MRI scans with respiratory immobilisation to contour radiotherapy organs-at-risk using oral contrast of hypo or hyper intense fluids including the patient perspective.

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Intellectual property and publication statements

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 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.

Chapter 2 is based on work from the jointly authored publication:

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Matthew Richard Beasley was responsible for conducting the scoping review, including screening, data charting and collation, analysis, drafting of the manuscript and responding to reviewers' comments. Carole Burnett independently screened 10% of abstracts for validation and assisted with data charting. All authors contributed to the interpretation of findings, critically reviewed the manuscript, and approved the final version.

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Publications and presentations arising from this thesis

Publications

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Beasley MR, Henry AM, Bestall J, Cosgrove VP, Murray LJ, Burnett C. Non-medicinal oral contrast in upper abdominal MRI for MR-guided radiotherapy: A scoping review. Radiography (London). 2025;31:102868. https://doi.org/10.1016/j.radi.2025.01.003.

Poster presentations

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Beasley MR, Burnett C, Cosgrove VP, Henry AM, Murray LJ, Bestall J. 1427 Patient perspectives of liver SABR: a qualitative study. Radiotherapy and Oncology. 206:S4165-S7. https://doi.org/10.1016/S0167-8140(25)00449-9. ESTRO 2025.

Oral presentations

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Abstract

Introduction

Stereotactic ablative body radiotherapy (SABR) has emerged as a promising treatment option for liver cancer. However, its use is challenging due to organ motion and poor visual discrimination between the tumour and surrounding healthy tissues. Whilst magnetic resonance imaging (MRI) and breathing immobilisation techniques have been employed to address these issues, there is a paucity of research exploring the patient experience and potential strategies to improve this. The aim of this PhD project was to explore improvements in visualisation of healthy tissues by reducing motion and improving conspicuity of organs in an acceptable way to patients.

Methods

Four studies were undertaken:

1. A scoping review mapped Non-medicinal Oral Contrasts (NMOC) for upper-abdominal MRI.
2. A single-centre retrospective analysis of 134 consecutive liver SABR patients compared liver motion with and without abdominal compression using planning CT data and multivariable modelling.
3. Semi-structured patient interviews explored experiences of planning and treatment.
4. A proof-of-concept healthy-volunteer study assessed candidate NMOCs on 1.5 T MRI.

Results

1. The review identified 31 distinct NMOCs, with no radiotherapy-specific evaluations, which signified a translational gap.
2. Abdominal compression reduced superior-inferior liver motion by a median of 4.4 mm. However, a large proportion of compressed patients had superior-inferior excursion > 5 mm, and motion ranges overlapped between compressed and uncompressed cohorts. This indicates heterogeneous benefit and supports further personalisation of immobilisation.
3. Ten patient interviews from a single radiotherapy centre revealed three themes of communication, discomfort, and coping and support. Recommendations include clearer pathway explanations and improved timing prompts for breath-hold.
4. Healthy-volunteer MRI suggested that NMOCs, notably yerba mate, produced the expected T_1-hyperintense and T_2-hypointense appearances, improved duodenal conspicuity by one point on a four-point visual grading scale for contouring confidence on T_1-weighted sequences, and were acceptable to participants.

Conclusions

Personalised motion management and pragmatic NMOC protocols warrant prospective evaluation to test effects on contouring confidence, margins, and patient-reported experience.

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Ethics approval

The required research ethics approvals were obtained (HRA 23/WM/0070) and are provided in Appendix A and Appendix B.

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Abbreviations

4DCT	4-dimensional computed tomography
ABC	Active Breathing Coordinator
AC	Abdominal compression
AP	Anterior-Posterior
ASTRO	The American Society for Radiation Oncology
BCLC	Barcelona Clinical Liver Cancer
BMI	Body Mass Index
CBCT	Cone beam computed tomography
CC	Cranio-caudal
CI	Confidence interval
CT	Computed tomography
df	Degrees of freedom
DICOM	Digital Imaging and Communications in Medicine
ECOG	Eastern Cooperative Oncology Group
ESTRO	European Society for Therapeutic Radiation Oncology
F	Female
FB	Free breathing
GBCA	Gadolinium-based contrast agents
GI	Gastrointestinal
HCC	Hepatocellular carcinoma
HIFU	High-intensity focused ultrasound
HL	Hodges-Lehman
HRA	Health Research Authority
HU	Hounsfield unit
Hz	Hertz
I-CVI	Item-level content validity index
IGRT	Image-guided radiotherapy
IR	Inversion recovery
IQR	Inter-quartile range
ITV	Internal target volume
IV	Intravenous
kV	Kilovoltage
LAT	Lateral
LTHT	Leeds Teaching Hospitals NHS Trust
LR	Left-right
M	Male
MR	Magnetic resonance
MRI	Magnetic resonance imaging
MRCP	Magnetic resonance cholangiopancreatography
ml	Millilitre
mm	Millimetre
ms	Milliseconds
MWA	Microwave ablation
NIHR	National Institute for Health and Care Research

NHS	National Health Service
NMOC	Non-medicinal oral contrast
OAR	Organs-at-risk
OR	Odds-ratio
PPIE	Patient and public involvement and engagement
PCC	Population, concept and context
PTV	Planning target volume
REC	Research Ethics Committee
RF	Radiofrequency
RFA	Radiofrequency ablation
R-IDEAL	Radiography-Idea Development Evaluation Assessment Long-term follow-up
RILD	Radiation induced liver disease
RTSTRUCT	Radiotherapy Structure Set files
SABR	Stereotactic ablative body radiotherapy
SBRT	Stereotactic body radiotherapy
SD	Standard deviation
SE	Spin echo
SI	Superior-Inferior
T	Tesla
TACE	Transarterial chemoembolisation
TE	Echo time
TNM	Tumour Node Metastasis
TR	Repetition time
TSE	Turbo spin echo
UK	United Kingdom
USA	United States of America

Chapter 1 Introduction

1.1 Treatment of liver cancer

1.1.1 Hepatocellular carcinoma (HCC)

1.1.1.1 Background

Liver cancer is considered a global and growing health challenge. Its incidence continues to rise worldwide [1]. In 2020, approximately 905,700 new cases were reported, with projections indicating a rise to 1.4 million new cases per year by 2040 [2]. Liver cancers include malignancies originating in the liver (primary liver cancer) or those that have spread from other organs (secondary or metastatic liver cancers) [3-7].

Primary liver cancers are predominantly hepatocellular carcinoma (HCC), comprising approximately 75% of all cases [3,4]. Intrahepatic cholangiocarcinoma accounts for 10-15% of cases [3,8], with rarer types making up the remainder [3,9]. It ranks among the leading causes of cancer-related mortality worldwide, with a particularly steep increase observed in developed countries experiencing rising incidence of chronic liver disease, cirrhosis and metabolic risk factors due to obesity [10-12]. The estimated five-year survival for primary liver cancer is below 20% [12,13]. Over the last decade, deaths from primary liver cancer have increased by approximately 50% and it is projected to be the cancer with the highest average annual increase over the next 15 years [14]. Surgical resection or liver transplantation are the first-line options for curative treatment in localised disease [12,15]. Worldwide HCC is predominantly associated with chronic hepatitis B and hepatitis C virus, but in the UK alcohol-related liver disease and metabolic dysfunction-associated liver disease are more common causes [12]. Excessive alcohol consumption is estimated to be the cause of approximately 36% of liver cancers in England and Scotland [16]. Approximately one third of cirrhotic patients develop primary liver cancer, with up to 20% of HCC cases estimated to occur in a non-cirrhotic liver [17,18]. Increasing age is also an associated risk of developing primary liver cancer, with the peak age incidence being in people over the age of 80 years [12].

1.1.1.2 Staging and treatment pathways

Primary liver cancers can be staged in different ways, but increasingly the Barcelona Clinical Liver Cancer (BCLC) system is used[19]. BCLC combines TNM (Tumour size, Nodal involvement, Metastases) with performance status and measures of liver function to stratify patients into five stages. Against common circumstances of poor baseline hepatic function and potential co-morbidities, treatment options are often limited. If primary liver cancers are diagnosed at an early stage, cure and/or long-term survival is possible, with at least 80% of patients surviving for more than one year [12].

Despite having potentially curative treatment options, the UK has no national surveillance programme for patients with cirrhosis and just 30% of patients diagnosed with HCC currently survive for greater than one year [12]. Curative treatment options include surgical resection, liver transplantation and local ablation [8,12,20,21]. Management of HCC has become more standardised, with the BCLC staging and treatment strategy (Figure 1) having been validated and widely adopted to guide therapeutic decisions and recommended for use by the British Society of Gastroenterology for the management of HCC [12,19,21]. The BCLC staging system integrates tumour burden, liver function (Child-Pugh), and the Eastern Cooperative Oncology Group (ECOG) performance status to assign five prognostic stages with linked treatment recommendations [19,22-24]. In the palliative setting transarterial chemoembolisation (TACE), Selective Internal Radiation Therapy and tyrosine-kinase inhibitors can palliate symptoms and provide a survival benefit [1,24-26].

Not all patients meet the therapeutic criteria aligned with their BCLC stage due to factors such as their age, co-morbidities, or anatomical location of their tumour(s), and so the importance of multi-disciplinary discussion is emphasised in the literature [21,24]. Liver transplantation may be used for fit patients with impaired liver function, whilst patients with a solitary tumour and preserved liver function are the preferred candidates for surgical resection [24]. Intra-arterial treatment using conventional TACE is the standard of care for most patients who have intermediate stage HCC [12]. Randomised controlled trials and meta-analyses have confirmed the benefits of intra-arterial treatments and TACE can also be considered for patients as a bridging therapy for those awaiting a liver transplant [12,25-27].

Ablative therapies offer a radical treatment alternative to surgery in patients with early-stage HCC [19]. Administered locally using image-guidance, local ablation can be delivered in the form of radiofrequency ablation (RFA), microwave ablation (MWA), cryotherapy and radiation therapy. Emerging non-invasive ultrasound-based ablative technologies, including high-intensity focused ultrasound (HIFU) and histotripsy, are also being investigated, although their role in routine HCC management is still evolving[28,29]. There is no significant difference in mortality between radiofrequency ablation and surgery for early-stage HCC, but local recurrence is higher albeit with fewer adverse effects in those receiving RFA [30-32]. A meta-analysis demonstrated no significant difference in overall survival when comparing MWA and RFA, but local recurrence rates might be lower in the MWA group but with higher complications [33].

Historically radiotherapy had not been used to treat liver cancer due to the risks of liver dysfunction. External beam radiotherapy in the form of high-dose stereotactic ablative body radiotherapy (SABR, also known as stereotactic body radiotherapy, abbreviated to SBRT) is an emerging alternative non-invasive local ablative option for patients unsuitable for surgery or conventional ablative techniques. The doses are considered 'ablative' because they are radiobiologically potent and better at killing cells compared to conventional radiotherapy fractionation regimes [34]. SABR involves delivering highly conformal, high-dose radiation in a small number of treatment fractions, thereby intensifying the local tumouricidal effect while minimising damage to surrounding healthy tissues, including the uninvolved liver parenchyma and limiting the risk of radiation-induced liver disease [35,36]. It has the advantages of being non-invasive and potentially widely available. The last official update of the BCLC published in 2023 acknowledges the potential ‘antitumoural activity’ of SABR but states that further prospective studies are needed to define its role [19]. Evidence supporting its use is growing.

A recent systematic review and meta-analysis of SABR for HCC found SABR to be a viable treatment option, with high local control rates and low rates of reported grade three or four toxicity [37]. NHS England’s clinical commissioning policies, published in March 2020, made SABR a routinely commissioned option for two groups: 1) adults with localised hepatocellular carcinoma who are

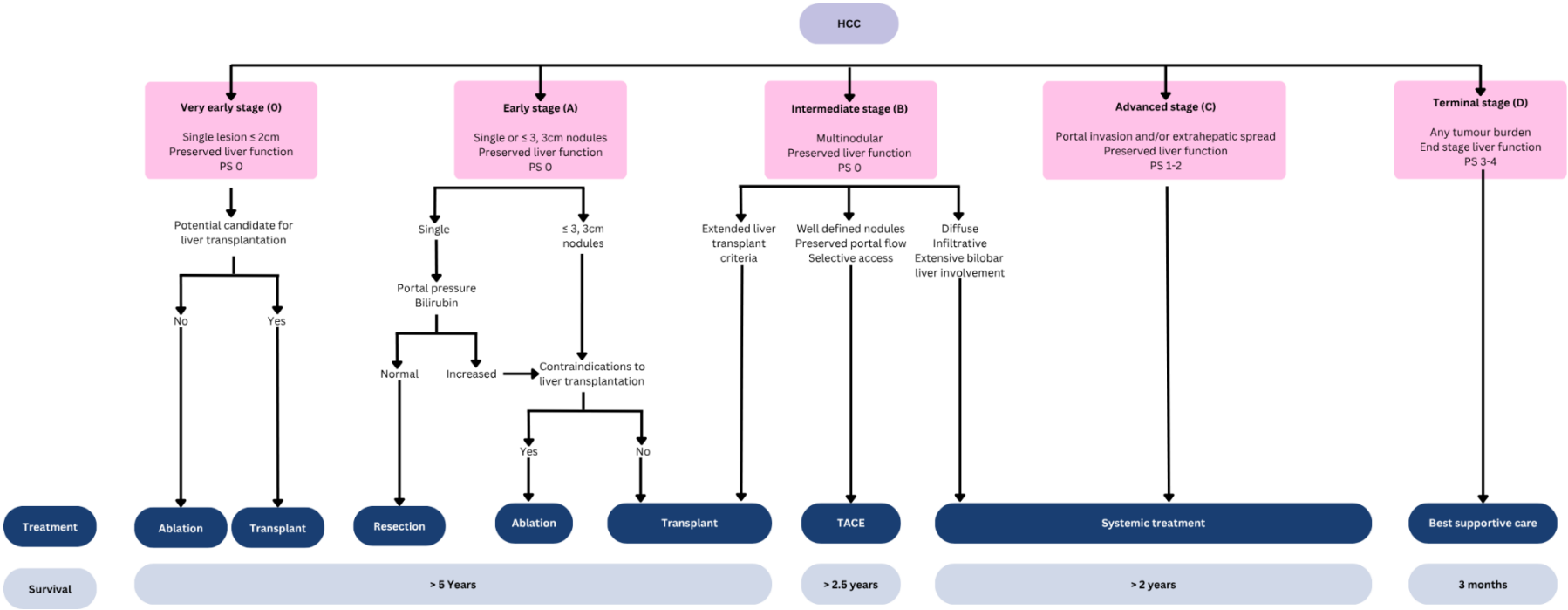
unsuitable for surgery, transplantation, RFA or other standard treatments, and 2) patients with up to three metachronous extracranial oligometastases, including lesions in the liver, where SABR can be used in place of radiofrequency ablation or systemic cancer therapy [38,39].

In a meta-analysis of 49 cohorts involving 2846 patients, Shanker et al. (2021) found the pooled three-year local control was 84.2% (95% CI 77.9-88.9) and overall survival for three-years was 48.3% (95% CI 39.0-57.0) after treatment with SABR [37]. Shanker et al. argued that further prospective trials were warranted to determine the optimal patient selection criteria and dose-fractionation regimens [37]. In a smaller transplant list cohort of 379 patients treated with SABR (n = 36), TACE (n = 99) or RFA (n = 244), Sapisochin et al. (2018) reported similar five-year overall survival across groups, with SABR and RFA both achieving 61% compared with 56% for TACE[40]. Likewise, in another retrospective study of 224 patients with inoperable, non-metastatic HCC treated with RFA (n = 161) or SABR (n = 63) Wahl et al. (2016) showed SABR and RFA also had similar local control and progression free survival, despite their SABR group having lower pre-treatment Child-Pugh scores, higher pre-treatment alpha-fetoprotein level, and having received a greater number of prior liver-directed treatments [41]. Importantly, the safety and efficacy of external beam radiotherapy have been demonstrated across all BCLC stages in retrospective and prospective studies (Figure 1) [42].

Since 2020, SABR has been commissioned by NHS England for patients with tumours <5 cm who have fewer than five HCC lesions, no extrahepatic disease and Child Pugh class A compensated liver function [38]. A multi-disciplinary taskforce led by The American Society for Radiation Oncology (ASTRO) and endorsed by the European Society for Therapeutic Radiation Oncology (ESTRO), the American Society of Transplant Surgeons and the Society of Surgical Oncology recommend using external beam radiotherapy as a potential first-line treatment in patients who are unable to have surgery but have liver-confined HCC. Treatment can also be delivered as a consolidative therapy following an incomplete response to liver-directed therapies, and as a salvage option for local recurrences [43].

Figure 1 The Barcelona clinical liver cancer (BCLC) staging and treatment strategy linked to the first-line treatment recommendation.

SABR is not included in the treatment options of the algorithm. Here the BCLC pathway has been adapted from Reig et al. (2022) [19] and the BCLC stages where the safety and efficacy of external beam radiotherapy have been demonstrated in both retrospective and prospective studies are highlighted in pink.



ASTRO, as a standalone association, individually recommends external beam radiotherapy for selected HCC cases. Indications include unresectable or liver-confined multifocal disease, macrovascular invasion, use in sequence with systemic or catheter-based therapies, palliation, and bridging to transplant or preoperative use [43]. The guidelines by the European Society for Medical Oncology and the American Association for the Study of Liver Disease recommend SABR as an option in selected BCLC stage 0 to A patients with HCC [23,44].

Despite this, the most recent 2022 updated BCLC guidelines do not include conventional radiotherapy or SABR as a treatment option in the algorithm. This has not gone unnoticed in the radiation oncology community. In a letter responding to the publication of the updated BCLC guidelines, Hallemeier et al. (2022) concluded the following:

> *'…the current available evidence supports the incorporation of EBRT into BCLC guidelines, especially when "first treatment options" are not feasible or suitable, or if there is progression after first treatment. For future updates of the BCLC guidelines, we propose inclusion of EBRT as per recommendations of the ASTRO Guidelines: 1) for patients with BCLC 0-A HCC, EBRT should be considered as an alternative non-surgical treatment (along with ablation or embolization), either as definitive therapy or as a bridge to transplant; 2) for patients with BCLC B-C, EBRT is a treatment option with or without embolization or systemic therapy; 3) for patients with BCLC D HCC, EBRT should be considered as a palliative treatment for tumor-related pain. We acknowledge the importance of current and future RCTs for all therapies in refining HCC treatment strategies, and we strongly support further RCTs of EBRT for HCC.'*
>
> Hallemeier et al. 2022 [42].

Evidence supporting the use of SABR for HCC continues to grow, and its inclusion in guidelines by national and international bodies underscores its emerging role in the management of liver cancers unsuitable for surgery or conventional ablative treatments. Although prospective phase III trials are lacking, ongoing research is clarifying optimal patient selection and dose-fractionation strategies. SABR has already benefited from technological

advances such as enhanced imaging, improved motion management, and more sophisticated treatment planning. Further innovation is likely. Continued refinements in these areas, coupled with clinical trials, may help maximise the therapeutic potential of SABR whilst minimising risks, ultimately improving outcomes for patients with liver malignancies.

Although advances in the management of HCC have expanded local treatment options, including SABR, the liver's anatomical and vascular characteristics also make it a common site for secondary malignancies. Understanding how these differ from primary liver cancers is also relevant for this thesis, as treatment intent, prognosis, and evidence supporting SABR can vary.

1.1.2 Secondary liver cancer and oligometastatic disease

Beyond primary liver cancers, the liver is also a common site for metastatic spread of colorectal, breast, oesophageal and stomach cancers [7,45-47]. Colorectal cancer is the most common primary source of oligometastatic disease of the liver [48]. Colorectal cancer is a significant contributor to cancer mortality worldwide, with over 1.9 million new cases in 2020, accounting for approximately 9.4% of all cancer-related deaths [11,48]. More than 20% of patients with colorectal cancer are diagnosed with metastatic disease at presentation, and a further 20% may relapse. Amongst those who have metastatic spread, more than 70% have liver involvement[48,49].

The concept of oligometastatic disease, characterised by a limited number of metastases that have spread to a limited number of sites, has led to a potential role for local ablative treatments. Weichselbaum and Hellman first proposed the term 'oligometastases' in 1995, defining it as an intermediate state between purely localised tumours and widely metastatic [50]. They argued that anatomy and physiology might limit or concentrate metastases to a single or limited number of organs before the further progression via increasing tumour seeding eventually leads to more widespread metastatic growth. Twenty-five years later, oligometastatic disease was subsequently defined through an ESTRO-ASTRO consensus as:

> '1-5 metastatic lesions, a controlled primary tumour being optional, but where all metastatic sites must be safely treatable.'
>
> Lievens et al. (2020) [51].

The time difference between the development of primary cancers and secondary cancers varies. Metastases that have developed by the time of diagnosis of the primary tumour are referred to as synchronous disease. Metachronous disease is where metastases have developed after treatment of a primary tumour [52]. The specific time interval used to define metachronous disease varies across studies. For example, some definitions consider metastases detected more than three months after the primary tumour diagnosis as metachronous, whilst others use intervals of six or 12 months [53].

Treatments for metachronous oligometastatic disease aim to control symptoms and extend life expectancy. Current treatments include surgical excision, RFA, systemic treatments and SABR [39,54]. Treatment of liver oligometastases of colorectal tumours using either surgical resection or RFA is well established [48,49]. The phase II randomised CLOCC trial reported improved overall survival at 30 months with RFA and systemic chemotherapy of 61.7% vs 57% in the systemic chemotherapy arm.

Similar to HCC, there is a growing body of evidence supporting the use of ablative therapies such as SABR, but larger phase III RCT are still required to conclusively prove survival benefits [55]. Results of a phase II randomised controlled trial in 99 patients comparing SABR to the standard of care palliative radiotherapy and/or chemotherapy for multiple primary cancer oligometastases (including liver), found that median overall survival was 28 months in the control group versus 41 months in the SABR group (hazard ratio 0·57, 95% CI 0·30-1·10; p=0·090) [56]. A comparative study of SABR to RFA for liver metastases provided evidence of non-inferiority. However, since this was a retrospective study and underpowered, further evidence is required [57]. In the absence of phase III clinical trials, an evidence review was commissioned by NHS England in 2019 [58]. As a result of this review, in 2020, NHS England concluded there was sufficient evidence to support a policy of routine commissioning of SABR to treat oligometastatic cancers, where the primary cancer is controlled with up to three extracranial metachronous oligometastases manifested following a disease-free interval following treatment of >6 months [39]. Results have been encouraging: SABR doses greater than 48 Gy in three fractions have been shown to provide local control above 90% at one year for colorectal liver tumours under 6 cm in diameter [59]. Accordingly, the Royal College of

Radiologists recommends 24-30 Gy in a single fraction, 40-60 Gy in three fractions over one week on alternate days or 50-60Gy in five fractions on alternate days or daily. Where oligometastatic disease is >6 cm in diameter or if organ at risk constraints cannot be met, the RCR recommend 40-60 Gy in 10 daily fractions [60].

1.1.3 Fundamentals of radiotherapy dose and radiobiology

Given the expanding evidence for SABR in HCC and oligometastatic disease, a concise background of the underlying dose and radiobiology principles is provided as the basis for later sections.

Radiotherapy is an effective treatment option used to treat approximately 50% of all cancer cases [61]. Radiotherapy involves the targeted delivery of a prescribed dose of ionising radiation, which damages tumour cell DNA either directly through single or double strand DNA breaks or indirectly by ejecting molecular electrons. These ejected electrons then trigger further ionisations forming free radicals, ultimately causing cellular apoptosis and death [34,62]. Radiotherapy affects both cancerous and normal tissues, but normal tissues generally repair sublethal damage more effectively between fractions [62,63]. A key challenge in radiotherapy is balancing the effective treatment of a defined tumour volume and any potential spread, whilst minimising the dose and potential risk, to surrounding normal healthy tissues [34,62,64]. In conventional radiotherapy regimens, the total prescribed dose is divided into fractions to allow for normal tissue repair between treatments [65]. Tumour size is a predictor of local control. Larger tumours require bigger radiotherapy treatment volumes, but the radiation dose which can be safely administered is limited by adjacent normal-tissue tolerances, and the tumour control probability decreases approximately linearly with the logarithm of the tumour volume [62]. Larger tumours are also more hypoxic, which reduces radiosensitivity [62].

1.1.4 SABR as a technological and radiobiological paradigm shift

Whilst conventional fractionation (1.8 Gy to 2 Gy per fraction) remains standard for many cancers, technological advances have enabled more precise targeting of cancers. This improved ability to localise the disease, together with other technological advances, has become a crucial component to help guide how clinical oncologists decide on the optimum dose delivery strategy and, where

appropriate, facilitates the safe use of higher doses per fraction (termed hypofractionation), including SABR [62].

SABR involves the accurate delivery of very high doses per fraction (e.g. >5 Gy per fraction; termed ultra-hypofractionation) to an extra-cranial target with millimetre precision over very few treatment sessions (often one to five) [34]. SABR has been used in multiple tumour sites, including in the liver. Delivering a small number of large dose fractions increases the biological effective dose to >100 Gy in a complete treatment course, often achieving a stronger tumouricidal effect, and in fewer treatments when compared to conventional dose regimens. Where doses per fraction are greater than 5 Gy, as with SABR, the effect of ionising radiation on microvasculature may also be an important factor in controlling tumour growth [62,66]. In addition, there is growing evidence to support the hypotheses that inflammatory and immunological responses triggered by such large doses per fraction may also enhance cancer cell death and generate abscopal[1] (immunogenic) effects on malignant cells outside the radiotherapy target volume(s) [69-73]. This departure from conventional fractionation for some tumour types to the delivery of ultra-hypofractionated doses of ionising radiation with SABR has been described as a paradigm shift [74,75]. As above, this shift has been made possible by technological advances in pre-treatment and on-treatment imaging, immobilisation, motion management, treatment planning and treatment delivery techniques [34,75-78]. These advances now allow large doses of ionising radiation to be delivered safely to smaller tumours (diameter <5 cm) with

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[1] The abscopal effect (from Latin ‘ab’ – away from and ‘scopus’ – target) refers to the phenomenon where localised radiotherapy at one site not only causes a direct tumour kill in the treated volume but also leads to a regression of tumour cells outside of the irradiated field. This effect is rare and thought to be immune-mediated, where immunogenic tumour cell death is induced by high-dose radiation, essentially turning the irradiated tumour into an in situ vaccine, stimulating anti-tumour immunity against distant cancer cells. The term was first used by R.H. Mole in 1953 to describe radiation effects ‘at a distance from the irradiated volume but within the same organism.’

Source: [67] Jatoi I, Benson JR, Kunkler I. Hypothesis: can the abscopal effect explain the impact of adjuvant radiotherapy on breast cancer mortality? npj Breast Cancer. 2018;4:8. https://doi.org/10.1038/s41523-018-0061-y. [68] Mole RH. Whole body irradiation; radiobiology or medicine? Br J Radiol. 1953;26:234-41. https://doi.org/10.1259/0007-1285-26-305-234.

reduced margins, whilst historically, wider margins were needed to compensate for greater setup and motion uncertainty, resulting in excessive normal tissue doses with high SABR dose regimens. Modern image guidance and motion management create a sharper dose fall-off beyond the target, limiting exposure to normal liver tissue [34,66,75,78]. With accurate and precise targeting and motion management, SABR has been shown to deliver tumouricidal doses to liver tumours [79-83].

Until SABR was developed at the Karolinska Hospital and first used clinically in the 1990s, radiotherapy had a limited role in the treatment of unresectable liver malignancies due to the radiosensitivity of the liver [83-86]. The tight dose fall-off characteristic of SABR spares more of the healthy liver parenchyma, reducing complications such as radiation-induced liver disease (RILD)[85]. RILD is defined as a clinical condition associated with hepatomegaly, jaundice, ascites and elevated liver enzymes that occur two weeks to three months following radiotherapy [85]. Although most cases of RILD are transient, it can lead to liver failure, and is the most common liver toxicity following conventional radiotherapy[85]. RILD remains a concern with SABR, and although those with more compromised liver function and larger target volumes have a higher risk of RILD, RILD remains difficult to predict [37].

1.2 SABR and challenges when treating cancers of the liver

Although evidence for the use of SABR to liver cancers (primary or metastatic) continues to grow, its implementation in the clinic is complex and SABR is not always clinically feasible. The liver's proximity to critical organ structures, including the duodenum, bowel, and stomach, coupled with its intrinsic motion during respiration can limit the safe escalation of radiation doses [7,87,88]. Furthermore, both the volume of uninvolved liver and the patient's baseline liver function are key determinants of hepatic tolerance to radiation, evaluated to determine suitability for liver SABR [43].

1.2.1 Uncertainties in planning and delivering liver SABR

Two major challenges in planning and delivering liver SABR arise from uncertainties related to organ motion and the visualisation of tumours and adjacent structures:

i. Respiratory and other organ motion:

The liver is a highly mobile organ that moves substantially with respiration [89-94]. Research has shown that liver motion due to breathing can be higher than 55 mm in the cranio-caudal (CC) direction [94]. Other abdominal organs, such as the bowel and stomach, also shift and change shape over time [95]. This motion introduces spatial uncertainties, increasing the risk of unintentionally irradiating healthy tissues. These uncertainties not only limit the escalation of radiation doses but also elevate the risk of radiation toxicity [95-97]. Breathing phase-specific dose delivery, respiratory gating or tumour tracking, and improved image guidance have been used to manage motion, yet motion still limits accurate and precise dose delivery [98].

ii. Poor visualisation of tumours and adjacent structures:

Distinguishing tumours from surrounding healthy tissues is another critical challenge in liver SABR and is compounded by organ motion. Conventional computed tomography (CT), whilst essential for dose calculation, often lacks sufficient soft tissue contrast to confidently delineate tumour boundaries, especially in complex anatomical regions [99]. Magnetic resonance imaging (MRI) provides superior soft tissue contrast enabling more accurate definition of target volumes and organs-at-risk (OARs) [99,100]. The UK SABR Consortium recommends the integration of MRI into the planning process for liver SABR [100]. However, even MRI-based planning is not without its limitations, as image quality can be affected by motion artifacts and variability between imaging sequences [101,102].

1.2.2 Motion uncertainties

The liver, along with other organs in the abdominal cavity is subject to the natural muscular motions within the body, including respiration, gastrointestinal (GI) motility, and cardiac motion. In the context of radiotherapy, motion is often categorised into two categories:

i. Inter-fraction motion:

This refers to variations in patient positioning or internal organ movement that occur between separate treatment fractions. Such discrepancies can arise from differences in daily setup, anatomical changes, or organ filling, potentially leading to misalignment of the radiation beams with the target volume across different treatment days [103].

ii. Intra-fraction motion:

This describes movements that happen during a single treatment fraction. These can result from patient or organ movement, such as breathing or other physiological motion, causing the tumour or surrounding organs to shift whilst radiation is being administered [103,104]. Intra-fraction motion poses significant challenges to the precision of dose delivery, because if the target moves more than anticipated, this may lead to underdosing of the tumour and overdosing of the normal tissues. Given SABR delivers a high-dose per fraction that takes longer to deliver in a single fraction compared to conventional radiotherapy, there is less room for error, and any deviation will have more impact on treatment efficacy and the risk of adverse effects [105].

Whilst both inter-fraction and intra-fraction motion are accounted for to some extent in added treatment margins around the gross tumour volume(s) (GTV), in the form of the planning target volume (PTV), effective management is essential to maintain the accuracy and safety of SABR treatments.

1.2.2.1 Reducing breathing motion to improve liver SABR accuracy and precision

Respiratory-induced motion is a primary source of geometric uncertainty in liver SABR. Traditional approaches involve adding margins around the tumour to ensure the cancer remains within the high-dose radiation field throughout the breathing cycle. Whilst margin expansion helps maintain tumour coverage, it also increases exposure to healthy tissues, potentially elevating the risk of

radiation-induced toxicity and constraining dose escalation[103,106-108]. This increased exposure can increase the incidence of treatment-related side-effects and limits the radiation dose that can be safely delivered to minimise harm to nearby healthy tissues and OARs [85,109]. By reducing respiratory motion, the positional uncertainty of the tumour decreases, allowing smaller margins to be applied around the clinical target volume. This, in turn, reduces the volume of normal tissue exposed to high-dose radiation. SABR takes advantage of this principle by employing minimal margins when forming the PTV.

1.2.2.2 Abdominal compression

This technique applies external pressure to the abdominal region with the use of abdominal compression devices [110]. Abdominal compression has become a widely adopted method to mitigate respiratory-induced liver motion during SABR. By applying external pressure to the abdomen, diaphragmatic excursion is restricted, thereby reducing liver displacement. It is used in over 50% of UK radiotherapy centres to treat liver, pancreas, and adrenal indications [100,111-113]. Studies have shown that compression can be applied simply by lying patients in a prone position. However, the use of commercially available devices with patients lying supine is more common as the supine position is thought to be more comfortable and stable [100,114,115]. Commercially available devices vary in their design, comprising of compression arches (Figure 2), compression belts (Figure 3), and less commonly, shells and corsets, all aiming to physically restrict diaphragmatic movement and decrease motion amplitude [111,116].

Figure 2 Abdominal compression arch device (Civco)
The device is a plastic plate placed on the patient's abdomen and screwed in place, effectively compressing the upper abdomen and diaphragm and thus reducing/restricting breathing motion.

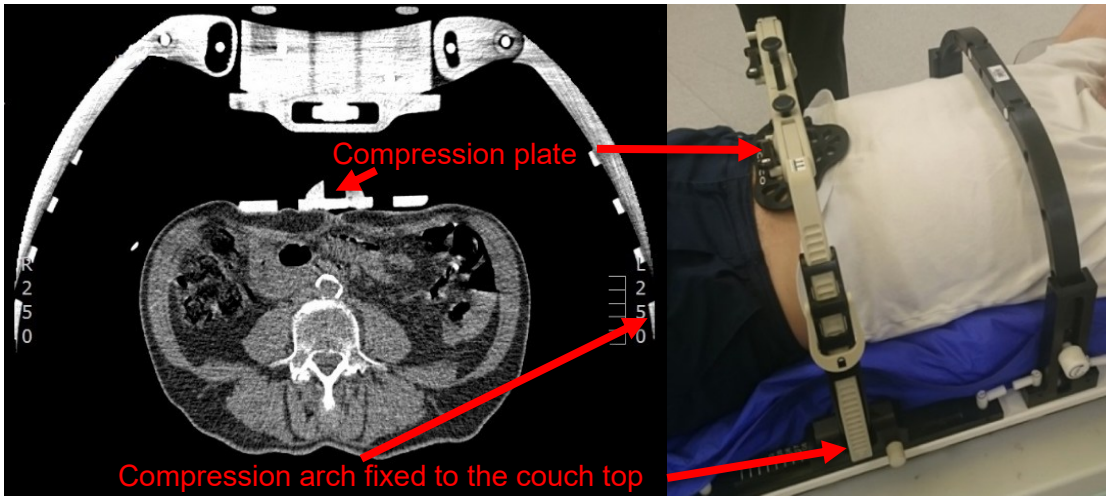
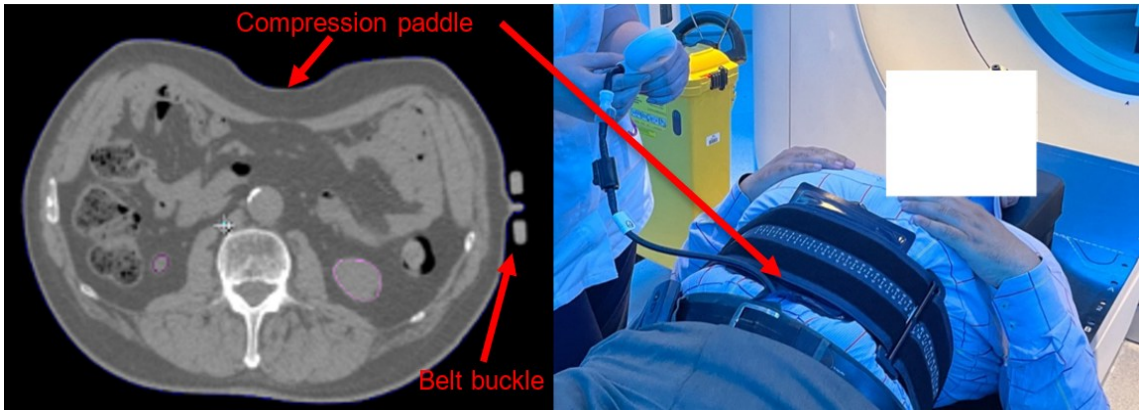


Figure 3 Abdominal compression belt (ZiFix). It comprises of a belt strap that wraps around the patient using a buckle.
A compression paddle, including an inflatable bladder, is attached via Velcro to the belt and inflated using a manometer pump to the desired compression pressure level.



A recent systematic review by Webster et al. (2024) investigating the effectiveness of both abdominal compression and breath-hold techniques was unable to perform a planned meta-analysis due to study heterogeneity. The group did observe, however, that practical use, patient compliance, and comfort are not well reported in the literature, raising questions about optimal clinical application [111]. There is limited data on the patient experience of abdominal compression, but some authors have reported that it can be uncomfortable, is poorly tolerated by some patients, and it does not eliminate motion completely [89,111,112].

Recent ESTRO Advisory Committee on Radiation Oncology Practice guidelines classify abdominal tumours as ‘very mobile’ if the excursion is >5 mm [117]. Webster et al.’s systematic review applied the same threshold and identified six abdominal compression pre-treatment studies where residual respiratory motion remained >5 mm in at least one direction despite compression, and two abdominal compression belt series with systematic inter-fraction set-up errors >5 mm [111]. In contrast, in the abdominal compression cohorts that reported intra-fraction motion, residual motion within a treatment fraction was consistently <5 mm [111].

However, these patterns need to be interpreted cautiously, because there is substantial heterogeneity in how motion and set-up error were quantified [111]. Studies used different image-guided radiotherapy (IGRT) match structures, including the liver contour, pancreas GTV, fiducials, and diaphragm, as well as different imaging modalities such as four-dimensional computed tomography

(4DCT), cone beam CT (CBCT), fluoroscopy, and MRI. 4DCT refers to CT imaging acquired across the respiratory cycle to estimate motion-related positional change. Studies also used difference error metrics, including the mean, systematic, random, range, maximum values, which limits direct comparison and complicates translation into robust margins [111].

MRI has considerable advantages for soft-tissue delineation as opposed to CT imaging, and it is considered an ideal modality for organ at risk contouring and potential margin reduction and motion management [118,119]. However, many studies have relied on x-ray-based modalities to identify structures and their motion, raising questions over the validity of some motion measurements. Just four of the studies that met the inclusion criteria in Webster's systematic review used MRI to evaluate motion uncertainty and most concerned the pancreas, not the liver [119-121].Aside from abdominal compression and breath-hold, motion-management strategies applicable to MR-guided radiotherapy include respiratory gating [122], tumour tracking/trailing [123-126], and online adaptive workflows [127,128], whilst AI-assisted methods for motion prediction, segmentation and dynamic motion estimation are emerging [129,130]. Recent work such as learning-based 3D motion modelling and high temporal resolution 4DCT reconstruction from in-treatment 2D cone-beam x-ray projections further illustrates the wider efforts still in development to quantify and potentially respond to real-time motion during radiotherapy [131]. MR-guided radiotherapy is particularly suited to adopting these approaches because it allows direct soft-tissue visualisation during treatment delivery [130,132].

Table 1 shows a synthesis of seven studies where superior-inferior (SI) liver-specific motion data have been extracted based on a variety of imaging modalities. These studies show that abdominal compression reduces motion in the SI direction whilst is less effective in the anterior-posterior (AP) and left-right (LR) directions [111]. To provide some context, an early study using ultrasound to determine abdominal organ motion found the liver to be the most movable organ in both normal respiration (25 mm, range: 10-40 mm) and if patients were asked to breathe with maximum respiration, its excursion was on average 55 mm (range: 30-80 mm) [94].

Hu et al., (2017) reported a decrease with a compression arch, from a mean liver movement of 9.9 mm (SD 3.0 mm) without compression to 5.11 mm (SD

2.05 mm) [133]. Although, contrary to these findings, van Gelder et al., 2018 reported an average amplitude of 5-7 mm in the SI direction of the kidneys. There was no significant difference in the average amplitude, with and without the abdominal compression belt, for the kidneys or the liver [134]. This was however limited by the small sample of 15 patients.

Across all seven of these studies, the average free-breathing SI motion was between 9 mm and 16 mm, ranging between 4 mm and 39 mm, and reduced by 8 – 62% with compression. However, between 7 – 79% of patients in these studies still had >5 mm residual motion or paradoxical increases, thus the effectiveness of abdominal compression being highly variable between patients. Proposed reasons for this include anatomical differences [135] and patient factors such as discomfort or anxiety when the compression device is applied [134]. Nevertheless, a further important consideration is the practical use and patient's experience and compliance. Van Gelder et al (2018) reported on patient experience with abdominal compression, highlighting that several of the patients reported discomfort [134]. However, few other studies have examined this in any detail. Patient comfort is not well reported, raising questions of how these devices are best used in the clinic [111,116] and the primary motivation for the study in Chapter 4.

Table 1 Studies comparing motion amplitudes of the liver using either abdominal compression (AC) or free breathing (FB) with liver motion measurements.

Study (year)	Imaging (surrogate) / compression method	Liver cohort size	Superior-Inferior (SI) motion FB	SI motion with AC	% >5mm or <1mm reduction	Significant difference between FB and AC?
Daly et al. (2024) [136]	T_2-w cine MRI (MR-linac) / compression belt	7/16 (3 healthy volunteers; 13 patients – 7 liver, 4 pancreas, 1 adrenal, 1 nodal metastasis)	Mean 15.7 mm (IQR 5.5 mm)	8 mm (IQR 4.1 mm)	12.5% - motion increased	p = 0.001
Hardcastle et al. (2023) [137]	Fluoroscopy (liver dome) / compression belt	26 liver patients	Not reported	Not reported. Reported a mean of 3.4 mm (range, -0.3 – 16 mm) reduction over FB	35% < 1 mm delta between FB and AC	Not tested
Van Gelder et al. (2018) [134]	4DCT (liver dome) / compression belt	14/15 (13 liver, 2 pancreas) but one unspecified patient excluded	Mean 8.7 mm ± 3 mm	Mean 8.0 mm ± 3.8 mm	79%	Reported as 'not significant' (but values not reported)

Study (year)	Imaging (surrogate) / compression method	Liver cohort size	Superior-Inferior (SI) motion FB	SI motion with AC	% >5mm or <1mm reduction	Significant difference between FB and AC?
Hu et al. (2017) [135]	4DCT liver / compression arch	99 liver patients (53 in AC, 46 in FB)	Mean 9.9 mm	Mean 8.0 mm	33%	Unreported. Did report significant gender and body mass index (BMI) relationship with effectiveness of compression (p <0.05).
Lovelock et al. (2014) [138]	Fluoroscopy / compression belt	42 liver patients	Mean 11.4 mm (range, 5-20 mm) (AC applied without pressure applied)	Mean 4.4 mm (range, 1-8 mm)	7%	p = < 0.001
Eccles et al. (2011) [110]	T2w cine MRI / compression arch	60	Mean 11.7 mm (range, 4.8-23.3 mm)	Mean 4.4 mm (range, 1.6 – 23.4 mm)	28%	Methods state Pearson statistics calculated but not reported – descriptive only.
Wunderink et al. (2008) [139]	Fluoroscopy and fiducials / compression arch	12	Mean 10.8 mm (range, 4.4-38.5 mm)	Mean 4.2 mm (range, 1.7-8.5 mm)	17%	Regression coefficient R ranged from -0.07 - -0.28 (median -0.11) (1cm adjustment ~ 1mm decrease in target excursion).

1.2.2.3 Breath-hold

An alternative approach to abdominal compression involves breath-hold techniques, in which patients suspend respiration at a particular phase of the breathing cycle to achieve a reproducible anatomical positioning during image acquisition and delivery of radiotherapy [111,116]. Suspending respiration whilst SABR is being delivered has been shown to efficiently reduce dose to OAR, but careful implementation is necessary to manage uncertainties [117]. One retrospective planning study found that eliminating respiratory motion from liver SABR treatment volumes allowed for dose escalation in the majority of patients studied and substantially increased tumour control probability [106].

Complex equipment is often not necessary, as has been demonstrated and now widely implemented across the UK with voluntary deep inspiration breath-holds to lower the heart dose frequently being used for left breast external beam radiotherapy [117,140,141]. An ESTRO patterns of practice survey, found voluntary inhale to a specified level and breath-hold during imaging and/or treatment delivery is the most commonly used technique to reduce intra-fraction breathing motion [117,142]. However, some authors claim there is high variation and considerable underutilisation of various breath-hold techniques [142]. One potential reason for this is that any implementation of breath-hold for abdominal cancers requires a surrogate measure for the position of the target. Equipment that can provide this has now become more widely commercially available in the form of spirometers or surface-guidance equipment, some of which can provide visual feedback to patients and even allow automatic gating [117].

Different systems have advantages and disadvantages and compatibility with pre-existing radiotherapy delivery systems, immobilisation equipment and cost all being important considerations. For example, spirometers such as Active Breathing Coordinator (ABC) devices have been used for at least two decades and were introduced as a mechanical means of controlling and monitoring patient breathing. Safety concerns related to magnetic components preclude their use inside MRI scanners with the exception of being attempted once in research conditions [117,143-146]. Consequently, MRI-based planning often relies on voluntary breath-hold manoeuvres (without ABC) that demand patient cooperation and stability in the chosen respiratory state. Aznar et al. (2020) have provided detailed descriptions of the equipment available but still

emphasise that image guidance to verify and localise the intended target is still necessary with all breath-hold approaches [117].

The abdomen is one of the most challenging sites for motion management in radiotherapy. Breath-hold has the potential to reduce treatment margins and improve the quality of pre-treatment and on treatment imaging [117]. UK SABR Consortium guidelines recommend exhale breath-hold for liver SABR[100] as evidence shows this is more reproducible [91,147-149]. However, limited evidence suggests that inhale breath-hold may achieve higher compliance and lengthier breath-holds due to improved comfort [91,116,150]. Physiologically, starting at a higher lung volume increases the intrapulmonary oxygen reservoir, dilutes accumulating carbon dioxide and provides reduced feedback from diaphragmatic afferents that drive the need to respire [151]. Breath-holding at total-lung-capacity can last two-to-three times longer than at end-expiration [151]. Despite this, comparing results across studies is challenging due to variations in reported data, staff and patient training, as well as differences in techniques and equipment used.

Lens et al. (2016) reported on breath-hold motion and concluded that not only was this reduced in exhale, but also that delaying irradiation until after the first 10 seconds of breath-holding to achieve stability may be advantageous for abdominal tumours [150]. However, given their volunteers were asked to hold their breath for up to 60 seconds, and since, as discussed previously, liver SABR patients are likely to present with multiple co-morbidities, the practicalities of prolonged breath-holds are challenging.

