLF He developed a post-operative chest infection requiring antibiotics and was discharged on day 7.

MRI report

Findings: the left lobe extends into the left sub phrenic space. There is 11 mm metastasis high within segment two. Within segment seven there is a 2.1 cm metastasis. Within segment four extending into segment two just above the left main branch of the portal vein there is a 3.5 cm metastasis. Within the caudate lobe there is a 2.3 cm metastasis abutting the IVC. In segment three immediately adjacent to the anterior capsular surface there is a 1.4 cm and 4 mm metastasis. Posteriorly within segment seven in a subcapsular location there is a 2.6 cm metastasis. No other lesions identified.

Pathology report

Macroscopic Description:

A: Liver segment 6 - Wedge shaped liver fragment measuring 6.5cm (superior to inferior) x 3.5cm (anterior to posterior) x 3.8cm (medial to lateral). A subcapsular, ill-defined white lesion is identified at the posterior aspect of specimen. Resection margin inked black. On slicing the lesion appears white and soft with central necrosis and measures 3.5 x 2.8 x 2.4cm (presumably

representing radiological lesion 7). The lesion appears to be very close to the presumed superior margin and appears to abut the presumed lateral margin.

B: Tumour on caudate lobe Wedge of liver measuring 3.6 x 2.8 x 3cm. Resection margin has been inked black. A subcapsular, ill-defined white lesion measuring 3 x 1.5 x 2.5cm is identified (presumably representing radiological lesion 4). On slicing the lesion appears to abut the resection margin.

C: Left lobe of liver

Left hemihepatectomy measuring 21cm superior to inferior x 10cm medial to lateral x 6cm anterior to posterior. Ligamentum teres is attached measuring 5 x 3.5 x 1.5cm. On the anteroinferior aspect of the specimen an incision is identified measuring 7.8cm in length. The cut surface reveals tumour and adjacent hepatic parenchyma sampling for research prior to receipt in the lab. as stated on the request form. Two subcapsular white lesions are noted within segment 3. The larger measures 1.2 x 1.3cm and the smaller measures 0.6 x 0.6cm. Excision margin measures 12 x 6cm and shows an area of incision measuring approximately 5cm in length and 1.5cm in depth. Area of incision inked orange and resection margin inked black. Specimen serially sliced from superior to inferior in 32 slices.

On slicing, three whitish, firm lesions are identified. The largest is in segments 2-4 (radiological lesion 3), measures 3.8 x 3.5 x 2.7cm and appears to abut the resection margin. The remaining two lesions are located in segment 3. The largest has been previously sampled as mentioned above and measures 1 x 1 x 1 cm (presumably radiological lesion 5). The smallest measures 0.8 x 0.6 cm (radiological lesion 6). Both lesions are well far from the resection margin.

Radiological lesion 1 was not visualised on initial sectioning, so segment 2 has been sliced after further fixation into 0.2cm intervals and three potential lesions are noted. Proceeding from superior to inferior, a subcapsular, multiloculated cystic lesion (pathological lesion 7) is identified measuring 0.8cm in maximum dimension, an area of portal tract fibrosis (pathological lesion 8), measuring 0.7cm and an area of dilated ductal formations (pathological lesion 9) measuring 0.9cm, are identified. All lesions in segment 2 are embedded in their entirety.

C1= small lesion segment 3 radiological lesion 6; C2= large and small lesion segment 3 radiological lesions 5 and 6; C3= large lesion segment 3 radiological lesion 5; C4-5-6= lesion segments 2-4 and resection margin radiological lesion 3; C7=cystic lesion segment 2 (pathological lesion 7); C8=portal tract thickening segment 2 (pathological lesion 8); C9-10= "ductal" lesion segment 2 (pathological lesion 9).

D: Liver, segment 7 metastasis Irregular fragment of liver measuring 3.8 x 2.3 x 2.3cm, partially covered by capsule. Resection margin is inked black. On slicing, a subcapsular, whitish ill-defined lesion with central necrosis is identified (presumably representing radiological lesion 2). This measures 2.5 x 2 x 2cm and appears to abut both capsule and resection margin.

Microscopic Description:

On sections six metastatic, moderately to poorly differentiated, partially necrotic, colorectal adenocarcinomas are identified as follows:

Pathological lesion 1: radiological lesion 7, segment 6, maximum dimension: 3.5cm, subcapsular, extends up to the lateral resection margin.

Pathological lesion 2: radiological lesion 4, segment 1, maximum dimension: 3cm, subcapsular, extends up to the resection margin.

Pathological. lesion 3: radiological lesion 3, segments 2-4, maximum dimension 3.8cm, extends up to the resection margin. Adjacent to the tumour a big blood vessel, most likely hepatic vein branch, with the lumen occluded by fibrous tissue is identified (block C6). No tumour involving the lumen, or the wall is identified.

Pathological. lesion 4: radiological lesion 5, segment 3, maximum dimension 1cm, excised

Pathological. lesion 5: radiological lesion 6, segment 3, maximum dimension 0.8cm, excised

Pathological. lesion 6: radiological lesion 7, segment 7, maximum dimension 3.8cm, extends up to the resection margin.

Pathological lesion 7 in segment 2 shows Von Meyenburg complex with a cystically dilated duct in keeping with simple biliary cyst. This is presumably radiological lesion 1.

Pathological lesion 8 in segment 2 show an expanded portal tract only.

Pathological lesion 9 in segment 2 shows dilated lymphatic vessels.

Summary:

- Number of tumour(s) present 6
- Maximum diameter 3.8cm
- Tumour grade - moderately to poorly differentiated
- Minimum distance from margin - At the margin (pathological lesion 1/segment 6, pathological lesion 2/segment 4, pathological lesion 3/segments 2-4)
- Vascular invasion - not seen
- Response to neoadjuvant therapy - not applicable
- Lymph nodes - not submitted
- Background liver - unremarkable

DIAGNOSIS:

Liver segments 6, 7, caudate lobe and left lobe, resection - Metastatic colorectal carcinoma x 6

Resect019

An 80-year-old male who had a left lateral sectionectomy for a segment 3 metastases. He received no preoperative chemotherapy. eGFR was 88. He had mild steatosis in his background liver. His FLR-volume was 82% and FLR-function was 82%. Day 5 bilirubin was 32, INR 1.1, Lactate 1.2, indicating mild PHLF. He had a normal post-operative course and was discharged day 5.

MRI report

Findings: there is a solitary metastasis in segment three with a maximal diameter of the 2.8 cm. This extends to the falciform ligament and the anterior aspect of the left main branch the portal vein, there is dilatation of the ducts in segment four suggesting that there is infiltration at the level of the falciform ligament. The rest of the liver appears unremarkable.

Pathology report

Macroscopic Description:

Specimen weighing 249.9g comprising segments II and III and a small area of segment IV. It measures 140 x 80 x 60mm. The falciform ligament is present measuring 40 x 20 x 10mm.

In segment III there is a tumour with a maximal diameter of 35mm. The closest distance to the tumour is 15mm. The tumour appears to have grown in structures ?bile duct and bears a satellite lesion approximately 15mm from the main tumour (1). In lower segment III close to the falciform ligament there is a small subcapsular whitish nodule measuring 5mm maximum and is 15mm from the closest resection margin (3).

Block 2 = liver to capsule including small satellite lesion above the tumour; 4 = background liver.

Microscopic Description:

The liver contains three lesions of moderately differentiated adenocarcinoma in keeping with metastases from a colorectal origin. The tumours show some central necrosis, haemorrhagic areas and fibrosis. The advancing edge of the tumour is diffusely infiltrating; the liver capsule is intact over the tumour. The nearest surgical resection margin is 14mm. The tumour grows in biliary ducts (1) and has two satellite lesions (1 and 3). The histology of the background liver (4) shows a normal architecture and some mild steatosis, but no evidence of chronic liver disease. Special stains have not been performed.

Summary:

- Number of tumour(s) present - Three
- Maximum diameter - 35mm
- Tumour grade - Moderate
- Minimum distance from margin - 14mm (assessed macro/micro combined)
- Vascular invasion - Not identified
- Response to neoadjuvant therapy - N/A
- Lymph nodes - None received
- Background liver - Mild steatosis

DIAGNOSIS:

Left lobe of liver - Metastatic adenocarcinoma consistent with colorectal origin, margin 15mm.

Resect020

A 78-year-old male who had a left lateral sectionectomy for an 11mm segment 2 resection. He received no preoperative chemotherapy. eGFR was 82. He had type 2 diabetes. He had mild steatosis in his background liver. His FLR-volume was 82 and FLR-function was 80%. Day 5 bilirubin was 14, INR 1, Lactate 1.2, with no evidence of PHLF. He had a normal post-operative course and was discharged day 3.

MRI report

Findings: Solitary 11 mm lesion in segment two away from major vascular structures 11 mm from the anterior capsules surface. The lesion is very bright on T2 with T2 shine through on diffusion. This is atypical for a "conventional" colorectal metastasis however I understand that the patient has had a mucinous primary and has had chemotherapy, this could account for this appearance. It also appears to have increased in size on earlier serial CTs. Following gadolinium, the enhancement pattern is against that of a haemangioma.

Pathology report

Macroscopic Description:

Left lobe of liver weighing 168g and measuring 13 x 7 x 4.5cm. Slicing shows one lesion 11mm diameter and it is 8mm from the resection margin. The lesion has a haemorrhagic periphery and some viable tumour in the middle.

Microscopic Description:

Summary:

- Number of tumour(s) present - One
- Maximum diameter - 11mm
- Tumour grade - Moderately differentiated mucinous
- Minimum distance from margin - 8mm (assessed macro)
- Vascular invasion - No
- Response to neoadjuvant therapy - Yes, partial
- Lymph nodes - None submitted
- Background liver - Mild steatosis

Comment:

The metastatic colorectal adenocarcinoma is moderately differentiated, present in a pool of extracellular mucin and is fairly circumscribed. The pool of extracellular mucin, which in many areas has no viable cells, will explain the radiological appearances described.

DIAGNOSIS: Left liver lobe - Metastatic mucinous colorectal adenocarcinoma. - Excised.

Resect021

A 64-year-old male who was found to be inoperable due extrahepatic disease on a repeat staging CT.

MRI report

Findings: There is a solitary 1.4 cm metastasis within segment eight extending just under the middle hepatic vein into segment four. The lesion is very close to the segment eight biliary radicle in addition to the middle hepatic vein. No other metastases demonstrated

Resect022

A 62-year-old female who underwent resection of segment 2, 6 and 4a for 3 metastases. She had undergone preoperative neoadjuvant chemotherapy. eGFR was >90. She had normal background liver. Her FLR-volume was 65.5% and FLR-function was 65.5%. Day 5 Bilirubin was 12, INR 1, Lactate 1.3, so had no evidence of PHLF. She had a normal post-operative course and as discharged home day 5.

MRI report

There are were multiple ring enhancing lesions on the CT of 5.7.13, the majority of there have disappeared with no residuum visible - a rare event.

The unequivocal the metastasis within segment four crossing into segment eight measuring 3.9 cm in diameter. There is a satellite metastasis inferior to this in relatively peripheral location. There are multiple lesions with benign characteristics elsewhere. A more indeterminate but probable benign lesion is present high within segment 8, this measures 4 mm in diameter and is well way from major vascular structures.

Pathology report

Macroscopic Description:

A: Liver segment 4a. A specimen of liver weighing 127g and measures 85mm medial to later, 85mm superior to inferior and 40mm anterior to posterior. Falciform ligament can be identified on the anterior aspect. The anterior of the liver shows a puckered lesion with depression of the surface measuring 22mm in maximum dimension. The resection margin inked black. Slicing reveals possible two foci of tumour, the first focus measures approximately 4cm from superior to inferior and 4cm medial to lateral. It has irregular boundaries and shows areas of haemorrhage and necrosis. A second focus is present in the inferior aspect which measures 15mm in maximum dimension. It is 2cm from away from the resection margin. Tumour 1 present at the capsular margin and is close to or present at resection margin in one of the other slices. There is no obvious vascular invasion in any of the sections examined.

B: Liver segment 2 metastasis. A small fragment of liver which measures 10 x 6 x 3mm. No obvious lesion is identified. It is painted black.

C: Liver segment 6 metastasis. A small fragment of liver measuring 7 x 6 x 2mm. It contains a circular white lesion in the middle which measures approximately 3mm in maximum dimension. Inked black.

Microscopic Description:

- Number of tumour(s) present - 2
- Maximum diameter - 40 mm
- Tumour grade - Moderately to focally poorly differentiated in keeping with metastatic colorectal carcinoma
- Minimum distance from margin - Less than 1mm, tumour 1 (assessed macro/micro combined)
- Vascular invasion - Yes
- Response to neoadjuvant therapy - None
- Lymph nodes - No
- Background liver -normal

B and C. These are pieces of liver tissue, each of which demonstrating an area of fibrosis within a septal portal tract. There is no evidence of viable metastatic carcinoma, and definitive histological features are not present in either lesion. Lesion 1 is most likely a small metastasis which has undergone complete response to therapy. Lesion 2 could represent a sclerosed haemangioma/solitary sclerotic nodule.

DIAGNOSIS:

- A. Liver segment 4a, metastatectomy - Metastatic adenocarcinoma.
- B. Liver segment 2, metastatectomy - Fibrosis; no evidence of viable metastatic carcinoma.
- C. Liver segment 6, metastatectomy - Fibrosis; no evidence of viable metastatic carcinoma.

