Using routinely collected national data to describe the surgical management and outcomes of patients with colorectal cancer liver metastases in the English National Health Service

Abigail Ella Vallance

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Department of Medicine and Health

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

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I was responsible for study conception, data collection (including conducting the survey of colorectal cancer service organisation), data analysis, drafting of manuscript and revision of manuscript. AK assisted in preparing the data. JH, IDB and DGJ assisted in the drafting and revision of the manuscript. KW and JvM assisted in study conception and drafting and revision of the manuscript.

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Abstract

Colorectal cancer (CRC) is the fourth most common cancer in the United Kingdom. Up to half of patients with CRC will develop liver metastases. For selected patients with liver metastases, liver resection can offer a chance of long-term cure. The aim of this thesis was to investigate the management and outcomes associated with the surgical treatment of patients with CRC liver metastases in England in an attempt to identify areas where care may be improved.

Four separate studies were performed describing i) the impact of centralisation of hepatobiliary surgical services on liver resections rates for patients with CRC liver metastases and patient survival, ii) the effect of socioeconomic deprivation on rates of liver resection in patients with CRC liver metastases ,and the impact on survival, iii) the timing of liver resection in relation to CRC resection in patients with synchronous CRC liver metastases and iv) the impact of advancing age on outcomes following liver resection. These studies were conducted by linking three national databases: the National Bowel Cancer Audit, Hospital Episode Statistics data and Office for National Statistics mortality data.

The results of these studies highlight that firstly, amongst patients with synchronous CRC liver metastases, those diagnosed at hospital sites with no on-site hepatobiliary services and those of higher socioeconomic deprivation have poorer survival than would be expected. This appears to relate to inequalities in provision of liver resection. Secondly, there is wide inter-hospital variation in the timing of liver resection in relation to CRC resection in England. Thirdly, although elderly patients are at increased risk of post-operative mortality following liver resection, cancer-specific and overall survival in patients between 65 and 74 years are comparable to younger patients. This thesis also discusses methodological issues associated with using national routine data for the analyses in this patient cohort.

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Abbreviations

A&E	Accident and Emergency
ACPGBI	Association of Coloproctology of Great Britain and Ireland
ACS-NSQIP	American College of Surgeons National Surgical Quality Improvement Program
AIDS	Acquired Immune Deficiency Syndrome
AJCC	American Joint Committee on Cancer
ASA	American Society of Anaesthesiologists
ASR	Age Standardised Rate
AUGIS	Association of Upper Gastrointestinal Surgeons
BMI	Body Mass Index
CAP	Clinical Audit Platform
CEA	Carcinoembryonic Antigen
CEU	Clinical Effectiveness Unit
CI	Confidence Interval
COSD	Cancer Outcomes and Services Dataset
CPET	Cardio-Pulmonary Exercise Testing
CRC	Colorectal Cancer
CT	Computed Tomography
DEBIRI	Irinotecan Loaded Drug-Eluting Beads
EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
FACS	Follow-up After Colorectal Surgery
FCE	Finished Consultant Episode
FDG-PET	Fluorodeoxyglucose-Positron Emission Tomography
FLR	Future Liver Remnant
GBIHPBA	Great Britain and Ireland Hepato-Pancreato-Biliary Association
GMC	General Medical Council
GP	General Practitioner
HAI	Hepatic Artery Infusion
HES	Hospital Episode Statistics
HIFU	High Intensity Focused Ultrasound
HIV	Human Immunodeficiency Virus
HQIP	Health Quality Improvement Programme
HR	Hazard Ratio
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
IMD	Index of Multiple Deprivation
IMPACT	Improving Management of Patients with Advanced Colorectal Tumours
IRE	Irreversible Electroporation
ISRCTN	International Standard Registered Clinical/soCial sTudy Number
LAVA	**L**iver **R**esection Surgery Versus Thermal Ablation for Colorectal Li**V**er Met**A**stases
LSOA	Lower Layer Super Output Area
MDT	Multi-disciplinary Team
MRI	Magnetic Resonance Imaging
MWA	Microwave Ablation
NBOCA	National Bowel Cancer Audit
NHS	National Health Service
NICE	National Institute of Health and Clinical Excellence
NSQIP	National Surgical Quality Improvement Programme
ONS	Office for National Statistics

OPCS-4	Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures (4th revision)
OR	Odds Ratio
PVE	Portal Vein Embolisation
RCS	Royal College of Surgeons
RFA	Radiofrequency Ablation
SIRT	Selective Internal Radiation Therapy
TACE	Transcatheter Arterial Chemoembolisation
TNM	Tumour, Nodal and Metastasis
TME	Total Mesorectal Excision
UGI	Upper Gastro-Intestinal
UK	United Kingdom
US	United States

1. Chapter 1: Introduction

1.1 Chapter overview

Colorectal cancer (CRC) is a common diagnosis in the Western world and is the fourth most common cancer in the United Kingdom (UK) (Cancer Research UK, 2014). Up to 20% of CRC patients have liver metastases at presentation and a further 30% of patients will be diagnosed with liver metastases as part of follow-up (Manfredi *et al*., 2006). Patients with CRC liver metastases may be classified into three groups: those with clearly resectable liver metastases, those with marginally resectable liver metastases and those with clearly unresectable liver metastases. The mainstay of treatment for patients in the second and third groups is systemic chemotherapy. This thesis is centered around the surgical management of patients, and therefore will focus on patients in the first group.

In many forms of cancer, a diagnosis of metastatic disease equates to a non-curative management strategy with the focus of care on extending life, maintaining quality of life and reducing symptoms. Isolated CRC liver metastases, however, can be considered quite unique among presentations of common malignant disease in this regard. In CRC patients with metastatic disease who undergo complete surgical resection, cure rates superior to those observed in non-metastatic primary cancer of other solid organs may be achieved (Lyratzopoulos *et al.*, 2007). This depends on the identification of such patients and subsequent referral to specialist teams. These teams must, in conjunction with the patient and the referring team, decide if the patient is to be treated with curative intent, usually consisting of one or more surgical procedures.

The management of patients with CRC liver metastases has become increasingly complex and relies upon these systems working smoothly to ensure patients have timely access to services. It is deficiencies in the treatment of patients with metastatic disease which is cited as one of the potential reasons that the UK is lagging behind much of Europe in the survival of patients with CRC (Angelis *et al*., 2014). The aim of this thesis was to investigate the management and outcomes associated with the surgical treatment of patients with CRC liver metastases in England in an attempt to identify areas where care may be improved in the future.

This introductory chapter will provide an overview of the incidence of CRC liver metastases, outline the current treatment options and describe the provision of services for these patients in England. This chapter will conclude by identifying a number of current evidence gaps in the literature and describe how the research presented in this thesis will address these.

1.2 Colorectal cancer

CRC accounts for 11% of new cancer diagnoses in the UK and it is the second most common cause of cancer-related deaths. Over 40,000 new cases of CRC are diagnosed in the UK per annum with 72 new cancer cases for every 100,000 males and 56 for every 100,000 females. (Cancer Research UK, 2014). When a patient is diagnosed with CRC, the extent of local disease and any metastatic spread must be determined to allow treatment planning.

The pathologist Cuthbert Dukes (1932) proposed a classification designed to represent a step-wise progression of locoregional invasion by rectal cancers, and later adapted it to include colon cancer. Many refinements of the original classification have now been reported in the surgical literature. The American Joint Committee on Cancer (AJCC) (2017) in an attempt to provide a uniform classification for CRC, proposed a staging system based on the TNM classification system (Table 1.1) (Sobin and Fleming, 1997). This assesses the extent of the primary tumour (T), the status of regional lymph nodes (N), and the presence or absence of distant metastases (M) and allows patients to be assigned to one of 4 stages (Table 1.2) (American Joint Committee on Cancer, 2017).

Table 1.1 The Tumour Node Metastases (TNM) classification system (Sobin and Fleming, 1997)

Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria
T1	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3	Tumour invades through the muscularis propria into the pericolorectal tissues
T4a	Tumour penetrates to the surface of the visceral peritoneum
T4b	Tumour directly invades or is adherent to other organs or structures
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1-3 regional lymph nodes
N1a	Metastasis in 1 regional lymph node
N1b	Metastasis in 2-3 regional lymph nodes
N1c	Tumour deposit(s) in the subserosa, mesentery, or nonperitonealised pericolic or perirectal tissues without regional nodal metastasis
N2	Metastasis in 4 or more lymph nodes
N2a	Metastasis in 4-6 regional lymph nodes
N2b	Metastasis in 7 or more regional lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to 1 organ or site
M1b	Metastases in more than 1 organ/site or the peritoneum

Table 1.2 The American Joint Committee on Cancer staging system (2017)

Stage	**TNM**
Stage I	T1 N0 M0
Stage I	T2 N0 M0
Stage II-A	T3 N0 M0
Stage II-B	T4 N0 M0
Stage III-A	T1-2 N1 M0
Stage III-B	T3-4 N1 M0
Stage III-C	any T, N2 M0
Stage IV	any T, any N, M1

Establishing the stage of disease is essential to formulate a treatment plan and inform prognosis. The presence of distant metastases at diagnosis, stage IV disease, has a significant impact, not only on the treatment plan, but also patient survival.

In CRC patients treated with curative intent, surgical excision is the mainstay of treatment and around two thirds of patients with CRC in England undergo a major resection (nboca.org.uk, 2016). Surgical excision of a colonic tumour along with the appropriate vascular pedicle and accompanying lymphatic drainage is the gold standard for colonic tumours (Nelson *et al.*, 2001). Total mesorectal excision (TME) is the optimal treatment strategy for patients with low or mid-rectal cancer (Heald and Ryall, 1986).

1.3 Colorectal cancer liver metastases

Metastasis (meta (μετά) = after, next and stasis (στάση) = arrest) is a word of Greek origin, describing the development of secondary malignant growths at a distance from the primary cancer site (Paschos *et al.*, 2014, National Cancer Institute, 2017). Metastases are the main cause of cancer-related mortality in CRC due to associated organ failure (Van Cutsem *et al.*, 2016). The presence of metastatic disease at the time of diagnosis of CRC is relatively common. The National Bowel Cancer Audit (NBOCA) reports 19% of patients in England and Wales have metastatic disease at diagnosis (nboca.org.uk, 2016). Around 50% of patients without metastases at presentation develop distant metastases within 3 years of diagnosis (McArdle, 2000).

The liver is one of the most frequent sites of organ-specific metastasis for many cancers. The preferential spread of CRC to the liver is thought to be partially attributable to circulation patterns with blood draining from the large bowel through the portal system to the liver (Nguyen *et al.*, 2009). In approximately 50- 80% of patients with CRC metastases, the liver is the only site of metastatic disease (Sjovall *et al*., 2004, Manfredi *et al*., 2006).

1.3.1 Current terminology

Liver metastases may be detected either at the time of diagnosis or at a later date. Although some experts are of the opinion that all metastases are synchronous and it is just our ability to detect them that renders their diagnosis metachronous (Adam *et al.*, 2015), in clinical practice synchronicity refers to those evident at the time of clinical presentation, and metachronous to those detected at a later time point (Siriwardena *et al.*, 2014).

In practical terms there are a variety of definitions of synchronous, and therefore metachronous disease. Synchronous metastases have been defined as those detected at pre-operative staging or during the primary tumour resection (Manfredi *et al*., 2006, Adam *et al*., 2015, van der Pool *et al*., 2010) or within 3 months (Ng *et al.*, 2009), 6 months (Wang *et al.*, 2007) or 1 year (Bockhorn *et al.*, 2008) of primary diagnosis. An international consensus group recently recommended synchronous disease should be termed, ‘synchronously detected metastases’ and defined as metastases detected at or before diagnosis of the primary tumour (Adam *et al.*, 2015). They recommend that *early* metachronous disease should be considered as that detected within 12 months of diagnosis or surgery to the primary tumour, and *late* metachronous disease, that detected at 12 months or more.

1.3.2 Incidence of liver metastases

The incidence of synchronous liver metastases is not fully known. Due to recruitment bias and differences in referral practices, the reported incidence in single centre studies tends to be over-estimated (Leporrier *et al*., 2006). In addition, cancer registries such as the NBOCA tend to report overall rate of metastases and not specifically liver metastases (nboca.org.uk, 2016).

The EUROCARE study reported 23% of patients to have synchronous liver metastases at diagnosis in 1990 (Gatta *et al.*, 2000). A more recent study performed in a German population diagnosed with CRC from 2002 to 2007 reported the rate of synchronous liver metastases as 18% (Hackl *et al.*, 2014). Other population-based studies have reported the rate to be lower. The incidence in two separate studies of French populations were described as 14.5% and 14.7% (Manfredi *et al*., 2006, Mantke *et al*., 2012). Similarly, results from a population based Swedish study reported the rate to be 15% (Sjovall *et al.*, 2004).

The majority of patients with no detectable metastatic disease at diagnosis who do develop liver metastases will do so within 3 years of diagnosis of primary CRC (Manfredi *et al*., 2006).

Again, the proportion of CRC patients reported to have metachronous disease varies, and comparisons must be made with caution due to differing follow up times and surveillance schedules. Amongst 3,655 patients undergoing a curative major CRC resection in a French population over a 25 year period, 13% developed metachronous liver metastases in the 5 years following diagnosis. The overall actuarial cumulative rate was 4% at 1 year, 12% at 3 years and 17% at 5 years (Manfredi *et al*., 2006). However, over a follow-up period of 10 years in a more recent German population the rate of metachronous liver metastases was much lower at 7% (Hackl *et al.*, 2014).

1.3.3 Risk factors for liver metastases

Stage of the primary tumour at diagnosis has been shown to be the greatest predictor of the development of both synchronous and metachronous liver metastases (van Gestel *et al*., 2014, Landreau *et al*., 2015). Manfredi *et al.* (2006) reported an almost 8-fold increase in the relative risk of liver metastases for patients with stage III CRC when compared to those with stage I disease at diagnosis. Patients who are diagnosed with synchronous metastases, compared to those with metachronous disease, tend to have more locally advanced primary CRC as well as a greater burden of liver metastases (Mantke *et al.*, 2012).

Liver metastases appear to be more common in men than in women (Manfredi *et al*., 2006, Mantke *et al*., 2012, van Gestel *et al*., 2014). Studies have also reported that younger patients are more likely to be diagnosed with liver metastases (Manfredi *et al*., 2006, Mantke *et al*., 2012). This may relate to younger patients more commonly having a later stage of disease at diagnosis, or undergoing more thorough staging investigations as they may be treated more aggressively than older patients.

Data regarding the propensity of patients to develop liver metastases based on the site of the primary tumour within the bowel is conflicting. Some studies report a higher rate of liver metastases in patients with a colonic primary when compared to those with a rectal primary (Mantke *et al*., 2012, Qiu *et al*., 2015), whereas other studies have found no association between location of the primary and the development of liver metastases (van Gestel *et al*., 2014, Landreau *et al*., 2015).

1.3.4 Diagnosis of liver metastases

1.3.4.1 Imaging

Adequate pre-treatment imaging is critical for patients with suspected CRC liver metastases for diagnosis, staging and treatment planning (Charnsangavej *et al.*, 2006). Computed tomography (CT) is widely used as the first cross-sectional imaging assessment in patients with CRC. The National Institute of Health and Clinical Excellence (NICE) (2014) recommends all patients should undergo a contrast-enhanced CT of the chest, abdomen and pelvis at diagnosis. In addition, patients who have undergone CRC resection with curative intent should undergo regular surveillance with a minimum of two CTs of the chest, abdomen and pelvis in the first 3 years after resection (National Institute for Health and Care Excellence, 2014).

When patients are suspected to have liver metastases, imaging should be undertaken to define the number and segmental/lobar distribution, determine surgical resectability and identify any extra-hepatic disease. As well as CT, further imaging options include ultrasound, magnetic resonance imaging (MRI) and fluorodeoxyglucose-positron emission tomography (FDG-PET). The use of these modalities in clinical practice varies according to local availability, expertise, and clinical indication.

MRI is the most accurate imaging technique for detection and characterisation of liver masses (Adams *et al.*, 2013), and can help in distinguishing malignant from benign lesions, and in establishing a road map of the anatomical distribution of lesions (Siriwardena *et al.*, 2014).

MRI is particularly sensitive in the detection of metastases in patients with steatosis or changes to the liver parenchyma secondary to pre-operative chemotherapy

FDG-PET, used with concurrent CT, has a high sensitivity and specificity for the detection of liver metastases (Bipat *et al.*, 2005). FDG-PET is particularly efficacious in the detection of extra-hepatic disease, which can have important implications for patient management. FDG-PET is currently recommended by the Royal College of Radiologists (2016) for use in staging of CRC patients with synchronous metastases at presentation or to detect recurrence in patients in whom there is clinical suspicion.

1.3.4.2 Carcinoembryonic antigen

Serum levels of the complex glycoprotein carcinoembryonic antigen (CEA) are widely used in post-resection surveillance. In the Follow-up After Colorectal Surgery (FACS) trial investigating follow-up methods for CRC patients who had undergone a curative resection, 1202 participants were randomised to one of four groups, CEA screening, CT screening, CEA and CT screening, or minimum (symptomatic) follow up (Primrose *et al*., 2014b). Among these patients, either CT or CEA screening each provided an increased rate of surgical treatment of recurrence with curative intent compared with minimal follow-up; there was no advantage in combining CEA and CT. It is therefore recommended that CRC patients have CEA tests at least every 6 months in the first 3 years following resection (National Institute for Health and Care Excellence, 2014). An increase in the serum CEA level has a reported sensitivity of 84% and specificity of 96% in the diagnosis of liver metastases (Arnaud *et al.*, 1980).

1.3.5 Patient survival with liver metastases

Untreated, the median survival time for patients with CRC liver metastases is around 5 months, with less than 30% of patients alive at 1 year (Bengtsson *et al*., 1981, Erlichman *et al*., 1988).

Patients with unilobar liver disease and those with a limited number of metastases have a better prognosis then those with more advanced disease (Stangl *et al.*, 1994). However even in patients with less disease burden, without treatment very few would be expected to be alive at 5 years. The median survival for patients with less than one quarter of their liver volume replaced by tumour without treatment is reportedly 11 months (Stangl *et al.*, 1994).

With the advent of modern chemotherapy regimens, the overall survival in patients with unresected metastatic disease who receive systemic treatment has improved over the past two decades. Median survival for these patients is now of the order of around 24 months (Cutsem *et al.*, 2011).

Wherever possible, treatment should be aimed toward complete excision of disease (Garden *et al*., 2006). Liver resection is commonly regarded as the only curative treatment modality for patients with liver-limited disease. Survival following resection of CRC liver metastases can be widely variable and is dependent on clinical, tumour and molecular factors. In addition, selection criteria for liver resection is not usually consistent between centres; staging algorithms vary, and there is a great deal of heterogeneity between treatment protocols. In a meta-analysis of outcomes after liver resection for CRC liver metastases based on 60 studies, 5-year survival ranged from 16% to 74% with a median of 38%, and 10-year survival ranged from 9% to 69% with a median of 26% (Vigano *et al.*, 2008). Many of the included studies were from single institutions and could not account for referral or selection bias. Population-based studies may be better placed to describe survival outcomes following liver resection, and recent publications using registry data from English and Swedish cohorts report 5-year survival rates of 44% and 45% respectively (Morris *et al.*, 2010, Norén *et al.*, 2016).

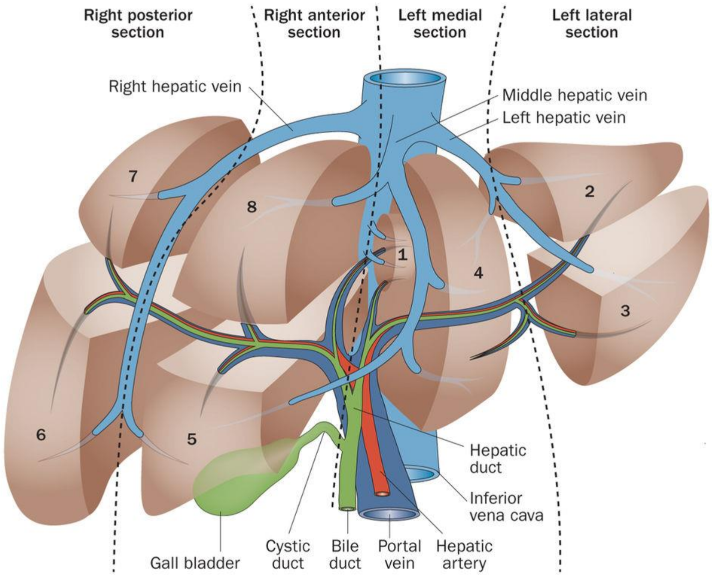
The comparison of survival in synchronous and metachronous disease is again limited by the lack of standardised definitions, however synchronicity is generally thought of to be a sign of poor prognosis, regardless of treatment (Manfredi *et al*., 2006, Adam *et al*., 2015). These patients have a cancer biology which is less favourable and therefore a reduced chance of long-term survival (Fong *et al.*, 1999). The natural history of patients with metachronous liver metastases is less well documented. The reporting of outcomes in this cohort is complicated by the fact it is generally accepted that a proportion of patients presenting with metachronous disease most likely had this at initial presentation. Similar to synchronous disease, however, liver resection is the most effective therapy with associated 5-year survival rates ranging from 28% to 58% (Mann *et al.*, 2007).

1.4 Treatment of colorectal cancer liver metastases

1.4.1 Surgical anatomy of the liver

Liver surgery is largely based on the contributions of two surgeon-anatomists, Couinaud (1957) and Healey (1953), to the understanding of liver anatomy. In their work on hepatic division, Couinaud used the portal and hepatic veins as the basis of division, while Healey used the hepatic arteries and bile ducts. The classification according to Couinaud, which has gained the widest acceptance, divides the liver into eight functional segments, each with its own blood supply, and venous and biliary drainage (Figure 1.1). Segment II, III and IV collectively form the functional left lobe of the liver, with the functional right lobe consisting of segments V, VI, VII and VIII. The caudate lobe, segment I, is located posteriorly.

Figure 1.1 The segments of the liver and the current surgical nomenclature. Image reproduced from Siriwardena et al. (2014).



1.4.2 Liver resection

There are no randomised controlled trials comparing surgical resection of liver metastases versus systemic treatment alone (Van Cutsem *et al.*, 2016). However, even in the absence of such, surgery is considered the gold-standard treatment for patients with CRC liver metastases.

Traditionally, liver resection was associated with high rates of morbidity and mortality, such that it was considered a challenging and high-risk procedure. The liver hosts the most complex vascular anatomy of any human organ, and consequently it has been control of haemorrhage, both in the past and present, which has posed the major challenge in liver surgery. The first successful hepatectomy was carried out by the German surgeon Carl Johann August Langenbeck (1888), who removed a left lobe lesion in 1888. Subsequent advances in blood transfusion services in the 20th century allowed the field of liver surgery to grow. Catell (1940) performed the first successful surgical excision of a CRC liver metastases in 1940, with the first left hepatectomy performed in 1941 and right hepatectomy in 1952 (Felekouras *et al.*, 2010).

Despite the anatomical discoveries of the 1950s, it was several decades until liver surgery gained momentum. This mainly relates to advances in techniques for the control and modulation of hepatic blood flow. In modern liver surgery, tumours that are positioned deep within liver parenchyma or close to critical vascular or biliary structures, may be resected with precision due to the use of specific tools such as the ultrasonic dissector, argon gas diathermy, magnifying loupes and intraoperative ultrasound, allowing precise delineation of the proper transection plane (Mentha *et al*., 2007, Aragon and Solomon, 2012). In addition, both the Pringle manoeuvre and the maintenance of low central venous pressure remain important adjunctive techniques in reducing blood loss during liver transection (Pringle, 1908).

1.4.2.1 Types of liver resection

1.4.2.1.1 Anatomical resection

Anatomic liver resections are largely based on our understanding of the liver segments as described by Couinaud. In an attempt to standardise definitions of anatomical liver resection, the Brisbane 2000 system was developed (Terminology Committee of the International Hepato-Pancreato-Biliary Association, 2000). This is a unified nomenclature for the classification of liver resection (as shown in Table 1.3), and has become generally accepted as a standardised reporting system.

Table 1.3 Nomenclature for hepatic anatomy and resections according to the Brisbane 2000 system (Terminology Committee of the International Hepato-Pancreato-Biliary Association, 2000)

Term for surgical resection	**Couinaud segments**
Right hepatectomy/ right hemihepatectomy	V, VI, VII, VIII
Left hepatectomy/ left hemihepatectomy	II, III, IV
Right anterior sectionectomy	V, VIII
Right posterior sectionectomy	VI, VII
Left median sectionectomy	VI
Left lateral sectionectomy	II, III
Segmentectomy	Any one of I - IX
Bisegmentectomy	Any two of I - IX in continuity
Right trisectionectomy/ extended hepatectomy/ extended hemihepatectomy	IV, V, VI, VII, VIII ± I
Left trisectionectomy/ extended hepatectomy/ extended hemihepatectomy	II, III, IV, V, VIII ± I

Many of the potential risks of liver resection relate to the volume of the remnant liver remaining. However, this measurement is inconsistent and is not reported in most resection series. The extent of resection is therefore used as a surrogate. Anatomical liver resections may be considered as ‘major’ or ‘minor’. Risk stratification by extent of resection has been used to analyse post-operative morbidity and mortality across multiple case series, with patients undergoing major liver resection at the highest risk of adverse outcomes (Aloia *et al.*, 2009). There is, however, a lack of consensus on the definitions of such terms with major liver resection being defined as the resection of two, three, four or five segments. Reddy *et al.* (2011) reported that the resection of four or more segments was independently associated with risk of post-operative morbidity and mortality. There were no significant differences in any post-operative outcome after resection of three, or two or fewer, segments. They therefore advocate that major hepatectomy should be defined as resection of four or more liver segments. Despite this, many recent reports continue to define major hepatectomy as resection of three or more segments. The 2014 recommendations from the Second International Consensus Conference on laparoscopic liver resection suggest the ‘classical definition’ for extent of liver resection should be used where a minor resection is the resection of two or fewer Couinaud segments, and major resection the resection of three or more (Wakabayashi, 2014).

1.4.2.1.2 Non-anatomical resection

Non-anatomic resection, also termed parenchymal-sparing hepatectomy, involves resection of the lesion along with a margin of uninvolved tissue (Alvarez *et al.*, 2016). This has the advantage of both preserving parenchyma and thus minimising the risk of post-operative hepatic insufficiency, and enabling a repeat hepatectomy at a later date if disease was to recur. Previously, this approach had raised concern for increased rates of local recurrence due to closer margins. This has not, however, been substantiated and in a recent study comparing outcomes of 156 CRC patients with a parenchyma-sparing approach to 144 patients undergoing an anatomical resection, the parenchyma sparing approach was not associated with recurrence in the liver remnant and in fact, improved 5-year survival in cases of recurrence (Mise *et al.*, 2016).

1.4.2.1.3 Laparoscopic liver resection

The use of laparoscopic techniques for liver resection has been relatively slow in comparison to other gastrointestinal surgical procedures where laparoscopy has been established as the standard of care (Wakabayashi *et al*., 2015a). Initial difficulties in laparoscopic liver resection related to the challenge of achieving haemostasis at the transection plane and controlling haemorrhage from intra-hepatic vessels. However, with advances in instrument technology and surgical technique, minimally invasive approaches for liver resection are now gaining momentum.

At the Second International Consensus Conference on laparoscopic liver resections held in 2014, the panel acknowledged that a minor liver resection performed laparoscopically has a sufficient safety and benefit record to achieve 'standard practice' level, whereas laparoscopic major resections were still to be considered innovative procedures with continued caution recommended for their introduction (Wakabayashi, 2014).

A recent meta-analysis of over 9000 cases showed a laparoscopic approach offered reduced overall rate of complications, blood loss, rate of transfusion, and hospital stay following minor resection, and reduced overall rate of complications, blood loss, and hospital stay following major resection (Ciria *et al.*, 2016). There were no observed differences in resection margins. There are several randomised controlled trials currently underway to evaluate the safety and the long-term oncological outcomes of laparoscopic liver resection in comparison to open surgery (Fretland *et al.*, 2015).

1.4.2.2 Complications associated with liver resection

Techniques to reduce blood loss and better understanding of hepatic anatomy have greatly improved the safety of liver resection. Post-operative mortality has gradually dropped from rates of 50% in 1963, to 20% in the 1990s (Thompson *et al.*, 1983, Fan *et al.*, 1995), to recent reports of up to zero mortality even for complex procedures (Imamura *et al*., 2003, Vauthey *et al*., 2004).

However, literature-based data on mortality may be misleading, as poor outcomes are less likely to be published. In an analysis of national mortality data following major hepatic resection in the United States (US) the mortality rate reported in the literature was found to be 3.6% compared to 5.6% in the National Inpatient Sample dataset (Asiyanbola *et al*., 2008). This suggests that actual population-based mortality rates may be higher than those reported in the literature. A recently published series of 4,152 patients undergoing liver resection reported a 90-day mortality of 5% before 1999, 2.3% from 2000 to 2006, continuing to decrease to 1.6% from 2007 to 2012 (Kingham *et al.*, 2015). In modern clinical practice, a patient undergoing liver resection would usually be advised of an associated 90-day mortality of 1-2%, with the exact figure depending on factors such as the extent of the liver resection, patient age and fitness, and the condition of the liver due to chemotherapy and cirrhosis (Dokmak *et al.*, 2013).

Despite the drop in mortality following liver resection, there remains significant associated morbidity, with large series reporting complications occurring in 24-56% of patients (Mullen *et al*., 2007, Dokmak *et al*., 2013, Kingham *et al*., 2015). This may partly reflect the increased complexity of modern liver surgery. Significant complications now more commonly relate to post-operative liver failure rather than bleeding. In a large recent series of patients undergoing liver resection, 23% of the 546 patients with CRC liver metastases experienced a serious complication (Clavien–Dindo class 3 or 4) (Dokmak *et al.*, 2013). Pulmonary complications were noted in 18% of patients, ascites in 18%, biliary fistula in 4%, liver failure in 2% and re-operation in 4%.