The systematic review by Webster et al. included studies on both abdominal compression and breath-hold. The group found no direct comparisons between the two methods, and study heterogeneity prevented meta-analysis [111]. A further source of uncertainty relating to breath-hold is having to acquire multiple breath-hold CT, MRI or CBCT scans to aid target delineation and calculate patient-specific treatment margins. Inter-breath-hold motion can be >3 mm [117,152,153] and intra-breath-hold uncertainties have been reported to reach 1 cm [154]. Further research is therefore required to determine which approach – inhale, exhale, deep inhale, or deep exhale, optimally balances patient comfort, reproducibility, and treatment accuracy [111,116,117].

1.2.3 Visualisation - MRI and its utility in liver SABR

MRI of the abdomen is well established and has become a useful tool in liver SABR planning because it provides superior soft-tissue contrast compared with CT, improving liver tumour visualisation and characterisation [155,156]. A brief overview of key MRI concepts explains why sequence parameters affect signal intensity and the relevance of this in the context of this thesis.

1.2.3.1 Relaxation and image contrast

Clinical MRI uses radiofrequency (RF) pulses and magnetic field gradients in the presence of a strong static field (B_0) to excite and detect signals from hydrogen nuclei, including those present in water and fat. Unlike CT, MRI does not use ionising radiation. It is incredibly flexible: thin slices can be acquired in any plane or 3D volumes can be reformatted in axial, coronal, sagittal, or oblique orientations. By adjusting pulse sequences and parameters, image contrast can be weighted to emphasise or suppress specific signals such as fat or fluids [157].

Images are acquired by exciting tissue and measuring the induced voltage in receiver coils. When a patient enters the scanner, mobile protons (hydrogen nuclei) align with its B_0. An RF pulse (B_1) tips this net magnetisation away from equilibrium in what is known as excitation. After the RF pulse, protons return towards equilibrium, and the changing magnetisation induces a voltage in the receiver coils. Gradients encode the position of these voltage signals, interpreted from raw data in as a spectrum consisting as an array or matrix of individual spatial frequencies called k-space, and a Fourier transform reconstructs the image [157].

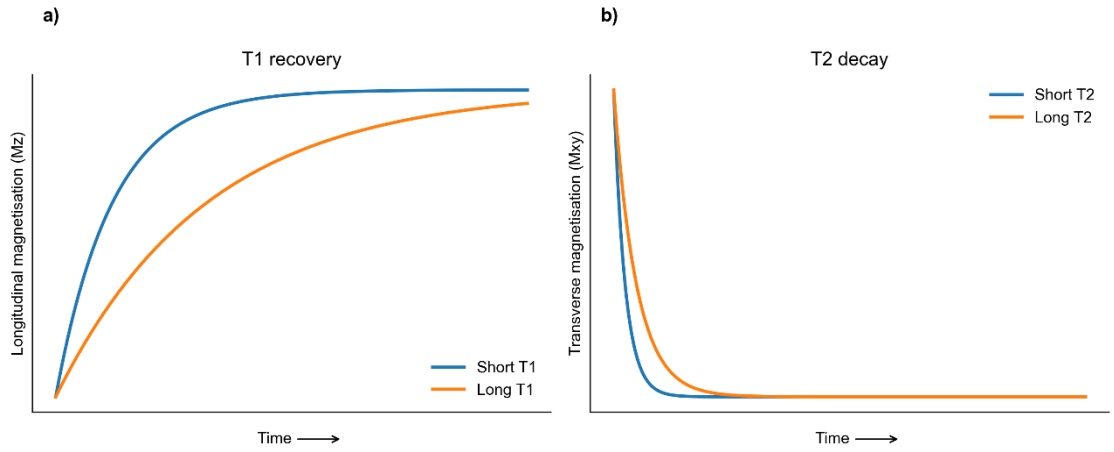
Three intrinsic tissue properties drive most anatomical contrast:

i. Proton spin density: the number of mobile, resonating protons available to emit a signal.
ii. T_1 relaxation time: the rate at which longitudinal magnetisation realigns with B_0 following an RF pulse.
iii. T_2 (transverse) relaxation time: the rate at which transverse magnetisation loses phase coherence[157,158].

After excitation, tissues regain longitudinal magnetisation (T_1 recovery) and lose transverse magnetisation (T_2 decay). By selecting the repetition time (TR) - the

time interval between successive RF excitation pulses and echo time (TE) - the time at which an echo is sampled, acquisitions can be biased toward T_1-weighting (short TR and TE) or T_2-weighting (long TR and TE). Because various tissues have different relaxation rates, this leads to different levels of signal intensity on the captured reconstructed image [157]. Signal intensity becomes more hyperintense (brighter) with increasing proton spin density and the T_1 decreases [159]. Conversely, the signal intensity becomes more hypointense (darker) when the proton spin density and T_2 decreases [159]. Where tissue has a high signal intensity and another has a lower signal intensity, the difference in signal intensities is called contrast. Field strength, bandwidth, chemical shift, susceptibility, and perfusion can also influence signal and image appearance, but adjustment of TR and TE allows for contrast manipulation between different tissues dependent on their inherent relaxation characteristics [157-160]. In most biological tissues T_2 decay is much shorter than T_1, so transverse signal falls quickly while longitudinal signal recovers more slowly (Figure 4). It is important to note that MR signal is dimensionless and not absolute [158]. With given parameters, images should therefore be interpreted relatively, described as hyperintense or hypointense, when compared with reference tissues such as fat or muscle [161].

Figure 4 Illustration of T_1 recovery (a) and T_2 decay (b).
Short TR/TE produces T1-weighted contrast; long TR/TE produces T_2-weighted contrast.



1.2.3.2 The current use of MRI in liver SABR planning

At the host-institution, MRI is acquired on a dedicated 1.5T MR simulator scanner, with a flat couch-top to match the radiotherapy treatment machines

and aid radiotherapy patient setup reproducibility, and a coil bridge to avoid abdominal deformation from receiver coil placement.

1.2.3.3 Exogenous contrast agents

Exogenous contrast agents can be used to modify MR signal that would otherwise reflect only intrinsic tissue properties [159]. In abdominal MRI relevant to liver SABR, the two predominant routes of administration are intravenous (IV) and oral.

Gadolinium-based contrast agents (GBCAs) are the most commonly used IV agents. They shorten T_1 of tissues where it accumulates, so enhancing tissues appear hyperintense on T_1-weighted images. They can also shorten T_2/ T_2*, but the T_1 effect dominates at routine concentrations.

1.2.3.3.1 IV contrast

Intravenous contrast agents distribute with blood flow [157,162]. IV GBCA is a useful contrast agent for liver cancer detection, characterisation and delineation owing to the vascular supply and composition of liver tissue[163]. The use of IV GBCA supports the acquisition of multiphase imaging. Multiphase imaging of the liver is where a series of T_1-weighted images are acquired at specific times following IV contrast injection to capture the different vascular and tissue enhancement over time. In liver MRI the different phases of liver perfusion can include:

i. Pre-contrast (unenhanced) phase: A baseline scan for comparison.
ii. Arterial phase (20-40 seconds after IV GBCA administration): Since 70% of the blood supply of the liver is via the portal vein, the liver parenchyma is relatively unenhanced so that hypervascular lesions, such as some HCCs, are hyperintense during the arterial phase.
iii. Portal venous phase (50-90 seconds after IV GBCA administration): hypovascular lesions (such as some metastases) appear hypointense compared to the normal liver tissue, which is enhanced via the portal venous Gd flow.
iv. Delayed phase (3-6 minutes after GBCA administration): Fibrotic tissue and certain benign lesions can retain contrast but many malignant tumours ‘wash-out’.

v. Hepatobiliary phase (10-20 minutes after GBCA administration): Tumours containing functioning hepatocytes become hyperintense in this phase, whereas lesions without hepatocytes remain hypointense against the surrounding liver tissue that becomes enhanced before GBCA is excreted into the bile ducts [163-166].

Intravenous GBCA is therefore frequently used to aid diagnosis and characterisation of liver tumours on MRI, particularly as they are challenging to visualise and characterise on CT [164], and therefore facilitate radiotherapy tumour volume delineation for SABR planning [98]. At the host-institution, gadoxetate disodium (Primovist) is the hepatospecific gadolinium based IV contrast agent used to acquire T_1-weighted image sequences. For multiphase imaging, a 3D T_1 mDIXON (multi-echo Dixon spoiled gradient-echo sequence) is used that can simultaneously provide water, fat, in-phase, and out-of-phase image reconstructions. Whilst IV GBCA enhances parenchymal and liver tumour contrast, adjacent GI OARs can remain challenging to delineate on MRI. In current practice these OARs are usually delineated on a co-registered CT, whilst the literature has acknowledged that some structures, including the duodenum, common bile duct and distal biliary tree, may be better distinguished on specific MRI sequences [155]. With MRI simulation and MR-guided radiotherapy becoming more common [127,167-169], there is a clear incentive to improve MRI-only OAR conspicuity. Accurate and precise definition of both the tumour and OARS is essential to ensure safe treatment [155,170,171]. Therefore, there might be a role for oral contrast in liver SABR planning MRI scans.

1.2.3.3.2 Oral contrast

Oral contrast agents are frequently used in diagnostic abdominal MRI examinations. Oral contrast agents are ingested to change intraluminal signal and, in some cases, distend the bowel. They are widely used in diagnostic abdominal MRI to make the bowel wall stand out against the lumen, improving visualisation of pathology and anatomical boundaries [172]. Options include water-based preparations (for example, mannitol or polyethylene glycol solutions), dilute barium, dilute GBCAs, manganese-containing juices (for example, pineapple), and high-fat milk. There is a consensus amongst the literature that optimal oral contrasts are palatable, provide an optimum level of

distension, have minimal side effects, are readily available and cheap [172-176]. The potential use of oral contrast in the context of liver SABR MR image guidance is discussed in more detail in Section 1.2.4.

1.2.4 The potential of using oral contrast to improve tissue visualisation of MRI to help plan liver SABR

Optimisation of imaging, implementation of standardised protocols, and delineation guidelines to help doctors draw around tissues more accurately, are reported strategies to improve target volume (the cancerous tumours) and OAR delineation [155,177]. Differentiating between tumours from normal liver, bowel loops, and bile ducts can be difficult on standard MRI sequences [155]. Accurate anatomical structure delineation is vital for the safe delivery of ablative doses [170,171]. Definition of delineated structures has been shown to be prone to interobserver variation and studies have demonstrated that peer review can identify gross errors in up to 30% of target volume definitions [171,178]. Furthermore, a recent study by Lukovic et al. found that cases where variability in delineation was observed in terms of whether or not contouring of the bowel was done inside or outside of the bowel wall and the omission of the caudate lobe of the liver. There was also evidence of a knowledge gap in the contouring of the common bile duct [155].

Medicinal oral contrasts (e.g. mannitol, polyethylene glycol, barium) have been described in diagnostic contexts, but they can induce adverse reactions such as nausea or diarrhoea [179,180]. Alternatives to the medicinal products, capable of improving anatomic delineation without side-effects [172,174,181] could be translated and applied in the context of MR-guided liver SABR (i.e. MR-based planning and motion/visualisation interventions that may or may not be paired with other modalities such as CT or MR-linac SABR delivery). Using non-medicinal oral contrasts (NMOCs) to help improve the quality of MRI in radiotherapy planning pathways may reduce radiotherapy treatment planning uncertainties and might offer a potential solution to enhance anatomical delineation. NMOCs such as water, pineapple juice, or milk can serve as inexpensive, safe, and patient-friendly agents that alter the MRI signal characteristics of the GI tract, enhancing organ boundaries and facilitating more accurate tumour and OAR delineation [23-25].

Unfortunately, as demonstrated in Chapter 2, there is no quantitative or qualitative research of NMOCs for liver SABR [161]. Despite decades of use in a diagnostic setting, NMOCs have never been systematically evaluated in MR-guided radiotherapy workflows. No published study has defined optimal drink type, volume or timing for SABR planning; nor has their effect on observer variability or dosimetric margins been evaluated. Given NMOCs are cheap, safe and readily available, addressing this knowledge gap could yield a simple yet impactful intervention to refine MRI-based planning for liver SABR.

1.2.5 Patient experience - Qualitative insights into the liver SABR experience

Despite its importance in the development of any new radiotherapy technique, patient experience in liver SABR has only recently been highlighted as an area lacking in research [111,112]. Although qualitative study of hepatocellular carcinoma has started to examine the patient journey, treatment goals, and decision-making [182-184], this evidence is not specific to liver SABR or to the practical demands of radiotherapy workflows.

In abdominal compression studies, there is a lack of patient accounts of lived experiences and feelings towards the immobilisation devices or techniques used in liver SABR. Although ‘discomfort’ from abdominal compression is often cited, there is no published evidence on incorporating qualitative patient experience into the evaluation of immobilisation equipment for liver cancer radiotherapy. Whilst equipment specifically designed to aid breath-hold procedures in radiotherapy have been evaluated in the literature, evidence suggests 30-38% of patients are unable to maintain or reproduce a suitable or stable breath-hold, making them ineligible for these procedures [91]. Reasons for patients being unsuitable for breath-hold include patient ‘intolerance’ of the procedure, poor reproducibility of the breath-hold position, or communication difficulties [185]. If the procedure could be made more comfortable while increasing the ability for the patient to accomplish a sufficient breath-hold, this could lead to more successful treatments, with more patients eligible for treatment [116]. The lack of qualitative insights into patients’ lived experiences of these immobilisation methods highlights the need for patient-centred inquiry [111].

Qualitative work in radiotherapy shows that patients' informational and emotional needs can shape treatment acceptance and satisfaction [186-192]. However, most studies have focused on conventional fractionation or other tumour sites, and they often centre on symptom burden rather than the logistics unique to SABR. Because SABR differs in intent, dose, and workflow complexity, findings from conventional radiotherapy are only partly transferable. The scarcity of qualitative evidence might be attributed to both the relatively recent more widespread introduction of liver SABR and the ongoing evolution of the concept of oligometastatic disease. Collectively, this gap supports targeted qualitative enquiry in liver SABR.

In general, the patient's voice is underrepresented in radiotherapy research [193]. Understanding patient experiences, preferences, and tolerances is crucial, as these factors influence treatment adherence, satisfaction, and potentially clinical outcomes [194,195]. The procedures used to address imaging and motion challenges such as fasting and drinking oral contrast before MRI, being constrained by abdominal compression, or performing repeated breath-holds can be burdensome. If patients experience significant discomfort, anxiety, or poor understanding of these procedures, their ability to comply and remain still during imaging and treatment may be affected. Additionally, patient perspectives can inform the design of educational materials, the refinement of communication strategies, and the selection of interventions that respect individual comfort and agency [196]. Liver SABR studies to date have underreported patient-centred outcomes, focusing mainly on technical and clinical endpoints. Only small, mixed-cohort studies have included liver SABR patients, typically reporting symptoms and tolerability of treatment in general, rather than specifically planning scans, immobilisation, or breath-hold procedures. This therefore also reinforces the need to explore the lived experience of liver SABR directly.

Qualitative research approaches, such as in-depth interviews, have the potential to provide rich insights into how patients perceive their SABR experience, including the emotional and psychological dimensions of undergoing complex imaging and treatment procedures. By coupling technical optimisations with patient-centred research, this thesis aims to incorporate a more holistic understanding of radiation therapy.

1.3 PhD thesis rationale

Five-year survival for liver cancer remains below 25% [172]. Cancer Research UK has added liver cancer to its priorities for cancers of unmet need [172]. Building on the premise that enhancing imaging precision and patient comfort can improve both the safety and effectiveness of radiotherapy, this thesis begins to address key knowledge gaps in MRI-based planning for liver SABR. Despite the implementation of advanced imaging and motion management strategies in current UK practice, uncertainties in tumour delineation and risks of unintended irradiation to healthy tissues persist. In this context, introducing NMOCs to improve MRI tissue contrast and exploring alternative breath-hold techniques emerge as plausible strategies to refine liver SABR planning. Coupling these technical refinements with qualitative insights into patient experiences could produce interventions that are both efficacious and acceptable [197].

By systematically investigating both the technological and human dimensions of liver SABR, this project hopes to produce evidence that can eventually inform clinical decision-making, shape clinical protocols, and ultimately improve patient outcomes. This thesis will add to the evidence base regarding the use of MRI in abdominal radiotherapy and for the first time, provide an insight into the experience of patients receiving SABR to treat liver cancer, something completely absent in the literature. By improving our understanding of the planning procedures that patients undergo, we may be able to provide more choice for patients to better select procedures that facilitate sparing of OAR and provide a more positive patient experience. If NMOCs can enhance the accuracy of MRI delineation, and if more comfortable or patient-preferred breath-hold strategies and immobilisation methods can be identified, clinicians may be able to reduce planning margins, escalate doses more safely, and potentially improve local control and quality of life. Embedding the patient voice ensures that advances align with patient values, enabling adoption of a translational set of perspectives with the potential to influence radiotherapy practice and care delivery.

This thesis describes the exploratory components of the MICROCHIPS study (MRI scans with respiratory immobilisation to contour radiotherapy OAR using oral contrast of hypo or hyper intense fluids including the patient perspective).

The MICROCHIPS study exemplifies the complexity of the proposed approach. Rather than focusing on a single intervention, it comprises exploration of potential improvements to multiple interacting components: MRI tissue contrast with NMOCs; immobilisation workflows; and patient experience. Enhanced imaging precision may inform the optimal breathing immobilisation approach, whilst adjustments in patient positioning can influence how images are acquired and used for SABR planning. Critically, this thesis also acknowledges that patient acceptance and comfort are integral to successful interventions [198]. In this thesis, imaging uncertainty, motion management, and patient experience are reframed as interrelated facets of one central problem: how to improve MR-guided liver SABR in a way that enhances tumour targeting and is acceptable for patients.

This approach aligns with the principles of complex interventions research [199,200]. According to frameworks such as the UK Medical Research Council's guidance, complex interventions benefit from iterative development, stakeholder engagement, and consideration of contextual factors that influence intervention success [200]. Here, complexity arises not only from the interplay of imaging methods and motion management techniques but also from integrating a novel imaging adjunct (NMOCs) and incorporating patient feedback into clinical decision-making and guidelines. In doing so, this thesis aims to build evidence toward the refinement of MRI liver SABR protocols through future research and clinical implementation. Ultimately it is hoped this will improve care delivery, shaped by patient experience, ensuring that progress in radiotherapy is both technically rigorous and genuinely responsive to patient needs.

1.4 Translational research framework: R-IDEAL

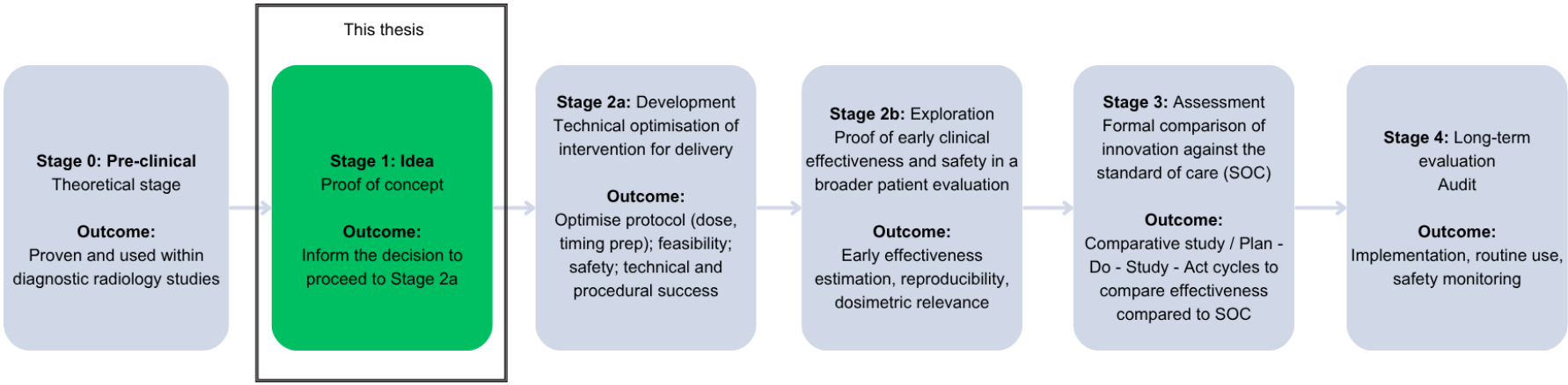
Innovations in radiotherapy, such as MR-guided SABR with novel contrast agents or modified motion-management workflows, are complex interventions with multiple interacting components [201]. Radiotherapy research also varies widely by disease site and comorbidity, dose cannot be fully standardised, and rapid technology change often undermines long clinical trials [201,202]. Since authors recommend application of a phased approach to the development and evaluation of complex interventions and the use of qualitative and quantitative evidence, this thesis follows the R-IDEAL framework [202,203]. R-IDEAL is a radiotherapy-specific adaptation of the surgical IDEAL model (Idea,

Development, Exploration, Assessment, Long-term) [202,203] that provides staged implementation of translational research in radiation oncology (Figure 5).

Briefly, Stage 0 studies involve pre-clinical or foundational investigations that establish the theoretical rationale (for example, phantom experiments, or retrospective planning studies). Stage 1 (Idea) is the first-in-human [204] or the first use of an innovation or intervention used to demonstrate the proof-of-concept [202]. Stage 2 (Development and Exploration) consists of implementing the innovation in a small cohort, case series or pilot study, refining the technique and procedures, and monitoring for safety; this stage often includes iterative improvements and may be subdivided into Stage 2a and 2b as the innovation is optimised and expanded to more patients in the form of a prospective study, preferably with a randomised cohort to measure effectiveness [202]. Stage 3 (Assessment) involves a prospective trial of effectiveness in the broader population to quantify the innovation's benefit and risks compared to standard practice [202]. Stage 4 (Long-term evaluation) includes implementation, audit, ongoing surveillance for long-term toxicity and safety, patient-reported reported outcomes and cost-effectiveness in routine use [202-204].

As shown in Figure 5, the work in this thesis corresponds to R-IDEAL Stage 1. This project, by mapping existing evidence on NMOC research, establishing baseline motion and patient-experience data, and presenting initial proof-of-concept MRI and NMOC results in volunteers and patients, consists of a set of exploratory predicate studies designed to build evidence to aid the development of further translational studies. It therefore aims to report exploratory studies designed to build evidence and inform Stage 2a development (i.e. evaluating NMOCs and personalised motion management in a clinical cohort).

Figure 5 Mapping the thesis to the R-IDEAL framework.
Translational stages used in radiotherapy innovation: Stage 0 shows preclinical theory, already established by diagnostic evidence, Stage 1 - proof-of-concept, Stage 2a - technical and procedural optimisation for delivery in a highly selected population, Stage 2b - early clinical effectiveness and reproducibility in a broader population, Stage 3 formal comparison with the standard of care, and Stage 4 long-term audit for implementation and safety monitoring. This thesis is mapped against the framework, highlighted in green. Since the pre-clinical stage being the components already been carried out in vivo in preceding diagnostic radiology studies, this thesis starts at R-IDEAL Stage 1. It reports diagnostic evidence in Chapter 2, baseline data of motion and patient experience presented in Chapter 3 and Chapter 4, respectively. Data from a proof-of-concept study of selected NMOCs is presented in Chapter 5.



1.5 Thesis aims, objectives, structure and overview

1.5.1 Aims

This thesis aims to systematically investigate approaches to enhance the planning and delivery of MR-guided liver SABR by comprehensively addressing imaging, motion management and patient experience factors in an integrated framework.

1.5.2 Objectives

1. **Scoping the evidence of NMOC usage.** To map existing knowledge on non-medicinal oral contrast agents for upper-abdominal MRI, including MR-guided radiotherapy.
2. **Quantification of liver motion under compression.** To measure respiratory-induced liver motion in SABR patients and evaluate how well abdominal compression reduces this movement, including analysis of patient variability and potential predictors of motion reduction. This can serve as a benchmark for future immobilisation methods to be compared against.
3. **Exploration of patient experiences.** To understand the patient experience of liver SABR, focusing on how patients perceive and cope with the preparatory and delivery procedures. The findings are intended to inform modifications to protocols and patient information in future components of the MICROCHIPS study.
4. **Proof-of-concept MRI technique development.** To establish proof-of-concept of using candidate NMOCs and evaluate their impact on anatomical conspicuity, image quality and experience in healthy volunteers.

Achieving these objectives might provide initial evidence on whether introducing NMOCs into MRI planning and refining motion management with patient input could reduce uncertainties in liver SABR in a patient-centred way.

1.5.3 Thesis structure and overview

To accomplish the aims above, the structure of this thesis is outlined below, together with a summary of each chapter.

Chapter 2 - Non-medicinal oral contrast in upper abdominal MRI for MR-guided radiotherapy: A scoping review: This chapter addresses the first objective. It presents a published scoping review that systematically maps the landscape of NMOC agents used to enhance MRI of the upper abdomen. The various non-medicinal oral contrast agents are identified within the literature to identify any existing knowledge gaps. This aids the identification of candidate NMOCs that might be applicable for translating their use from diagnostic imaging contexts to liver SABR, investigated further in Chapter 5.

Chapter 3 - Quantifying liver motion in SABR: Study Quantifying the use of abdominal breathing suppression for hepatic motion equipment development: This chapter addresses the second objective. It describes a motion analysis study using retrospective data from 134 liver SABR patients at our institution. Chapter 3 evaluates how a standard rigid compression arch impacts liver motion, using in-house developed python code to measure liver structure excursions on routinely collected radiotherapy planning data, with and without compression. This chapter provides a real-world baseline of motion management efficacy for future comparison.

Chapter 4 - Patient experience of liver SABR: a qualitative interview study. Supporting the third objective, Chapter 4 discusses a qualitative study capturing the patient's voice in the liver SABR pathway. It reveals important insights that can be used to inform future adaptations for future protocols and clinical practice.

Chapter 5 - Evaluation of non-medicinal oral contrast agents: This chapter addresses the fourth objective by presenting preliminary findings from an exploratory proof-of-concept investigation of proposed NMOCs in MR-guided liver SABR. The results provide an indication to the potential viability of the concept and support further investigation in patient populations.

Chapter 6 - Discussion: major findings, limitations and future developments: The final chapter synthesises the major findings from all studies, discusses their implications in the context of current literature, and outlines the next steps for research and clinical implementation. In Chapter 6, the work within this thesis is reflected upon within the R-IDEAL pathway. Future research is proposed to integrate an MRI NMOC protocol (from Chapter 5) and a personalised motion management approach (informed by Chapter 3 (data on

the effectiveness of compression), and Chapter 4 (patient feedback to improve on the overall experience)). Chapter 6 also reflects on limitations and how these might be addressed in subsequent research. Finally, this chapter emphasises the importance of ongoing patient and public involvement as the research program moves towards a further study, ensuring that innovations in liver SABR truly align with patient needs and ultimately contribute to improving the liver SABR cancer treatments.

Chapter 2 Non-medicinal oral contrast in upper abdominal MRI for MR-guided radiotherapy: A scoping review

2.1 Preface

The chapter is derived from work published in Radiography (2025) [161] and a poster presented at ESTRO 2024 [205].

2.2 Introduction

MRI provides superior soft-tissue contrast compared with CT and is widely used for cancer diagnosis and staging [206,207]. In radiotherapy, CT has been the planning standard because it supplies electron-density information for dose calculation. Recent adoption of MRI in radiotherapy workflows, via MR-simulators and MR-linacs, improves soft-tissue definition and supports more accurate contouring [155,172,208-211].

Utilising MRI, especially in MR-guided upper abdominal radiotherapy, presents challenges such as interobserver variation in accurately delineating tumours from OARs [155]. These difficulties arise from the complexity of abdominal anatomy, tissue conspicuity, and the impact of motion on image quality [155]. Advances in diagnostic strategies have enhanced the visualisation of the gastrointestinal (GI) tract by modifying luminal signals through oral administration of contrast agents, aiding the identification of specific anatomical structures and/or pathologies [173,212]. The signal from these agents can vary based on the type used and the MRI sequence employed, appearing hyperintense or hypointense when compared to reference tissues such as the psoas muscle. Oral contrast agents range from pharmaceutical medicines to naturally derived substances and foods such as fruit juices and milk-based products. Ideally, oral contrast agents should not only enhance anatomical visualisation but also be palatable and cost-effective [172-176].

When selecting oral contrasts to optimise image quality, it is important to consider their impact on patient experience. Some medicinal oral agents are effective, but they can cause gastrointestinal side effects [213]. Non-medicinal oral contrasts (NMOCs) may offer a practical alternative, potentially reducing adverse reactions and improving comfort and adherence [172,176,179,214].

The use of oral contrast agents for upper-abdominal MR-guided radiotherapy remains underexplored.

Preliminary searches indicated that the literature on NMOCs in diagnostic radiography was heterogeneous, and that, in a radiotherapy context, research was absent. Consequently, a scoping review was deemed the most suitable approach to systematically map the breadth of existing evidence. Scoping reviews have proven especially valuable for synthesising broad or complex research fields that feature diverse study types, limited prior syntheses, and significant heterogeneity [215-217]. By capturing the extent, range, and nature of prior work, and highlighting key knowledge gaps [218], this method supported the aim of this thesis: to investigate ways to enhance MR-based SABR planning for liver cancer. In doing so, the review identified evidence gaps that shape later studies in this thesis and may inform other MR-guided radiotherapy research.

2.2.1 Aims and objectives

2.2.1.1 Aims

This scoping review aims to systematically map and synthesise the current evidence on the use of NMOC agents in upper-abdominal MRI, with a specific focus on their potential applicability to radiotherapy planning. By identifying the types of NMOCs studied, their imaging characteristics, and reported patient experiences, this scoping review aims to identify existing knowledge gaps, particularly in the context of upper-abdominal MR-guided radiotherapy - an area where there is a notable paucity of research.

2.2.1.2 Objectives

To achieve these aims, the scoping review had the following objectives:

- Identify and characterise NMOCs:
    - Catalogue the different types of NMOCs used in upper-abdominal MRI.
    - Summarise the reported signal characteristics of NMOCs across different MR sequences.
- Identify research and clinical effectiveness assessment methods:
    - Record how NMOCs have been evaluated.

    - Record for what purpose NMOCs were studied (e.g. to improve tissue conspicuity).
    - Determine the range of clinical or research settings such as radiotherapy, noting any limitations or evidence gaps.
- Examine patient experience and acceptability:
    - Explore the extent to which studies have reported patient-centred outcomes, including side-effects, comfort, and compliance.
- Identify gaps and future research needs:
    - Highlight where empirical data is lacking, especially relevant or related to the use of NMOCs for MR-guided radiotherapy planning.
    - Provide recommendations for further research that integrates both technical and patient perspectives, potentially informing future protocols or clinical trials.

2.3 Methods

A pre-defined protocol based on Arksey and O'Malley's framework was followed and published on the Open Science Framework [215,219]. The Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocols (PRISMA-P) statement and the extension for Scoping Reviews (PRISMA-ScR) reporting guidelines were followed in producing the written report [220]. Since this study was extracting data from existing publicly available published papers, ethical approval was unnecessary.

2.3.1 Search and screening strategy

A search strategy (See supplementary material A, provided in the original publication [161]) was developed with assistance from an information specialist. In line with the recommendations of the Joanna Briggs Institute, with respect to the broad topic and review question, the objectives were assigned to the population, concept and context (PCC) framework shown in Table 2 [221]. Manual bidirectional citation searching was undertaken to ensure a thorough search and identify studies potentially missed by bibliographic database search methods [222]. The literature was searched from inception to 01/05/2024 using MEDLINE (Ovid), EMBASE, CINAHL (EBSCOhost), CAB Abstracts databases. To aid with mitigating publication bias, additional sources included Google

Scholar and ProQuest Dissertations & Theses. The search included potentially relevant research in all languages. Where the full text was unavailable or not in English, it was excluded at the full text review stage. Animal studies were excluded. All database records were transferred to EndNote 20 (Clarivate, Philadelphia, PA) and duplicates were removed using the Bramer method [223,224].

Studies published in peer reviewed journals which met the eligibility criteria in Table 2 were included for title and abstract screening. Screening was conducted by the first author, with a minimum proportion of 10% of results being independently checked by a second reviewer (CB) using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) [225]. Testing for inter-screening reliability of the screened proportion was quantified using Cohen's kappa scores [226]. Disagreements were resolved with consensus. Reasons for full-text exclusion were recorded.

Table 2: Population, Concept, and Context (PCC) framework specifying inclusion and exclusion criteria for the scoping review.
Each row outlines the eligibility criteria for the study population, the targeted concept and contextual requirements, alongside the corresponding exclusion criteria.

Objective	Inclusion criteria	Exclusion criteria
Population	Adults aged 18 or over, any condition, any country.	Animal studies.
Concept	Upper-abdominal MRI with natural (non-medicinal) oral contrast agent ingestion – how were they perceived and when, how, and why were they used?	Non-medicinal oral contrast not used as part of the empirical evaluation studied.
Context	Studies to have taken place in a hospital - clinical or academic.	Full text unavailable. Studies not published in English.

2.3.2 Data charting

An a priori charting framework form was developed for intended use on the first 10% of the included studies and was modified until the codes were coherent and explicit. Cohen's Kappa statistic was used to test the level agreement. The objectives of this scoping review did not encompass the assignment of quality grading scores. Utilising risk of bias tools was considered unnecessary and potentially inappropriate due to the substantial methodological variability across

the included studies [227]. Data were charted and aggregated to provide an account of the utilisation of NMOC use in upper-abdominal MRI. Data items extracted included: oral contrasts tested; type of publication, year of publication, country, method (in vitro, in vivo); participants; themes; aims; design; funding; conflicts of interest; inclusion and exclusion criteria; participant preparation; intervention details; MRI acquisition details (including manufacturer and sequences used); participant positioning; if IV contrast was used; anatomical site of interest; reference anatomy; plane of imaging; signal properties and appearance; quantitative imaging results; methods of evaluation; statistical analysis details; reported outcomes; participant experience details and outcome. Studies were grouped by NMOC and summarised by thematic aim (for example, visualisation vs motility), design, and population.

2.4 Results

The results are provided in accordance with the review objectives. Firstly, the range and frequency of NMOCs are summarised. Secondly, the study aims and evaluation approaches are described, including the study designs and populations. Thirdly, signal characteristics and reported imaging effects are synthesis across sequences. Finally, patient experience and acceptability data is reported.

2.4.1 Literature search results

Figure 6 presents the PRISMA flow diagram illustrating the search and screening process. Initially, 1,955 unique citations were identified. Following the review of titles and abstracts, 1,756 citations were excluded. The first author screened 77% of abstracts, with 449 out of 1,955 (23%) being subjected to independent screening by two reviewers, resulting in a proportionate agreement of 97.3% and a Cohen’s Kappa coefficient of 0.88. Full-text screening was performed on 199 articles, of which 153 were excluded for failing to meet the inclusion criteria, and one article was retracted due to plagiarism. An additional article was incorporated into the full-text review following citation searching. A total of six studies were excluded due to not being written or translated into English [228-233]. A final total of 47 studies were included for data charting, comprising 44 research articles, two conference abstracts, and one short communication paper. Characteristics of the evidence including details of

funding sources and statements of conflicts of interest are reported in Supplementary Material A of the original publication [161]).

2.4.2 Frequency of non-medicinal oral contrasts (NMOCs) reported in the literature

A total of 31 distinct NMOCs were utilised across the studies reviewed. The frequency of studies reporting the use of various NMOCs, distinguishing between in vitro (NMOCs imaged in phantoms) and in vivo applications (NMOCs imaged in humans) is summarised in Figure 7.

All included studies performed in vivo testing in humans, with 18 of these studies (58% of NMOCs used) reported preliminary in vitro evaluations. In vitro evaluations, although not the focus of our review, provided foundational data that informed the progression to in vivo applications. Twenty-nine studies (62%) reported the use of oral contrasts in vivo only and publications often included more than one candidate NMOC for evaluation.

Figure 6: PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flow diagram illustrating the search, screening, and inclusion process for the scoping review.
Reproduced from [161]. © Crown Copyright 2025. Published by Elsevier Ltd on behalf of The College of Radiographers. Licensed under CC BY 4.0. This shows the number of records identified via database and citation searching, how many were excluded at each screening stage and why, as well as the final set of studies included in the scoping review.

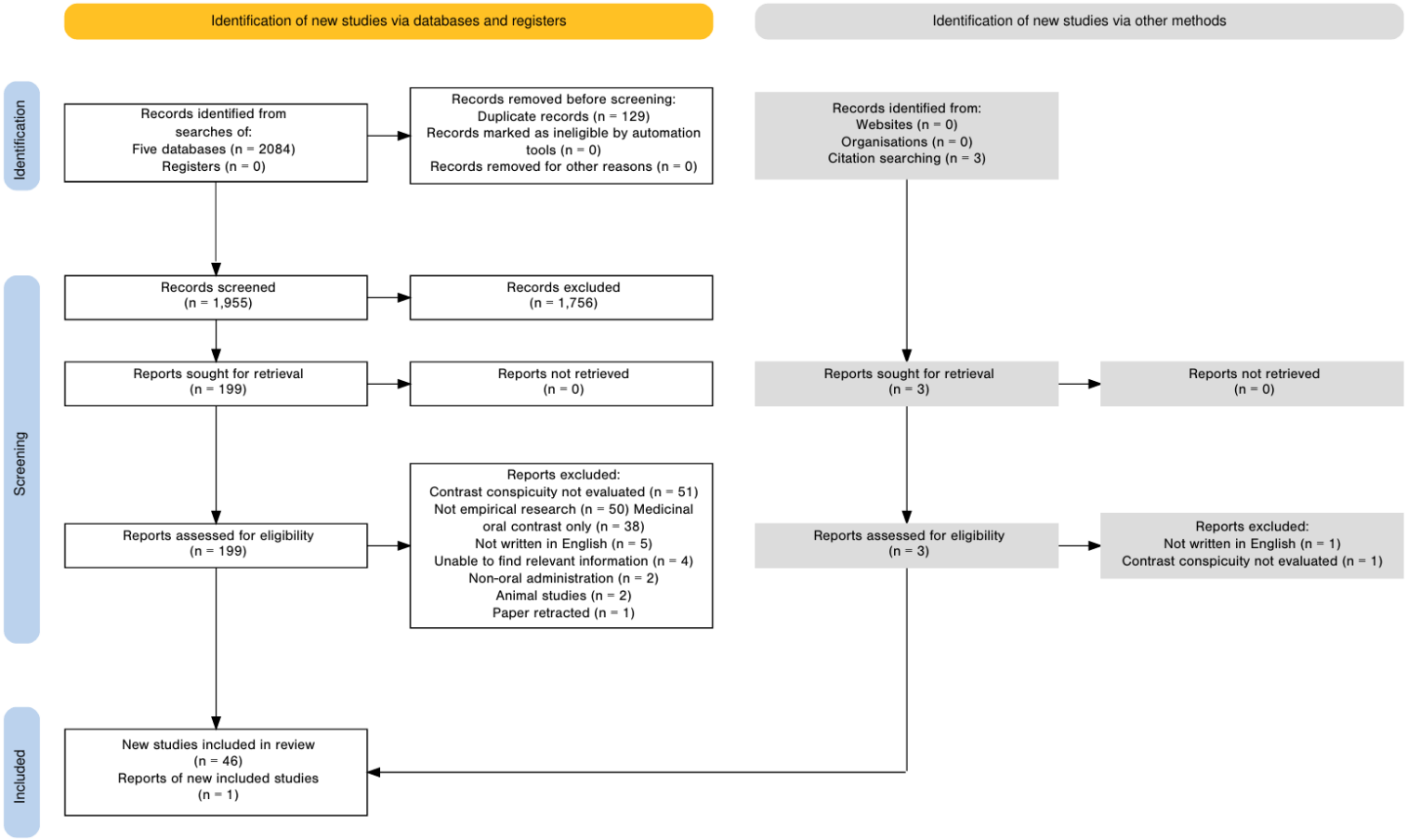
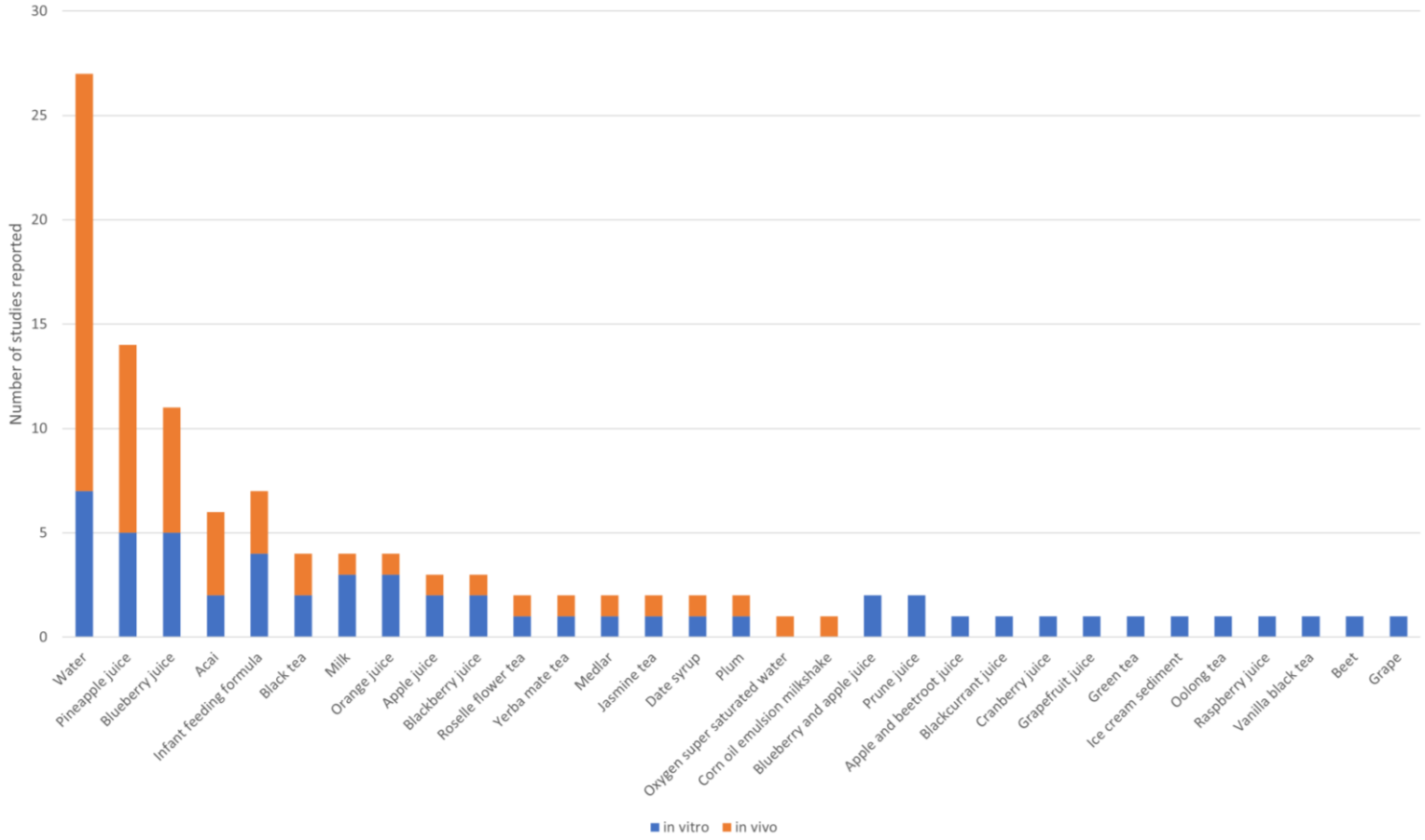


Figure 7: The number of studies reporting the utilisation of NMOCs.
 Each bar represents a specific contrast medium, with blue segments indicating the number of NMOCs studied in vitro studies and orange segments representing the number of NMOCs studied in vivo.



Water was the most frequently studied NMOC, with a total of 27 studies. Fruit juices included pineapple juice (10 studies) and blueberry juice (8 studies) with a relatively balanced distribution between in vitro and in vivo study components. Other fruit juices such as acai juice appeared in multiple studies but with far fewer total reports compared to pineapple and blueberry juices. Infant feeding formula featured in earlier MRI contrast studies (three were in vivo studies) between the years 1989 and 1992.

NMOCs studied less frequently, including various teas (e.g. green tea, jasmine tea, yerba mate tea), and other substances such as ice cream emulsion or oxygen-supersaturated water have only been reported once each in the literature. The specific NMOCs used, grouped by food types along with their corresponding references are detailed in Table 3.

2.4.3 Study aims

All studies could be broadly categorised into two themes based on their aims: investigating either motility (5/47 (11%) [234-238] or tissue visualisation (42/47, 89%)[174,181,213,214,239-276]. In this review, motility referred to the utility of NMOCs to observe the activity of the gastrointestinal tract during MRI, whereas tissue visualisation referred to the visibility of anatomical structures on MRI, including their conspicuity, namely the degree to which they could be distinguished from adjacent tissues or luminal contents.

Twenty-eight percent of the tissue visualisation studies (13/47) specifically aimed to investigate luminal signal suppression properties of NMOC for T2-weighted magnetic resonance cholangiopancreatography (MRCP) sequences [174,214,239,250,251,254,262,264-266,268,272,273].

Table 3: Overview of non-medicinal oral contrast (NMOC) agents identified in the literature, with counts of publications focusing on tissue visualisation or motility.
Each row corresponds to a distinct NMOC sub-type, with columns indicating the number of studies addressing visualisation or motility aims, and the total publications reported.

NMOC	Visualisation publications	Motility publications	Total publications
Water			28
Water	25 [174,213,236,240,241,243-249,255-261,263,267,269,270,272,274,275]	3 [234,236,238]	
Oxygen super-saturated water	1 [263]		
Fruit/vegetable juice			21
Pineapple juice	9 [174,214,240,241,246,248,262,265,276]	1 [235]	
Blueberry juice	8 [174,214,241,246,252-254,258]		
Acai juice	5 [239,244,245,264,268]		
Orange juice	3 [174,240,241]		
Apple juice	2 [174,246]	1 [237]	
Blackberry juice	2 [240,246]		
Blackcurrant juice	1 [240]		
Blueberry and apple juice	2 [174,240]		
Prune juice	2 [174,240]		
Apple and beetroot juice	1 [240]		
Beet juice	1 [246]		
Cranberry juice	1 [174]		

NMOC	Visualisation publications	Motility publications	Total publications
Date syrup	1 [251]		
Grape juice	1 [246]		
Grapefruit juice	1 [174]		
Medlar	1 [245]		
Plum	1 [246]		
Raspberry juice	1 [240]		
Milk/emulsion			10
Milk	5 [174,242,243,248,251]		
Ice cream sediment	1[243]		
12% corn oil emulsion	1[271]		
Infant feeding formula	4[240,242,243,249]		
Teas			5
Black tea	3[250,272,273]		
Green tea	1[272]		
Jasmine tea	1[272]		
Oolong tea	1[272]		
Roselle flower tea	1[266]		
Vanilla black tea	1[272]		
Yerba mate	1[181]		

2.4.4 Study designs

Table 4 shows the breakdown of studies by design and their participant types. Each row categorises the studies by design, whilst the columns indicate whether the study enrolled only healthy volunteers, a mix of healthy volunteers and patients, or only patients. The grand total row shows the overall number of studies. Healthy volunteers were the most studies population. The most common study design was an uncontrolled before-after study, where outcomes were measured before and after the intervention in the same group of participants, without the use of a control or comparison group (35/47, 74%) [174,213,214,234,236,238-240,244-248,250-259,262-264,266-273,275]. One study described itself as an ‘observational comparative analytical study,’ however it was also recorded as an uncontrolled before-after study, as it evaluated before and after images following a pineapple juice intervention[262]. There were five uncontrolled studies (11%) without comparators [181,235,242,260,261], three controlled before-after studies (7%) [241,265,274], one retrospective uncontrolled study (2%) [249], one study that included both an uncontrolled before-after design and an uncontrolled study (2%) [243], and one randomised controlled trial (2%) [237]. One study was recorded as a comparative cohort study despite the authors stating it was a case-control study, since it tracked outcomes of group exposed to different treatments forward in time, rather than looking backward and there being no control group [276].