Resect023

A 60-year-old man who underwent a left hepatectomy and caudate metastatectomy. He did not receive any chemotherapy prior to liver surgery. eGFR was >90. He had an 11mm metastasis in segment 2, a 3.5cm segment 4/2 metastasis just above the left portal vein, a 2.3cm metastasis in the caudate lobe. His FLR-volume was 54% and FLR-function was 56%. Background liver was

unremarkable. Day 5 bilirubin was 21, INR was 1.7. This indicates Moderate PHLF. He developed a post-operative chest infection requiring antibiotics. He was discharged 8 days' post-surgery.

MRI report

Lesion 1: Segment 3 posteriorly- unchanged from previous and measures 14mm.

Lesion 2: Segment 8 - smaller in size and measures 12mm (16mm previously).

Lesion 3 & 4: Two adjacent lesions in Segment 8 – reduced in size and now measures 15mm (23 mm previously).

Lesion 5: There is a new lesion in segment 2 anteriorly measuring 11mm which was not present on previous CT or MRI.

There are two small peripheral wedge-shaped areas of reduced Primovist concentration in segment 7 (present previously) and medially in segment 6. These are unlikely to represent metastases. No intrahepatic biliary duct dilatation. Normal adrenal glands.

Comment: Mixed response with interval improvement in segment 8 lesions but segment 3 lesion unchanged with new lesion in segment 2.

Pathology report

Macroscopic Description:

A: Gall bladder- Distended 100 x 40 x 40mm gall bladder with a short 10mm length of cystic duct. The serosa is smooth, the wall is 2mm thick and the mucosa is velvety with no focal lesions. One 7mm gallstone seen.

B: Segment V- 158g segment of liver 75mm supero-inferior, 65mm antero-posterior and 75mm medio-lateral. The lower anterior surface in continuity with the posterior surface inferiorly is covered by capsule. Three ?surgical defects are noted anteriorly largest 12mm. Margins inked, and specimen serially sliced into 19 slices. Two nodules are identified:

Lesion one, slices 1-4, 20mm maximum, at surgical margin, distant from capsule (blocks B1 and B2). Lesion two, slices 8-13, 24mm maximum, firm and cream-coloured, 11mm from capsule, 15mm from nearest margin (block B3).

C: Segment II- 9.9g disc of liver with capsule on one side 40 x 32 x 12mm. The capsule is puckered by an underlying cream-coloured lesion. Serially sliced into 10 slices. Tumour nodule is seen in slices 2-9, 26 x 18 x 22mm. It has a firm cut surface and extends to the capsular surface and surgical margin (slices3-6).

D: Segment III- 1.7g disc of liver measuring 7mm with smooth glistening capsule on one surface. Inked with silver nitrate and serially sliced into 5 slices. Pale nodule is identified in slices 2-5 measuring 9 x 9 x 10mm, reaching the margin in slices 2 and 3, and within 1mm of the capsule.

E: Segment IIb- 11.4g cuboid piece of liver 30 x 27 x 25mm with capsule on one surface bearing a 2mm area of puckering. Serially sliced into 6 to reveal a firm cream-coloured tumour in slices 3-6, 14 x 14 x 16mm. The capsule puckering is unrelated to the tumour. The tumour lies at the surgical margin (slices 4 and 6).

Block E1 = slice 4, tumour to margin; E2 = slice 6, tumour to margin.

Microscopic Description:

A. The gall bladder shows unremarkable epithelium with a mild chronic inflammatory cell infiltrate in the lamina propria. There is no evidence of dysplasia or malignancy. The features are those of mild chronic cholecystitis.

B-E. Sections of liver resections confirm five tumour deposits with features consistent with moderately- to poorly differentiated metastatic colorectal adenocarcinoma. The tumour shows central necrosis and fibrosis in areas and there is a peripheral cuff of lymphoplasmic cells at the outer edges.

Three of the deposits in segments II, III and IIb (parts C-E) show tumour at the resection margins. In Part B, one of the two deposits in segment V ('Lesion 1') lies within 0.1mm of the inked resection margin and 'Lesion 2' lies 9mm from the resection margin. No definite bile duct or vascular space invasion are identified.

The background liver shows occasional macrovesicular steatosis in less than 2% of hepatocytes.

The portal tracts show no significant pathology.

Summary:

- Number of tumour(s) present - Five
- Maximum diameter - 20mm, 24mm, 26mm;
- Tumour grade - poorly differentiated
 - Minimum distance from margin - 0mm (assessed combined)
- Vascular invasion - Not identified
- Response to neoadjuvant therapy - cannot comment
- Lymph nodes - None submitted
- Background liver - steatosis

DIAGNOSIS:

Liver segments V, II, III, IIB - Metastatic colorectal adenocarcinoma x5 - three at the resection margins

Resect024

A 63-year-old male who underwent a right hepatectomy for a 5.6 cm metastasis within segment 7/8, a peripheral 2.3 cm metastasis high in segment eight and a 1.8cm metastasis posteriorly in the sub capsular location in segment six. He did not receive any preoperative chemotherapy. He had type 2 diabetes. eGFR was 73. His background liver was normal. His FLR-volume was 49% and FLR-function was 49%. His day 5 bilirubin was 18, INR 1.7, Lactate 2.5. This indicates mild PHLF. He developed a post-operative chest infection requiring antibiotics and was discharged on day 5.

MRI report

Findings: there is a 5.6 cm metastasis within segment 7/8, a peripheral 2.3 cm metastasis high in segment eight and a 1.8 cm metastasis posteriorly in the subcapsular location in segment six.

The previously noted lesion within the left lobe has benign features.

Features of chronic pancreatitis with dilated PD noted.

Pathology report

Macroscopic Description:

Liver, right hemihepatectomy

A right hemihepatectomy specimen (140mm anterior to posterior x 90mm medial to lateral x 170mm superior to inferior, weight 1068g). A large incision has been made on the anterior surface of the specimen prior to receipt in the laboratory (140mm) from which samples of tumour and normal tissue have been sampled (approximately 15mm each in size).

Externally the liver has a smooth contour. On sectioning 3 tumours are identified in keeping with the MRI appearances as follows:

Tumour 1, segment 7, size 80 x 60 x 60mm, free of resection margin by 30mm, block B1.

Tumour 2, anterior part of segment 8, size 30 x 20 x 20mm. Free of resection margin by 15mm. Sampled in block B2.

Tumour 3, posteriorly in segment 6, size 30 x 30 x 10mm. Free of margin. Sampled in block B3.

The background liver appears unremarkable grossly and sampled in block B4.

Microscopic Description:

Liver, right hemihepatectomy

All 3 of the tumours sampled show similar histological features of metastatic moderate to poorly differentiated adenocarcinoma in keeping with a colorectal primary. There is a moderate amount of tumour necrosis. Focal lymphovascular

invasion is seen in tumour 1. Tumour 1 also surrounds and destroys a large vessel, which looks like a large branch of the hepatic vein.

The background liver shows a mild degree of steatosis occupying approximately 2% of the liver.

There is no evidence of significant progressive chronic liver disease or fibrosis.

Summary:

- Number of tumour(s) present 3
- Maximum diameter - 80
- Tumour grade - moderate/poor
- Minimum distance from margin 15mm (assessed macro/micro combined)
- Vascular invasion - Focal
- Background liver - Unremarkable

DIAGNOSIS:

Liver, right hemihepatectomy, metastatic adenocarcinoma x3, see report

Results of Whole Liver DGE-MRI output dependant variables

Patient reference	Whole Liver Volume (ml)	Whole Liver Total Plasma Flow (ml/100 ml/min)	Whole Liver Arterial Flow Fraction (%)	Whole Liver Extra Cellular Volume (ml/100ml)	Whole Liver Uptake Rate (ml/100 ml/min)	Whole Liver Arterial Plasma Flow (ml/100 ml/min)	Whole Liver Venous Plasma Flow (ml/100 ml/min)	Whole Liver MT T (secs)	Whole Liver Uptake Fraction (%)	Whole Liver Uptake Function (ml/min)
PILOT/001	2140	135.0	62.83	31.5	11.1	84.8	50.2	13.0	7.6	236.6
PILOT/003	1329	158.5	10.72	31.1	12.5	17.0	141.5	10.9	7.3	166.1
PILOT/005	1045	55.7	57.53	36.5	4.3	32.1	23.7	36.5	7.1	44.6
PILOT/008	1758	62.6	69.61	32.9	18.4	43.6	19.0	24.4	22.7	323.8
RESECT/001	2339	123.9	63.84	41.7	7.8	79.1	44.8	19.0	5.9	182.4
RESECT/002	1511	110.2	16.11	32.9	20.5	17.8	92.5	15.1	15.7	310.1
RESECT/003	1389	94.6	68.86	33.5	13.3	65.1	29.4	18.6	12.3	184.9
RESECT/006	1167	133.5	29.80	32.8	15.9	39.8	93.7	13.2	10.6	185.6
RESECT/007	1341	206.5	13.15	35.7	12.0	27.1	179.3	9.8	5.5	161.2
RESECT/008	1780	84.9	42.89	55.2	16.0	36.4	48.5	32.8	15.8	284.4
RESECT/009	1486	89.9	100.00	28.4	9.3	89.9	0.0	17.2	9.4	138.1
RESECT/010	1902	171.1	14.63	52.5	16.2	25.0	146.1	16.8	8.7	308.7
RESECT/012	1815	101.4	36.45	40.7	16.5	37.0	64.5	20.7	14.0	299.2
RESECT/013	1517	159.0	16.14	33.8	16.6	25.7	133.4	11.5	9.5	252.2
RESECT/015	1467	53.2	51.24	31.0	20.7	27.2	25.9	25.2	28.0	303.1
RESECT/016	1244	86.7	N/A	29.6	10.5	N/A	N/A	18.3	10.8	130.4
RESECT/017	1296	101.0	N/A	29.8	6.1	N/A	N/A	16.7	5.7	78.6
RESECT/018	1651	70.0	N/A	30.4	10.6	N/A	N/A	22.6	13.1	174.5
RESECT/019	1500	151.6	4.30	38.4	13.3	6.5	145.1	14.0	8.1	199.9
RESECT/020	1400	71.5	3.95	12.2	3.9	2.8	68.7	9.7	5.2	54.8
RESECT/022	966	185.1	5.94	31.5	10.1	11.0	174.1	9.7	5.2	98.0
RESECT/023	1451	144.1	11.82	40.4	12.5	17.0	127.1	15.5	8.0	181.0
RESECT/024	1585	241.8	17.24	38.3	18.4	41.7	200.1	8.8	7.1	292.3

Results of FLR DGE-MRI output dependant variables

Patient reference	FLR Volume (ml)	FLR Total Plasma Flow (ml/100 ml/min)	FLR Arterial Flow Fraction (%)	FLR Extra Cellular Volume (ml/100 ml)	FLR Uptake Rate (ml/100 ml/min)	FLR Arterial Plasma Flow (ml/100 ml/min)	FLR Venous Plasma Flow (ml/100 ml/min)	FLR MT T (secs)	FLR Uptake Fraction (%)	FLR Uptake Function (ml/min)
PILOT/001	397	199.8	18.8	31.16286	9.741465	37.5437	162.2	8.9	4.6	39
PILOT/003	336	132.1	13.4	30.68444	14.55285	17.7048	114.4	12.6	9.9	49
PILOT/005	189	71.3	54.4	39.79971	5.907	38.8065	32.5	30.9	7.6	11
PILOT/008	1026	64.2	64.5	31.05426	17.14271	41.3595	22.8	22.9	21.1	176
RESECT/001	1018	176.1	57.7	48.61431	8.174894	101.608	74.5	15.8	4.4	83
RESECT/002	1393	117.6	14.2	32.69485	21.29727	16.7024	100.9	14.1	15.3	297
RESECT/003	254	99.1	44.7	36.74374	13.76477	44.3065	54.8	19.5	12.2	35
RESECT/006	703	123.2	34.6	33.257	17.27907	42.621	80.6	14.2	12.3	122
RESECT/007	819	234.3	8.9	35.27952	11.57826	20.8599	213.4	8.6	4.7	95
RESECT/008	951	93.0	43.2	54.65135	15.91923	40.2168	52.8	30.1	14.6	151
RESECT/009	1027	92.5	94.1	27.42064	8.703721	86.9595	5.5	16.3	8.6	89
RESECT/010	1178	181.7	11.7	53.06105	16.44956	21.2751	160.5	16.1	8.3	194
RESECT/012	1163	89.7	40.4	38.52246	15.38517	36.2731	53.5	22.0	14.6	179
RESECT/013	1402	157.8	16.6	34.10796	16.72601	26.1631	131.7	11.7	9.6	235
RESECT/015	1075	47.2	56.7	29.55027	19.36135	26.7253	20.4	26.7	29.1	208
RESECT/016	677	91.8	N/A	26.75846	9.81929	N/A	N/A	15.8	9.7	66
RESECT/017	517	85.3	N/A	26.10864	5.628059	N/A	N/A	17.2	6.2	29
RESECT/018	658	73.3	N/A	32.43474	11.43357	N/A	N/A	23.0	13.5	75
RESECT/019	1225	146.7	4.4	36.70581	12.90905	6.43183	140.3	13.8	8.1	158
RESECT/020	1118	71.7	6.6	12.47333	3.859188	4.77013	67.0	9.9	5.1	43
RESECT/022	665	180.4	9.9	31.36166	9.703141	17.7854	162.6	9.9	5.1	65
RESECT/023	973	155.0	8.4	41.73778	12.97362	13.0655	142.0	14.9	7.7	126
RESECT/024	564	243.5	12.1	38.17356	18.79321	29.3634	214.1	8.7	7.2	106

FLR function, Volume and Functional bias

Patient reference	FLR volume %	FLR Function %	functional bias (%)	Mean FLR Function & Volume (%)
PILOT/001	18.6	16.4	2.21	17.5
PILOT/003	25.3	29.4	-4.16	27.4
PILOT/005	18.1	25.1	-6.95	21.6
PILOT/008	58.3	54.3	4.04	56.3
RESECT/001	43.5	45.6	-2.10	44.6
RESECT/002	92.2	95.7	-3.50	93.9
RESECT/003	18.3	18.9	-0.62	18.6
RESECT/006	60.2	65.5	-5.21	62.8
RESECT/007	61.1	58.8	2.25	59.9
RESECT/008	53.4	53.2	0.20	53.3
RESECT/009	69.1	64.7	4.36	66.9
RESECT/010	61.9	62.8	-0.83	62.3
RESECT/012	64.1	59.8	4.26	62.0
RESECT/013	92.4	93.0	-0.59	92.7
RESECT/015	73.3	68.6	4.61	71.0
RESECT/016	54.4	50.9	3.46	52.7
RESECT/017	39.9	37.0	2.91	38.4
RESECT/018	39.9	43.1	-3.26	41.5
RESECT/019	81.7	79.1	2.57	80.4
RESECT/020	79.8	78.6	1.19	79.2
RESECT/022	68.9	65.9	3.00	67.4
RESECT/023	67.1	69.7	-2.68	68.4
RESECT/024	35.6	36.3	-0.68	35.9

Appendix B
Pilot Ethics Application
REC Approval



Health Research Authority

NRES Committee South Central - Hampshire A

Bristol Research Ethics Committee Centre
Level 3, Block B
Whitford
Law Ins Road
Bristol
BS1 2HT
Telephone: 01173 421303

23 April 2014

Mr David Longbotham
Leeds Teaching Hospitals
Beckett Street
Leeds
LS9 7TF

Dear Mr Longbotham

Study title: Pilot study for determining the best method of acquisition of Dynamic Contrast-Enhanced Liver MRI
REC reference: 14/8C/0243
IRAS project ID: 148186

The Proportionate Review Sub-Committee of the NRES Committee South Central - Hampshire A reviewed the above application on 23 April 2014.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the REC Manager Vicky Canfield-Duthie at nrescommittee.southcentral-hampshirea@nhs.net.