1.4.2.3 Criteria for resectability

Ultimately, eligibility for surgery is determined by taking into account three aspects: the operative risk to the patient, the technical resectability and the oncological benefit. The presence of four or more metastases within the liver, extra-hepatic disease, large size of hepatic metastases and the inability to achieve a cancer free resection margin (R0) were previously considered contraindications to resection (Ekberg *et al.*, 1986). However, over the past 10 years the criteria for defining resectability in patients with CRC liver metastases has been expanded (Pawlik *et al.*, 2008). Advances in systemic chemotherapy, and adjunctive techniques such as thermal ablation and portal vein embolisation have resulted in a paradigm shift in resectability. Now resectability is determined by whether complete resection of the disease may be performed and if an adequate liver remnant will remain following surgery.

Pawlik *et al.* (2008) suggest four main criteria that determine resectability:

1) Macroscopic and microscopic complete resection of the liver disease and any extra-hepatic metastases must be achievable
2) Two or more segments of the liver should be spared
3) Vascular inflow and outflow and biliary drainage must be preserved
4) The future liver remnant (FLR) (i.e. the volume of liver remaining after resection) must be adequate. This usually means at least 20% of the total estimated liver volume for normal parenchyma and between 30% and 60% if the liver has been injured by chemotherapy.

A multidisciplinary panel of experts meeting in 2012 proposed a new system, as shown in Table 1.4, for determining eligibility in a bid to simplify treatment decisions and standardise care across centres and reporting in clinical trials (Adam *et al.*, 2012).

Table 1.4 Contraindications to hepatic resection in patients with CRC liver metastases. Any patient should be categorised as A1 or A2/B1, B2, or B3. Adapted from Adam et al (2012).

Category	**Contraindication**
Technical (A)	
1. Absolute	Impossibility of R0 resection with 25%–30% liver remnant
	Presence of unresectable extrahepatic disease
2. Relative	R0 resection possible only with complex procedure (portal vein embolisation, two-stage hepatectomy, hepatectomy combined with ablation (includes all methods, including radiofrequency ablation)
Oncological (B)	
1.	Concomitant extrahepatic disease (resectable)
2.	Number of lesions ≥5
3.	Tumour progression

With regard to patient risk, medical fitness for general anaesthesia and major abdominal surgery should be carefully evaluated pre-operatively. Obese patients and those who have undergone previous chemotherapy, should be considered at increased risk and the volume of the predicted FLR should be appropriately adjusted (Tucker and Heaton, 2005).

1.4.3 Metachronous liver metastases

The management of patients with metachronous liver metastases is often considered more straightforward than in those with synchronous disease. Resectability will be assessed according to the criteria discussed above and a treatment plan will be formulated through discussion with a hepatobiliary multidisciplinary team (MDT) meeting. Metachronous liver metastases tend to be more commonly unilobar, and present in smaller numbers (Tsai *et al.*, 2007). This may relate to the fact that metachronous lesions are diagnosed when they are less advanced due to the regularity of post-operative follow up. The resection of liver metastases is performed more frequently in patients with metachronous than synchronous disease, (17% vs. 6%) (Manfredi *et al.*, 2006).

1.4.4 Synchronous liver metastases

The optimal management of patients diagnosed with CRC and synchronous liver-limited metastases is complex. There are multiple factors which must be considered, such as the presence of symptoms, the location and extent of the CRC primary and the liver metastases, and the patient's underlying fitness. Patients should be offered multimodal treatment as appropriate, comprising surgery, chemotherapy and, if the patient has rectal cancer, radiotherapy.

1.4.4.1 The timing of liver resection

Advances in radiological and surgical techniques, systemic chemotherapy and anaesthesia, over the last decade have allowed more possibilities in the management of CRC patients with synchronous liver metastases (Siriwardena *et al.*, 2014). Now, it is not only enough to decide if liver metastases are potentially amenable to surgical resection, but how the liver resection will be timed in relation to resection of the primary tumour must also be considered.

1.4.4.1.1 Bowel-first

The traditional management of CRC with synchronous liver-limited metastases involves the resection of the primary CRC followed by resection of the secondary liver metastases at a later date (Lambert *et al.*, 2000). This approach is termed the 'bowel-first', or the 'classical' approach. The rationale for this strategy is that the primary neoplasm should be managed first as the patient will have symptoms, such as partial obstruction, bleeding, lethargy and diarrhoea, therefore necessitating a timely bowel resection. Some studies have reported the rate of complications related to the primary CRC if resection is delayed, as high as 20% (McCahill *et al.*, 2012).

Within the bowel-first strategy, two approaches may be undertaken. The first involves resection of the primary tumour followed by a period of recovery and then a liver resection.

No systemic treatment is given between the surgical procedures. This is mainly undertaken when technical considerations, such as a CRC resection involving pelvic dissection, or the necessity to perform a major liver resection, preclude a simultaneous resection. The second approach, the delayed approach, involves administration of chemotherapy between the two operations. Scheele *et al.* (1995) advocate a ‘test of time’ strategy, where 3 to 6 months is waited following primary resection before liver resection, acting as a means of natural selection for operable disease.

A commonly cited disadvantage of the bowel-first approach, particularly with a delay, is the potential for progression of the liver metastases beyond resectability whilst dealing with the primary tumour. This may not be the case however, as a study of 318 patients with CRC liver metastases, 73 of whom had resectable disease, did not show any patients undergoing delayed resection of synchronous liver metastases to become unresectable due to the growth of initial metastases (Lambert *et al.*, 2000). This may be more of a concern however in patients who have a delay in systemic chemotherapy owing to morbidity associated with the CRC resection.

1.4.4.1.2 Simultaneous resection

The ‘simultaneous’ approach involves the resection of the liver metastases and CRC in the same procedure and may provide several advantages to both patients and healthcare providers. This strategy involves only one anaesthetic and post-operative recovery period, reduced overall hospital stay and possible reduction of healthcare resources (Martin *et al*., 2003, Reddy *et al*., 2007, Slesser *et al*., 2013). A simultaneous approach can be adopted with or without neoadjuvant treatment.

Even when a margin free liver resection appears technically achievable at the time of surgery for the primary CRC, the patient will not benefit from surgical resection if occult extrahepatic disease is present (Alberts and Poston, 2011). Proponents of a staged approach argue that delaying the resection of synchronous disease may allow such disease to become clinically overt (Lambert *et al.*, 2000). In this approach patients in whom disease becomes irresectable in this interval may be spared from undergoing an operation, with its associated risks, which would not provide a survival benefit. A simultaneous resection also increases the complexity of the surgical procedure as well as the operative time. This approach can increase the risk of infected haematoma due to contamination from translocation of intestinal bacteria (Klein *et al.*, 2012). In addition, the Pringle manoeuvre causes an increase in portal hypertension thus resulting in intestinal oedema, potentially compromising the colonic anastomosis (Nakajima *et al.*, 2012).

1.4.4.1.3 Liver-first

Recently there has been increasing interest in the 'liver-first', or 'reverse' approach as first described by Mentha *et al. (2006)*. This is where liver metastases are resected, usually after a period of down-staging chemotherapy, before resection of the primary.

Whether further disease progression is driven by the primary CRC or by the liver metastases is an important consideration in the adoption of the liver-first approach. This strategy is based on a belief that it is the metastatic disease, and not the primary CRC, which results in further systemic metastases and thus determining the patient's survival (de Jong *et al.*, 2011). It is postulated that the primary tumour produces anti-angiogenic molecules and with resection this inhibition is lost thus resulting in proliferation of metastases (Peeters *et al.*, 2006). The evidence to support this concept is limited however, and there is counter-evidence to suggest the presence of the primary tumour drives an angiogenic environment in the liver, perpetuating metastatic tumour growth (van der Wal *et al.*, 2012).

A more accurate description of the liver-first approach would in fact be the 'chemotherapy-first approach'. Preoperative systemic chemotherapy will treat both the CRC primary and the liver metastases. The liver-first strategy particularly lends itself to a rectal cancer primary as the post-radiation waiting period provides a window of opportunity for a liver resection procedure (Jegatheeswaran *et al.*, 2013). The increasing use of colonic stenting also facilitates the use of the liver-first strategy. Stents can palliate symptoms of partial obstruction without the need for surgery therefore allowing patients to be candidates for systemic chemotherapy at an early stage in their treatment pathway (Karoui *et al.*, 2007). Patients with non-obstructive colonic cancer with extensive liver disease that necessitates down-staging to achieve negative margins may also benefit from this approach as it could provide a narrow window of resectability (De Rosa *et al.*, 2013).

1.4.4.2 Decisions regarding strategy

NICE recommends that the decision on whether a patient has a synchronous or staged approach to resecting their CRC and liver metastases should be made by the site-specialist MDTs in consultation with the patient (National Institute for Health and Care Excellence, 2014). Due to the differences in patient and disease characteristics in those typically considered eligible for a liver-first or simultaneous approach, very few patients would be a candidate for all three strategies. In most clinical circumstances the choice of strategy for an individual patient is between the bowel-first approach and the liver-first approach, or the bowel-first approach and the simultaneous approach. The optimal timing of resection of liver metastases from CRC has been identified as a research priority in a modified Delphi approach by the Association of Coloproctology of Great Britain and Ireland (ACPGBI) (Tiernan *et al.*, 2014).

1.4.4.3 Outcomes according to surgical strategy

When considering the surgical approach for patients with synchronous CRC liver metastases the associated post-operative and oncological outcomes should be considered. Early reports comparing the bowel-first and the synchronous approach predate the use of neoadjuvant chemotherapy and more sophisticated imaging modalities such as PET-CT, and therefore the findings are no longer generally applicable. For example, Norlinger *et al.* (1996) compared outcomes in 115 patients undergoing a simultaneous approach to 893 patients with a bowel-first approach. The 90-day mortality reported in the simultaneous group was significantly higher at 7% compared to 2% in the bowel-first group.

Ten years later, Reddy *et al. (2007)* published one of the largest studies to date comparing the post-operative outcomes from 135 simultaneous and 475 staged patients undergoing liver resection across three hepatobiliary institutions. Rates of 90-day mortality were similar following simultaneous CRC resection and minor liver resection compared to minor liver resection alone (1% vs. 0.5%), whereas for major liver resection, simultaneous CRC resection significantly increased mortality (8.3% vs. 1.4%). Conversely Capussotti *et al.* (2007) compared outcomes in 31 patients undergoing simultaneous major hepatectomy and primary CRC resection, and 48 who underwent delayed major hepatectomy. They reported no difference in mortality between the groups, with 0% mortality in the 9 patients undergoing major hepatectomy concurrently with anterior rectal resection. Thelen *et al.* (2007) reported outcomes in 219 patients, 40 of whom underwent simultaneous resection and 179 bowel-first approach. They found the mortality to be significantly higher (10% vs. 1%) in patients undergoing simultaneous approach, with all patients who died in this group undergoing a major resection. These authors also reported 5-year survival of 53% in the simultaneous group and 39% in the bowel-first group, but this was not a statistically significant difference.

Similar studies published in more recent years have described no difference between 90-day mortality across surgical strategies, even when including major liver resection in the simultaneous group (Martin *et al.*, 2009). To control for the often wide differences in patient characteristics in patients undergoing a simultaneous or bowel-first approach, Moug *et al.* (2010) performed a case-matched analysis of 32 patients undergoing a simultaneous approach to bowel-first patients, demonstrating no difference in 90-day mortality and comparable median survival (39 months in the synchronous group vs. 42 months in the bowel-first group).

Several recent studies have also reported the outcomes of patients undergoing a liver-first approach. These demonstrate a wide range of reported long-term survival, but appear to show similar long-term outcomes when compared to patients undergoing a bowel-first approach. Andres *et al.* (2012), using data from the LiverMetSurvey, a prospective international registry of patients undergoing surgery for CRC liver metastases, compared patients with two or more liver metastases diagnosed from 2000 to 2010, including 729 in the bowel-first group, and 58 in the liver-first group. Overall survival and disease-free survival were reportedly similar in the liver-first and bowel-first group (48% vs. 46% and 30% vs. 26% at 5 years respectively). Two systematic reviews reporting the outcomes of patients treated with the liver-first approach showed 5-year overall survival rates to range widely from 31% to 89% despite apparently similar protocols (Lam *et al*., 2010, Jegatheeswaran *et al*., 2013). Welsh *et al.* (2016) in a propensity score-matched analysis of outcomes of the liver-first approach, reported that after matching according to the Basingstoke Predictive Index, there was no difference in long-term outcomes between the liver-first and bowel-first approach.

There are only three studies published to date comparing the outcomes of the three strategies. Brouquet *et al.* (2010) compared the post-operative mortality and 5-year survival in 156 consecutive patients. In this cohort, 73 patients underwent a bowel-first approach, 43 a simultaneous resection and 27 a liver-first approach. There was no significant difference in 90-day mortality (5%, 3% and 1% respectively). The authors grouped patients undergoing either a bowel or liver resection into a single ‘staged’ group for the analysis of long-term outcomes. There was similarly no difference in 5-year survival between the staged and simultaneous group with reported rates of 48% and 55% respectively. In the same year, van der Pool *et al.* (2010) published an analysis of the outcomes of rectal cancer patients, in whom

29 patients had a bowel-first approach, 8 a simultaneous approach and 20 patients a liver-first approach. The authors reported no in-hospital mortality associated with any strategy and 5-year survival rates of 28% (bowel-first) 73% (simultaneous) and 67% (liver-first). In the largest study to date comparing the use of the three strategies, Mayo *et al.* (2013) analysed 1,004 patients with synchronous CRC liver metastases undergoing surgical management across 4 institutions. Of the 647 patients who had a bowel-first approach, 28 liver-first and 329 simultaneous resection, there was no significant difference in 90-day mortality (3%, 0% and 3% respectively). There was also no difference in 5-year survival in patients managed with simultaneous or staged approach (42% vs. 44%) (Mayo *et al.*, 2013).

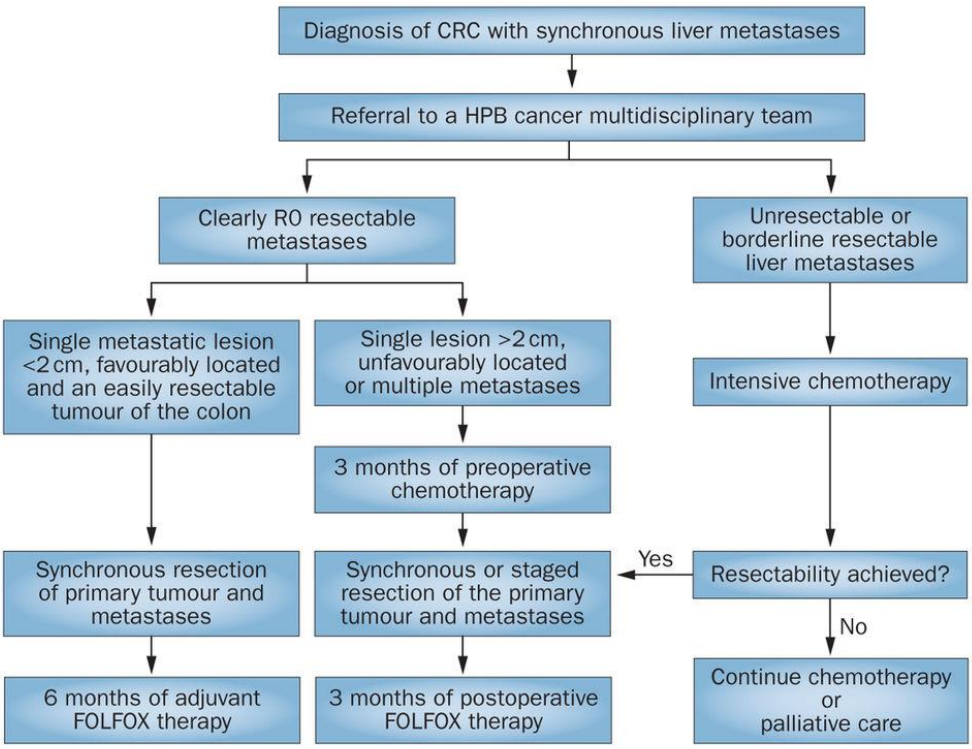
Although there appears to be evidential equipoise around the three surgical treatment options, these previous studies are largely single institution, include patients diagnosed over a long time period and have very small numbers in the liver-first or simultaneous group, or they group the liver-first and bowel-first patients together as a ‘staged’ cohort. The limited studies previously comparing survival between the three strategies are also hampered by direct comparison of strategies without accounting for selection bias.

1.4.4.4 Current recommendations

As with many aspects of modern hepatic surgery, there are no randomised control trials guiding clinicians in the selection of surgical strategy (Alberts and Poston, 2011). It is generally accepted that a practical approach should be taken to these decisions based on the nature of the surgery required (Pathak *et al.*, 2010). Patient fitness and the anatomical location and extent of liver metastases and primary CRC largely govern which of the alternative strategies is a possible treatment option. However, there are certain clinical situations in which it is generally agreed a staged approach would be indicated. When a patient is found to have synchronous liver metastases at the time of emergency CRC resection it would not be considered appropriate to resect liver metastases in a simultaneous procedure. These patients have a high likelihood of extra-hepatic and peritoneal disease, and, due to their emergency presentation, may have not have undergone thorough pre-operative staging. In addition, in patients in whom there is a higher risk of post-operative hepatic failure, such as those with cirrhosis, it would be inadvisable to perform a synchronous bowel and liver resection.

The European Society for Medical Oncology published a suggested treatment algorithm in 2012 for patients with synchronous liver metastases (Schmoll *et al.*, 2012). A modified version by Siriwardena *et al.* (2014) is shown in Figure 1.2. In summary, this suggests that patients with clearly R0 resectable metastases who have a single metastatic lesion less than 2cm which is favourably located and an easily resectable tumour of the colon, should be considered for synchronous resection followed by adjuvant chemotherapy. Patients with a greater burden of liver disease, even if resectable are suggested to undergo neoadjuvant systemic chemotherapy followed by a staged resection.

Figure 1.2 A flowchart of recommended management of patients with CRC and liver-limited metastases from Siriwardena et al. (2014)



More recently consensus recommendations formulated using a modified Delphi by a multidisciplinary expert panel for the management of patients with CRC and synchronous liver metastases were published (Adam *et al.*, 2015). This group suggested that a simultaneous approach would not be advocated for patients with resectable liver metastases and an asymptomatic CRC requiring complex surgery, in high-risk patients, or for those when hepatectomy would be major. They advise that simultaneous resections may be considered in selected patients requiring limited hepatectomy. No guidelines exist regarding the use of the liver-first approach.

1.4.5 Strategies to improve resectability

It is estimated that only around 10-30% of patients presenting with CRC liver metastases are candidates for curative resection (Adam and Vinet, 2004, Simmonds *et al.*, 2006). A multimodal approach which includes chemotherapy and aggressive surgical techniques may improve resectability rates by 10-50% in patients with bilobar metastases who would otherwise not be candidates for a curative approach (Karoui *et al.*, 2010).

1.4.5.1 Conversion chemotherapy

Patients with initially unresectable CRC liver metastases who sufficiently respond to chemotherapy to allow surgical resection have superior long-term survival to patients treated with chemotherapy alone (Nordlinger *et al.*, 2007). Therefore systemic chemotherapy, given with the aim of converting unresectable liver metastases to resectable, may be given to patients with liver-limited disease who would otherwise be a candidate for curative treatment (Van Cutsem *et al.*, 2016). Adam *et al.* (2004) reported that 138 out of 1,104 patients (12.5%) with initially unresectable disease managed at a single centre over an 11-year period, underwent liver resection after treatment with either FOLFOX (folinic acid (leucovorin), fluorouracil (5-FU), oxaliplatin) or FOLFIRI (folinic acid, 5-FU, irinotecan). The authors reported 5- and 10-

year survival rates of 33% and 23 % respectively in these patients, only slightly lower than that in patients with initially resectable disease.

1.4.5.2 Portal vein embolisation

Many patients with extensive liver metastases may not be candidates for surgical resection at initial presentation due to insufficient FLR volume; a strong, independent predictor of post-operative hepatic dysfunction (Shoup *et al.*, 2003). As outlined in the criteria for resectability described above, an adequate FLR volume, usually at least 20% of the total estimated liver volume for normal parenchyma, must remain following liver resection. Portal vein embolisation (PVE) is an image guided procedure used in patients with marginal FLR. The procedure uses embolisation to induce atrophy of the lobe of the liver to be resected and thus resulting in hypertrophy of the non-embolised lobe. The use of PVE may allow major hepatectomy in patients with previously technically unresectable disease due to small FLR, as well as lowering the risk of liver insufficiently post-operatively due to borderline FLR (Adam *et al.*, 2015). PVE is usually performed under conscious sedation by interventional radiologists, with resection typically occurring 3-6 weeks following embolisation. The overall technical and clinical success rate of PVE are reportedly close to 100% with 85% of patients proceeding to liver resection (van Lienden *et al.*, 2013).

1.4.5.3 Two stage hepatectomy

A two-stage hepatectomy can accomplish complete resection of liver metastases previously deemed unresectable because the remnant liver volume would be too small (Adam *et al.*, 2000). The first-stage is resection of all metastases from the part of the liver which will constitute the FLR in the form of minor metastasectomy with or without locally destructive techniques. In patients with synchronous disease this first stage may be combined with bowel resection. This may be followed by PVE to induce primary hypertrophy of the future liver, thus allowing the second-stage resection to be completed with minimal risk of post-operative hepatic insufficiency. The second stage is completed in 76-87% of patients undergoing stage one. For patients who complete the second stage, long-term survival is equivalent to patients with more limited disease treated with a conventional single-stage strategy (Brouquet *et al.*, 2011).

1.4.6 Loco-regional therapies

Loco-regional, also known as liver-directed, therapies may be used in patients with unresectable liver metastases to prolong survival, and also as adjuncts to surgical resection to aid local control in patients with resectable disease. The most common loco-regional therapies: ablation and intra-arterial therapy are discussed below.

1.4.6.1 Ablative therapies

Ablative therapy involves the delivery of localised destructive treatment to a tumour. The precise role of ablative techniques is not clearly defined but common consensus is that its use should be limited to an adjunct to surgery in patients with widespread disease or a means of achieving local control in patients with unresectable disease either due to wide-spread liver metastases or extra-hepatic disease (Pathak *et al.*, 2011). While radiofrequency ablation (RFA) and microwave ablation (MWA) are the most commonly used ablative therapies, there are a range of additional techniques, including high intensity focused ultrasound (HIFU), irreversible electroporation therapy (IRE) (Nanoknife), focussed radiotherapy (Cyberknife), cryoablation and laser ablation.

RFA is the most widely used tumour ablation technique. It involves applying localised high frequency alternating current to the tumour to produce heat, resulting in coagulative necrosis (Guenette and Dupuy, 2010). Ten-year follow-up results of the randomised phase II European Organisation for Research and Treatment of Cancer (EORTC) 40004 CLOCC study demonstrated a promising role for ablation in patients who are ineligible for resection. Patients with unresectable CRC liver metastases were randomly assigned to systemic treatment alone (standard arm) or systemic treatment plus local treatment by RFA with or without additional resection (experimental arm). Progression-free survival was improved in the experimental arm at 16.8 months, compared to 9.9 months in the standard arm (Ruers *et al.*, 2010).

Due to concerns regarding a high rate of local recurrence (local recurrence rates of 47% following ablation have been demonstrated compared to 13% after surgery (Nishiwada *et al.*, 2014)), RFA is not currently used as an alternative to surgical resection in patients with potentially operable disease (Lee *et al.*, 2015).

There is evidence to suggest that RFA is associated with lower complication rates and an improved health-related quality of life than surgery (Loveman *et al.*, 2014). It has therefore been proposed that ablation may be a feasible alternative to surgery in high-risk patients who would currently be considered for liver resection but are likely to have poorer short- and long-term outcomes after surgery. The LAVA (**L**iver **R**esection Surgery Versus Thermal Ablation for Colorectal Li**V**er Met**A**stases) trial is currently seeking to address this (ISRCTN registry, 2017).

MWA uses heat generated by microwaves for localised destruction of the tumour (Petre and Sofocleous, 2017). MWA has been reported to have lower rates of local recurrence and major complications than RFA but a higher rate of minor complications (Pathak *et al.*, 2011). There is a single randomised controlled trial comparing MWA to liver resection, which suggested MWA to be equally effective in the treatment of CRC liver metastases (Shibata *et al.*, 2000). These findings are limited however, as the trial did not describe allocation concealment or blinding, and excluded 25% of participants from analysis after random assignment (Bala *et al.*, 2013).

1.4.6.2 Intra-arterial therapy

The concept of intra-arterial therapy is based on the knowledge that the blood supply to hepatic tumours originates predominantly from the hepatic artery, in contrast to normal healthy liver tissue which is supplied by the portal vein (Ackerman, 1974).

Hepatic artery infusion (HAI) therapy involves directed chemotherapy (either 5-FU or leucovorin) via a pump attached to a catheter which gets implanted through the gastroduodenal artery. The administration of therapy via the hepatic arterial system may enhance drug delivery to the tumour and reduce the occurrence of systemic side-effects. A Cochrane review of randomised trials reported that despite an improved tumour response rate in patients treated with HAI when compared to systemic chemotherapy, HAI does not provide a survival advantage over systemic chemotherapy in patients with unresectable CRC liver metastases (Mocellin *et al.*, 2009). HAI has therefore not gained widespread acceptance.

Transarterial chemoembolisation (TACE) involves selective administration of chemotherapy, usually combined with embolisation of the hepatic artery, resulting in ischemic and chemotherapeutic effects on liver metastases, leaving normal parenchyma virtually unaffected. Fiorentini *et al.* (2012) randomly assigned 74 patients with CRC liver metastases to either receive TACE in the form of irinotecan loaded drug-eluting beads (DEBIRI) or systemic chemotherapy. At 50 months, overall survival was significantly longer for patients treated with DEBIRI than for those treated with systemic chemotherapy. No trials have yet compared liver resection with TACE.

Selective internal radiation therapy (SIRT) is a form of brachytherapy in which the radiation source yttrium-90 is coupled with an embolic particle, termed a microsphere. This allows the delivery of the therapeutic dose of radiotherapy to the tumour to induce cytotoxicity with minimal damage to the uninvolved tissues. At present, patients are not eligible to receive SIRT funded by the National Health Service (NHS). A randomised trial of 74 patients with nonresectable CRC liver metastases by Gray *et al.* (2001) demonstrated that those randomised to HAI with floxuridine with the addition of SIRT had significantly improved response rate and time to progression of disease within the liver than those undergoing HAI with no SIRT. There was, however, no improvement in overall survival.

1.4.7 Hepatic transplant

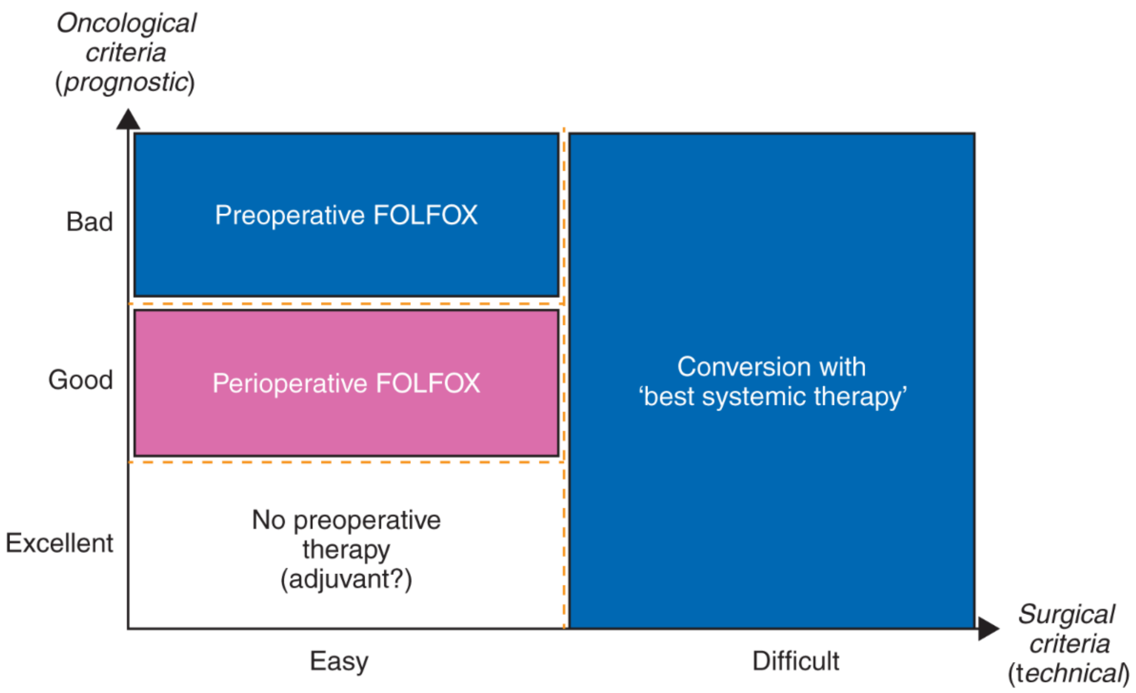
A small number of patients with unresectable CRC liver metastases have undergone liver transplantation. Transplantation in this cohort has been the subject of a recent systematic review which pooled the results of 11 studies including 66 patients (Moris *et al.*, 2017). The largest study, conducted by Muhlbacher *et al.* (1991) which included 25 patients, reported 1-, 3- and 5-year post-transplant survival of 76%, 32% and 12% respectively (Muhlbacher *et al.*, 1991). A more recent study of 21 patients by Hagness *et al.* (2013) reported superior survival with 1-, 3- and 5-year post-transplant survival of 95%, 68% and 60% respectively (Hagness *et al.*, 2013). Recurrence, however, across all studies was high at 67%, with time to recurrence being less than a year in most cases. The most common site of recurrence was the lung. As there are only a small number of patients who have undergone transplantation for CRC liver metastases, a lack of comparative studies and a shortage of donor organs, liver transplantation is not currently supported in patients with unresectable CRC liver metastases.