Motility studies were typically small, within-subject designs that assessed short-term changes after ingestion, whereas tissue visualisation studies spanned a broader range of designs but were also predominantly uncontrolled before-after evaluations.

2.4.5 Study populations

Twenty-six out of forty-seven (55%) studies conducted their research in healthy volunteers [174,213,214,234-239,245,247,248,250,252,253,257-261,263,266,271-273,275], while 6/47 (13%) combining healthy volunteers for preliminary research before progressing to utilising patient populations [181,241,249,253,266,268] and 15/47 (30%) conducting research exclusively in patient populations [242,246,251,254-256,262,264-267,269,270,274,276].

Cohort sizes were heterogeneous across the included literature, with a median of 13 participants (IQR 7 - 24.5; range 1 - 613). The mean size was 31.4 participants, reflecting the influence of a small number of larger studies. Nine studies (35%) reported the mean age of their healthy volunteer participants [174,213,236,241,247,252,261,271,275], and 12 studies reported the mean age of their patient participants [242,250,251,254-256,262,264,266-268,270].

Table 4 Distribution of study designs and participant populations in the included literature.
Each row categorises the studies according to their design method, whilst the columns indicate whether the study enrolled only healthy volunteers, a mixture of healthy volunteers and patients, or exclusively patients. The grand total column shows the spread of publications for each design, illustrating both the diversity of methods and the composition of participant groups across the reviewed literature.

Study design	Healthy volunteers	Healthy volunteers & patients	Patients	Total
Controlled before-after study		1	2	3
Other: Retrospective uncontrolled study		1		1
Other: Combined uncontrolled before after study for two of the volunteers (5 min and 40 min after ingestion and uncontrolled study for two other volunteers.	1			1
Randomised controlled trial	1			1
Uncontrolled before-after study	20	3	13	36
Uncontrolled study (no comparator)	3	1	1	5
Grand Total	25	6	16	47

2.4.6 Non-Medicinal Oral Contrast signal properties

Figure 8 presents an overview of the signal appearance properties of the NMOCs when imaged using different MRI weighting sequences reported in 37/47 (78.7%) studies.

2.4.7 T_1-weighted sequences:

In T_1-weighted MRI sequences, agents such as acai, blueberry juice, and pineapple juice reportedly exhibited hyperintense signals, indicating a shorter T_1 [241,252,253,258]. Conversely, medlar, orange juice, and water demonstrated hypointense signals, reflecting a longer T_1 [241,245,258,267,269,271,274].

2.4.8 Proton density-weighted sequences:

Infant feeding formula was the only agent reported with a proton density weighted sequence, and it was noted to be hyperintense [243].

2.4.9 T_2-weighted sequences:

In T_2-weighted sequences, agents like water and infant feeding formula appeared hyperintense [213,234,238,241,247,261,267]. Conversely, teas such as black tea and yerba mate were reported as hypointense [239,250,264,268,273].

Nine out of forty-seven (19%) of studies reported in vitro measurement of relaxation times, facilitating a comparison of the intrinsic properties of NMOCs without interference of biological tissues or physiological processes, potentially in a more controlled environment [174,181,214,240-243,249,265]. Signal characteristics reported at a field strength of 1.5T were obtained for 17/31 (55%) NMOCs, using either tabulated data or a graph plot digitiser, and were collated and synthesised in Table 5. Although there is a large amount of missing and limited data, yerba mate exhibited the lowest reported T_1 (155 ±7 ms)[181], followed by pineapple juice (185 ms – 295.6 ms) [174,214,240,241,265], with the longest T_1 being water (2512 ms – 4100 ms) [174,240,241,243,249]. The shortest reported T_2 was pineapple juice (48 ms) [240], however the range of pineapple juice reported T_2 values was large owing to studies using different concentrations of pineapple juice. The longest T_2 reported was water (2040 ms) [174].

Figure 8: Tree diagram illustrating in vivo NMOC signal characteristics across T1-, proton density-, and T2-weighted MRI sequences in vivo.

Adapted from [1]. Each branch indicates whether an agent was reported to appear hyperintense or hypointense, with the associated references noted in brackets. The diagram highlights which specific NMOCs displayed particular signal intensities under the observed sequence types (where available in vivo), providing an overview of the variety of signal properties observed in the literature.

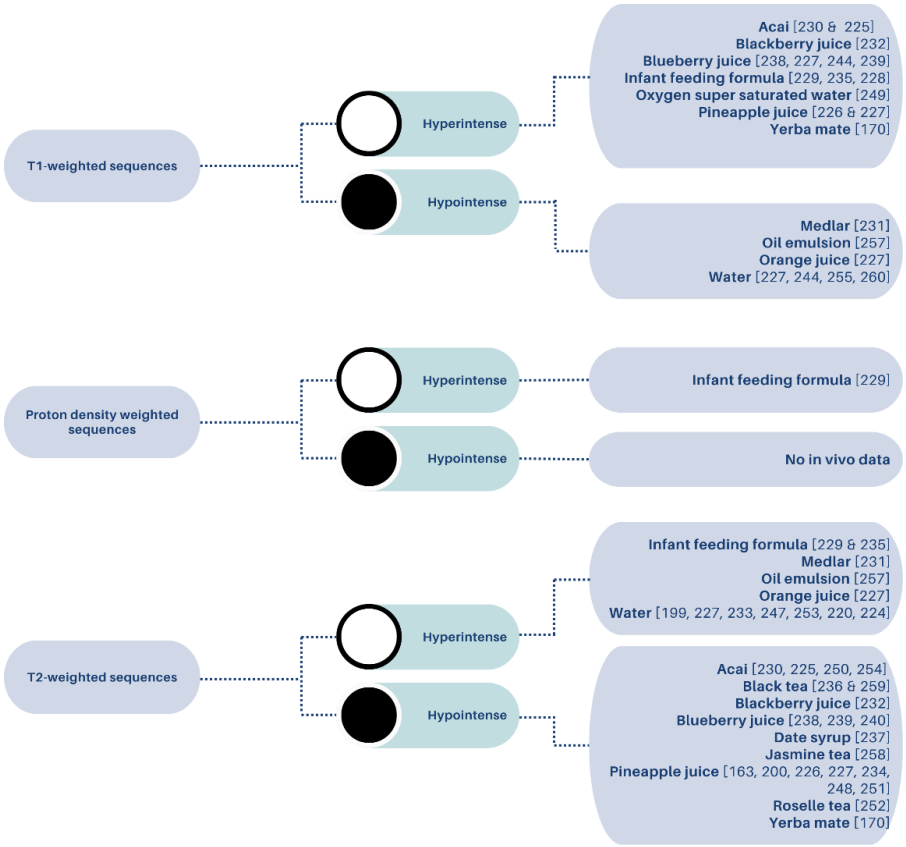


Table 5: Relaxation times (T_1, T_2, and proton density [PD]) of NMOC media measured at 1.5 T.
Data were collated from measurements reported in the literature; the '~' symbol indicates values were derived from graphical data using a plot digitiser.

Non-medicinal contrast media	T_1 values (ms)	T_2 values (ms)	PD values (ms)	References
12% Corn oil emulsion	-	-	-	-
Acai juice	-	-	-	-
Apple and beetroot juice	1679	518	-	Arthurs et al. (2014) [240]
Apple juice	~1753	~543	-	Riordan et al. 2004) [174]
Black tea	-	-	-	-
Blackberry juice	831	103	-	Arthurs et al. (2014) [240]
Blackcurrant juice	2803	1480	-	Arthurs et al. (2014) [240]
Beet	-	-	-	
Blueberry and apple juice	~359	~72	-	Riordan et al. 2004) [174]
Blueberry juice	573	80	-	Arthurs et al. (2014) [240]
	356	64.1	-	Asbach et al. (2006) [241]
	-	86±9	-	Renzulli et al. (2019) [214]
Cranberry juice	~2235	~800	-	Riordan et al. 2004) [174]
Date syrup	-	-	-	
Grape	-	-	-	
Grapefruit juice	~2388	~656	-	Riordan et al. 2004) [174]
Green tea	-	-	-	

Non-medicinal contrast media	T_1 values (ms)	T_2 values (ms)	PD values (ms)	References
Ice cream sediment	670	53	-	Bisset (1989) [243]
Infant feeding formula				
SMA Gold	930	148	-	Arthurs et al. (2014) [240]
Humana 1 (Nestle)	1220	400	-	Balzarini et al. (1992) [242]
Nidina 1 (Nestle)	640	210	-	Balzarini et al. (1992) [242]
Isomil with iron	994	112	-	Bisset (1989) [243]
Similac with iron	580	90	-	
Similac with low iron	1438	103	-	
Similac 20	1484	104	1200	Gerscovich et al. (1990) [249]
Jasmine tea	-	-	-	
Medlar	-	-	-	
Milk				
Condensed milk	920	130		Balzarini et al. (1992) [242]
Whole milk	1739	92		Bisset (1989) [243]
Skimmed milk	1893	95	-	
	~1804	~144	-	Riordan et al. 2004) [174]
Orange juice	1796	440	-	Arthurs et al. (2014) [240]
	2720	690	-	Asbach et al. (2006) [241]
	~2071	~635	-	Riordan et al. 2004) [174]
Oolong tea	-	-	-	

Non-medicinal contrast media	T_1 values (ms)	T_2 values (ms)	PD values (ms)	References
Oxygen super saturated water	-	-	-	
Pineapple juice				
Brand 1	243	48	-	Arthurs et al. (2014) [240]
Brand 2	258	53	-	
	295.6	79.1	-	Asbach et al. (2006) [241]
Brand 1	-	60±6	-	Renzulli et al. (2019) [214]
Brand 2	-	59±6	-	
Brand 3	-	68±7	-	
Brand 4	-	51±5	-	
Brand 4 (75% concentration)	-	59±6	-	
Brand 4 (62.5% concentration)	-	67±7	-	
Brand 4 (50% concentration)	-	80±7	-	
Brand 4 (37.5% concentration)	-	101±10	-	
Brand 4 (25% concentration)	-	140±15	-	
100% concentration	-	95	-	Renzulli et al. (2022) [265]
50% concentration	-	172	-	
25% concentration	-	330	-	
12.5% concentration	-	747	-	
6.3% concentration	-	1261	-	
	~185	~72	-	Riordan et al. (2004) [174]

Non-medicinal contrast media	T_1 values (ms)	T_2 values (ms)	PD values (ms)	References
Plum	-	-	-	
Prune juice	1245	324	-	Arthurs et al. (2014) [240]
	~666	~205	-	Riordan et al. 2004) [174]
Raspberry juice	1055	146	-	Arthurs et al. (2014) [240]
Roselle flower tea	-	-	-	-
Vanilla black tea	-	-	-	
Water	2831	1950	-	Arthurs et al. (2014) [240]
	3800	1800	-	Asbach et al. (2006) [241]
	2512	352	-	Bisset (1989) [243]
	2978	386	1082	Gerscovich et al. (1990) [249]
	~4100	~2040	-	Riordan et al. 2004) [174]
Yerba mate	155 ±7	-	-	Nestle et al. (2004) [181]

2.4.10 MRI study participant preparation

Table 6 illustrates the various participant preparation methods reported in studies, segregated into those focused on tissue visualisation and those focused on motility. Four out of five studies reported a pre-imaging fasting requirement ranging between three to twelve hours to try to ensure the stomach was empty. The use of erythromycin or metoclopramide in two papers was attributed to the known efficacy of these agents in enhancing gastric emptying, thereby retaining less contrast in the stomach. Of these two studies, Young et al. (2008) also referenced the potential for these agents to increase small bowel distension to improve visualisation [257,275]. Other preparation methods included asking participants not to consume caffeine or tobacco during the day of the study (2/47, 4%) [245,246], and positioning of the participants in the right decubitus position for 15 minutes [253], or 60 seconds prior to the examination to speed up gastric emptying (2/47, 4%) [247].

2.4.11 Oral contrast ingestion

The range of NMOC volume administered across all studies is summarised in Table 7 and varied between 100 ml to 2000 ml, ingested between 0 and 180 minutes prior to MRI examination. For visualisation studies specifically, a slightly wider range of volumes of 100 ml to 2000 ml were reported, compared to motility studies, where 500 ml to 1200 ml were used. Both motility and visualisation themed studies reported a mode time of consumption prior to the MRI exam as zero minutes. A complete extraction relating to methods of NMOC agent ingestion, including the anatomical sites of interest, volume, and timing of administration of NMOCs is provided in Supplementary material E of the original publication [161]).

Table 6: Overview of participant preparation protocols reported by visualisation and motility studies.
The rows detail whether bowel preparation methods such as motion stimulants, antispasmodics, or fasting were used before upper-abdominal MRI. The variation in prior preparation highlights the diverse strategies employed to optimise imaging quality or capture specific gastrointestinal functions, depending on the study aim.

Prior preparation	Visualisation studies (42/47)	Motility studies (5/47)
Bowel motion stimulant	Two studies (5%) reported the use of medicines to stimulate gastric emptying of oral contrasts, asking participants to consume either 10 ml of metoclopramide syrup (10 mg/ml) immediately prior to consumption of the oral contrast [275], or IV administration of erythromycin (100mg) immediately after oral contrast ingestion [257].	Zero
Antispasmodics	Six studies (15%) reported the administration of hyoscine butylbromide (Buscopan) (three intramuscularly, two IV and one did not report the route of administration) with doses ranging between 10mg to 40mg [247,255,256,267,269,270]. One study reported using either IV hyoscine (10mg) or IV glucagon (0.25mg)[276].	Zero
Fasting	Thirty-one studies (74%) reported a fasting requirement. Mean and mode time of fasting was 6.9 hours and 6 hours, respectively, with a range of 3 – 12 hours. Seven studies (17%) required fasting for 12 hours or overnight fasting [239,244,247,255,256,259,268] and 11 studies (26%) did not report any fasting requirements [181,214,242,243,250,261,266,269,273-275].	Four out of the five motility studies (80%) reported a requirement for fasting [234-238]. Two of those studies required overnight fasting [237,238] and the other two required fasting for 6 hours prior to examination [234,235].

Table 7 Summary of oral contrast ingestion volume and timing in upper-abdominal MRI studies.
Data are grouped according to the study focus, either tissue visualisation (n=41) or motility (n=5). The mean and mode total ingestion volumes, along with the mean, mode, and range of pre-exam timing, illustrate the differences in oral contrast protocols used for the two main study aims observed in the scoping review (visualisation or motility).

Oral contrast administration	Visualisation studies (41/47)	Motility studies (5/47)
Mean total volume	657 ml	760 ml
Mode total volume	1000 ml	500 ml
Volume range	100 ml – 2000 ml	500 ml – 1200 ml
Mean time of consumption prior to MRI	29.7 min	6.7 min
Mode time of consumption prior to MRI	0	0
Range of consumption time prior to MRI	0 – 180 min	0 – 20 min

2.4.13 Motion management

Twenty-two studies (47%) utilised breath-hold to acquire the MRI images [174,213,234-237,241,246,254-261,264,266,269-272], four studies did not[240,247,252,274], and 19 studies (40%) did not state if imaging was acquired using breath-hold or any other form of respiratory compensation [181,214,239,242-245,248-251,253,262,263,265,268,273,275]. One study (2%) reported that participants were asked to use ‘quiet breathing’ together with an abdominal compression band [267]. One study (2%) reported that participants were asked to voluntarily time their respiration with the scan; however, specific details on how this was achieved were not provided [238].

2.4.14 Impact on tissue conspicuity

NMOCs were administered to aid GI structure delineation or conspicuity in 42/47 studies (89%). Of the remaining five studies, two utilised oral contrast as a mechanism to study motility and were not specifically measuring tissue conspicuity of the oral contrast [236,237]. One further study did not measure tissue conspicuity but was focussed on the amount and timing of distention of

the small bowel [275]. Similarly, one enterography study evaluated bowel distension and image quality, focusing on artefacts with different oral contrast media; it lacked a control group and mainly compared pineapple juice with varying mannitol concentrations [276]. Another study investigated the fate of oxygen-supersaturated water in the GI tract, and it also evaluated luminal signal intensity [263].

2.4.15 Participant experience

Twenty-four studies (51%) did not report any data on participants' experiences. Ten studies (21%) measured participant experience specifically related to oral contrasts [174,213,237,248,251,257,258,271,275,276]. Of these, eight reported using questionnaires or scoring systems to assess participant experience [213,237,248,257,258,271,275,276]. Only one of these studies [237] provided references to the sources upon which their questionnaire was based, and just one study included the questionnaire itself in their appendix [258]. The remaining 13 studies (28%) briefly mentioned tolerability, focusing on side-effects [242,243,247,250,252-256,259,260,264,268].

2.5 Discussion

2.5.1 Summary of evidence: Mapping existing knowledge

This scoping review systematically mapped the literature on NMOCs in upper-abdominal MRI. The review identified 31 distinct NMOCs. Eighty-nine percent of studies evaluated tissue visualisation; 11% assessed gastrointestinal motility. The data demonstrated a diverse range of NMOCs, with water most frequently used and evaluated, followed by pineapple and blueberry juice. In some studies, the rationale was the lack of clinically available medicinal oral agents. Study heterogeneity produced a rich variety of stated uses. Although this diversity precluded direct efficacy comparisons, potential applications of NMOCs in MR-guided radiotherapy were identified, an area notably absent from the radiotherapy literature.

2.5.2 Characteristics of NMOCs and their range of applications

The most common objectives were to identify contrast agents for enterography or MRCP by achieving adequate distension and/or signal suppression

[172,173]. Terminology for NMOC appearance was occasionally inconsistent (see Supplementary Material F in [161]). There was a consensus in terminology, where terms such as ‘positive’ or ‘negative’ were used to indicate luminal hyperintensity or hypointensity, respectively, but caution should be used where no relative reference has been provided. Ensuring clear and consistent terminology is used, potentially as described in Table 8, is recommended for future authors, although it is accepted signal appearance is relative and open to interpretation. To compare the appearance of contrast agents, the same magnet strength, sequences type and weighting should be used, as well as an appropriate reference such as abdominal muscle [277,278].

Table 8: Recommended terminology to describe and reference the luminal appearance of NMOCs relative to abdominal muscle, illustrating the effect of T_1 and T_2 relaxation times on spin echo sequences.
Shorter T_1 relaxation times yield hyperintense (lighter) T_1-weighted signals but hypointense (darker) T_2-weighted signals, whereas longer T_1 times have the opposite effect.

Relaxation times (T_1 & T_2)	T_1w appearance		T_2w appearance	
Shorter	○	Lighter/Hyperintense	●	Darker/Hypointense
Longer	●	Darker/Hypointense	○	Lighter/Hyperintense

2.5.3 Identification of gaps in the evidence

2.5.3.1 Absence of radiotherapy-specific research:

Despite almost 90% of publications focussing on tissue visualisation, with some demonstrating promising performance for improving conspicuity in diagnostic MRI (e.g. pineapple juice and yerba mate), there is a paucity of evidence on the use of NMOCs in MR-guided radiotherapy, and their potential to improve radiotherapy planning and delivery remains unexplored. This finding highlights a key knowledge gap, especially given the increasing reliance on MRI for high-precision radiotherapy planning in the upper abdomen, including liver SABR. Distinguishing between different abdominal structures can be challenging [155],

making this an important area for future targeted research, particularly given the growing integration of MRI into the radiotherapy pathway.

Although no empirical evaluations of NMOCs in MR-guided radiotherapy were found in this scoping review, it is possible that clinical adoption within MR-guided radiotherapy has already taken place without substantial research to support it. For instance, a review by Boldrini et al. (2021) suggested that administering a glass of water prior to MR-guided radiotherapy may help visualise the stomach and duodenum due to the hyperintense signal of water [95]. Similarly, an adaptive radiotherapy study using an MR-Linac to treat 30 patients with locally advanced pancreatic cancer described giving patients half a cup of water prior to treatment to better differentiate between the duodenum and gross tumour volume interface [279]. Therefore, whilst water is occasionally referenced in the MR-guided radiotherapy literature, more substantial investigations are missing.

The optimal selection of NMOC for MR-guided radiotherapy appeared context dependent, varying with disease location, the intended delineation benefit, and patient preference. These factors were not examined comprehensively in the reviewed studies. Whether diagnostic gains translated to MR-guided radiotherapy planning or treatment remained uncertain. Interpreted within the R-IDEAL framework [202], this suggested a need for Stage 1 exploratory work before introduction to the radiotherapy pathway in the clinic. Accordingly, future work could determine which NMOCs best improve OAR conspicuity; how dosing, timing, and patient preparation affect image quality and comfort; and whether side-effects occur in older or comorbid patients typical of SABR.

It is also notable that some of the NMOCs detailed (e.g. pineapple juice, yerba mate) in this review are biphasic, exhibiting different relative signal intensities dependent on the MR sequence employed. In the context of MR-guided radiotherapy planning or treatment, there are potential benefits of utilising biphasic agents that warrant further investigation. Firstly, co-registered sequences where a biphasic NMOC appears hyperintense on one weighting and hypointense on another might help clinicians differentiate luminal structures from adjacent tissues, potentially reducing OAR boundary uncertainty. In adaptive workflows, agents that give strong delineation across different

sequences could allow clinicians to select the sequence that best fits the daily need. Secondly, where MR-guided radiotherapy involves daily plan adaptation with the patient on the treatment couch, having an oral contrast agent that might provide strong delineation on different imaging sequences means clinicians may have an option to choose whichever sequence best suits the workflow need. Future research could evaluate the co-registration of T_1w and T_2w sequences. Once co-registered, by switching between sequences, biphasic NMOC could cause the GI lumen to be hyperintense on T_1w and hypointense on T_2w imaging (or vice versa). This signal difference might improve recognition and delineation of OARs for MR-guided radiotherapy.

2.5.3.2 Limited patient-centred perspectives

Optimising both patient comfort and treatment precision in radiotherapy is important, particularly in the context of complex cancer treatment where patients often present with multiple comorbidities. This review revealed a lack of information regarding participant or patient experiences with NMOC ingestion. Studies frequently presented limited information on side-effects, palatability, tolerance, and compliance, with very limited reporting of patient-reported experience or acceptability. Despite 13% of studies using a questionnaire to measure participant experience of ingesting oral contrast media, there was insufficient information reported to determine whether any of these instruments were validated. This lack of reporting limits the ability to accurately and reliably interpret and compare data on participant experience across studies [280], highlighting another gap in the evidence base. Woolen et al. (2017) explored the patient-centred value of oral contrast media used in CT, incorporating questions from the Testing Morbidities Index; validated measures of temporary health disutility [281,282]. Their findings suggested that if oral contrast material offered a diagnostic benefit, most patients would prefer to ingest it rather than risk missing important findings [281]. However, the risk, burden, and acceptability of NMOC ingestion, especially in the context of liver SABR and MR-guided radiotherapy, remains uncertain.

To facilitate future evaluations and comparisons of MRI oral contrast media, the development and use of validated questionnaires is recommended. Additionally, qualitative methods could provide further validation and offer a more holistic and

nuanced understanding of patient perspectives [283]. Although some authors claimed to have conducted ‘qualitative’ analysis, they appear to have been referring to quantitative measures of image quality, rather than employing true qualitative methodologies [241,251,276]. Importantly, none of the studies included in this review utilised genuine qualitative methods in relation to NMOCs. Given that additional burdens or discomforts might reduce compliance or potentially complicate MR workflows, qualitative patient data should be sought to ensure that any proposed NMOC intervention is both clinically feasible and patient centred.

2.5.4 Limitations

This review has several limitations. Although an information specialist supported the development of a search strategy, the literature search was conducted by one reviewer, with only 23% of abstracts independently screened by a second. Relevant data may have therefore been missed. Furthermore, due to the possibility of introducing errors resulting from inaccurate translation, the search and exclusion strategy identified six full-text papers that were excluded because no English translation was available [228-233], raising the possibility that key information may have been lost.

The heterogeneity of studies and their methods prevented a meta-analysis of multiple outcomes related to NMOCs, and this was outside the scope of this review. There was also inconsistency in study methods when comparing image quality, and limited information on the clinical significance of reported results. Whilst extracting more data on tolerability and experience was intended, this information was either only briefly covered or entirely absent from most studies.

Given this scoping review aimed to develop a comprehensive overview of the evidence surrounding NMOCs rather than a complete synthesis of outcomes data, a methodological appraisal or risk of bias assessment of studies was not conducted. Although this approach is in line with supporting guidance for scoping reviews, some data, such as the likely appearance and reported relaxometry of specific NMOCs were synthesised to facilitate further research. However, these results should be interpreted with caution, as they lack the quality and reliability evaluations that ensure greater validity [284,285].

This scoping review is the first to systematically summarise the properties of NMOCs and highlights their potential use in MR-guided radiotherapy. By providing a comprehensive overview of the current evidence, this review has established a foundation for future research and offers insights into the emerging applications of NMOCs in radiotherapy planning and delivery.

2.6 Conclusion

NMOCs have been extensively used in diagnostic MRI to enhance GI visualisation and assess motility, with this review identifying 31 distinct NMOCs primarily used to aid tissue visualisation. Their promising characteristics, such as the potential to improve tissue conspicuity and having fewer side effects than their medicinal counterparts, suggests their application in MR-guided radiotherapy may be beneficial. Further research is needed to evaluate NMOCs in this context, considering imaging requirements, as well as patient experience and acceptability.

To translate this evidence into a radiotherapy context, the next chapters establish uncertainties that NMOCs would interact with in the broader context of liver SABR as a complex intervention. In MR-guided liver SABR, any gain in conspicuity from NMOCs, and in general image quality, will be impacted by motion management and patient experience. Chapter 3 therefore quantifies motion uncertainty with current immobilisation practice and Chapter 4 examines what this experience is like from the patient perspective.

Chapter 3 Quantifying liver motion in SABR: Study Quantifying the use of abdominal breathing suppression for hepatic motion equipment development

3.1 Introduction

In Chapter 1, the challenge of respiratory-induced motion and its impact on liver SABR was introduced. Respiratory-induced displacement of the liver can exceed 20 mm, compromising target coverage and normal tissue sparing during SABR [140,286,287]. Current motion mitigation techniques fall into two types: 1) 'active' measures, such as breath-hold/or gating, and 2) 'passive' techniques, including abdominal compression [142]. The passive technique of abdominal compression is the most common method used in the UK to reduce diaphragm excursion and therefore liver motion for SABR [288].

A systematic review by Daly et al. (2022) focussed on six studies of hepatobiliary or pancreatic context and found that abdominal compression reduced cranio-caudal (CC) tumour motion in most patients [112]. In terms of magnitude, some studies have shown that abdominal compression can often reduce average peak excursions in the CC direction by up to 62% [139]. This often enables internal target volume (ITV) reduction, potentially sparing more healthy tissues [112,138].

To explore this further, an extracted summary of data from eight studies, all of which have aimed to measure how effective abdominal compression is at reducing motion during liver SABR, is shown in Table 9. There are various abdominal compression devices that include rigid compression plates, belts/bands, vacuum cushions with compression, some of which are couch attachable [112]. No clear overall difference in motion-reduction efficacy between different compression device types has been found [112]. Authors have suggested potential reasons for increased motion are due to initial discomfort and anxiety associated with abdominal compression [289,290].

Research suggests that patient-specific factors and equipment differences can contribute to the variability of response. In total, three studies have explored the impact of patient anatomy or body habitus on the effectiveness of compression [135,136,138]. However, their conclusions were mixed. The largest study of 99

patients hypothesised that patients with a high body-mass index (BMI) might respond less to abdominal compression as the compression force could be absorbed by adipose tissue. Abdominal compression was significantly less likely to succeed in overweight patients and men [135]. In their cohort, patients with a BMI ≥25 had a higher chance of motion >5 mm. Conversely, others with fewer participant numbers and different methods of analysis, have found no such correlation [136,138].

Multiple studies have reported a proportion of populations experience negligible or paradoxical motion change [110,134,136,137,139]. This has been summarised in the final column of Table 9. As can be seen, a sub-set of patients show <2 mm of residual benefit from abdominal compression or even worsening motion[134,137]. In a single-institution study by Hardcastle et al. (2023), abdominal compression produced minimal motion reduction (<1 mm) in 9 out of 26 evaluated liver SABR patients [137]. Similarly, Van Gelder et al. (2018) observed inconsistent motion reductions using a pneumatic abdominal compression belt. Amongst 14 patients treated for upper-abdominal tumours, many had negligible (<2 mm) or even increased organ motion under compression. Only six patients showed a clear decrease in liver motion, whilst others saw no improvement or a slight worsening [134].

Meta-analyses have been precluded by the marked methodological heterogeneity amongst these studies [112]. Heterogeneity refers to differing compression techniques or equipment amongst studies. It also includes variations in participant selection criteria, imaging protocols, response assessment metrics and statistical testing. A key limitation of the current literature is the lack of standardised protocols to assess motion. Therefore, whilst the published data has demonstrated efficacy of abdominal compression is not uniform across all patients [110,112,134-139], cross-study comparisons, and indeed Table 9, should be interpreted with caution. Some authors have acknowledged this and consequently recommended evaluating respiratory motion strategies on a per patient and/or local population rather than relying on data in the literature [134,137]. In practice, this requires performing internal audits and perhaps individual tests of how each patient responds to abdominal compression or other available motion management techniques at radiotherapy simulation. Current guidelines broadly support this, by recommending

verification of the effectiveness of any motion mitigation technique for each patient during the setup and planning process and investigate sources of variability [98,100,117].

Direct comparisons between abdominal compression and breath-hold are limited, with studies often focussing on individual strategies. Accordingly, Webster et al. (2024) emphasised the need for further studies comparing abdominal compression and breath-hold, since breath-hold can offer greater immobilisation leading to smaller treatment volumes. However, this comes with higher patient selection demands [111]. Understanding potential factors that might mediate compression in a local cohort might lead to further technique optimisation. This could lead to developing a protocol whereby breath-hold or gating are offered to patients who can manage the demands. This could potentially avoid needless discomfort or potentially improve the reproducibility of liver SABR [134,137].

In the host institution, abdominal compression has been delivered with a rigid ‘bridge’ or ‘arch’: the ONEBridge compression device (CIVCO Medical Instruments Co., Inc., Kalona, Iowa, U.S.A), shown in Figure 9. The recent installation of a new magnetic resonance (MR)-simulator, with its narrow bore and positional difficulties in fitting the compression device along with the abdominal coil, necessitated a switch to a new system, an MR-compatible compression belt. When integrating a new device or technique into clinical practice, current guidelines recommend conducting thorough evaluations and audits to assess patient movement, setup errors, and margin accuracy, with subsequent re-auditing as necessary [98,291]. Apart from the study by Hu et al. (2017) [135], there is a lack of large-scale investigations that systematically quantify liver motion in contemporary 4D CT amongst an unselected SABR population. An analysis of the ONEBridge arch provides a baseline for comparison for liver SABR motion studies, including the MICROCHIPS study.

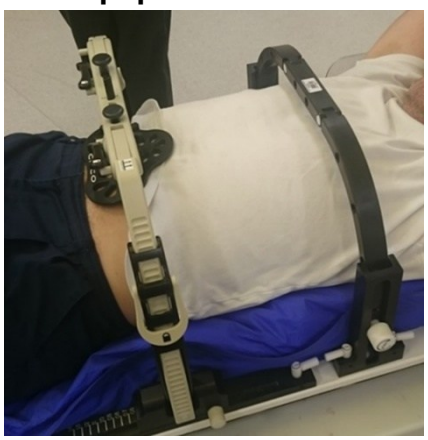
Table 9 Studies comparing motion amplitudes of the liver using either abdominal compression (AC) and free breathing (FB) in liver SABR.

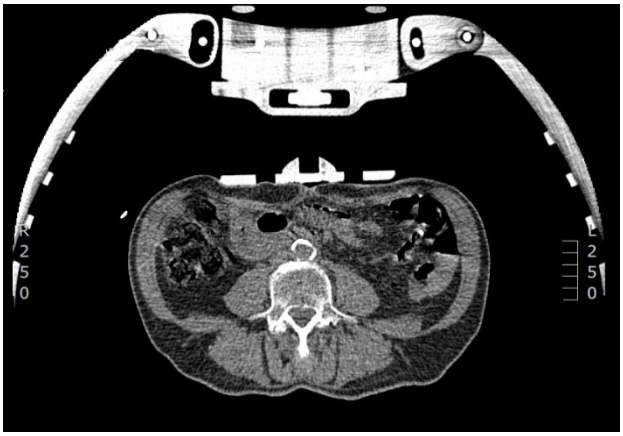
Study	Imaging modality/method	Liver cohort size (n)	Motion reduction[1]	% Non-responders (>5mm residual CC motion or <1mm reduction)
Daly et al. (2024)[136]	T_2w cine MRI (MR-linac) / compression belt	16	Mean -40.3% CC (15.7 mm FB vs 8 mm AC) and 7.8 mm reduction	12.5%
Hardcastle et al. (2023)[137]	Fluorscopy (liver dome) / compression belt	26 with and without AC	-3.5 mm CC (-0.3 mm – 16 mm. 9/26 patients < 1 mm	35% < 1mm or an increase in motion with AC
Van Gelder et al. (2018)[134]	4DCT (liver dome / compression belt)	15 (14 comparable)	Mean – 8% sup inf (SI) (8.7 mm FB vs 8.0 AC), +13% AP (4.7 FB vs 5.4 mm AC), 0% LR (0.7 mm FB vs 0.7 mm AC).	79% < 2mm or increase in motion with AC
Hu et al. (2017)[135]	4DCT liver / compression arch/plate	99	46% CC (9.9 mm FB vs 5.3 mm AC), -20.7% AP 2.9 mm FB vs 2.3 mm AC) 6.5% LR (3.1 mm FB vs 2.9 mm AC).	33% CC motion remained >5 mm

[1] Authors frequently used and reported mixed terms of motion as cranio-caudal (CC) or superior-inferior (SI). AP refers to anterior-posterior motion, LR refers to left-right motion.

Study	Imaging modality/method	Liver cohort size (n)	Motion reduction[1]	% Non-responders (>5mm residual CC motion or <1mm reduction)
Lovelock et al. (2014)[138]	Fluoroscopy / belt	42	60% CC (11.4 AC no pressure vs 4.4 mm AC pressure applied).	7% CC > 5mm
Eccles et al. (2011)[110]	T_2w cine MRI / compression arch/plate	60	Mean -19.7% CC (11.7 FB vs 9.4 AC), -12.5% AP (4.9 mm FB vs 5.6 mm AC).	28%
Wunderink et al. (2008)[139]	Fluoroscopy and fiducials / compression arch/plate	12	Median/mean -62% CC (mean 10.8mm FB vs 4.2 mm AC), -38% AP (4.2 mm FB vs 2.6 mm AC) and +15% LR (FB vs AC < 1 mm.	0%
Heinzerling et al. (2008)[292]	4DCT	6	Mean SI tumour motion -49.2% in high compression; -37.5% in medium compression.	0%

Figure 9: The CIVCO OneBridge device demonstrated in situ on a model (left) and an axial CT image (right) showing the positioning of the equipment.





3.2 Study objectives

1) Establish local ranges of liver motion with and without abdominal compression to enable future research into motion management.
2) Examine whether sex or body-habitus metrics (external body AP/LAT diameters, regional fat/body fraction) moderate the abdominal compression effect. By understanding whether these factors act as covariates or predictors, it may be possible to refine patient selection criteria for compression, potentially avoiding needless discomfort or potentially improving the reproducibility of liver SABR.

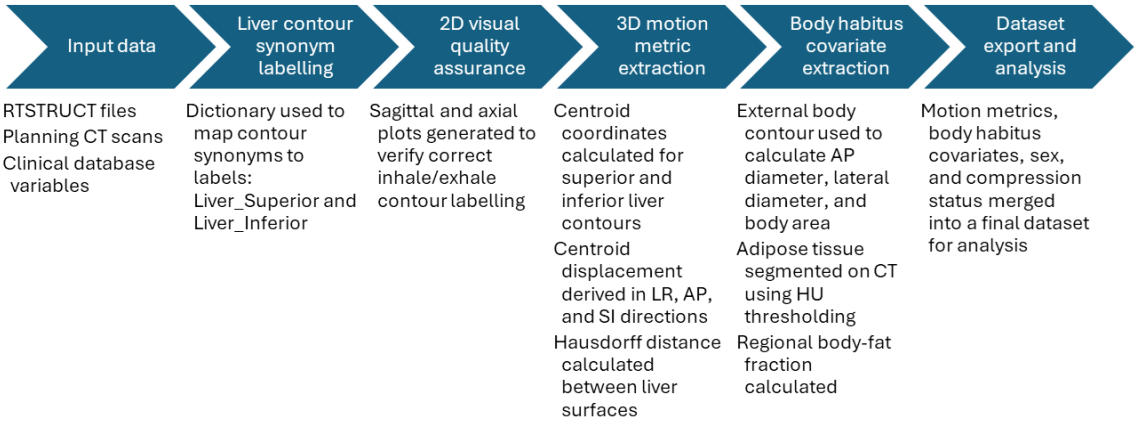
3.3 Methods

3.3.1 Study design overview

This retrospective evaluation extracted respiratory motion metrics and body habitus covariates from the CT and radiotherapy Structure Set object files (RTSTRUCT) of 134 consecutive liver SABR patients treated in a single centre. This data was then compared across abdominal compression status using non-parametric statistics and multivariable generalised linear regression models. The analysis workflow is summarised in Figure 10.

Figure 10 Workflow of the analysis pipeline.

RTSTRUCT and planning CT data were processed using author-developed python scripts to distinguish between superior and inferior liver positions captured during radiotherapy planning and extract 3D motion and body-habitus metrics before exporting a dataset to SPSS for statistical analysis.
Abbreviations: LR, left-right; AP, anterior-posterior; SI, superior-inferior, HU, Hounsfield Unit.



3.3.2 Ethical considerations

The study was a retrospective analysis, conducted with the LeedsCAT research database ethical approval (REC reference: 19/YH/0143 and IRAS project ID: 342888, Research database ethical approval) (approval letter provided in Appendix A). All patient data was deidentified and stored on secure LeedsCAT infrastructure.

3.3.3 Patient population and inclusion/exclusion criteria

Consecutive patients who underwent liver SABR at LTHT from 1st January 2017 until 31st December 2024 were identified using a Structure Query Language (SQL) query of the MOSAIQ radiotherapy electronic patient record (MOSAIQ,

Elekta AB, Stockholm, Sweden) and associated DICOM data was queried using Nexus (Pukka-j, 2023, Darlington, United Kingdom).

Patients were eligible for inclusion if they had completed liver SABR and had structures within the RTSTRUCT and a corresponding planning CT that represented the most superior and inferior liver positions used to aid registration and treatment localisation. Exclusion criteria comprised incomplete RTSTRUCT information, inconsistent or missing data. Supporting lookup tables were generated to clarify any ambiguous compression information.

Compression status was obtained from the setup information recorded in the radiotherapy record and verify treatment system, MOSAIQ (Elekta AB, Stockholm, Sweden). These criteria ensured that only patients with reliable imaging and a confirmed compression status (whether the patient was treated with or without abdominal compression) were included. Each record was de-identified in accordance with local policy. Only the most recent plan dataset per patient was used, thereby excluding older or superseded plans. The dataset did not include the clinical rationale for using or omitting abdominal compression.

3.3.4 Compression technique

Patients in the compression group were treated using a ‘ONEBridge’ compression device (CIVCO Medical Instruments Co., Inc., Kalona, Iowa, U.S.A). This device provides external pressure on the abdominal region to limit diaphragmatic excursion and, by extension, hepatic motion. This comparative design, compressed versus non-compressed, facilitated a direct assessment of the compression arch’s effectiveness in controlling liver motion.

3.3.5 Clinical image acquisition protocol

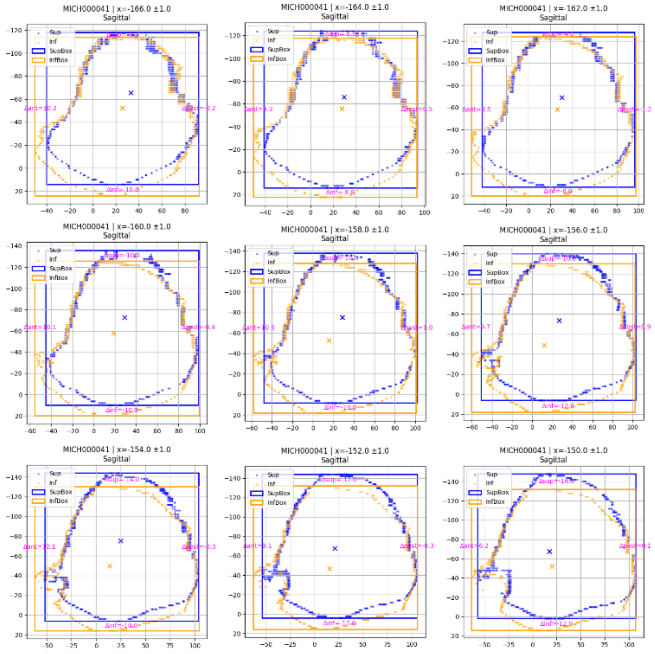
All patients underwent a 3D exhale breath-hold scan and a 4DCT simulation, in which a reconstructed CT is acquired along with a 4D bellows breathing trace and binned into ten distinct respiratory amplitude phases or bins spanning from full inspiration to full expiration. Slice thickness was 2 mm. A cine loop of the 4DCT reconstruction provided a temporal representation of respiratory-induced organ motion which the medical physicists used to determine the maximum tidal exhale (superior liver position) and the maximum tidal inhale (inferior liver position) phases for delineation to aid image co-registration and enable contouring and treatment planning. This includes the delineated tumour and

organs-at-risk volumes, including the liver. All liver structures were the clinically approved contours used for treatment planning. Experienced clinical oncologists delineated the inferior and superior liver positions acquired during tidal respiration established from the 4DCT.

3.3.6 Liver position mapping and validation

Within each RTSTRUCT dataset, the canonical organ labels ‘Liver_Superior’ and ‘Liver_Inferior’ represented the extremes of tidal liver motion. The author-developed python code to create a dictionary that mapped any synonyms found within the RTSTRUCT datasets of inferior and superior liver contours where names of the structures differed to normalise so comparisons could be made. For example, ‘liver_sup’ or ‘liver_maxex’ were mapped to ‘Liver_Superior’. 2D sagittal and axial plots of all liver contours, shown in Figure 11, were generated and manually cross-checked to ensure the aliasing and original labelling were accurate. These 2D sagittal and axial plots were used solely as a visual quality-assurance step to verify contour identity and inhale/exhale labelling before subsequent 3D centroid and surface-distance analysis.

Figure 11 An example vignette of sagittal plots used to verify the contour labelling.
Sequential contours delineated on 2 mm slices along the x dimension are shown with the superior (SupBox) and inferior (InfBox) bounding boxes and centroid positions (x). These were manually checked to ensure the liver contours were correctly assigned to the inhale (inferior) and exhale (superior) positions for subsequent 3D analysis.

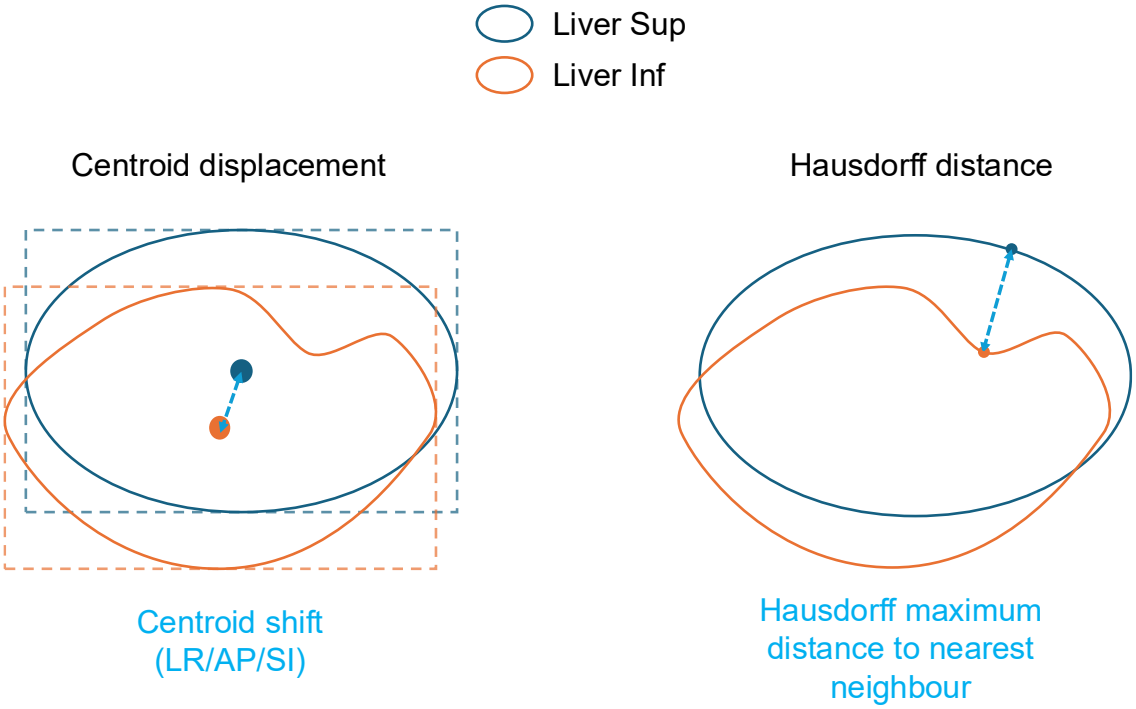


3.3.7 Motion metric extraction

For each patient, superior and inferior liver contours (Liver Sup and Liver Inf, respectively) were extracted using author-developed Python 3.10.11 scripts with pydicom 2.4.4 [293]. This enabled analysis of respiratory motion. Three-dimensional bounding boxes and centroids for both contours were calculated. The range of motion (measured in mm) in the LR, AP, and SI axes was determined by calculating the absolute differences in centroid coordinates between Liver Sup and Liver Inf. To include a measure of liver shape changes as well as the translational direction provided by the centroids, the symmetric Hausdorff distance (also measured in mm) between the 3D surfaces of the Liver Sup and Liver Inf were also calculated. This captured the maximum pointwise motion, representative of worst-case movement of any part of the liver, that might for example correspond to a peripheral tumour at the dome. The Hausdorff distance was calculated using the directed Hausdorff function called from the scipy.spatial.distance library of scipy, version 1.15.3 [294]. Figure 12 shows a schematic of how both the centroid displacement and Hausdorff distance between a superior (blue) and inferior (orange) liver contour were established.