Ethical opinion - Favourable Opinion with Additional Conditions

The Sub-Committee considered whether the research team should be allowed access to patient records, however it was agreed that this was fine as it is mentioned in the PIS and Consent form, and the research team will also be part of the patients' clinical care team.

On behalf of the Committee, the Sub-Committee gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

1. Please proof-read the Participant Information Sheet.
2. Please include an additional item in the Consent Form for participants to be able to agree to their GP being informed.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ('R&D approval') should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at <http://www.inforum.nhs.uk>.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ('participant identification centre'), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publicly accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list



Health Research Authority

- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Information is available at National Research Ethics Service website > After Review

14/SC/0243

Please quote this number on all correspondence

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at <http://www.hra.nhs.uk/01m-training/>

With the Committee's best wishes for the success of this project.

Yours sincerely

Dr Ronja Bahadori
Chair

Email: nrescommittee.southcentral-hampshirea@nhs.net

Enclosures: *List of names and professions of members who took part in the review*
"After ethical review – guidance for researchers"

Copy to: *Dr Derek Norfolk*
Ms Anne Gowing, Leeds Teaching Hospitals NHS Trust

Pilot Protocol

St James's University Hospital: Department of
HPB and Transplantation

RESEARCH PROTOCOL

Version 1.7
26th March 2014

Study Full Title:

Pilot study for determining the best method of acquisition of Dynamic Contrast-Enhanced Liver MRI

Protocol Number: 1.7

Principal Investigator: David Longbotham
Clinical Research Fellow
HPB and Transplantation Unit
St James University Hospital
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Beckett Street
Leeds
LS9 7TF

Tel:

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Lecturer in MRI Physics

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1.0 RESEARCH SUMMARY

General Information

Pilot study for determining the best method of acquisition of Dynamic Contrast-Enhanced Liver MRI

Investigator:

David Longbotham

Version: 1.7, 26/3/14

Centre:

St James's University Hospital (SJUH), HPB and Transplantation Unit
R&D Department, Leeds Teaching Hospitals

Study Information

Type: Pilot Study

To determine the most appropriate data acquisition protocol for Dynamic Contrast MRI

Prospective, single centre, randomised

Objectives:

Comparison of three MRI protocols on quality of data to determine which is the most suitable to be used in the clinical setting.

Study Timelines

Expected Start Date: May 2014

Subject Enrolment Phase: May-August 2014

End of Study: August 2014

Expected Completion Date: September 2014

Study Subject Information

Number of trial subjects: ~15

Age group of study subjects: 18 years and above

Criteria:

Patients undergoing MRI for investigation into Colorectal Liver Metastasis

Exclusion:

Current Pregnancy, Allergy/intolerance to Gadolinium based contrast agents, Inability to undergo MRI (see appendix for list)

2.0 INTRODUCTION

2.1 Background

Colorectal Liver Metastases (CRLM) is a common and potentially fatal disease. There are around 40,000 new cases of colorectal cancer diagnosed a year¹. A third of patients of all patients diagnosed with Colorectal Cancer will have metastatic liver disease at time of presentation.

Surgical Resection of CRLM remains the only curative option for this group of patients². Due to advances in surgical, radiological and oncological techniques and technology, increasingly radical liver resections are being considered. Due to the large volume of liver that is being considered for resection it is vitally important to know pre-operatively that the remnant liver volume (RLV) will be sufficient to be compatible with life.

In current practice, 75% of total liver volume (TLV) can be safely resected (or to leave a remnant weighing 0.5% of total body weight) in patients with apparently healthy liver. The percentage of TLV resectable reduces to 70% in patients with known liver disease or having received chemotherapy pre-operatively, and 65% in patients with established cirrhosis³. Those patients requiring larger resections would need to be considered for techniques to induce liver hypertrophy (such as portal vein embolisation or two-stage hepatectomy) or to be deemed unresectable.

Dynamic Contrast MRI (DCE-MRI) of the Liver is a new technique using Gadoteric Acid (Primovist™) – a liver specific contrast agent. Rapidly acquired images at short interval can calculate rate of flow of contrast into hepatic arterial architectures, portal venous flow and diffusion into hepatocytes. Diseased, fibrotic liver tissue will have altered blood flow and diffusion rates from normal healthy tissue. A region of interest (ROI) within each liver segment can be identified and the data derived provides a limited number of parameters that characterise the physiological state of the tissue. Calculation of the function of each segment can be used as a numerator over the total calculated liver function as its denominator⁴⁻⁷.

Previous studies⁸ have shown good levels of correlation of DCE-MRI against global measures of hepatic function Indocyanine Green (ICG) testing and nuclear medicine Galactosyl Serum Albumin scintigraphy (GSA).

However, there is little concordance about the method of acquisition for DCE-MRI in the literature. Previous studies have involved times that require over an hour to obtain the necessary data: impractical for routine clinical work. This means its current use is only limited to research.

2.2 Rationale for Study

Using three different designed acquisition protocols that use differing sequences that can be incorporated into a pre-existing protocol for Liver MRI, a shortening of the acquisition time could

be obtained. If the quality of the images obtained is adequate in providing the necessary data that is needed to complete the DCE-MRI, then these shorter MRI scans may be able to be both more tolerable to patients and potentially suitable for clinical practice.

For those patients who are undergoing a staging Liver MRI, their acquisition protocol can be amended to include the DCE-MRI sequences as the only delayed phase of the MRI acquisition is necessary for radiological staging, and the initial phases (arterial and portovenous phase) are not required. As a result, could be altered to obtain dynamic data without changing the required radiological images in these patients to stage these patients accurately.

Continuous data over a set period of time can be acquired, collecting 'semi-quantitative' and quantitative data.

Semi-quantitative: This is the information includes: The maximal signal intensity (S_{MAX}), the time to reach S_{MAX} (T_{MAX}), the half-life ($T_{1/2}$) and the area under the curve for the data⁶. This can be directly compared with comparative signal in other organs (e.g. Heart, Spleen) for a calculated fraction of contrast within the liver at that given time. This would allow corrections for deviations in timing of the data acquisitions.

Quantitative measurements calculate the hepatic extraction fraction (HEF), input-relative blood flow (irBF) and mean transit time (MTT) of the segments as method of assessing hepatic function^{5, 6}. This estimates the slope of the arterial perfusion divided by the sum of the slope of the arterial and portal perfusions⁷. These values could correlate with liver function.

This study will analyse 3 different methods on adequacy of images prior to a subsequent study that aims to determine its effectiveness in obtaining the following values: S_{MAX} , T_{MAX} , $T_{1/2}$, AUC, HEF, irBF, MTT, and RLE. The ability to accurately calculate these values with narrow confidence ranges shall demonstrate which of the 3 protocols is the most appropriate to be used in a clinical trial.

- Standard 3D Sequence obtaining images every 2 seconds with normal breathing - this is the type of sequence used currently in St James' University Hospital
- TWIST 3D Sequence obtaining images every second with normal breathing, in a method used in other studies^{6,8} into Liver MRI
- Pre-bolus 2D slice sequence with a multi-slice 2D sequence every 6 seconds with normal breathing - used in DCE-MRI of kidneys.^{18,19}

2.3 Hypothesis – One of the three acquisition methods will provide good quality data and images to be used in clinical practice to be utilised in further planned studies.

3.0 STUDY OBJECTIVES AND AIMS

3.1 Primary objective

- 3.1.1 To assess 3 separate DCE-MRI acquisition protocols to determine which would be the most suitable for shortening the sequence with no compromise on the quantitative result.

- 3.1.2 The following values shall be calculated:
 S_{MAX} , T_{MAX} , $T_{1/2}$, HEF, irBF, MTT, and RLE
 Reproducibility of results and accuracy will be calculated
- 3.1.3 Image quality and artefacts will be qualitatively assessed

4.0 STUDY DESIGN

4.1 Randomised, non-blinded

4.2 Single centre

4.3 Prospective data collection:

- 4.3.1 Patient characteristics (such as age, medical history, BMI, alcohol intake (units/week), medications and any known liver/biliary disease) will be collected
- 4.3.2 Diagnosis of Colorectal Liver Metastases will be confirmed from the St James Specialist hepatobiliary Multi-disciplinary Meeting (MDT)

4.4 Dynamic Contrast Enhanced MRI

- 4.4.1 Patients will be randomised to one of the three pre designed DCE-MRI protocols
- 4.4.2 5 patients in each group.
- 4.4.3 Use of MRI in St James' University Hospital Radiology department.
- 4.4.4 Brief Explanation of how MRI works
- 4.4.4.1 Utilises paramagnetic qualities of water molecules within tissue to demonstrate liver anatomy and pathology
- 4.4.4.2 Utilises intravenous liver specific contrast agent (Gadoxetic Acid) to demonstrate blood flow and diffusion in the liver
- 4.4.4.3 This agent is taken up by hepatocytes via organic anion transporting polypeptide OATP and excreted into bile canaliculi via multidrug resistant protein (MRP) system
- 4.4.4.4 This acquisition will be added onto the participants routine MRI scan for staging of their CRLM – no additional MRI will need to be requested
- 4.4.4.5 A study⁸ has shown strong correlation of DCE-MRI with validated methods of global hepatic function ICG and GSA
- 4.4.4.6 Acquisition will be taken dynamically during the arterial and portovenous phases (first 5 minutes).
- 4.4.5 This phase is not utilised on a routine MRI scan and 3 acquisition protocols written by Dr Dan Wilson and Dr Steven Sourbron will be used
- 4.4.5.1 Standard 3D Sequence obtaining images every 2 seconds with normal breathing
- 4.4.5.2 TWIST 3D Sequence obtaining images every second with normal breathing
- 4.4.5.3 Pre-bolus 2D slice sequence with a multi-slice 2D sequence every 6 seconds with normal breathing

- 4.4.5.4 In addition 3 extra breath hold sequences shall be obtained to provide a comparison against movement artefacts.
- 4.4.6 Analysis of the DCE-MRI data will take place in in-house computer system at University of Leeds MRI Physics Department by Steven Sourbron and DL.
- 4.4.7 The interpreting consultant radiologist will be blinded to the results of the DCE-MRI phase to prevent this data being used in their reporting of patients MRI

5.0 STUDY SUBJECT SELECTION

5.1 Patient List:

- 5.1.1 Patients will be identified from the hepatobiliary outpatient clinic from tertiary referrals for patients with potentially resectable liver metastases
- 5.1.2 Information regarding the study will be provided to potential participants at this stage via post

5.2 Eligibility criteria

- 5.2.1 Inclusion criteria
 - 5.2.1.1 Confirmed diagnosis of Colorectal Liver Metastasis:
 - 5.2.1.1.1.1 Histological confirmation of adenocarcinoma of the large bowel
 - 5.2.1.1.1.2 Radiologically diagnosed CRLM at time of diagnosis of Large bowel tumour or subsequent time
 - 5.2.1.1.1.3 Needing a staging Liver MRI
 - 5.2.1.1.2 Able and willing to provide informed consent
- 5.2.2 Exclusion criteria
 - 5.2.2.1 Current pregnancy
 - 5.2.2.2 Allergy/intolerance to Gadolinium based intravenous contrast agents
 - 5.2.2.3 Intolerance to MRI
 - 5.2.2.4 Unable to undergo MRI due to safety concerns (see appendix for complete listing)

5.3 Sample Size

- 5.3.1 Approximately 160-180 patients undergo resection of their CRLM a year in St James' University Hospital (as per local prospectively maintained databases)
- 5.3.2 Due to availability of obtaining MRI to allow DCE-MRI to be performed the anticipated recruitment shall be ~1-2 patients per week
- 5.3.3 The aim of recruiting ~15 patients that will allow the study to be completed and analysed within 3 months

5.4 Recruitment

Potential participants will be identified at the Hepatobiliary Specialist MDT as potentially needing a liver resection. They must have plan for a Liver MRI in Leeds to stage their metastasis.