1.4.8 Systemic chemotherapy in patients with resectable liver metastases

Although treatment decisions regarding liver resection must be made with consideration of the role of systemic chemotherapy, optimal practice remains undefined. The EPOC (EORTC 40983) trial compared oxaliplatin/5FU given both prior to and after surgery, to surgery alone in patients with liver-limited CRC liver metastases, and reported a marginal improvement in progression free survival in the chemotherapy group (Nordlinger *et al.*, 2008). The new EPOC trial which compared patients with resectable liver metastases all of whom received peri-operative chemotherapy either with or without the addition of the biological agent cetuximab, closed early after revealing a worse disease free survival in the cetuximab group (Primrose *et al*., 2014a).

The detailed use of systemic chemotherapy in patients with liver metastases is outside the remit of this thesis. However, in brief, European Society for Medical Oncology (ESMO) guidelines recommend decisions regarding the use of peri-operative chemotherapy should be based on prognostic and surgical considerations, as shown in Figure 1.3 (Van Cutsem *et al*., 2016). Prognostic considerations relate to the FONG score (Fong *et al*., 1999), as discussed below, with surgical criteria based on the technical difficultly of resection. Patients with easily resectable liver metastases with an excellent prognosis often proceed directly to liver resection with no pre-operative therapy.

Figure 1.3 Categorisation of patients according to technical and oncological criteria. FOLFOX (5-fluorouracil, leucovorin, oxaliplatin). Adapted from Van Cutsem et al. (2016).



1.4.9 Recurrence

Although a proportion of patients following liver resection will achieve long-term cure, disease will recur in 50-70% of patients, with the majority in the first 2 years (Galjart *et al.*, 2016). The mechanism of recurrence includes involved resection margins, missed or undetected lesions at the first resection, or natural progression of micrometastases from the primary colorectal tumour (Lintoiu-Ursut *et al.*, 2015).

Despite a patient having technically resectable disease, the concern remains that not all patients with technically resectable disease will actually benefit from surgical resection. Fong *et al.* (1999) developed a clinical score to predict recurrence after hepatic resection identifying seven factors with a significant impact on survival. Positive margin and the presence of extrahepatic disease, both increased risk of death by 1.7 times, and thus were suggested to be a relative contraindication to resection. The five factors contributing to the overall score were lymph node positive primary, <12 months disease-free interval from primary to metastases, number of hepatic tumours >1, size of hepatic tumour >5cm and CEA >200ng/ml. A scoring system assigning 1 point for each of the five factors was devised with patients scoring 0 points having a 5-year survival of 60% vs. 14% in patients with 5 points. Although this score is not routinely used in decisions regarding patient selection for resection, it may highlight patients in whom neoadjuvant chemotherapy is a better option than upfront surgery.

The overall strategy for managing patients with disease recurrence is the same as that for the first presentation of metachronous liver metastases and involves full staging followed by discussion at an MDT meeting. Surgical resection is the treatment of choice and up to 40% of patients with disease recurrence will be candidates for re-resection (Viganò *et al.*, 2014).

1.5 Care provision in England

1.5.1 Colorectal cancer multidisciplinary team

In the mid-1990s two documents were published that had a significant impact on the structure and provision of cancer care within the NHS. The Calman-Hine report from the Department of Health (1995) and the Guidance on Commissioning Cancer Services from NHS Executive (1997) were strategic frameworks for creating a network of cancer care in England and Wales. They led to significant changes in the way that care was provided, from being predominantly organised and delivered by individual surgeons, to a MDT based approach.

It is now expected that the management of all patients with CRC should be the responsibility of a CRC MDT (National Institute for Health and Care Excellence, 2004). The MDT model is a patient-centred approach in which relevant specialists will work together to identify the appropriate tests and treatment options available. Important benefits to patients with CRC from effective MDT working have been identified, including enhanced quality of life (Rummans *et al.*, 2006), increased use of adjuvant chemotherapy (MacDermid *et al.*, 2009)' and improved post-operative (Wille-Jørgensen *et al.*, 2013) and long-term survival (Munro *et al.*, 2015). The importance of MDT assessment for patients with metastatic CRC has also been demonstrated. In a population-based study of Swedish registry data, patients with metastatic CRC discussed in a CRC MDT were more commonly referred for surgery to resect secondary metastases than those who were not (Segelman *et al.*, 2009). The extent of the implementation of the Calman-Hine report has been studied in a region of England, and although its recommendations were found to be associated with improvements in processes and outcomes of care for CRC patients, the extent of implementation was reportedly variable (Morris *et al.*, 2006).

CRC MDTs should consist of a core team of members who have particular interest and expertise in this area. Core members of the team include CRC surgeons, an oncologist, a diagnostic radiologist, a pathologist, clinical nurse specialists and a meeting co-ordinator (The Association of Coloproctology of Great Britain and Ireland, 2007). Every patient with a new diagnosis of CRC should be discussed as well as patients with newly identified recurrent or metastatic disease. This team will determine whether a patient has clearly resectable, borderline resection or unresectable metastatic disease and if referral to a further specialist team is warranted.

There are more than 1500 cancer MDTs currently active in the United Kingdom, and the annual cost, in staff time alone, is over £100 million (Taylor *et al*., 2010). As well as being resource intensive, a scarcity of administrative support and variable team member attendance may be further barriers to efficient MDT functioning. In a 2004 report, half of the UK Cancer Networks surveyed described an absence of administrative support for MDTs and problems with MDT coordinator funding (National Audit Office, 2002). Attendance at colorectal MDT meetings is particularly variable with some core members, especially oncologists, reportedly participating infrequently (Kelly *et al*., 2003).

1.5.2 Organisation of hepatobiliary services

At the same time that CRC services were being overhauled within the NHS, it was recognised that upper gastrointestinal (UGI) (an umbrella term for oesophagogastric and hepatobiliary) cancer services in England were fragmented in their delivery and complex UGI procedures were often being undertaken by general surgeons working as lone practitioners in small and medium sized hospitals (Siriwardena, 2007). Multiple studies have demonstrated an association between hospital volume and operative mortality following certain surgical procedures (Birkmeyer *et al.*, 2002), with much of the apparent effect attributable to individual surgeon volume (Birkmeyer *et al.*, 2003). Evidence of the impact of high-volume providers on patient outcome following both oesophagogastric and hepatobiliary procedures led to major changes in UGI cancer service structure at the turn of the millennium (Strong *et al*., 1994, Sosa *et al*., 1998).

In 2001 the Clinical Outcomes Group in the UK set out a reform strategy including several specific recommendations, primarily that UGI services should be delivered by units with sufficiently large catchment populations (Department of Health, 2001). This move toward service centralisation, with the aim of concentrating skills, technologies and MDT in one location, led to major changes in the delivery of UGI cancer services in England (Palser *et al*., 2009). Membership of the hepatobiliary MDT usually consists of two or more specialist liver surgeons, a diagnostic and interventional radiologist with expertise in hepatobiliary disease, an oncologist, a histopathologist and a clinical nurse specialist (Garden *et al.*, 2006). The Association of Upper Gastrointestinal Surgeons (AUGIS) (2016) now recommends each hepatobiliary centre in the UK should serve a minimum population of two million, and should be performing in excess of 100 liver resection for primary and metastatic liver tumours per year. In recently published plans to improve cancer services, the NHS in England has recommended an evaluation of whether cancer surgery would benefit from further centralisation (NHS England, 2016).

1.5.3 Referral practices

It is expected that each CRC MDT should identify a hepatobiliary MDT which will receive referrals and provide surgery for patients suitable for hepatic resection. In addition to this a liver surgeon is considered part of the 'extended team' of a CRC MDT (The Association of Coloproctology of Great Britain and Ireland, 2007). NICE (2011a) have published guidelines regarding the referral of patients with metastatic CRC to specialist MDTs. These state that "if both primary and metastatic tumours are considered resectable, anatomical site-specific MDTs should consider initial systemic treatment followed by surgery, after full discussion with the patient". There may also be specific guidelines issued from individual hepatobiliary MDTs to their referring CRC MDTs regarding referral criteria. It is important that any decisions regarding the planning of treatment from both the CRC MDT and the hepatobiliary MDT are communicated effectively to patients in a prompt manner.

1.6 Factors influencing surgical resection rate

The true number of patients presenting with CRC liver metastases who have potentially surgically resectable disease is not known. Neoadjuvant down-staging chemotherapy, two-stage hepatectomy and portal vein embolisation have resulted in a patient subgroup with potentially resectable disease who were previously thought to be ineligible for surgery. These advances may have increased the proportion of patients for whom surgical resection is possible by up to 20% (Bismuth *et al*., 1996, Fusai and Davidson, 2003, Adam *et al*., 2004). Improvements in pre-operative staging and increased utilisation of PET-CT may conversely have reduced the number of patients classified as having potentially resectable disease due to better detection of irresectable disseminated disease at presentation (Lykoudis *et al.*, 2014). Population based studies from Sweden and the US reported 4% and 6% of patients with CRC undergo liver resection respectively (Cummings *et al.*, 2007, Hackl *et al.*, 2011). There is evidence to suggest that liver resection in patients with CRC liver metastases may be under-utilised (Morris *et al*., 2010). The advances in patient management, the expanding criteria for resection and the centralisation of hepatobiliary services have resulted in new complexities for CRC MDTs in the management of patients with CRC liver metastases.

1.6.1 Inter-hospital and geographical variation in liver resection rates

The NBOCA reports wide inter-hospital and regional variation in many aspects of the management and outcomes in patients with CRC in England and Wales. Two-year mortality rates are particularly variable and it may be that the care received by patients with metastatic disease contributes towards this disparity (nboca.org.uk, 2016). It is known that the implementation of guidelines has the potential to influence the utilisation of surgery and reduce variation in patient care across geographic areas (Reames *et al.*, 2014). Therefore, the lack of consensus guidelines in many aspects of the management of patients with CRC liver metastases may contribute to regional variation in care in this patient cohort.

Regional variation in liver resection rates in CRC patients was initially studied by Morris *et al.* (2010). The reported liver resection rates amongst 114,115 patients undergoing major resection for CRC in the English NHS between 1998 and 2004 varied significantly across regions (1.1-4.3%) and hospitals (0.7-6.8%). Significant variation in rates of liver resection has also been reported in more recent studies of European cohorts ('t Lam-Boer *et al*., 2015, Norén *et al*., 2016, Angelsen *et al*., 2017). Although Noren *et al.* (2016) reported similar liver resection rates across regions of Sweden in 3,149 patients with liver-limited synchronous CRC liver metastases, patients treated at university hospitals were more likely to undergo liver resection than those treated at district hospitals thus contributing to inter-hospital variation in care. In a study of 10,520 patients in the Netherlands Cancer Registry with synchronous CRC liver metastases, t' Lam-Boer *et al.* (2015) reported inter-hospital variation of 2-26% in liver resection rates.

1.6.2 Advancing age

The fastest growing subset of the Western population is that of people living over the age of 65 years. Although the overall age structure of the population is evolving, the common cancer types will remain, such that CRC will continue to be the third most common cancer diagnosis (Anaya *et al.*, 2011). Therefore, the number of elderly patients requiring CRC treatment is likely to rise substantially. At present, the median age for diagnosis of CRC in England is 72 years with over 40% of patients aged 75 years or over at diagnosis (nboca.org.uk, 2016).

The effect of an aging population on the epidemiology of CRC liver metastases has not been formally studied, however considering the growth of the elderly population and improvement in diagnostic techniques, the number of elderly patients with CRC liver metastases will likely increase over the coming years. Long-term survival in patients with synchronous metastatic CRC appears to be improving in younger patients. The same trend, however, is not seen in the elderly population, thus raising concerns over our ability to adapt available treatments for older patients (Sorbye *et al.*, 2013).

Studies have consistently demonstrated elderly patients to be less likely to undergo liver resection than younger patients (Leporrier *et al.*, 2006, Morris *et al.*, 2010, Norén *et al*., 2016, Angelsen *et al*., 2017). Morris *et al.* (2010) reported each 10-year increase in age of CRC patients to be associated with an odds ratio (OR) of 0.63 for undergoing liver resection.

This negative selection towards elderly patients may be clinically appropriate. Liver surgery is not without risk, and must be balanced against the potential for improvement in survival. The aging process is associated with a gradual decline in organ system reserve and our ability to respond to stressful stimuli (Leal *et al.*, 2016). In terms of the liver, advancing age is associated with a decline in physiological reserve, alterations in hepatic microcirculation, and a reduction in liver volume, capacity to eliminate free radicals and response to growth factors (Aalami *et al*., 2003, Schmucker and Sanchez, 2011). This is thought to result in delayed hepatic regeneration in the elderly population, leading some to question whether advanced age should be a relative contraindication to liver resection (Petrowsky and Clavien, 2005). As our understanding of the biology of liver repair in the elderly has developed, so too has critical care management, thus improving operative safety.

The current evidence regarding the outcomes of elderly patients undergoing hepatectomy is conflicting and studies evaluating liver resection for CRC liver metastases in this group specifically present differing results. In studies including both minor and major liver resection there are reports that age has no association with 90-day mortality (Leal *et al.*, 2016) and conversely that advancing age is associated with a poor outcome (Booth *et al.*, 2015, Cook *et* *al*., 2012). Similarly, in studies restricted to major hepatic resection there are reports showing no association between advancing age and 90-day mortality (Menon *et al*., 2006, Bell *et al*., 2017) and that age is independently associated with increased risk of 90-day mortality (Reddy *et al*., 2011a).

Many of these previous studies are single centre, categorise patients into one of two groups based on an age cut off (usually 70 years) and include only a small number of patients in the elderly group. Also, due to an under-representation of high-risk patients in such studies, it is acknowledged that these results may not be realised in the general population (Asiyanbola *et al*., 2008).

There is a paucity of population-based studies reporting outcomes in this cohort. Those that are published restrict the analysis to patients 65 years and older or do not describe outcome according to age group. In a recent population-based study, Booth *et al.* (2017) studied 1,310 patients classified into three age groups, younger than 65 years, 65 to 74 years, and 75 years or older, undergoing liver resection for CRC liver metastases between 2002 and 2009 in Ontario, Canada. There were comparatively few patients aged 75 years and older included (n=174). In addition, the role of minimally invasive, and parenchyma sparing techniques in liver resection in the elderly population has not been established.

1.6.3 Social deprivation

Even in the UK where there is a universal entitlement to healthcare within the NHS, the health inequalities between the most deprived and least deprived areas are showing little sign of reducing (Newton *et al*., 2015). People living in the most deprived areas of England in 2013 have not yet reached the levels of life expectancy that less deprived groups had in 1990 (Newton *et al*., 2015). The reported life expectancy for men in 2013 ranged from 75 years in the most deprived area in North West England to 83 years in the least deprived area of East of England.

Socioeconomic inequalities in survival have been reported for most adult cancers worldwide (Kogevinas and Porta, 1997, Coleman *et al*., 2004, Woods *et al*., 2006). The improved cancer survival that has occurred over the last two decades has been reflected more in patients living in affluent areas than for those living in deprived areas. It is estimated that 11% of deaths from common cancers would be avoided if survival for all patients was as high as in the most affluent group (Ellis *et al*., 2012).

Poorer cancer-specific and overall survival in CRC patients in lower socioeconomic groups has been reported in US (Aarts *et al*., 2010), European (Eloranta *et al*., 2010, Dejardin *et al*., 2014) and UK (Jeffreys *et al*., 2006, Møller *et al*., 2012, Dejardin *et al*., 2014) populations. The origins of these disparities in survival are still not fully understood. Although late stage at presentation is a commonly cited cause of the lower survival amongst more deprived patients, studies applying multiple regression analysis to correct for stage have reported this difference to remain (Hole and McArdle, 2002, Wrigley *et al*., 2003). Evidence now also points to differential access to treatment within the healthcare system (Lejeune *et al*., 2010) . Access to specialist care is known to favour the affluent (Dixon *et al*., 2007) and lower rates of primary CRC resection (Pollock and Vickers, 1998, Tilney *et al*., 2009, Raine *et al*., 2010) and use of chemotherapy (Lemmens *et al*., 2005, McGory *et al*., 2006, Aarts *et al*., 2010) in less affluent patients have been demonstrated.

Relatively little is known about the influence of socioeconomic status on liver resection rates, with population-based studies reporting conflicting findings. A study of selection for liver resection in an English CRC population diagnosed from 1998-2004 demonstrated higher socioeconomic status to independently predict liver resection (Morris *et al*., 2010). Similarly, Wiggans *et al*. (2015), reported that affluent patients were over-represented amongst a regional English cohort of patients undergoing liver resection when compared to the demographics of the local population. In contrast, a population-based study of patients with synchronous liver-limited metastases in Sweden did not find either income, or education, to be independently associated with liver resection (Norén *et al*., 2016).

1.6.4 Access to specialist input

As highlighted in this introduction, the treatment pathway to be negotiated for patients with CRC liver metastases, particularly those with synchronous metastases, may be complex with a lack of consensus regarding multiple aspects of care. Providing these patients optimal treatment requires increasingly specialised expertise.

There is evidence to suggest that some patients with resectable liver disease are not referred to hepatobiliary teams for discussion (Jones *et al.*, 2012, Young *et al.*, 2013). These patients may therefore be denied potentially curative treatment. A survey of the attitudes of colorectal surgeons in the UK towards referral practices for patients with CRC liver metastases performed in 2000, reported that only half of surgeons would refer a patient with bilobar metastases and only a quarter would refer if the patient had bilobar disease and more than three metastases (Heriot *et al.*, 2004).

The complexities of the technical and oncological rationale influencing decision-making in CRC patients was highlighted by Jones *et al.* (2012). These authors analysed regional CRC MDT data from 2009, and out of 53 patients with CRC liver-limited metastases who had undergone palliative chemotherapy at a regional UK oncology centre without previous hepatobiliary MDT discussion, 63% were found by a panel of blinded liver surgeons to have potentially resectable disease prior to commencement of chemotherapy. The following year, Young *et al.* (2013) published an analysis of patients presenting with new CRC liver metastases across a 12 month period in a cancer network which consisted of a hepatobiliary specialist centre and seven attached hospitals. There were 131 patients identified who were deemed by the CRC MDTs to be fit for liver resection but to have inoperable disease and therefore were not referred to the hepatobiliary MDT. When the cases of these patients were reviewed by hepatobiliary surgeons and radiologists at the specialist centre, 29% were considered to have operable disease with a further 15% having equivocal imaging. A recent regional study in the UK, similarly demonstrated 42% of CRC patients with liver-limited metastatic disease not referred to a hepatobiliary MDT over a 6 month period had resectable or potentially resectable disease. A further 36% may have been suitable for a clinical trial (Thillai *et al.*, 2016).

1.7 Aim of thesis

The literature search performed in this Chapter has highlighted several gaps in the current evidence regarding the management and outcomes of patients with CRC liver metastases. The overall aim of this thesis was to describe several aspects of the surgical management and outcomes of patients with CRC liver metastases in England using routinely collected national data. This thesis examines four specific clinical topics in depth and can be broadly grouped into the domains: service provision, accessibility, and outcomes.

1.7.1 The impact of the centralisation of hepatobiliary services in England on colorectal cancer patients with synchronous liver metastases

The positive impact of assessment by specialist MDT on outcomes for CRC patients is well documented. Local studies have demonstrated that patients with potentially operable liver metastases may be missing out on surgical resection due to their cases not being discussed within a hepatobiliary MDT.

Liver surgical services in England have undergone a complete restructure over the last two decades with the centralisation of such services to create higher-volume units. This may have particularly impacted upon CRC MDTs based at hospitals that do not offer liver specialist services.

Little is known about the impact of the centralisation of hepatobiliary services on CRC patients in England, although limited European data suggests on-site access to liver surgery may increase the rate of liver resection. The first study of this thesis investigated how the presence of hepatobiliary surgical services on-site at the hospital of diagnosis of CRC effects the rate of liver resection in patients with synchronous CRC liver metastases, and importantly, if this changes patient survival.

1.7.2 Effect of socioeconomic status on selection for liver resection and survival in patients with synchronous colorectal cancer liver metastases

As discussed above, social deprivation is associated with poorer long-term survival in CRC patients in the UK. The cause of this disparity is not fully understood. More deprived patients are known to be at a higher risk of emergency and delayed presentation of CRC (Wallace *et al.*, 2014) resulting in more advanced disease at diagnosis (Clegg *et al.*, 2009). However stage at presentation only appears to partly explain the poorer survival and process factors such as access to services may also contribute (Lejeune *et al.*, 2010).

Studies of the impact of socioeconomic deprivation on liver resection rates and survival have reported conflicting results (Morris *et al*., 2010, Wiggans *et al*., 2015). No previous study has examined socioeconomic status as an independent predictor of mortality in this cohort. The study presented in Chapter 4 investigates how socioeconomic deprivation is associated with rate of liver resection and overall survival in patients with synchronous CRC liver metastases. This study also examines if any survival inequalities related to deprivation within this cohort are explained by differences in rates of liver resection.

1.7.3 The timing of liver resection in relation to colorectal cancer resection in patients with colorectal cancer and synchronous liver metastases

Without widely accepted guidelines for clinicians regarding the surgical timing of bowel resection in relation to liver resection for patients with synchronous disease, patient management can be challenging. Although the popularity of alternative strategies for the timing of resection of synchronous CRC metastases in relation to colorectal cancer resection has increased in recent years, it is not known how these approaches are being used in England and how patients are being selected for each strategy.

The study presented in Chapter 5 was therefore undertaken to investigate temporal trends in the surgical strategy used in CRC patients with synchronous liver metastases, and the demographic and clinical characteristics of the patients selected for each approach. The study used landmark analysis and propensity matching techniques in comparing the long-term outcomes of patients, thus addressing several of the methodological flaws in previous publications of this nature.

1.7.4 The impact of advancing age on outcomes in patients undergoing hepatectomy for colorectal cancer liver metastases

The reported post-operative and long-term outcomes in the elderly undergoing liver resection for CRC liver metastases vary. This may reflect that previous studies have been limited by small patient numbers, long-recruitment periods and a single centre design.

Within an aging population it is critical that the role of newer interventions such as laparoscopic surgery and parenchyma sparing techniques, and outcomes of common surgical procedures in the older patient are well characterised to allow clinicians to present accurate information regarding the potential risks and benefits to patients.

The final study of the thesis aimed to compare characteristics of patients having liver resection by age and to investigate advancing age as a prognostic factor for post-operative outcomes and long-term survival in patients with CRC liver metastases.

2. Chapter 2: Methods

The general methodology of this thesis is described below, and the specific methodology for the analysis conducted in each individual study is detailed in the relevant chapter.

2.1 Data sources

The primary source of data for the research presented in this thesis was the NBOCA database. Data derived from the audit dataset was linked with other data sources, to provide the comprehensive dataset required for further analysis.

2.1.1 The National Bowel Cancer Audit

The NBOCA collects data on over 30,000 patients diagnosed with CRC in England and Wales each year and has been running in its current form since 2010. The aim of the audit is to measure the quality of care and survival of patients with CRC treated within the NHS in England and Wales. The NBOCA is commissioned by the Healthcare Quality Improvement Partnership (HQIP) and funded by NHS England and the Welsh Government. Participation in the NBOCA is mandatory for hospital trusts and the NBOCA is listed as one of the 58 programmes which NHS England advises trusts to prioritise for participation and inclusion in their quality accounts (NHS England, 2017). In addition to this, it is data from the NBOCA that is published by ACPGBI as part of Clinical Outcomes Publication (The Association of Coloproctology of Great Britain and Ireland, 2016). This has improved clinician engagement in NBOCA data collection, therefore increasing both data completeness and accuracy.

The NBOCA is carried out by the Clinical Effectiveness Unit (CEU) of the Royal College of Surgeons (RCS) of England in partnership with the ACPGBI and NHS Digital. The ACPGBI provides clinical leadership and direction, while NHS Digital provide project management and technical infrastructure. A project team, comprised of clinicians, epidemiologists and data analysts, work together to run the audit. The audit meets on a biannual basis with a clinical advisory group which includes clinicians, commissioners, and charity and patient representatives.

2.1.1.1 Inclusion criteria

The audit includes all patients with a new diagnosis of primary CRC. Included patients must be:

- Aged 18 or over
- Diagnosed with CRC, with one of the following International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes (World Health Organisation, 2011):
    - C17.0 Malignant neoplasm of caecum
    - C18.2 Malignant neoplasm of ascending colon
    - C18.3 Malignant neoplasm of hepatic flexure
    - C18.4 Malignant neoplasm of transverse colon
    - C18.5 Malignant neoplasm of splenic flexure
    - C18.6 Malignant neoplasm of descending colon
    - C19.0 Malignant neoplasm of colon with rectum
    - C20.0 Malignant neoplasm of rectum

2.1.1.2 Exclusion criteria

Patients with recurrent CRC, or a second primary CRC are not included in the audit.

2.1.1.3 Audit dataset

The majority of data items are collected by NHS trusts in England as part of the Cancer Outcomes and Services Dataset (COSD).

The following data items are included in the final NBOCA dataset:

Patient variables: NHS number, date of birth, surname, forename, postcode and gender. These data items are predominantly used for linkage purposes and, apart from gender, are not available to the analysts.

Tumour variables: Site of cancer, pre-treatment T-stage, pre-treatment N-stage, pre-treatment M-stage. This also includes data regarding the source of diagnosis, date of diagnosis, the treatment intent (curative/ palliative), planned treatment and anaerobic threshold (if applicable).

Surgery variables: Date of surgery, American Society of Anesthesiologists (ASA) class, surgical urgency, consultant General Medical Council (GMC) code, primary procedure, surgical access and post-operative care.

Pathological variables: Circumferential excision margin, number of lymph nodes examined, number of lymph nodes positive, pathological T-stage, pathological N-stage, pathological M-stage, size of lesion, tumour type, differentiation, vascular or lymphatic invasion.

Neo-adjuvant and adjuvant treatment variables: Neo-adjuvant treatment provider, neo-adjuvant treatment type, adjuvant treatment provider and adjuvant treatment type.

2.1.1.4 Major colorectal cancer resection

Major resection is defined in NBOCA data according to the below procedures:

- Right hemicolectomy

- Extended right hemicolectomy
- Transverse colectomy
- Left hemicolectomy
- Sigmoid colectomy
- Anterior Resection
- Abdomino Perineal Excision of Rectum
- Pelvic exenteration
- Hartmann's procedure
- Total colectomy and ileorectal anastomosis
- Total excision of colon and rectum ± anastomosis of ileum to anus + pouch

2.1.1.5 Data collection

The NBOCA data is prospectively collected. The dataset is designed to collect information at the time of the CRC MDT meeting. Since March 2014, patient data has been collected via NHS Digital’s Clinical Audit Platform (CAP) system.

The Health Act 2009 requires that trusts demonstrate their participation National Clinical Audits via their Quality Accounts (Government, 2009). Since 2012 it has been a requirement that these Quality Accounts are externally audited.

2.1.1.6 Case ascertainment

The case ascertainment reported by the NBOCA audit has remained consistently high over the last five years. This is expressed as a ratio of the number of patients registered in the NBOCA (the numerator) to the number of patients newly recorded in HES data with an ICD-10 code indicating a diagnosis of CRC. The case ascertainment for the NBOCA was reported to be 95% for patients diagnosed from 31st March 2015 to 1st April 2016 resection (nboca.org.uk, 2016). The results of the studies presented in this thesis therefore may be considered generalisable and representative of the current management and outcomes of CRC patients.

2.1.1.7 Type two objections

Patients who do not want their personal confidential information to be shared, for purposes other than for their direct care, can register a type 2 opt-out with their GP practice. These patients are not included in the calculation of case ascertainment. This is estimated to be around 2% of the UK population, and therefore the exclusion of patients who have registered a type 2 objection, although should be considered, is not likely to have had a significant influence on the overall results presented (NHS Digital, 2016).

2.1.1.8 Ethical Approval

The NBOCA is considered to be exempt from the UK National Research Ethics Committee approval as it involves analysis of data for services. Section 251 approval was obtained for the collection of the personal health data from the Ethics and Confidentiality Committee.

2.1.2 Organisation of services

Data regarding the services available at hospital trusts was collected in November 2015. An electronic survey was designed and then initially piloted at 10 sites. Feedback was gathered from those who completed the pilot survey and the survey was modified. The final survey was circulated to the CRC clinical lead for all 142 English NHS hospital trusts treating more than 10 CRC patients per year. Those who failed to respond within 1 month were followed up with a telephone reminder.

2.1.3 Hospital Episode Statistics

The studies presented in this thesis derive much of the presented data from the Hospital Episode Statistics (HES) inpatient database. HES is described as a ‘data warehouse’ containing details of patients' demographic characteristics as well as their main and supplementary diagnoses and operations (NHS Digital, 2017). The HES database is linked to NBOCA data to allow more in-depth analyses to be performed.

Each record in HES describes a period of care for a patient under a particular hospital consultant and is known as a Finished Consultant Episode (FCE). For each FCE, administrative data is captured, including date of admission and discharge (allowing length of stay to be determined). Clinical information is captured in the HES database in the form of alphanumeric codes.

The International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) (World Health Organisation, 2011) is used to record diagnoses in the HES dataset. Within each episode there is a data field to record a primary diagnosis, and a further 19 data fields for secondary diagnoses.

Operative and other interventional procedures are recorded using Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures (4th revision) (OPCS-4) codes in up to 24 operative fields (NHS Classifications Service, 2007). These correspond to primary procedure, secondary procedure and so on. Each of the operative fields is associated with a ‘date of operative procedure’ data field.

2.1.4 Mortality database from the Office for National Statistics

Patient date of death and cause of death was obtained from the Office for National Statistics (ONS) records (Office for National Statistics, 2014). In this dataset the underlying cause of death is listed as a single ICD-10 code based on the death certificate generated from an automated programme operated by the ONS. The codes listed in Table 2.1**Error! Reference source not found.** were considered to represent a CRC cancer related death.