Figure 12 Illustration of the two motion metric methods used in the study. The Liver Sup and Liver Inf contours differ in both position and shape because the liver deforms during respiration. Each contour was delineated on clinically selected inhale and exhale phases of the 4DCT. The two motion metrics, centroid displacement and Hausdorff distance, were selected to capture both translational displacement and shape-related surface change.

Left: The Liver Sup and Liver Inf contours are shown with their bounding boxes (dashed). Liver position deemed to be at its most superior (Liver Sup) and inferior (Liver Inf) position during respiration and contoured in the clinic. The solid dots represent the centroids of each surface. The dashed arrow represents the 3D centroid shift, which is reported separately for the LR, AP and SI axes.
Right: For each pair of contours, the dashed arrow represents the Hausdorff distance (the maximum distance from a point in one contour to the closest in the other contour).



3.3.8 Body habitus covariate extraction

Sex was obtained as recorded in the patient's medical record using a de-identified SQL query of the MOSAIQ database, whilst the regional external anterior-posterior and lateral diameters (mm) and body area (mm^2) was calculated from the patient's external body structure already segmented/contoured for radiotherapy planning purposes in the RTSTRUCT sets using author-developed python scripts with pydicom. A metric representing volumetric adipose tissue across all CT slices within the segmented body contour (both sub-cutaneous and visceral fat) was calculated by summing

segmented voxels from the reference CT scan within a widely supported range used to segment adipose tissue on abdominal CT images using a Hounsfield unit (HU) interval window of -190 to -30 HU [295-297]. Since the scan length varied between patients, the volume of adipose tissue could not be directly compared across patients. A regional 'body fat fraction' volume was calculated by calculating the ratio of the segmented fat by the pre-existing segmented external body structure. These covariate data were merged with the motion metrics into a final spreadsheet for analysis.

3.3.9 Statistical analysis

Analyses were performed in IBM SPSS Statistics, version 29.0.2.0 (Build 20). Motion metrics prepared in python as described in 3.3.7 and 3.3.8 were imported. Sex was coded as 0 = Male, 1 = Female. Compression status was coded as 0 = Uncompressed, 1 = Compressed.

A combination of descriptive statistics and Mann Whitney U tests of motion metrics were used to answer the first objective and describe the local ranges of liver motion with and without compression. Binary logistic regression of compression use, and a generalised linear model of motion metrics were performed to examine whether body habitus metrics, including sex moderate the use and effect of abdominal compression.

3.3.10 Descriptive statistics and assumption tests

For each continuous motion variable (LR, AP, SI and Hausdorff distance), the mean ± standard deviation (SD), median, interquartile range (IQR) and range were reported. To determine if parametric or non-parametric tests were required normality was assessed with the frequency histograms and Shapiro-Wilk tests. Homogeneity of variance between the compression groups was checked with Levene's test.

3.3.11 Group comparison on sex and body habitus covariates

Mann-Whitney U tests were conducted to confirm if the groups differed and if any magnitude and direction of the unadjusted effect could be observed without covariate adjustment. Compressed vs uncompressed groups were also compared using Welch's unequal variance t-tests for the continuous co-variates. Welch's test was selected since Levene's test was significant for size

metrics. Effect size was reported as Cohen's d with 95 % confidence intervals (CI). Sex distribution was tested with χ^2.

3.3.12 Binary logistical regression across body habitus metrics

Compression use was modelled with binary logistic regression to explore the differences in proportions seen between compression selection across the sexes and so any potential selection bias could be contextualised.

3.3.13 Multivariate generalised linear model analyses

Whilst the univariate Mann-Whitney U tests described the raw compression effect without adjusting for covariates, a generalised linear model was necessary to quantify whether the compression effect persisted after accounting for sex and body-habitus differences. A gamma-distributed generalised linear model with a log-link was fitted separately for each motion metric since this could account for the right-skewed motion variables and provide adjusted and clinically interpretable estimates of effect for the multiple predictors. Gamma models are known to be appropriate for non-normal, continuous data and when combined with a log-link, can model multiplicative (proportional increase or decrease) effects. These effects were reported as ratios of means (Exp B) so they were more easily interpretable [298]. Predictors entered were compression status, sex, anterior-posterior body diameter (centred and re-scaled per 10 mm) and regional body fat fraction (centred and re-scaled per 10%). Multicollinearity was checked and all variance inflation factors were found to be moderate (≤2.4). A compression x sex interaction was tested but proved non-significant (p >0.24) and was subsequently removed.

3.4 Results

3.4.1 Patient characteristics

From the potential list of 201 patients in the initial SQL query, the final dataset comprised of 134 patients who met the inclusion criteria.

The compression status of the included patients was unequal. One hundred and four patients (78%) received abdominal compression, with 30 (22%) patients being uncompressed. Table 10 shows how the body-habitus characteristics by compression status and sex were distributed. Hepatobiliary cancers are more

prevalent in males and Table 10 reflects this with the larger proportion of males (77%) in this cohort. Sex distribution did not differ between compression groups (Pearson $\chi^2 = 2.26$, degrees of freedom (df) = 1, p = 0.13; $\varphi = 0.13$).

As shown in 0 Table 28, compared with females, males had significantly larger AP body dimensions (Cohen's $d = -1.22$ (–1.64 to –0.79 CI), $p = < 0.001$)), lateral body dimensions (LAT 95 ($d = -0.55$, $p = 0.027$)) and maximum body cross-sectional area (Max area ($d = -0.52$, $p = 0.039$)). Regional body-fat fraction (fat fraction) did not differ significantly ($d = 0.09$, $p = 0.70$).

Table 26 and Table 27 in Appendix C and Appendix D show the results of normality and variance testing on the body habitus and motion metrics, along with outcomes guiding the subsequent statistical approach in the final column. Normality assumptions were violated for at least one compression group across all motion displacement metrics (Shapiro-Wilk $p < 0.05$), and variances were unequal for SI displacement (Levene $p = 0.023$). This necessitated the need for non-parametric testing, because parametric tests become sensitive to normality violations with unbalanced data [298]. Consequently, group differences were assessed with the Mann-Whitney U test. As shown in Table 11 and Table 12, regional body fat fraction and maximum cross-sectional area were significantly higher in uncompressed patients, with small but significant effect sizes (r = 0.28, $p = 0.001$; r = 0.23, $p = 0.007$, respectively), although the wide variability in the maximum area indicated heterogeneity across patients, limiting precision of the effect size. There were also borderline differences in lateral body diameter (Cohen's d = 0.52, $p = 0.051$) and anterior-posterior diameter ($p = 0.055$) between the groups.

Table 10 Body-habitus characteristics by compression status and sex.
N= 134. Values include the median (50%) for the 95th-percentile anterior-posterior diameter (AP 95, cm), 95th-percentile lateral diameter (LAT 95, cm), maximum cross-sectional body area (Maximum area, cm²) and whole-body fat fraction. The last column gives the number of participants and row % within each compression group.

Compression	Sex[1]	AP (cm) Median	LAT (cm) Median	Maximum area (cm²) Median	Body-fat fraction Median	n (%)
Uncompressed	Female	23.9	32.7	651	0.48	10 (7.5%)
	Male	31.0	41.3	1000	0.53	20 (14.9%)
Compressed	Female	24.7	35.7	672	0.45	21 (15.7%)
	Male	28.9	37.6	858	0.45	83 (61.9%)

[1]Pearson $\chi^2 = 2.26$, $p = 0.13$ (no significant difference in female:male ratio between the compression groups).

Table 11 Comparison of the LAT 95% diameter between uncompressed and compressed patients using Welch's unequal-variance t-test and the effect size.
Mean ± SD values are shown for each group, followed by Welch's t statistic with adjusted degrees of freedom in brackets, two-tailed *p* value, and Cohen's *d* with 95% confidence intervals in brackets. Positive t and d indicate larger values in the uncompressed group. Only lateral body diameter showed a borderline difference at the 5% significance level; other size metrics are similar between the two cohorts.

Body habitus metric	Mean ± SD uncompressed (cm)	Mean ± SD compressed (cm)	Welch's *t* (df)	*p* (two tailed)	Cohen's *d* (95% CI)
LAT (cm)	39.9 ± 6.1	37.5 ± 4.0	2.02 (36.7)	0.051	0.52 (0.11 – 0.93)

Table 12 Comparison of the AP 95%, maximum area and body fat fraction between uncompressed and compressed patients using the Mann-Whitney U test.
The Hodges-Lehmann median differences and effect size have also been calculated.

Body habitus metric	Mean ± SD	Hodges-Lehmann median difference (95% CI)	Mann-Whitney U	Z	*p* (two tailed)	Effect size (r = |Z|/√134)
AP (cm)	28.4cm ± 3.4cm	1.77cm (-0.04 cm – 3.30 cm)	1200	-1.922	0.055	-0.17
Maximum area (cm^2)	906cm ± 284cm	148.0cm^2 (52.0 cm^2 – 261.3 cm^2)	1055	-2.695	0.007*	-0.23
Body-fat fraction	0.46 ± 0.09	0.06 (0.03 - 0.09)	960	-3.203	0.001*	-0.28

These results indicate that uncompressed patients tended to have larger body habitus and higher adiposity, which may have influenced the reason for not receiving abdominal compression in those patients within the uncompressed group. In practice, the compression arch did not accommodate some larger anterior-posterior body sizes, and at certain settings it was known that the combined arch and patient could not pass through the MRI bore. The observed association with body fat fraction may therefore reflect these equipment limits. A review of the uncompressed cohort, (Table 13), did indeed demonstrate that omission was most commonly due to body habitus and device fit constraints (46.7%) followed by anatomical contraindications such as a stoma, aneurysm or hernia (30%).

Table 13 Documented reasons for omission of abdominal compression in the uncompressed cohort (n = 30). Reasons were obtained retrospectively from routine clinical information.

Documented reason for omission of abdominal compression	Count	Proportion (%)
Body habitus device constraints	**14**	**46.7%**
Large body habitus	11	36.7%
Small body habitus	3	10.0%
Anatomical contraindications	**9**	**30.0%**
Stoma	6	20.0%
Aneurysm	2	6.7%
Hernia	1	3.3%
Unable to tolerate compression	**1**	**3.3%**
Technique limitation	**4**	**13.3%**
Breathing trace poor	2	6.7%
Arm down	1	3.3%
Breath hold restricted by compression	1	3.3%
Not recorded	**2**	**6.7%**

3.4.2 Primary motion metric differences

Figure 4 compares the distribution of LR, AP, and SI centroid motion and the Hausdorff motion for compressed vs uncompressed patients. It illustrates that SI centroid motion is generally lower with compression, but as with LR, AP and Hausdorff distance, the plots of the raw motion data showed overlapping distributions. Compression produced statistically significant reductions in AP centroid motion (Hodges-Lehmann (HL) median difference = 1.45mm, 95% CI 0.05–2.96) and SI centroid motion (HL = 4.37mm, 95% CI 1.84–6.78). The interquartile range of SI motion was also smaller (6.1mm vs 8.3mm), which suggests there were fewer large motion cases in the compressed group. A large proportion of compressed patients had SI excursion >5 mm (Figure 13). LR centroid motion and Hausdorff distance showed CIs that crossed the 0 mm line, indicating no clear median difference between the two groups (see Table 14, Figure 13 and Figure 14).

Sex stratification similarly showed compression reduced SI centroid motion in both males and females, although females exhibited overall smaller Hausdorff distances with the medians being approximately 19 mm vs 22 mm, ($p < 0.01$) (see Table 15 and Figure 15).

Since body habitus metrics were not normally distributed, correlations between the body habitus metrics were checked for using Spearmans r. Body-size metrics were highly correlated with a Spearman's ρ up to 0.82 (Appendix E, Table 29). Of the body size metrics, only AP was retained as the representative of body size in the multivariable models because it was significantly correlated with the other metrics. This would be practically easy to measure and implement in clinical practice. Fat-fraction showed modest correlation with size ($\rho \approx 0.60$) and weak correlation with motion ($\rho \leq 0.19$).

3.4.3 Multivariable analysis of motion metrics

The independent contribution of each predictor was estimated using a gamma log-link generalised linear regression model. The results are shown in Table 16.

The regression coefficient, B, was expressed on the natural-log scale. The exponent ($\text{Exp B} = e^{B}$) gives the ratio of geometric means between comparison groups (for categorical predictors) or per-unit increase (for the continuous

predictors). Values of Exp B > 1 therefore indicated a proportional increase in motion, whereas Exp(B) < 1 indicated a decrease. Figure 16 shows the adjusted effects of compression as a forest plot of Exp(B) with confidence intervals on each motion metric.

All models showed a satisfactory fit (Pearson χ^2 / df ≈ 1 and deviance / df ≈ 1), and no evidence of multicolinearity was present (maximum VIF ≤ 2.4, see 0 Table 30).The AP diameter was rescaled to a per 10 mm increase and regional fat-fraction was similarly rescaled to a per 0.10 unit (10%) to provide effect sizes that were more interpretable as the original unit size of the variables was so small. An interaction between compression and sex was initially tested and was not significant for all outcomes (Wald's $p > 0.24$). It was therefore excluded from the final model.

After adjusting for sex, anterior-posterior body diameter and regional fat-fraction, abdominal compression remained a strong independent determinant of motion. SI centroid motion was confirmed by the model to be 58% higher when uncompressed (Exp B = 1.58; 95% CI 1.15–2.17; $p = 0.005$). Consistent with the univariate analysis where the median was 19.1 mm vs 22.8 mm, sex was a significant predictor of overall Hausdorff distance derived motion, being 14% lower in females compared to males (Exp B = 0.86; 95% CI 0.75–0.98; $p = 0.022$) and showed an approaching but non-significant increase of 12% without compression ($p = 0.064$). However, sex was not significantly associated with the SI, AP or LR centroid motions in the adjusted model. The compression effect on AP centroid motion, which was marginally significant in the univariate analysis, did not remain significant after adjustment (Exp B = 1.27, $p = 0.11$). This might suggest that the small difference in AP motion might have been influenced by other factors or random variation. Compression had no significant effect on LR centroid motion either in the model (Exp B = 0.81, $p = 0.29$). AP diameter and fat fraction showed no significant association with any motion metric, with p levels of 0.49 and 0.32, respectively, and confidence intervals both crossing 1.0.

3.4.4 Logistical regression – compression usage by sex and body habitus

0 Table 31 shows the results of the binary logistic regression exploring factors associated with being treated with compression. Male patients had higher odds of receiving compression than females (OR = 3.03), but this did not reach significance (p = 0.062, CI = 0.95–9.67). Similarly, although for every 10 mm increase in AP diameter, the odds of compression appeared to decrease by 9.9%, these results were not statistically significant (p = 0.278, CI = 0.97 – 1.01). Also not significant was the ratio metric of fat (OR = 0.005, p = 0.15, CI = 0.00 – 6.69). This suggests a tendency to avoid compression in larger AP-sized patients and potentially those who were female, but since the sample of uncompressed patients was limited, this cannot be concluded.

Figure 13 Liver motion by compression status.
Boxplots show inter-quartile range (IQR), median (line), whiskers to 1.5 × IQR, and outliers (n=134).

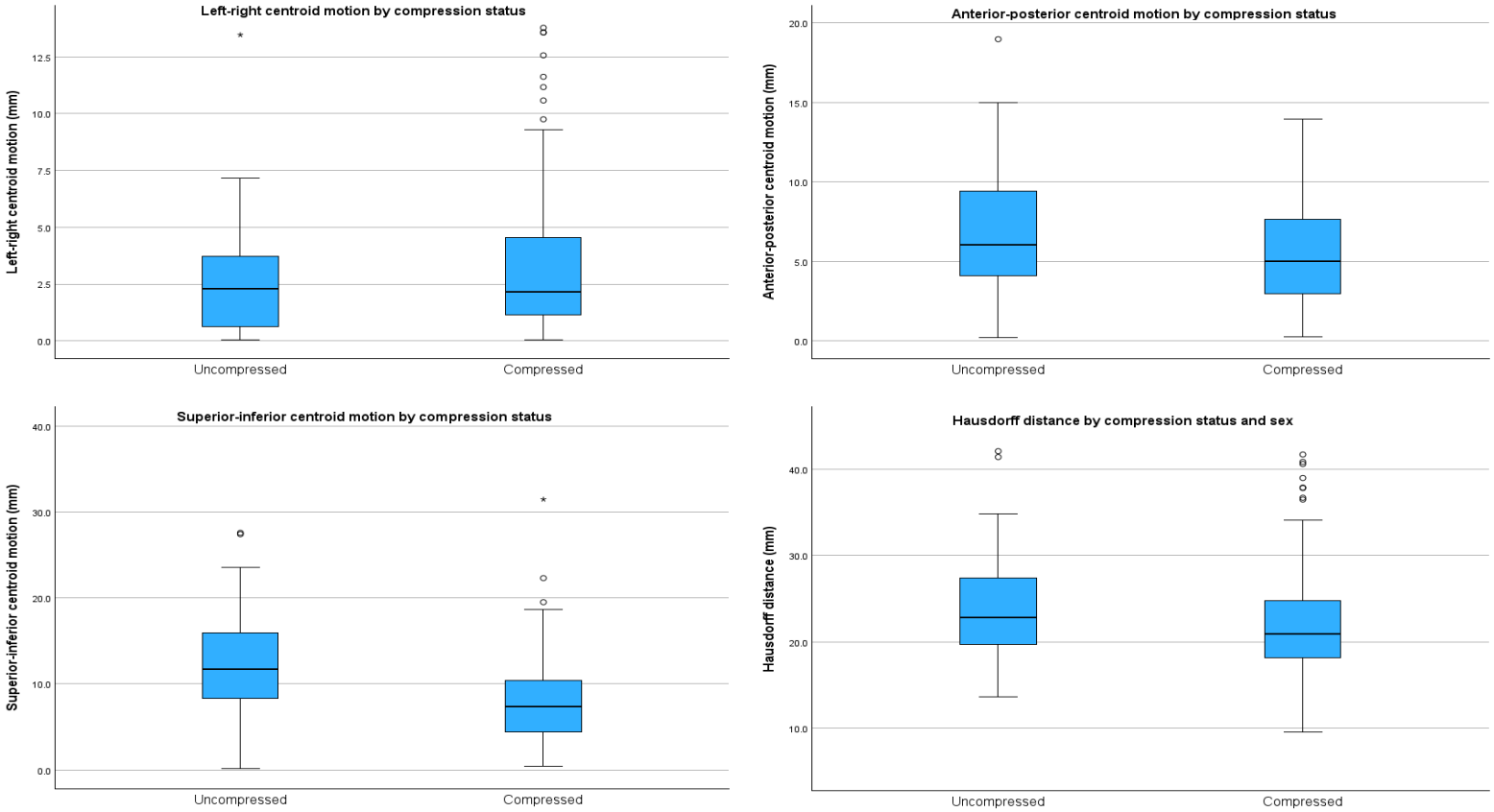


Table 14 Descriptive and univariate statistics of the motion metrics by compression.
The counts (n), mean, standard deviation (SD), standard error (SE) mean, lower (25%) quartile, median (50%), upper quartile (75%) and interquartile range (IQR) by compression status. Nonparametric tests including the Hodges-Lehmann median differences excluding outliers beyond 95%, and the Mann-Whitney U (MWU), across the motion metrics LR, AP and SI motion, and Hausdorff distance (mm)).

Motion by compression status		N	Mean (mm)	SD (mm)	SE Mean (mm)	25% (mm)	50% (mm)	75% (mm)	IQR (mm)	HL median difference (95% CI, mm)	MW U	*Z*	p	*r = |Z|/√134)*
LR centroid motion (mm)	Uncompressed	30	2.78	2.88	0.53	0.60	2.30	3.92	3.32	-0.410 (-1.17-0.46)	1748	-1.00	0.316	-0.087
	Compressed	104	3.41	3.30	0.32	1.14	2.15	4.60	3.46					
AP centroid motion (mm)	Uncompressed	30	7.19	4.13	0.75	4.08	6.05	9.71	5.63	1.45 (0.05-2.96)	1185	-2.00	0.045 *	-0.17
	Compressed	104	5.48	3.28	0.32	2.95	5.03	7.69	4.74					
SI centroid motion (mm)	Uncompressed	30	12.06	7.36	1.34	8.05	11.68	16.31	8.26	4.37 (1.84-6.78)	971	-3.14	0.002 *	-0.27
	Compressed	104	7.90	5.16	0.51	4.30	7.34	10.38	6.08					
Hausdorff distance (mm)	Uncompressed	30	24.60	7.32	1.34	19.31	22.81	27.74	8.42	2.05 (-0.71-0.48)	1283	-1.48	0.139	-0.13
	Compressed	104	22.49	6.73	0.66	18.17	20.90	24.80	6.63					

Figure 14 Forest plot of the unadjusted effect (Hodges–Lehmann median differences) of abdominal compression on the liver-motion metrics.
The HL median difference (uncompressed - compressed) for each metric: LR centroid motion, AP centroid motion, SI centroid motion, and Hausdorff distance. The dots mark the medians and the horizontal lines represent the 95% confidence intervals. Values to the right of the line at 0 mm indicate a great motion when patients are uncompressed.

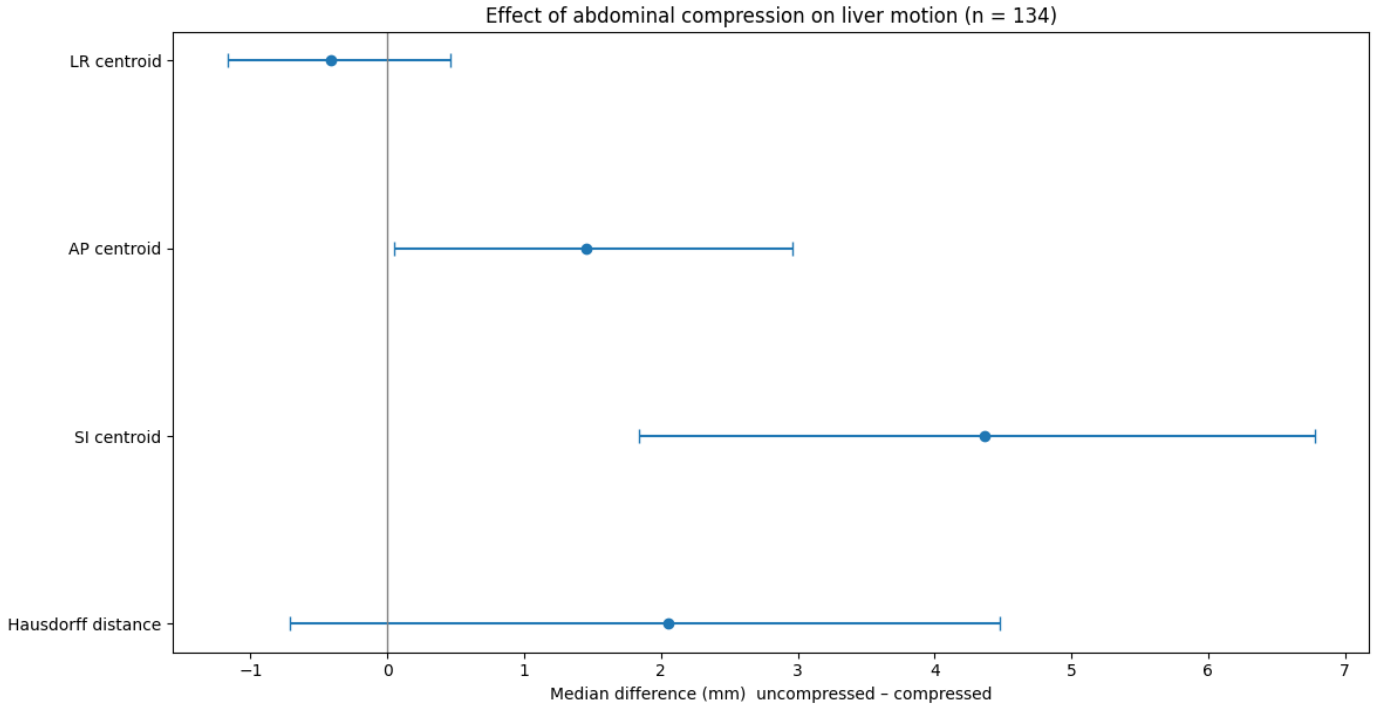


Figure 15 Liver motion by compression status stratified by sex.
Boxplots show inter-quartile range (IQR), median (line), whiskers to 1.5 x IQR and outliers.

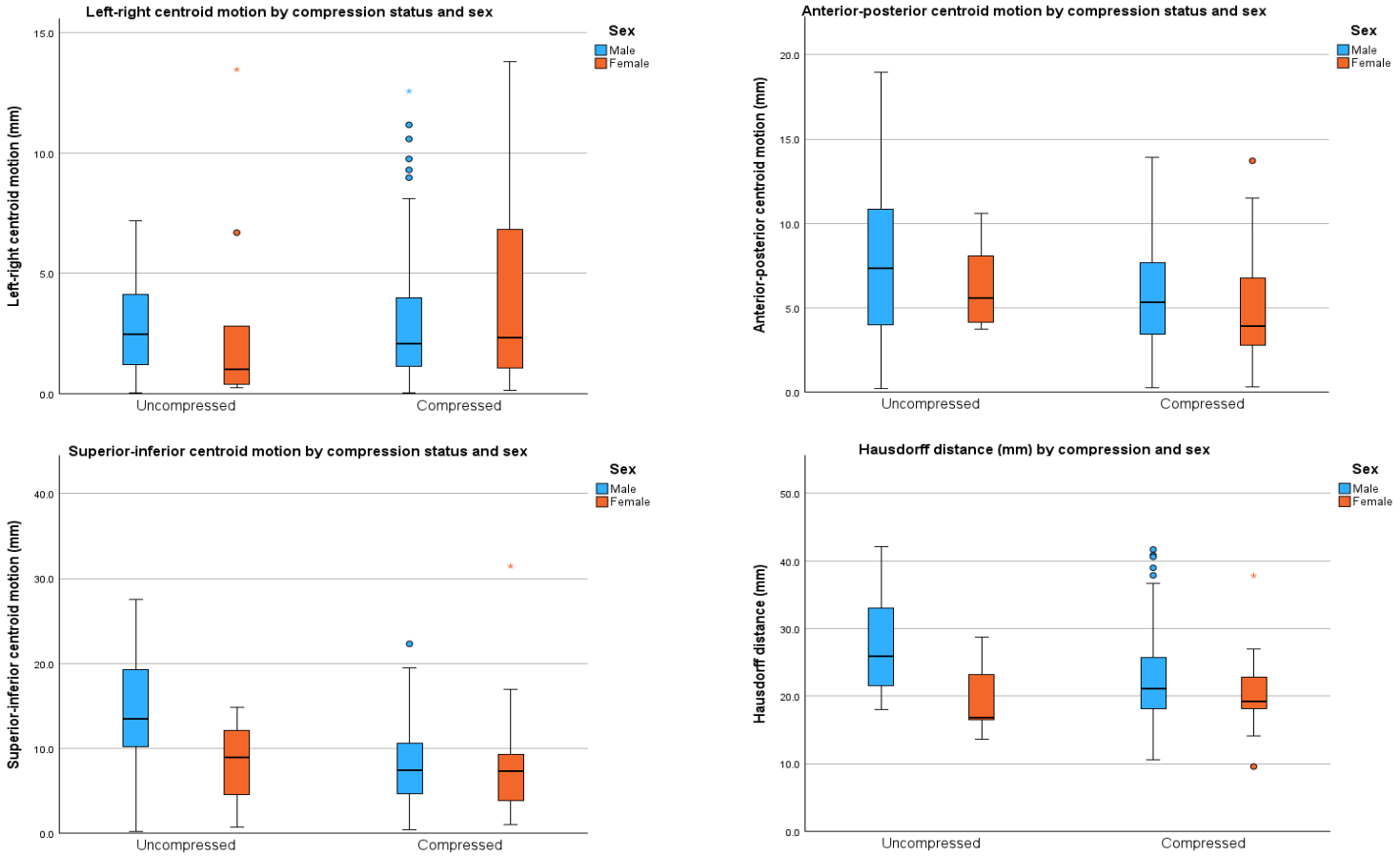


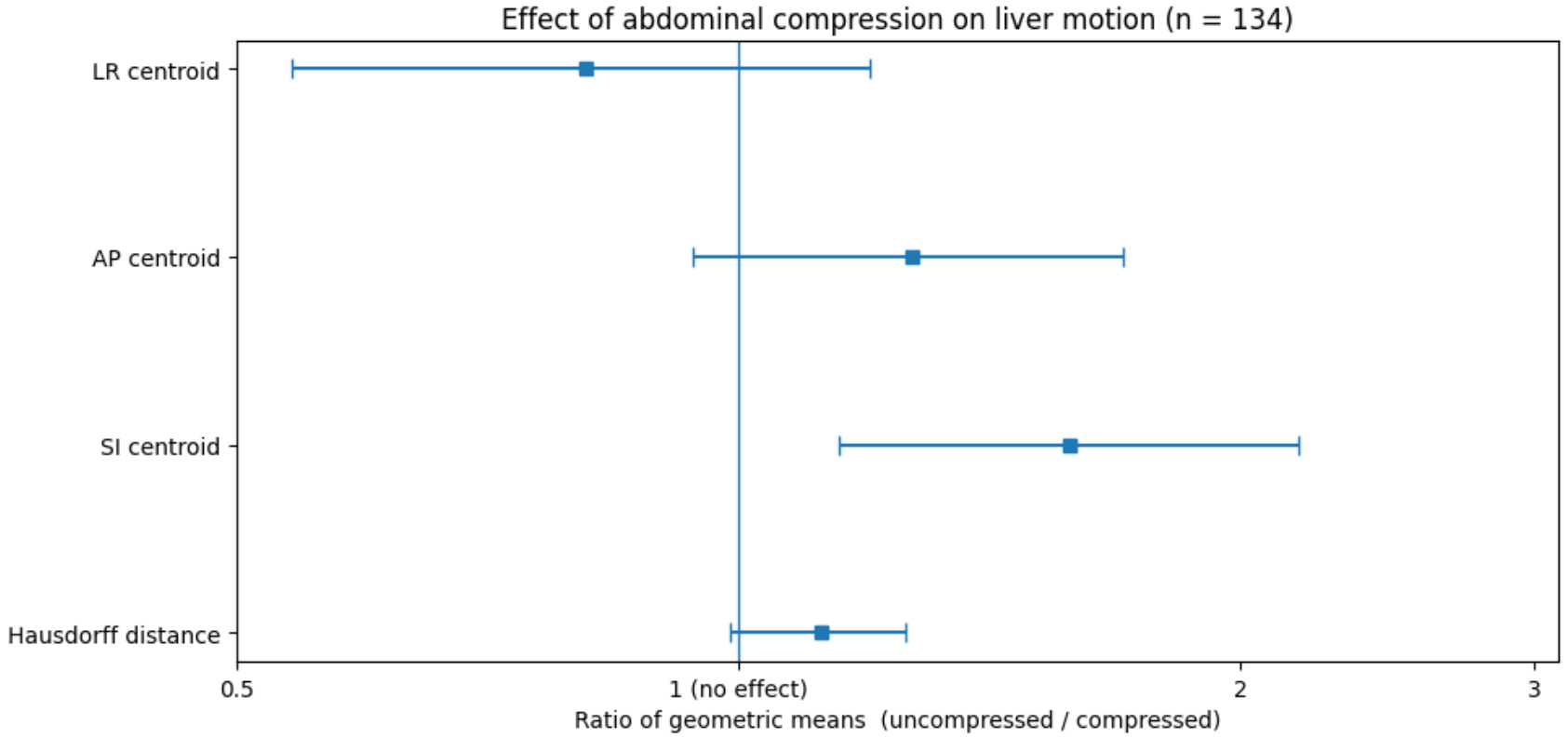
Table 15 Descriptive and univariate statistics of the motion metrics by sex.
The counts (n), mean, standard deviation, standard error mean, lower (25%) quartile, median (50%), upper quartile (75%) and interquartile range (IQR). Nonparametric tests including the Hodges-Lehmann median differences excluding outliers beyond 95%, and the Mann-Whitney U (MWU), across the motion metrics (LR, AP, and SI motion, and Hausdorff distance (mm)).

Motion by sex		N	Mean	SD	SE	25%	50%	75%	IQR	HL median difference (95% CI)	MWU	*Z*	p	*r* = |*Z*|/√*134)*
LR centroid motion (mm)	Female	31	3.99	4.59	0.82	0.64	1.71	6.69	6.05	-0.15 (-0.89 - 0.84)	1541	-0.29	0.77	0.03
	Male	103	3.05	2.66	0.26	1.14	2.22	4.08	2.94					
AP centroid motion (mm)	Female	31	5.21	3.37	0.61	2.94	4.12	8.05	5.11	-0.84 (-2.22 - 0.49)	1374	-1.17	0.24	0.10
	Male	103	6.06	3.59	0.35	3.57	5.56	8.08	4.51					
SI centroid motion (mm)	Female	31	8.22	6.09	1.09	3.84	8.03	10.95	7.11	-0.75 (-2.92 - 1.38)	1472	-0.66	0.51	0.06
	Male	103	9.01	5.93	0.58	5.07	8.01	12.46	7.38					
Hausdorff distance (mm)	Female	31	20.09	5.35	0.96	16.48	19.13	22.81	6.32	-3.1 (-5.35 - -0.99)	1075	-2.75	<0.01*	0.24
	Male	103	23.83	7.09	0.70	18.57	22.37	27.35	8.78					

Table 16 Adjusted gamma log-link regression results for the four liver-motion metrics.
Gamma-distributed generalised linear models with a log-link were fitted separately for each motion metric. Values shown are the log-scale coefficients (B), their standard errors (SE), Wald p-values, and exponentiated regression coefficient (Exp B) with 95 % confidence intervals. Exp B represents the change in ratio of the geometric-mean motion associated where there is an increase in the predictor.

Motion metric	Predictor	B (log scale)	SE	*p*	Exp B (ratio of means)	95% CI Exp(B)
Left-Right centroid motion (mm)	Compression (0:1)	-0.21	0.20	0.29	0.81	0.54-1.20
	Sex (F vs M)	0.35	0.25	0.17	1.41	0.86-2.32
	AP	0.02	0.04	0.64	1.02	0.94-1.10
	Fat fraction	-0.08	0.13	0.53	0.92	0.72-1.19
Anterior-Posterior centroid motion (mm)	Compression (0:1)	0.24	0.15	0.11	1.27	0.94-1.70
	Sex (F vs M)	-0.18	0.17	0.30	0.84	0.60-1.17
	AP	0.00	0.03	0.96	1.00	0.95-1.05
	Fat fraction	0.08	0.09	0.36	1.08	0.91-1.29
Superior-Inferior centroid motion (mm)	Compression (0:1)	0.46	0.16	<0.01*	1.58	1.15-2.17
	Sex (F vs M)	-0.20	0.18	0.26	0.81	0.57-1.16
	AP	-0.03	0.03	0.33	0.97	0.92-1.03
	Fat fraction	0.05	0.10	0.65	1.05	0.86-1.27
Hausdorff distance (mm)	Compression (0:1)	0.11	0.06	0.06	1.12	0.99-1.26
	Sex (F vs M)	-0.16	0.07	0.02*	0.86	0.75-0.98
	AP	0.01	0.01	0.49	1.01	0.99-1.03
	Fat fraction	-0.04	0.04	0.32	0.96	0.90-1.04

Figure 16 Forest plot of the adjusted effect of abdominal compression on liver motion: ratios of geometric-mean displacement (Exp B).
The squares mark the point estimate of Exp B for compression (uncompressed / compressed states). The horizontal bars represent the 95% CI. The values great than the vertical line at 1 indicate greater motion when uncompressed.



3.5 Discussion

3.5.1 Summary of key findings

This single-centre study analysed liver motion in 134 SABR cases, 104 with a compression arch and 30 without. Compression resulted in lower SI centroid motion, median 4.37 mm (95% CI 1.84 to 6.78, $p = 0.002$), equivalent to 58% higher mean SI motion when patients were uncompressed (Exp B = 1.58, 95% CI 1.15 to 2.17, $p = 0.005$). Effects in the AP and LR axes were not significant after adjustment. Whole-liver analysis showed larger absolute excursion when measured with the Hausdorff distance metric, with a lower value in females (Exp B = 0.86, 95% CI 0.75 to 0.98, $p = 0.022$). In compressed patients, motion was not associated with AP diameter or regional fat fraction. We observed that uncompressed patients tended to have larger body habitus. Physical constraints such as MRI bore clearance, clinical preference, tolerance, contraindications, or workflow factors could have all contributed as confounders. Indeed, retrospective review of the rationale for omitting abdominal compression obtained from the patient records showed that omission was most commonly related to body habitus related device fit constraints and abdominal contraindications.

3.5.2 Contextual interpretation of results

3.5.2.1 Compression motion when compared to other literature

The average centroid SI reduction corroborates earlier plate-based studies reporting clinically meaningful dampening of CC motion, while neutral AP and LR effects reflect several mixed findings across the literature [110,135,139,292]. Compression belt studies have reported variable results [134,136-138]. Compression device design and setup may therefore be important, but heterogeneity in methods and small samples limit direct comparisons [111,112,136]. It has previously been reported that doubling the respiratory motion can correspond to almost an eightfold increase in intrahepatic tumour ITVs [115]. Therefore, reducing SI motion could substantially reduce the necessary ITV margin. Although the data from this study demonstrated that the legacy arch exhibited lower SI liver excursion, its effect was minimal in other directions. Whereas centroids might not represent the areas of the liver that

move most but provide a measure of directionality, Hausdorff distance was used as the surrogate for the highest point of liver deformation. As Figure 13 and Table 14 show, the Hausdorff distances were greater than the centroid motion with medians of 23 mm and 21 mm in uncompressed and compressed patients, respectively. The SI benefit of compression validates the findings of several authors who used abdominal compression arch plates [110,135,139,292]. It contrasts with the compression belt study of Van Gelder et al. (2018), who found a negligible difference between the SI motion and slightly increased AP motion and recommended individual patient assessment as a result [134]. This divergence might not be due to the belt since other studies have demonstrated improved motion reduction with compression belts [136-138]. Heterogeneity across study designs and amongst the different motion metrics utilised, as well as the relatively small numbers of participants in those studies makes comparisons challenging [134-139].

3.5.2.2 Cohort attributes

Body habitus

Patients with greater AP diameter were more likely to be in the uncompressed group. Physical limitations, such as inability to use the compression arch whilst still achieving CT or MRI bore clearance in some larger AP body sizes, likely contributed to this. There was, however, overlap in body size between compression groups, which indicates that body habitus alone did not determine compression use, and decisions about compression were potentially influenced by other factors. Patient tolerance, contraindications, radiographer judgement and resources could also have been considerations. With compression applied, neither regional fat fraction nor AP diameter predicted residual motion, which may reflect triage of non-compressible patients out of the arch workflow.

Sex

Potential differences in motion across the sexes were observed, but confined to a lower Hausdorff distance in females, possibly reflecting anatomical or biomechanical differences. Males and females have been shown to exhibit differences in breathing patterns, with males breathing tending to use greater diaphragmatic motion and females with more thoracic motion at rest in healthy individuals [299-302]. The underlying mechanisms for any difference in motion

across the sexes was not investigated in this study. The relatively small number of uncompressed females further limits precision for subgroup analysis.

3.5.2.3 Clinical implications

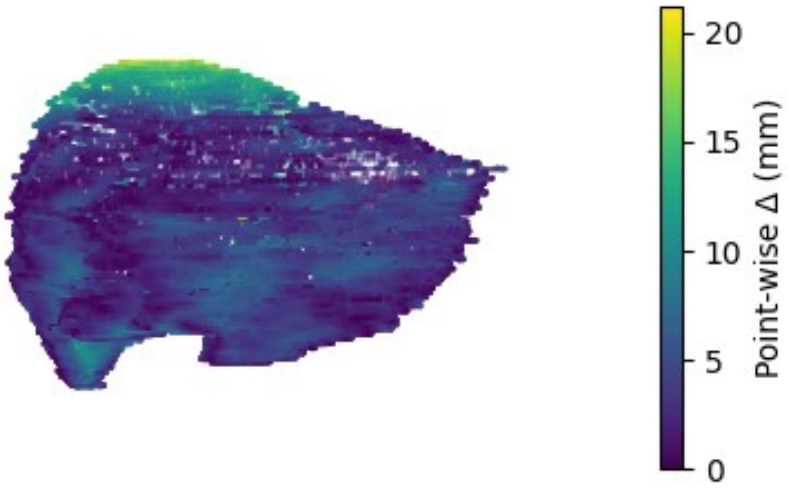
An average centroid SI reduction of approximately 4 mm could translate into smaller ITV margins if reproducible from simulation to treatment. Importantly, lower motion averages in the compressed group might not guarantee individual benefit from compression. Since motion distributions overlapped between groups, not all patients exhibited smaller motion than that of uncompressed patients. This potentially supports a need for personalised motion management strategy with patient-specific compression assessment rather than universal use. Doing so would require additional imaging sequences (assuming MRI is available), time and additional resources. Further research is required to establish if any non-responders to compression could be triaged to alternative breath-hold methods or uncompressed planning.

The data from this study has achieved the aim of providing a baseline for evaluating a new MR-compatible compression belt and for planning subsequent MICROCHIPS R-IDEAL Stage 2 study analyses (see Chapter 6), where paired designs, richer covariates, such as decision rationale, can be included. An alternative belt system, with fewer physical constraints might prove more equitable to patients with a larger body habitus, where the existing compression arch would not fit through the bores of the MRI or CT scanners.

In a patient group with multiple co-morbidities, other factors, not accounted for in this study might also affect motion. Data was notably lacking on fibrosis or cirrhosis, tumour pathology and lesion segment, all of which might possibly modulate the elastic behaviours of the liver motion. On this latter point, a recent study has quantified respiration-induced motion in each Couinaud liver segment using 4DCT in 20 free-breathing patients with various tumours [90]. Although the authors found that all segments moved cranially and slightly posteriorly on exhalation, different segments moved by varying amounts, with the largest motion observed in segment VII (the posterior-superior part of the right lobe near the dome) of a mean of 8.6 mm in the SI direction in free breathing (FB). Central segments moved least, and Tsai et al., (2018) described the liver's motion pattern as being like a 'flying seagull', noting that the lateral superior segments under the domes of the diaphragm are less physically constrained by

ligaments than those located more medially [90]. Only two of the 20 patients in their study had tumours of the liver. Nonetheless, such data suggest motion is heterogeneous across the liver. Tsai et al. (2018) suggested segment-specific ITVs might be possible [90], but none of the studies evaluating abdominal compression have stratified results by the Couinaud segments nor given their sample sizes. Future studies (including the MICROCHIPS study) could incorporate segment-specific motion analysis to ultimately refine ITV margins. Such data on potential confounders or moderators might be retrievable in the existing dataset by reviewing the individual patient electronic records and mapping the target volumes with the liver using co-registered images and using manual or automated delineation of the liver segments. To explore this further, Figure 17 shows a single patient's 3D plot where the motion of the liver has been coloured by its nearest point distance from the superior instance to the inferior instance of its radiotherapy Structure set. If all images were co-registered and a segment structure applied with which tumour locations and their motion could be compared, the motion of liver with and without compression could be evaluated further.

Figure 17 Exemplar 3D plot of the liver for a single patient in its most superior state coloured by the nearest point distance to the inferior surface.



3.5.3 Strengths and limitations

This study is the largest analysis of motion comparing compressed and uncompressed patients receiving liver SABR. It was achieved using manual but routinely acquired end-of-respiratory phase liver contours in which the whole liver surface was analysed, not just excursion metrics or arbitrary regions of interest as has been used in prior studies. The use of clinically validated segmented livers minimised segmentation misalignment and all contours were verified to ensure the data was labelled accurately. However, relying on the respiratory phases during a single, short period of time at the 4DCT to characterise liver tumour motion has known limitations. Breathing patterns might vary and the positions might not encompass the full range of tumour motion [90,303]. It also fails to account for respiratory hysteresis – the discrepancy between tumour paths during inhalation and exhalation, so intermediate trajectory deviations are not captured [131,304].

It is believed that this is the first time Hausdorff distance has been applied in the context of determining worst case motion in the context of liver SABR. Hausdorff distance is a well-documented metric typically used in contour comparison studies, and is possible to measure in a python pipeline, enabling repeated measurements as part of future analysis for direct comparison. A phantom validation of Hausdorff distance as a worst-case motion indicator would strengthen the rationale for the metric's use in this context. The retrospective, unpaired nature of the design also precluded within-participant efficacy estimates, and responder identification. The imbalance between compressed and uncompressed patient groups may also have introduced bias. A body fat fraction metric aimed to reduce bias from differing scan lengths, but it was only a loco-regional fat measure rather than a whole-body composition metric and was non-normally distributed. Although non-parametric comparisons for the skewed raw data and fit of adjusted gamma log-link regression models were explored for potential confounders based on the findings of prior studies (sex, AP diameter and fat fraction), residual confounding is possible. For example, data regarding fibrosis, ascites, or pulmonary comorbidities were not available for association testing. One study indicated that covariates of age, transarterial chemoembolisation history, liver resection history, tumour area, tumour number and number size were not significantly associated with the effectiveness of abdominal compression. Therefore, they were not retrieved for

analysis. It was also in a different ethnic population compared to this study [135]. Future studies could attempt to reduce bias further through prospective paired designs of motion on MRI, or through propensity score-based covariate adjustment with a larger cohort [305].

The variance in motion described by previous authors might suggest findings are not generalisable to other forms of compression. No intra-fraction repeat scans were available, meaning temporal reproducibility was not tested. Hu et al. (2016) found that more superior positioning of the compression plate was more effective. In this study there was no attempt made to assess the effect of the position in which compression was applied [115]. Radiographers in the host institution positioned the plate inferior to the xiphisternum and adjusted position and pressure to achieve a tolerable fit that would still clear the CT and MRI bores. However, plate position, contact point, and applied settings were not recorded in structured fields, nor were they extracted from images in this study. As a result, it has not been possible to quantify the effect of plate placement or evaluate whether deviations from a superior position attenuated the benefit of compression. Future work could extract compression plate position from planning images and test its association with motion metrics. Prospective studies should also include compression settings, number of fit attempts, and MRI/CT bore clearance outcome if it impacted on the decision to use compression.