A Patient Information Sheet and letter of invitation (see appendix) will be posted out to patients prior to their attendance at their outpatient MRI appointment explaining the study and need to adapt their MRI to one of the 3 acquisition protocols.

They will be invited to attend their appointment 15 minutes early, and approached on the day of their MRI to consent them into the study, at which time they will be randomised to one of the 3 acquisition protocols.

This process will be clearly documented onto PPM (patient pathway manager) – hospital database with patient information and clinic letters that can be printed out easily and also kept in their medical case notes.

5.5 Consent

Informed written consent will be obtained when patients attend their outpatient Liver MRI appointment. The right of the patient to refuse consent without giving reasons will be respected. Furthermore, the patient will remain free to withdraw from the study at any time without giving reasons. The rights and welfare of the patients will be protected by emphasising to them that the quality of medical care will not be adversely affected if they decline to participate in this study. A copy of the consent will be given to the patient, the original filed in the Trial Master File (TMF), and one filed in the hospital notes. The written consent will be taken by a clinician, who has signed / dated the staff authorisation / delegation log. The process of obtaining written consent will be clearly documented in the patient's medical notes.

The participant's General Practitioner (GP) will also receive confirmation of the patient's inclusion into the trial.

6.0 STUDY SCHEDULE

6.1 Patients identified from Hepatobiliary clinic referrals from Colorectal Surgery/Oncology as to possible resectability of CRLM

6.2 Recruitment of patients over 3 months:

- 6.2.1 Initial identification of needing staging Liver MRI for Colorectal Liver Metastasis
- 6.2.2 Letter posted to patient containing information sheet and consent form
- 6.2.3 Highlighted patients as potential participants will be logged onto prospectively maintained database as a potential and their date of MRI will be obtained
- 6.2.4 Potential participants will have their MRI requested as per radiology department guidelines for including patients in research
- 6.2.5 Once written informed consent has been obtained, participants will have their sequence modified as per their randomly allocated MRI protocol
- 6.2.6 Participants will be randomised but not blinded to one of the 3 DCE-MRI protocols

6.3 Analysis of data over 1 months

6.4 Write up of results over 1 months

7.0 DATA COLLECTION, SOURCE DATA AND CONFIDENTIALITY

7.1 General

- 7.1.1 All information collected during the course of the trial will be kept strictly confidential.
- 7.1.2 Information will be held securely on paper and electronically on secure university and hospital servers.
- 7.1.3 A database of all information will be anonymised with patients allocated to a study number. Identification of the patients to their number will be kept on a separate password protected file on secure servers accessible only to the principal investigator.
- 7.1.4 The HPB and Transplant Unit, SJUH will comply with all aspects of the Data Protection Act 1998, International Conference on Harmonization (ICH) of Good Clinical Practice (GCP) guidelines and Declaration of Helsinki (2008). Operationally this will include:
- 7.1.4.1 Consent from patients to record personal details including name, date of birth, address and telephone number, NHS ID, hospital ID, GP name and address.
- 7.1.4.2 Appropriate storage, restricted access and disposal arrangements for patient personal and clinical details.
- 7.1.4.3 Consent from patients for access to their medical records by responsible individuals from the research staff, the sponsor or from regulatory authorities, where it is relevant to trial participation that have received ICH GCP training and are thus aware of the importance of patient confidentiality.
- 7.1.4.4 Consent from patients for the data collected for the trial to be used to evaluate safety and develop new research.

7.2 Archiving

In line with the principles of ICH-GCP / UK Clinical trial Regulations guidelines, at the end of the trial, data will be securely archived at each participating centre for a minimum of 10 years. Arrangements for confidential destruction will then be made. If a patient withdraws consent for their data to be used, it will be confidentially destroyed immediately.

8.0 DATA ANALYSIS

8.1 Patient characteristics

8.2 Statistical Analysis

- 8.2.1 The pilot study is aiming for 15 patients over 7-8 weeks
- 8.2.2 There shall be 3 arms of the research DCE-MRI protocol (information in Appendix
- 8.2.3 Each protocol will calculate the following values: S_{MAX} , T_{MAX} , $T_{1/2}$, HEF, irBF, MTT, and RLE
- 8.2.4 The reproducibility of the data will be assessed for its variance as to maintaining narrow confidence intervals of the spread of the data
- 8.2.5 Image quality and artefacts will be assessed qualitatively by SS, DW, AG and DL

8.2.6 Comparison on each ability to produce reproducible data will be compared

8.3 Randomisation of patients as per radiology research methods – an in house computer program will allocate patients to protocol 1, 2 or 3. 5 patients will be allocated to each protocol.

9.0 DATA MONITORING & QUALITY ASSURANCE

The nature of the proposed study aims to primarily assess which DCE-MRI protocol gives the most reproducible data and can be used for a further clinical trial.

The scientific and academic quality of the proposal has been reviewed by all of the clinical and academic supervisors for the study.

The components of the study will involve and be led by members of the research team with the appropriate experience. Interpretation of MRI images will be performed by Dan Wilson and Steven Sourbron. Statistical analysis will be overseen by Mr David Longbotham with help from Helene H Thygesen (Leeds Cancer Research UK Centre Statistician).

This study is being used as part of a research degree for DL. Routine Regular research meetings will be held every 4 weeks from an academic point of view and clinical meetings will be held every 4 weeks. This will ensure good lines of communication between the different aspects of the study with regular review of progress.

10.0 ETHICAL CONSIDERATIONS

There are no risks for participants taking part in the study as there shall be no difference between planned MRI. The three MRI acquisition protocols are designed to obtain the planned necessary data required for accurate Liver MRI staging as planned. They shall last for around 10 minutes longer than a standard liver MRI.

The study will be performed in accordance with the recommendations guiding ethical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 48th General Assembly, Somerset West Republic of South Africa; October 1996. All participants will be volunteers. Informed written consent will be obtained from the patients prior to registration into the study.

The right of a patient to refuse participation without giving reasons must be respected. The patient must remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment.

The study will be submitted to and approved by a main Research Ethics Committee (REC) and the appropriate REC for the participating centre prior to entering patients into the study.

11.0 PUBLICATION POLICY

We reserve the right to present and publish the results of our study. At the end of the study, the results will form part of an MD degree thesis. We will also disseminate the results in peer reviewed medical and scientific journals. No individual patient information will be identified in any publications or documents.

12.0 TABLE OF DEFINITIONS AND ABBREVIATION

Acronym	Full name	Definition
MRI	Magnetic Resonance Imaging	
DCE-MRI	Dynamic Contrast Enhanced Magnetic Resonance Imaging	
CRLM	Colorectal Liver Metastasis	
TLV	Total Liver Volume	The volume(cm ³) of the liver before any surgery
RLV	Remnant Liver Volume	The volume (cm ³) of the liver after surgery
TLF	Total Liver Function	The function of the liver calculated by the result of the DCE-MRI before surgery
RLF	Remnant Liver Function	The function of the liver calculated by the result of the DCE-MRI after surgery
ICG	Indocyanine Green Test	A measure of global liver function
GSA	Galactosyl Serum Albumin scintigraphy	
RLE %	Relative Liver Enhancement	$=((SI_{hp}-SI_{un})/SI_{un}) \times 100$ SI is signal intensity, _{hp} is hepatobiliary Phase, _{un} is unenhanced.
S _{MAX} ,	maximal signal intensity	
T _{MAX}	time to reach S _{MAX}	
T _{1/2}	Half life	
AUC	Area under curve	
HEF	hepatic extraction fraction	
irBF	input-relative blood flow	
MTT	mean transit time	
GCP	Good Clinical Practice	

13.0 FUNDING APPLICATION

An application to the Pelican Foundation has been undertaken for up to £20,000 for the cost of running this study. The outcome is pending at this time.

14.0 REFERENCES

1. *Cancer Research UK Incidence of Colorectal cancer data*
<http://www.cancerresearchuk.org/cancerinfo/cancerstats/types/bowel/incidence>

2. R. A. Adair, A. L. Young, A. J. Cockbain, D. Malde, K. R. Prasad, J. P. A. Lodge, G. J. Toogood **Repeat hepatic resection for colorectal liver metastases** *British Journal of Surgery Volume 99 Issue 9 (September 2012)*
3. Capussotti, MD; Andrea Muratore, MD; Alessandro Ferrero, MD; Giovanni Carlo Anselmetti, MD; Andrea Corgnier, MD; Daniele Regge, MD **Extension of Right Portal Vein Embolization to Segment IV Portal Branches** *Arch Surg. 2005;140(11):1100-1103. doi:10.1001/archsurg.140.11.1100*
4. Sommer WH, Sourbron S, Huppertz A, Ingrisch M, Reiser MF, Zech CJ **Contrast agents as a biological marker in magnetic resonance imaging of the liver: conventional and new approaches.** *Abdom Imaging. 2012 Apr;37(2):164-79*
5. Sourbron S, Sommer WH Reiser MF, Zech CJ. **Combined quantification of liver perfusion and function with dynamic gadoxetic acid-enhanced MR imaging.** *Radiology 2012 Jun;263(3):874-83*
6. H Nilsson, L Blomqvist, L Douglas, A Nordell, E Jonas **Assessment of liver function in primary biliary cirrhosis using GD-EOB-DTPA enhanced liver MRI** *HPB 2010 October; 12(8): 567–576.*
7. Goh V, Gourtsoyianni S, Koh DM **Functional Imaging of the Liver.** *Semin Ultrasound CT MRI 34:54-65*
8. Saito K, Ledsam J, Sourbron S, Hashimoto T, Araki Y, Akata S, Tokuyue K **Measuring hepatic functional reserve using low temporal resolution Gd-EOB-DTPA dynamic contrast-enhanced MRI: a preliminary study comparing Galactosyl human serum albumin scintigraphy with indocyanine green retention.** *Eur Radiol. 2013 Aug 15*
9. Rahbari NN, Garden OJ, Padbury R, et al. **Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS).** *Surgery.* 2011; 149:713–724.
10. M J Schindl, D N Redhead, K C H Fearon, O J Garden, S J Wigmore, on behalf of the Edinburgh Liver Surgery and Transplantation Experimental Research Group (eLISTER) **The value of residual liver volume as a predictor of hepatic dysfunction and infection after major liver resection** *Gut* 2005;54:289–296
11. Balzan S, Belghiti J, Farges O, et al. **The “50–50 criteria” on postoperative day 5: an accurate predictor of liver failure and death after hepatectomy.** *Ann Surg.* 2005; 242:824–828; discussion 828–829.
12. Ribero D, Amisano, Bertuzzo F, Langella S, Lo Tesoriere R, Ferrero A, Regge D, Capussotti L **Measured Versus Estimated Total Liver Volume to Preoperatively Assess the Adequacy of the Future Liver Remnant Which Method Should We Use?.** *Annals of Surgery, Volume 00, Number 00, 2013*
13. Allard, Marc-Antoine; Adam, René, Bucur, Pétru-Octav, Termos, Salah, Cunha, Antonio Sa; Bismuth, Henri; Castaing, Denis; Vibert, Eric **Posthepatectomy Portal Vein Pressure Predicts Liver Failure and Mortality after Major Liver Resection on Noncirrhotic Liver** *Annals of Surgery*: November 2013 - Volume 258 - Issue 5 - p 822–830
14. Alastair L. Young, Dan Wilson, Janice Ward, John Biglands, J. Ashley Guthrie, K. Rajendra Prasad, Giles J. Toogood, Philip J. Robinson & J. Peter A. Lodge **Role of quantification of**

- hepatic steatosis and future remnant volume in predicting hepatic dysfunction and complications after liver resection for colorectal metastases: a pilot study *HPB* 2012, 14, 194–200
15. Wibmer A, Prusa A, Notz R, Gruenberger T, Schindl M, Ba-Ssalaman A **Liver Failure after Major Liver Resection: Risk Assessment by Using Preoperative Gadoteric Acid-enhanced 3-T MR Imaging** *Radiology: Volume 269: Number 3—December 2013*
 16. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei A (2002) "Hepatic encephalopathy- definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998". *Hepatology* 35 (3): 716–21
 17. Daniel Dindo, MD, Nicolas Demartines, MD, and Pierre-Alain Clavien, MD, PhD, FRCS, FACS **Classification of Surgical Complications A New Proposal with Evaluation in a Cohort of 6336 Patients and Results of a Survey** *Ann Surg* 2004;240: 205–213
 18. Attenberger UI¹, Sourbron SP, Michaely HJ, Reiser MF, Schoenberg SO. **Retrospective respiratory triggering renal perfusion MRI.** *Acta Radiol.* 2010 Dec;51(10):1163-71. doi: 10.3109/02841851.2010.519717.
 19. Khalifa F, Abou El-Ghar M, Abdollahi B, Frieboes HB, El-Diasty T, El-Baz A. **A comprehensive non-invasive framework for automated evaluation of acute renal transplant rejection using DCE-MRI.** *NMR Biomed.* 2013 Nov;26(11):1460-70. doi: 10.1002/nbm.2977. Epub 2013 Jun 18.

Pilot Patient Information Sheet

Pilot study for determining the best method of acquisition of Dynamic Contrast-Enhanced Liver MRI

Can a new way of taking MRI pictures of the Liver tell us how well the Liver is working?

PARTICIPANT INFORMATION SHEET AND INFORMED CONSENT DOCUMENT

HELPING YOU DECIDE WHETHER OR NOT TO JOIN OUR STUDY

- Before you decide whether to take part, it is important for you to understand why the research is being done and what it will involve.
- Please take time to read the following information carefully. Discuss it with friends and relatives if you wish. Take time to decide whether or not you wish to take part.
- You are free to decide whether or not to take part in this research study. If you choose not to take part, this will not affect the care you receive from your own doctors.
- Ask us if there is anything that is not clear or if you would like more information.
- Thank you for reading this information. If you decide to take part you will be given a copy of this information sheet and your signed consent form.