Table 2.1 ICD-10 codes used to identify CRC cancer specific deaths

4-digit code	Description
C180, C181, C182, C183, C184, C185, C186, C187, C188, C189	Malignant neoplasm of colon
C19X	Malignant neoplasm of rectosigmoid junction
C20C	Malignant neoplasm of rectum
C260	Malignant neoplasm of intestinal tract, part unspecified
C269, C768	Malignant neoplasm of ill-defined sites within digestive system
C762	Malignant neoplasm of abdomen
C770, C771, C772, C773, C774, C775, C778, C779	Secondary and unspecified malignant neoplasm of lymph nodes
C780, C781, C782, C783, C784, C785, C786, C787, C788	Secondary malignant neoplasm of respiratory and digestive organs
C790, C791, C792, C793, C794, C795, C796, C797, C798	Secondary malignant neoplasm of other sites
D374	Neoplasm uncertain colon
D375	Neoplasm uncertain rectum
D377	Neoplasm uncertain/ unknown behaviour other digestive organs
C97X	Malignant neoplasms of independent (primary) multiple sites

2.1.5 Methods for administrative data

2.1.5.1 Royal College of Surgeons Charlson comorbidity score

The Royal College of Surgeons (RCS) Charlson comorbidity score was used to calculate patient comorbidity. This is a comorbidity score consisting of 14 disease categories developed for use with administrative data in the UK by the RCS Comorbidity Consensus Group (Armitage and van der Meulen, 2010). The RCS Charlson score was developed with surgical patients in mind, and validated in patients undergoing elective surgery.

A patient is considered to have a comorbid condition if an ICD-10 code included in the RCS Charlson Score, as shown in Appendix 9.1, was present in any of the first seven diagnosis fields of either the index admission or a hospital admission in the year preceding diagnosis. The original score includes ‘metastatic solid tumour’ and ‘any malignancy’ but this item is routinely excluded when the score is applied to cancer patients. The Charlson comorbidity score was considered in three categories: 0, 1 or 2 and more.

2.1.5.2 The Index of Multiple Deprivation

Socioeconomic status was calculated according to the English Indices of Deprivation and was based on the patient's postcode (Noble M *et al*., 2007). This measure is based on 37 indicators organised across 7 distinct domains of deprivation. These are combined to calculate the Index of Multiple Deprivation (IMD). The 7 domains of deprivation are combined using the following weights:

1) income deprivation (22.5%)
2) employment deprivation (22.5%)
3) education, skills and training deprivation (13.5%)
4) health deprivation and disability (13.5%)
5) crime (9.3%)
6) barriers to housing and services (9.3%)
7) living environment deprivation (9.3%)

This is an overall measure of deprivation experienced by those living in a particular area and is calculated for 32,844 neighbourhoods (termed Lower layer Super Output Area (LSOA)) in England. Every such neighbourhood, which covers an average population of around 1500 people or 400 households, is ranked according to its level of deprivation relative to that of other areas. Patients are grouped into five socioeconomic categories based on quintiles of the national ranking of these areas.

2.1.5.3 Emergency readmission

An emergency readmission was defined as one where the hospital admission within 30-days of liver resection in the HES record was coded as one of the following: 'Emergency: via Accident and Emergency (A&E) services' (21), 'Emergency: via general practitioner (GP)' (22), 'Emergency: via Bed Bureau, including the Central Bureau' (23), 'Emergency: via consultant outpatient clinic' (24) or 'Emergency: other means, including patients who arrive via the A&E department of another healthcare provider' (28).

2.1.5.4 Return to theatre

Reoperation was defined as any return to theatre for an intra-abdominal procedure or wound complication on the index admission, or on a subsequent admission to hospital within 30 days of the initial liver resection. The codes used to define return to theatre were those used by Burns *et al*. (2012) with additional codes previously identified using a strategy to identify frequent procedure codes amongst patients with poor outcomes (Burns *et al*., 2013). Procedure codes indicating a return to theatre occurring up until midnight on the day of liver resection could not be distinguished from the original procedure, resulting in a requirement of at least one day between the liver resection and the procedure code identifying return to theatre.

2.1.5.5 Data linkage

The NBOCA database was linked to HES and the ONS death register for each patient. Data were linked using a hierarchical deterministic approach (Li *et al*., 2006). Deterministic methods are based on exact-match comparisons of a combination of variables that allow unique discrimination. The patient identifiers used for linkage were NHS number, date of birth, sex and postcode. In 2016, 93% of patients undergoing major surgery at English trusts in the audit could be linked to HES. Multiple imputation (as discussed in Section 2.2.5) was used to impute data for patients who could not be linked to HES.

2.1.5.6 Coding accuracy within Hospital Episode Statistics data

HES data provided information regarding the site of metastases, and liver resection procedures, allowing analyses which would not have been possible using the NBOCA dataset alone. The primary use of the HES database, as well as the premise on which it is designed, is for administrative purposes. Therefore, despite its increasing use in epidemiological research, the potential for coding inaccuracies and the impact of such errors must be considered.

The routine coding of information about episodes of hospital care has now become a central feature of the NHS. In recent years there have been changes to coding practices which may have improved the accuracy of coding. In the white paper "Equity and excellence: Liberating the NHS" the government showed a strong commitment to ensuring that information is collected and used to inform patient choice (Department of Health, 2010). As a result NHS Choices now publishes metric and quality indicators in the public domain. These are based largely upon HES data (gov.uk, 2017). Furthermore, hospitals trusts are now paid based on coding data. Errors in coding are known to have a significant impact on payment accuracy and as a result there is significant interest from commissioners in ensuring accuracy (Payment by Results data assurance framework, 2014).

Given the increased engagement from trusts in improving administrative data accuracy in recent years, HES data is generally considered sufficient for use in most circumstances. A systematic review of studies comparing routine discharge statistics about an episode of hospital care with the original medical record, reported the coding accuracy to be high, with an accuracy of 80% for diagnoses and 84% for procedures (Burns *et al*., 2012).

HES data was used to capture information regarding the presence of synchronous liver metastases for the analyses presented in Chapters 3, 4 and 5. In the study in Chapter 3, which includes patients diagnosed from 2010 to 2014, 13% of CRC patients were found to have a HES code recorded for liver metastases at the time of diagnosis. In Chapter 4, a slightly more recent cohort of patients were included (those diagnosed from 2011 to 2015), and a higher proportion of patients, 15%, were found to have liver metastases at diagnosis. Although the true proportion of CRC patients with synchronous liver metastases at diagnosis is unknown, these figures are similar to those reported by previous European population-based studies using registry data (Manfredi *et al*., 2006, Norén *et al*., 2016).

Despite this, as only 40 to 50% (depending on the time period examined) of patients with metastatic disease recorded in NBOCA data had an ICD-10 code for a metastasis recorded in HES, it must be inferred that liver metastases are under-recorded in HES data. There were however several strategies used to validate the findings and to reduce the risk of bias from the use of incomplete data. As discussed in Chapter 3 and 4, although the true incidence of synchronous liver metastases in this patient cohort is unknown, the odds ratio to estimate likelihood of undergoing liver resection remains a valid measure of association in the same way that it is valid in a case control study if under-recording is not dependent on the risk factor under investigation. This is demonstrated in Table 3.2 to be the case for both on-site hepatobiliary services and socioeconomic status which are the focus of investigation in Chapters 3 and 4 respectively.

Due to the under-recording of metastases in HES data, patients with liver metastases detected during the course of follow up were excluded when investigating patient access to liver resection. This is because NBOCA collects data on only the presence of metastases at the time of diagnosis, and not on metachronous disease detected as part of follow up. Therefore, the validation step of comparing the characteristics of patients with metachronous disease in the HES dataset to the NBOCA dataset, as performed in Chapter 3 for patients with synchronous disease, was not possible.

2.2 Statistical analysis

The statistical methods used throughout this thesis are discussed below. Further details may also be found in the specific chapter. STATA® version 14.1 (StataCorp, College Station, Texas, USA) was used for all analyses.

2.2.1 Multi-level models

The analyses in Chapter 3 and Chapter 4 include individual patient variables as well as an institutional variable (presence of hepatobiliary surgical services on-site). This is considered a multi-level model. Observations from data with a hierarchical structure may be correlated with one another, termed 'clustering'. With clustered data, estimated standard errors in a conventional regression are smaller than actual standard errors due to failure to account for the similarity of responses among observations within the same cluster (Vaughn, 2008). This underestimation of standard errors causes an increase in likelihood of a Type I error. Hence for the analyses used in Chapters 3 and 4, multilevel logistic regression models with random intercepts, and Cox regression with shared frailty, were used to allow for clustering within hospital trusts.

2.2.2 Competing risks analysis

Kaplan-Meier survival analysis and Cox proportional hazard regression models were originally developed to describe all-cause mortality, as opposed to incident disease. When these approaches are used to describe outcomes other than all-cause mortality, the presence of a related competing risk, such as death, may lead to biased results (Gooley *et al*., 1999, Southern *et al*., 2006). In Chapter 6 where the primary outcome was death attributable to a CRC related cause, death attributable to a non-CRC cause serves as a competing event. For example, a CRC patient who dies of a myocardial infarction is no longer at risk of death attributed to CRC. This is a particular consideration when studying a geriatric population, in whom the risk of death from other causes is higher. The use of traditional methods, without accounting for the competing risk of death, can overestimate the risk of the outcome of interest. Therefore, for the analysis of cancer-specific mortality in the 3 years following liver resection according to patient age, a competing risks model was used to reduce the risk of such bias.

2.2.3 Propensity score-matched analysis

Propensity score-matching was used to control for imbalances between the patient cohorts in Chapter 5. This presented several advantages to logistic regression. In propensity score-matching, the collection of confounders which may predict the outcome of interest are collapsed into a single variable, the propensity score (Austin, 2011a). This therefore allows more confounders to be accounted for than in a logistic regression model. For the analysis in Chapter 5, components of the Charlson comorbidity score were included individually rather than in a cumulative single value. In addition, it would be very unlikely that a patient in the bowel-first group would have the demographic, clinical and pathological characteristics to be eligible for both a simultaneous and a liver-first approach. Therefore, a further advantage of propensity score-matching was that it allowed the comparison to be restricted to only bowel-first patients eligible for a specific alternative approach.

2.2.4 Landmark survival analysis

To compare long-term survival between patients undergoing the bowel-first, liver-first and simultaneous surgical strategies, the analysis in Chapter 4 uses a landmark analysis to correct for the bias inherent in the time-to-event outcome between patient cohorts. In the landmark method, a fixed time after a baseline data is selected as a landmark for conducting the analysis of survival. Only patients alive at the landmark time are included in the analysis (Anderson *et al*., 1983, Dafni, 2011). As this study only includes patients in the staged groups who survive to undergo a second intervention, a traditional survival analysis from date of diagnosis would introduce bias in favour of bowel- and liver-first patients. This is because patients who die after the first procedure would be excluded by definition. Furthermore, patients in the staged cohorts have their interventions at different time points following diagnosis, again introducing bias in a traditional survival analysis.

2.2.5 Dealing with missing data

There are a number of proposed methods for dealing with missing data. The simplest is known as a complete case analysis and involves omitting all cases with missing data. The primary problem with this approach is that data may not be missing at random. For example, elderly patients, those with more comorbidities and more advanced disease have been shown to be more likely to have missing staging data (Gurney *et al*., 2013). Therefore, excluding these patients can result in lack of generalisability in the results. Furthermore, the effect of missing data in several domains may result in the exclusion of large proportion of the original sample, reducing study power (Sterne *et al*., 2009).

The National Clinical Audit Advisory Group (2011) recommends the use of multiple imputation using chained equations for approaching missing data in registries. This method uses a patient's other risk factors to predict the information that is missing, whilst taking into account the uncertainty due to their missing data. Firstly, chained equations were used to create 10 copies of the dataset with the missing values replaced by imputed values. Following this, the model of interest was fitted to each of the imputed datasets and standard errors were calculated using Rubin's rules (White *et al*., 2011). Multiple imputation was used throughout this thesis to fill in risk factor information when reporting adjusted outcomes.

3. Chapter 3: The impact of hepatobiliary service centralisation on treatment and outcomes in patients with colorectal cancer and liver metastases

3.1 Introduction

Evidence has emerged over the last decade that centralisation of specialist surgical services to create higher volume units improves patient outcomes (Birkmeyer *et al*., 2003, Munasinghe *et al*., 2015). This has had a significant effect on both organisational infrastructure and clinical practice within the NHS (Siriwardena, 2007, Palser *et al*., 2009). The English Department of Health (2001) published guidelines recommending that hepatobiliary surgery services should be delivered by units with sufficiently large catchment populations. As a result, hepatobiliary services have been centralised in a hub-and-spoke arrangement. In recently published plans to improve cancer services the NHS in England has recommended an evaluation of whether cancer surgery would benefit from further centralisation (National Cancer Transformation Board, 2016).

NICE recommends that if a CRC MDT considers both primary and metastatic tumours are potentially resectable, the patient should be referred to a specialist hepatobiliary surgery team (National Institute for Health and Care Excellence, 2011b). If referral pathways are working effectively, patients diagnosed with CRC and liver metastases at hospital trusts with a specialist hepatobiliary team on site should have similar liver resection rates and survival as those diagnosed at hospital trusts without a specialist hepatobiliary team. However, there is evidence from regional studies to suggest that there is considerable inter-hospital variation in referral rates from colorectal MDTs to hepatobiliary MDTs (Young *et al*., 2013).

The aim of this study was to outline the structure of hepatobiliary services for patients with CRC liver metastases in England and then use this data to compare the liver resection rate and survival outcomes in patients diagnosed with CRC and synchronous metastases limited to the liver at a centralised hepatobiliary centre (hub) with those at hospital trusts without hepatobiliary services (spokes).

3.2 Methods

3.2.1 Study population

All patients registered in the NBOCA dataset diagnosed with primary CRC between 1st April 2010 and 31st March 2014 with synchronous liver metastases who underwent a major CRC resection in English NHS hospitals were considered for inclusion in this study.

3.2.2 Data items and definitions

3.2.2.1 Secondary metastases

The site of metastases was identified from HES data using diagnostic information coded according to ICD-10. Liver metastases were identified in HES data because the NBOCA records only the presence, but not the site, of metastatic disease. Patients were considered to have metastatic disease at diagnosis if a HES code was recorded up to 1 year before and 30 days after diagnosis of CRC. A year before CRC diagnosis was chosen to include patients who are found to have metastases before determining the site of the primary CRC. The codes detailed in Table 3.1 were used to identify those with secondary metastases. Patients were considered to have liver-limited metastases if an ICD-10 code for liver metastases (C787) was recorded in HES, with no further secondary metastases also recorded, in the period of 1 year before and up 30 days following CRC diagnosis.

Table 3.1 ICD-10 diagnostic codes recorded in HES data used to identify patients with secondary metastases

4-digit code	Description
C780	Secondary malignant neoplasm of lung
C781	Secondary malignant neoplasm of mediastinum
C782	Secondary malignant neoplasm of pleura
C783	Secondary malignant neoplasm of other & unspecified respiratory organs
C784	Secondary malignant neoplasm of small intestine
C786	Secondary malignant neoplasm of retroperitoneum & peritoneum
C787	Secondary malignant neoplasm of liver
C788	Secondary malignant neoplasm of other & unspecified digestive organs
C790	Secondary malignant neoplasm of kidney & renal pelvis
C791	Secondary malignant neoplasm of other & unspecified urinary organs
C792	Secondary malignant neoplasm of skin
C793	Secondary malignant neoplasm of brain & cerebral meninges
C794	Secondary malignant neoplasm of other & unspecified parts nervous system
C795	Secondary malignant neoplasm of bone and bone marrow
C796	Secondary malignant neoplasm of ovary
C797	Secondary malignant neoplasm of adrenal gland
C798	Secondary malignant neoplasm of other specified sites

Of all patients undergoing major surgery for CRC identified in the NBOCA database to have metastatic disease at diagnosis, 41.1% (4,098 of 9,966) had a metastasis code recorded in HES data. This highlighted the under-recording of metastases in HES data.

Cohort study designs usually allow for the direct calculation of relative risk from incidences, however in this study the true incidence of liver metastases in the population was not known. This therefore likens the design to a case-control study in which the proportion of cases in the entire population-at-risk is unknown. In such circumstances it is the odds ratio, and not the risk ratio, that provides a valid measure of relative risk (Pearce, 1993). This approach would be valid in investigating the impact of on-site hepatobiliary surgical services on liver resection dependent on two conditions being met. Firstly, the completeness of recording of metastases in HES must be independent of the patient being diagnosed in a hub or spoke. Secondly, patients recorded in HES data as having liver metastases must be representative of all patients with liver metastases. This was evaluated by two methods. The first was by comparing the completeness of recording of metastases in HES between hub and spoke hospital trusts. The second was comparing the characteristics of patients with metastases, irrespective of their site, identified in the NBOCA database and corresponding patients in the HES database

3.2.2.1.1 Completeness of recording of metastases between hub and spoke hospital trusts

Of the 9966 patients who underwent resection of the primary CRC and had a record of metastatic disease in the NBOCA data set, 41.1% of those from spoke hospital trusts (3,141 of 7,644) and 41.2% of those from hub hospitals trusts (957 of 2,322) had a metastasis code recorded in HES. Therefore, the recording of metastases appeared to be consistent between both types of hospital.

3.2.2.1.2 Characteristics of patients with metastases in NBOCA and HES data

For the second step in the validation of the use of HES data for capturing metastases, the demographic and clinical characteristics of patients with metastases recorded in NBOCA data were compared with those with metastases recorded in HES data. There were slightly more patients who had an emergency admission, urgent surgery and T4 disease identified in the HES database with metastatic disease than in the NBOCA, but patient characteristics were otherwise similar, as shown in Table 3.2.

Table 3.2 Comparison of characteristics of patients recorded as having metastatic disease at diagnosis in the NBOCA compared to those with a metastasis code in HES, restricted to those patients undergoing major resection

		Patients recorded as having metastatic disease in NBOCA N=9,966	**Patients recorded as having metastatic disease in HES N=6,001**
Hepatobiliary services	Hub	2,322 (23.3)	1,401 (23.3)
	Spoke	7,644 (76.7)	4,600 (76.7)
Sex	Men	5,455 (54.7)	3,252 (54.2)
	Women	4,511 (45.3)	2,749 (45.8)
Age group	18-64	3,589 (36)	2,120 (35.3)
	65-74	3,163 (31.7)	1,892 (31.5)
	75-84	2,618 (26.3)	1,592 (26.5)
	>=85	596 (6)	397 (6.6)
Index of Multiple Deprivation	1 (least deprived)	1,590 (16.0)	989 (16.6)
	2	1,791 (18.1)	1,115 (18.7)
	3	2,107 (21.2)	1,236 (20.7)
	4	2,208 (22.3)	1,326 (22.2)
	5 (most deprived)	2,226 (22.4)	1,303 (21.8)
	Missing	44	32
Admission	Elective	6,323 (66.3)	3,202 (55.8)
	Emergency	3,218 (33.7)	2,532 (44.2)
	Missing	425	267
CRC resection surgical urgency	Elective/ scheduled	6,439 (65.5)	3,354 (57)
	Urgent/ emergency	3,396 (34.5)	2,529 (43)
	Missing	131	118
Charlson co-morbidity score	0	6,810 (70.7)	4,009 (69.1)
	1	2,174 (22.6)	1,361 (23.5)
	≥2	644 (6.7)	434 (7.5)
	Missing	338	197
ASA grade	1	1,070 (12)	545 (10.4)
	2	4,564 (51)	2,512 (47.7)
	3	2,812 (31.4)	1,832 (34.8)
	4	506 (5.7)	376 (7.1)
	Missing	1,011	736
Cancer site	Ascending colon	1,098 (11)	722 (12)
	Caecum	2,218 (22.3)	1,541 (25.7)
	Rectosigmoid	695 (7)	360 (6)
	Descending colon	335 (3.4)	217 (3.6)
	Hepatic flexure	439 (4.4)	286 (4.8)
	Rectum	1,673 (16.8)	690 (11.5)
	Sigmoid colon	2,453 (24.6)	1,463 (24.4)
	Splenic flexure	309 (3.1)	214 (3.6)
	Transverse colon	746 (7.5)	508 (8.5)
T-stage at diagnosis	T0	53 (0.6)	28 (0.5)
	T1	116 (1.2)	51 (0.9)
	T2	454 (4.7)	206 (3.6)
	T3	3,845 (39.7)	1,911 (33.6)
	T4	5,228 (53.9)	3,492 (61.4)
	Missing	270	313
N-stage at diagnosis	N0	2,516 (25.9)	1,304 (22.9)
	N1	3,125 (32.2)	1,788 (31.4)
	N2	4,058 (41.8)	2,595 (45.6)
	Missing	267	314

3.2.3 Liver resection

All HES records including admissions up to 31 March 2015 were searched for codes indicating a liver resection. The OPCS-4 codes detailed in Table 3.3 were used to identify those patients who underwent liver resection.

Table 3.3 OPCS-4 codes recorded in HES data used to identify liver resection

4-digit code	**Description**
J021	Right hemihepatectomy
J022	Left hemihepatectomy
J023	Resection of segment of liver
J024	Wedge excision of liver
J026	Extended right hemihepatectomy
J027	Extended left hemihepatectomy
J028	Other specified partial excision of liver
J029	Unspecified partial excision of liver
J031	Excision of lesion of liver NEC
J035	Excision of multiple lesions of liver
J038	Other specified extirpation of lesion of liver
J039	Unspecified extirpation of lesion of liver

3.2.4 Hepatobiliary services

Data regarding the location of a specialist hepatobiliary teams were collected in November 2015 as part of the organisational audit discussed in Chapter 2.1.2. For hospital trusts not offering hepatobiliary services, the hospital trust to which the majority of patients were referred was ascertained. Survey responses were validated using two approaches.

The first was by using linked HES records. Patients who underwent liver resection were grouped by their trust of diagnosis according to NBOCA data. Following this, the hospital trust at which the majority of liver resection procedures were performed for patients in that trust (according to the provider code recorded in HES data) was identified.

The second was by comparing the employing trusts of the consultant members of the Great Britain and Ireland Hepato-Pancreato-Biliary Association (GBIHPBA) to those trusts identified as providing hepatobiliary services in the organisational survey.

This allowed the hospital trusts with and without a specialist hepatobiliary team on-site to be mapped in a 'hub and spoke' model.

3.2.5 Statistical analysis

The statistical significance of differences in patient characteristics in hub and spoke hospital trusts were assessed using the χ^2 test. Multivariable random-effects logistic regression was used to estimate the odds ratio of liver resection by presence of specialist hepatobiliary services on site, adjusted for the following risk factors: sex, cancer site, IMD quintile, age group, admission type, surgical urgency, Charlson comorbidity score, T-stage, N-stage and ASA class. A random intercept was modelled for each hospital trust to reflect the possible clustering of results within hospital trusts. Missing values for the risk factors were imputed with multiple imputation.

Survival was compared between patients with liver metastases diagnosed at hospital trusts with versus without a specialist hepatobiliary team. To avoid the need to censor patients, survival analyses were restricted to patients diagnosed before 1st April 2013 (with a minimum follow-up of two years from the last date of death available from ONS data). Survival curves were estimated using the Kaplan–Meier method and differences were tested using the log rank test. Comparisons were made adjusting for other risk factors using a multivariable Cox proportional hazards model with a shared frailty factor, again to reflect the possible clustering of results within hospitals.

3.3 Results

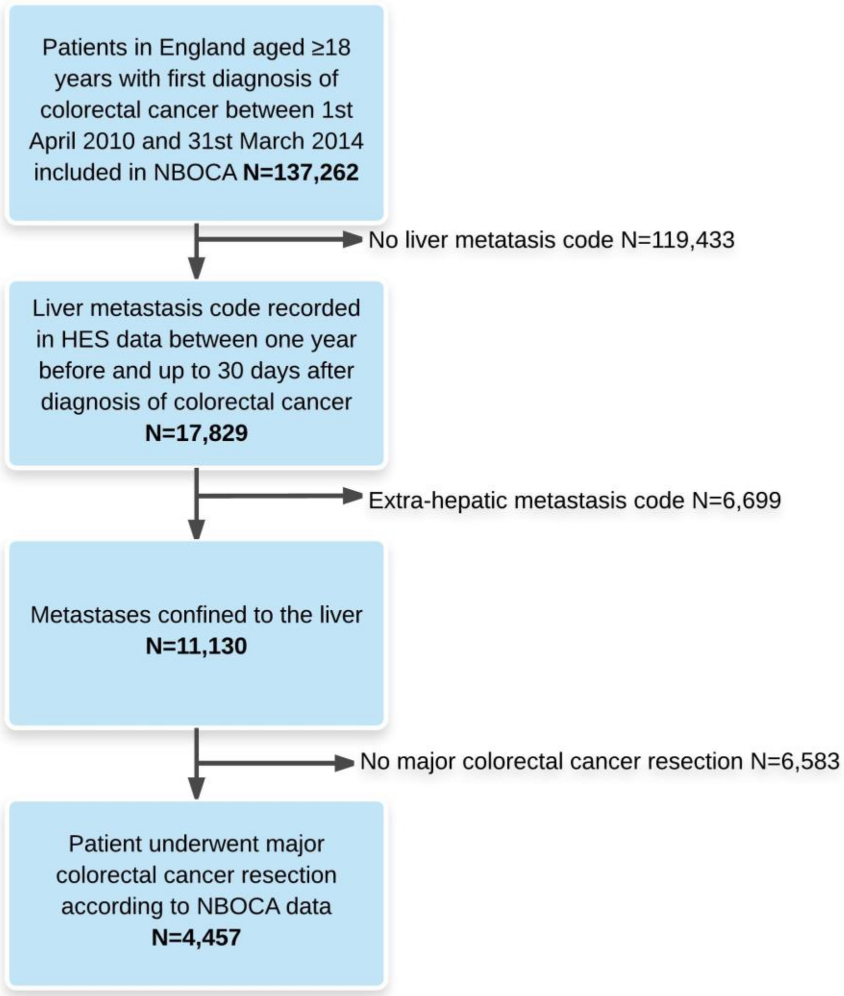
3.3.1 Structure of hepatobiliary services

All 142 English hospital trusts treating more than ten patients with CRC per year responded to the 2015 electronic survey. There were 23 hospitals trusts identified that diagnose and treat patients with CRC and provide on-site hepatobiliary surgical services, known as hubs. This number corresponded with the site in the procedural codes of the liver resection episode according to HES data. There were 27 trusts with consultant hepatobiliary surgeons registered in GBIHPBA. Four of these trusts were found to be no longer offering liver resection services in 2015 as further centralisation has occurred over recent years, therefore corresponding with survey responses and HES data.

3.3.2 Study cohort

The NBOCA contained linked HES records of 137,262 patients aged 18 years or more with a primary CRC diagnosed between 1st April 2010 and 31st March 2014. Some 17,829 patients (13.0%) with a code of secondary malignant neoplasm of the liver (C787) recorded up to 1 year before and 30 days after a diagnosis of CRC were identified. Of these, 6,699 patients with a HES code of another site of metastasis were excluded. A further 6,583 patients who did not have a CRC resection were excluded. As a result, data from 4,547 patients were available for analysis (Figure 3.1). Liver resection was performed in 1,956 of these patients (43.0%).

Figure 3.1 Flow chart of patient inclusion and exclusion



3.3.3 Patient characteristics

Patients diagnosed in hubs tended to have higher ASA class (P=0.026) and lower deprivation (P<0.001) compared with those diagnosed elsewhere (Table 3.4). There was no statistically significant difference in any other patient or tumour characteristic.

Table 3.4 Demographic, clinical and tumour characteristics of patients with liver metastases undergoing CRC resection according to whether a specialist hepatobiliary surgery team was available on site

		Spoke hospitals (n = 3,466)	**Hub hospitals (n = 1,081)**	**P-value**
Age (years)	18–64	1,319 (38.1)	449 (41.5)	0.150
	65–74	1,161 (33.5)	376 (34.8)	
	75–84	813 (23.5)	217 (20.1)	
	≥ 85	173 (5.0)	39 (3.6)	
Sex ratio	M : F	2,059 : 1407	633 : 448	0.636
Index of Multiple Deprivation	1 (least deprived)	450 (13.10)	224 (20.7)	**<0.001**
	2	657 (19.1)	225 (20.8)	
	3	729 (21.2)	219 (20.3)	
	4	792 (23.1)	210 (19.4)	
	5 (most deprived)	806 (23.5)	202 (18.7)	
	Missing	32	1	
Admission	Elective	2,227 (66.0)	702 (67.2)	0.474
	Emergency	1,145 (34.0)	342 (32.8)	
	Missing	94	37	
Urgency of CRC resection	Elective/scheduled	2,256 (66.0)	721 (68.4)	0.152
	Urgent/emergency	1,161 (34.0)	333 (31.6)	
	Missing	49	27	
Charlson comorbidity score	0	2,400 (70.6)	760 (72.0)	0.336
	1	776 (22.8)	220 (20.8)	
	≥ 2	222 (6.5)	76 (7.2)	
	Missing	68	25	
ASA fitness grade	I	404 (13.3)	100 (10.1)	**0.026**
	II	1,603 (52.6)	524 (53.0)	
	III	871 (28.6)	316 (32.0)	
	IV or V	168 (5.5)	49 (5.0)	
	Missing	420	92	
Cancer site	Ascending colon	388 (11.2)	110 (10.2)	0.212
	Caecum	665 (19.2)	191 (17.7)	
	Rectosigmoid	273 (7.9)	75 (6.9)	
	Descending colon	126 (3.6)	37 (3.4)	
	Hepatic flexure	156 (4.5)	52 (4.8)	
	Rectum	551 (15.9)	194 (17.9)	
	Sigmoid colon	938 (27.1)	326 (30.2)	
	Splenic flexure	112 (3.2)	26 (2.4)	
	Transverse colon	257 (7.4)	70 (6.5)	
T-stage	T0	22 (0.7)	7 (0.7)	0.727
	T1	32 (1.0)	6 (0.6)	
	T2	156 (4.7)	50 (4.8)	
	T3	1,577 (47.4)	507 (48.9)	
	T4	1,540 (46.3)	466 (45.0)	
	Missing	139	45	
N-stage	N0	819 (24.6)	249 (24.1)	0.889
	N1	1,136 (34.1)	361 (34.9)	
	N2	1,374 (41.3)	425 (41.1)	
	Missing	137	46	

3.3.4 Liver resection

Liver resection was performed more frequently in hubs: 545 of 1,081 patients (50.4%) who were diagnosed in the 23 hospital trusts with a specialist hepatobiliary surgery team had a liver resection, compared with 1,411 of 3,466 (40.7%) diagnosed elsewhere (crude OR 1.48, 95% confidence interval (CI) 1.29 to 1.70). With adjustment for differences between the patient groups, those diagnosed at hubs remained more likely to undergo liver resection (adjusted odds ratio 1.52, 95% CI 1.20 to 1.91).