Finally, when used, compression was applied to a level that patients could ‘comfortably tolerate’. Only one patient in this study had compression omitted due to being unable to tolerate it, but a routinely acquired measure of compression level and comfort was unavailable. One study has examined the impact of the level of compression applied in six liver SABR patients [292]. Acknowledging the small sample size of the uncompressed group in this study, the raw data and logistic regression showed a higher proportion of females (not significant), were uncompressed. Further data pertaining to the reasons why abdominal compression is not used should thus be sought so it may be factored into the model. Since no data on comfort is routinely recorded, aside from the potential of random variation, tolerance or clinical bias could also have been potential reasons behind why the proportion of uncompressed females trended higher than males. Attempts to explore this further should be made.

3.5.4 Future directions

Further prospective work is currently underway to determine how a new compression belt compares using the method developed here. The routine nature of clinically available contours in RTSTRUCT data sets could help with the comparison of institutional practices and the effectiveness and impact of abdominal compression devices. ProKnow, recently procured by NHS England, could support such a comparison [306].

Based on published data, tumours exhibit different ranges of motion dependent on their location within the liver [90]. Further study is recommended to produce a segmented motion atlas using deformable registration of inhale and exhale pairs, onto a common template to characterise variability by segments that links tumour location and dose to motion. This could be explored in future work to determine the clinical significance of the motion differences observed. Such data could be potentially linked to tumour control and toxicity data. Additional unanswered questions such as how intra- and inter-faction motion compares across compression states as well as with inhale and exhale breath hold in the same individuals to provide paired data using MRI is also underway as part of the MICROCHIPS study. A prospective study of 15 patients has been designed to derive a true responder/non-responder rate and validate segmented-specific ITV margins. This study made no attempt to assess the relationship with treatment volumes or dose, also a missing factor from other published work. General health conditions can impact treatment experience and an older patient with poor mobility or cognitive impairment may find it hard to attend daily sessions or follow complex breath-hold instructions [307]. Thus, it is plausible that tailored, patient-specific comfort measures combined with effective communication and patient support might enhance both adherence and overall treatment experiences. Practical barriers, such as difficulty lying still for extended periods or challenges complying with breath-hold instructions as discussed further in Chapter 4, may affect patients' ability to complete treatment protocols [112]. Furthermore, T_1 mapping of the liver [308,309] or the use of MR-elastography [97] could be explored in the future to test the hypothesis that increased liver stiffness might reduce deformation and impact inter-patient variability dependent on the location of disease.

Finally, since MR-linacs now have gating capabilities, real-time cine imaging could be informed by prior surface-distance maps, potentially eliminating compression and enhancing comfort [310]. However, given the scarcity of MR-linac platforms, potentially integrating either a novel 4D MRI or 4D CT approach with kV projection data on a standard linac could benefit more patients [311].

3.6 Conclusion

This study has demonstrated that for liver SABR patients, where the abdominal compression arch was used, SI centroid liver motion was approximately 4 mm smaller compared to uncompressed patients. There was no significant LR or AP centroid motion difference between cohorts. The SI difference was observed broadly across the population, with no strong dependence on body size or sex, although female patients exhibited slightly lower Hausdorff distance derived motion. These results have established an important benchmark for motion management and corroborate the prior findings of others that have suggested that abdominal compression is an effective tool for limiting SI liver tumour motion for many patients. Uncertainties remain however: it is not effective in all patients, and measures to determine its effectiveness could be incorporated into the exiting liver SABR planning pathway to avoid unnecessary compression. Alternatively, patients could be triaged to alternative means of motion mitigation, such as breath-hold. These findings serve as a baseline for comparison in the MICROCHIPS study as well as the clinical implementation of a new more universally MR-compatible compression belt that facilitates it. The methodologies developed, including motion quantification using Hausdorff distances, can be further validated to facilitate ongoing analysis and research in this domain.

The heterogeneity in compression use and effectiveness highlights that motion management is part of a wider complex intervention, where technical efficacy is dependent on physical constraints, tolerability and understanding within a broader care pathway. Chapter 4 therefore explores the lived experience of liver SABR procedures through the patient lens, focusing on how communication, discomfort and coping may shape what is practically achievable.

Chapter 4 Patient experience of liver SABR: a qualitative interview study

4.1 Preface

The work from this chapter was presented as a poster at ESTRO 2025 [312].

4.2 Introduction

Despite increasing knowledge and advances in the technical delivery of SABR and research affirming its clinical effectiveness, the experiential dimension of undergoing this treatment remains underexplored [111,313]. Few qualitative studies explicitly examine liver SABR; published reports or reviews have focused on toxicity or feasibility metrics rather than patients lived experiences [111,112,187,191,288,313-316]. Therefore, this highlights a gap, and a need to explore how patients understand, endure, and navigate SABR's unique planning processes and techniques, including the addition of MRI protocols to more traditional CT planning, abdominal compression immobilisation and breath-hold procedures used [111,313].

This gap provided the rationale for this study. One study included only two liver SABR patients out of 25 interviewees and focused on symptoms and tolerability, not planning scans, immobilisation, or breath-hold procedures [184]. A US study in 2023 interviewed 26 HCC patients receiving various loco-regional therapies, including six who underwent SABR, but it focused on post-treatment symptom monitoring rather than procedural experience [191]. An international interview study of 50 HCC patients documented care journeys and priorities; SABR was not among the reported options. Notably, participants asked for information in more accessible formats, and most decisions were physician-led with high trust in clinicians [182].

Managing internal organ motion is critical in liver SABR because of the large ablative doses. Breath-hold and abdominal compression are used to minimise tumour motion and enable smaller margins [140,286,287]. Although widely reported, these strategies can be physically and cognitively demanding, and breath-hold is implemented in varied ways [100,117,137]. Most reports emphasise compliance/feasibility metrics rather than patients' comfort or experience, and outcomes vary across studies in part because protocols differ.

For example, patients may be asked to hold their position after deep or end-tidal exhalation, end-tidal inhalation, or deep inhalation, each with distinct implications for lung volume, achievable duration, and comfort [117]. In practice, although breath-hold procedures are feasible with training, they can prove challenging for patients, particularly for those with multiple comorbidities. This might suggest that there is no single ‘ideal’ motion-management intervention. Selection could be personalised to patient physiology, comorbidity requirements, and workflow constraints, with scope for coaching and adaptation. In a prospective series of 41 patients receiving liver SABR using surface-guided deep-inspiration breath-hold, all patients completed the technique and rated it ‘tolerable’, with training improving comfort. However, no data were provided for the longer MRI planning process [286]. Similarly, a multi-year series reported approximately 95% breath-hold feasibility using spirometry for inspiration holds [137].

Although deep inhale strategies offer a potential comfort benefit, breath-hold, whether at inhale or exhale, may still be intolerable for patients, particularly those with poor pulmonary function or other co-morbid conditions [91,140]. In contrast to studies reporting 100% feasibility when using inhale breath-hold, one prospective study reported that only 62% of screened patients could consistently meet the strict exhale breath-hold criteria during SABR [91]. Conversely, end-exhale breath-hold imaging is often recommended for liver SABR due to its reproducibility and stability advantages, as well as smaller residual abdominal organ motions during the hold [100,144,150,317]. Exhale breath-holds can limit the hold duration due to lower lung volumes, potentially exacerbating patient fatigue and discomfort [112]. By contrast, breath-holding at deep inspiration has been shown to produce significantly larger lung volumes than breath-holding at end expiration [318]. Patients might struggle to hold their breath at end-exhale much beyond 20 seconds, whereas inhale breath-holds of 20-30 seconds are achievable and sometimes can be extended with further training or supplemental oxygen [111,112,116,150,319-321]. Farrugia et al. (2021) demonstrated that a pre-treatment personalised breath-hold screening approach could significantly improve breath-hold reproducibility and patient comfort. Inhale-based techniques were selected for over half of patients undergoing upper abdominal radiotherapy, pragmatically challenging the assumption that exhale breath-hold is universally superior [116]. Abdominal

compression devices, used alongside or as an alternative to breath-hold, are another common motion management tool in liver SABR. Although they can effectively stabilise the diaphragm, the experience may be uncomfortable [288], and their comfort and tolerability are not well understood. Systematic reviews show that abdominal compression can reduce respiratory motion in many patients, but effectiveness varies and patient factors are not well characterised. Comorbidities are rarely reported and have not been analysed systematically [111,112]. Abdominal compression may be unsuitable in specific clinical situations such as certain vascular or abdominal contraindications, and use is typically individualised to a level of compression a patient can tolerate. However, the included studies in systematic reviews rarely listed comorbidity-based exclusions. This data was not synthesised and so generalisation to multimorbid cohorts remains uncertain [111,112].

Evidence on patient comfort and tolerability of liver SABR is therefore sparse. Hepatobiliary cancer patients often present with underlying co-morbid conditions such as cirrhosis, arthritis, or respiratory impairments. These may negatively impact their ability to adhere to radiotherapy procedures, however, no studies to date have addressed patient co-morbidities or comfort [112,288,307,322]. Practical barriers, such as difficulty lying still for extended periods or challenges complying with complex breath-hold instructions, may affect patients' ability to complete treatment protocols [112]. Additionally, general health conditions can impact treatment experience. An older patient with poor mobility or cognitive impairment may find it hard to attend daily sessions or follow complex breath-hold instructions [307]. Thus, it is plausible that tailored comfort measures, effective communication, and patient support might enhance both adherence and overall treatment experiences.

By listening to patient voices, this chapter seeks to uncover how individuals engage with planning procedures, interpret technical instructions, cope with the demands of abdominal immobilisation, and make sense of their circumstances from diagnosis through treatment completion. The aim was to reveal salient factors that influence patients’ experiences, satisfaction, and tolerance of liver SABR. In doing so, this study intends to offer an honest and in-depth account of how clinical practice and future research could become more patient-centred in this rapidly evolving field.

4.3 Study aim

To explore how patients experience and manage liver SABR planning and treatment procedures, with a focus on breath-hold and immobilisation techniques.

4.4 Study objectives

The objectives are to describe perceived burdens and enablers, identify communication and comfort needs, and highlight practical opportunities for patient-centred optimisation.

4.5 Methods

4.5.1 Study design and theoretical approach

Acknowledging that patient experiences are subjective, context-bound, and shaped by social and interpersonal factors [323-327], this study explored how patients construct meaning around liver SABR procedures. As previously mentioned, patients are exposed to multifaceted phenomena such as immobilisation, breath-hold, MRI and CT techniques in liver SABR. These procedures are not experienced in isolation. Broader evidence across cancer pathways shows that stages of care are experienced within a wider context of living with cancer. The uncertainty of waiting for diagnosis, treatment, results, and resultant prognosis can be emotionally burdensome and can shape how patients interpret and tolerate clinical procedures[182,328-330]. As a result, these procedural experiences may be interpreted through emotions rather than purely procedural tasks. To capture this complexity, semi-structured interviews were combined with reflexive thematic analysis using an adapted framework method [326,331-333]. This approach has been reported to provide straightforward and accessible yet context-rich accounts of patient experiences [326,332,334], allowing the researcher to probe unanticipated emergent themes whilst still being guided by the pre-defined foci of physical, psychological/emotional and information themes [335,336].

A subtle, realist stance was adopted, balancing recognition of an external clinical reality (planning and treatment processes) with the understanding that patient interpretations provide the lens through which that reality is experienced [331]. Accounts were treated as meaningful descriptions of participants'

experiences, acknowledging that they were most likely shaped by context and memories. The analysis therefore aimed to produce a credible and useful interpretive account of how liver SABR is experienced.

4.5.2 Researcher characteristics and reflexivity

The author (MB), a therapeutic radiographer with 17 years' experience of working within radiotherapy services, had no direct role in the participants' care, and conducted all interviews. This clinical background supported a strong understanding of the SABR pathway and facilitated rapport, encouraging open disclosure. It also helped MB interpret nuanced references in patients' accounts while maintaining an empathetic stance. Potential sources of bias included assumptions formed through prior clinical experience and existing working relationships with the clinical team. Familiarity with the workflows aided rapport and interpretation of the technical accounts which were at times challenging for participants to describe but may have predisposed attention towards practical and procedural aspects of the pathway. The author was aware that prior professional assumptions about radiotherapy processes, communication and tolerability might have shaped questioning and interpretation and resulted in interviewer, response and reflexivity biases. To mitigate these, a reflexive stance was maintained to minimise role-related assumptions. Reflexive memoing was undertaken during and after interviews [337-339]. These memos included recording of non-verbal cues, emotions expressed, emerging ideas, contradictory statements and reflections on the interview. A second qualitative expert (JB) periodically reviewed and discussed coding decisions. Any differences were discussed to agreement to enhance credibility.

4.5.3 Context and setting

Participants were recruited at Leeds Teaching Hospitals NHS Trust, a regional centre offering liver SABR, not yet routinely offered at all UK radiotherapy centres. Approximately five liver SABR patients are treated locally per month. Patients often travelled long distances from across Yorkshire and the Humber, introducing additional logistical considerations.

4.5.4 Sampling strategy and rationale of information power

A purposeful sampling approach, within pragmatic recruitment constraints, targeted adult (≥18 years) patients who had completed both MRI and CT

planning scans for liver SABR. Sample size was guided by the principle of information power, where an adequate sample is influenced by the specificity of the study aim, sample specificity, quality of dialogue and the analytic strategy[340]. Given the narrow study aim, focusing on experiences of liver SABR planning and treatment procedures, and a sample specific to individuals who had experienced the relevant imaging and motion management demands, the study was expected to provide high information power [340]. The relative paucity of prior qualitative research in liver SABR also meant participants were likely to contribute experience-based insights of high relevance to the study aim, further supporting this rationale.

Clinical teams introduced the study, and the lead researcher then approached interested individuals. [340-343].

4.5.5 Ethical considerations

Ethical approval was obtained through the West Midlands - Black Country Research Ethics Committee (HRA 23/WM/0070, Appendix B – HRA approval). All participants received a participant information sheet detailing the study purpose, procedures and confidentiality measures. Participants were informed that their participation was voluntary, that they could withdraw at any time, and that non-participation would not affect their clinical care. Participant codes (M101-M110) were used to replace identifiable information in transcripts and analysis to protect confidentiality, and all transcripts were securely stored on NHS systems.

Since interviews involved discussion of patient history, including diagnosis, treatment and potentially emotive experiences, there was a possibility of triggering distress. This risk was explicitly addressed in the participant information sheet, and the interview process was designed to minimise harm. Participants were reminded at the start of the interview that they could pause, skip elements they were uncomfortable with discussing or stop the interview at any time, without providing a reason. A pre-specified support pathway was in place. If a participant had become distressed or requested further support, the team were able to offer the radiotherapy department’s patient support team and the clinical teams, who were made fully aware of the study and potential for referral.

4.5.6 Patient and public involvement and engagement

Patient and public involvement and engagement (PPIE) informed the design of this study. PPIE discussions with patients who had received liver SABR and in follow-up helped prioritise areas likely to matter to patients during liver SABR. These included comfort, context, emotional and physical responses, side effects and information needs. This input influenced the wording and ordering of topic guide questions and initial coding framework, but most crucially helped ensure that interviews address not only the technical procedures but also how patients understood and coped with them. PPIE also informed decisions about the acceptable interview length, how best to explain the purpose of the study, and to offer and provide further support from our patient support team should any of the topics trigger distress.

4.5.7 Data collection methods

Ten semi-structured interviews were conducted (January–November 2024), guided by a pre-designed topic guide. The topic guide drew on prior patient and public involvement input and clinical discussions, where former patients and clinicians highlighted practical tolerability, emotional impact, and information needs as the aspects they felt most likely to shape the experience of liver SABR procedures. These considerations informed an initial set of domains (Table 17), used to construct the interview topic guide. The domains ensured that interviews explored issues relevant to complex workflows, including comfort and experience of breath-hold and immobilisation and communication across the various pathway stages. The topic guide was refined with input from the research team, approved by the PPIE group consulted and approved by the ethics committee.

Questions were open-ended and probing to elicit rich, candid narratives [333]. The topic guide is provided in Appendix F. Participants chose in-person or telephone interviews based on preference and convenience. Previous research shows telephone and face-to-face qualitative interviews yield comparable content and analytic quality, when conducted with good practice (for example, clear consent, rapport-building, and careful probing) [344-346]. All interviews were recorded on an encrypted Dictaphone, lasting between 34 – 90 minutes. Field notes documented contextual details such as interruptions and non-verbal

cues. Interviews were scheduled during or shortly after treatment completion in order to minimise recall bias [347].

Table 17 A priori coding framework developed for the MICROCHIPS study, showing analytic domains and initial categories used to inform the topic guide and analysis.

A priori theme	Categories
Physical	Health context, comfort, pain, physiological reaction, side-effects
Psychological/Emotional	Control, side-effects
Information	Written, verbal, training, feedback

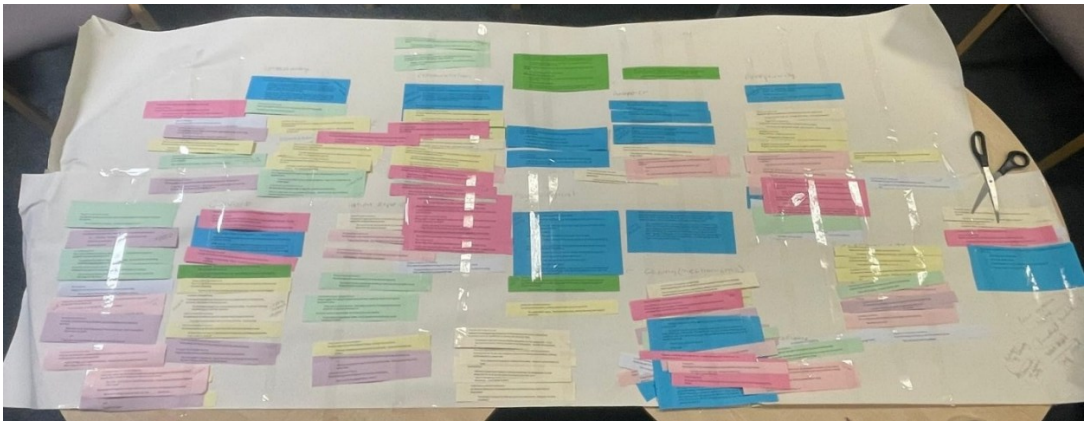
4.5.8 Data processing and analysis

All interviews were transcribed verbatim by the lead researcher and de-identified prior to analysis. Analysis proceeded iteratively. A reflexive thematic approach was used, supported by the framework method as a pragmatic way to organise, chart, and compare the data cross participants and pathway stages[326,327,333,336]. Transcripts were read repeatedly for familiarisation, along with reflexive memos taken during and after the interviews.

Initial line-by-line, then iteratively refined into themes. Coding was managed in NVivo (Version 12, QSR International Pty Ltd (2018)). As analysis progressed, codes were grouped and compared across accounts and were charted using a combination of NVivo concept output and printed excerpts to support comparison across participants. The initial framework was treated as modifiable

and was revised iteratively to reflect the dataset, resulting in high-level themes of communication, discomfort and coping/support.

Figure 18 Paper charting. Colour coded paper representing different participants was used to aid the interpretation and refinement of the thematic account.



Credibility was enhanced by code-checking with a second researcher where any discrepancies were discussed until to challenge assumptions and refine analytic judgements. To aid transparency of the research, data was reported in accordance with the Standards for Reporting Qualitative Research guidelines [348].

4.6 Results

4.6.1 Overview of themes and the patient journey

Ten participants (M101–M110) were interviewed either during or shortly after liver SABR course completion, comprising a range of ages, ethnic backgrounds, and comorbidities (Table 18). Ten additional patients were approached but did not enter the study. Five declined participation (most commonly citing ‘too much going on’) and five were deemed ineligible due to medical events or issues with imaging/planning. Of these ten, six were female and four were male. Co-morbidity data of the participants were collected to provide contextual information on factors that might influence the participant’s experience such as the tolerance of breath-hold, immobilisation, or repeated imaging. No interviews were terminated due to distress and no referrals to the patient support or clinical teams were necessary.

Similar to previous findings in general radiotherapy studies [349,350], participants described the overall SABR experience along a chronological

journey. The journey encompassed the pre-treatment phase (including CT and MRI planning scans), the treatment course itself, and the immediate post-treatment period, when they awaited follow-up. From these narratives, three interrelated themes emerged (Figure 19):

1. **Communication**: The clarity, timing and depth of information.
2. **Discomfort**: Sub-themes included breath hold strain, arm or shoulder discomfort, compression discomfort, and MRI claustrophobia.
3. **Coping and support**: Subthemes included patient strategies, external support, staff reassurance and personalisation.

Although the themes are presented separately, these three themes overlapped considerably. Technical and emotional dimensions of liver SABR were clearly intertwined and difficult to separate. Emotional responses of frustration, fear, uncertainty and trust were revealed at various points when participants were discussing how procedures were understood and tolerated across the pathway. Communication shaped how patients understood or tolerated discomfort, and coping strategies depended on whether they felt they had the information or reassurance needed to endure physically demanding parts of liver SABR.

Figure 19 Patient experience themes during liver SABR and their interactions.
Communication shaped how discomfort was interpreted. Coping drew on family and clinician support, which fed back into experience.

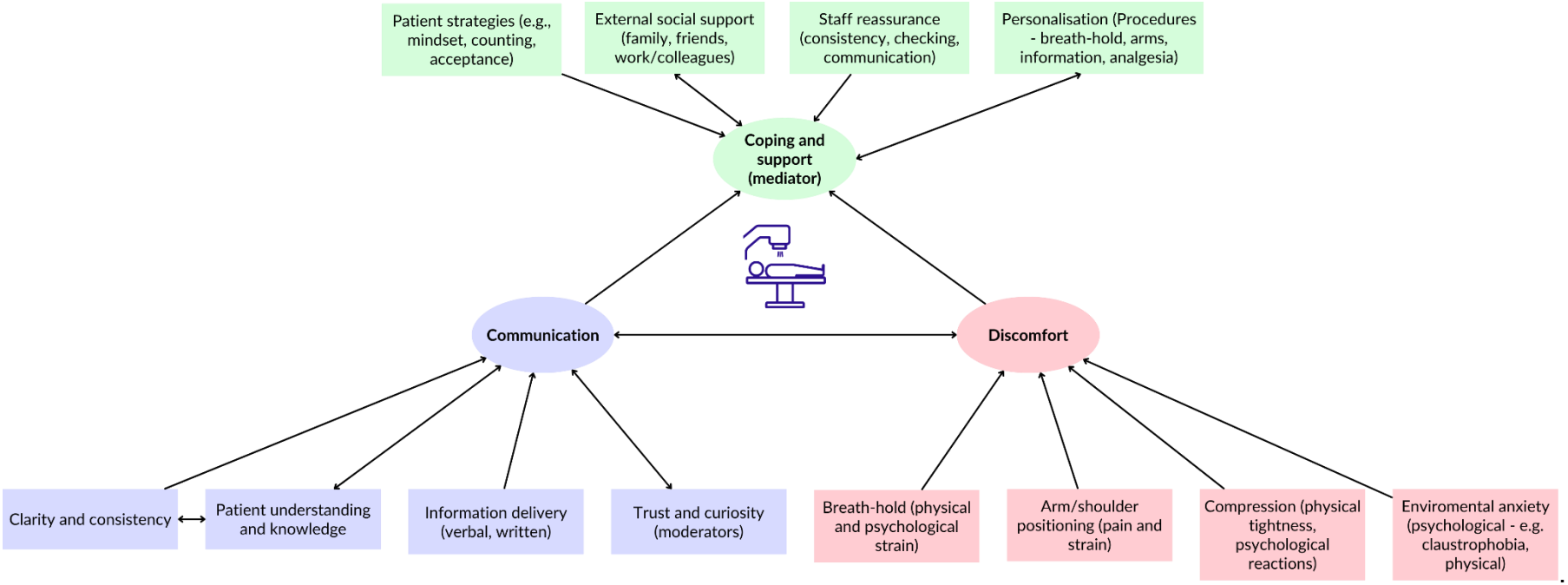


Table 18 Participant case classifications including demographic data, radiotherapy equipment used, if MRI scans required repeating and co-morbidities.

Participant	Gender	Age	Diagnosis	Ethnicity	Immobilisation	MRI breath-hold length	Repeated MRI breath-hold sequences?	Co-morbidities	Interview timing
M101	Male	80-89	Oligometastatic cancer	Asian or Asian British	Vac-bag only	Long	Repeated	Chronic kidney disease, T2 diabetes, hypertension, heart failure	Post fraction 4/5
M102	Male	90-99	Primary HCC	White British	Compression arch + Vac Bag	Long	Not repeated	Not Applicable	Post fraction 5/5
M103	Male	70-79	Primary HCC	White British	Compression arch + Vac Bag	Long	Not repeated	T2 diabetes, hypertension, cirrhosis	Post fraction 3/5
M104	Male	50-59	Primary HCC	White British	Vac-bag only	Other	Repeated	Metabolic dysfunction-associated steatotic liver disease, cirrhosis, hypertension, T2 diabetes	Post fraction 5/5
M105	Male	50-59	Oligometastatic cancer	White British	Vac-bag only	Long	Repeated	Hypertension, atrial fibrillation, asthma, osteoarthritis, depression	7 days post SABR
M106	Male	70-79	Primary HCC	White British	Compression arch + Vac Bag	Long	Repeated	T2 diabetes, peripheral vascular disease, chronic obstructive pulmonary disease	Post fraction 5/5
M107	Male	80-89	Primary HCC	Other ethnic group	Compression arch + Vac Bag	Long	Not repeated	Hypertension, hypercholesterolaemia	Post fraction 3/5
M108	Male	70-79	Primary HCC	White British	Compression arch + Vac Bag	Short	Repeated	Hypertension, pre-diabetes, glaucoma, squamous cell lung cancer	Post fraction 5/5
M109	Female	60-69	Primary HCC	White British	Compression arch + Vac Bag	Long	Not repeated	Metabolic dysfunction-associated steatotic liver disease, cirrhosis, T2 diabetes, hypertension	9 days post SABR
M110	Male	50-59	Primary HCC	White British	Compression arch + Vac Bag	Long	Repeated	Pre-diabetes, cirrhosis	3 days post SABR

4.6.2 Communication

A theme of communication ran through the whole SABR pathway, shaping how patients interpreted procedures, navigated appointments, and managed uncertainty. Mismatches between what staff explained and what letters said often created confusion. Many participants expressed strong trust in their oncology teams even whilst holding gaps in understanding. Consistent with prior work [188], participants simultaneously and consistently reported high confidence in their clinical team's expertise, yet they expressed confusion about details of procedures, particularly around the rationale for appointments such as 'day zero'[1] or 'review' appointments, immobilisation, follow-up timelines or the technical aspects of SABR treatment. Where confusion or perhaps a lack of knowledge driven by their curiosity existed, patients often combatted any discord by reaffirming their trust in the healthcare staff, that 'they know what they're doing'.

4.6.2.1 Uncertainty about 'day zero', 'dummy runs' or 'dress-rehearsals'

Multiple participants commented on 'day zero' (or 'dummy run') sessions and expressed confusion over their necessity:

> *'I was disappointed with the dummy run. I just wanted to get it on the way. Crack on and do the treatments as well.'* (M101)

Others discovered only during the event that the first session was a 'dummy run,' having assumed they were starting their actual treatment:

> *'Well, I didn't realise it was a dummy run, that first one… Well, actually, I thought I was having five treatments. So, I thought that it were… it was just five, but with a dummy run, it was six. So, … I didn't realise that. But that's not a problem. It's not to me anyway.'* (M103)

> *'I thought: "They aren't gonna send me to have a preten- a dummy run before I go and get it are they?" Before I get the… scan. I'll just get in there and get scanned? And I could never understand, when I'm thinking*

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[1] A 'day zero', or 'dummy-run', as often described by patients and healthcare professionals, is an appointment on a radiotherapy machine, where the patient is set-up in the same way they were planned and will have their radiotherapy, however, they are only imaged using on-board image verification such as cone-beam CT; no radiotherapy treatment is given. The purpose is to check the treatment can be safely delivered; that no significant anatomical change has occurred that would preclude continuing with treatment, especially since it has likely been some weeks since the patient was planned on CT (and MR) imaging. Liver SABR patients are informed of day zero at Leeds Teaching Hospitals NHS Trust verbally and using written information in liver SABR information leaflets.

> *back, "Why did I go for these dummy runs?"... I presume there's got to be a reason why. But for the life of me, I can't understand why I've had them.'* (M105)

Radiographers often used the day zero to reassure patients that later sessions would be similar or easier. Some participants found this accurate and comforting, though a few felt the rationale for Day zero was under-explained or perhaps unnecessary:

> *'… on that day zero, why they do it? … They say, "It's no worse than this", and they were right. It's fine, not a problem at all. Dead easy.'* (M104)

Similarly, participant M109 reflected on the reassuring language used by the radiographers to contextualise the day zero as a 'dress rehearsal' for the remaining SABR treatment sessions:

> *'Yeah, dress rehearsal or a day- day zero. …. the following day, when I was having the day one, um, it would be like that but then I'd have my treatment after that, so it would be a little bit longer, explaining that that it would be a little bit longer on the day - you know the treatment days.'* (M109)

4.6.2.2 Uncertainty about 'review' and other appointments

Participants likewise mentioned confusion surrounding 'review appointments.' Some believed these would be detailed consultations or perhaps getting feedback or insight into how well the treatment was working, but found that, in practice, these appointments often entailed only blood tests. The term 'review' as stated on their appointment schedule thus felt misleading:

> *'I thought I was going to be having a chat about how my treatment was going … it should have said "bloods" … I'm not bothered [by having blood taken], but some people get agitated. A review is a chat to me.'* (M109)

During one interview, prior to the 'review' appointment taking place, participant M103 anticipated receiving detailed information about how his treatment was progressing, explaining that he was uncertain what would happen:

> *'No, I'd like to … I don't know what they're going to tell me when I get in the nurses' review … They might say it's going well, or it's not … I don't know if they're in a position to do that. … It might be that I have to wait for the doctor.'* (M103)

Similarly, M104 believed the planned 'nurse review' would offer reassurance regarding his treatments' efficacy, alongside a more traditional consultation format:

> *'I presume they're going to … because I thought, 'Oh, nurse review, this is where they will tell me, it's looking alright, we'll take some bloods. Any questions?' Blah, blah, blah. But no, they just did that.'* (M104)

One participant speculated that their appointment letter was merely an administrative document, written more for internal use than for patients. Participant M106 reflected on how the letters 'AGL', present alongside all their SABR appointment dates and times, was incomprehensible to someone unfamiliar with departmental nomenclature. He also felt that the term 'review' was misleading when, in fact, he required a blood test:

> *'I didn't know they had that, then I had two the next time I came … I didn't know they were coming. It just said 'see the nurse' … I've got one here [referring to the appointment letter]. … Telling me it's an 'AGL.' I've never been before … it doesn't mean so much to me. Is it an MRI? … it is an internal document … It's supposed to be a patient document.'* (M106)

Whilst some participants simply expressed confusion, others suggested that clearer communication about the appointment purpose might reduce anxiety. Participant M107 specifically noted that seeing images or discussing treatment with the clinician would have been more reassuring:

> *'Yes, yes. I prepared to see the doctor who saw me … it is nice for a patient to look at [the computer images], to see what is going on … Psychologically, yeah.'* (M107)

Overall, confusion stemmed from mislabelling, unexplained internal codes, and misalignment between verbal explanations and appointment letters. Upon further questioning, some participants recognised that the information might have already been communicated at an earlier stage (e.g. an oncologist mentioning blood tests).

4.6.2.3 Unclear follow-up procedures

Uncertainty about the future was a pressing concern for many, often brought out by discussing the next steps after treatment: the follow-up appointment. As briefly touched upon in the accounts of the 'review' appointments, the lack of a forthcoming progress report was a frequently discussed theme. Participants commonly voiced uncertainty over when or how they would learn about treatment outcomes. Some expected real-time feedback from radiographers during each session, whilst others wondered how soon they would receive a post-treatment scan or see a doctor:

> *'Because at the moment, I don't know when they will contact me. My last one's [treatment] Thursday. When are they going to contact me to tell me*

> *what's what? I presume I'll get some more MRI and CT scans coming through the post, but at the moment I don't know whether that will be next week, two weeks, three weeks, four, I have no idea at this point. Because I've only got Thursday left.'* (M104)

> *'And, but a little bit of a progress report, maybe? But I don't know if they're allowed to do that, the nurses. And I don't know. I'm not going to ask them. I don't like putting people in position where it makes it a bit awkward for them. I'll just wait while the- the doctors see me. I don't know how long that is. I don't know what, when they will, - when we will- 'll be having further scans. I don't know how many more times I'll have to come here.'* (M103)

M106 characterised the post-treatment period as anti-climactic and expressed her struggle to comprehend the rationale for the delay in between completing SABR and further diagnostic scans:

> *'I don't know what's going to happen now just go away and we'll ring you in 6 weeks and we'll call you back in 3 months. I don't know, is that it? Do we just walk out and wait for 3 months because I haven't got any symptoms? In the Macmillan book it said you will come back for an MRI or a CT scan just to check if everything is ok in 3 months' time. I find that hard to comprehend that's how you do it if that is the case. There should be somebody but now at the end, it's like an anti-climax.'* (M106)

M109 was looking for guidance about the process after completing their SABR:

> *'I just hope it works that's all. I just hope that, what- um- what I'm having done works and has a good outcome at the end of it so fingers crossed. When I finish the treatment on the Monday do I get anything? Do I get notice to say that I have to go back or do I do I get that later on down the line or? I'm not 100% sure about that.'* (M109)

M110 divulged their anticipated anxiety about waiting to find out the impact of the treatment whilst waiting for their follow-up appointment before going on to question the physical and perhaps radiobiological technicalities of radiotherapy:

> *'No, I've got a thing for a scan on the [date redacted]. Which I'm assuming they're going to tell me if it's worked or it hasn't. That's the thing as well. It's like from the first or whatever to the [date redacted], you're thinking, has it worked? Is it still working now, the radiotherapy? Is it still going on in my body now? Or is that it, once you come off that machine, it's switched off and your therapy's finished then?'* (M110)

This latter point likely relates to either written or verbal explanations of why patients need to wait several months before further diagnostic scans. Indeed, this was also reflected upon by other patients including M102, M105, and M109:

> *'And then, er, and so... So that six weeks, she's getting back to erm, to see where things went. I know I read on a book, on a leaflet that it carries on after, well, I think it's on that booklet I got. It carries on after the treatment, still working.'* (M105)

> *'I feel, I, yeah, they said, when we, the daughter rang about asking about going on the cruise, and the girl and the counter? said, "Well, it still keeps working, you know, after you finish." I didn't know that.'* (M102)

The necessary delay required to allow for the effects of SABR to have been realised and before follow-up scans or clinical consultations can therefore take place was not well understood, felt anticlimactic to some, and perhaps reinforces the need for better signposting of timelines and next steps.

4.6.2.4 Equipment and techniques

Patients diverged in how much detail they wanted about the SABR machinery (e.g., linear accelerators, imaging and immobilisation equipment). A few found staff explanations too brief, prompting them to search online for more technical knowledge:

> *'I've even been… online and looked them all up, these linear accelerators and all the other stuff. I'm looking at it, because you like to know, you see, what you're dealing with. Well, I do anyway. And see how it's helping.'* (M105)

Others only realised mid-treatment that they had questions which they wanted more comprehensive answers:

> *'I was expecting somebody to tell me more about it. How they work, for example. I mean, it is important to the patient to know what is going on behind the wall.'*
>
> *'… So how it works... That's why, when I finished the first time, I told them what was going on. "You put me in this machine - nobody told me about anything.""* (M107)

Whilst trust in healthcare professionals was consistently high, the varying communication styles and differing levels of detail offered either in written or verbally by staff members might have contributed to uneven patient understanding and satisfaction. Several participants commented on the timing and tailoring of information. Indeed, M101, M102, and M104 were very positive about the information provision and how it was communicated. For example, M104 stated:

> *'… it's fine, I've not got a problem with that. It's just lots of information. And the videos and the stuff from the Leeds Teaching Hospital's online you can find, there's a lot of stuff. There's a lot of Macmillan stuff online as well, which a lot of people do today.'* (M104)

For participant M106 felt that there was, however, too much information, too early in the pathway and a preference for practical guidance closer to treatment:

> *“There's no point necessarily giving you a leaflet with loads of information in - too much information. So there's too much at the beginning. Put it into practice when we get here. Nobody else wants to read it - you can only pass on experience.* (M106)

Other patients (M102, M105, M107) described seeking additional explanations about their radiotherapy after treatment began:

> *‘… I've asked one lady when I get in, I said, “Do you start off on a low dose and build me way up?” She says, “No, you get standard dose like everyone else.” And that was, that were her explanation. So that didn't leave me with much.* (M105)
>
> *‘So you still feel like you'd need more information about what you have had?’* (Interviewer)
>
> *‘It’s mainly the technical side – that’s’ just my preference. I’ve looked things up online: the different types of radiation, and there’s a tool where you can estimate how much you’ve had over your life – dental x-rays, sun exposure, all that. It says I’m getting quite a good dose now, but it’s concentrated in one area, not the whole body.’* (M105)

Similarly, M102 expressed frustration at an absence of explanation of the linac machinery:

> *‘...I just wondered what they were doing, because I didn't… There's hardly any noise. And I thought, well, they must be doing something, but I don't know which one's doing it. ‘[laughs] I did mention it. … So, I don't know what's happening, like. Because, to me, things just keep going around. I don't know what they're doing.’* (M102)

M109 spoke of not knowing what to expect:

> *‘I really I just didn't know what to expect. Um, I got the I got the leaflet… of the treatment that I was having… and there's like a picture of the equipment and stuff and I'm thinking oh crikey! But you know, like the thing that goes over your tummy and things like that and I'm thinking oh crikey! Um- I don't know. First of all, I thought oh is it gonna hurt or and I did ask I did ask, um, and they went no you won't feel or anything like that. I don't know. I just I didn't know what to expect.’* (M109)

As shown by these differing accounts, the overall picture was mixed, with some wishing for more granular detail and others feeling that staff should simply ‘get on with it’. Personalisation and provision of information at the right time for the patient therefore may help improve the patient experience.

4.6.2.4.1 The breath-hold procedures at CT and MRI planning scans:

Breath-hold techniques are integral to achieving good quality images in the same position across CT, MRI and linac platforms, and are crucial for accurate treatment planning. However, breath-hold often proved confusing or challenging for participants, particularly in the MRI scanner where audio clarity was sub-

optimal or no clear countdown was given to tell them how long they were expected to hold their breath.

For some participants, the clarity of the breathing instructions was a particularly challenging element:

> *'With me practically deaf in one earhole and not so good in the other, even though I could hear it with the earplugs in and the headphones on, I could hardly hear them telling me instructions about breathe or take a breath and all that.'* (M105)
>
> *'Right, the CT was all right, but in the MRI they put earplugs in. But I could still hear.'* (M103)
>
> *'So, I was a little bit worried inside, whether I am doing right, doing everything in the right way or not. The machine always... For me, it wasn't understandable.'* (M107)

When audio was unclear, some participants felt they had to prompt staff to adjust communication.

> *'I had to say, "I can't hear you very well", But it should be clear, as I said before. …The voice should be clear.'* (M107)

Some participants (M106, M108, M110) indicated the pace of the instructions to breathe in and out before holding their breath may have been challenging:

> *She was talking fast. I got the impression that she was talking fast. I think the clarity, the volume was ok, but it wasn't clear enough it just needs a bit of a bit of a kick as if it's an old machine have it rewired.* (M106)

Like M103, M104 noticed the differences between the breath-hold communication and length of breath-hold practised in CT and MRI.

> *'I couldn't hold my breath to save my life. There was no counter on there. On the CT machine, it counts. So, if I said, lay on your back, stressed out, and it's 15, 14, 13, you can probably hold your breath. But when there's no counter, it's really bloody hard to hold your breath [laughs] for 15 seconds or whatever it is. And the kids said, "Oh, you'll have to hold it longer". … CT's easy. MRI's hard when you're holding your breath…. The CT one had a little counter. "10, 9, 8," and you could hold it.'* (M104)

This led to some participants describing their coping strategy of counting due to a lack of additional support in the form of countdowns or time cues:

> *'In fact, I did actually count them in my head every time, so I had a rough idea myself, how long, when can I start breathing again. …They didn't tell me. I was counting them. I presume everybody did that.'* (M105)

Participants also pointed to a need for improved breath-hold instructions such to avoid acquiring images in the incorrect breathing phase:

> *'…Because you're not having a deep breath and, oh yeah, what I was doing was I was doing it wrong and they told me I was doing it wrong.'* (M105)

> *'Erm, I was taking a deep, deep breath and holding it. And they said, and they weren't getting the, the images right, they says it was a normal breath I had to take [breath out] and then hold it. …Well, the one where you've exhaled it all and you don't know when you're going to draw your next breath. …you're thinking, oh, this is 13 seconds, you know, and it's in your head that. Cor!'* (M110)

Not only were there communication components which often contributed to making the breath-hold procedures challenging, but patients frequently spoke of the challenging physical demands of the process. These issues fed directly into the next major theme: discomfort.

4.6.3 Discomfort

4.6.3.1 Breath-hold challenges

Breath-holding was required for image quality in both CT and MRI, but the physical demand described varied across the participants. Many participants found exhale holds harder than inhale holds, describing chest wall effort, the reflex drive to breathe, and strain when repeated in quick succession. A sense of 'failure' was also described by some patients.

4.6.3.1.1 Links with co-morbidities

Some of the patients, particularly those with comorbidities found breath-holds particularly difficult, linking their struggles to underlying breathlessness:

> *'No, I think, I know the reason why, because I've been for quite a few years having breathing problems associated with my cardiac situation. So, I realised why I had difficulty in holding my breath for so long. And likewise exhaling and holding it for so long. I just automatically associated it with my breathlessness.'* (M101)

4.6.3.1.2 Timing of breath-holds

Some reported the pace and timing of the repeated breath-holds, as previously highlighted and interlinked with the communication theme, potentially manifesting in patients struggling to breathe in time with the instructions:

> *'I mean, there seemed to, when on the previous times when I've had MRI or the CT, it seemed to come around a lot quicker on that one for that day. You know, the holding of the breath and that seemed to come pretty quick on top of each other.'* (M110)

'I could just nearly… I was breathing in before they asked me to breathe in again.' (M108)

'You know, there comes a point where you just can't, and you have to breathe. …and then you're out of breath and he says, 'Breathe in, breathe out, hold your breath.' And you're like, 'Oh, I haven't even taken six breaths in between that.' Yeah, a little bit more time in between that bit or that bit.' (M104)

4.6.3.1.3 Thoughts and feelings

Several patients struggled, requiring repeated breath-holds during MR simulation. M102 reflected on the feeling that they'd 'mucked it up a bit':

'I think it mucked it up a little bit, like, you know. I don't know how, but he said, "Not so good."' (M102)

M107 expressed some concern about their breath-holds:

'So I was a little bit worried inside, whether I am doing right, doing everything in the right way or not.' (M107)

Patient M110 found they were doing the opposite of what was asked:

'… it was me. I was just, I don't know about the, like, bloomin' brain freeze or what, but I was breathing out when I should have been breathing in and breathing in when I should have been breathing out. I finally did get it. …whether it was a bit of anxiety or something, I don't know. I just couldn't seem to grasp it straight away.' (M110)

4.6.3.1.4 Comparing different breath-hold procedures throughout their SABR pathway

Patients often lamented about the procedure asking for exhale breath-holds as opposed to inhale like they had found was typically done in diagnostic examinations:

'I couldn't hold the breath or with MRIs for this - it was a reversal: exhaling.' …I just wasn't able to, on the exhaling on one of them, holding the breath thing, I wasn't able to hold it or exhale it for that long.' (M101)

'No, this is breathe out which is even worse. So, if you breathe in and hold your breath, I think it's easier than breathing all out and holding your breath. Have you tried it? It's easier if you breathe in and hold your breath. I don't know why.' (M104)

'No, I'd rather have it the other way around where you was holding your breath with a lungful because I used to swim a lot underwater. Yeah, I mean, swimmers don't do it – you do it the other way. No, they do it with their full lung, don't they?' (M108)

Patient M110 referred to exhale breath-hold as 'the opposite way around' potentially being unnatural and referring to previous examinations where they have been given the choice of either inhale or exhale:

> *'No, they've said whichever you feel comfortable.…That's what I usually do. Deep breath in and hold it. And then, yeah, but I was doing it the opposite way around. Then they said, "no, that's right, do it again". Then going back in the scans where they can see what's going on, tell you to do it, and then I wasn't doing it. So, you know, that happened two or three times. And then as I say, I finally cracked it.'* (M110)

M109 reflected on finding the first breath-hold challenging in MRI and then being able to manage with subsequent requests, potentially highlighting the need for practice:

> *'With every MRI that I've had I always find the first bit when they ask me to do the inhale, that's always the- the most awkward one for me I don't know why. I can't explain it. I find that the most awkward one and then after that I'm fine.'*

Only three patients went on to compare the differences between the planning scans and the SABR treatment, the latter not requiring any breath-holds at all:

> *'There is nothing here. [referring to the linac]*
>
> *… It is very, very easy for me. … Because it is easier here.'* (M107)

M104 commented that if the planning scans could be performed in free breathing, as on the linac, that might improve the process:

> *'Here [referring to the linac], it's a lot more…, you're not thinking about your breaths at all. Whether I don't know whether it's doing it in or when you're breathing in and out or not, but, because you're not told it, or if it's not doing it, you just breathe normally. You just lay there like a plank and that's it, really. It's, it's dead easy. …If, if MR and CT were like that, it'd be a million times better.'* (M104)

4.6.3.2 Positional discomfort: arm and shoulder positioning

The current immobilisation technique for liver SABR requires patients to hold their arms above their head, supported by a vac-bag to primarily ensure the patient's arms are removed from the radiotherapy treatment beam's 360-degree arc, bringing the diaphragm more superior. This arm and shoulder position was frequently described as one of the most uncomfortable aspects of the entire process. Participants frequently describe having to 'stretch' or 'hold' arms in a raised position as inherently uncomfortable. Even those who claimed the discomfort was minimal acknowledged it as being 'awkward' or caused an 'ache'. Some patients found it painful. For most patients, the physical demands of extended their arms above their head for SABR became more salient the lengthier period they were required to lie in this position, especially during longer MRI sessions. Pre-emptive analgesia improved the tolerance for some

patients, evident because some forgot and noticed the difference. Where small, personalised modifications to support were made, such as an extra shoulder or hand support, or allowing one arm across the chest, these made a tangible difference to those patients. Several were explicit that they would trade temporary discomfort for potential survival or quality-of-life gains.