Important things that you need to know

- You are to undergo an MRI scan of your Liver to investigate the lesions found in your Liver
- We would like to know more about a new way of getting of MRI scan data. We feel it may provide more information to accurately assess the how the liver is functioning.
- The care you receive will be the same if you take part in the study or not.
- You can stop taking part in the study at any time, without giving a reason. Your treatment and care will not be affected in any way.
- This is an initial (also known as a pilot) study done at St James' University Hospital looking to provide information about a new type of MRI scan works.
- It has yet to be shown if the information gained from this type of scan can be used in care of patients, this is what this study aims to assess.
- We aim to recruit 15 patients into this study.

Contents

- 1 Why we are doing this study
- 2 Why am I being asked to take part?
- 3 What will happen to me if I take part?
- 4 Are there any drawbacks of taking part?
- 5 Benefits of taking part
- 6 What happens with my data?
- 7 Who has reviewed the project?
- 8 More information about taking part
- 9 Contact for further information

How to contact us

Our researcher, Mr David Longbotham, would be available to answer any questions that you may have. He can be contacted via 0113 20XXXXX.

Why we are doing this study

Your Consultant needs detailed pictures from a Liver MRI to plan further treatment for the lesions found in the liver. We would like to know whether the pictures that a new technique called Dynamic Contrast Enhanced MRI (DCE-MRI) could be used to tell us how well the liver is working as a whole. We feel that knowing how well the liver is functioning may be helpful for us to plan treatment in the future.

Why am I being asked to take part?

You have been asked to take part in this study because your consultant has asked us to perform an MRI of the liver to provide us more information of the lesion/s in your to plan further treatment. We would like to adapt your MRI scan to provide us with extra information.

What will happen to me if I take part?

The care of your condition will not be any different whether you decide to take part in the study or not. If you wish to take part, the MRI scan you have will be adapted in a way that the information we need to plan your treatment is entirely unaffected.

Your scan will be altered to take lots of different pictures in addition to the ones that we would normally take of your Liver. You will notice no difference in the MRI – it will not differ from the experience of any other person undergoing a Liver MRI. The scan itself may take 10 minutes longer than a routine scan. At times you may be asked to hold your breath for up to 20 seconds. This is standard practice that is often asked in MRI scans and is nothing to be concerned about.

After the scan we will have all the information and pictures to allow your consultant to make decisions on your care as normal, in addition there will be the extra pictures that will be used for this research study.

Following the scan you will be seen in the outpatient clinic of your consultant. They will be able to make the decision on your care based on the MRI results **as normal**.

There is no need for you to attend any extra clinics or scan appointments if you wish to take part in this study.

Are there any drugs or additional tests involved?

You will be given a contrast agent into a needle (also known as a cannula) placed in a vein in your arm. This is part of routine liver scanning and will happen whether you take part in the study or not. There are no other drugs or contrast agents given. You will not need any extra scans as part of this study, although the time of your MRI may take around 10 minutes longer than the routine scan.

Will I be paid for taking part?

You will not be paid for taking part in this study.

Informing your General Practitioner

Your GP will be aware that you have been invited to take part in the study as they will be copied into all the invitations. Results of the scan will also be relayed to your GP so they have a complete record of your health.

Are there any drawbacks of taking part?

There are no drawbacks to taking part in this study. The care of your liver condition will not change and you will be followed up as planned as any other patient. There is no risk to your health from taking part in this study.

What are the advantages of taking part?

There will be no direct benefit to you from this research study. However the information obtained from the study will potentially help people in the future who have the same disease as you. Once all the data has been analysed it is hoped that we will be able to understand better how this type of MRI works. We are hopeful that it will be able to help guide our treatment of these liver lesions.

What happens with my data?

Will my taking part be kept confidential?

All information collected about you during the course of this research will be kept strictly confidential. Your information will be entered into a computer database on a password-protected computer at St James' University Hospital. This information will be unavailable to anyone outside the research team. You will be allocated a unique study identifier on entry into the study and your name will be removed from the study images.

Will the researchers have access to my clinical data?

As part of the study protocol we will need to gather clinical information relating to your treatment which may require access to your medical notes. We will only access your notes if it is absolutely essential. Case notes will only be accessed by the following members of the research team. Any information will be entered in a password protected computer as described above. As you will be allocated a study number we will not keep any personal identifiable information on the computer.

What will happen to the results of the research study?

The results of the study will be published in peer reviewed journals and presented at scientific meetings nationally and internationally. All data will be fully anonymised.

Who has reviewed the study?

All research in the NHS is looked at by independent research ethics committee to protect your safety, rights and dignity.

More information about taking part

Who is organising the research?

The study is being organised by Mr Raj Prasad, Consultant Hepatobiliary and Transplant Surgeon in collaboration with Mr David Longbotham, Clinical Research Fellow, Mr Ernest Hidalgo - Consultant Hepatobiliary and Transplant Surgeons and Dr Ashley Guthrie, Consultant Radiologist at St James University Hospital. The study has been reviewed by an NRES approved Ethics Committee and the Research and Development Department situated in Leeds Teaching Hospitals NHS Trust.

What will happen to the data I have provided?

In line with Good Clinical Practice guidelines, at the end of the study, your data will be securely archived. For the purpose of this study, data will be archived for a minimum of 10 years after which arrangements for confidential destruction will be made

Your data will **not** be used for commercial purposes.

Additional research

Your data may also be stored, and may provide a resource for future surgical research. If any information from this study is used to develop new research, data protection regulations will be observed and strict confidentiality maintained; your data will have your personal details removed, but will be coded so it may be linked back to your details. This would also be with your consent. You will not be identified in the results of future studies. Ethical approval will be obtained for any future studies involving your data or samples.

Contacts for further information

If you would like any further information about this study, please contact:

Mr David Longbotham on 0113 20XXXXX

You will be given copies of this information sheet and your signed consent form to keep

Thank you for taking the time to read the information sheet and for considering taking part in this study.

The Leeds Teaching Hospitals

NHS Trust

Pilot Consent

: Pilot study for determining the best method of acquisition of Dynamic Contrast-Enhanced Liver MRI
(Consent Form; Version 1.7; 26th March 2014)

Participant ID:	Initials:
Date of Birth:	NHS/Hospital Number:
Principal Investigator: Mr David Longbotham Clinical Research Fellow – HPB and Transplant	Supervising Clinician: Mr Raj Prasad Consultant in HPB and Transplant Surgery

Participant consent form for research study

confirm that I have read and understand the information sheet (Version 1.7, 26th March 2014) for *Please initial each box* had the opportunity to ask questions.

understand that my participation in this study is voluntary and that I am free to withdraw at any time without my medical care or legal rights being affected. I understand that even if I withdraw from the above study, the data and samples collected from me will be used in analysing the results of the study.

understand that my healthcare records may be looked at by authorised individuals from the study team, regulatory bodies, funder or Sponsor in order to check that the study is being carried out correctly.

agree to allow any information or results arising from this study to be used for healthcare and/or further medical research upon the understanding that my identity will remain anonymous.

agree to my General Practitioner being contacted by letter about my inclusion in this study.

6. I agree to take part in the study.

Participant:
Signature.....

Date.....

Investigator:
I have explained the study to the above named participant and he/she has indicated his/her willingness to participate.

Signature.....
 (1 copy for participant; 1 to be kept in medical notes and original stored in Investigator Site File)

Pilot GP information sheet
 GP Letter; Version 1.7; 26th March 2014

The Leeds Teaching Hospitals

NHS Trust

Re: Patient

Mr David Longbotham
 Clinical Research Fellow
 3th Floor, Bexley Wing Building
 St James's University teaching Hospital
 Beckett Street
 LS9 7TF
 Email: david.longbotham@leedsth.nhs.uk

29th July 2014

Dear General Practitioner

Information regarding recruitment of patient to Participate in Dynamic Contrast Enhanced MRI of the Liver and predicting liver dysfunction study

I am writing to inform you that your patient has agreed to take part in a research study by the Leeds Teaching Hospitals Trust. This study has been approved by the above institutions and by the National Research Ethics Service ethics committee.

Our aim is to determine if a new type of Dynamic Contrast Enhanced MRI scan can be used to predict Quantitative Segmental Liver function is able to help us work out before surgery the residual function. Their routine staging MRI scan has been modified into one of 3 acquisition protocols that we use. This scan will be slightly adapted to obtain more information that the scan would normally take, however it still get the same information that is necessary to plan your surgery in the best way

We have included the patient information sheet for you. It explains the study and tells you why we are doing it, how you can help and how we will carry out the research. Please contact me if there is anything that is not clear, if you need help or have any queries or if you would like more information.

Yours sincerely

David Longbotham (Principal Investigator)
 MBBS MRCS
 Clinical Research Fellow
 For Mr Hidalgo, Consultant HPB and Transplant Surgeon and
 Mr Prasad, Consultant HPB and Transplant Surgeon and Chief Investigator

Appendix C: Resection Study Ethics Application REC Approval

Part of the research infrastructure for Wales funded by the National Institute for Social Care and Health Research, Welsh Government.

Yn rhan o seilwaith ymchwil Cymru a ariannir gan y Sefydliad Cenedlaethol ar gyfer Ymchwil Gofal Cymdeithasol ac Iechyd, Llywodraeth Cymru



Wales REC 6
Floor 8
36 Orchard Street
Swansea
SA1 5AQ

Telephone : 01792 607416
Fax : 01792 607533
E-mail : penny.beresford@wales.nhs.uk
Website : www.nres.nhs.uk

09 September 2014

Mr David
Longbotham
Research Fellow

Leeds Teaching Hospitals NHS
Trust Level 3 Bexley Wing

St James' University
Hospital Leeds

LS9 7TF

Dear Mr Longbotham

Study title: Can use of Dynamic contrast Enhanced MRI (DCE-MRI) of the Liver accurately predict Quantitative Segmental Function to determine post operative remnant liver function after major resection for Colorectal Liver Metastasis?
REC reference: 14/WA/1141
IRAS project ID: 146183

Thank you for responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved by the sub-committee.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the REC Manager Ms Penny Beresford, penny.beresford@wales.nhs.uk.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.



Cynhelir Cydweithrediad Gwyddor Iechyd Academaidd y Sefydliad Cenedlaethol ar gyfer Ymchwil Gofal Cymdeithasol ac Iechyd gan Fwrdd Addysgu Iechyd Powys

The National Institute for Social Care and Health Research Academic Health Science Collaboration is hosted by Powys Teaching Health Board



Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at <http://www.rdforum.nhs.uk>.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" above).

Approved documents

The documents reviewed and approved by the Committee are:

<i>Document</i>	<i>Version</i>	<i>Date</i>
GP/consultant information sheets or letters [Resection GP letter]	V1.7	23 July 2014
IRAS Checklist XML [Checklist_08092014]		08 September 2014
Letter from statistician [Helene Thygesen Letter]		12 March 2014
Letters of invitation to participant [Resection study Invitation letter]	V1.8	05 September 2014
Participant consent form [Resection Consent form]	V1.7	23 July 2014
Participant information sheet (PIS) [Resection Patient Information Sheet]	V1.8	05 September 2014
REC Application Form [REC_Form_28082014]		28 August 2014
Research protocol or project proposal [Resection study protocol]	V1.7	23 July 2014
Response to Request for Further Information		
Summary CV for Chief Investigator (CI) [CI CV David Longbotham]		14 April 2014
Summary CV for student [Mr Prasad CV - included here as could not upload 2 files for supervisor CV section. CI CV is same as students]		11 November 2013
Summary CV for supervisor (student research) [Dr Sourbron CV]		11 February 2014

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document “After ethical review – guidance for researchers” gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial
- amendments Adding new sites
- and investigators
-
- Notification of serious breaches of the protocol Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:

<http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance>

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at <http://www.hra.nhs.uk/hra-training/>

14/WA/1141

Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Yours sincerely



pp

Roy L. Evans Chair

Email: penny.beresford@wales.nhs.uk

Enclosures: *"After ethical review – guidance for researchers" [SL-AR2]*

Copy to: *Dr Derek Norfolk, Leeds Teaching Hospitals NHS Trust
Anne Gowing, Research and Development Leeds Teaching Hospitals NHS Trust*

Resection Protocol

St James's University Hospital: HPB and Transplantation

RESEARCH PROTOCOL

Version 1.7
23rd July 2014

Can use of Dynamic contrast Enhanced MRI (DCE-MRI) of the Liver accurately predict Quantitative Segmental Function to determine post-operative remnant liver function?