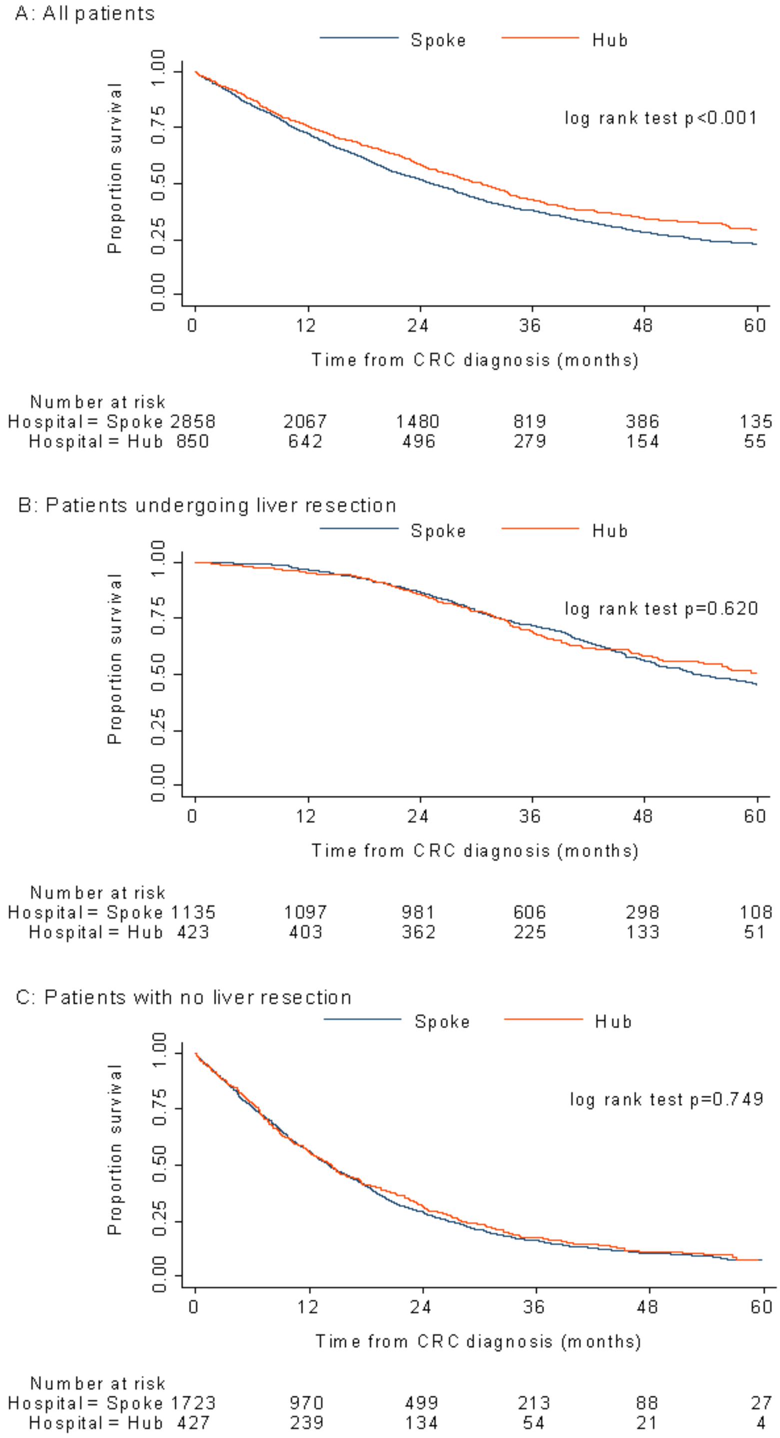
A difference in liver resection rates between hubs and spokes was seen across most regions of the country. Comparison of liver resection rates in hubs with the average rates in spokes that referred to them, indicated that 17 of 23 hubs had higher liver resection rates than their respective spokes' average.

3.3.5 Survival

Median follow-up for surviving patients was 41.9 months. Survival was better in hubs (median 30.6 months compared with 25.3 months in spokes; P<0.001) (Figure 3.2), and remained so when differences in patient and tumour characteristics were taken into account (adjusted hazard ratio (HR) 0.83, 95% CI 0.75 to 0.91).

There was no difference in median survival between patients diagnosed at hubs and spokes when the analysis was restricted to only patients who had liver resection (P= 0.620) and only those who did not undergo liver resection (P=0.749).

Figure 3.2 Kaplan-Meier curves of survival after CRC diagnosis in patients with synchronous liver metastases, according to diagnosis at hub or spoke: ***A*** *all patients,* ***B*** *patients who had liver resection and* ***C*** *patients who did not undergo liver resection.* ***A*** *P<0.001,* ***B*** *P=0.620,* ***C*** *P=0.749 (log rank test)*



3.4 Discussion

3.4.1 Summary of findings

In this national cohort of patients with CRC and liver metastases, those who were diagnosed at hubs were more likely to undergo liver resection and have better survival than patients diagnosed at spokes, after adjusting for patient and tumour characteristics. This discrepancy was present in over three-quarters of hubs and spokes in the country. As there was no difference between hubs and spokes in the survival of patients in this cohort who underwent liver resection and in those who did not, the improved overall survival for patients diagnosed at hubs was likely to be due to the increased rate of liver resection.

3.4.2 Study limitations

13% of CRC patients from this study period were found to have a HES code recorded for liver metastases at the time of diagnosis, whereas others have found corresponding percentages ranging from 14% to 20% (Leporrier *et al*., 2006, Manfredi *et al*., 2006). Despite it appearing likely that metastases are under-recorded in HES data, almost all patients who had a liver resection had a recorded liver metastases code thus potentially creating a source of bias. Although this will result in an underestimate of the risk ratio (the ratio of the observed percentages of patients who had a liver resection following diagnosis in a hub (50%) and the corresponding percentage in spokes (41%), it will not affect the odds ratio presented. As explained in the Section 3.2.2, this odds ratio is a valid measure of the relative risk if patients with liver metastasis recorded in HES are representative, and if the likelihood that a liver metastasis is recorded in HES is the same in hub and spoke hospitals. If liver metastases were more likely to be recorded in the hubs than in the spokes (which is the most probable situation if the assumption is not met), this would underestimate the odds ratio and only further strengthen the conclusion that liver resection rates were higher in hospital trusts with specialist hepatobiliary services.

A further limitation of HES data is that it does not contain information regarding the volume and distribution of liver metastases. It is therefore not possible to know which of the patients who did not undergo a liver resection had potentially operable disease. It is, however, unlikely that the burden of liver metastases in patients would vary substantially between hospital trusts after risk-adjustment for IMD quintile. As chemotherapy is often administered on an out-patient basis, reliable information regarding its use is also not available in HES data and therefore unknown for this patient cohort.

The patients diagnosed in spoke hospitals were more socially deprived than patients diagnosed in hub hospitals. This may reflect the demography of the areas served by the spoke hospitals, or may indicate that less deprived patients are more likely to travel to a specialist hub unit. The comparisons of the liver resection rates and survival across spokes and hubs were risk adjusted for deprivation and other factors, so that this difference in deprivation did not bias the results.

3.4.3 Comparison to other studies of service centralisation

These results mirror those of a study of 95,818 patients diagnosed with lung cancer in English NHS Trusts between 2008 and 2012 (Khakwani *et al.*, 2015). The study demonstrated differences in access to surgery according to hospital of diagnosis. 17% of patients who were first seen in a ‘surgical centre’ underwent resectional surgery compared to 12% of patients who were first seen in a ‘non-surgical centre’. The present study of CRC patients with liver metastases demonstrates not only differences in access to liver surgery between patients diagnosed in hospital trusts with and without a specialist team but also significant differences in patient survival.

The results of the present study, conducted on a national level, confirm the findings of previous single-centre or single-region studies demonstrating the need to improve referral rates from spoke hospital trusts to hub hospital trusts with specialist hepatobiliary services on-site (Lordan *et al*., 2009, Jones *et al*., 2012, Young *et al*., 2013, Thillai *et al*., 2016). A national study of 27,990 CRC patients treated in Sweden between 2007 and 2011 also demonstrated higher liver resection rates in patients treated at hub hospitals with on-site hepatobiliary services (Norén *et al*., 2016). However, they did not find improved patient survival in hub hospitals compared to those diagnosed at spoke hospitals.

3.4.4 Conclusions

The present study, restricted to CRC patients with synchronous liver-limited metastasis at diagnosis, demonstrates that variation in the rate of liver resection in England is still present. Furthermore, it indicates that hepatobiliary service centralisation, with the existence of a hub-and-spoke arrangement, may be part of the explanation. Any further centralisation of cancer services should take into consideration the impact on equity of access to services. These findings suggest that access to specialist hepatobiliary services is inadequate for patients diagnosed in spoke hospitals trusts.

4. Chapter 4: Effect of socioeconomic status on selection for liver resection and survival in patients with synchronous colorectal cancer liver metastases

4.1 Introduction

Reducing health inequities has been a longstanding priority of the UK government with more than 20 billion pounds spent between 1997 and 2007 on a dedicated strategy to target this (Mackenbach, 2011). Moving forwards, the Cancer Research Taskforce for England, which is working to develop a cancer survival improvement strategy on behalf of NHS England, has recommended that tackling of variation is a top priority over the next five years (National Cancer Transformation Board, 2016). The relationship between cancer and socioeconomic status has been studied extensively, with agreement that social factors strongly influence treatment and survival (Jeffreys *et al*., 2006, Aarts *et al*., 2010, Eloranta *et al*., 2010, Ellis *et al*., 2012, Møller *et al*., 2012, Dejardin *et al*., 2014).

Relatively little is known of the impact of socioeconomic status on liver resection rates and no previous study has examined socioeconomic status as an independent predictor of mortality in patients with metastatic CRC. The aim of the study detailed in this Chapter was to describe how socioeconomic deprivation is associated with rates of liver resection and survival in patients with synchronous CRC liver metastases in England. This study also examines if any survival inequalities related to deprivation within this cohort are explained by differences in rates of liver resection.

4.2 Methods

4.2.1 Study population

Data from patients included in the NBOCA were linked to Hospital Episode Statistics (HES) data. In this study all patients recorded in the NBOCA dataset with a diagnosis of primary CRC from 1st January 2011 to 31st December 2015 with synchronous liver-limited metastases were included.

4.2.2 Data items and definitions

4.2.2.1 Secondary metastases

HES records were used to identify the presence of synchronous liver and extra-hepatic metastases as detailed in Chapter 3.2.2.1. Patients identified with extra-hepatic metastases were excluded from the analysis.

Of all patients identified in the NBOCA to have metastatic disease at diagnosis, 50.3% (12,301 out of 24,476) had a metastasis code recorded in HES data. This was higher than found in the analysis in Chapter 3 (41.1%), due to the use of a more recent patient cohort. Given the under-recording of metastases in HES data, the use of odds ratios are a valid measure of the impact of socioeconomic status on liver resection rates in this cohort as long as: i) the data completeness of recording of metastases in HES is independent of socioeconomic status, and ii) patients recorded as having metastases in HES are representative of all patients with metastases. This was validated in the same ways as previously described in Chapter 3 and detailed below.

4.2.2.1.1 Completeness of recording of metastases in according to deprivation

The first validation step was to compare the completeness of recording of metastases in HES between the most deprived quintile and the least deprived quintile. In the most deprived quintile 51.4% (2,148 out of 4,179) of patients recorded as having metastatic disease in NBOCA data had a metastasis code recorded in HES, compared to 48.4% (2,513 out of 5,196) in the least deprived quintile.

4.2.2.1.2 Characteristics of patients with metastases in NBOCA and HES data

The second step was to compare the characteristics of patients with metastases, irrespective of their site, identified in the NBOCA database and corresponding patients in the HES database. As shown in Table 3.2, there was no difference in the distribution of IMD quintile between patients recorded as having metastatic disease in NBOCA data and patients recorded as having metastatic disease in HES data.

4.2.2.2 Procedural codes

All HES records in the year following the date of CRC diagnosis were searched for codes indicating a liver resection, as detailed in Chapter 3.3.4.

4.2.3 Study endpoints

The primary endpoints were undergoing liver resection within one year of date of CRC diagnosis and three-year all cause survival from date of CRC diagnosis. These two outcomes, as well as demographic and tumour characteristics, were compared between IMD quintiles to highlight any differences between groups of increasing deprivation.

As a sensitivity analysis, patients who died within 90-days of CRC resection were excluded from the analysis of likelihood of undergoing liver resection.

4.2.4 Statistical analysis

The statistical significance of differences in patient characteristics according to IMD quintile were assessed using the χ^2 test. Multivariable random-effects logistic regression was used to estimate the odds ratio of liver resection by IMD quintile, firstly adjusted for the following risk factors: gender, age, Charlson comorbidity score, primary cancer site within the colon and rectum, admission type, T-stage and N-stage. A further model was fitted additionally adjusting for the presence of hepatobiliary surgical services on-site. A random intercept was modelled for each hospital trust to reflect the possible clustering of results within trusts. Missing values for the risk factors were imputed with multiple imputation using chained equations. Survival curves were estimated using the Kaplan–Meier method. Difference in 3-year survival after diagnosis between IMD quintiles was tested with the log rank test. Comparisons were made adjusting for other risk factors using a multivariable Cox proportional hazards model with a shared frailty factor, again to reflect the possible clustering of results within hospitals.

4.3 Results

4.3.1 Study population

There were 18,899 patients out of the 130,554 patients diagnosed with primary CRC from 1st January 2011 to 31st December 2015 with synchronous liver metastases (14.5%) identified from NBOCA linked HES data. Of these, 5,243 patients were excluded due to recorded extra-hepatic metastases, resulting in a final cohort of 13,656 CRC patients with synchronous liver-limited metastases. This group formed the study population, and the demographic data divided into quintiles of deprivation, is summarised in Table 4.1. Patients in the lower socioeconomic quintiles tended to be younger, have more comorbidities, have rectal cancer, and more commonly had an emergency presentation leading to CRC diagnosis.

Table 4.1 Characteristics of patients according to IMD quintile

		IMD quintile					
		1 (most deprived) N=2,233 (%)	**2 N=2,628 (%)**	**3 N=2,886 (%)**	**4 N=3,009 (%)**	**5 (least deprived) N=2,890 (%)**	**P-value**
Sex	Male	1,398 (62.6)	1,561 (59.4)	1,764 (61.1)	1,810 (60.2)	1,711 (59.2)	0.089
	Female	835 (37.4)	1,067 (40.6)	1,222 (38.9)	1,199 (39.9)	1,179 (40.8)	
Age	<65	830 (37.2)	889 (33.8)	1,004 (34.8)	888 (29.5)	934 (32.3)	**<0.001**
	65-74	671 (30.1)	752 (28.6)	846 (29.3)	915 (30.4)	829 (28.7)	
	>74	732 (32.8)	987 (37.6)	1,036 (35.9)	1,206 (40.1)	1,127 (39.0)	
Site	Right	762 (34.1)	871 (33.1)	1,015 (35.2)	1,130 (37.6)	1,074 (37.2)	**0.002**
	Left	886 (39.7)	1,100 (41.9)	1,196 (41.4)	1,190 (40.0)	1,110 (38.4)	
	Rectum	585 (26.2)	657 (25.0)	675 (23.4)	689 (22.9)	706 (24.4)	
Charlson comorbidity score	0	1,130 (55.4)	1,364 (56.5)	1,695 (63.5)	1,777 (64.1)	1,711 (65.3)	**<0.001**
	1	604 (29.6)	743 (30.8)	671 (25.1)	717 (25.9)	676 (25.8)	
	2	306 (15.0)	308 (12.8)	305 (11.4)	279 (10.1)	233 (8.9)	
	Missing	193	213	215	236	270	
T-stage	0-2	104 (6.1)	133 (6.6)	135 (6.0)	161 (6.9)	186 (7.9)	0.170
	3	880 (51.7)	1,043 (51.7)	1,164 (51.9)	1,203 (51.5)	1,262 (53.8)	
	4	719 (42.2)	842 (41.7)	943 (42.1)	970 (41.6)	898 (38.3)	
	Missing	530	610	644	675	544	
N-stage	0	340 (19.8)	461 (22.7)	473 (20.9)	501 (21.4)	502 (21.4)	0.495
	1	710 (41.4)	820 (40.3)	887 (39.1)	936 (39.9)	943 (40.1)	
	2	665 (38.8)	754 (37.1)	906 (40.0)	908 (38.7)	905 (38.5)	
	Missing	518	593	620	664	540	
Emergency admission	No	1,257 (61.7)	1,539 (63.8)	1,752 (65.5)	1,835 (66.2)	1,880 (71.3)	**<0.001**
	Yes	782 (38.4)	875 (36.3)	921 (34.5)	936 (33.8)	757 (28.7)	
	Missing	194	214	213	238	253	
Hepatobiliary services on-site	No	593 (26.6)	482 (18.3)	507 (17.6)	506 (16.8)	590 (20.4)	**<0.001**
	Yes	1,640 (73.4)	2,146 (81.7)	2,379 (82.4)	2,503 (83.2)	2,300 (79.6)	
Liver resection	No	1,937 (86.7)	2,217 (84.4)	2,411 (83.5)	2,517 (83.7)	2,351 (81.4)	**<0.001**
	Yes	296 (13.3)	411 (15.6)	475 (16.5)	492 (16.4)	539 (18.7)	

4.3.2 Liver resection

Overall 2,213 out of 13,656 patients with synchronous liver-limited CRC metastases had a liver resection (16.2%). Liver resection was performed more frequently in patients in the least deprived IMD quintile when compared to those in the most deprived quintile (18.7% vs. 13.3%, $p<0.001$).

With adjustment for differences in patient and institutional characteristics, patients in the least deprived quintile remained more likely to undergo liver resection than patients in the most deprived quintile, with a trend of increasing chance of liver resection with decreased quintile of deprivation (least deprived vs. most deprived IMD quintile OR 1.42, 95% CI 1.18 to 1.70) (Table 4.2).

Table 4.2 Odds ratio of undergoing liver resection adjusted for patient, tumour and hospital characteristics

		Odds ratio (95% CI)	P-value	Odds ratio (95% CI) adjusted for patient and tumour characteristics	P-value	Odds ratio (95% CI) adjusted for patient, tumour and hospital characteristics	P-value
IMD quintile	1 (most deprived)	1	**<0.001**	1	**0.005**	1	**0.003**
	2	1.21 (1.02-1.42)		1.22 (1.02-1.46)		1.24 (1.03 to 1.48)	
	3	1.29 (1.10-1.52)		1.30 (1.09-1.56)		1.32 (1.1 to 1.58)	
	4	1.30 (1.11-1.53)		1.29 (1.08-1.54)		1.30 (1.09 to 1.56)	
	5 (least deprived)	1.47 (1.25-1.73)		1.41 (1.18-1.68)		1.42 (1.18 to 1.70)	
Gender	Male	-	-	1	0.18	1	0.187
	Female	-	-	1.07 (0.97-1.20)		1.07 (0.97 to 1.20)	
Age	<65	-	-	1	**<0.001**	1	**<0.001**
	65-74	-	-	0.66 (0.59-0.74)		0.66 (0.59 to 0.74)	
	75-84	-	-	0.32 (0.27-0.36)		0.31 (0.27 to 0.36)	
	>=85	-	-	0.07 (0.05-0.11)		0.07 (0.05 to 0.11)	
Emergency admission	No	-	-	1	**<0.001**	1	**<0.001**
	Yes	-	-	0.44 (0.38-0.50)		0.44 (0.38 to 0.5)	
Charlson comorbidity score	0	-	-	1	0.469	1	0.454
	1	-	-	0.99 (0.88-1.12)		0.99 (0.87 to 1.12)	
	2	-	-	0.89 (0.73-1.07)		0.88 (0.73 to 1.07)	
Cancer site	Right	-	-	1	**<0.001**	1	**<0.001**
	Left	-	-	1.21 (1.08-1.38)		1.22 (1.07 to 1.38)	
	Rectum	-	-	0.96 (0.83-1.10)		0.96 (0.83 to 1.1)	
T-stage	0-2	-	-	1	**<0.001**	1	**<0.001**
	3	-	-	1.11 (0.91-1.36)		1.1 (0.9 to 1.35)	
	4	-	-	0.84 (0.68-1.04)		0.84 (0.68 to 1.04)	
N-stage	0	-	-	1	**<0.001**	1	**<0.001**
	1	-	-	0.62 (0.54-0.70)		0.62 (0.54 to 0.7)	
	2	-	-	0.41 (0.36-0.48)		0.42 (0.36 to 0.48)	
Hepatobiliary services on-site	No	-	-	-	-	1	**0.003**
	Yes	-	-	-		1.38 (1.12 to 1.7)	

4.3.2.1 Sensitivity analysis

When patients who died within 90-days of CRC resection (N=795) were excluded from the analysis, patients in the least deprived quintile remained more likely to undergo liver resection than patients in the most deprived quintile (Table 4.3).

Table 4.3 Odds ratio of undergoing liver resection with the exclusion of patients who died within 90-days of major CRC resection

IMD quintile	Odds ratio (95% CI)	P-value
1 (most deprived)	1	**<0.001**
2	1.18 (1.00-1.39)	
3	1.29 (1.10-1.52)	
4	1.27 (1.08-1.50)	
5 (least deprived)	1.46 (1.24-1.72)	

4.3.3 Survival

Median follow up was 45 months. There was a significant difference in all-patient survival, regardless of receipt of liver resection, according to IMD quintile. Three-year survival for patients in the most deprived quintile was 17.4% compared to 22.3% for patients in the least deprived quintile ($p<0.001$) (Table 4.4). This remained so when differences in patient and institutional characteristics were taken into account (least deprived vs. most deprived IMD quintile hazard ratio (HR) 1.20, 95% C.I. 1.11 to 1.30) (Table 4). Adding liver resection as a covariate in the multivariable model attenuated this effect (least deprived vs. most deprived IMD quintile HR 1.15, 95% C.I. 1.06 to 1.24).

When survival analysis was restricted to patients undergoing a liver resection, there was no significant difference in unadjusted (Table 4.4) or adjusted (Table 4.5) survival according to IMD quintile. In patients not undergoing liver resection, patients in the least deprived group had better 3-year survival then those in the most deprived group (7.3% vs. 9.3%; $P<0.001$). This difference remained after adjusting for differences in patient characteristics.

Table 4.4 Unadjusted 3-year survival from date of colorectal diagnosis according to IMD quintile for all patients (P<0.001) and restricted to patients undergoing liver resection (P=0.742) and those not undergoing liver resection (P<0.001)

IMD quintile	**All patients**	**Patients undergoing liver resection**	**Patients not undergoing liver resection**
	3-year survival % (95% CI)		
1 (most deprived)	17.4 (15.7-19.1)	65.5 (59.7-70.1)	7.3 (6.0-8.8)
2	19.0 (17.4-20.7)	71.3 (66.7-75.4)	6.8 (5.6-8.0)
3	19.0 (17.4-20.5)	67.7 (63.2-71.8)	7.2 (6.1-8.4)
4	19.5 (18.0-21.1)	69.0 (54.6-72.9)	7.8 (6.5-8.9)
5 (least deprived)	22.3 (20.7-24.0)	69.3 (65.1-73.2)	9.3 (8.0-10.7)

Table 4.5 Hazard ratio of 3-year survival after CRC diagnosis adjusted for demographic, tumour and intuitional factors, for all patients and restricted to patients undergoing liver resection and not undergoing liver resection

		All patients	P-value	Liver resection patients	P-value	No liver resection patients	P-value
IMD quintile	**1 (most deprived)**	**1**	**<0.001**	**1**	**0.568**	**1**	**<0.001**
	2	**1.05 (0.97 to 1.14)**		**1.02 (0.79 to 1.32)**		**0.98 (0.91 to 1.06)**	
	3	**1.08 (0.99 to 1.15)**		**0.89 (0.7 to 1.14)**		**1.02 (0.93 to 1.1)**	
	4	**1.14 (1.05 to 1.23)**		**0.93 (0.74 to 1.19)**		**1.1 (1.01 to 1.19)**	
	5 (least deprived)	**1.20 (1.11 to 1.30)**		**0.97 (0.76 to 1.23)**		**1.16 (1.08 to 1.27)**	
Gender	Male	1	0.220	1	0.572	1	0.142
	Female	0.97 (0.93 to 1.02)		0.93 (0.8 to 1.06)		0.96 (0.92 to 1.01)	
Age	<65	1	**<0.001**	1	**<0.001**	1	**<0.001**
	65-74	0.78 (0.74 to 0.82)		0.89 (0.76 to 1.05)		0.85 (0.8 to 0.91)	
	75-84	0.5 (0.47 to 0.53)		0.65 (0.53 to 0.79)		0.62 (0.58 to 0.66)	
	>=85	0.31 (0.47 to 0.53)		0.3 (0.17 to 0.52)		0.45 (0.49 to 0.49)	
Emergency admission	No	1	**<0.001**	1	**<0.001**	1	**<0.001**
	Yes	0.56 (0.53 to 0.59)		0.69 (0.57 to 0.83)		0.63 (0.6 to 0.66)	
Charlson comorbidity score	0	1	**<0.001**	1	0.484	1	**<0.001**
	1	0.95 (0.9 to 1)		0.93 (0.78 to 1.1)		0.93 (0.88 to 0.99)	
	2	0.85 (0.79 to 0.91)		0.79 (0.61 to 1.04)		0.85 (0.79 to 0.92)	
Cancer site	Right	1	**<0.001**	1	**0.003**	1	**<0.001**
	Left	1.22 (1.16 to 1.28)		1.32 (1.11 to 1.56)		1.15 (1.09 to 1.22)	
	Rectum	1.10 (1.04 to 1.18)		0.99 (0.81 to 1.2)		1.14 (1.06 to 1.2)	
T-stage	0-2	1	**<0.001**	1	**0.022**	1	**0.012**
	3	1.05 (0.95 to 1.16)		0.71 (0.51 to 0.98)		1.06 (0.96 to 1.18)	
	4	0.91 (0.83 to 1.01)		0.57 (0.41 to 0.81)		0.99 (0.88 to 1.1)	
N-stage	0	1	**<0.001**	1	**<0.001**	1	**<0.001**
	1	0.69 (0.65 to 0.74)		0.64 (0.53 to 0.78)		0.79 (0.74 to 0.85)	
	2	0.56 (0.52 to 0.6)		0.49 (0.4 to 0.6)		0.69 (0.65 to 0.75)	
Hepatobiliary services on-site	No	1	**0.040**	1	0.411	1	0.215
	Yes	1.10 (1.00 to 1.20)		0.92 (0.77 to 1.09)		1.06 (0.97 to 1.15)	

4.4 Discussion

4.4.1 Summary of findings

In this study it is demonstrated that socioeconomic deprivation is associated with lower rates of liver resection and poorer 3-year survival amongst CRC patients with synchronous liver-limited metastases. This was irrespective of differences in demographic, tumour related and institutional factors. Socioeconomic deprivation was no longer associated with poorer outcomes when only patients undergoing liver resection were considered.

4.4.2 Patient survival according to socioeconomic status

The findings in this study show that socioeconomic differences in survival in patients with CRC liver metastases can be explained in part by inequalities in rates of liver resection. These findings, which mirror those reported in non-metastatic CRC (Nur *et al*., 2008), ovarian cancer (Abdel-Rahman *et al*., 2014) and lung cancer (Forrest *et al*., 2015) suggest equal treatment yields equal outcome, regardless of deprivation. For patients who did not undergo liver resection, socioeconomic deprivation continued to be associated with poorer survival after controlling for differences in patient and tumour characteristics. For this palliative cohort survival outcomes may relate to utilisation of chemotherapy (Lemmens *et al*., 2005, McGory *et al*., 2006, Aarts *et al*., 2010, Paterson *et al*., 2014), or enrolment in clinical trials (Sharrocks *et al*., 2014), both reportedly lower in more deprived patients. Data regarding these variables were not available and therefore not included in the multivariable model.

4.4.3 Explanation for disparity in liver resection rates

There are a number of obstacles to overcome for a patient with CRC liver metastases to undergo a liver resection. In patients undergoing the traditional bowel-first approach for resection of liver metastases, they must survive the resection of their primary tumour, they must recover sufficiently from this operation to potentially undergo further surgery, they must be referred to a hepatobiliary multidisciplinary team (MDT) for consideration of surgical resection and finally their metastases must be deemed operable. A patient’s socioeconomic status may influence how they negotiate this complex pathway. Within a publicly-funded health system it is an uncomfortable notion that socioeconomic status can influence treatment, and thus survival, for patients with CRC liver metastases. There are several mechanisms to explain why a patient’s socioeconomic status may influence rates of liver resection, including stage of disease at presentation, presence of comorbidities, access to local services, clinical decision making and health-seeking behaviour.

4.4.3.1 Patient factors

Although clinical and pathological characteristics in CRC patients are associated with both socioeconomic status and likelihood of liver resection, controlling for such differences did not account for the differences in liver resection rates. The presence of comorbidity, more prevalent in patients in lower socioeconomic groups in our cohort, can impact upon a patient's fitness for liver resection. After adjusting for differences in both ASA class and Charlson comorbidity score, the association between less deprivation and increased likelihood of liver resection remained. Patients with higher levels of deprivation are also more likely to suffer post-operative complications and mortality related to primary CRC resection that render them unfit for liver resection (Møller *et al*., 2012). However, as shown in the sensitivity analysis, when patients who died within 90 days of major CRC resection were excluded, the difference in rates of liver resection remained. More advanced disease stage at diagnosis is cited as one of the main causes of disparity in cancer related treatment and outcomes according to social status (Mitry and Rachet, 2006). However, this was not a factor in this study cohort, where there was not a statistically significant difference in stage according to level of deprivation.