> ‘*The only thing that I find difficult is the arms, keeping the arms up. …It’s awkward. It's just, you know, it's like saying to someone, “Hold your hands out.” For an age you'll put your hands out.’* (M101)

4.6.3.2.1 Discomfort and time

The length of time the arms were held had an impact.

> *As I said, the only criticism I had was that sort of time span. Other than that, no criticism.* (M101)

M102 also referred to the impact of time on their discomfort, but for them, the MRI simulation was the lengthiest and most uncomfortable process:

> *I can manage it. I've managed it all right today, with no trouble. But the last few, I've been all right. But some... I think MRI took a bit longer, and I felt it a bit more… It did feel a bit more then like, you know.* (M102)

M103 stated the MRI took longer, and it was the position made this challenging.

> *‘The first MRI scan, that takes about, well, I think it's about 45 minutes. And it, that's a bit uncomfortable when you're laid like that for 45 minutes… The MR was the most difficult with the arm position.’* (M103)

4.6.3.2.2 Analgesia

M103 was more assertive in describing it as pain, in which to cope, he was advised to self-medicate with paracetamol and also provided with an explanation as to justify why he was required to be in this position:

> *‘What it gets is your shoulders because I'm like that [puts his arms up] They're not just at the back of here, they have to stretch 'em out. And that does... It hurts my shoulders and the top of me hands. They have told me to take some paracetamols before I come, which I have done. …they've told me to take a couple of paracetamols and I can take ibuprofen as well, at the same time as paracetamol, which I do. Although today I forgot. I never took them. I left them in the room and never bothered. I should have took them half an hour before. That's the only uncomfortableness for me is here.’* (M103)

M106 also described how they were advised by the radiographer to take analgesia to help cope and reduce the pain:

> *‘I had two sessions yesterday my arms and my back, at the time it was just my shoulders but… she said what you need to do before you come*

today was take two paracetamol and ibuprofen at the same time. She said those complement one another.' (M106)

4.6.3.2.3 Trading transient discomfort for treatment-related gains

M103 went on to suggest their discomfort was a necessary element of their treatment and worth trading discomfort for extending quality-of-life:

> *'I am feeling them now, and I know when I come, I'm going to feel it again. But I can tolerate it. If it's going to cure what I've got and give me and my missus it a few more happy years. It's a- a bit of stiffening of the shoulders, it's nothing, is it?* (M103)

4.6.3.3 Discomfort related to co-morbidities and request for more personalisation

There was perhaps a variance in coping with the pain caused by the arm positioning, with some pointing to their age, prior injuries (e.g., M104's nerve damage from a motorcycle accident), or general musculoskeletal condition affecting their ability to cope. Patients were stoical, but many were left wondering if they could be made more comfortable or better explained. For example, M104 wanted additional support, on top of the existing vac-bag they already had, expressing a feeling the existing equipment was ineffective:

> *'So something like that knee rest is really good. But if there was something for your arms, it'd be better. … they ache… six out of ten for me [referring to pain level experienced]. … I'm conscious about my shoulders and not moving. It's just my shoulders. So, something to hold your shoulders would be nice. …I don't understand that blue bag. Because you spend all that time moulding it and then you never seem to be in the same… you can feel you're not in the same position. So, if that's meant to hold you still, it may well do, but you're not in the position it was moulded into. It's a bugger to get in and out of anyway. …It's not particularly comfortable.'* (M104)

In one case, a participant was allowed to keep one arm by their chest, which relieved substantial discomfort (M108), highlighting how a more individualised approach to immobilisation might help:

> *'I couldn't put both arms up like I did in [location redacted]. That really killed me. Dr. [redacted] actually suggested that as long as it stretches and pulls, this arm had to be pulled up. The other one could be put across the chest. And if that worked, that was brilliant. I enjoyed that. But this arm was going absolutely dead. It was cold and it's completely dead there somehow. … my arm was dead.'* (M108)

4.6.3.4 Abdominal compression discomfort

Seven-out-of-ten patients interviewed in this study had an abdominal compression arch applied to reduce liver and tumour motion. From those who received treatment in compression, it elicited mixed responses. Although one participant stated they felt they were being held in place by the compression arch which hurt their neck (M110), no other participants reported any pain from the device.

4.6.3.4.1 Emotional experience

Abdominal compression was most often described as tight but tolerable once fitted. M109 felt some apprehension but was reassured by the staff before experiencing compression:

> *'There's like a picture of the equipment and stuff and I'm thinking "oh crikey!" but you know, like the thing that goes over your tummy, and I'm thinking "oh crikey!" …First of all, I thought, "oh is it gonna hurt?" and I did ask… and they went "no you won't feel or anything like that". …When you first look at it looks a bit, not very nice when you're looking at it – 'crikey, what they're going to do with that!?'* (M109)

4.6.3.4.2 Importance of communication

The communication with staff was often spoke of by the patients as a mediator aiding them to stoically cope with the abdominal compression and perhaps accept it as a necessity:

> *'And they did ask me, they were screwing it for them, telling me when to stop. I thought, "Oh, that was nice," cause, cause, cause they don't know how, what it's, how it's pressing on you.'* (M102)

> *'When they're trying to fit it all over you and … then obviously they're turning, turning it round, you know like they're turning the screw… but keep… going – "are you comfortable?" They did keep, you know, asking me questions and am I all right? – "is it okay, is it?" – "you're all right to breathe properly?" Obviously, they don't want you to know I'm not being able to breathe properly, but no I was fine with that… it just looks a little bit, you know, but yeah, but once it's on, yeah, it's fine – no problem with that.'* (M109)

When asked if they'd had any thoughts or issues with the device, M103 responded:

> *'No, because I… know why they're doing it. I know it's necessary. And I know that if I don't keep everything in place, it could move and then… the radiotherapy might not pinpoint where it wants to be. So I understand what it is. And it in't a painful thing.'* (M103)

Despite not being treated with the abdominal compression, its use was attempted, (aborted since it would not fit through the MRI at simulation) with M104 who stated:

> *'I've not had any of the compression thing. And to be honest, that were alright as well, I didn't think it were a problem at all.'* (M104)

4.6.3.4.3 Impact on breathing and physical sensation

A minority felt compression interacted with breath-hold tasks as well as comfort, potentially suggesting value in modification of pressure and pacing instructions for those affected.

M110 also proposed the compression might have added to their difficulty in breath-holding during simulation:

> *'I mean, I must admit though, for some reason, I don't know if it's because he had the weight, you know, across your stomach, but I seemed to be struggling with breathing in and out, holding my breath and then breathing out, which I found quite amusing, because usually it wasn't a problem. But they had to go over that a bit, but the staff was all good. He was joking about it. But no, as I've had that many of them now, it's pretty straightforward, really.'* (M110)

Like M109, M108 reported some potential anxiety and that it 'took a bit of getting used to.' They also described the impact on their breathing and the feeling that they just wanted to get through their treatment as fast as possible:

> *'I was shallow breathing. I was shallow breathing. And then I wanted a cough, and I thought, damn, I'll get this over with. And he's trying to back out what the machine's doing. That's why I said, bang it in overdrive. Come on, don't mess about.'* (M108)

Patients often used the word 'tight' to describe how it felt:

> *That's a bit tight, but it, it, it's not uncomfortable, if you know what I mean.… just a little bit of pressure, nothing much to worry about (M102)*
>
> '*It's like, we're going to put this on you and you're going to talk. It's pretty, it's tight.'* (M110)

4.6.3.5 Claustrophobia and MRI

The MRI scanner environment emerged as a source of claustrophobia for four out of the ten participants (M101, M108, M109, M110). Unlike the relatively 'open' feel of the linac or CT scanner, MRI was described as confining and noisy. The MRI scans were often compared to familiar situations patients had experienced, particularly where they had felt uncomfortable such as in a Pharo's tomb in Egypt. It was frequently described as a 'tunnel' or once, a

'sewer'. The enclosed environment, coupled with extended scan times and unfamiliar noises, exacerbated anxiety. M109 disliked having the additional equipment such as the abdominal MRI coil, placed near over face, a sentiment shared by M107:

> *'I know it has to be done… it was when they had to put something like nearly over my face as I was going through the machine. Didn't like that bit – didn't like that bit at all.'* (M107)

Conversely, some patients (M101, M107, M108) were clear on pointing out their preference for CT or the linac to MRI because of the openness, or as M101 put it, it's 'just a doughnut thing.'

> *'No, the only bugbear I had was going through that tunnel. … This was a nice surprise. [referring to the linac] … I'm pleased you haven't got a tunnel. Don't you dare put one on!'* (M108)
>
> *'It's more relaxed. More relaxed. Because it's more open.'* (M107)
>
> *'CT is alright, yeah. I think that's only because it's narrow and even if you understand, you can see daylight on the sides.'* (M101)

Participant M108 compared the day zero on the linac to the prior CT and MRI planning scans, describing their relief at being in the more open treatment room:

> *'Do you know how relieved I was when we first came here? …I was waiting for it. I was dreading that because that's the bit I don't like – the hole. I said, "You're not putting me in there?" I went, "Oh wow, I can manage that then."'* (M108)

4.6.3.6 Scan preparation

Fasting was unproblematic, and cannulas/IV contrast were familiar to most participants. No patient reported any issue at all with regards to fasting or drinking water to potentially act as an oral duodenal contrast agent for their treatment. Patients frequently explained they were 'used to' having cannulas and intravenous (IV) contrast administered. One patient out of the ten experienced an immediate reaction from the IV contrast:

> *'I think that's when they put the contrast in. I got a bit of an effect from it then. But after that I was fine. … I was breathing a bit heavy. I was hot. I did go hot because that contrast made me go hot in the head as well. I say that was uncomfortable, but er I don't complain about it because I know it's necessary. And if it weren't for these things, I couldn't spot what they're doing, could they? So, it's a necessary thing. But yes, it was a little bit uncomfortable having the contrast.'*

4.6.4 Coping and support

Patients drew on a range of coping strategies throughout their SABR journey. Participants used practical mindsets (‘just get on with it’), distraction (work, routines, future plans), and self-talk such as counting and rationalising their experience to themselves to manage the demands of planning and treatment. Communication and trust in staff were also important to patients. Family support provided reassurance, transport, and emotional buffering. Participants were often keen to discuss their relatives’ anxiety and coping. Discussions about coping with treatment often followed on from discussion about more broadly coping with their cancer diagnosis. Many participants also relied on family members’ emotional support, practical assistance, or simply the comfort of knowing someone was there for them.

4.6.4.1 Patient psychological strategies

Mindset

Many participants adopted a practical, stoic mindset, emphasising the necessity of ‘just getting on with it.’

> *‘You’ve got to get on with it… look forward to things. I don’t want to sit and wallow; I want to carry on as normal.* (M109)
>
> *‘I can’t just sit in the house, it drives me mad.’* (M110)
>
> *‘… you crack on…’* (M104)

Patients looked forward to upcoming events after their treatment, potentially as a coping mechanism.

> *‘You've got to have treatment and look forward to things and that's what I keep doing. I keep thinking right, I've got got my holiday coming, Christmas is coming, things to look forward to, you know?*’ (M109)
>
> *‘And hopefully we'll be going on holiday later on this year, maybe September time. I'm okay. I know what it's doing. I know that I'm getting radio beams... er, put into my liver. And then it's going to hopefully break these things up. And then that's gonna er... well, if if don't cure it, it's going to give a few more years. So, I'll have a few more years of burnt fish fingers or whatever she cooks. So, we'll be okay. No, I'm happy.’* (M103)

Distraction and external support

Distraction, potentially linked to looking at other present or future events outside of their treatment, was also a technique used by some patients as a coping mechanism. M104 spoke of his work being very supportive, encouraging him to

take time off. However, like M109, he too questioned what else he would be doing:

> *'Even HR said, "What are you doing here? Why aren't you off for two weeks while they have this treatment?" And I was like, Well, what would I do? I'd just sat at home staring at a floor, what's the point of it? So, I've been going to work in the morning, so I've been starting at 8 o'clock as normal. … And everybody says, "Well, you're really positive about it." And the answer is, "Well, in my brain, what else would you do?" You either go in a dark room and cry for six months, or you crack on and do whatever's doing.'* (M104)

The link of distraction to mindset was evident in the case of M104:

> *'We're going on holiday for just over two weeks. I'm looking forward to that so much. Can't wait. That's where I am every time I'm having my treatment.'* (M104)

Family members however, often provided emotional support or transportation and often were crucial buffers against stress and helped with a positive mindset.

> *'Everybody keeps saying you just look the same and I thought, well, that's how I want to be. I just want to be me. Just be the same.'* (M109)

But patients were keen to point out the impact their diagnosis and subsequent treatment. Family members' distress sometimes added to anxiety.

> *'Well, she worries, she worries more than me to be fair.'* (M110)
>
> *'My husband was worse than me. He's not coped very well. It's alright now, but I couldn't cope with how he was… I know he couldn't help it… He's been to the doctors, and they've sorted him out and he's fine – back to his normal self, which has made me feel better. …My husband just keeps saying I don't know how you can keep getting on with it, but what can you do?'* (M109).

In some cases, there was value of simple, shareable explanations that support both patients and relatives, but this did not work for everyone. M104 commented that information and explanations helped his wife, but others didn't want to engage to the same extent:

> *'My wife, obviously very upset, but once she read all the pamphlets and been explained, she's been okay. Mum and Dad, they don't really like to talk about it at all. My Dad won't engage with me at all about it, because he doesn't like death or illness or anything. But my mum's been alright with it.' (M104)*

M110 spoke of his wife's concern and his preference for being at work:

> *'But I can't, like she said, just call it a day and just forget work and just get over all this but I can't just sit in house, it just drives me mad.'* (M110)

4.6.4.2 Trust in clinical teams

High trust in clinicians was a common coping resource for patients. Clear, calm demeanour and small relational behaviours (explaining steps, checking comfort, offering music) increased confidence and helped patients tolerate breath-holds, positioning, and unfamiliar environments.:

> *'I've always... I'm always of the belief that, well, perhaps naively, I just trust that the person who's going to do the procedure, if you like, is suitably trained and qualified and knows what they're going to do. I got that feeling.'* (M101)
>
> *'He talked to me, "What music do you want? Oh, this is what we're going to do. I'm just doing this now." And it makes you feel a lot more easy. …here in radiotherapy, they've been brilliant. You know, day zero, they explained everything that was going to happen. First time you go in, you explain this and what's going to happen. And then you come in and you automatically do what you need to do, and you're great.'* (M104)
>
> *'I got the feeling the people in charge of the MRI were more experienced they gave me more confidence the way they conducted themselves and the way they greeted me and said this is what we're going to do so yeah well let's go on with it. I could speak to them.'* (M106)

The general support from healthcare professionals was echoed by several of the patients, and often coincided with remarks about trust or the importance of confidence and demeaner of staff where participants consistently valued staff warmth and competence, which they said eased worries and reinforced adherence:

> *'… it's great to see, you know …smiling faces.'* (M103)
>
> *'By the way, all of them… were very, very nice in their treatment, in smiling. This gives a big help to the person. If you see somebody just to put you in the machine and stop, quite different. I felt at home.* (M107)
>
> *'And there's a lot of support out there, because in my case, there's liver nurses, there's Macmillan. I've had the liver nurses from [redacted] - various people at [redacted]. The diabetic people there, because I've told them, so they asked me how I am. And obviously, the liver people here, who are very good anyway. So there's all that support around, isn't there? I don't think there's a lack of support for patients in that respect, if you want it.'* (M104)

To show where specific experiences arose along the pathway, themes were mapped onto the clinical workflow stages, from diagnosis to follow-up (Table 19). Some issues were stage specific. Day-zero confusion occurred at the treatment stage of within radiotherapy. Claustrophobia and most breath-hold problems clustered in MRI, not CT. Information needs and analgesia occurred

across more than one part of the pathway, from CT to treatment. Trust in staff was referred to across the entire pathway.

Table 19 Summary of key patient experience findings mapped against the liver SABR clinical workflow.
Black dots mark the stages where each experience occurred in this cohort. The matrix highlights stage-specific occurrences of sub-themes.

Mapped experiences	Diagnosis	Consent	CT	MRI	Radiotherapy	Follow-up
Day zero rationale unclear					●	
Clarity of information ('review' vs bloods, treatment schedule/letters)					●	
Follow-up timeline					●	●
Volume/timing of information - some want less now, some more later/technical			●	●	●	●
Breath-hold - Physical discomfort, feeling of failure, lack of countdown timer, audio clarity of instructions, pace of repeated breath-holds				●		
Arms-up discomfort/pain				●	●	
Analgesia				●	●	
Physical setup personalisation aid (extra supports, one arm down)			●	●	●	
Compression			●	●	●	
Claustrophobia				●		
Family distress	●				●	
Trust and staff behaviour	●	●	●	●	●	●

4.7 Discussion

4.7.1 Major findings

Liver SABR patients described their journey across planning scans, treatment, and the early post-treatment period through three overlapping themes: communication, discomfort, and coping and support.

4.7.2 Interpretation of patient experiences in context

There is a notable gap in the literature regarding qualitative studies specifically addressing upper-abdominal cancer patients undergoing complex immobilisation such as with breath-hold techniques [111,116,313,351]. Recent studies investigating the patient experience of voluntary breath-hold on an MR-guided linacs have typically employed unvalidated questionnaires or focussed predominantly on other tumour sites such as breast cancer [352,353]. To date, no studies have qualitatively investigated the experiences of abdominal compression or breath-hold techniques specifically within a liver SABR cohort. This research is therefore potentially the first qualitative insight to focus explicitly on liver SABR patients' perspectives on these critical aspects, beginning to address a significant gap in patient-centred care.

Although participants' accounts of liver SABR procedures have been reported against various procedural elements of the liver SABR pathway, it is evident that they were experienced through a broader context of emotional, relational and cancer-related phenomena, including uncertainty, fear, trust and anticipated outcomes. Whilst liver SABR's clinical outcomes and feasibility are increasingly well-documented, this study found that liver SABR patients' subjective experiences are shaped by overlapping concerns of communication, physical (and psychological) discomfort, and access to resources or strategies that help them cope with their journey. For example, breath-hold is a task that relies on good communication between the patient and radiographers in which the physiological effort and experience can be shaped by pacing, and presence of comorbidities. It has highlighted how these experiences emerge through interactions with healthcare staff, institutional policies or documents, and broader personal (external/family/work) contexts.

Communication consistently emerged as pivotal to patient experience. Participants indicated increased comfort when they received clear explanations from healthcare staff, particularly regarding the purpose and procedures involved in their treatment pathway. Conversely, unclear rationales for ‘day zero’ or ‘dummy runs’ or ambiguous descriptions of procedures within appointment letters contributed notably to patient anxiety, reinforcing findings from previous research in radiotherapy [187,350]. Similarly, patients commonly questioned what would happen next, even if they acknowledged they were aware of the procedural ‘follow-up’ process. Their anxiety was more related to the potential outcomes, echoing established evidence that uncertainties about clinical follow-up can exacerbate patient anxiety [184,188]. The patients in this study frequently spoke of uncertainty in knowing what would happen in the future following their treatment and this is aligned with similar findings in a broader context investigating more elderly patients [342].

Across the patient narratives, the simultaneous expressions of trust in healthcare professionals, that often followed examples where communication or understanding was sub-optimal, emerged as a coping mechanism and a possible buffer against uncertainty. For example, when communication could have been improved to reinforce or clarify the rationale behind ‘day zero’ appointments or resolve ambiguous appointment descriptions, patients frequently deferred to the expertise of their clinical team, expressing a confidence and trust in their clinical team.

This phenomenon is also consistent with the literature, being well-documented in cancer care. Trust has long been acknowledged as helpful in maintaining treatment adherence, navigating decisions, and tolerating discomfort [182,354-356]. Adapting information to suit patient needs so it is communicated in an understandable manner, as well as has been found to be crucial in trusting health services [342,357]. In the radiotherapy and liver SABR setting, this trust may be particularly important due to the technical complexity and increased length of procedures that differ from prior diagnostic procedures. Again, although the contexts are slightly different, studies by Halkett et al. (2010) and Bolderston et al. (2020) explained how patients’ trust in their radiographers was not grounded in both the perceived technical competence but also in relational care, preferring staff who explain procedures clearly treat patients with dignity

and provide reassurance [355,356]. Halkett et al. (2010) posed a similar theme: ‘a need for information and strategies for coping with uncertainty’. This study adds further support for this theme. Trust potentially functioned prominently as a coping mechanism, enabling patients to tolerate discomfort and manage uncertainty about complex procedures, even when they did not fully understand the technical rationale behind them. Patients tolerated discomfort and uncertainty, not necessarily because they were fully informed, but because they trusted their clinical team’s intentions and expertise, a potential substitute for understanding their situation. In this study, trust allowed patients to reconcile their limited personal understanding with their willingness to ‘get on with it’, consistent with studies that have previously demonstrated the importance such pragmatic reliance and relational reassurance provided by their clinical team [355]. Nonetheless, participants often gave examples of both positive and negative interpersonal interactions and, when coupled with clear explanations, appeared to mediate their discomfort.

Studies have shown that improving comfort can correlate with significant increase in radiotherapy accuracy, demonstrating a need to explore patient comfort prior to developing interventions [358]. Physical discomfort, particularly related to overhead arm positioning and, to a lesser degree, breath-hold combined with abdominal compression, was notably challenging for some, though not severe enough to result in any of the participants from not completing treatment. However, it was a notable source of distress for some patients. Discomfort was present in longer MRI sessions and in patients with comorbidities. These findings align with previous radiotherapy studies highlighting the need for improved positioning devices or more flexible immobilisation strategies [349,359]. Furthermore, MRI-based planning emerged as particularly challenging due to environmental factors such as scanner noise, confined spaces, and the physical demands of repeated breath-holds, especially exhale breath-holds which some participants found especially taxing. Thus, this study reinforces recent calls for more personalised and patient-adapted motion management approaches, supported by clearer communication, enhanced patient coaching, and tailored comfort interventions [116,321,351].

4.7.3 Strengths and limitations

To the author's knowledge, this is the first qualitative interview study focused on liver SABR procedures such as breath-hold, compression, and positioning from the patient perspective. Semi-structured interviews were chosen because they allowed detailed exploration of individual experiences, including uncertainty, fear, discomfort and previously private reflections that may have been less accessible in focus groups or observational methods. Interviews provided the flexibility to probe the technical aspects of SABR, such as breath-hold and immobilisation in detail and what undergoing those processes felt like in their own words. As shown by Table 19, the results from this study could be used to translate its qualitative themes into improving components of the patient pathway. MRI revealed burdens including exhale breath-hold difficulty, lack of audio clarity and claustrophobia. Pathway misunderstandings from patients were evident, particularly around day zero and 'review' appointments. However, the mapping only presents patient reports. A parallel staff process map could highlight where staff expectations and understanding conflict or support with patient experience. Future work could overlay with the patient experience matrix with a complementary staff map of workflow tasks, information and constraints.

A limitation of this study is the relatively small sample size. Ten participants were sufficient to capture the major themes, but this modest cohort may limit the range of perspectives. This is particularly relevant given the heterogeneity of the liver SABR population in terms of diagnoses, comorbidities, treatment techniques, support networks and emotional responses. There was no stratification by comorbidity, which may have influenced tolerance to procedures. However, the purpose of this embedded study was to gain an in-depth understanding rather than statistical representation, and qualitative research can still utilise such small samples when information power is high to generate rich data [327,338,360].

The composition of the sample is a further limitation. With only one female interviewed out of the ten patients, females were underrepresented whilst men were overrepresented compared with the local liver SABR cohort described in Chapter 3 (90% male in the interview sample versus 70% in the treated population). Although females were not under-approached, six out of the ten patients who did not enter the study following approach were female. Four of

these female patients declined participation, most commonly stating that they had ‘too much going on’ at the time. It is possible practical burdens, and competing demands may have disproportionately limited female participation in this study, reducing transferability of findings to female patients and limiting insight into potentially sex or gendered aspects of experience. This gender skew might have influenced the themes that emerged; for example, issues of modesty and vulnerability as highlighted in breast cancer radiotherapy studies [361], were not prominent, possibly due to the majority male sample. As a pragmatic study, recruitment relied on clinical oncologists to introduce the study and on voluntary participation. Therefore, some participation bias is possible. Patients with higher trust in clinicians or more positive care relationships may have been more inclined to take part, whilst less engaged or more sceptical patients may be underrepresented. These findings should therefore be viewed as a foundation that has identified core themes and areas for improvement, which could be addressed in future work that purposively recruits a larger and more diverse sample.

Although purposeful sampling facilitated recruitment of participants with relevant experience, participation may have over-represented individuals who felt able to, comfortable or motivated to discuss their experiences, whilst under-representing those who were more distressed, fatigued, unwell, or less able to engage in an interview. This is a recognised challenge in health research recruitment, and a potential source of selection bias[362,363].

Since all interviews were conducted with patients recruited from a single cancer centre, the findings may be context-dependent, reflecting institutional practices or the culture specific to this setting and thus may limit transferability. Other radiotherapy centres might have different protocols that might include breath-hold coaching or alternative patient information and methods of delivery which could yield somewhat different patient experiences. However, many sub-themes, such as side-effects and relationships with family and external support networks are likely relevant in other settings, even if specific technical or operational methods differ.

A further limitation was the use of an initial a priori framework informed by pathway stages and PPIE discussions, which may have influenced the balance of the analysis by drawing more attention to procedural aspects of the SABR

experience. Although emergent coding was used to remain open to unanticipated concepts, the analytic structure may still have shaped what was most visible in the final thematic account. Other limitations include retrospective nature of interviews and the potential for recall bias, which might have affected their recall of certain experiences at the time of procedures such as CT and MRI scans.

4.7.4 Implications for practice - Recommendations for Improving patient comfort and acceptance

Despite the limitations of this study, small, practical changes could mitigate patient burdens or potential triggers of discomfort. For instance, participants suggested:

- **Clear, plain language communication with simple explanations of appointment/procedure/equipment purpose:** Patients wanted to know why they have a ‘dummy run’, what a ‘review’ really entailed, and how each step fitted into the overall pathway. Offering enhanced explanations could help alleviate anxiety and confusion. Additionally, a family-facing explainer could be developed: a one-page sheet for relatives and patients can reduce anxiety and help coping.
- **Enhanced clarity in letters and schedules:** Suggestions from PPIE work suggested minimising department-centric abbreviations and providing plain-language definitions (such as ‘You will have blood tests on this visit; you won’t speak with your clinical oncologist until six weeks after your treatment’) might pre-empt confusion. Further public and patient involvement is highly recommended to facilitate co-design and validation of communication.
- **Positioning comfort - personalised immobilisation:** Although equipment is often selected and a level of personalisation provided to provide comfort and reproducibility for patients, where feasible, radiographers should ensure those with shoulder issues or comorbidities are assisted as much as possible, actively discussing with the wider multi-disciplinary team the option of offering additional adjustments, clearly explaining to the patient the available options during the planning

phase. This may also include pre-emptive analgesia or allowance for ‘one-arm-up’ treatments where feasible.

- **Personalised breath-hold support:** Offering a real-time countdown and confirming audible clarity and patient comprehension is recommended, especially for those with hearing difficulties. Research into alternative communication methods for hard-of-hearing patient is warranted. Patients who struggle with exhale holds might benefit from inhale techniques, aligning with recent evidence advocating for adaptive breath-hold approaches [116]. Additionally, providing short instructional videos, diagrams, or dedicated pre-treatment breath-hold coaching sessions could help reduce patient anxiety, enhance breath-hold reproducibility, and improve overall treatment experience.

4.7.5 Future directions

Future studies could use purposive sampling across more than one centre to achieve a more diverse sample, particularly with increased representation of women, to better understand potential gender-related differences in patient experience.

Clinical implementation of liver SABR should actively engage patients in the co-design of educational materials (such as single-page leaflets, checklists, and perhaps online modules). Additional coaching and countdowns for facilitating breath-hold could be explored, as well as prompts for pre-emptive analgesia and additional support. Furthermore, clinical workflows should incorporate routine assessments of shoulder mobility or claustrophobia to facilitate more individualised immobilisation choices. Whilst trust in staff often compensated for imperfect communication, ensuring consistent, empathetic, and transparent explanations could deepen patient engagement, improve satisfaction, and potentially enhance treatment adherence and quality of life. Such interventions could be systematically evaluated to determine if they enhance comfort and reduce anxiety using the R-IDEAL framework.

4.8 Conclusion

Patient experience in liver SABR is shaped by how clearly the pathway is explained, how physically demanding the procedures feel, and how patients and families are supported to cope. Small, low-cost changes, such as countdown time cues for MRI breath-holds, analgesia prompts, minor support adjustments, and improvements to plain-language letters and liver SABR pathway information leaflets, could lead to an improved patient-centred experience.

If communication, discomfort and coping can influence how reliably patients engage with demanding procedures such as breath-hold and abdominal compression, these procedures should be understandable and tolerable in practice. Chapter 5 therefore aims to provide a proof-of-concept evaluation of whether selected NMOCs can improve upper-GI conspicuity relevant for liver SABR under a practicable and acceptable protocol, as predicate evidence before testing in patients.

Chapter 5 Evaluation of non-medicinal oral contrast agents

5.1 Introduction

Magnetic resonance imaging (MRI) is integral to liver stereotactic ablative radiotherapy (SABR) planning because its superior soft-tissue contrast improves delineation of tumours and organs-at-risk (OARs) [155,208,211,364]. However, even with MRI, the borders of the gastrointestinal (GI) tract (duodenum, stomach and small-bowel loops) often remain indistinct, and this can lead to uncertainty in contouring [155,365,366].

Chapter 2 identified candidate NMOCs that might have utility to aid contouring. This chapter is purposefully positioned after the motion (Chapter 3) and patient experience (Chapter 4) to reflect the logic of this thesis: technical optimisation should be developed alongside an understanding of practicability and patient burden. Together, Chapter 2 – 4 provide the predicate evidence that justifies this proof-of-concept evaluation prior to patient testing.

5.1.1 The use of oral contrast in abdominal MRI

In diagnostic GI MRI, oral contrast is used fill or distend structures so the bowel wall can be seen against the lumen and to predictably change the signal inside the bowel lumen so can be better distinguished. It is important that the oral contrast agent and MRI sequence are chosen together, because the same liquid can appear hyperintense (bright) on a T_1-weighted image and hypointense (dark) on a T_2-weighted image, or vice-versa. This property can be exploited to either accentuate or suppress the GI lumen depending on the sequence. Palatability, cost and adverse effects are also important considerations, since some oral contrasts can cause nausea, bloating, or diarrhoea may be distressing for patients [174].

5.1.2 Types of oral contrast

The term oral contrast includes two broad groups. Firstly, medicinal agents which includes iron or barium formulations, but they can cause GI side effects[160]. Secondly, non-medicinal oral contrasts (NMOCs) which are readily available liquids like water, fruit juices and teas [161]. As reported in Chapter 2, the use of NMOCs can change the signal of bowel lumen on MR imaging. Chapter 2's scoping review of the literature identified 31 distinct NMOCs across

47 studies, with water most often studied, followed by pineapple and blueberry juice. Side effects from NMOCs are rare, NMOCs are cheap and produce comparable image qualities [161,174,367]. Diagnostic radiology studies have explored numerous NMOCs for improving abdominal GI tract visualisation on MRI examinations [161]. Some NMOCs, notably pineapple juice and yerba mate tea, are naturally rich in paramagnetic ions and are biphasic [161,174,214,230,240,241,248,253,254,258,262,265]. Their naturally high manganese (Mn^{2+}) content shortens both T_1 and T_2, rendering the ingested fluid hyperintense on T_1-weighted (T_1w) images, and hypointense on T_2w images. Conversely, water, has a long T_1/T_2 and appears hypointense on T_1 and hyperintense on T_2 images. This property might, in theory, make boundaries between the gastrointestinal lumen and adjacent tissues easier to distinguish across different co-registered MRI sequences, though this specific impact within radiotherapy planning remains untested.

5.1.3 The gap in radiotherapy

Despite the wide diagnostic use, the scoping review in Chapter 2 found there were no radiotherapy specific studies of NMOCs for MR-guided radiotherapy planning or treatment in the upper abdomen. This indicates a gap between diagnostic and radiotherapy practice.

5.1.4 Why oral contrast could help in radiotherapy

Radiotherapy planning and adaptive treatment workflows rely on reproducible anatomy positioning and confident delineation of boundaries to identify bowel from other abdominal structures [161]. Selection of an NMOC with desired properties may offer clinical oncologists the opportunity to either accentuate or suppress the GI lumen, potentially improving boundary definition of adjacent OARs, reducing geometric uncertainty, and helping clinicians to contour with more confidence. Patient experience is relevant, since anything added to the patient pathway must be acceptable and cause minimal, preferably no, adverse effects.

5.1.5 How the prior chapters informed this study

The scoping review (Chapter 2) found that water was the most studied NMOC. Investigators also evaluated several juices, most often pineapple and blueberry, and a small number of teas [161]. Evidence on some NMOCs was sparse. For

example, a single proof-of-concept paper reported a tea brewed from *Ilex paraguariensis* (yerba mate) at 1.5 T [181]. There was little consensus on ingested volume, timing of ingestion to imaging and images appearance. Reported drinking volumes ranged from 100 to 2000 ml. The timing of ingestion and patient preparation varied widely. To translate this evidence into a radiotherapy-relevant workflow, NMOC ingestion parameters were adopted pragmatically whilst aligning with existing guidance. In hepatobiliary radiotherapy planning CT scans, 'On Target 2' radiotherapy guidance recommends 125-200 ml of water diluted gastrografin approximately 15 – 20 minutes before CT planning scans to aid consistent visualisation of the upper GI tract [98]. The Royal College of Radiologists' diagnostic abdominopelvic imaging examination recommendations suggest patients fast for four hours [368]. Informed by these sources, a 200 ml volume and 20 minute interval were pragmatically selected for this study to standardise gastric contents across sessions.

Most studies used qualitative labels to describe how the NMOC looked on MRI, for example 'bright' or 'dark'. Terminology was inconsistent across papers and sequences, and reporting of sequence parameters was often limited [161].

Comparisons of NMOC appearance often relied on subjective conspicuity scores. Quantitative relaxation mapping offers an objective alternative. This approach acquires a series of images while systematically varying inversion time, echo time, or flip angle, then fits the signal curve to estimate the absolute T_1 and T_2 relaxation times in milliseconds [157,369,370]. These values are independent of windowing and observer judgement, so they allow direct comparison across agents at a given field strength. Performing this mapping in vitro, under controlled conditions, reduces confounders such as motion, variable gastric contents, and metabolism, and it avoids burdening participants [371]. Such values are relevant because they predict how an NMOC will appear on commonly used sequences and whether it will create the desired hyperintense or hypointense contrast against surrounding tissues.

5.1.5.1 Relevance to MR-guided radiotherapy and patient experience

Critically, the scoping review found no studies of NMOC use within MR-guided radiotherapy [161]. Patient-reported outcomes were also scarce and lacked depth. For any candidate contrast to be feasible in a radiotherapy workflow, it

needs to enhance visualisation and be acceptable to patients who are ingesting it [173,176]. Studies have emphasised that medicinal contrast agents can cause GI side effects including bloating, nausea, vomiting, and diarrhoea, whereas NMOCs have capacity to improve these aspects of patient comfort [213]. Factors like taste and tolerability are therefore aspects which could be measured to assess if a contrast agent is feasible for use and to confirm if people are willing to ingest it.

5.1.5.2 Study rationale

Given the complete lack of comparative evidence of NMOC use for liver SABR, a brief in vitro evaluation of NMOC T_1 and T_2 signal characteristics to corroborate published reports was necessary. Therefore, a sequential evaluation over two steps was undertaken: Step 1 – in-vitro selection using relaxometry to evaluate NMOC signal characteristics at 1.5 T, followed by Step 2 – an in-vivo volunteer study to determine whether candidate NMOCs alter conspicuity of upper-abdominal structures.

5.1.6 Study framework

This study adopted the R-IDEAL framework (Radiotherapy - Idea, Development, Exploration, Assessment, Long-term evaluation) [202,203]. It enables a stepwise approach to evaluating innovations rapidly, without exposing patients to unwarranted risks. This is justified as it is acknowledged that the traditional phase I-IV framework used in drug evaluation studies often does not lend itself as an efficient framework for clinical and technological evaluations in radiotherapy [202]. Figure 5 shows how the MICROCHIPS study commenced at the R-IDEAL development stage, since the pre-clinical theoretical components of the study have already been established in diagnostic radiology studies identified in the scoping review of Chapter 2. In keeping with the R-IDEAL development stage, exploratory proof-of-concept in vivo data in volunteers under radiotherapy-like conditions was obtained, before potentially moving toward broader evaluation in patients.

This proof-of-concept study was carried out using radiographer evaluation of image quality and abdominal structure conspicuity as well as data from participants regarding sensory acceptability, to evaluate the feasibility of using the selected NMOCS in the radiotherapy pathway prior to obtaining a larger

sample with a more clinically relevant metric relating to radiotherapy contouring, such as the Dice similarity coefficient metric [372].

5.2 Aims

The aim of this chapter was to present a proof-of-concept evaluation of potential NMOCs. This process involved two steps: a systematic progression from controlled in-vitro NMOC signal characterisation and protocol optimisation (Step 1) to preliminary assessment in a healthy-volunteer study, incorporating both technical image interpretation findings and volunteer acceptability (Step 2).

5.3 Objectives

To address this aim, the following objectives were set:

Step 1: Characterise NMOCs through quantification of the T_1 and T_2 relaxation times in a clinical 1.5 T MR-simulator to determine their suitability for further investigation in vivo.

Step 2: Healthy volunteer exploratory evaluation of NMOCs to:

- Assess the conspicuity of upper-abdominal structures on T_1- and T_2-weighted sequences across NMOC interventions by two blinded radiographers
- Assess and compare the participant experience of consuming the NMOCs.

5.4 Step 1: In vitro screening of NMOCs

5.4.1 Step 1 Methods

5.4.1.1 NMOC evaluation

Based on the Chapter 2 scoping review, the following NMOCs were chosen due to their biphasic appearance on T_1- and T_2-weighted MRI:

- Blueberry juice [174,214,241,246,252-254,258]
- Ilex paraguayensis (yerba mate) [181]
- Pineapple juice [174,214,240,241,246,248,262,265,276]
- Cranberry juice [174]
- Grape juice [246]
- Beetroot juice [240].

Biphasic signal characteristics were selected because of their potential utility, for example improved co-registration of T_1- and T_2-weighted or using different sequences to aid anatomical contouring. Candidates with the shortest measured T_1 were expected to appear hyperintense on T_1-weighted imaging. Two NMOCs with the shortest measured T_1 and T_2, water as a T_1-weighted hypointense and T_2-weighted hyperintense comparator, and a no-NMOC condition as a control were carried forward into Step 2.

5.4.1.2 MRI data acquisition and relaxometry

All imaging was performed on a 1.5T clinical MR simulator (Philips Ingenia) with a dStream 'HeadNeckSpine' coil. NMOC samples were placed in standard test tubes held by an acrylic phantom fabricated specifically for this purpose (Figure 20). The phantom was filled with distilled water to ensure proper coil loading. Calibrated agarose gels doped with gadolinium (Leeds Test Objects, UK) were positioned together with the NMOC samples as reference standards. The phantom was stored at scanner room temperature for two hours to minimise temperature-induced variability in relaxation times. To measure the intrinsic properties of each NMOC, B1-corrected T_1 and T_2 relaxometry sequences were acquired. For T_1 estimation, an inversion recovery spin echo (IR-SE) sequence with repetition time (TR) of 5000 ms and a range of inversion times (TI 20–2500 ms) was acquired. For T_2 estimation, a multi-echo turbo spin echo (TSE) sequence (TR 5000 ms, flip angle 90°, echo times 10–90 ms, echo train length 9) was acquired. These sequence acquisitions enabled generation of voxel-wise T_1 and T_2 maps.

T_1 and T_2 values were estimated using a peer-reviewed curve-fitting approach [373] implemented in MATLAB code (MATLAB, version 9.14.0.2306882 (R2023a) Update 4 (The MathWorks Inc., Natick, MA, USA, 2023)) with code developed in-house by a clinical MR physicist, Dr David Broadbent. Mean T_1 and T_2 values (± standard deviation) were derived from region of interests placed centrally in each NMOC sample and each agarose gel reference. Comparing NMOC values against the calibrated reference gels confirmed that the mapping process was stable and reproducible, enabling objective comparison across liquids.

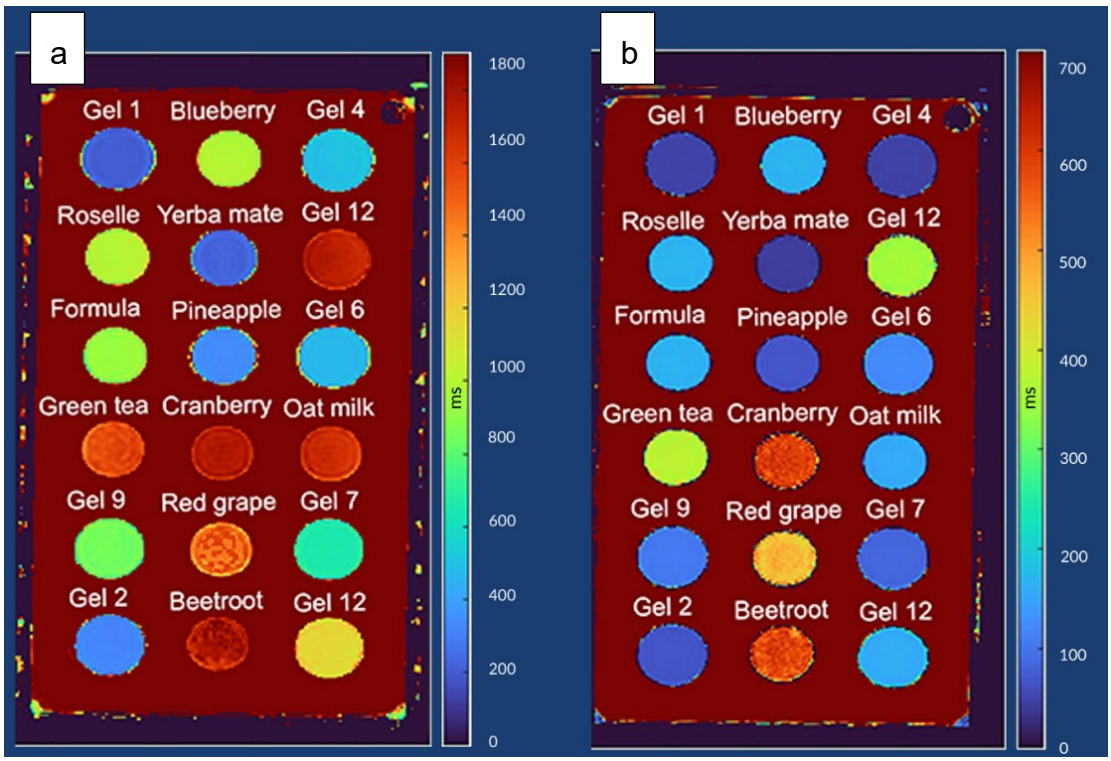
Figure 20 The MICROCHIPS acrylic phantom; test tube holder manufactured for this study.

5.4.2 Step 1 Results

5.4.2.1 In vitro relaxometry screening

A T_1 and T_2 map acquired during the in vitro relaxometry screening is shown in Figure 21. Figure 21 presents two quantitative maps acquired of the test-tube phantom, a T_1 map in Figure 21a and a T_2 map in Figure 21b. Each pixel's colour encodes the measured relaxation time in milliseconds, not image brightness. Cooler colours (blue to green) represent shorter relaxation times. Warmer colours (yellow to red) represent longer relaxation times. The scale on the images tells you the relaxation times. The surrounding bath of water appears red on both maps, confirming that water has relatively long T_1 and T_2. Relaxometry indicated yerba mate and pineapple juice as having the shortest T_1 / T_2 (mean 222.3 ± 5.4 ms / 42.8 ± 0.6 ms, respectively) / (mean 341.4 ± 4.2 ms / 68.2 ± 0.8 ms, respectively).

Figure 21 A T_1 IR SE map (a) and T_2 TSE map (b) of potential candidate NMOCs obtained during relaxometry mapping.
Quantitative T_1 map (left, a) and T_2 map (right, b) of candidate non-medicinal oral contrasts calibrated gel tubes measured in a test-tube phantom. The colour represents the relaxation time in milliseconds. Yerba mate and pineapple juice fall at the short- T_1 /short-T_2 end of both scales, predicting bright appearance on T_1-weighted images and dark appearance on T_2-weighted images. Water shows long T_1 and T_2.



5.4.2.2 Step 1 Interpretation

A shortened T_1 and T_2, as exhibited by the blue average signal of yerba mate and pineapple juice potentially indicated these substances would appear relatively hyperintense on T_1w MRI scans, but hypointense on T_2w sequences.

5.4.3 Translating the relaxometry findings into Step 2

Pragmatism informed the final protocol, restricting each volunteer to four MRI sessions to balance scientific value and participant burden. This enabled evaluation of four NMOC conditions in the next step: yerba mate, pineapple juice, water, and a no-drink control, within the same individual.

5.5 Step 2: In vivo proof-of-concept evaluation of NMOCs

5.5.1 Step 2 Methods

5.5.1.1 Study design

A single-centre, non-randomised exploratory efficacy study was undertaken in the host institution, Leeds Teaching Hospitals NHS Trust. The study was registered on the National Institute for Health Research (NIHR) Clinical Research Network Portfolio (Portfolio ID: 55694), Appendix B.

5.5.1.2 Participants

Healthy adult volunteers (age >18 years, with no known contraindications to MRI, Buscopan and/or candidate NMOCs) who were able to provide written informed consent were recruited from the staff and students within the radiotherapy department of the host institution. Healthy volunteers were recruited as this R-IDEAL Stage 1 evaluation sought to establish proof-of-concept and an understanding of acceptability under radiotherapy conditions before introducing potentially unnecessary added burden in patients.

5.5.1.3 Ethical considerations

Ethical approval was obtained through the West Midlands - Black Country Research Ethics Committee (HRA 23/WM/0070). All participants received a participant information sheet detailing the study purpose, procedures and confidentiality measures. They were informed that their participation was voluntary, that they could withdraw at any time, and, since they were employees at the host institution, that non-participation would not affect their employment rights. All participants were also informed their imaging data would be reported by a radiologist to manage any incidental findings appropriately, which included making scan reports available to their general practitioner with potential health and life insurance implications. Participant codes (M201-M210) were used to replace identifiable information in Digital Imaging and Communications in Medicine (DICOM) and other data used for analysis to protect participant confidentiality. All data were securely stored on NHS systems and demographics were reported in aggregate to preserve participant confidentiality.