Protocol Number: 1.7

Principal Investigator: David Longbotham
Clinical Research Fellow
HPB and Transplantation Unit
St James University Hospital
Bexley Wing, 3rd Floor
Beckett Street
Leeds
LS9 7TF
Tel:
Email: david.longbotham@leedsth.nhs.uk

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TEAM CONTACT

Principal Investigator: Mr David Longbotham

Primary Supervisor: Mr Raj Prasad
HPB and Transplant Consultant
3rd Floor, Bexley Wing
St James's University Hospital
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Dr Steven Sourbron
Lecturer in MRI Physics
Leeds Institute of Genetics, Health and Therapeutics (LIGHT)
University of Leeds

Dr Ashley Guthrie
Consultant Radiologist
3rd Floor, Bexley Wing
St James's University Hospital
Beckett Street
Leeds
LS9 7TF

1.0 RESEARCH SUMMARY

General Information

David Longbotham

Version: 1.7, 23/7/14

St James's University Hospital (SJUH), HPB and Transplantation Unit
 University of Leeds, Faculty of Graduate School,
 Faculty of Medicine and Health

Study Information

Type: Prospective Correlation/Prediction Study

To investigate if a new form of Liver MRI can lead to accurate predictions of liver function after major liver resection for patients with Colorectal Liver Metastasis

Prospective, single centre, non-randomised

Comparison and correlation of results of DCE-MRI based predicted liver quantitative segmental function compared with clinical scoring systems of post-operative hepatic dysfunction

Comparison and correlation of results of DCE-MRI based predicted liver quantitative segmental function compared with general post-operative complications, length of stay, morbidity and mortality

Study Timelines

Expected Start Date: November 2014

Subject Enrolment Phase: November 2014

End of Study: July 2015

Expected Completion Date: Oct 2015

Study Subject Information

Number of trial subjects: ~32

Age group of study subjects: 18 years to no upper limit

For major liver resection (defined as >3 liver segments) for Colorectal Liver Metastasis with curative intent

Current Pregnancy, Allergy/intolerance to Gadolinium based contrast agents, Inability to undergo MRI (see appendix for list), Concurrent enrolment in other research trial

2.0 INTRODUCTION

2.1 Background

Colorectal Liver Metastases (CRLM) is a common and potentially fatal disease. There are around 40,000 new cases of colorectal cancer diagnosed a year¹. A third of patients diagnosed with Colorectal Cancer will have metastatic liver disease at time of presentation.

Surgical Resection of CRLM remains the only curative option for this group of patients². Due to advances in surgical, radiological and oncological techniques and technology, increasingly radical liver resections are being considered. Due to the large volume of liver that is being considered for resection it is vitally important to know pre-operatively that the remnant liver volume (RLV) will be sufficient to be compatible with life.

In current practice, 75% of total liver volume (TLV) can be safely resected^{3,18} (or to leave a remnant weighing 0.5% of total body weight¹⁹) in patients with apparently healthy liver. The percentage of TLV resectable reduces to 70% in

patients with known liver disease or having received chemotherapy pre-operatively, and for patients with established cirrhosis there is need to be extremely selective³. Those patients potentially requiring larger resections would need to be considered for techniques to induce liver hypertrophy (such as portal vein embolisation or two-stage hepatectomy) or to be deemed unresectable.

Dynamic Contrast MRI (DCE-MRI) of the Liver is a new technique using Gadoteric Acid (Primovist™) – a liver specific contrast agent. Rapidly acquired images at short interval can calculate rate of flow of contrast into hepatic arterial architectures, portal venous flow and diffusion into hepatocytes. Diseased, fibrotic liver tissue will have altered blood flow and diffusion rates from normal healthy tissue. A region of interest (ROI) within each liver segment can be identified and the data derived provides a limited number of parameters that characterise the physiological state of the tissue. Calculation function of each segment can be used as a numerator over the total calculated liver function as its denominator⁴⁻⁷.

Previous studies⁸ have shown good levels of correlation of DCE-MRI against global measures of hepatic function Indocyanine Green (ICG) testing and nuclear medicine Galactosyl serum albumin scintigraphy (GSA).

Other methods based on DCE-MRI such as relative liver enhancement (RLE) have recently shown that a lower RLE has a relationship with an increased risk of liver failure post hepatectomy^{15, 20}.

In order to objectively define Liver dysfunction following resection, many different clinical scoring systems have been developed. The 3 most commonly used scoring systems are the International Study Group of Liver Surgery (ISGLS) definition and grading system⁹, the Edinburgh Hepatic Dysfunction score¹⁰, and Balzan's 50/50 criteria definition¹¹.

2.2 Rationale for Study

Currently, preoperative assessment of RLV is mainly done by CT Volumetry – which gives detailed anatomical and volumetric data. In Japan, ICG testing is used; however this is not licensed in the UK. However this seems to underestimate the risk of post resection insufficiency by 11% even when compared to an estimated value from the patient's weight¹². This indicates that the volume of liver does not equate to function; therefore a more accurate assessment is required. It is conceivable that many patients have a degree of subclinical hepatic dysfunction that we are currently underestimating in purely volumetric analysis.

Post Hepatectomy Liver Failure (PHLF) is a serious complication with significant morbidity and mortality associated¹³. There is need to identify more accurate assessments of function of the liver in operative planning to reduce its incidence.

Recent studies have been published looking at steatosis preoperatively¹⁴ and different static MRI techniques¹⁵ in patients who undergo liver resection; however the role of DCE-MRI in this setting has not been established.

2.3 Hypothesis

DCE-MRI can predict quantitative segmental function and hence predict risk of PHLF.

3.0 STUDY OBJECTIVES AND AIMS

3.2 Primary objective

2.1 To calculate participants quantitative segmental hepatic function, and thus predict the remnant liver function (RLF). Correlation will be calculated against Edinburgh hepatic dysfunction score (see section 4.4.1), ISGLS classification of hepatic dysfunction (section 4.4.2) and Balzan's 50/50 criteria (section 4.4.3).

3.3 Secondary objectives

- 3.1 To calculate a comparison in clinical outcomes between the calculated result of quantitative segmental function of DCE-MRI against the result of Relative Liver Enhancement (RLE)
- 3.2 To calculate participants quantitative segmental hepatic function, and predict the remnant hepatic function (RHF). Correlation will be calculated against general surgical complications (Clavien classification¹⁷ - see section 4.6) length of stay, readmission to critical care, mortality
- 3.3 Cost effectiveness of use of DCE-MRI in assessment of CRLM.

4.0 STUDY DESIGN

4.5 Non randomised

4.6 Single centre

4.7 Prospective

- 7.1 Patient characteristics (such as age, medical history, BMI, alcohol intake (units/week), medications and any known liver/biliary disease) will be collected
- 7.2 Baseline calculations of the 3 clinical hepatic dysfunction scores. The following investigations will need to be collected: Bilirubin, Prothrombin Time, Lactate (can be taken from venous or arterial sample), U&Es, Encephalopathy grade (as per West Haven Criteria)
- 4.8 Clinical Scoring System

4.8.1 Edinburgh hepatic dysfunction score

Score	0	1	2
Bilirubin (mmol/L)	<20	21-60	>60
PT (seconds above normal)	<4	4-6	>6
Lactate	<1.5	1.6-3.5	>3.5
Encephalopathy	0	1-2	3-4

Severity (the four values above are added together to give a sum value – this then stratifies patients into 4 groups range is 0 to 8)

None	Mild	Moderate	Severe
0	1-2	3-4	>4

This is based on patients without chronic liver diseases. Based on the findings of the original authors of this system total dysfunction occurred in 74.1% of cases. Mild dysfunction occurred in 40.4%, moderate in 21.2%, and severe hepatic dysfunction was evident in 12.5% of patients.

4.4.2 ISGLS classification

Grade	Definition
A	PHLF resulting in abnormal laboratory parameters but requiring no change in the clinical management of the patient
B	PHLF resulting in a deviation from the regular clinical management but manageable without invasive treatment
C	PHLF resulting in a deviation from the regular clinical management

A patient's PHLF is graded by the worst identified criteria (i.e., by fulfilling at least 1 criterion of non-invasive or invasive intervention, patients are classified to have PHLF grade B and C, respectively).

	Grade A	Grade B	Grade C
Specific treatment	Nil	Required any of the following: FFP, HAS, NIV, Level 2 Care related to hepatic insufficiency	Required any of the following: Inotropes/vasopressor use, Glucose infusion, I&V, Extracorporeal liver support, rescue hepatectomy/transplant
Hepatic function	INR <1.5 No encephalopathy	INR ≥1.5 but <2 Mild encephalopathy	INR >2 Encephalopathy
Renal Function	Ur <8.3mmol/L UO > 0.5ml/kg/hr	Ur <8.3mmol/L OU ≤0.5ml/kg/hr	Ur ≥8.3mmol/L Renal Replacement Therapy
Respiratory function	O ₂ >90% (can be given via nasal/mask)	O ₂ <90% via nasal/mask	≤85% on high O ₂
Additional info	n/a	Unplanned Abdo USS/CT, CXR, cultures, Head CT	ICP monitoring

Slightly modified from Rahbari – converted into units used in UK

Using ISGLS classification, 11% of liver resections meet the criteria to diagnose PHLF. Of these 8% were diagnosed with grade A PHLF. 72% had grade B PHLF, because they required a change in their clinical management without need for invasive therapy. Grade C PHLF was diagnosed in 13 patients (20%). The perioperative mortality of patients with PHLF grades A, B, and C was 0%, 12%, and 54% respectively.

4.8.2 Balzan's 50/50 criteria - prothrombin time ratio less than 50% (this corresponds to an INR of 1.7) and serum bilirubin greater than 50µmol/L at postoperative day 5 is defined as post-operative Liver failure

3.2.1.1 In the original study **5.5% of patients undergoing resection** fulfil the criteria of both raised INR >1.7 and Bilirubin >50, 9.8% have a raised INR >1.7 on day 5, and 21.5% have a raised bilirubin >50 on day 5.

3.2.1.2 Mortality was 59% in the population with both raised INR and bilirubin, 33% in those with raised INR only, and 15% in raised bilirubin, compared to mortality of 1.5% in those with neither.

4.4.4 West Haven Criteria¹⁶

Grade 1 - Trivial lack of awareness; euphoria or anxiety; shortened attention span; impaired performance of addition or subtraction

Grade 2 - Lethargy or apathy; minimal disorientation for time or place; subtle personality change; inappropriate behavior

Grade 3 - Somnolence to semi stupor, but responsive to verbal stimuli; confusion; gross disorientation

Grade 4 - Coma (unresponsive to verbal or noxious stimuli)

4.9 Dynamic Contrast Enhanced MRI

- 9.1 Part of the study that calculates predicted RLF.
- 9.2 Use of MRI in St James' University Hospital Radiology department.
- 9.2.1 Utilises paramagnetic qualities of water molecules within tissue to demonstrate liver anatomy and pathology
- 9.2.1.1 Utilises intravenous liver specific contrast agent (Gadoxetic Acid) to demonstrate blood flow and diffusion in the liver
- 9.2.1.2 This agent is taken up by hepatocytes via organic anion transporting polypeptide OATP and excreted into bile canaliculi via multidrug resistant protein (MRP) system – the same uptake and excretion as bilirubin.
- 9.2.2 This acquisition will be added onto the participants routine MRI scan for staging of their CRLM – no additional MRI will need to be requested
- 9.2.3 A study has shown strong correlation **8** of DCE-MRI with validated methods of global hepatic function ICG and GSA
- 9.2.4 Acquisition will be taken dynamically during the arterial and portovenous phases (first 5 minutes).
- 9.2.5 This phase is not utilised on a routine MRI scan and an acquisition protocol written by Dr Dan Wilson and Dr Steven Sourbron will be used
- 9.2.6 Delayed contrast data for the hepatobiliary phase (30-40 minutes) using relative liver enhancement (RLE) techniques
- 9.2.6.1 RLE **15, 20** calculated as the ratio of signal intensity (SI) measurements of the liver parenchyma before (SI DCE) and 20 minutes after intravenous administration of gadoteric acid.
- 9.2.6.2 $RLE (\%) = (SI_{DCE} - SI) / SI * 100$
- 9.2.7 Analysis of the DCE-MRI data will take place on an In-House computer system at University of Leeds MRI Physics Department by Steven Sourbron and David Longbotham
- 4.9.3 All research team will be blinded to patients' baseline scoring results to reduce observer bias in analysis
- 4.9.4 The interpreting radiologist will be blinded to the results of the DCE-MRI phase to prevent this data being used in their reporting of patients MRI

4.6 Clavien Classification¹⁷

Grade	Definition
I	Deviation from normal postoperative course without need for intervention (although including antiemetics, antipyretics, analgesics, diuretics, IV fluid, Physio, local wound management)
II	Pharmacological intervention
III	Surgical/Endoscopic/Radiological intervention
a	No GA
b	GA
IV	Life-threatening complications needing ICU management
a	Single organ dysfunction
b	Multiorgan dysfunction
V	Death
Suffix d	Prolonged disability after discharge (e.g. cardiac insufficiency post MI, faecal incontinence post injury of nerves, stroke etc)

5.0 STUDY SUBJECT SELECTION

5.6 Patient List:

- 5.6.1 Patients will be identified from the hepatobiliary outpatient clinic from tertiary referrals for patients with potentially resectable liver metastases

6.2 Baseline characteristics such as age, sex, alcohol intake, medication history, prior liver disease, chemotherapy status (type, time scale and duration)

6.3 Information regarding the study will be provided to potential participants at this stage

5.7 Eligibility criteria

7.1 Inclusion criteria

7.1.1 Confirmed diagnosis of Colorectal Liver Metastasis:

7.1.1.1 Histological confirmation of adenocarcinoma of the large bowel

7.1.1.2 Radiologically diagnosed CRLM at time of diagnosis of Large bowel tumour or subsequent time

7.1.1.2 Confirmed potential resectability of liver that involves at least 3 or more liver segments

7.1.1.3 Able and willing to provide informed consent

7.2 Exclusion criteria

7.2.1 Current pregnancy

7.2.2 Unresectable CRLM

7.2.3 Extra-hepatic colorectal metastases that are unresectable

7.2.4 Other concurrent malignancy of any kind

7.2.5 Allergy/intolerance to Gadolinium based intravenous contrast agents

7.2.6 Intolerance to MRI

7.2.7 Unable to undergo MRI due to safety concerns (see appendix)

7.2.8 Inclusion in other clinical trials related to liver disease or surgical intervention running concurrently

5.8 Sample Size

8.1 Approximately 250 patients undergo resection of their CRLM a year in St James' University Hospital

8.2 Approximately 130 patients will have a major liver resection

8.3 Due to availability of obtaining MRI to allow DCE-MRI to be performed the anticipated recruitment shall be ~1 patient per week

8.4 The aim of recruiting ~32 patients that will allow the study to be completed and analysed within a year

5.9 Recruitment

Potential participants will be identified from the Specialist Hepatobiliary Multi-disciplinary team (MDT) meeting and information regarding participation will be mailed.