4.4.3.2 Access to specialist care

Differences in liver resection rates according to socioeconomic status in this cohort may also relate to access to specialist care. This is particularly pertinent when considering services, such as hepatobiliary surgery, that exist in a centralised system. There is now evidence to suggest that the presence of specialist hepatobiliary services on-site at the hospital of treatment increases liver resection rates amongst patients with CRC liver metastases (Norén *et al*., 2016). Deprived patients were more commonly diagnosed at a hospital trust with no hepatobiliary services on site. Ability to travel for healthcare may be lower amongst more deprived patients and therefore the necessity to travel to access hepatobiliary services may preferentially disadvantage those of a lower socioeconomic status (Crawford *et al*., 2009). However, controlling for the on-site presence of specialist services in the study cohort did not reduce the effect of deprivation on likelihood of liver resection.

4.4.3.3 Clinical decision making

A patient's socioeconomic status may also modify the behaviour of the treating clinicians and cause inequalities in access to specialist care. There is an element of discretion by clinician practitioners in many stages of the patient pathway prior to surgery for CRC liver metastases. Although few surgeons would admit to altering their management of patients due to deprivation, clinicians may consider more deprived patients to have a lack of social support (Cavalli-Björkman *et al*., 2012), or be less able to travel to specialist services (Crawford *et al*., 2009) and therefore be less likely to refer these patients to a hepatobiliary MDT for consideration of liver resection.

4.4.3.4 Health-seeking behaviour

Finally, a patient's health seeking behaviour may partly explain this finding. Low health literacy is associated with less use of healthcare services and poorer health outcomes (Berkman *et al*., 2011). As a result, more deprived patients may be less likely to actively seek referral to a hepatobiliary unit than more affluent patients (Wiggans *et al*., 2015).

4.4.4 Study limitations

HES data does not contain information regarding the distribution or size of liver metastases, an important factor in determining the operability of liver metastases. It was therefore not possible to ascertain whether liver resection rates reflected clinically appropriate decision making or inequity. In addition, around 20% of T-stage and N-stage data is missing from NBOCA data. Importantly, there was no difference in proportion of missing data according to IMD quintile. Missing values were imputed using multiple imputation to minimise the bias associated with excluding patients with missing values. As chemotherapy is usually administered on an outpatient basis, the HES dataset does not contain details regarding its provision. Adjuvant chemotherapy is less frequently used in more deprived patients and differences in its use may account in part for the reported variation in rates of liver resection and survival inequality in patients who did not undergo liver resection (Lemmens *et al*., 2005, McGory *et al*., 2006, Aarts *et al*., 2010, Paterson *et al*., 2014). A further limitation of HES is the under-reporting of liver metastases. Some 15% of patients with CRC were found to have a HES code recorded for liver metastases at the time of diagnosis, whereas other population-based studies have reported corresponding percentages of up to 20%. However, as explained in the methods section, the odds ratio can be used as a valid measure of the impact of socioeconomic status on resection rates as socioeconomic status does not affect the recording of metastases in HES.

4.4.5 Conclusions

In conclusion, this study has demonstrated that more deprived CRC patients with synchronous liver metastases have worse survival than more affluent patients in England. Lower rates of liver resection in poorer CRC patients is likely to be a major contributory factor. As both the patient and tumour characteristics and institutional variables included in the multivariable model in this study did not account for the differences in liver resection rates according to socioeconomic status, this suggests that is it is differences in the availability of services or in decision making by socioeconomic status that account for the differences observed. Targeted efforts should be made by healthcare providers to ensure equitable access to specialist care for this cohort.

5. Chapter 5: The timing of liver resection in relation to colorectal cancer resection: current practice and survival

5.1 Introduction

The traditional approach to managing patients with CRC and synchronous liver metastases has been to resect the primary tumour, and then in the absence of disease progression, perform a liver resection. In recent years, improvements in surgical, radiological and anaesthetic techniques have resulted in a challenge to this approach, with the feasibility of both a liver-first approach and a simultaneous resection having been demonstrated.

Despite the fact that around 20% of patients with CRC are reported to have synchronous liver metastases at the time of initial diagnosis, selection criteria for each modality are not well defined. There is an absence of randomised evidence comparing the three strategies and the literature investigating both the liver-first and simultaneous approach is derived largely from high-volume single centres (Brouquet *et al*., 2010) and multi-institutional case series. (Mayo *et al*., 2013). Several studies have failed to include, or only have very small numbers in their liver first or simultaneous groups (Reddy *et al*., 2007, Mayo *et al*., 2013, Silberhumer *et al*., 2016, Welsh *et al*., 2016), or they group the liver-first and bowel-first patients together as a "staged" cohort (Lykoudis *et al*., 2014). The largest previous population based study of the characteristics and outcomes of patients with synchronous CRC and liver metastases included patients diagnosed over a twenty year period (1982-2011) with only 28 patients in the liver-first group (Mayo *et al*., 2013).

It is not known how these approaches are being utilised in England, how patients are being selected for each strategy and whether comparable outcomes are being achieved. The aim of the study presented in this chapter was to describe trends in surgical strategy in the management of patients with synchronous liver-limited CRC over time and factors influencing patient selection. The study also sought to compare long-term survival in patients undergoing either the liver-first or simultaneous approach compared to the bowel-first strategy.

5.2 Methods

5.2.1 Study population

All patients registered in the NBOCA dataset diagnosed with primary CRC between 1st January 2010 and 31st December 2015 who underwent an elective major CRC resection and liver resection for synchronous liver-limited metastases in English NHS hospitals were considered for inclusion in this study.

5.2.2 Data items and definitions

5.2.2.1 Liver resection

All HES records including admissions up to 1st January 2017 were searched for codes indicating a liver resection. Liver resection was stratified into 'major' and 'minor' according to the definition suggested by the Second International Consensus Conference on laparoscopic liver resection in which a minor resection is one in which 2 or fewer Couinaud segments are removed and a major resection is one in which 3 or more segments are removed (Wakabayashi, 2014). The extent of liver resection and its corresponding OPCS-4 description and code is shown in Table 5.1.

Table 5.1 Liver resection type according to OPCS-4 code and description

4-digit code	**Description**	**Liver resection type**
J021	Right hemihepatectomy	Major
J022	Left hemihepatectomy	Major
J023	Resection of segment of liver	Minor
J024	Wedge excision of liver	Minor
J026	Extended right hemihepatectomy	Major
J027	Extended left hemihepatectomy	Major
J028	Other specified partial excision of liver	Minor
J029	Unspecified partial excision of liver	Minor
J031	Excision of lesion of liver NEC	Minor
J035	Excision of multiple lesions of liver	Minor
J038	Other specified extirpation of lesion of liver	Minor
J039	Unspecified extirpation of lesion of liver	Minor

Patients were considered to have a simultaneous resection when a liver resection code was recorded on the day of CRC resection, a liver-first approach if a liver resection code was recorded within the year preceding resection of CRC, or a bowel-first approach if a liver resection code was recorded within the year following CRC resection.

5.2.2.2 Additional liver procedures

HES records were searched for evidence of ablative procedures performed on the same day as liver resection and portal vein embolisation performed in the 6 months preceding liver resection. The OPCS-4 codes used are displayed in Table 5.2.

Table 5.2 OPCS-4 codes used to indicate thermal ablation or portal vein embolisation

4-digit code	Description
J033	Thermal ablation of single lesion of liver
J034	Thermal ablation of multiple lesions of liver
J083	Endoscopic microwave ablation of lesion of liver using laparoscope
J102	Percutaneous transluminal embolisation of portal vein
J124	Percutaneous radiofrequency ablation of lesion of liver
J125	Percutaneous thermal ablation of lesion of liver NEC
J126	Percutaneous chemical ablation of lesion of liver
J127	Percutaneous microwave ablation of lesion of liver

5.2.2.3 Secondary metastases

As described in Chapter 3, patients were considered to have liver-limited metastases if an ICD-10 code for liver metastases was recorded in HES, with no further code for secondary metastases also recorded, in the period of 1 year before and up 30 days following CRC diagnosis.

5.2.2.4 Hepatobiliary services

An electronic survey completed by the CRC lead for each hospital trust as described in Chapter 3 was used to collect data regarding the presence of an on-site hepatobiliary MDT.

5.2.3 Statistical analysis and outcome measures

As discussed in Section 2.2.4 a landmark analysis was undertaken to compare survival. Individuals who survived a minimum of 1 year after diagnosis or, if the second procedure had not been undertaken in the year following diagnosis, more than 90-days from their second procedure, were included in the landmark analysis. Patients who died during the exposure window were excluded from analysis. Median follow-up from the date of diagnosis was 50 months. Therefore, four-year survival was presented to avoid censoring the majority of patients.

Characteristics of the treatment groups were compared using the χ^2 test. Due to differences in patient and disease characteristics in patients typically considered eligible for a liver-first or simultaneous approach, the choice of strategy for an individual patient is usually between the bowel-first approach and the liver-first approach, or the bowel-first approach and the simultaneous approach. Therefore, two separate long-term survival comparisons were made: bowel-first vs. liver-first and bowel-first vs. simultaneous. The potential biases to the survival analysis associated with differences in patient characteristics were accounted for by propensity score matching. Multivariable logistic regression models were used to generate the propensity scores. The following variables were candidates for inclusion: sex, primary CRC site within the colon or rectum, IMD quintile, age group, T-stage, N-stage, ASA grade (at time of CRC resection), major/minor liver resection. Instead of including Charlson comorbidity score, the individual indicator variable for each comorbidity was entered. One to one nearest neighbour matching without replacement was performed. The one to one ratio was chosen to minimise bias in accordance with recommendations (Austin, 2010) and callipers of 0.33 were used (0.2 of the standard deviation of the logit of the propensity score) (Austin, 2011b). The distribution of all the model factors in the bowel-first and the simultaneous group and the bowel-first and the liver-first group were compared. The balance in the covariates across the treatment groups was considered to be achieved if the standardised differences were less than 10% (Austin and Mamdani, 2006).

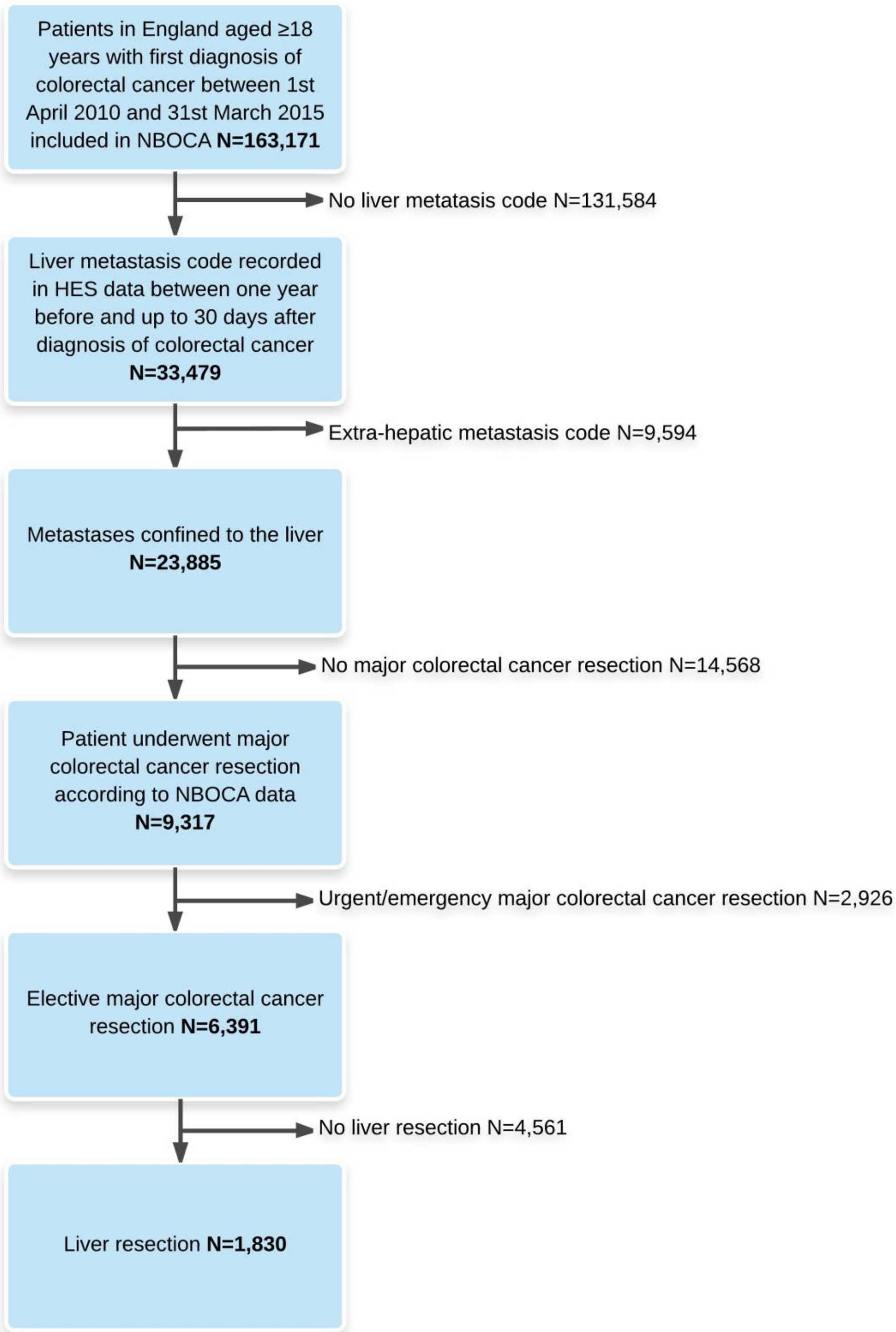
The Kaplan-Meier method was used to compare long-term survival in the matched and pre-matching cohort. Comparison of survival probabilities in the pre-matching group was performed with the log rank test. A Cox regression analysis was performed on the propensity matched cohort using a robust standard error to allow for the clustering on the pairs.

5.3 Results

5.3.1 Study cohort

A flow diagram detailing study inclusion and exclusion is shown in Figure 5.1. Of the 163,171 patients in the NBOCA database diagnosed with CRC between 1st April 2010 and 31st March 2015, there were 1,830 patients with synchronous liver-limited metastases who underwent an elective CRC and liver resection.

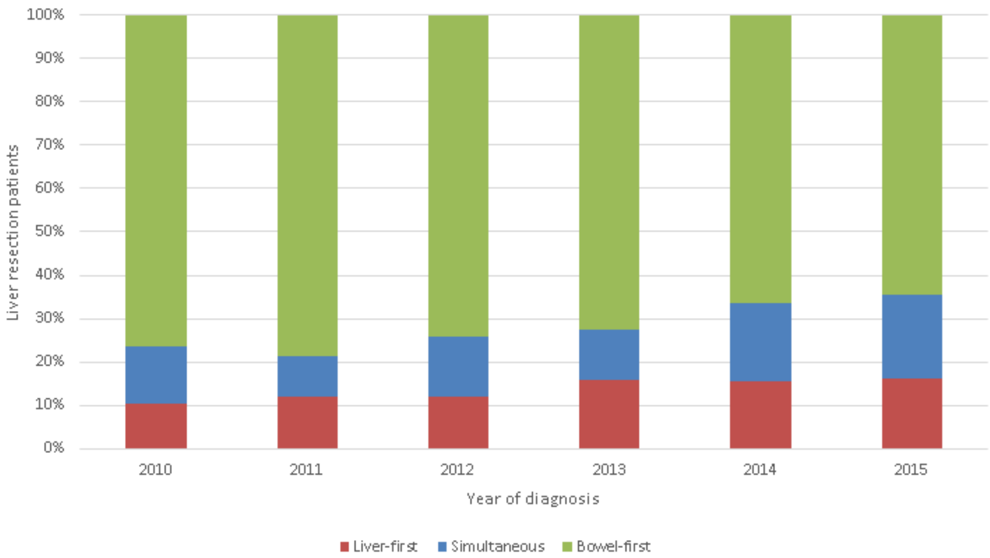
Figure 5.1 Flow chart of patient inclusion and exclusion



5.3.2 Patient selection and characteristics

Of 1,830 patients who underwent both a CRC and liver resection, 270 (14.8%) patients underwent a liver-first approach, 259 (14.2%) a simultaneous approach and 1,301 (71.1%) a bowel-first approach. The proportion of patients undergoing either a liver-first or simultaneous approach increased over the period, from 59 out of 249 patients (26.8%) in 2010 to 99 out of 278 patients (35.6%) in 2015, p<0.001 (Figure 5.2).

Figure 5.2 Trends in surgical strategy over study period according to year of diagnosis



Baseline demographics and clinico-pathological characteristics for patients having both a liver resection and CRC resection according to treatment strategy are outlined in Table 5.3. Patients in the liver-first group were younger, had lower T-stage and N-stage and more commonly had a rectal cancer primary than patients in the bowel-first and simultaneous cohorts. In addition, a higher proportion had rectal cancer and underwent a major liver resection. Combined liver ablation, two-stage resection and portal vein embolisation, were used more frequently in the liver-first cohort.

In comparison, patients in the simultaneous group tended to be older, had a right sided CRC primary tumour and typically underwent a minor liver resection. These patients were more commonly diagnosed in hospital trusts with on-site hepatobiliary services when compared to patients undergoing a bowel-first or liver-first approach.

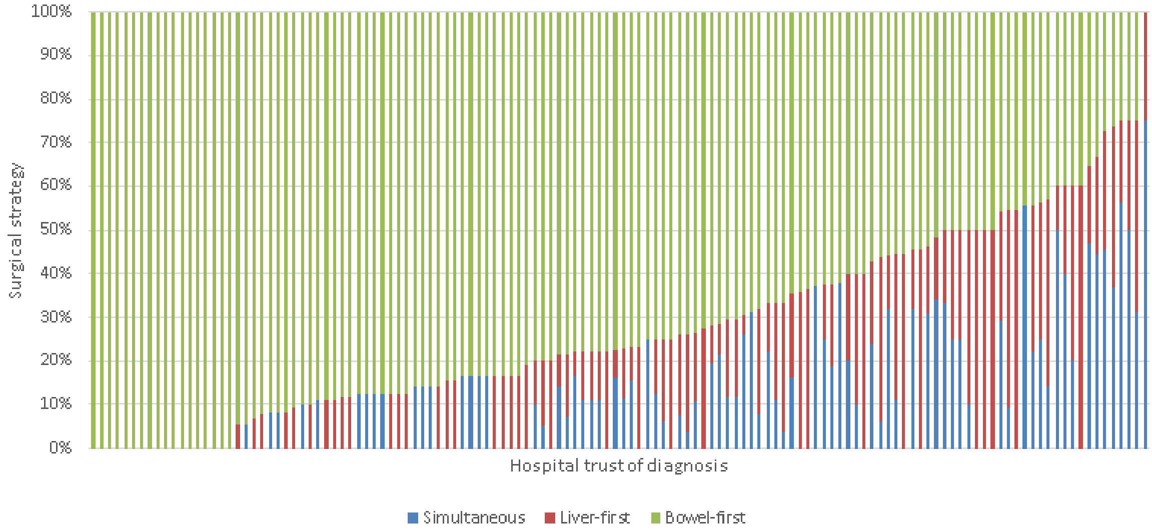
Table 5.3 Clinico-pathological characteristics and surgical details of patients diagnosed with synchronous liver metastases undergoing CRC resection and liver resection (n=1,830)

		Liver-first n=270 (%)	Simultaneous n=259 (%)	Bowel-first n=1,301 (%)	P-value
Sex	Male	173 (64.1)	141 (54.4)	814 (62.6)	**0.033**
	Female	97 (35.9)	118 (45.6)	487 (37.4)	
CRC site	Right side	21 (7.8)	134 (51.7)	356 (27.4)	**<0.001**
	Left side	97 (35.9)	71 (27.4)	630 (48.4)	
	Rectum	152 (56.3)	54 (20.9)	315 (24.2)	
IMD quintile	1 (most deprived)	27 (10.1)	45 (17.5)	153 (11.8)	0.110
	2	53 (19.9)	51 (19.8)	233 (18.0)	
	3	56 (21.0)	52 (20.2)	269 (20.8)	
	4	71 (26.6)	54 (21.0)	293 (22.6)	
	5 (least deprived)	60 (22.5)	55 (21.4)	346 (26.7)	
	Missing	3	0	11	
Age (years)	<60	122 (45.2)	73 (28.2)	397 (30.5)	**<0.001**
	60-70	88 (32.6)	81 (31.3)	472 (36.3)	
	>70	60 (22.2)	105 (40.5)	432 (33.2)	
Charlson comorbidity score	0	163 (61.1)	158 (61.7)	849 (66.6)	0.097
	1	85 (31.8)	70 (27.3)	325 (25.5)	
	≥2	19 (7.1)	28 (10.9)	100 (7.9)	
	Missing	3	3	27	
T-stage	T0-2	45 (17.3)	21 (8.2)	102 (8.0)	**<0.001**
	T3	173 (66.5)	146 (56.8)	790 (62.0)	
	T4	42 (16.2)	90 (35.0)	382 (30.0)	
	Missing	10	2	27	
N-stage	N0	100 (38.5)	78 (30.5)	390 (30.6)	**0.042**
	N1	94 (36.2)	110 (43.0)	484 (38.0)	
	N2	66 (25.4)	68 (26.6)	401 (31.5)	
	Missing	10	3	26	
ASA class (at CRC resection)	1/2	187 (75.1)	169 (70.4)	995 (81.0)	**<0.001**
	3/4	62 (24.9)	71 (29.6)	234 (19.0)	
	Missing	21	19	72	
Major liver resection		127 (47.0)	40 (15 4)	535 (41.1)	**<0.001**
Combined ablation		41 (15.2)	20 (7.7)	148 (11.4)	**0.026**
Two stage resection		10 (3.7)	2 (0.8)	21 (1.6)	**0.026**
Portal vein embolisation		31 (11.5)	16 (6.2)	153 (11.8)	**0.030**
Hepatobiliary surgery on-site		72 (26.7)	138 (53.3)	269 (20.7)	**<0.001**

5.3.3 Variation by hospital trust of diagnosis

There was wide variation in surgical strategy according to hospital trust of diagnosis (Figure 5.3). In 18 out of 132 (13.6%) of hospital trusts, all patients diagnosed with synchronous liver-metastases who underwent a liver resection, were treated with the bowel-first approach. There were 19 hospital trusts (14.4%) in which more than 50% of patients underwent either the simultaneous or the liver-first approach.

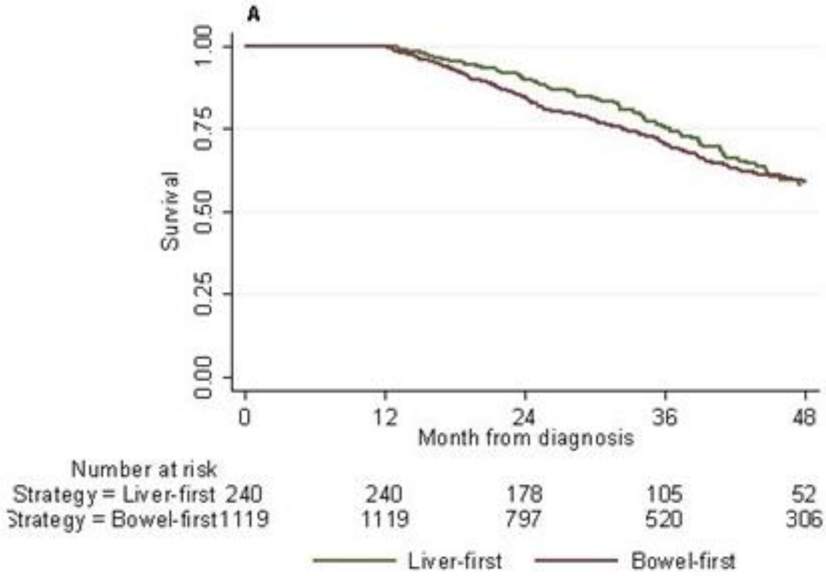
Figure 5.3 Variation in surgical strategy according to English National Health Service hospital trust of diagnosis

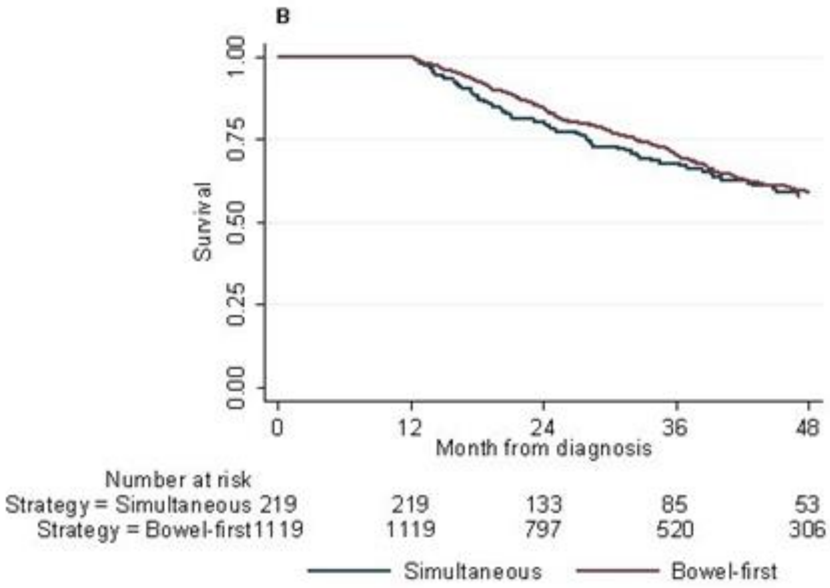


5.3.4 Survival

Four-year survival in the landmark analysis for the unmatched cohort was 59.2% (95% CI 56.5-62.1) in the bowel-first group, 58.8% (95% CI 50.6-66.1) in the liver-first group and 59.6% (95% CI 50.4-66.7) in the simultaneous group. Kaplan-Meier survival curves for the unmatched cohorts are shown in Figure 5.4.

Figure 5.4 Landmark analysis of survival according to surgical strategy in all patients, A P=0.638, B P=0.788 (log rank test)





5.3.4.1 Matched survival analysis

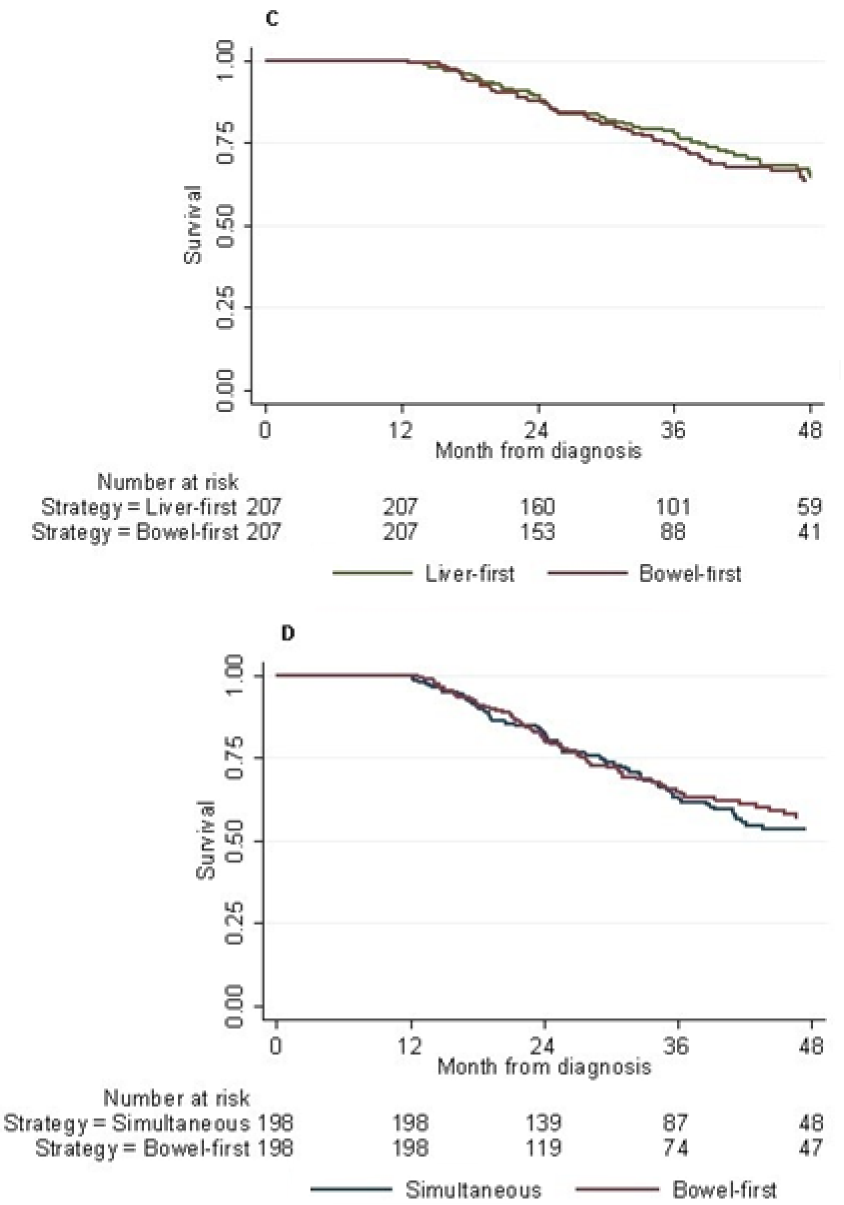
After propensity score-matching was performed across patients included in the landmark analysis, there were 198 matched bowel-first patients in the bowel-first vs. simultaneous comparison, and 207 matched bowel-first patients in the bowel-first vs. liver-first comparison. The patient, tumour and operative characteristics of the bowel-first patients matched to the simultaneous cohort and those of the bowel-first patients matched to the liver-first cohort were quite different. Table 5.4 shows that the characteristics of the matched bowel-first patients reflect the patients in each of the simultaneous and liver-first cohorts.