5.5.1.4 Interventions

All three NMOCs administered to participants were commercially available non-medicinal products. Each participant completed four MRI sessions, each testing one of the three NMOC interventions and the no NMOC control. The sequence of NMOC administration was determined in a randomised order generated in python to minimise order effects. The assigned NMOC (200 ml) was ingested 20 minutes before positioning on the MRI scanner.

5.5.1.5 MRI participant preparation

Participants were asked to fast for four hours before NMOC administration. IV Buscopan was administered once the participant was positioned on the MRI couch. Time from NMOC administration to IV Buscopan administration was recorded.

5.5.1.6 MRI scanning

MRI was performed on a 1.5 T Philips Ingenia scanner (Software Version 5.7.1) using a dStream Torso coil. To explore the effect of NMOCs on MRI images, two sequences were taken T_1- and T_2-weighted. T_2-weighted images were acquired with an axial respiratory-gated turbo spin-echo sequence (T_2_AX_MVXD_HR_RT): TR/TE = 2867/100 ms, turbo factor 39, receiver bandwidth 333 Hertz per pixel (Hz/pixel), in-plane SENSE factor 2, field-of-view 450 x 450 mm, acquisition matrix 576 x 576 (reconstructed voxel 0.78 x 0.78 mm), slice thickness 5 mm (0 mm gap). The total predicted scan time was 153 seconds, but with respiratory belt triggering this time varied across participants. Dual-echo T_1-weighted opposed-phase images were obtained with an axial spoiled gradient-echo sequence (T_1 in/out_EXBH CS 2): TR = 228 ms, TE_1/TE_2 = 2.3 / 4.6 ms, flip angle 75 °, bandwidth 543 Hz/pixel, Compressed-SENSE factor 2, FOV 350 x 350 mm, matrix 528 x 528 (voxel size 0.66mm x 0.66mm x 5 mm); right-left phase-encoding; acquired in a single end-expiratory breath-hold of approximately 20 seconds.

5.5.1.7 Outcome metrics – anatomical conspicuity

Quantitative Likert scores for tissue visibility (conspicuity) on MRI and participant experience questionnaires were collected.

The conspicuity metrics assessed seven anatomical and imaging features; visibility of liver, stomach, duodenum, pancreas, small/large bowel conspicuity, artefact severity and overall image quality. All related to radiotherapy contouring confidence. These were individually assessed on a T_1w (in phase) and T_2w MR sequence for the four NMOC interventions (no NMOC administered (control), pineapple juice, yerba mate and water), using a four-point ordinal image quality scale (Table 20). The four-point scale was used following guidance frameworks of image assessment in MRI [374] and cone-beam CT (CBCT) image quality for SABR [375].

Conspicuity metrics were evaluated concurrently by two experienced observers [Mr Matthew Beasley (MB) and Dr Carole Burnett (CB), an experienced MRI radiographer (over 30 years) and academic supervisor]. Prior to formal scoring, the readers assessed the suitability of the scoring framework using four exemplar pilot cases, achieving consensus on all outcome metrics before formal grading began. The assessors were blinded to the oral contrast type, volunteer details and acquisition order, with DICOM tags independently de-identified. Scores were attributed as a consensus method, disagreements resolved by discussion; a method chosen because it reflects routine clinical image guided radiotherapy practice, where paired radiographers agree target positioning before treatment and which MB had previously had experience with, and validated, a similar tool in CBCT-guided SABR study [375].

5.5.1.8 Outcome metrics – participant experience

Twelve questions describing the experience of drinking NMOCs were developed with patient and public involvement and engagement (PPIE) input. The questions used a four-point scale (1 = Strongly disagree, 2 = Disagree, 3 = Agree, 4 = Strongly agree) and contained a mixture of both positive and negative sentiment phrasing to avoid acquiescence bias. To enable direct comparison and aggregation of responses, negatively phrased questions were reverse-scored so that, after recoding, higher numbers consistently indicated greater acceptability (e.g. 4 = strongly agree that the experience was favourable). Given the exploratory phase of this study, and to aid further development of the questionnaire prior to use in a patient population, content validity was also evaluated where every question was independently scored once on a 4-point relevance scale: 1 = Not relevant, 2 = Somewhat relevant, 3 =

Quite relevant, 4 = Highly relevant. For each question item, the content validity index was calculated [376,377].

Prior to participation, participants received written and verbal information cover the purpose and design of the study, fasting requirements, NMOC details including timing and volume requirements, IV Buscopan administration and common side effects, and the incidental findings reporting pathway. This information formed the baseline for the acceptability item ‘adequacy of prior information’.

5.5.1.9 Statistical analysis – anatomical conspicuity

As MICROCHIPS is a proof-of-concept (R-IDEAL Stage 1) evaluation, hypothesis-driven sample-size calculation was not required. Allowing for 20% attrition, a pragmatic recruitment aim was for 12-15 volunteers, consistent with early-phase imaging studies [378]. Analysis was limited to descriptive statistics and tentative non-parametric testing of the ordinal Likert visual grading scores. All ordinal ratings (1 = poor, 4 = excellent) were summarised by frequency, median and interquartile ranges (IQR). The Wilcoxon signed-rank tests (two-tailed, $\alpha = 0.10$) and effect size (r) was calculated to compare each NMOC to the control. Statistical testing was performed using IBM SPSS Statistics, Version 29.0.2.0 (20) (IBM Corp., 2023) and Python 3.10.11 (pandas 2.3 and scipy 1.16) with the heat-maps (colour-bar ticks = 1, 2, 3, 4) generated via matplotlib 3.9. Because each NMOC makes an independent claim of efficacy and positive findings only trigger further patient-based evaluation (MICROCHIPS Work Package 3), in line with other exploratory or hypothesis generating imaging studies, multiplicity corrections were deemed unnecessary at this stage [379].

5.5.1.10 Statistical analysis – participant experience

The sensory experience questionnaire data was analysed using descriptive statistics and plots in Python 3.10.11 (pandas 2.3, and matplotlib 3.9), with medians and IQR calculated. Stacked bar charts were calculated in python to show the spread of responses across all domains.

Table 20 Four-point visual-grading scoring framework used to score the MR images.
For each sequence, an organ-specific conspicuity, artefact severity, and overall image quality score was provided. Scores range from 1 = Impossible to use, where borders were indistinct or artefacts too severe, making the image unsuitable, to 4 = Excellent, where structure boundaries, artefacts were absent and overall image quality were deemed to result in no limitations for radiotherapy contouring purposes.

Category	Structure conspicuity (per organ)	Artefact severity	Overall image quality
4 – Excellent	Boundary of the structure is clear. High confidence that the structure can be contoured.	None	Image suitable for contouring; no limitations anticipated.
3 – Satisfactory	Boundary is clear along most of it; small areas might be challenging. Acceptable for contouring.	Mild and doesn't obscure the structure's conspicuity.	Adequate for contouring with some caution
2 – Poor quality	Boundary indistinct and edges blend with adjacent tissue in much of the structure with limited use.	Moderate artefact partially obscuring structures or causing edge confusion; likely to affect contour accuracy.	Contouring possible but with uncertainty; would repeat sequence if feasible.
1 – Impossible to use	Structure cannot be confidently separated from neighbouring tissues along the boundary; contouring impossible.	Severe artefact or signal loss that prevents structure delineation.	Image unusable for radiotherapy planning; repeat acquisition required.

5.5.2 Step 2 – Results

5.5.2.1 Participants

The MICROCHIPS study schema is shown in Figure 22.

Ten volunteers completed all four scheduled MICROCHIPS MRI scans. The demographic details of participants are provided in Table 21. Two participants (one female, one male) were recruited for the purpose of sequence-development only and therefore excluded from the main analysis. All eight participants completed the consumption of 200 ml of every NMOC and all corresponding imaging sequences, providing paired data for all four NMOC conditions on both T_1w and T_2w sequences. In total, 64 MR images were evaluated. All NMOCs were well tolerated, with no participants reporting any adverse effects.

Figure 22 Participant flow diagram for the MICROCHIPS.
The diagram shows the number of participants who were approached, excluded, recruited and completed the study. Thirteen individuals volunteered to be approached, seek further information and were screened for eligibility. Three were excluded – one because they were ineligible to receive Buscopan and two who following consideration, declined participation. Following two participants aiding sequence development, ten participants completed the study.

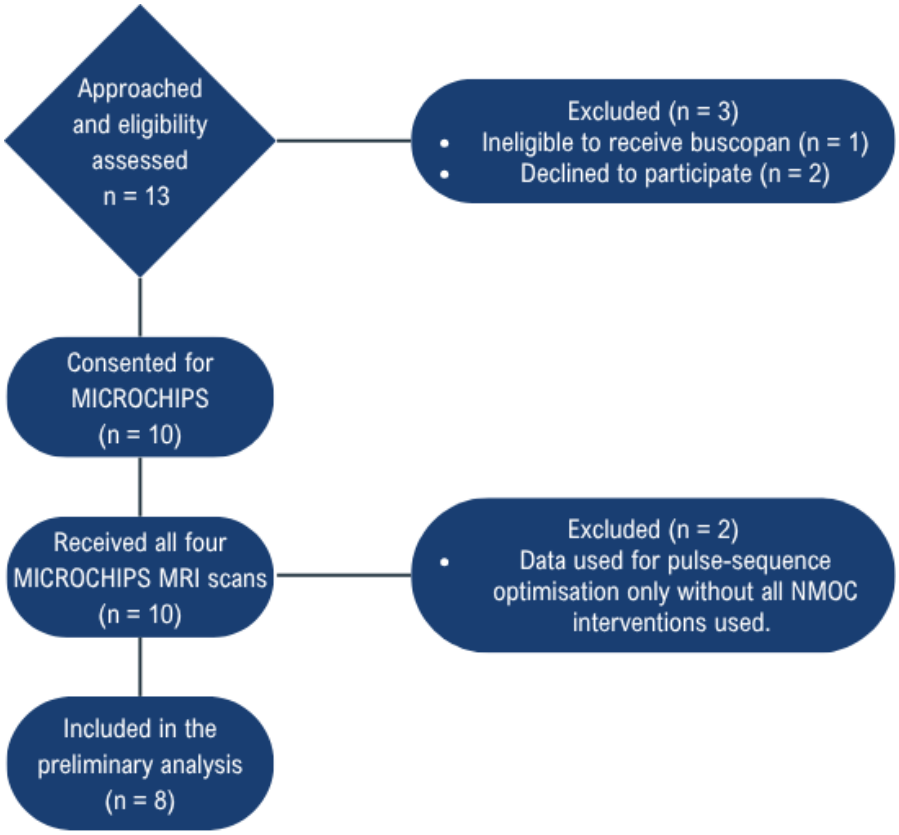


Table 21 Participant demographic data.
The participant demographics, including sex, age and ethnicity are presented as raw data and percentages.

Characteristic	Analysed cohort (n = 8)
Sex, n (%)	Female: 4 (50%) Male: 4 (50%)
Age, years	Mean ± SD: 43 ± 9.1 Range: 31-58
Ethnicity, n (%)	White British: 7 (88%) Other white background: 1 (12%)

5.5.2.2 Image evaluation

Figure 23 and Figure 24 demonstrates the image appearance on the GI structures with the NMOC intervention (baseline – no NMOC, water, yerba mate, and pineapple juice) in T_1w and T_2w MRI sequences.

Table 22 shows the median and inter-quartile ranges of the scores across the metrics. Scores have also been presented as stacked bar charts in Figure 25 - Figure 31. The bar charts demonstrate the proportional scoring across all metrics scored with 92.2% (413 / 448) of all ratings graded a 3 or 4 (above satisfactory).

5.5.2.3 Overall image quality

Median scores for overall image quality were clustered at ≥ 3 across NMOCs and both MRI weightings in 62 / 64 (96.9%) images, indicating that most images were at least ‘satisfactory’ for radiotherapy contouring.

5.5.2.4 T_1w conspicuity

Yerba-mate produced a median improvement in duodenal conspicuity (median Likert $\Delta = +1$ (IQR = 0.25); $r = 0.9$; $p = 0.023$), and the overall highest sum of median scores across all categories, joint highest for liver, and highest for stomach, duodenum, and bowel.

5.5.2.5 T_2w conspicuity

The T_2w median scores with no contrast were ‘excellent’ (median = 4, IQR range = 0.0 – 1.0) in all metrics except for the pancreas (median = 3, IQR 1.25), which showed the widest variability in terms of conspicuity. Water and

pineapple juice yielded a 0.5 median gain in two volunteers, but effects were not significant. Yerba mate was the poorest performing NMOC in terms of pancreatic conspicuity.

5.5.2.6 Artefact severity

Under all NMOC conditions, the median artefact scores remained 3 – 4 in all T_1w images (Table 23), and consistently at 4 in T_2w images (Table 24). NMOCs did not appear to show a trend for increasing artefacts on either weighting.

5.5.2.7 NMOC acceptability questionnaire

Twelve sensory experience questions were piloted in this cohort, of which five exceeded the item-level content validity index (I-CVI) threshold of 0.8 and were therefore retained for analysis:

- the adequacy of prior information (I-CVI = 0.80)
- absence of nausea (I-CVI =0.80)
- taste (I-CVI =1.0)
- texture (I-CVI =0.8)
- smell (I-CVI =0.8).

There was a total of 15 missing responses (12.5%), resulting in 105 / 120 (85%) valid question responses available for analysis. The detailed responses of these five items are presented in Figure 32, whilst the medians and interquartile ranges are shown in Table 25.

Palatability of all three NMOCs was positive in 87% (91/105) of responses which were given Likert ratings of 3-4. No nausea was reported, with every participant scoring ≥3 for all NMOCs (median = 4, IQR ≤1). Water achieved the highest median rating for texture (median = 4 [IQR = 0.75]) and the narrowest dispersion across all questions (all IQR ≤0.75). Pineapple juice showed all medians were ≥3 but showed greater variability for smell with an IQR of 1 and as shown in Figure 32, scored the only single selected report of a Likert score of 1. Yerba mate showed medians of ≥3 for all categories except for smell (median = 2.5 [IQR = 1], with 4 / 8 participants expressing some dislike of its smell. One volunteer felt under-informed about pineapple juice and yerba mate (Likert = 2) whilst all others scored prior information as being ≥ 3.

Figure 23 Axial MR images from a single participant (M208) demonstrating the effect of the four NMOC conditions on GI signal intensity.
Rows (from top to bottom): No NMOC (control), water, yerba mate, pineapple juice. Columns (left to right): T_1w in-phase (used for T_1w assessment) (TE = 2.3 ms); T_1w out-of-phase (TE = 4.6 ms); and T_2w TSE (respiratory gated, TE = 100 ms). Note the hyperintense signal intensity of the stomach (yellow arrows) on T_1w imaging with yerba mate and pineapple juice when compared to the no-NMOC (control) and water NMOC. Subtle difference in stomach volume should also be noted.

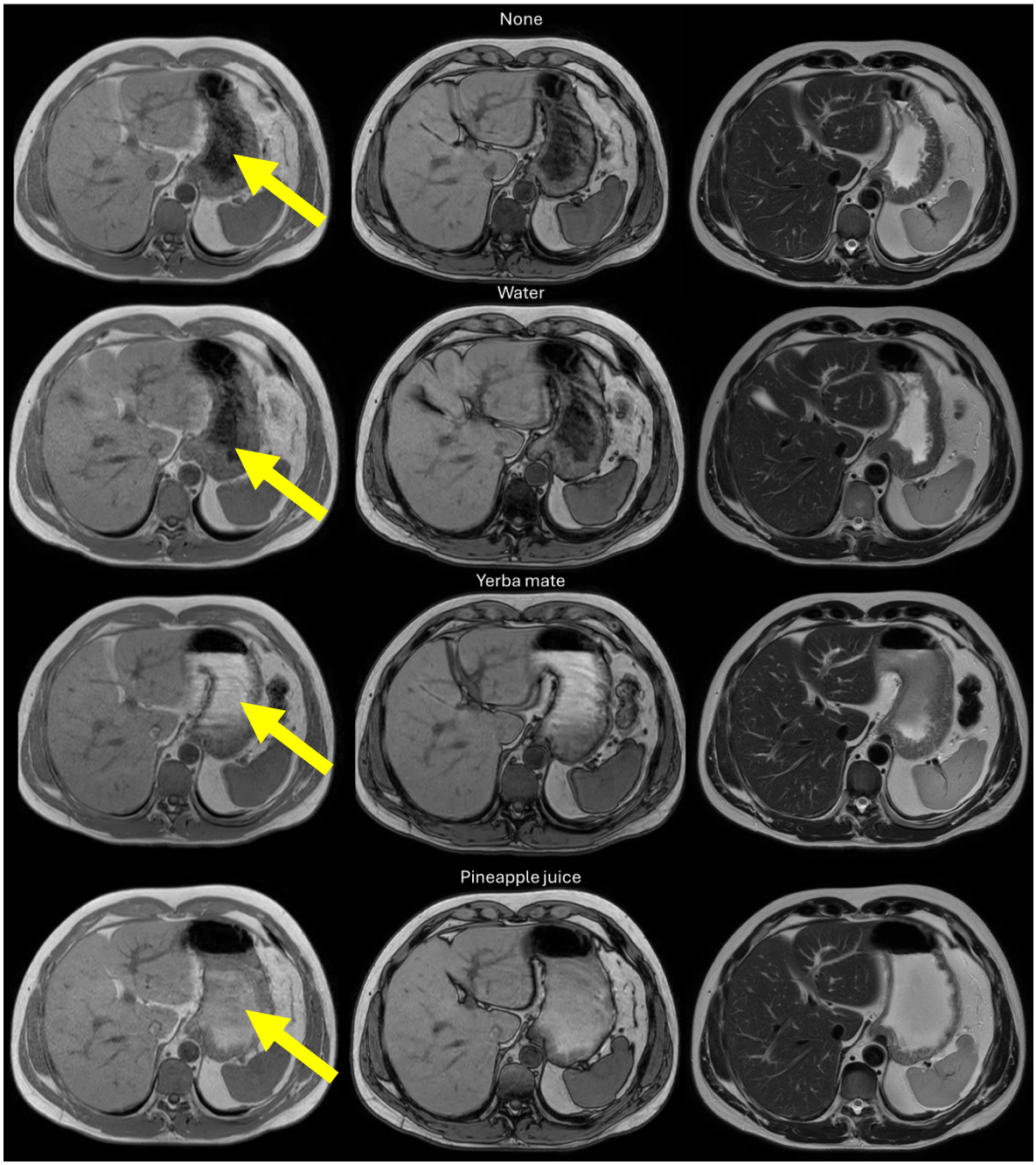


Figure 24 Axial MR images from a single participant (M206) demonstrating the effect of the four NMOC conditions on GI signal intensity.
Rows (from top to bottom): No NMOC (control), water, yerba mate, pineapple juice. Columns (left to right): T_1w in-phase (used for T_1w assessment) – TE = 2.3ms; T_1w opposed-phase – TE = 4.6 ms; and T_2w TSE (respiratory gated, TE = 100 ms). Note the hyperintense signal intensity of the duodenum (blue arrows) on T_1w imaging with yerba mate and pineapple juice when compared to the non-NMOC and water NMOC conditions.

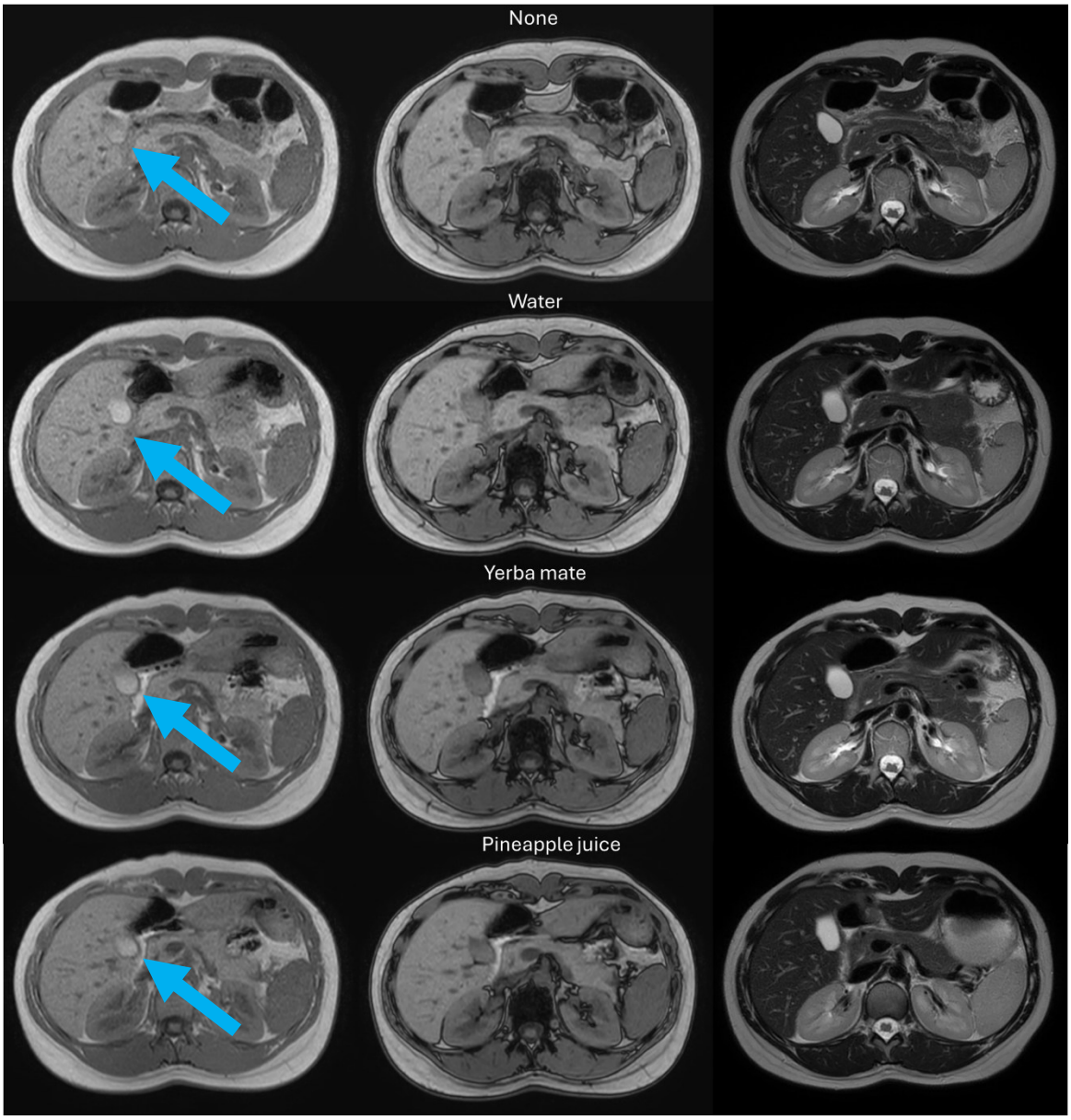


Table 22 Median [IQR] or Likert scores for each assessment variable by NMOC and sequence type.
N=8. Scores ranged from 1 = Impossible to use, 2 = Poor quality, 3 = Satisfactory and 4 = Excellent. IQR = inter-quartile range.

Sequence	NMOC	Liver conspicuity	Stomach conspicuity	Duodenum conspicuity	Pancreas conspicuity	Bowel conspicuity	Artefact severity	Overall quality
T_1-weighted	None	4 [0.25]	3 [1.0]	3 [1.0]	3 [0.5]	3.5 [1.0]	3 [1.0]	3 [0.25]
	Water	4 [0.25]	3.5 [1.0]	3 [0.25]	3 [1.25]	4 [0.25]	4 [1.0]	3 [1.0]
	Pineapple	4 [0.0]	3 [1.0]	3 [0.5]	3 [1.5]	4 [1.0]	3 [1.25]	3 [1.0]
	Yerba-mate	4 [0.0]	4 [1.0]	4 [0.25]	3 [1.25]	4 [0.25]	3 [1.0]	3 [1.0]
T_2-weighted	None	4 [0.0]	4 [0.25]	4 [0.25]	3 [1.25]	4 [0.25]	4 [0.0]	4 [1.0]
	Water	4 [0.0]	4 [0.0]	4 [0.25]	4 [2.25]	4 [1.0]	4 [0.0]	4 [1.0]
	Pineapple	4 [0.0]	4 [0.0]	4 [0.25]	4 [1.0]	3.5 [1.0]	4 [0.0]	4 [0.25]
	Yerba-mate	4 [0.0]	4 [1.0]	3 [1.0]	3 [1.5]	4 [1.0]	4 [0.0]	4 [1.0]

Figure 25 Stacked bar charts showing the distribution of visual grading scores of overall image quality for T1- and T2-weighted MRI sequences across all participants (n = 8) for each NMOC condition (none, water, pineapple juice, yerba mate).
Scores were assigned on a 4-point Likert scale (1 = impossible to use, 2 = poor quality, 3 = satisfactory, 4 = excellent). Across all conditions and sequences, most images (62 / 64, 96.9%) were graded as ≥ 3, indicating at least satisfactory quality for radiotherapy contouring.

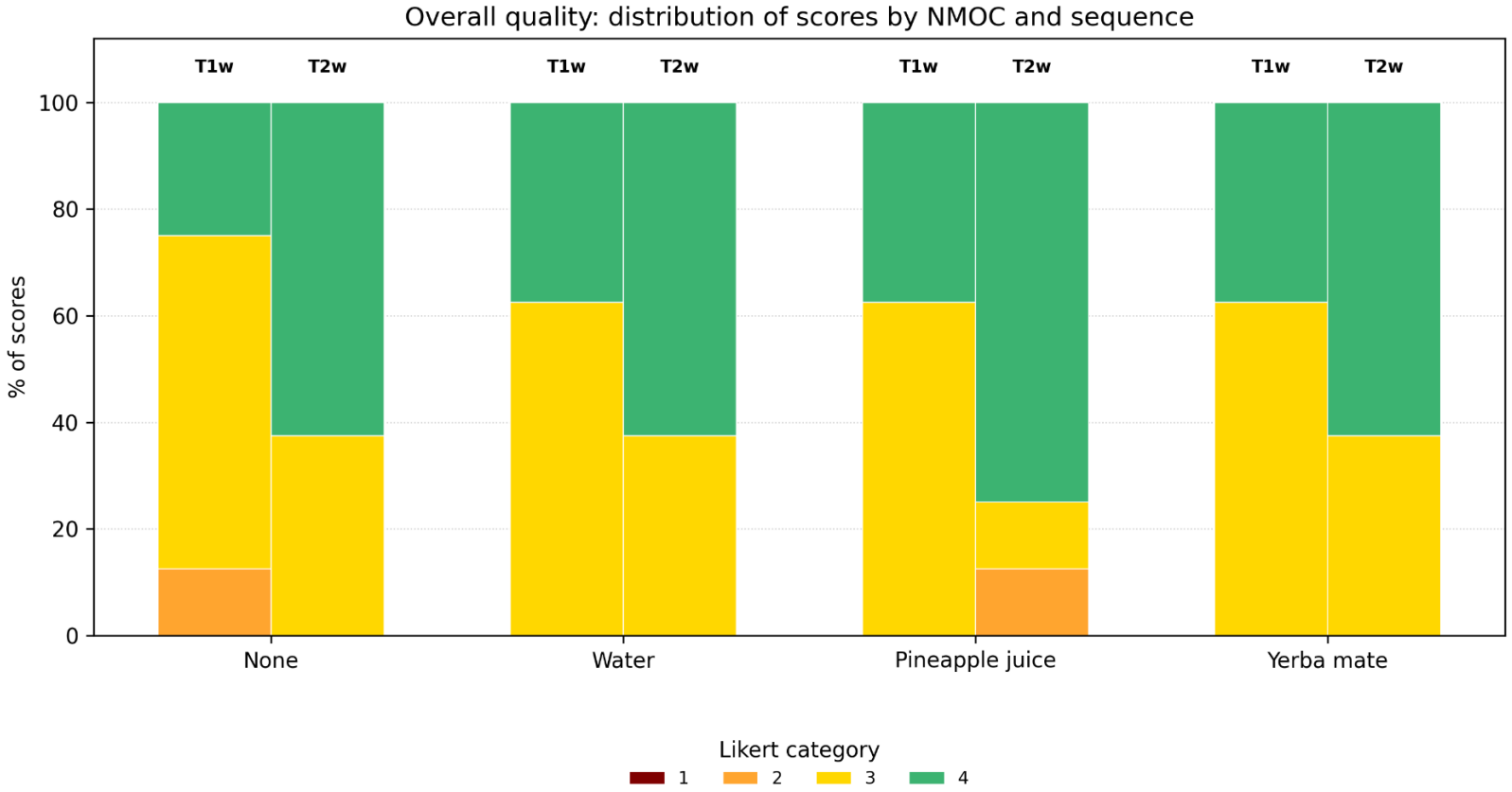


Figure 26 Stacked bar charts showing the distribution of visual grading scores for liver conspicuity on T1- and T2-weighted MRI sequences across all participants (n = 8) for each NMOC condition (none, water, pineapple juice, yerba mate).
Scores were assigned on a 4-point Likert scale (1 = impossible to use, 2 = poor quality, 3 = satisfactory, 4 = excellent). Liver conspicuity was at least satisfactory (≥ 3) across all NMOC interventions in both MR sequence weightings, with 8 / 64 being Likert 3, and 56 / 64 (87.5%) Likert 4.

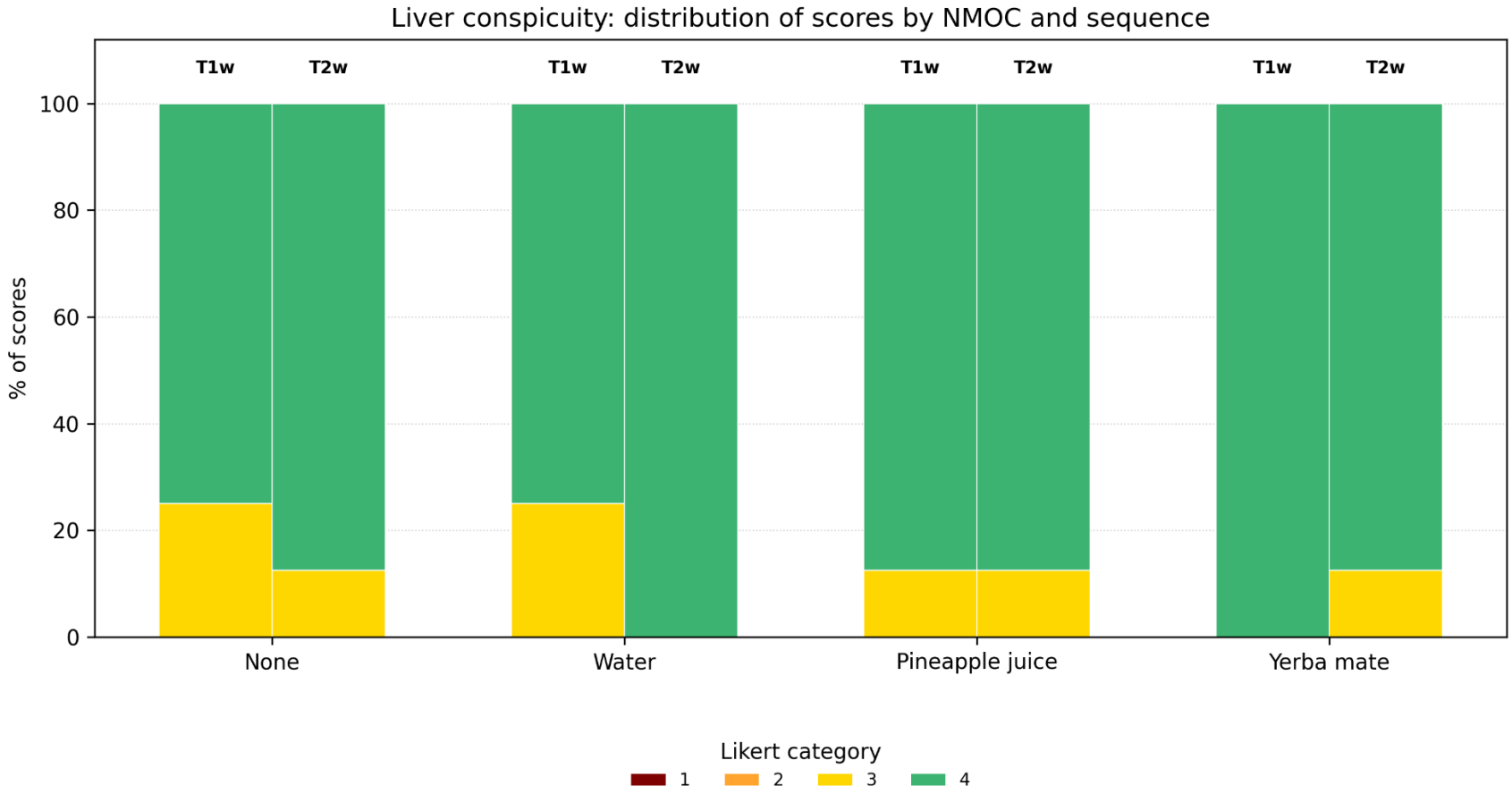


Figure 27 Stacked bar charts showing the distribution of visual grading scores for stomach conspicuity on T1- and T2-weighted MRI sequences across all participants (n = 8) for each NMOC condition (none, water, pineapple juice, yerba mate).
Scores were assigned on a 4-point Likert scale (1 = impossible to use, 2 = poor quality, 3 = satisfactory, 4 = excellent). Stomach conspicuity was rated ≥ 3 in 63 / 64 (98.4%) T1-weighted images and in all T2-weighted images. A greater proportion of T2-weighted images were scored as 4 (26 / 32, 81.3%) compared to T1-weighted images (15 / 32, 46.9%).

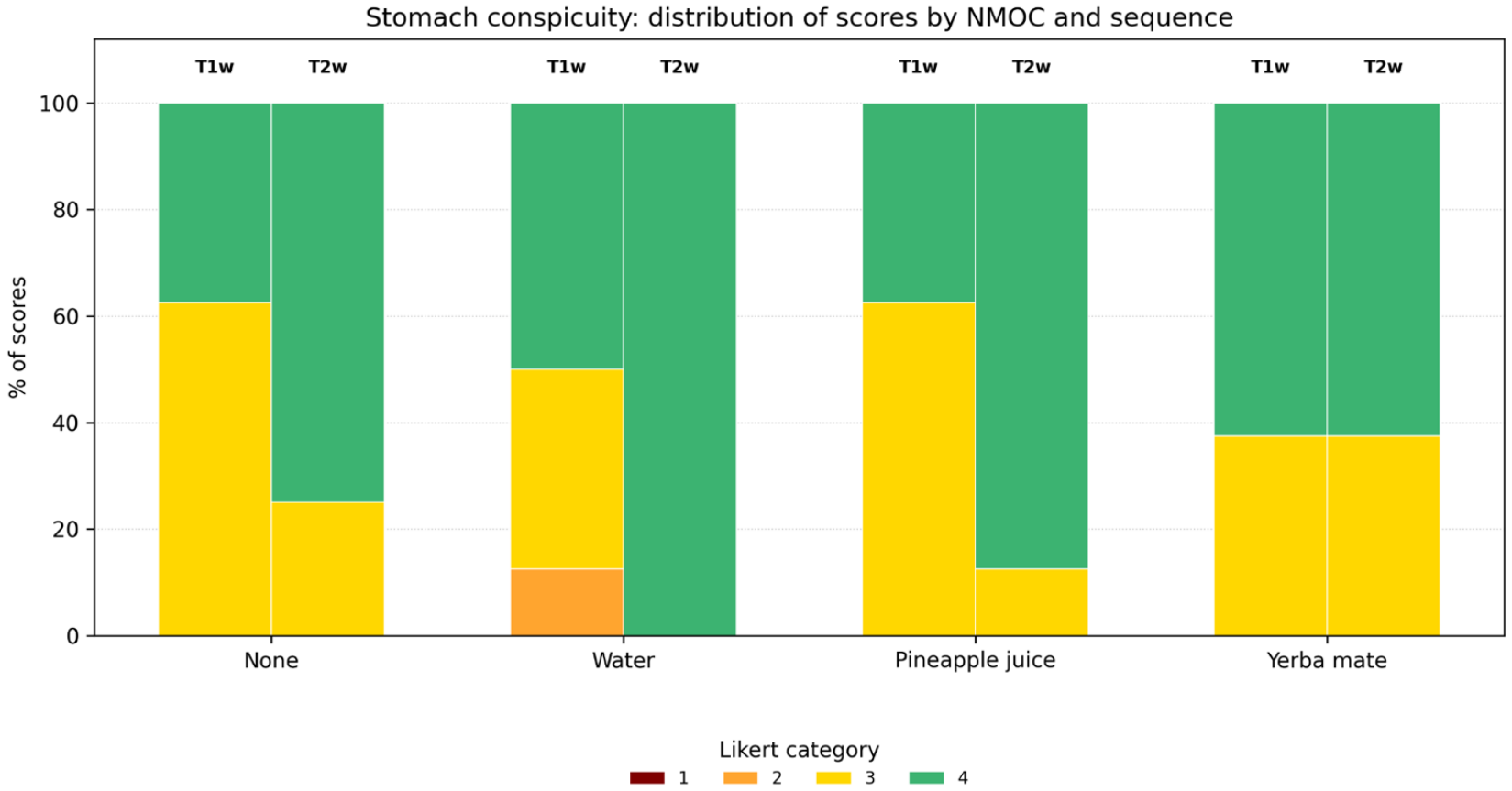


Figure 28 Stacked bar charts showing the distribution of visual grading scores for duodenal conspicuity on T1- and T2-weighted MRI sequences across all participants (n = 8) for each NMOC condition (none, water, pineapple juice, yerba mate).
Scores were assigned on a 4-point Likert scale (1 = impossible to use, 2 = poor quality, 3 = satisfactory, 4 = excellent). On T1-weighted imaging, duodenal conspicuity was rated ≥ 3 for all participants with yerba mate, whereas lower conspicuity scores were observed with the other NMOCs. This difference was less apparent on T2-weighted imaging, where conspicuity was more consistently rated as satisfactory or excellent across conditions.

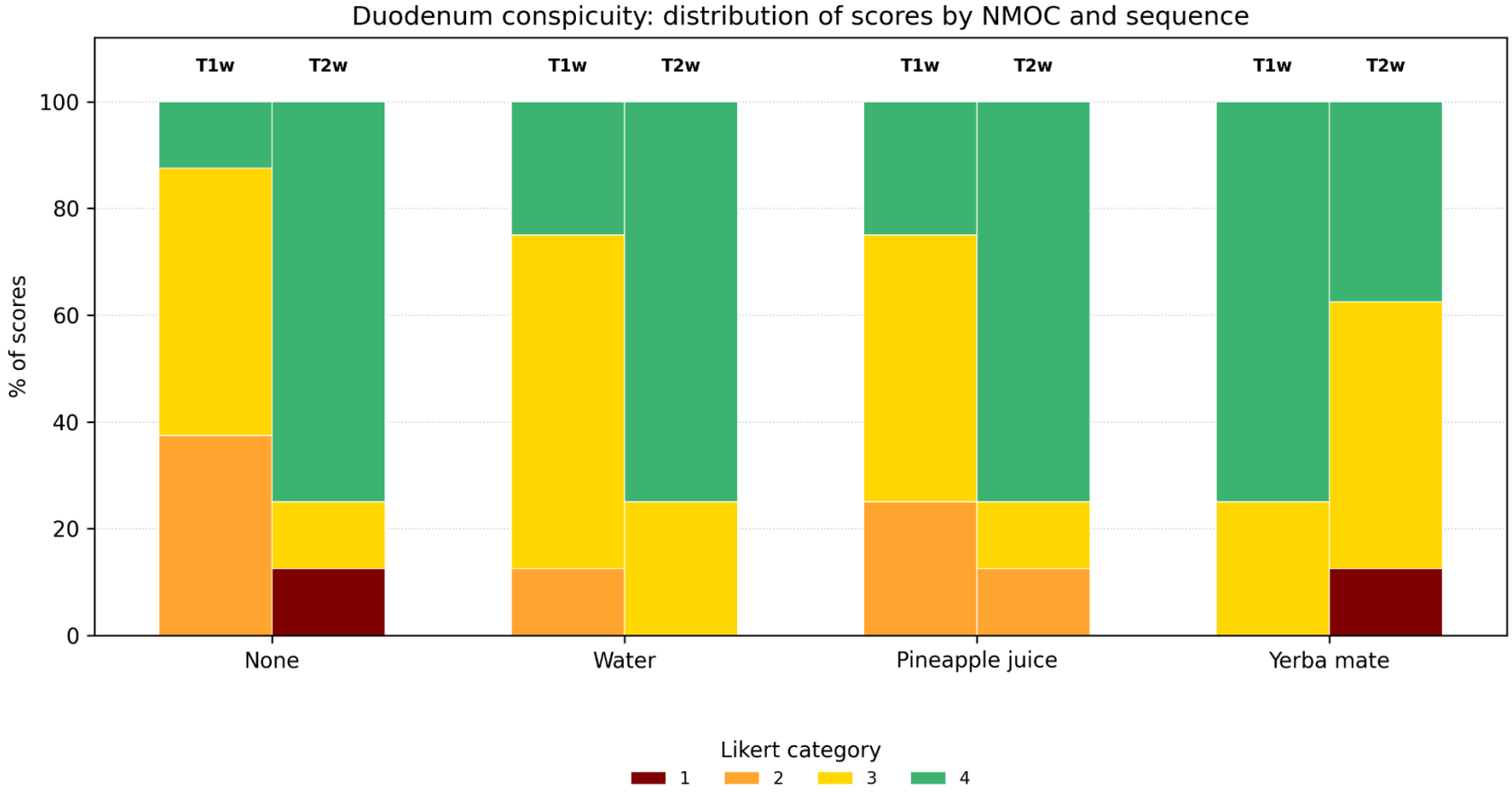


Figure 29 Stacked bar charts showing the distribution of visual grading scores for pancreatic conspicuity on T1- and T2-weighted MRI sequences across all participants (n = 8) for each NMOC condition (none, water, pineapple juice, yerba mate). Scores were assigned on a 4-point Likert scale (1 = impossible to use, 2 = poor quality, 3 = satisfactory, 4 = excellent). Compared to the liver, stomach, and duodenum, pancreatic conspicuity showed greater inter-participant variability, with a larger proportion of images rated ≤ 2 across all NMOC conditions.

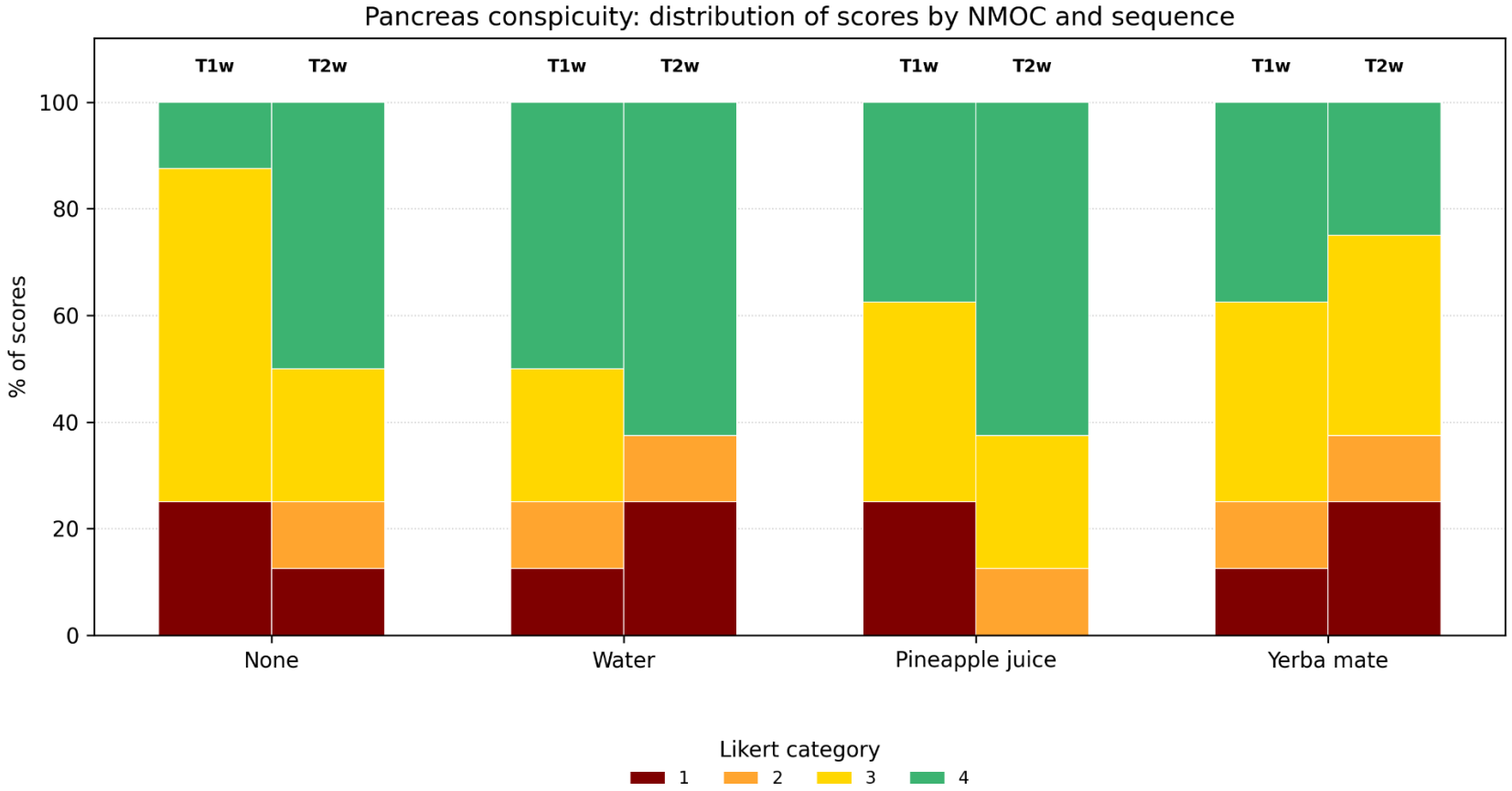


Figure 30 Stacked bar charts showing the distribution of visual grading scores for bowel conspicuity on T1- and T2-weighted MRI sequences across all participants (n = 8) for each NMOC condition (none, water, pineapple juice, yerba mate).
Scores were assigned on a 4-point Likert scale (1 = impossible to use, 2 = poor quality, 3 = satisfactory, 4 = excellent). Bowel loops were generally well visualised, with 21 / 32 (66%) of T1-weighted images and 20 / 32 (63%) of T2-weighted images rated as 4 (excellent). Across both sequences, 31 / 32 (97%) images were graded ≥ 3, indicating satisfactory or better conspicuity.