A Patient Information Sheet and letter of invitation will be provided by the authorised trial clinician for the patient to consider participation (appendix). Following information provision, patients will have at least 24 hours to consider participation and will be given the opportunity to discuss the trial with their family and healthcare professionals before they are asked whether they would be willing to take part in the trial. This process will be clearly documented onto PPM (patient pathway manager) – hospital database with patient information and clinic letters that can be printed out easily and also kept in their medical case notes. Clarification to potential participants that the DCE-MRI will have no

implications of the standard of care they will receive. They will be contacted by to confirm understanding of the study, ask any immediate questions and confirm acceptance onto study.

5.10 Consent

Informed written consent will be obtained when patients attend their MRI appointment. A copy of the consent will be given to the patient, the original filed in the Trial Master File (TMF), and one filed in the hospital notes. The written consent will be taken by a clinician, who has signed / dated the staff authorisation / delegation log. The process of obtaining written consent will be clearly documented in the patient's medical notes.

All members for the research team are Good Clinical Practice (CGP) Trained

The participant's General Practitioner (GP) will also receive confirmation of the patient's inclusion into the trial.

7.0 STUDY SCHEDULE

6.5 Patients identified from Hepatobiliary clinic referrals from Colorectal Surgery/Oncology as to possible resectability of CRL

6.6 Recruitment of patients over 12 months:

6.1 Initial contact after discussion in MDT - patients who have yet to undergo a diagnosis staging MRI in St James' Hospital

6.2 Informed consent for inclusion into the trial

6.3 Once written informed consent has been obtained, patients will be listed for their MRI using specific radiology department approved Lilac forms.

6.4 Their DCE-MRI will occur <8 weeks and >1 day before their surgery

6.5 On the day of their DCE-MRI scan they will have their Edinburgh Hepatic Dysfunction Score, ISGLS score and Balzan's 50/50 score calculated, including lactate, oxygen saturations (non-invasive) – to ensure there is no obvious preoperative hepatic dysfunction.

6.6 At time of Surgery data will be obtained – time of operation, intra-operative complication, unexpected procedures, use of Pringle Manoeuvre, Blood loss, need for transfusion, use of Inotropes

6.7 Post-operative, daily calculations of the 3 hepatic dysfunction scores will be obtained for up to 7 days and/or discharge

6.8 This will include blood tests as defined as above, Oxygen use, lactate levels, Critical care input, blood and blood products (FFP, platelets, Cryoprecipitate), non-routine radiology requests, unanticipated pharmacological use (e.g. Antibiotics), urine output, need for renal replacement therapy, any observed medical complication (e.g. myocardial infarction, pulmonary embolus) need for input from other specialists (e.g. cardiology, respiratory)

6.9 Other information, length of patient stay, mortality

6.10 Post-operative histology reports on the resected live

6.7 Analysis of data over 2 months

7.0 DATA COLLECTION, SOURCE DATA AND CONFIDENTIALITY

7.3 General

7.3.1 All information collected during the course of the trial will be kept strictly confidential.

7.3.2 Information will be held securely on paper and electronically on secure university and hospital servers.

3.3 A database of all information will be anonymised with patients allocated to a study number. Identification of the patients to their number will be kept on a separate password protected file on secure servers accessible only to the research team members as listed above.

3.4 The HPB and Transplant Unit, SJUH complies with all aspects of the Data Protection Act 1998, International Conference on Harmonization (ICH) of Good Clinical Practice (GCP) guidelines and Declaration of Helsinki (2008). Operationally this will include:

4.1 Consent from patients to record personal details including name, date of birth, address and telephone number, NHS ID, hospital ID, GP name and address.

4.2 Appropriate storage, restricted access and disposal arrangements for patient personal and clinical details.

4.3 Consent from patients for access to their medical records by responsible individuals from the research staff, the sponsor or from regulatory authorities, where it is relevant to trial participation that have received ICH GCP training and are thus aware of the importance of patient confidentiality.

4.4 Consent from patients for the data collected for the trial to be used to evaluate safety and develop new research.

7.1.5 Data will be stored in a locked filing cabinet behind a keypad access only door in the John Goligher Academic Unit

7.4 Archiving

In line with the principles of ICH-GCP / UK Clinical trial Regulations guidelines, at the end of the trial, data will be securely archived at each participating centre for a minimum of 10 years. Arrangements for confidential destruction will then be made. If a patient withdraws consent for their data to be used, it will be confidentially destroyed immediately.

8.0 DATA ANALYSIS

8.2 Patient characteristics

8.4 Statistical Analysis

4.1 The pilot study is aiming to recruit ~32 patients over 15-30 weeks

4.2 Outcome data will be presented as correlation between predicted function of the remnant liver (RLF) given as a percentage (%) as calculated by the Liver DCE-MRI (Provided as a percentage of overall function) versus each of the 3 validated clinical post hepatectomy hepatic dysfunction scoring systems

4.2.1 Balzan's 50/50 Criteria (raised INR to 1.7 and bilirubin >50mmol/L on post-operative day 5) will be presented as either being: no rise in either, raised bilirubin >50 but no rise in INR above 1.7, raised INR above 1.7 but no rise in bilirubin, or both elevated.

4.2.2 In analysis of this test, patients will have their RLF compared to their result of their 50/50 criteria

4.2.2.1 In the original study **5.5% of patients undergoing resection** fulfil the criteria of both raised INR >1.7 and Bilirubin >50, 9.8% have a raised INR >1.7 on day 5, and 21.5% have a raised bilirubin >50 on day 5.

4.2.3 ISGLS classification will be represented as 3 results – group A, B and C

4.2.3.1 Total hepatic dysfunction scores A, B or C are expected in **11% of cases of liver resection**, ~1% fell into Group A, 8% into group B and 2% in Group C

- 4.2.4 Edinburgh Hepatic Dysfunction score shall be 4 results – no dysfunction, mild, moderate and severe
- 4.2.5 Based on the findings of the original authors of this system total dysfunction occurred in **74.1% of cases**. Mild dysfunction occurred in 40.4%, moderate in 21.2%, and severe hepatic dysfunction was evident in 12.5% of patients.
- 4.3 Any significant differences in proportions will be demonstrated by correlation – Spearman’s Rank Coefficient
- 4.4 Each group will be compared against the RLF as calculated by the DCE-MRI
- 8.5 RLE values will also be calculated and analysed against each of the 3 clinical scoring systems as similar study to Wibmer and colleagues¹⁵ that will allow a comparison between RLE and DCE-MRI

For 32 participants:

Assuming that the overall risk of moderate to severe liver dysfunction is 33.7% **10**, and assuming that the MRI results are dichotomized as (above median, below median), risks of moderate or severe liver dysfunction of 53.4% in the high-MRI group versus 14.0% in the low-MRI group, can be detected with 80% power at 95% confidence (two-sided Fisher test). This corresponds to a relative risk of 3.8 or an odds ratio of 7.0. *Applying a Spearman Rank correlation test will make the power slightly better than this.*

The power calculations were carried out with the statmod package for R (version 3.0.2 for OS/X).

9.0 DATA MONITORING & QUALITY ASSURANCE

The nature of the proposed study aims to primarily assess if DCE-MRI can be used to predict post-operative hepatic dysfunction

The scientific and academic quality of the proposal has been reviewed by two clinical and academic supervisors for the study.

The components of the study will involve and be led by members of the research team with the appropriate experience. Interpretation of MRI images will be performed by Dan Wilson and Steven Sourbron. Statistical analysis will be overseen by Mr David Longbotham with help from Helene H Thygesen (Leeds Cancer Research UK Centre Statistician).

Regular research meetings will be held every 4 weeks from an academic point of view and clinical meetings will be held every 2 weeks and informally during weekly liver surgery clinics. This will ensure good lines of communication between the different aspects of the study with regular review of progress.

15.0 ETHICAL CONSIDERATIONS

There are minimal risks for participants taking part in the study as there shall be no difference between planned MRI and blood investigations. The MRI acquisition protocol is designed to obtain the planned necessary data required for effective clinical decision making as is currently performed.

This study is not interventional in nature - no change to patients’ care will be undertaken. It is using the information from participants MRI in a novel way only.

The study will be performed in accordance with the recommendations guiding ethical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 48th General Assembly, Somerset West Republic of South Africa; October 1996. All participants will be volunteers. Informed written consent will be obtained from the patients prior to registration into the study.

The right of a patient to refuse participation without giving reasons must be respected.

The patient must remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment.

The study will be submitted to and approved by a main Research Ethics Committee (REC) and the appropriate REC for the participating centre prior to entering patients into the study.

Table of terminology used

Acronym	Full name	Definition
MRI	Magnetic Resonance Imaging	
DCE-MRI	Dynamic Contrast Enhanced Magnetic Resonance Imaging	
CRLM	Colorectal Liver Metastasis	
TLV	Total Liver Volume	
RLV	Remnant Liver Volume	
TLF	Total Liver Function	
RLF	Remnant Liver Function	
ICG	Indocyanine Green Test	
GSA	G	
RLE %	Relative Liver Enhancement	$=((SI_{hp}-SI_{un})/SI_{un}) \times 100$ SI is signal intensity, hp is hepatobiliary phase, un is unenhanced.
ISGLS	International Study Group of Liver Surgery	
PHLF	Post Hepatectomy Liver Failure	
INR	International normalised ratio	
FFP	Fresh Frozen Plasma	
HAS	Human Albumin Solution	
NIV	Non-invasive Ventilation	

Study funding

There is no external funding available for this study

16.0 PUBLICATION POLICY

We reserve the right to present and publish the results of our study. At the end of the study, the results will form part of an MD degree thesis. We will also disseminate the results in peer reviewed medical and scientific journals. No individual patient information will be identified in any publications or documents.

12.0 REFERENCES

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20. Cancer Research UK *Incidence of Colorectal cancer data*
<http://www.cancerresearchuk.org/cancerinfo/cancerstats/types/bowel/incidence>
21. R. A. Adair, A. L. Young, A. J. Cockbain, D. Malde, K. R. Prasad, J. P. A. Lodge, G. J. Toogood **Repeat hepatic resection for colorectal liver metastases** *British Journal of Surgery* Volume 99 Issue 9 (September 2012)

22. Capussotti, MD; Andrea Muratore, MD; Alessandro Ferrero, MD; Giovanni Carlo Anselmetti, MD; Andrea Corgnier, MD; Daniele Regge, MD **Extension of Right Portal Vein Embolization to Segment IV Portal Branches** *Arch Surg.* 2005;140(11):1100-1103. doi:10.1001/archsurg.140.11.1100
23. Sommer WH, Sourbron S, Huppertz A, Ingrisich M, Reiser MF, Zech CJ **Contrast agents as a biological marker in magnetic resonance imaging of the liver: conventional and new approaches.** *Abdom Imaging.* 2012 Apr;37(2):164-79
24. Sourbron S, Sommer WH Reiser MF, Zech CJ. **Combined quantification of liver perfusion and function with dynamic gadoxetic acid-enhanced MR imaging.** *Radiology* 2012 Jun;263(3):874-83
25. H Nilsson, L Blomqvist, L Douglas, A Nordell, E Jonas **Assessment of liver function in primary biliary cirrhosis using GD-EOB-DTPA enhanced liver MRI** *HPB* 2010 October; 12(8): 567–576.
26. Goh V, Gourtsoyianni S, Koh DM **Functional Imaging of the Liver.** *Semin Ultrasound CT MRI* 34:54-65
27. Saito K, Ledsam J, Sourbron S, Hashimoto T, Araki Y, Akata S, Tokuyue K **Measuring hepatic functional reserve using low temporal resolution Gd-EOB-DTPA dynamic contrast-enhanced MRI: a preliminary study comparing galactosyl human serum albumin scintigraphy with indocyanine green retention..** *Eur Radiol.* 2013 Aug 15
28. Rahbari NN, Garden OJ, Padbury R, et al. **Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS).** *Surgery.* 2011; 149:713–724.
29. M J Schindl, D N Redhead, K C H Fearon, O J Garden, S J Wigmore, on behalf of the Edinburgh Liver Surgery and Transplantation Experimental Research Group (eLISTER) **The value of residual liver volume as a predictor of hepatic dysfunction and infection after major liver resection** *Gut* 2005;54:289–296
30. Balzan S, Belghiti J, Farges O, et al. **The “50–50 criteria” on postoperative day 5: an accurate predictor of liver failure and death after hepatectomy.** *Ann Surg.* 2005; 242:824–828; discussion 828–829.
31. Ribero D, Amisano, Bertuzzo F, Langella S, Lo Tesoriere R, Ferrero A, Regge D, Capussotti L **Measured Versus Estimated Total Liver Volume to Preoperatively Assess the Adequacy of the Future Liver Remnant Which Method Should We Use?** *Annals of Surgery, Volume 00, Number 00, 2013*
32. Allard, Marc-Antoine; Adam, René, Bucur, Pétru-Octav, Termos, Salah, Cunha, Antonio Sa; Bismuth, Henri; Castaing, Denis; Vibert, Eric **Posthepatectomy Portal Vein Pressure Predicts Liver Failure and Mortality after Major Liver Resection on Noncirrhotic Liver** *Annals of Surgery*: November 2013 - Volume 258 - Issue 5 - p 822–830
33. Alastair L. Young, Dan Wilson, Janice Ward, John Biglands, J. Ashley Guthrie, K. Rajendra Prasad, Giles J. Toogood, Philip J. Robinson & J. Peter A. Lodge **Role of quantification of hepatic steatosis and future remnant volume in predicting hepatic dysfunction and complications after liver resection for colorectal metastases: a pilot study** *HPB* 2012, 14, 194–200
34. Wibmer A, Prusa A, Notz R, Gruenberger T, Schindl M, Ba-Ssalaman A **Liver Failure after Major Liver Resection: Risk Assessment by Using Preoperative Gadoxetic Acid-enhanced 3-T MR Imaging** *Radiology: Volume 269: Number 3—December 2013*
35. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei A (2002) "Hepatic encephalopathy- definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998". *Hepatology* 35 (3): 716–21
36. Daniel Dindo, MD, Nicolas Demartines, MD, and Pierre-Alain Clavien, MD, PhD, FRCS, FACS **Classification of Surgical Complications A New Proposal with Evaluation in a Cohort of 6336 Patients and Results of a Survey** *Ann Surg* 2004;240: 205–213