Table 5.4 Clinico-pathological characteristics and surgical details of propensity score-matched patients

		Liver-first N=207 (%)	**Bowel-first N=207 (%)**	**Bowel-first N=198 (%)**	**Simultaneous N=198 (%)**
Sex	Male	132 (63.8)	140 (67.6)	108 (54.6)	104 (52.5)
	Female	75 (36.2)	67 (32.4)	90 (45.5)	94 (47.5)
CRC site	Right side	12 (5.8)	8 (3.9)	94 (47.5)	84 (42.4)
	Left side	77 (37.2)	54 (26.1)	58 (29.3)	69 (34.9)
	Rectum	118 (57.0)	145 (70.1)	46 (23.2)	45 (22.7)
IMD quintile	1 (most deprived)	20 (9.7)	22 (10.6)	37 (18.7)	48 (24.2)
	2	40 (19.3)	41 (16.8)	35 (17.7)	34 (17.2)
	3	45 (21.7)	52 (25.1)	35 (17.7)	37 (18.7)
	4	54 (26.1)	52 (25.1)	45 (22.7)	42 (21.2)
	5 (least deprived)	48 (23.2)	40 (19.3)	46 (23.2)	37 (18.7)
Age group	18-64	95 (45.9)	98 (47.3)	55 (27.8)	63 (31.8)
	65-74	66 (31.9)	65 (31.4)	65 (32.8)	57 (28.8)
	75-84	46 (22.2)	44 (21.3)	78 (39.4)	78 (39.4)
Charlson comorbidity score	0	131 (63.3)	126 (60.9)	121 (61.1)	128 (64.7)
	1	61 (29.5)	65 (31.4)	56 (28.3)	52 (26.3)
	≥2	15 (7.3)	16 (7.7)	21 (10.6)	18 (9.1)
T-stage	T0-2	37 (17.9)	49 (23.7)	18 (9.1)	18 (9.1)
	T3	140 (67.6)	130 (62.8)	113 (57.1)	117 (59.1)
	T4	30 (14.5)	28 (13.5)	67 (33.8)	63 (31.8)
T-stage	N0	79 (38.2)	85 (41.1)	64 (32.3)	72 (36.4)
	N1	77 (37.2)	73 (35.3)	84 (42.4)	80 (40.4)
	N2	51 (24.6)	49 (23.7)	50 (25.3)	46 (23.2)
ASA class (at CRC resection)	1/2	160 (77.3)	153 (73.9)	145 (73.2)	148 (74.8)
	3/4	47 (22.7)	54 (26.1)	53 (26.8)	50 (25.3)
Liver resection type	Major	98 (47.3)	106 (51.2)	27 (13.6)	26 (13.1)
	Minor	109 (52.7)	101 (48.8)	171 (86.4)	172 (86.9)

Kaplan-Meier survival curves for the matched cohorts are shown in Figure 5.5. Survival analysis on the propensity score-matched groups showed there to be no evidence of a difference in four-year survival between the bowel-first and simultaneous cohort (HR 0.92 (95% CI 0.80-1.06)), or between the bowel-first and liver-first cohort (HR 0.99 (95% CI 0.82-1.19)). Note that in Figure 5.5 the survival curve of the matched bowel-first patients is different due to the different patient characteristics of the two matched cohorts.

Figure 5.5 Landmark analysis of survival in propensity score-matched patients according to surgical strategy



5.4 Discussion

5.4.1 Summary of main findings

This population-based cohort study is the first to provide an overview of national practice in the management of patients presenting with CRC and synchronous liver-limited metastases. This study shows a growing popularity of the liver-first and simultaneous approach, yet wide inter-hospital variation in patient management. The clinico-pathological characteristics of patients undergoing alternative strategies were quite distinct, confirming that these are generally performed in highly selected patients. There was no evidence of a long-term survival difference of the bowel-first strategy compared to the liver-first or simultaneous strategy.

5.4.2 Study limitations

The HES database does not include information regarding the extent or distribution of liver metastases, an important factor in determining management decisions particularly regarding the use of simultaneous resection. It is, however, unlikely that the burden of liver metastases and other patient and surgical characteristics, would vary sufficiently across the country to account for the inter-hospital differences in surgical approach.

Patients were only included in this study if they underwent both CRC resection and liver resection. When comparing both operative mortality and long-term mortality in this cohort, it should be considered that to complete the treatment, patients in both the liver-first and bowel-first group must survive, and recover sufficiently from, the initial operation. There is inevitably patient ‘drop-out’ from such complex and prolonged treatment pathways, which may be significant. Several single centre cohort studies have reported that between 16 to 35% of liver-first and bowel-first patients fail to proceed to the second operation (Brouquet *et al*., 2010, Welsh *et al*., 2016, Sturesson *et al*., 2017). This is not only related to operative morbidity. Proponents of a staged approach argue that the assessment of disease progression during the interval between first resection and second resection allows those with a poor prognosis to be excluded from surgery (Slesser *et al*., 2013). A potential disadvantage of the simultaneous approach is that it does not allow for such an assessment period. Studies comparing outcomes between staged and simultaneous cohorts will therefore over-sample patients with favourable tumour biology in the staged population, leading to selection bias in favour of the staged approaches.

The direct comparison of survival in these groups from time of diagnosis is a common feature of studies in patients with synchronous CRC liver metastases, and leads to bias in favour of the staged cohorts. Although the use of a landmark survival analysis addresses this bias it does come with its own disadvantages. These include the need to set a, somewhat arbitrary, choice of landmark time point. One year following the date of diagnosis was selected for the analysis in Chapter 5 as over 90% of patients have undergone their second operation by this time point. The choice of landmark time point must also take into account that the longer the time period set from diagnosis, the more patients die before this time and therefore are excluded from the study, thus losing statistical power.

5.4.3 Survival according to surgical approach

The landmark survival analysis of the matched cohorts in the present study showed no evidence of a difference in long-term survival between patients undergoing an alternative strategy to those undergoing a bowel-first approach.

At which time point to begin the comparison of the three groups varies throughout the literature. In the analysis of 1,004 patients who completed one of the three treatment strategies, Mayo and co-authors (2013) analysed long-term survival from 90-days after the date of the liver-directed operation. This analysis therefore included the post-operative mortality associated with CRC resection for patients in the liver-first group, yet no post-operatively mortality for patients in the liver-first and simultaneous cohort. Brouquet and co-authors (2010) analysed survival in 142 patients from the date of the last surgery, therefore comparing post-operative mortality of a combined liver and CRC resection in simultaneous patients to a single procedure in staged patients. In both of the aforementioned methods, the survival analysis start date for each patient varied from the date of diagnosis. In this study, survival in each cohort was estimated conditional on a patient's survival to the landmark time to reduce such time bias.

5.4.4 Patient characteristics according to surgical approach

The clinico-pathological characteristics of patients undergoing a simultaneous and liver-first strategy were quite distinct. A liver-first approach is commonly used in patients with more extensive hepatic disease (De Rosa *et al*., 2013). This was suggested in the present cohort by the high rate of major liver resection in the liver-first group as well as increased used of techniques to maximise the future liver remnant. Liver-first patients will have been deemed by the colorectal and hepatobiliary MDTs fit enough to withstand systemic chemotherapy followed by two major operations. It therefore follows that liver-first patients in the present cohort were younger and had less comorbidities than those in the bowel-first cohort. There also may be more treatment directed at attempting to cure a younger fitter patient. Synchronous resection increases the complexity of the surgical procedure and it is therefore notable that patients selected for a simultaneous approach tended to be older and have a higher ASA grade than patients undergoing alternative approaches. The safety of simultaneous resection when involving a minor resection in combination with high or low risk CRC resection has been demonstrated (Shubert *et al*., 2015, Kelly *et al*., 2015) and it may be considered clinically appropriate to offer this strategy to higher risk patients with low volume liver disease to avoid the cumulative morbidly and mortality of separate interventions.

5.4.5 Inter-hospital variation in surgical strategy

There was wide variation in surgical approach according to hospital trust of diagnosis reflecting no clear consensus as to optimal management. The presence of a hepatobiliary team on-site appeared to impact upon decision-making, as patients diagnosed at hospital trusts with such services on-site were more likely to undergo a simultaneous or liver first approach. Patients diagnosed at hospital trusts with no hepatobiliary MDT on-site may be undergoing CRC resection prior to referral to a hepatobiliary MDT for consideration of liver resection.

5.4.6 Conclusions

This study shows that a liver-first or synchronous approach can achieve similar survival rates in selected cases to the conventional bowel-first approach for CRC patients with synchronous liver limited metastases. The study has also indicated there to be substantial variation in how patients with synchronous disease are managed. This suggests that there is scope for increased resection rates of liver metastases in either the liver-first or the simultaneous settings. To achieve this patients with synchronous disease should be discussed by a hepatobiliary MDT early in their pathway.

6. Chapter 6: The impact of advancing age on outcomes in patients undergoing hepatectomy for colorectal cancer liver metastases

6.1 Introduction

There are noticeable differences in the incidence trends of CRC between countries. These differences are particularly marked in the individual risk at a given age, known as the age-standardised rate (ASR) (Papamichael *et al*., 2015). Over the last 25 years the ASR fell by more than 30% in the United States, while over the same period in the UK although unchanged in women, the ASR rose by 30% in men (Cancer Research UK, 2017). As mortality from non-cancer causes such as heart disease reduces, an elderly population at a high risk of developing bowel cancer remains. Currently in the UK the highest incidence of colorectal cancer diagnosis is in older patients and more than 40% of diagnoses are made in patients 75 years and over (nboca.org.uk, 2016).

The older population is consistently under-represented in clinical trials and institutional case series, and as a result outcomes in this cohort are also less well characterised (Aapro *et al*., 2005). It is well accepted that in general, major surgery in the elderly can be associated with significant risk. A study of more than 4 million patients in the UK found hospital mortality after surgery to be 1.9% (0.44% in elective procedures and 5.4% in emergency procedures). In patients with a mean age of 75 years, mortality rose to 12.3% (Pearse *et al*., 2006).

Elderly patients with CRC liver metastases are less likely to undergo liver resection (Leporrier *et al*., 2006, Morris *et al*., 2010, Norén *et al*., 2016, Angelsen *et al*., 2017). Concerns over their physical and mental frailty may preclude specialist referral. Surgical risk stratification remains one of the most important aspects of management in elderly patients and there is therefore a need to better characterise outcomes in this patient cohort (Tan *et al*., 2012). This information is used to inform operative decisions, choice of peri-operative management and to discuss risk with patients.

The aim of this chapter was to investigate the impact of age on surgical risk and long-term survival following liver resection, in patients with resected primary colorectal cancer.

6.2 Methods

6.2.1 Study population

Patients diagnosed with primary CRC between 1st April 2010 and 31st March 2016 in English NHS hospital trusts included in the NBOCA dataset who had undergone major CRC resection were eligible for inclusion.

6.2.2 Liver procedure

All HES records including admissions up to 31st March 2016 were searched for codes indicating a liver resection, portal vein embolisation and ablation procedure as described in Chapters 3 and 5. Liver resection was stratified into 'major' or 'minor' according to the resection of three or more Couinaud segments as described in Chapter 4.

6.2.3 Surgical access

To ascertain surgical access, the additional procedural codes shown in Table 6.1 indicating a minimally invasive technique were searched for. When these were in the same spell as a procedure code for resection this was assumed to represent a minimally invasive liver resection.

Table 6.1 OPCS-4 procedure codes used to identify minimally invasive liver resection

4-digit code	Description
Y751	Laparoscopically assisted approach to abdominal cavity
Y752	Laparoscopic approach to abdominal cavity
Y753	Robotic minimal access approach to abdominal cavity
Y754	Hand assisted minimal access approach to abdominal cavity
Y758	Other specified minimal access to abdominal cavity
Y759	Unspecified minimal access to abdominal cavity

6.2.4 Outcome measures

To investigate age as a risk factor for poor post-operative outcomes, 90-day mortality, 30-day emergency readmission, 30-day unplanned return to theatre, length of stay and overall and cancer specific 3-year survival was compared between age groups.

6.2.5 Statistical analysis

Comparisons of patient and tumour characteristics between different age groups undergoing liver resection were performed using the χ^2 test. The Kaplan-Meier method was used to describe overall survival and the log rank test for overall survival differences.

The Cox-proportional hazards model was used to evaluate the impact of age on 90-day mortality and 3-year mortality adjusted for differences in patient, tumour and surgical characteristics. The following variables were included: gender, age, IMD quintile, year of diagnosis, comorbidities, primary tumour site, primary tumour pathological T-stage, N-stage and M-stage, laparoscopic/ open liver resection and major/ minor liver resection. The model for three-year mortality additionally included an interaction between follow-up time (0-90 days after surgery vs. 90 days-3 years after surgery) and each of the above risk factors. This allowed risk factors to have a different effect shortly after surgery and in the longer term.

A Fine and Gray (1999) competing risks proportional hazards model was used to evaluate the impact of age on cancer-specific 3-year mortality adjusted for differences in patient, tumour and surgical characteristics (26). The competing risks model allows the effect of deaths from other causes to be accounted for. The same risk-factors were included in the competing risks model as the Cox regression model, including interactions between follow-up time (0-90 days after surgery vs. 90 days-3 years after surgery) and each risk factor. The cumulative incidence of cancer-specific mortality according to age and extent of liver resection was determined after adjusting for competing risks.

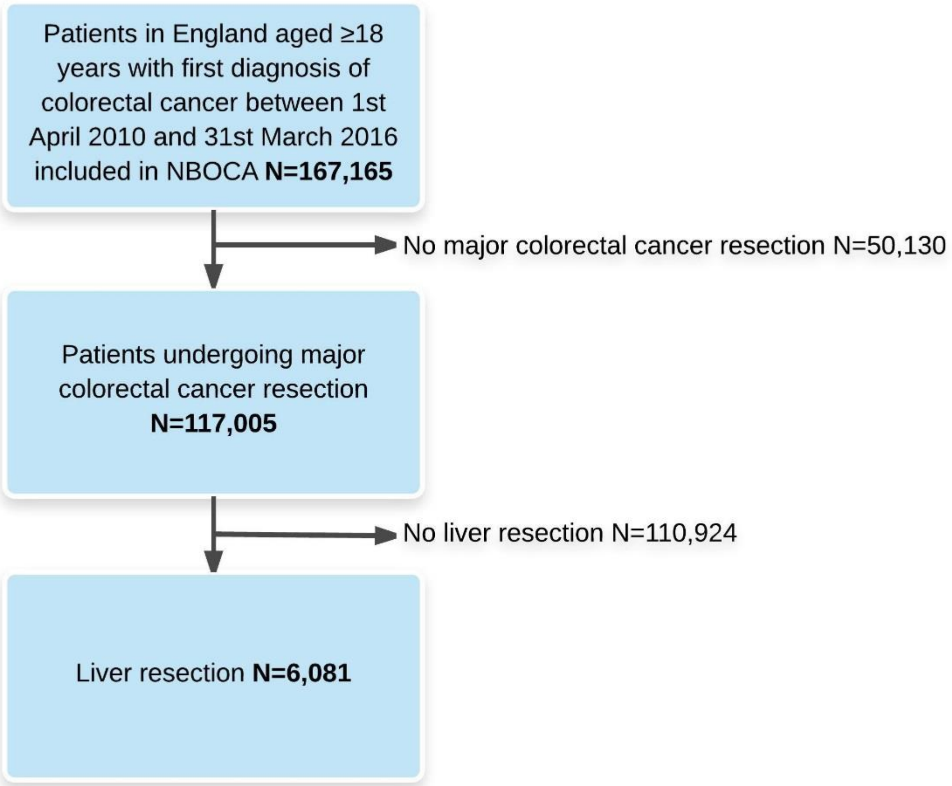
Missing values for the risk factors above were imputed with multiple imputation using chained equations creating 10 datasets and using Rubin's rules to combine estimates (27). The same variables included in the final multivariable model were included in the imputation model.

6.3 Results

6.3.1 Study cohort

Of the 117,005 patients undergoing major resection of CRC from 1st April 2010 to 31st March 2016, a total of 6,081 (5.9%) underwent liver resection (Figure 6.1).

Figure 6.1 Flow diagram of patient inclusion and exclusion



6.3.2 Patient characteristics

The characteristics of study patients undergoing liver resection are shown in Table 6.2. Patients aged ≥75 years tended to have more comorbidities (Charlson comorbidity score ≥2, ≥75 years vs. <65 years, 12.5% vs. 4.1%, P<0.001) and a higher ASA class (ASA 3/4/5, ≥75 years vs. <65 years, 31.4% vs. 15.7%, P<0.001), and more commonly had right sided colonic primary tumour (≥75 years vs. <65 years, 37.4% vs. 20.4%, P<0.001) and less advanced nodal disease (N2 ≥75 years vs. <65 years, 30.7s% vs. 20.7%, P<0.001) than younger patients.

Patients aged ≥75 years more commonly underwent a liver resection for metachronous disease (M0 at CRC diagnosis ≥75 years vs. <65 years, 64.8% vs. 49.4%, P<0.001). There was no significant difference in the proportion of patients undergoing a major or minor liver resection according to age (minor liver resection ≥75 years vs. <65 years, 67.0% vs. 64.3%, P=0.105). Laparoscopic liver resection was used more commonly in the elderly (≥75 years vs. <65 years, 17.7% vs. 13.8%, P=0.006) but both thermal ablation (≥75 years vs. <65 years, 9.0% vs. 12.9%, P<0.001) and portal vein embolisation (≥75 years vs. <65 years, 7.5% vs. 10.5%, P=0.005) were used less commonly with advancing age.

Table 6.2 Clinico-pathological characteristics of patients diagnosed with primary CRC undergoing liver resection (N=6,081)

		<65 years N=2,829 (%)	**65-74 years N=2,070 (%)**	**≥75 years N=1,182 (%)**	**Total N=6,081 (%)**	**P-value**
Gender	Male	1,706 (60.3)	1,389 (67.1)	755 (63.9)	3,850 (63.3)	**<0.001**
	Female	1,123 (39.7)	681 (32.9)	427 (36.1)	2,231 (36.7)	
Charlson comorbidity score	0	1,987 (72.2)	1,227 (60.9)	670 (58.7)	3,884 (65.7)	**<0.001**
	1	653 (23.7)	601 (29.8)	328 (28.8)	1,582 (26.8)	
	≥2	114 (4.1)	188 (9.3)	143 (12.5)	445 (7.5)	
	Missing	75	54	41	170	
IMD quintile	1 (most deprived)	421 (15.0)	275 (13.4)	155 (13.2)	851(14.1)	**<0.001**
	2	570 (20.3)	321 (15.6)	192 (16.3)	1,083 (17.9)	
	3	606 (21.5)	440 (21.4)	263 (22.3)	1,309 (21.6)	
	4	574 (20.4)	516 (25.1)	293 (24.9)	1,383 (22.9)	
	5 (least deprived)	644 (22.9)	504 (24.5)	274 (23.3)	1,422 (23.5)	
	Missing	14	14	5	33	
Primary CRC site	Right side	578 (20.4)	603 (29.1)	442 (37.4)	1,623 (26.7)	**<0.001**
	Left side	1,381 (48.8)	879 (42.5)	490 (41.5)	2,750 (45.2)	
	Rectum	870 (30.8)	588 (28.4)	250 (21.2)	1,708 (28.1)	
Emergency presentation of CRC	No	2,324 (83.5)	1,776 (87.1)	986 (85.8)	5,086 (85.2)	**0.002**
	Yes	459 (16.5)	264 (12.9)	163 (14.2)	886 (14.8)	
	Missing	46	30	33	109	
ASA class (at CRC resection)	1	609 (25.7)	236 (13.3)	77 (7.4)	922 (17.8)	**<0.001**
	2	1,398 (58.9)	1,107 (62.4)	634 (61.1)	3,139 (60.5)	
	3	340 (14.3)	406 (22.9)	303 (29.2)	1,049 (20.2)	
	4/5	27 (1.4)	26 (1.5)	23 (2.2)	76 (1.5)	
	Missing	455	295	145	895	
T-stage	0-2	278 (10.4)	243 (12.5)	133 (11.9)	654 (11.4)	**0.030**
	3	1,640 (61.1)	1,220 (62.6)	684 (61.0)	3,544 (61.6)	
	4	767 (28.6)	486 (24.9)	304 (27.1)	1,557 (27.1)	
	Missing	144	121	61	326	
N-stage	0	883 (32.9)	724 (37.0)	474 (42.1)	2,081 (36.1)	**<0.001**
	1	978 (36.4)	753 (38.5)	418 (37.2)	2,149 (37.3)	
	2	824 (30.7)	478 (24.5)	233 (20.7)	1,535 (26.6)	
	Missing	144	115	57	316	
Liver resection indication	Metachronous disease	1,291 (49.4)	1,073 (55.8)	704 (64.8)	3,068 (54.6)	**<0.001**
	Synchronous disease	4,320 (50.6)	851 (44.2)	383 (35.2)	2,554 (45.4)	
	Missing	218	149	95	459	
Liver resection type	Minor resection	1,795 (63.5)	1,324 (64.0)	792 (67.0)	3,911 (64.3)	0.105
	Major resection	1,034 (36.6)	746 (36.0)	390 (33.0)	2,170 (35.7)	
Liver resection access	Open	2,440 (86.3)	1,751 (84.6)	973 (82.3)	5,164 (84.9)	**0.006**
	Laparoscopic	389 (13.8)	319 (15.4)	209 (17.7)	917 (15.1)	
Combined ablation		365 (12.9)	176 (8.5)	106 (9.0)	647 (10.6)	**<0.001**
Portal vein embolisation		296 (10.5)	176 (8.5)	89 (7.5)	561 (9.2)	**0.005**

6.3.3 Crude outcomes

Unadjusted post-operative outcomes are displayed in Table 6.3. Overall 90-day mortality was 2.1% (130/6,081) in patients undergoing liver resection. The 90-day mortality increased with advancing age (<65 years: 0.9% (26/2,829), 65-74 years: 2.8% (57/2,070) and ≥75 years: 4.0% (47/1,182); P<0.001). There was no significant difference in rates of either return to theatre within 30-days or emergency readmission within 30-days according to patient age. The median length of stay following liver resection was 6 days (inter-quartile range (IQR) 5-8), and there was no significant difference according to patient age.

Table 6.3 Post-operative outcome following liver resection according to age

	Total N=6,081 (%)	**<65 years N=2,829 (%)**	**65-74 years N=2,070 (%)**	**≥75 years N=1,182 (%)**	**P-value**
90-day mortality	130 (2.1)	26 (0.9)	57 (2.8)	47 (4.0)	**<0.001**
Emergency readmission (30-days)	91 (1.5)	53 (1.9)	31 (1.5)	12 (1.0)	0.205
Return to theatre (30-days)	204 (3.4)	76 (3.7)	42 (3.6)	86 (3.0)	0.438
Median length of stay in days (IQR)	6 (5-8)	6 (4-8)	6 (5-9)	7 (5-10)	0.835

There was increased unadjusted 90-day mortality for older patients undergoing both major and minor liver resection, as shown in Table 6.4.

Table 6.4 90-day mortality according to extent of liver resection and age

	All patients (%)	**<65 years (%)**	**65-74 years (%)**	**≥75 years (%)**	**P-value**
Major liver resection	65/ 2,170 (3.0)	14/ 1,034 (1.4)	27/ 746 (3.6)	24/ 390 (6.2)	**<0.001**
Minor liver resection	65/ 3,911 (1.7)	12/ 1,795 (0.7)	30/ 1,324 (2.3)	23/ 792 (2.9)	**<0.001**

Median follow up was 36.4 months. Overall 3-year survival (<65 years: 60%; 65-74 years: 56%, and ≥75 years: 51%) decreased with advancing age (P<0.001).

6.3.4 Risk-adjusted outcomes

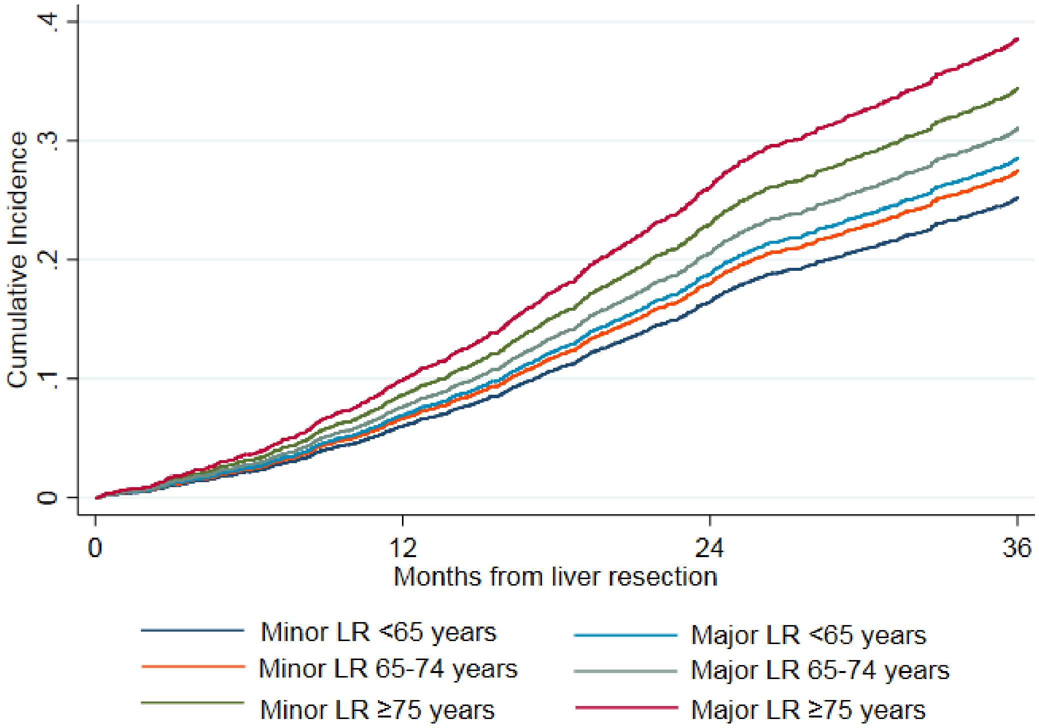
The effect of advancing age on outcomes following liver resection when adjusted for differences in patient and tumour characteristics was most pronounced early in the follow-up period (90-day mortality ≥75 years vs. <65 years HR 4.65 95% CI 2.7-8.1) (Table 6.5). The results from the full multivariable models are presented in Appendix 9.2.

Table 6.5 The impact of age upon mortality amongst patients undergoing liver resection adjusted for other patient and tumour characteristics

Age (years)	0-90 days All-cause mortality Hazard Ratio (95% CI)	P-value	90 days-3 years All-cause mortality Hazard Ratio (95% CI)	P-value	90 days-3 years Cancer-specific mortality Hazard Ratio (95% CI)	P-value
<65	1		1		1	
65-74	2.88 (1.67 to 4.97)	**P<0.001**	1.07 (0.90 to 1.17)	**P<0.001**	1.01 (0.90 to 1.14)	**P<0.001**
≥75	4.25 (2.38-7.57)		1.41 (1.23 to 1.61)		1.26 (1.09 to 1.45)	

Age was an independent risk factor for mortality (P<0.001), however, in the period of 90-days to 3-years following liver resection, mortality in patients aged 65-74 years was similar to those aged <65 (overall mortality: HR 1.07, 95% CI 0.90-1.17; cancer-specific mortality: HR 1.03, 0.92-1.16). Age ≥75 years was associated with both increased risk of overall mortality (HR 1.47, 95% CI 1.30-1.68) and cancer-specific mortality (HR 1.30, 95% CI 1.13-1.49). The 3-year cumulative incidence of cancer-specific mortality stratified by age and extent of liver resection is demonstrated in Figure 6.2.

Figure 6.2 Cumulative incidence curves for cancer-specific mortality stratified according to age group and extent of liver resection



Sub-group analysis confirmed age to be an independent prognostic factor for both 90-day and longer term mortality in patients undergoing major and minor liver resection.

6.4 Discussion

6.4.1 Summary of findings

This population based cohort study using prospectively collected national audit data, included over 6,000 patients, 3,252 of whom were aged 65 years and over. Estimates of surgical risk and long-term survival are presented by age group, both crude and adjusted for other risk factors. Although elderly patients were at increased risk of post-operative mortality following liver resection, the length of stay and rates of return to theatre and emergency readmission were comparable to younger patients. Over half of patients 75 years and over undergoing liver resection for CRC liver metastases were alive 3 years following their resection.

6.4.2 Post-operative outcomes in the older patient

Clinicians will frequently have to decide if major surgery is justified in an elderly patient. Balancing the post-operative risks with the oncological benefits is a key step in the decision-making process. Studies have consistently demonstrated elderly patients to be less likely to undergo liver resection than younger patients (Leporrier *et al*., 2006, Morris *et al*., 2010, Norén *et al*., 2016, Angelsen *et al*., 2017). This may be due to later presentation of disease, physiological fitness, or a perception that radical surgery is less likely to be of benefit. Elderly patients undergoing liver resection in this cohort had more comorbidities and higher ASA class than younger patients suggesting that elderly patients are not being refused liver resection due to the presence of pre-existing health conditions.

For elderly patients undergoing major liver resection, 3-year survival reaches nearly 50%, thus far exceeding median survival in patients who do not undergo liver resection (Stillwell *et al*., 2010). Despite this, post-operative mortality needs to be acceptable. Previous reports of 90-

day mortality in elderly patients undergoing liver resection present conflicting results. Some have shown no association between age and post-operative mortality (Leal *et al*., 2016) and in others age is reported to be a predictive factor (Cook *et al*., 2012, Booth *et al*., 2015). Even when the study population is restricted to patients undergoing major liver resection, reported outcomes in the elderly compared to younger patients are mixed (Menon *et al*., 2006, Reddy *et al*., 2011a, Bell *et al*., 2017). This study supports the view that age is an independent predictor of 90-day mortality following both minor and major liver resection.

This study found no increase in measures of morbidity such as return to theatre, length of stay and emergency readmission in elderly patients undergoing liver resection. This is supported by previous literature demonstrating that although elderly patients experience similar major morbidity to younger patients, they are more likely to experience minor complications including urinary tract and chest infections (Mann *et al*., 2008). The increased post-operative mortality in the elderly cohort suggests that those patients who do suffer a complication of surgery are more likely to die as a result due to poorer physiological reserve.

6.4.3 Thermal ablation

Despite there being no significant difference in the proportion of patients undergoing major liver resection according to age, combined thermal ablation was used less commonly in the elderly. Advancing age is associated with a decline in physiological reserve, hepatic size, blood flow and rate of liver regeneration (Aalami *et al*., 2003, Schmucker and Sanchez, 2011). This places the older patient at an increased risk of post-operative liver failure, the most common cause of significant morbidity and mortality following liver resection (Rahbari *et al*., 2011, Anaya *et al*., 2011). Thermal ablation of small lesions in combination with a liver resection may facilitate complete tumour clearance, whilst preserving parenchyma (Evrard *et al*., 2014). This strategy may be an acceptable alternative to a higher risk major liver resection in the elderly population. This study did not examine patients undergoing ablative techniques alone with no liver resection, but there is evidence that thermal ablation is associated with lower complication rates and an improved health-related quality of life than surgery (Loveman *et al*., 2014). The LAVA (**L**iver **R**esection Surgery Versus Thermal Ablation for Colorectal Li**V**er Met**A**stases) trial is currently seeking to address this (ISRCTN registry, 2017).

6.4.4 Laparoscopic liver resection

Laparoscopic liver resection is rapidly gaining momentum (Wakabayashi *et al*., 2015b). Randomised trials of laparoscopic versus open liver resection are awaited, but there is recent evidence to suggest that a laparoscopic approach in the elderly population is associated with lower morbidity and a shorter hospital stay than an open approach (Cauchy *et al*., 2016, Martínez-Cecilia *et al*., 2017). This study shows that 18% of liver resections for CRC liver metastases in the elderly population are performed laparoscopically, significantly higher than the 14% observed in the younger cohort. This suggest that hepatobiliary surgeons in the UK prefer a minimally invasive approach in the older population.

6.4.5 Study limitations

Elderly patients undergoing liver resection are reportedly less likely to receive both neoadjuvant and adjuvant chemotherapy (Adam *et al*., 2010). As chemotherapy is often administered on an outpatient basis, reliable information regarding its use is not available in HES and therefore unknown for this patient cohort. Differences in its use according to age may account for the poorer cancer-specific survival demonstrated in patients aged ≥75 years.

The analysis included only including patients undergoing major CRC resection and liver resection within the same time period, patients with metachronous disease will be under-represented. To reduce bias associated with this, year of diagnosis was included as a variable in the multivariable model.

6.4.6 Conclusions

Patients aged 65-74 years were not at increased risk of long term mortality following liver resection compared to younger patients after taking into account patient and tumour characteristics. Although an age of greater than 75 years was a predictor of poorer survival particularly in the early post-operative period, elderly patients undergoing liver resection had 3-year survival of over 50%. This study highlights the need for improved predictors of early post-operative mortality to aid patient selection and better inform both clinicians and patients.

7. Chapter 7: Discussion

The aims of this thesis were to investigate the surgical management and outcomes of patients with CRC liver metastases in England using routinely collected national data. Having reviewed the current literature in Chapter 1, several knowledge gaps were identified which this thesis addresses in four individual studies. These broadly investigate service provision, selection for liver resection, trends and utilisation of surgical approaches, and post-operative outcomes in patients with CRC liver metastases. The results of these studies have highlighted several important issues which may have significant future implications for clinical practice.

7.1 Implications for clinical practice

7.1.1 Achieving equitable access within a centralised system

There are longstanding recommendations to centralise specialist services for both cancer and non-cancer care within the English NHS (Department of Health, 2001). High volume is associated with improved outcome particularly for cancer types involving complex surgery such as oesophagogastric, urological and hepatobiliary (Sosa *et al*., 1998, Glasgow *et al*., 1999, Birkmeyer *et al*., 2002, Birkmeyer *et al*., 2003). Increased patient volumes in specialist centres allows greater experience and expertise across teams working at these sites.

Equity in access to healthcare is an important policy objective in England where specialist services should be available to everyone regardless of location. The centralisation of services into higher volume units can place increased travel demands on patients. The Calman and Hine (1995) report states that "*All patients should have access to a uniformly high quality of care as close to the patient's home as possible'* and that *'services should be planned to minimise travelling times whilst maintaining the highest standards of specialist care'* (Calman and Hine, 1995). These recommendations have introduced a challenge with regard to the delivery of high quality specialist care whilst ensuring that travel times are minimised. Although some geographical inequalities in access to healthcare are inevitable due the travel required for patients living in rural areas, these are unacceptable when they disproportionately impact upon particular patient groups, such as the elderly and more socioeconomically deprived (Exworthy and Peckham, 2006). There is evidence to suggest that in the UK longer distance to a specialist cancer centre is associated with more advanced disease at diagnosis and poorer survival and a recent study examining the geographical location of specialist services for four common cancers within the UK, including colorectal, found areas with longer mean travel times also to have poorer relative survival rates after adjustment for area deprivation (Murage *et al*., 2016).

The Cancer Research Taskforce is working to develop a five year cancer survival improvement strategy on behalf of NHS England with recommendations in place to evaluate whether service configuration for surgery merits further centralisation (National Cancer Transformation Board, 2016). The results presented in Chapter 3 suggest centralisation of surgical services may act as a double-edged sword. Further centralisation should therefore be undertaken with caution. As the Cancer Research Taskforce moves forward with its five-year plan it is imperative to ensure that specialist services are able to deliver equitable care to those not based at the specialist centre. The results presented in this thesis highlight several possible areas where services may be restructured to achieve this and which are discussed below.

7.1.1.1 Routine hepatobiliary MDT referral

Previous evidence from local studies in the UK suggests that it is variation in rates of referral from CRC MDTs to hepatobiliary MDTs which may contribute towards regional variation in liver resection rates (Jones *et al*., 2012, Young *et al*., 2013). Colorectal MDTs based at hospital trusts with no on-site hepatobiliary services may have less awareness of the availability of novel chemotherapy agents and sophisticated interventional radiological techniques which have resulted in a widening of the definition of resectable liver metastases (Pawlik *et al*., 2008). The routine referral of all patients diagnosed with CRC and liver metastases for discussion at a hepatobiliary MDT meeting would be an effective strategy for improving equity of access for those diagnosed at non-specialist centres. A survey of hepatobiliary surgeons within the UK reported 65% would support this (Qureshi *et al*., 2012). However, as the majority of patients with metastatic CRC would not benefit from resection but rather palliative treatment, this strategy may delay palliative therapy for these patients and would also prove resource intensive for hepatobiliary MDTs. More feasible future strategies to ensure the timely input from hepatobiliary surgeons into the care of patients with CRC liver metastases would include the regular attendance of hepatobiliary surgeons at spoke CRC MDTs, the delivery of education programmes from hepatobiliary MDTs to CRC surgeons, and the routine use of video-conferencing between hepatobiliary and CRC MDTs.

7.1.1.2 Increased cross-site working

The analysis in Chapter 5 which demonstrates higher simultaneous resection rates in patients diagnosed at trusts with on-site hepatobiliary surgical services, suggests that patients may be undergoing CRC resection at spoke trusts prior to a referral to a hepatobiliary MDT. There are national guidelines in place recommending that colorectal surgeons perform a minimum of 20 elective CRC resections per year (The Association of Coloproctology of Great Britain and Ireland, 2007). This is important to ensure that skills are kept up to date and quality standards are maintained. At present, if patients with synchronous liver metastases diagnosed at a spoke hospital are deemed suitable to undergo a simultaneous bowel and liver resection, this will usually occur at the hub hospital. The bowel resection component of this procedure is therefore unlikely to be performed by a CRC surgeon based at the spoke trust. Colorectal surgeons working at spoke hospitals may favour a staged approach to ensure that their minimum numbers are met. Future attention should therefore be given to improving the opportunity for cross-site working for both hepatobiliary and colorectal surgeons within hub and spoke hospitals, to ensure that such targets are not a consideration in the management of patients with synchronous disease.

7.1.1.3 Nationally agreed referral guidelines

Inequalities in specialist referrals have been found to be more likely to occur in the absence of explicit guidelines (McBride *et al*., 2010). NICE recommended for the diagnosis and management of patients with CRC that "*if both primary and metastatic tumours are considered resectable, anatomical site-specific MDTs should consider initial systemic treatment followed by surgery*" (National Institute for Health and Care Excellence, 2014). There are, however, an absence of widely accepted guidelines for colorectal MDTs of what should be considered 'resectable' disease, leaving referral practices to local policy and a clinician's own judgement. The implementation therefore of clearly defined and nationally agreed referral protocols may reduce inequity in access (Siriwardena, 2007).

7.1.1.4 Advanced colorectal cancer MDT

Since 2013 Aintree University Hospital NHS Foundation Trust has operated a weekly MDT meeting specifically for patients with advanced CRC in the Mersey area (Hore *et al*., 2014). The move away from the traditional organ-specific approach to a disease specific approach, may act to streamline patient management and improve equity of access. In addition, all specialists (including a hepatobiliary surgeon, thoracic surgeon and colorectal cancer surgeon) involved in the treatment of patients with advanced cancer are present at each meeting. If this Liverpool model can be demonstrated to be both feasible, cost-effective, and result in improved patient outcomes, this structure may be rolled out across other regions.

7.1.2 Targeting specific patient groups

It is not only patients who are geographically remote from specialist surgical centres who appear to be disadvantaged in terms of access to specialist treatment. The results presented in Chapter 4 demonstrate that more socioeconomically deprived patients are also less likely to undergo liver resection, independent of other risk factors such as patient comorbidity and stage of primary cancer. This difference was also independent of the presence of hepatobiliary specialist services on site. The positive influence of providing the same care to more deprived patients as less deprived patients was clearly highlighted; social deprivation was no longer associated with increased risk of long-term mortality when the analysis was restricted to patients undergoing liver resection.

Reducing health inequalities in England is an ambitious task. In the summer of 2016 the UK's new Prime Minister announced that tackling health inequalities and addressing unwarranted variations in cancer outcomes was to be a key priority for the current government (Barr *et al*., 2017). In addition, equity in the delivery of care is outlined as a key strategy in the Cancer Research Taskforce's five year plan (National Cancer Transformation Board, 2016). The findings presented in this thesis suggest that a concerted effort from healthcare professionals to ensure equitable access to specialist care for more deprived patients with CRC liver metastases may serve to improve survival in this patient cohort.

7.1.3 Reducing the risks of liver resection

The results presented in Chapter 6 confirm that advancing age is a risk factor for poorer outcomes following liver resection, particularly in the early post-operative period. However, long-term survival may be achieved in these elderly patients. This raises the question of how to firstly predict, and then optimise, patients at particular risk of poor post-operative outcomes so that this potential survival benefit may be achieved for more patients.

New knowledge is emerging that frailty, a syndrome characterised by a decreased physiological reserve, is a better predictor of mortality and morbidity than chronological age (Partridge *et al*., 2012). Traditionally, frailty has been measured by combining a patient's past medical history, physical examination, and an assessment of physical and functional status. These factors however may be time consuming to measure and are often subjective (Amrock *et al*., 2014). In 2011, 70 variables included within a frailty index developed by the Canadian

Study of Health and Aging were mapped onto the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) dataset (Velanovich *et al*., 2013). However, due to the significant extra burden of data collection and the lack of consensus regarding the optimal frailty assessment tool, particularly for use in population-based data, this was not incorporated into later versions of the database. There have subsequently been further attempts to use population-based data to measure frailty in patients undergoing liver resection. Gani *et al*. (2017), using the NSQIP hepatectomy targeting database, developed a frailty index to predict adverse post-operative clinical outcomes following liver resection. The model included ASA class, Body Mass Index (BMI), serum albumin, haematocrit, underlying pathology and type of liver resection, demonstrating an Area under Receiving Operating Characteristics curve of 0.68 on validation. Further evaluation of this index in external cohorts will be required for its use to become routine in the elderly population considering liver resection.

The association between low functional capacity, as determined by cardiopulmonary exercise testing (CPET), and poor patient outcome following non-cardiopulmonary surgery is well established (Older *et al*., 1993). A recent randomised clinical trial reported improvements in the scores achieved in CPET following a 4-week pre-habilitation programme in a cohort of patients undergoing liver resection for CRC liver metastases (Dunne *et al*., 2016). The further assessment of pre-habilitation as a tool to improve outcomes following liver resection with the focus on an elderly cohort is warranted.

The results presented in Chapter 6 demonstrate that thermal ablation in combination with liver resection is used less frequently in the elderly population. Combining thermal ablation with liver resection takes advantage of the ability of ablation to destroy small tumours whilst sparing parenchyma. This may be a rational de-escalating strategy compared to more extensive hepatectomy and has been shown to be well tolerated and achieve adequate tumour clearance (Evrard *et al*., 2014). It is not clear why ablation was used less often in elderly patients in the study cohort, but considering the 6% post-operative mortality following major liver resection demonstrated in patients over 75 years compared to 4% following minor liver resection, there may be scope for an increased role of this strategy.

7.1.4 Need for randomised evidence of timing strategies

The lack of consensus guidelines and the complexities involved in the care of patients with CRC and synchronous liver metastases is not only reflected in the variation in specialist referrals. The results shown in Chapter 5 highlight wide regional variation in the timing of liver resection in relation to resection of the primary CRC. This suggests lack of consensus on two key decisions in the surgical management of patients with synchronous liver metastases: firstly, if a staged or simultaneous resection should be performed, and secondly, whether the bowel or the liver should be operated first. The logical next step in producing quality evidence to guide hepatobiliary MDTs about the optimal management for these patients would be a randomised trial. The data presented in Chapter 5 provides evidence of equipoise in long-term survival between treatment options, as well as data regarding national practice and trends. This will be important in guiding future studies in this cohort.

7.2 Methodological considerations

7.2.1 Registry data

The results presented in this thesis are based on data collected specifically for the NBOCA and administrative data. There are several advantages to using such data for epidemiological research. Having large cohorts of patients to study allows the statistical power to perform subgroup analysis and, in regression analyses, the ability to adjust for a wide range of clinico-pathological characteristics.

There are, however, general limitations in using registry data. Primarily, these datasets were not designed to answer any specific scientific question, therefore desirable data for a particular study may have not been collected. There are several important examples in this thesis when individual studies may have benefited from more detailed information in specific areas.

Firstly, the use of chemotherapy was not able to be analysed. Systemic treatment is an important aspect of the management of patients with CRC liver metastases. It may be offered both in the neoadjuvant and adjuvant setting, and also with the aim of converting patients with inoperable disease to resectable. Although the NBOCA collects data regarding chemotherapy use for the primary CRC, it does not collect data regarding chemotherapy directed at metastases. As chemotherapy is often administered on an outpatient basis, reliable information regarding its use is also not available from HES data. Chemotherapy data would have been particularly informative when analysing outcomes in the elderly population undergoing liver resection. Elderly patients undergoing liver resection in a US and a French cohort were found to be less likely to undergo both neo-adjuvant and adjuvant chemotherapy (Adam *et al*., 2010, Booth *et al*., 2015). Therefore, the poor cancer-specific survival following liver resection reported in Chapter 6 may in part reflect less frequent chemotherapy use in the elderly.

The second important item of data that was not available relates to MDT referral and discussion. As highlighted in this thesis, the management of patients with CRC liver metastases is complex and can involve input from a range of subspecialty teams based at different geographical sites. The results from Chapter 3 suggest patients diagnosed at hospital trusts with no on-site hepatobiliary surgical services are less likely to undergo liver resection. There may be a range of mechanisms behind this which cannot be fully explored without analysing referral practices. The NBOCA or HES data does not include information regarding if and when a patient was referred to a site-specific MDT. The inclusion of this data would help differentiate whether it is a lack of referral from the local CRC MDTs to hepatobiliary MDTs, a delay in referral from the CRC MDTs, or differences in decision-making according to referral centre at the hepatobiliary MDTs, that is contributing to this finding.

A further potential limitation of using routinely collected national data is the impact of missing data. Particularly relevant for this thesis is under-recording of metastases, as discussed in Chapter 3, and missing staging data. Despite stage at diagnosis being integral to guiding treatment options and to the likelihood of survival, missing staging data in NBOCA is a particular issue in patients not undergoing major resection. In 2015/16 NBOCA data, 10% of patients who did not undergo major CRC resection did not have recorded T-stage (either radiological or pathological), compared to just 2% in patients who underwent surgery (nboca.org.uk, 2016). As the analyses in Chapters 3, 5 and 6 were restricted to patients who had undergone a CRC resection, data completeness for these studies were generally good. In the analysis of the impact of socioeconomic status on rates of liver resection presented in Chapter 4, all CRC patients with synchronous liver metastases were included, regardless of whether they had undergone CRC resection. As a result, around 20% of patients in this study had missing T-stage and N-stage data. Importantly, there was no difference in the proportion of missing data according to IMD quintile thus limiting the bias associated with this missing data.

7.2.2 Definitions

To perform analyses and create subgroups within the study population several rules were applied. Although these were based on recommendations, as highlighted in Chapter 1 there is a board range of terminology and definitions currently in use in patients with CRC liver metastases.

7.2.2.1 Synchronous versus metachronous disease

Understanding of what constitutes synchronous, and therefore metachronous liver metastases, varies. In this thesis, patients were considered to have synchronous disease when a metastasis code was recorded in HES data up to a year before, and up to 30-days after the diagnosis of CRC. This was based on recommendations from an international consensus group (Adam *et* *al.*, 2015). The inclusion of patients with recorded metastases at a longer time period, for example 3 months from diagnosis, would have the benefit of capturing more patients. However, retaining a tighter time interval for the definition of synchronous reduced the risk of including patients with metachronous disease and as discussed previously, the use of HES data to identity metachronous disease could not be validated. In addition, the analysis in Chapter 5 investigates the timing of liver resection in relation to CRC resection. It was therefore important to only include patients who had clinically detected liver metastases at the time of diagnosis to ensure they would also potentially be candidates for a simultaneous or liver-first approach. Relaxing the definition of synchronous metastases would artificially increase the number of patients in the bowel-first group due to including patients with metachronous disease.

7.2.2.2 Major versus minor liver resection

As discussed in Chapter 1 there is a range of definitions used in the literature to define major liver resection. Major liver resection for the analyses performed in this thesis was defined as resection of three or more segments. This includes left hemihepatectomy, which was not reported by Reddy *et al.* (2011b) to increase the risk of morbidity and mortality when compared to resection of two segments or less. Categorising this cohort of patients as undergoing a major liver resection, as done in Chapter 6, may have resulted in an underestimation of the true risk of major liver resection in the elderly cohort.

With evidence suggesting that parenchymal sparing liver resection does not increase the risk of local disease recurrence, there are an increasing number being performed (Mise *et al.*, 2016). If a non-anatomical resection of three or more non-adjoining segments of the liver is made, this would constitute a major resection, with the associated risks, yet could not be accounted for by OPCS-4 codes used in the HES dataset. Such a procedure may be coded as

J023 “resection of segment of liver”, J024 “wedge excision of liver” or J028 “unspecified partial excision of liver” and would be classified as a minor resection in the analysis.

7.2.3 Estimating risk in elderly patients

Chapter 6 examines the impact of advancing age on post-operative and long-term outcomes following liver resection. The study population was divided into three groups, those less than 65 years, those 65 to 74 years, and those 75 years and more. There are however several limitations associated with this arbitrary division.

Firstly, the cut-off point at which an adult is considered ‘old’ or ‘elderly’ has not been well defined (Pallis *et al*., 2010). Previous studies reporting the outcomes of liver resection in the older population, use an age of 65, 70 or 75 years to define elderly. This limits the conclusions that may be drawn from comparing these results.

Secondly, although it has long been recognised that advanced age can carry increased risk of mortality and morbidity after surgery, the aging process is not a uniform phenomenon. Chronological age fails to address the heterogeneity in the overall health of the older population (Huisingh-Scheetz and Walston, 2017). For the prediction of surgical complications amongst the older population, a number of measures may be considered, only some of which may be derived from NBOCA data. In the study presented in Chapter 6, age related differences in ASA class and Charlson comorbidity score were able to be accounted for. Although these assessments go some way towards determining the physical function of a patient in the pre-operative setting, they have not been adapted for specific use in the elderly population (Mistry *et al*., 2017). Given that the NBOCA or HES database does not include haematological or biochemical measures, the hepatectomy frailty score described above was not able to be replicated in the analysis for Chapter 6. Until such time as a validated measure of surgical risk in the elderly which may be applied to large UK national datasets is developed, the use of chronological age as a proxy measure is necessary.

7.3 Future work

Although these studies have highlighted several important issues relating to access to services for CRC patients, further investigation into the cause of these disparities will be important in determining future strategy. The development of the NBOCA dataset as well as current and future linkages with other administrative databases provides several opportunities for future research. Areas that may warrant further investigation are discussed below.

7.3.1 Targeting local practice

The use of audit and administrative datasets for the work in this thesis have allowed a picture of the management of patients with CRC liver metastases on a national level to be presented. However, this data alone cannot provide the level of detail required to establish the reasons behind the differences in liver resection rates according to hospital of diagnosis and further investigation at a local level is required. A prospective audit performed by individual regions, could capture information regarding the number of patients referred from CRC MDTs to hepatobiliary MDTs and the timeliness of these referrals. A concurrent review both of the physical systems in place for these referrals and the local guidelines regarding referral practices could accompany this. Local data from regions found to have higher rates of liver resection at a national level using NBOCA linked HES data could be compared to those with lower rates to establish key differences in these systems. This could then facilitate a targeted quality improvement programme to be delivered at a local level.

7.3.2 Evaluating the impact of “IMPACT”

The ACPGBI and the Pelican Cancer group are together working on a new programme aimed at improving the outcomes for patients with advanced and metastatic colorectal cancer. Part of the IMPACT (Improving the Management of Patients with Advanced Colorectal Tumours) initiative will involve an education programme for members of the CRC MDT. During 2018 and 2019, 14 regional one-day workshops will be delivered across the UK, to which key members (surgeon, palliative care, radiologist, oncologist, pathologist and clinical nurse specialist) from each local CRC MDT will be invited. At these workshops a range of clinical presentations of advanced CRC will be discussed, including synchronous and metachronous liver metastases. It is hoped that this programme will act to improve communication between MDTs and raise awareness of treatment options, particularly in developing concept such as the widening criteria for resection of CRC liver metastases. NBOCA linked HES data could evaluate the effect of the IMPACT programme by comparing local and national liver resection rates and survival in CRC patients with liver metastases, before and after its implementation.

7.3.3 Timing surgical resection in rectal cancer patients

The management of patients with synchronous liver-limited metastases secondary to a primary rectal cancer presents specific challenges when compared to patients with a primary colonic cancer. Firstly, the majority of patients with stage IV rectal carcinoma will have an advanced rectal tumour that should be treated locally with long-course chemoradiotherapy. Secondly, symptomatic patients with rectal cancer and synchronous liver-limited metastases may be managed initially by decompression with a colostomy or self-expanding metal stent instead of primary resection. Thirdly, there is growing evidence to support that the liver first strategy in stage IV rectal cancer may enable more patients to complete full treatment protocols. Fourthly, there is contention regarding the safety of performing a resection involving pelvic dissection as a synchronous procedure with liver resection. Finally, particularly pertinent in patients managed according to a bowel-first or synchronous approach, there is the consideration of stoma creation, and the feasibility and timing of stoma reversal.

Most studies, similar to that performed in Chapter 5, investigate the practice and outcomes regarding the timing of liver resection and bowel resection in a combined cohort of colonic and rectal cancer patients. In the future an analysis could be performed focusing on rectal cancer patients with the aim of describing at a national level aspects of the management and outcomes, as detailed above, that are specific to rectal cancer patients. With the benefit of an extra two years' worth of NBOCA data to that presented in Chapter 5, there would be a final cohort of around 800 rectal cancer patients with synchronous liver-limited metastases. No previous population based study has described the outcomes specifically of rectal cancer patients. Furthermore, the NBOCA has been recently granted access to the Systemic Anti-Cancer Therapy and the Radiotherapy database. Use of these datasets, linked to NBOCA and HES data, would allow the inclusion of data regarding neoadjuvant chemotherapy, chemoradiotherapy, and adjuvant chemotherapy. The HES database could be used to analyse national practice regarding emergency decompression, as well as defunctioning stoma formation and subsequent reversal.

7.4 Concluding comments

The use of linked national datasets for the research presented in this thesis has allowed a unique insight into the current trends, management and outcomes of patients with CRC liver metastases in England over the last seven years. This has highlighted several key areas where care may be improved in the future.

Firstly, amongst patients with synchronous CRC liver metastases, there are specific patient populations who have poorer survival than would be expected. This appears to relate to inequalities in provision of liver resection. It is important therefore as cancer services undergo further centralisation in coming years that healthcare professionals are aware of this inequity and take responsibility to ensure that these patients are offered equal care.

Secondly, there is currently wide inter-hospital variation in the timing of liver resection in relation to CRC in England. This is not only influenced by patient factors, but also institutional factors, such as the on-site presence of hepatobiliary services. This highlights the impact of the absence of clear guidelines and referral pathways for managing patients with synchronous CRC liver metastases.

Finally, major liver resection, even within a highly selected population of patients 75 years and over, is associated with 90-day mortality of 6%. This analysis highlighted there may be further scope to use strategies to reduce the extent of liver resection in the elderly population and that there is a need for improved predictors of early post-operative mortality to aid patient selection.

8. References

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9. Appendix

9.1 Charlson comorbidity score

Table 9.1 Charlson comorbidity score

Disease category	ICD-10 codes
Myocardial infarction	I21, I22*, I23*, I252
Congestive cardiac failure	I11, I13, I255, I42, I43, I50, I517
Peripheral vascular disease	I70–I73, I770, I771, K551, K558, K559, R02, Z958, Z959
Cerebrovascular disease	G45, G46, I60–I69
Dementia	A810, F00–F03, F051, G30, G31
Chronic pulmonary disease	I26, I27, J40–J45, J46*, J47, J60–J67, J684, J701, J703
Rheumatological disease	M05, M06, M09, M120, M315, M32–M36
Liver disease	B18, I85, I864, I982, K70, K71, K721, K729, K76, R162, Z944
Diabetes mellitus	E10–E14
Hemiplegia or paraplegia	G114, G81–G83
Renal disease	I12, I13, N01, N03, N05, N07, N08, N171*, N172*, N18, N19*, N25, Z49, Z940, Z992
Any malignancy	C00–C26, C30–C34, C37–C41, C43, C45–C58, C60–C76, C80–C85, C88, C90–C97
Metastatic solid tumour	C77–C79
AIDS/HIV infection	B20–B24

*Indicates an acute condition that should be used to define comorbidity only if present in a record of a previous hospital admission within the preceding 12 months.
AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus.

9.2 Multivariable model for risk of mortality following liver resection

Table 9.2 Multivariable model for risk overall mortality within 0-90 days and 90-days- 3-years, and cancer specific mortality 90-days- 3-years following liver resection

		90-day mortality (95% CI)	90-days to 3-year mortality (95% CI)	90-days to 3-year mortality cancer specific mortality (95% CI)
Age	<65 years	1	1	1
	65-74 years	2.88 (1.67 to 4.97)	1.11 (0.90 to 1.17)	1.01 (0.90 to 1.14)
	≥75 years	4.25 (2.38 to 7.57)	1.41 (1.23 to 1.61)	1.26 (1.09 to 1.45)
Gender	Male	1	1	1
	Female	0.72 (0.47 to 1.12)	0.97 (0.87 to 1.07)	0.99 (0.89 to 1.10)
IMD quintile	1 (most deprived)	1	1	1
	2	1.13 (0.55 to 2.33)	0.84 (0.71 to 1.00)	0.83 (0.69 to 0.99)
	3	1.21 (0.61 to 2.39)	0.87 (0.74 to 1.02)	0.87 (0.73 to 1.03)
	4	1.20 (0.61 to 2.37)	0.85 (0.72 to 0.99)	0.9 (0.76 to 1.07)
	5 (least deprived)	1.24 (0.63 to 2.44)	0.84 (0.71 to 0.98)	0.83 (0.70 to 0.98)
Charlson comorbidity score	0	1	1	1
	1	1.17 (0.72 to 1.91)	0.98 (0.86 to 1.11)	0.92 (0.8 to 1.06)
	≥2	2.22 (1.19 to 4.16)	1.09 (0.86 to 1.11)	0.95 (0.8 to 1.06)
Emergency CRC presentation	No	1	1	1
	Yes	1.14 (0.68 to 1.94)	1.23 (1.08 to 1.41)	1.26 (1.10 to 1.45)
ASA class (at CRC resection)	1	1	1	1
	2	1.2 (0.58 to 2.51)	1.17 (1.01 to 1.36)	1.17 (1.00 to 1.37)
	3	2.04 (0.95 to 4.37)	1.37 (1.15 to 1.64)	1.26 (1.05 to 1.52)
	4/5	2.02 (0.43 to 9.42)	2.07 (1.37 to 3.14)	1.82 (1.18 to 2.82)
Primary CRC site	Right side	1	1	1
	Left side	1.07 (0.67 to 1.71)	0.83 (0.74 to 0.94)	0.84 (0.74 to 0.95)
	Rectum	1.26 (0.73 to 2.19)	1.02 (0.89 to 1.18)	1.03 (0.89 to 1.2)
T-stage	0-2	1	1	1
	3	1.47 (0.66 to 3.29)	1.04 (0.87 to 1.25)	0.98 0(.82 to 1.19)
	4	1.75 (0.73 to 4.16)	1.29 (1.06 to 1.57)	1.24 (1.01 to 1.52)
N-stage	0	1	1	1
	1	1.41 (0.88 to 2.27)	1.45 (0.76 to 2.77)	1.34 (0.61 to 2.97)
	2	1.13 (0.63 to 2.03)	1.91 (1.67 to 2.18)	2.04 (1.78 to 2.35)
Liver resection indication	Metachronous	1	1	1
	Synchronous	1.07 (0.72 to 1.60)	1.1 (1.00 to 1.22)	1.14 (1.03 to 1.27)
Liver resection type	Minor resection	1	1	1
	Major resection	1.86 (1.25 to 2.76)	1.19 (1.07 to 1.31)	1.24 (1.11 to 1.37)
Liver resection access	Open	1	1	1
	Laparoscopic	0.28 (0.10 to 0.76)	0.87 (0.75 to 1.02)	0.81 (0.68 to 0.95)