37. R. Robles*, C. Marin, A. Lopez-Conesa, A. Capel, D. Perez-Flores, P. Parrilla **Comparative study of right portal vein ligation versus embolisation for induction of hypertrophy in two-stage hepatectomy for multiple bilateral colorectal liver metastases** *EJSO* 38 (2012) 586e593
38. Junichi Shindoh, MD, PhD, Jean-Nicolas Vauthey, MD, FACS, Giuseppe Zimmitti, MD, Steven A Curley, MD, FACS, Steven Y Huang, MD, Armeen Mahvash, MD, Sanjay Gupta, MD, Michael J Wallace, MD, Thomas A Aloia, MD, FACS **Analysis of the Efficacy of Portal Vein Embolization for Patients with Extensive Liver Malignancy and Very Low Future Liver Remnant Volume, Including a Comparison with the Associating Liver Partition with Portal Vein Ligation for Staged Hepatectomy Approach** *Vol. 217, No. 1, July 2013*
39. N. Verloh, M. Haimerl, F. Zeman, M. Schlabeck, A. Barreiros, M. Loss, A. G. Schreyer, C. Stroszczyński, C. Fellner, P. Wiggermann **Assessing liver function by liver enhancement during the hepatobiliary phase with Gd-EOB-DTPA-enhanced MRI at 3 Tesla** *European Radiology February 2014*

Resection Patient Information Sheet

Can use of Dynamic contrast Enhanced MRI (DCE-MRI) of the Liver accurately predict Quantitative Segmental Function to determine post-operative remnant liver function?

Can a new way of taking MRI pictures of the liver tell us how well the Liver is working?

PARTICIPANT INFORMATION SHEET AND INFORMED CONSENT DOCUMENT

HELPING YOU DECIDE WHETHER OR NOT TO JOIN OUR STUDY

- Before you decide whether to take part, it is important for you to understand why the research is being done and what it will involve.
- Please take time to read the following information carefully. Discuss it with friends and relatives if you wish. Take time to decide whether or not you wish to take part.
- You are free to decide whether or not to take part in this research study. If you choose not to take part, this will not affect the care you receive from your own doctors.
- Ask us if there is anything that is not clear or if you would like more information.
- Thank you for reading this information. If you decide to take part, you will be given a copy of this information sheet and your signed consent form.

Important things that you need to know

- You are to undergo an MRI scan of your Liver to investigate your Liver condition.
- We would like to know more about a new way of getting of MRI scan data. We feel it may provide more information to accurately assess the how the liver is functioning.
- We will work out how your liver is working on the day of your MRI in the form of routine blood and memory tests. If you require an operation for your condition, we would look at your blood and memory tests every day for your hospital stay
- You will not require any extra tests or investigations as part of this study.
- The care you receive will be the same if you take part in the study or not.
- You can stop taking part in the study at any time, without giving a reason. Your treatment and care will not be affected in any way.
- This is an initial (also known as a pilot) study done at St James' University Hospital looking to provide information about a new type of MRI scan works.
- It has yet to be shown if the information gained from this type of scan can be used in care of patients, this is what this study aims to assess.
- **The results of this study form part of a higher research degree (MD).**
- We aim to recruit 32 patients into this study.

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How to contact us

Our researcher, Mr David Longbotham, would be available to answer any questions that you may have. He can be contacted via 0113 20XXXXX

10 Why we are doing this study

Your Consultant needs detailed pictures from a Liver MRI to plan further treatment for the lesions found in the liver. We would like to know whether the pictures that a new technique called Dynamic Contrast Enhanced MRI (DCE-MRI) could be used to tell us how well the liver is working as a whole. We feel that knowing how well the liver is functioning may be helpful for us to plan treatment in the future.

11 Why am I being asked to take part?

You have been asked to take part in this study because your consultant has asked us to perform an MRI of the liver to provide us more information of the lesion/s in your to plan further treatment. We would like to adapt your MRI scan to provide us with extra information.

12 What will happen to me if I take part?

The care of your condition will not be any different whether you decide to take part in the study or not. If you wish to take part, the MRI scan you have will be adapted in a way that the information we need to plan your treatment is entirely unaffected. We will take some routine blood tests on the day of your scan. People having an MRI of their liver routinely have a plastic needle (cannula) inserted for the scan and bloods can be taken at this time. In addition we will perform an assessment of your liver function that involves a simple test of your memory. Your scan will be altered to take lots of different pictures in addition to the ones that we would normally take of your Liver. You will notice no difference in the MRI – it will not differ from the experience of any other person undergoing a Liver MRI. The scan itself may take 10 minutes longer than a routine scan. At times you may be asked to hold your breath for up to 20 seconds. This is standard practice that is often asked in MRI scans and is nothing to be concerned about. After the scan we will have all the information and pictures to allow your consultant to make decisions on your care as normal, in addition there will be the extra pictures that will be used for this research study. Following the scan you will be seen in the outpatient clinic of your consultant. They will be able to make the decision on your care based on the MRI results as normal. If the findings of the scan show that your consultant can offer an operation for your condition then we would follow your progress in your first week after surgery, looking at your routine blood results and to retest your memory scoring as was done on the day of your MRI. You won't have to have any extra tests as part of this study. There is no need for you to attend any extra clinics or scan appointments if you wish to take part in this study.

Will I be paid for taking part?

You will not be paid for taking part in this study.

Will any genetic tests be done?

No.

Informing your General Practitioner

Your GP will be aware that you have been invited to take part in the study as they will be copied into all the invitations. Results of the scan will also be relayed to your GP so they have a complete record of your health.

13 Are there any drawbacks of taking part?

There are no drawbacks to taking part in this study. The management of your liver lesions will not change and you will be followed up as normal. If there are any changes to the liver these will be discussed in detail during routine follow up. There is no risk to your health from taking part in this study.

14 What are the advantages of taking part?

There will be no direct benefit to you from this research study. However the information obtained from the study will potentially help people in the future who have the same disease as you. Once all the data has been analysed it is hoped that we will be able to understand better how this type of MRI works. We are hopeful that it will be able to make surgery even safer in the future.

15 What happens with my data?

Will my taking part be kept confidential?

If you decide to participate in study, the information collected about you will be handled strictly in accordance with the consent that you have given and also the 1998 Data Protection Act.

Information will be collected from your hospital notes on your past medical history and diagnostic tests you may have had previously. This information will be stored in a password protected University and hospital computers. You will be allocated a unique study number, which will be used along with your date of birth as a code to identify you on all paper forms. Only the research team will be able to identify you from this study number. With your permission, your relevant medical records may be inspected by authorised individuals from the research team or the University of Leeds (the study Sponsor). They may also be looked at by the relevant regulatory authorities and by authorised people from the Trust or other NHS bodies to check that the study is being carried out correctly. This data will have your name removed so that you cannot be identified from the information.

The information collected about you may be shared with other research teams to answer new research questions in the future. Information will be anonymised (for example, your full name will not be disclosed with this information). These records will be stored for a minimum of 10 years and after which they will be securely removed. Within this period, your medical records may also be looked at, if required, by the researcher or a member of your clinical care team under the direction of Mr Prasad, Consultant Hepatobiliary and Transplant Surgeon.

What will happen if I don't want to carry on with the study?

You can decide to leave the study at any time. You do not need to give a reason. This will not have any effect on any subsequent treatment you receive.

If you decide to leave the study after your liver has been scanned then your data collected up until that time will remain on file and will be included in the final study analysis and follow up information will continue to be collected from your medical records.

If you decide to leave the study and do not wish for any further data to be collected about you, you should inform your clinical care team of this in order that no further follow up information is collected from your medical records.

What will happen to the results of the research study?

When the study is complete the results will be published in a medical journal, but no individual participants will be identified. If you would like to obtain a copy of the published results, please ask your doctor.

What will happen if I lose mental capacity during the study period?

This is expected to be a very rare occurrence. It could however happen to any patient whether or not they are a participant in this study, for example due to an entirely separate event (e.g. a head injury). If this did occur before your liver scan we would withdraw you from the study. However, if it occurs after the liver scan, we would like to continue to use the data we have collected for the study and would like you to let us know on the consent form if you would be happy for us to do so.

What if something goes wrong in the study?

In the very unlikely event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against The Leeds Teaching Hospitals Trust but you may have to pay your legal costs. The normal National Health Services complaints mechanism and Patient Advice and Liaison Service (PALS) will still be available to you (if appropriate).

16 Who has reviewed the study?

All research in the NHS is looked at by an independent research ethics committee to protect your safety, rights and dignity.

The study has been reviewed by an NRES approved Ethics Committee, Wales REC 6, and the Research and Development Department situated at Leeds Teaching Hospitals NHS Trust.

The study has been independently peer reviewed by Professor JPA Lodge for its scientific merit. He is a Professor of Surgery at the University of Leeds and St James' University Hospital.

17 More information about taking part

Who is organising the research?

The study is being organised by Mr David Longbotham in collaboration with Mr Raj Prasad, Mr Ernest Hidalgo - Consultant Hepatobiliary and Transplant Surgeons, Dr Ashley Guthrie, Consultant Radiologist at St James University Hospital.

What will happen to the data I have provided?

In line with Good Clinical Practice guidelines, at the end of the study, your data will be securely archived. For the purpose of this study, data will be archived for a minimum of 10 years after which arrangements for confidential destruction will be made

Your data will **not** be used for commercial purposes.

Additional research

Your data may also be stored, and may provide a resource for future surgical research. If any information from this study is used to develop new research, data protection regulations will be observed and strict confidentiality maintained; your data will have your personal details removed, but will be coded so it may be linked back to your details. This would also be with your consent. You will not be identified in the results of future studies. Ethical approval will be obtained for any future studies involving your data or samples.

18 Contacts for further information

If you would like any further information about this study, please contact:
Mr David Longbotham on 0113 20XXXXX

Thank you for taking the time to consider taking part in this study.

The Leeds Teaching Hospitals

NHS Trust

Resection Consent

Research Study: Can use of Dynamic contrast Enhanced MRI (DCE-MRI) of the Liver accurately predict Quantitative Segmental Function to determine post-operative remnant liver function?
(Consent Form; Version 1.7; 23rd July 2014)

Participant ID:	Initials:
Date of Birth:	NHS/Hospital Number:
Principal Investigator: Mr David Longbotham Clinical Research Fellow – HPB and Transplant	Supervising Clinician: Mr Raj Prasad Consultant in HPB and Transplant Surgery

Participant consent form for research study

Please initial each box

confirm that I have read and understand the information sheet (Version 1.7, 23rd July 2014) for the above study and I have had the opportunity to ask questions.

understand that my participation in this study is voluntary and that I am free to withdraw at any time without my medical care or legal rights being affected. I understand that even if I withdraw from the above study, the data and samples collected from me will be used in analysing the results of the study.

understand that my healthcare records may be looked at by authorised individuals from the study team, regulatory bodies, funder or Sponsor in order to check that the study is being carried out correctly.

I agree to allow any information or results arising from this study to be used for healthcare and/or further research upon the understanding that my identity will remain anonymous wherever possible.

I agree to my General Practitioner being contacted by letter about my inclusion in this study.

6. I agree to take part in the study.

Participant:

Signature.....

Name (block capitals).....

Date.....

Investigator:

I have explained the study to the above named participant and he/she has indicated his/her willingness to participate.

Signature.....

(1 copy for participant; 1 to be kept in medical notes and original stored in Investigator Site File;)

Resection GP Information Sheet

GP Letter; Version 1.7; 23th July 2014

The Leeds Teaching Hospitals

NHS Trust

Re:

Mr David Longbotham
 Clinical Research Fellow
 3th Floor, Bexley Wing Building
 St James's University teaching Hospital
 Beckett Street
 LS9 7TF
 Email: david.longbotham@leedsth.nhs.uk

Date

Dear General Practitioner

Information regarding recruitment of patient to Participate in Dynamic Contrast Enhanced MRI of the Liver and predicting liver dysfunction study

I am writing to inform you that your patient has agreed to take part in a research study by the Leeds Teaching Hospitals Trust. This study has been approved by the above institutions and by the National Research Ethics Service ethics committee.

Our aim is to determine if a new type of Dynamic Contrast Enhanced MRI scan can be used to predict Quantitative Segmental Liver function is able to help us work out before surgery the residual function. Their routine staging MRI scan has been modified into a different acquisition protocol that we hope shall correlate to their clinical post-operative function.

We have included the patient information sheet for you. It explains the study and tells you why we are doing it, how you can help and how we will carry out the research. Please contact me if there is anything that is not clear, if you need help or have any queries or if you would like more information.

Yours sincerely

David Longbotham (Principal Investigator)
 MBBS MRCS
 Clinical Research Fellow
 For Mr Hidalgo, Consultant HPB and Transplant Surgeon and
 Mr Prasad, Consultant HPB and Transplant Surgeon and Chief Investigator