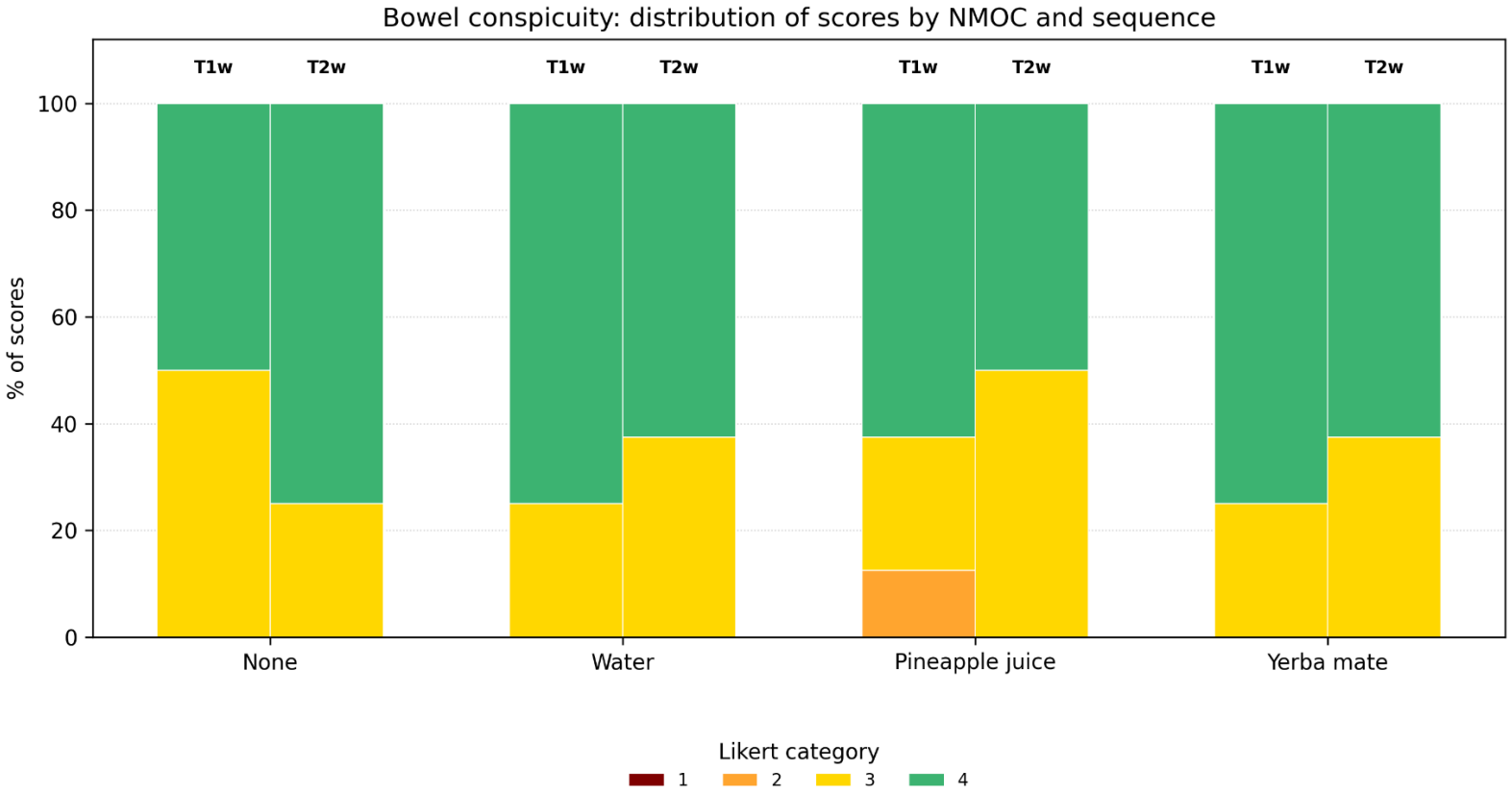


Figure 31 Stacked bar charts showing the distribution of visual grading scores for artefact severity on T1- and T2-weighted MRI sequences across all participants (n = 8) for each NMOC condition (none, water, pineapple juice, yerba mate).
Scores were assigned on a 4-point Likert scale (1 = severe artefact, 2 = moderate, 3 = mild, 4 = none). On T1-weighted imaging, a small proportion of images (4 / 32, 13%) were rated ≤2, but no consistent trend was observed between NMOCs. Artefact severity on T2-weighted imaging was minimal, with 31 / 32 (97%) images rated ≥ 3.

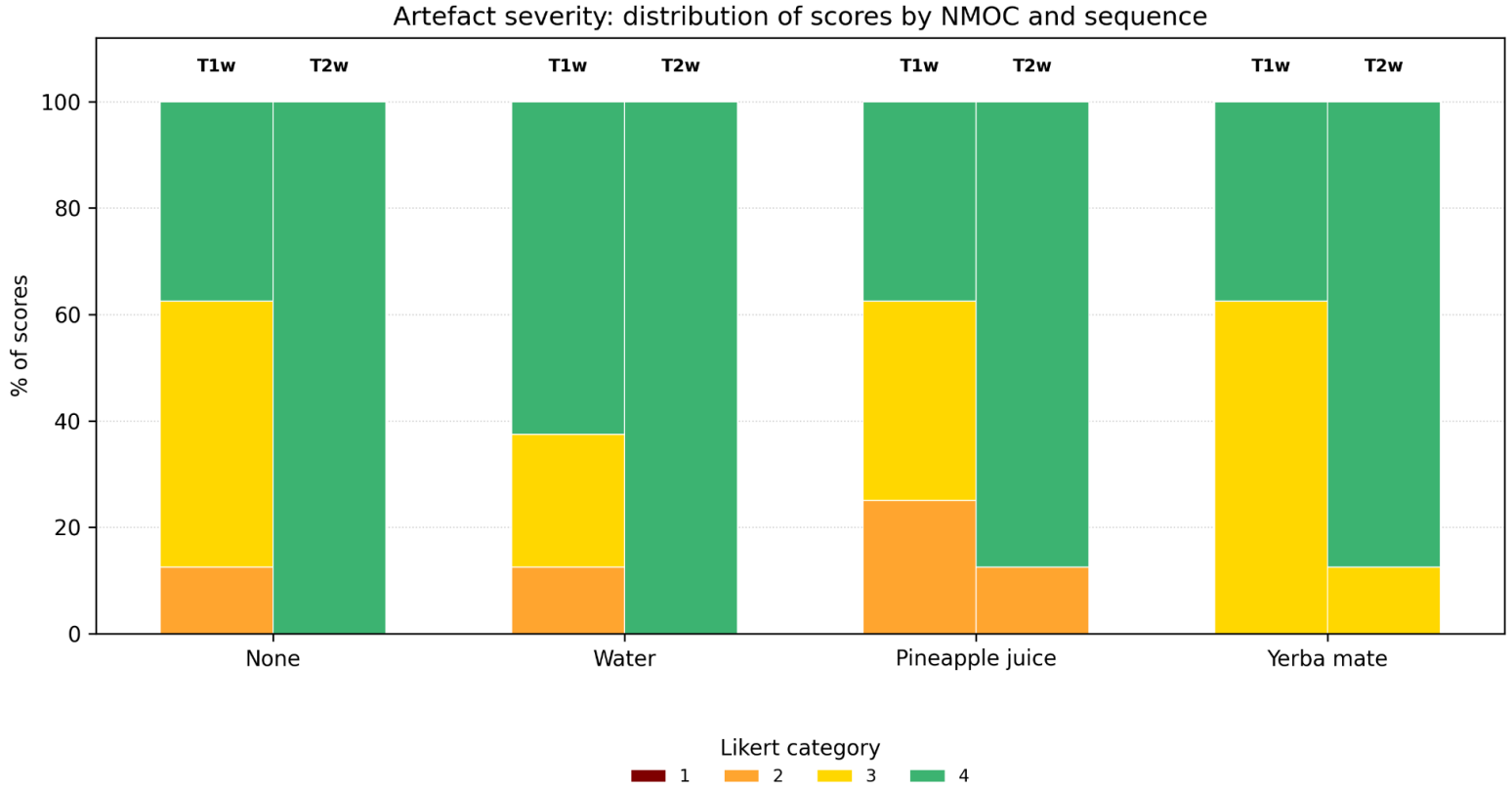


Table 23 T_1w NMOC medians vs None/control medians.
N = 8. The NMOC median Δ is the (NMOC median) – (None/control median). The effect size *r* and Wilcoxon *p* are shown only for the three

T_1w outcome metric	None/control median [IQR]	Water median Δ	*r*	*p*	Pineapple median Δ	*r*	*p*	Yerba-mate median Δ	*r*	*p*
Liver conspicuity	4.0 [0.25]	0	-	-	0	-	-	0	-	-
Stomach conspicuity	3.0 [1.0]	+0.5	0.00	1	0	0.00	1	**1**	-0.3	0.41
Duodenum conspicuity	3.0 [1.0]	0	-0.95	0.18	0	-0.5	0.32	**1**	**-0.9**	**0.023***
Pancreas conspicuity	3.0 [0.5]	**+0.5**	-0.91	**0.046***	0	-0.5	0.32	0	-0.6	0.26
Bowel conspicuity	3.5 [1.0]	+0.5	-0.95	0.16	+0.5	0.00	1	+0.5	-1	0.16
Artefact severity	3.0 [1.0]	+1.0	-0.46	0.32	0	-0.1	0.74	0	-0.3	0.56
Overall quality	3.0 [0.25]	0	-0.46	0.41	0	-0.3	0.48	0	-0.5	0.32

NMOCs. Bold numbers met the α = 0.10. A hyphen indicates the test was not calculated since there was no paired difference due to the scores being the same.

Table 24 T_2w NMOC medians vs None/control medians.
N = 8. The NMOC median Δ is the (NMOC median) – (None/control median). The effect size *r* and Wilcoxon *p* are shown only for the three NMOCs. Bold numbers met the α = 0.10. A hyphen indicates the test was not calculated since there was no paired difference due to the scores being the same.

T_2w outcome metric	None/control median IQR	Water median Δ	*r*	*p*	Pineapple median Δ	*r*	*p*	Yerba-mate median Δ	*r*	*p*
Liver conspicuity	4.0 [0.0]	0	-	-		0	1	0	0	1
Stomach conspicuity	4.0 [0.25]	0	0.95	0.16	0	-	-	0	-	-
Duodenum conspicuity	4.0 [0.25]	0	-	-	0	0.1	0.85	-1	0.5	0.18
Pancreas conspicuity	3.5 [1.25]	**0.5**	0.31	0.56	**0.5**	0.5	0.41	-0.5	0.4	0.28
Bowel conspicuity	4.0 [0.25]	0	-	-	-0.5	1	0.16	0	-	-
Artefact severity	4.0 [0.0]	0	-	-	0	-	-	0	-	-
Overall quality	4.0 [1.0]	0	-	-	0	0	1	0	0	1

Figure 32 Participant ratings of sensory and acceptability items for each NMOC. Stacked bars show the distribution of responses across a four-point Likert scale (1 = strongly disagree, 2 = disagree, 3 = agree, 4 = strongly agree). Items assessed were adequacy of prior information, texture, smell, taste, and absence of nausea. Each bar represents one NMOC condition (water, pineapple juice, yerba mate). Percentages are displayed along the x-axis, with total valid responses (n) indicated to the right of each bar. Higher Likert scores reflect greater acceptability. Overall, responses were predominantly positive (Likert 3 – 4). Water scored consistently high across all domains, pineapple juice showed greater variability for smell, and yerba mate had mixed ratings, particularly for smell.

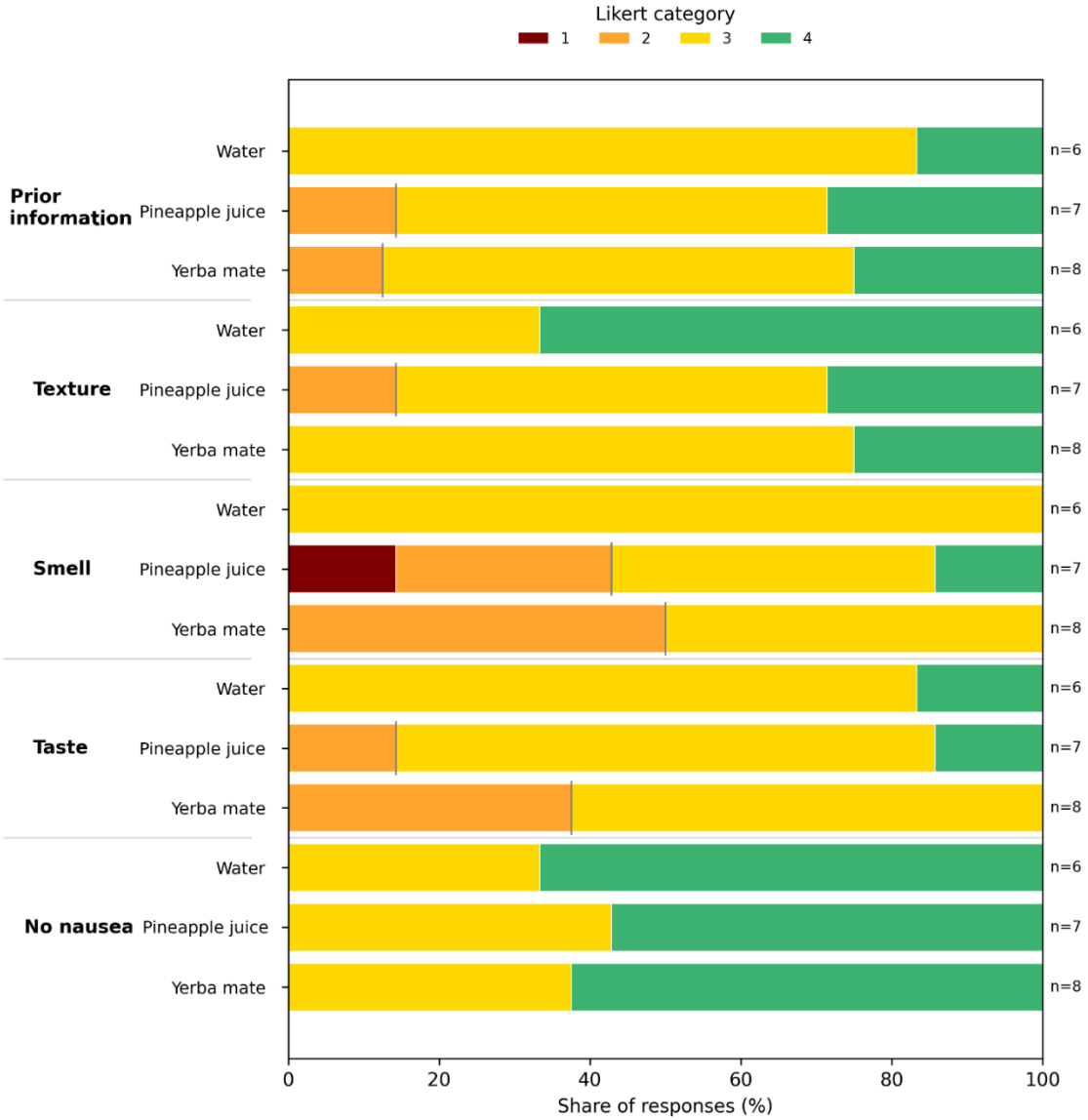


Table 25 Participant median [IQR] ratings for the five questionnaire items that met the content-validity threshold (I-CVI ≥0.80) on the four-point Likert scale.
1 = strongly disagree, 2 = disagree, 3 = agree, 4 = strongly agree). Note that negatively phrased items were reverse-scored so higher numbers consistently denote greater acceptability. The effective sample size for each cell ranged from 7 – 8 due to missing responses. Water achieved the highest texture score (4 [0.75]), whereas yerba-mate recorded the lowest score for its smell (2.5 [1]). All other medians were clustered at ≥ 3, indicating overall acceptability in those categories.

Contrast	Pineapple juice	Water	Yerba mate
Questionnaire item	**Median [IQR]**		
Nausea	4 [1]	4 [0.75]	4 [1]
Prior information	3 [0.5]	3 [0]	3 [0.25]
Smell	3 [1]	3 [0]	2.5 [1]
Taste	3 [0]	3 [0]	3 [1]
Texture	3 [0.5]	4 [0.75]	3 [0.25]

5.6 Discussion

5.6.1 Study overview and interim scope

This proof-of-concept study is the first to evaluate inexpensive and readily available NMOCs (yerba mate, pineapple juice, and water) for their impact on soft-tissue conspicuity in an MR-guided liver SABR planning context. The results from a small, healthy volunteer cohort, indicate a potential enhancement of duodenal conspicuity on T_1-weighted images with yerba mate, whilst water showed a possible benefit for improving visibility of the pancreas. All three NMOCs tested were well tolerated by the healthy volunteers, indicating that patients might find them acceptable. All tested NMOCs were commercially available non-medicinal products, supporting practical procurement. Pineapple juice is widely available in UK supermarkets, with an approximate retail cost at the time of writing of £0.47 per 200 mL carton serving. Yerba mate is less available, but was acquired via online or specialist retailers, typically supplied as tea bags or loose leaves prepared as an infusion. The estimated cost per 200 mL serving was approximately £0.15. Water was standard tap water and therefore had negligible consumable cost. These results support the potential of a simple intervention (NMOC ingestion prior to MR-planning) which could lead to improvements in delineation of OAR such as the duodenum and stomach in

liver SABR. Future work will evaluate if there is any change in inter-observer delineation agreement based on hand-drawn contours. However, at this stage, the following proof-of-concept outcomes data has been reported:

1. radiographer-rated conspicuity, artefact severity and overall image quality on T_1- and T_2-weighted sequences, and
2. participant-reported experience of each NMOC.

This data provides pragmatic but preliminary evidence to generate hypotheses and refine methodology for future clinical study rather than to definitively prove clinical benefit at this stage. Many uncertainties remain regarding the magnitude of benefit and its translation to patient outcomes. It does however support the continuation of recruitment and pursuit of the next stage of this research, a study in liver SABR patients, warranted to develop the intervention, and confirm the efficacy of NMOCs in a clinical setting in relation to whether their use can reduce contouring uncertainty and/or improve dosimetric sparing of OARs.

5.6.2 Interpretation of findings

The quantitative MRI screening measurements in phantoms confirmed that yerba mate and pineapple juice provided the shortest T_1/T_2 relaxation times at 1.5 T evaluated in this study. These relaxation properties led to their selection as the three NMOC interventions, along with a control condition, in which no NMOC was administered. Based on published guidance [98,368] and prior experience from the sequence development phase, 200 ml of each NMOC ingested 20 minutes prior to MRI was chosen as a pragmatic starting volume to observe proof-of-concept signal behaviour that also minimised the burden on participants. The study's MRI acquisition protocol was therefore locked in to acquire exploratory T_1- and T_2-weighted imaging as outlined in the MRI data acquisition and relaxometry methods section. Two NMOCs with the shortest measured T1 and T2, water as a T_1-weighted hypointense and T_2-weighted hyperintense comparator, and a no-NMOC condition as a control were carried forward into Step 2.

All the NMOC agents selected for study in this chapter were biphasic. Biphasic oral contrast agents are potentially important in this context because their signal intensity changes on T_1- and T_2-weighted imaging, appearing hyperintense on one and hypointense on the other. This dual behaviour offers flexibility in MR-

guided SABR planning, where both sequences could be used. By co-registering both T_1- and T_2-weighted image sequences, the GI lumen can be either accentuated or suppressed, possibly helping to define organ-at-risk boundaries more clearly and potentially reducing uncertainty in contouring. This was not explored in this chapter but should be evaluated in future work.

Although this study successfully recruited eight of the planned twelve participants, it is possible that continuing recruitment could change the trends observed. With a small crossover design, each additional volunteer contributes four full data points across all NMOC conditions, so the relative gain in power is not trivial. An expanded sample may reduce the wide interquartile ranges observed for some outcomes, clarify whether apparent trends (for example, yerba mate improving duodenal conspicuity on T_1w imaging) persist across a more heterogeneous group, and mitigate the risk of false positives from a small dataset. At the same time, all eight participants completed their scans successfully, and the fact that trends of consistent within-person effects across the NMOCs suggests that the broad patterns are unlikely to reverse with more participants. Instead, further recruitment would provide greater confidence around the effect size estimates and improve the precision of exploratory statistics, rather than fundamentally altering the direction of the findings. This sample should therefore be interpreted as hypothesis-generating rather than definitive, in keeping with the R-IDEAL stage of this work.

Overall, the baseline image quality without any NMOC was already high in many cases. This was expected, the study optimised protocol provided good soft-tissue contrast, particularly on T_2-weighted sequences, which can be inherently advantageous for depicting fluid-filled structures and soft tissue interfaces [157,380]. Median baseline scores for organ conspicuity on T_2-weighted images were ‘excellent’ (Likert = 4) for nearly all structures except the pancreas, which had slightly lower and more variable visibility.

Observers frequently noted that the stomach and proximal bowel/duodenum appeared well distended across the NMOC interventions, which may itself have aided differentiation from surrounding tissues. Because distension was not quantified volumetrically, it is currently difficult to determine whether observed improvements in conspicuity were due to the intrinsic signal properties of the NMOCs, the degree of luminal distension, or a combination of both. The T_1w

images, perhaps present more of an opportunity for an oral contrast to make a difference. The most prominent finding was with yerba mate on the T_1w sequence, which produced a median one-point delta improvement in duodenum conspicuity compared to the no-contrast control, and did so across most of the participants (Wilcoxon $p = 0.023$, effect size $r = 0.90$), suggestive of a trend despite the currently small sample. The descending duodenum, as depicted in Figure 23 often appeared hyperintense on the T_1w images, making it more obvious to distinguish from surrounding tissue (statistical results are shown in Figure 28 and Table 23). In terms of facilitating hypothesis generation, one could therefore consider proposing using a hyperintense contrast will help delineate the duodenum on MRI – a structure of high clinical importance in liver SABR due to its dose constraints if it lies near the tumour.

Yerba mate did not improve, but worsened, duodenal conspicuity on the T_2w image sequence in this preliminary dataset. This is likely a result of its effect rendering fluid hypointense on T_2w scans. The observers' median scores for the duodenal conspicuity on T_2w imaging were lower with yerba mate than without, but still mostly within the satisfactory to excellent range. Pineapple juice did not perform as poorly in terms of duodenal conspicuity on the T_2w image sequence. However, because the baseline T_2w images were already excellent for bowel visualisation, with this Likert scale, pineapple juice's effect might not have translated to a significant conspicuity change in this current sample. There was a potential negative trend in bowel conspicuity with pineapple on the T_2w sequence (median Δ -0.5, $p = 0.16$, Table 24), which could indicate that in some cases the juice's darkening of luminal fluid made the bowel wall less conspicuous against other dark structures. It is also plausible that the transit of fluids in some volunteers meant that by the time of T_2-weighted imaging, the pineapple juice had moved distally or been diluted, reducing its effect.

The pancreas is challenging to segment [120,128,155] and was included in the analysis. In T_1w images, water ingestion may improve pancreatic visibility, resulting in another nominally significant finding. Water led to a median pancreatic conspicuity score increase of +0.5 on T_1w images (from median 3.0 to 3.5) and achieved a Wilcoxon $p = 0.046$ ($r = 0.91$) in this small, incomplete sample. From comments recorded by the observers, some water scans demonstrated good distension of the duodenum that might have helped make

the pancreas more discernible. The potential benefit from water on pancreatic conspicuity was, however, inconsistent across participants (and overall resulted in a currently non-significant trend), and more data would be needed to determine its effect and reliability. MRI used for target volume delineation in pancreatic cancer has been shown to reduce interobserver variation and result in smaller target volumes [381,382]. If this signal of improved conspicuity is confirmed with further research, this study may have additional utility in being translated further into the context of pancreatic SABR.

Apart from the duodenum and potentially the pancreas, no other differences in conspicuity of other metrics with these NMOCs were observed. Liver conspicuity was unchanged. Stomach conspicuity was not consistently improved with any NMOC. The 20-minute transit time did not allow sufficient time for the NMOCs to reach more of the small bowel, but bowel loops in general were well visualised, in particular on T_2w imaging (Figure 30). In the case of pineapple juice on T_2w imaging, the scoring system may therefore have lacked sufficient range. With baseline Buscopan-optimised sequences already providing images adequate for contouring, the metric may not have been sensitive enough to detect further incremental improvements in conspicuity.

None of the tested NMOCs appear to show an association with image artefacts, with median artefact severity scores in the satisfactory to excellent range across conditions. The median scores were however lower on T_1w imaging compared to T_2w, but with no differences between the NMOCs. This indicates that introducing the NMOCs did not adversely affect the MR sequences and is consistent with the findings of previous studies relating to pineapple juice [248,276].

In addition to the imaging results, no adverse effects from NMOC ingestion were observed or reported. Participant feedback was collected using questionnaires to assess NMOC acceptability. Although the questionnaire was effectively a pilot measure (with a currently limited sample), it has provided insight into the practical demands of asking patients to ingest NMOCs. A content validity index approach was used to retain five key items that were deemed most relevant and had good expert agreement (I-CVI ≥ 0.80) from the 12 sensory-experience questions comprised the original questionnaire developed with patient and public involvement. These covered: (1) adequacy of

information given beforehand, (2) nausea, (3) taste, (4) texture, and (5) smell of the contrast. Despite 15 missing responses across all forms (some participants skipped certain items without providing a reason, 105 item responses were obtained in total.

As shown in Table 25, with the exception of the smell of the NMOCs, the median responses all scored above Likert 3 (‘agree’) or 4 (‘strongly agree’) (once reverse scoring had been applied to negatively phrased questions). The raw data showed 91% (229 / 251) responses were in the positive Likert 3 – 4 range across all domains. Reinforcing the lack of reported adverse effects from consuming the NMOCs, no volunteer reported nausea from any NMOC. This is consistent with most studies that simply report NMOCs are well tolerated [213,248,275,276], and is reassuring for the potential of yerba mate, since no data on its acceptability in this context has been published to date.

In terms of taste, water received uniformly good taste and texture scores (median Likert = 3), with the narrowest variability in acceptability scores (IQR 0 – 1). Pineapple juice also was largely positive (median taste Likert = 3, IQR = 0), but three participants rated it negatively on smell, and one strongly so. Yerba mate, a drink less familiar to the participants, was the least favoured in terms of smell. Its median smell rating was 2.5 (between ‘disagree’ and ‘agree’ on liking the smell), with half of all participants indicating some level of dislike (Likert = 2). Yerba mate’s median taste Likert score was 3, with average agreement representing that participants liked the taste, and its texture was also Likert = 3. Like the pineapple juice, this suggests that whilst its aroma was off-putting to some, the overall drinking experience was acceptable. The interquartile ranges reflect the variability in acceptability responses, and yerba mate had slightly wider variability than pineapple juice, indicating personal taste differences. This could potentially be mitigated by adjusting the preparation, but further research is required to confirm the signal characteristics are not adversely affected by doing so.

One volunteer indicated additional information before consuming the pineapple juice and yerba mate would have been preferred, though they did not specify what details were lacking. Given the high content validity score of this question, the findings suggest that providing comprehensive information, including the

purpose and characteristics such as yerba mate's tea-like bitter taste and smell or pineapple juice's aroma could better inform participants and patients.

These results should, however, be interpreted cautiously; given the exploratory nature of our analysis with multiple endpoints, the *p*-values presented do not account for multiple-testing and could therefore represent a false-positive statistical correlation. For the purpose of transparency, if applying a post-hoc Holm correction for the comparisons on each sequence, the water-pancreas finding no longer meets the large $\alpha = 0.10$ threshold (adjusted $p = 0.14$). Only the yerba mate versus control effect of duodenal conspicuity on T_1w sequences remains below 0.10 after adjustment, but still with a non-significant *p* value of 0.069 in the current sample. Thus, any statistically significant differences presented within these results should be treated as hypothesis-generating rather than conclusive evidence.

5.6.3 Strengths and limitations

A key strength was conducting this investigation within the structured R-IDEAL framework for radiotherapy innovations as a development and early exploration stage study, a systematic progression from background research to an in vivo study [202]. Relaxometry and protocol optimisation was conducted first. Following the selection of NMOC interventions, a first-in-human feasibility study in healthy volunteers was completed, and in line with Stage 1 of the R-IDEAL framework to check imaging effects and acceptability. The next step is to move along the R-IDEAL pathway into patient cohorts to optimise NMOC volume, timing and preparation, then into multi-centre cohorts, followed by comparative assessment. It helped avoid premature testing in healthy volunteers or patients without validating prior research findings and meant evidence from phantoms and the literature regarding the safety and MRI effect was available before any scanning was performed in humans.

Another strength was that each volunteer served as their own control, undergoing all four contrast conditions in a randomised, within-subject crossover design, which can mitigate against inter-individual variability [375,383-385]. Anatomical differences could confound the results, and that is potentially seen within these results in the case of participant M202, whose pancreas was not visible on T_1w imaging under any NMOC condition. The

paired statistical analysis benefits from increased power to an unpaired design and within-person changes were detectable across the NMOC interventions. Additionally, the design eliminated selection bias concerns since every participant contributed to every intervention. Care was taken to avoid any remaining effects of previously administered NMOC by ensuring the GI tract would be cleared of the previous NMOC intervention by scheduling the scans at least 24 hours apart. Participants were also asked to fast for a minimum of four hours prior to scanning and utilised IV Buscopan to limit motion which could have led to confounding motion artefacts [375,386].

Blinded image evaluation with two observers was a further strength. Consensus scores for conspicuity were used to provide some clinical context. By comparison, Nestle et al. (2006) primarily reported signal intensity measurements and a qualitative description of mate's effect [181] without blinded multiple observer evaluation. Our approach provided more quantitative and clinically interpretable data with regards to conspicuity for the purpose of contouring rather than simply stating the signal intensity has increased or decreased.

Despite these strengths, this study has important limitations. First and foremost, this was a proof-of-concept study with a limited sample size of healthy volunteers. The study did not reach aimed accrual (n = 8 / 12) and further research is required to evaluate not just GI conspicuity, but perhaps the more relevant impact of NMOCs on OAR contouring reproducibility across observers by calculating Dice similarity coefficient differences [372]. The sample is unlikely to capture the variability that might be observed in a broader patient population who have cancer with or without additional co-morbidity. The statistical power to detect differences is therefore limited, and there is a possibility of type II error (missing a real but limited effect) for some comparisons. Conversely, the multiple endpoints and lack of adjustment in the initial analysis means there is also a risk of type I errors (false positives). This was partly addressed by using an exploratory significance level ($\alpha = 0.10$), but to demonstrate the potential attenuation, although not pre-specified, a post-hoc Holm correction results in none of the comparisons meeting a conventional 0.05 *p* value threshold, and only the yerba mate effect of duodenal conspicuity on T_1w remained under an α of 0.10.

In addition, patients who require liver SABR may differ in several ways from the healthy volunteers studied. As highlighted in Chapter 1, they are likely to be older, may have compromised liver function or ascites, could have prior abdominal surgeries (adhesions or altered anatomy), and might suffer conditions like diabetes that affect gastric emptying. It is also likely that biological variability in gastric emptying and GI transit amongst the participants affected the observable impact on bowel and pancreas visibility. Despite instructing a four-hour fasting time, and a wait of 20 minutes following NMOC consumption prior to administration of Buscopan and commencement of imaging, it was noted that some had less fluid present in the stomach than others (as well as occasional food remnants). Distension volumes were not quantified, but could be through actual delineation and volume calculation, and integrated into statistical analysis, potentially with a larger sample. Individual differences in GI motility and differential absorption of NMOCs are an important consideration going forward [387]. This could be extremely important in patients. Absorption rates are known to differ in patients who have diabetes and associated gastroparesis [388] so this could be an area requiring further investigation for protocol optimisation. Obtaining additional imaging sequences, perhaps a series of scout scans to track fluid distribution following consumption to observe motility and standardise anatomical structure volumes could yield more reproducible and informative results to guide development of future research (and clinical) NMOC protocols. Prior enterography research has indicated that achieving uniform bowel distension using oral contrast agents is challenging, and larger volumes, potentially split over a longer time and/or use of alternative medicinal agents (something purposefully avoided in this study) are often used for that reason [248,275,276]. In addition, since the participants were recruited from a pool of staff and students, it should be acknowledged that they may have possessed further information than what was provided in the participant information sheet and verbal discussions at recruitment, which could have skewed the results regarding the adequacy of information. Since the findings from healthy volunteers might not translate directly to liver SABR patients, these healthy volunteer results should therefore be treated as predicate evidence to suggest further patient evaluation is required rather than any claim of clinical effectiveness.

In terms of technical limitations, the current imaging protocol may have impacted results. A relatively thick (5 mm) slice for MRI sequences was used to ensure adequate signal to noise ratio and reasonable scan times under breath-hold in this exploratory setting. In radiotherapy planning, thinner slices (≤ 2 mm) are often requested to facilitate image co-registration with radiotherapy planning CT. With such compromised sequence parameters, it is possible certain subtle differences could be more evident on higher resolution imaging. This will, however, be addressed in a future clinical cohort.

Another limitation is the lack of an objective standard for comparison in terms of organ visibility. This study has thus far relied on subjective scoring relative to what the observers deemed was satisfactory for contouring and could vary by observer experience. Due to its exploratory nature, no dosimetric or outcome improvement by using NMOCs has been investigated. Segmentation errors are well recognised as one of the largest sources of geometric uncertainty in radiotherapy [389] and can introduce more uncertainty than patient setup or motion in some cases [390]. In the context of liver SABR, variation in image segmentation can distort dose-volume and potentially outcome relationships for the liver and nearby organs [391]. The onus is therefore on subsequent research to explore whether potential organ conspicuity benefits are associated with improved segmentation.

5.7 Conclusion

This proof-of-concept study suggested improved conspicuity of abdominal structures using NMOCs for the purpose of MR-guided liver radiotherapy planning. The next steps, as outlined in the final chapter, is to incorporate more relevant contour comparison metrics such as the Dice similarity coefficient [372] as the primary outcome metric for analysis and comparison of uncertainties in volume delineation and begin subsequent R-IDEAL stage evaluation in a patient cohort.

Chapter 6 synthesises the technical and experiential findings across this thesis to define the next steps, clinically meaningful outcome metrics and provide a pathway to clinical implementation for evaluating NMOCs and personalised motion management in liver SABR patients.

Chapter 6 Discussion: major findings, limitations and future developments

6.1 Synopsis

This thesis set out to improve MR-guided liver SABR by addressing three interrelated concepts: anatomical uncertainty in MRI, abdominal organ motion, and the patient experience. In line with the problems outlined in Chapter 1, two technical barriers were prioritised:

i. distinguishing soft-tissue boundaries on planning MRI and
ii. uncertainty caused by motion.

A third, and previously unexamined dimension – patients' experiences with liver SABR procedures, was investigated to identify potential areas of the liver SABR pathway for improvement.

Pandemic-related delays to MR-sim installation constrained the scope of MRI work. The MICROCHIPS study was prospectively framed within the adopted R-IDEAL framework [202] introduced in Chapter 1 (Figure 5). 'Pre-clinical' elements were already established by preceding diagnostic radiology studies, so this thesis began at R-IDEAL Stage 1 (the idea stage, demonstrating the proof-of-concept). Chapter 2 provided the diagnostic evidence, whilst also establishing the lack of research in therapeutic radiography, Chapters 3 and 4 reported baseline motion and patient experience, and Chapter 5 presented the first proof-of-concept study of selected NMOCs. Together, these data represent the predicate evidence to inform subsequent R-IDEAL Stage 2 development studies, despite the reduced MRI component originally anticipated.

Within this framework, the thesis has achieved the following objectives:

1. mapped the evidence for non-medicinal oral contrast agents (NMOCs) for abdominal MRI,
2. quantified how much abdominal compression reduces liver excursion
3. captured patient perspectives on immobilisation, breath-hold and communication, and
4. provided proof-of-concept data demonstrating the potential feasibility of candidate biphasic NMOCs to improve conspicuity of upper-GI structures relevant to liver planning whilst being well tolerated.

Methodologically, this thesis is a multi-methods programme of research. The studies were sequenced using the R-IDEAL framework to generate predicate evidence for a complex intervention in MR-guided liver SABR. Evidence synthesis in Chapter 2 identified candidate NMOCs and importantly defined a translational gap. A local quantitative evaluation in Chapter 3 established motion benchmarks and heterogeneity in compression response and supporting the need to consider further personalisation. Qualitative interviews in Chapter 4 added the patient-centred lens of the patient by establishing where communication and comfort can conflict with breath-hold and immobilisation, and what might undermine compliance or deliverability. Together, these components informed Chapter 5 which has established the proof-of-concept that NMOCs may have potential benefit that is tolerable in healthy volunteers. Chapter 6 synthesises these findings to integrate the technical and experiential findings to justify the next steps and implementation priorities.

The studies included within this thesis ultimately provide preliminary support for exploration of more personalised modifications to MR-protocols and motion-management workflows. Specifically, they indicate a potentially measurable gain in duodenal visibility with selected NMOCs on planning-relevant (T_1w) sequences; clinically meaningful but heterogeneous motion reduction with abdominal compression, with a sub-group deriving little benefit when compared to an uncompressed cohort; and communication and comfort factors that, with relatively minor modifications, could improve the experience for future liver SABR patients and potentially modulate compliance and, by extension, geometric accuracy. The remainder of this chapter presents an overview of the contents of each subsequent chapter, summarises the key findings, discusses the limitations of the thesis, outlines future directions within the R-IDEAL framework, and provides the overall conclusions.

6.2 Overview of each chapter

Chapter 1 defined the clinical problems and provided a foundation of knowledge regarding potential methods that had previously been used to investigate motion and tissue visualisation, highlighting the unrealised potential of MRI in the context of liver SABR. Chapter 2 mapped uses of 31 distinct NMOCs from 47 studies, none of which had assessed utility in radiotherapy, and postulated that there was novel potential of biphasic juices and lesser-known teas as a

promising but untested hypothesis to improve visualisation of MRI in liver SABR (and possibly other) radiotherapy contexts [161]. Chapter 3 evaluated 134 consecutive liver SABR patient treatments and established that a compression arch which was found to be incompatible with new MRI equipment limited liver SI motion by a median of 4.4 mm compared with the uncompressed cohort. However, a large proportion of the compressed cohort had >5 mm SI excursion. Chapter 4 investigated the patient perspective. In total, ten patient narratives were included. Patients described how unclear terminology was frequently used by therapeutic radiographers, how the compression arch and process of waiting for the next steps in their treatment journey can generate anxiety even though trust in staff was high. Chapter 5 provided data from an explorative proof-of-concept study: in vitro phantom relaxometry and a subsequent in vivo healthy volunteer crossover study that showed that yerba mate and pineapple juice produced the expected T_1-hyperintense / T_2-hypointense signals, with yerba mate potentially improving duodenal conspicuity by one Likert grade. In addition, all agents (yerba mate, pineapple juice and water) were well-tolerated and accepted. Finally, the present chapter distils these findings and, together with the MICROCHIPS protocol, lays out the plans for further research.

From this thesis, three over-arching insights emerge. Firstly, readily available biphasic NMOC fluids can either accentuate or suppress the luminal signal of the gastrointestinal tract on standard 1.5T MRI, thereby enhancing anatomical borders to aid delineation for the planning of liver SABR. This is a novel area of research not previously investigated in the context of liver SABR. Secondly, abdominal compression (using a rigid compression arch) helps reduce motion but is inconsistent. More patient-specific application in the clinic is therefore recommended. Alternative devices such as compression belts could be compared using the same methods. Thirdly, this thesis, in attaining the first account from the perspective of liver SABR patients, suggests that clearer explanations of procedures, investigation of patient-centred option-based motion management choices and providing more attention to comfort could aid whether technical protocols succeed in routine clinical practice and warrants further research. Methodologically, this thesis has therefore begun to demonstrate a systematic approach that links theory, healthy-volunteer imaging and blinded radiographer scoring with the conception of patient-reported

acceptability metrics for NMOCs, and this approach can continue into future translational studies.

Several important gaps remain. Only proof-of-concept data on NMOC utility for liver SABR organ at risk (OAR) conspicuity has so far been obtained. A new potentially more inclusive compression belt system requires to be compared against the benchmark data now acquired from Chapter 3. Data from MICROCHIPS, using this belt, is currently being acquired and could be compared against voluntary breath-hold methods to determine if motion control may be individualised further as opposed to imposing a one-size fits all approach. Patient data, not just that so far seen in healthy volunteers are required to demonstrate whether or not NMOC-enhanced contours are reproducible. Broader demographic recruitment, including a representative sample of the current patient cohort that includes patients with multiple lesion types and co-morbidities, as well as a formal assessment of intravenously administered Buscopan (currently not used in the clinical protocol) have not been tested and multi-centre validation is required to confirm generalisability of motion ranges, NMOC effectiveness and patient narratives. Furthermore, the cost-utility of adding NMOCs via fluid preparation, staff training and the additional sequences potentially necessary is unknown. These areas require further research to quantify if there is a justifiable return in planning accuracy and patient experience.

6.3 Major findings

6.3.1 Mapping of non-medicinal oral contrast agents for MRI

The scoping review in Chapter 2 is the first systematic mapping of NMOCs identified 31 distinct agents. The scoping review summarised which NMOCs have been evaluated and established that a gap exists for use of NMOCs in the liver SABR context. Most studies pursued a single aim of improving tissue visualisation while a minority utilised these readily available and well-tolerated agents to investigate motility. Three agents dominated the literature: water – cheap and universally available – featured in 27 studies, and behaves as a hypointense T_1, but hyperintense T_2 medium. Pineapple and blueberry juices followed as the second and third most frequently researched NMOCs. Both fruit juices are naturally rich in manganese and therefore biphasic, showing a

hyperintense signal on T_1-weighted sequences and hypointense signal on T_2. By contrast, some candidate NMOCs, such as açaí juice and teas, were evaluated far less frequently. Despite the importance of the relaxation properties of these agents, only nine studies quantified T_1 or T_2 values. Yerba-mate tea, which was only evaluated in a single exploratory study in 2006, had the shortest T_1 (~155 ms) with more specific T_2 relaxation data not reported, whereas water exhibited the longest T_1/T_2 pair (~4100 / 2040 ms). Most authors of NMOC studies have resorted to subjective, or erroneously termed them, 'qualitative', descriptors [241,251,276]. This approach, however, precluded cross-study comparison due to heterogeneity of methods and scoring systems. Almost three-quarters of studies reviewed used uncontrolled before-after designs; just over half enrolled only healthy volunteers; and fewer than one-third recruited patient-only cohorts. Acquisition protocol details varied widely, with breath-holds like those used for radiotherapy MR-acquisition being reported in fewer than half of papers, whilst fasting requirements ranged widely from none to 12 hours. Patient-centred outcomes were noticeably limited. Half of all studies failed to report any participant experience, and of the ten that used questionnaires, only one deployed a validated instrument. Preparation regimens were inconsistent: volumes spanned 100 – 2000 ml, and ingestion timing ranges from immediately before scans commenced to three-hours pre-scan, and some protocols added antispasmodics. Consequently, tolerability, palatability and practical workflow effects of standardised regimens remain largely unquantified. From a radiotherapy perspective, no empirical study had assessed NMOCs within an MR-guided radiotherapy workflow. Occasional narrative reviews have suggested water could be used for organ delineation, but these citations lack primary data, which signals a clear opportunity for exploring biphasic agents further on MRI, as Chapter 5 have begun to explore.

6.3.2 Motion-management and patient experience research

In Chapter 3, the largest single-centre evaluation to date, the liver motion of 134 consecutive liver-SABR patients was retrospectively analysed to establish a robust baseline for future motion-management studies. Of these, 104 patients were treated with a rigid ONEBridge abdominal-compression arch, whilst 30 received no compression. A novel method of extracting motion from routinely acquired clinical radiotherapy datasets was developed for this study which could

be expanded to compare immobilisation techniques across multiple centre cohorts: respiratory motion was obtained from paired inhale/exhale 4DCT datasets by tracking liver-surface centroids in the LR, AP and SI axes, and by calculating a 3D Hausdorff distance to capture worst-case excursion.

In line with previous research, abdominal compression delivered its largest benefit along the SI axis: median displacement fell by 4.4 mm, and, after covariate adjustment, uncompressed livers moved 58% more than those in compressed patients (Exp B = 1.58, p = <0.01). A small raw reduction in AP motion (1.5 mm) lost significance once potential covariates were controlled, and LR motion remained unchanged. Using Hausdorff distance as an adapted 3D metric to represent overall liver motion, compression achieved a non-significant 2 mm (12%) reduction in worst-case motion (median = 23 mm to 21 mm, p = 0.064). This study validates the findings of smaller studies that used various methods to measure the motion reduction of abdominal compression plates [110,135,139,292] or compression belts [136-138]. By contrast, the compression belt study of Van Gelder et al. (2018) reported a negligible difference in SI motion and slight increase in AP motion [134].

Sex appeared to influence how much motion remained after mitigation: female patients showed a 14% lower Hausdorff distance than males, regardless of whether or not compression was used (Exp B = 0.86, p = 0.022). Surrogates for body habitus measures showed no predictive value in residual excursion. Neither anterior–posterior body diameter nor total fat fraction predicted residual excursion in our cohort, echoing some previous reports whilst contradicting others. Across the literature only three studies have investigated anatomy-related predictors of compression success [135,136,138] and their conclusions diverge. The largest study of 99 patients hypothesised that patients with a high body-mass index (BMI) would respond less to abdominal compression as the compression force could be absorbed by adipose tissue. Indeed, the study found that abdominal compression was significantly less likely to succeed in overweight patients and men [135]. Patients with a BMI ≥25 had a higher chance of residual motion >5 mm. Conversely, other studies in smaller cohorts, using different analytic methods found no clear link between BMI or body shape and compression efficacy [136,138]. Notably, a subset of patients gained little or fared worse with compression compared to those in the

uncompressed group, echoing findings from previous, smaller studies [110,134,136,137,139]. Some authors have acknowledged this effect previously, consequently recommending the evaluation of respiratory motion strategies on a per patient and/or local population basis rather than relying on data in the literature [134,137]. If the results of this thesis and the mixed findings of other published series studies are taken together, perhaps the need for personalised verification, rather than reliance on simple anthropometric cut-offs, is reinforced. This study does not refute that abdominal compression is not a useful tool to reduce motion and treatment margins [89,110,135], but its use could be personalised to avoid unnecessary application where it is ineffective and to route non-responders to alternative workflows. Alternative abdominal compression belts might differ in effectiveness and could be more inclusive of larger body types, owing to having fewer physical constraints that can conflict with medical equipment such as bore size and MRI coil placement. A basic radiological assessment, such as use of simple MR cine image sequences may help determine whether abdominal compression is beneficial for each patient in the clinic. This cohort and motion data resulting from this study now serves as a benchmark for an MR-compatible belt that has been selected for clinical practice in the host institution and for the subsequent breath-hold comparison study within the following stages of the MICROCHIPS study.

Complementing this quantitative study, a qualitative study explored how patients experience liver SABR in Chapter 4. From interviewing ten consecutive patients with either primary hepatocellular carcinoma or liver oligometastatic disease in a single UK radiotherapy centre, three themes emerged from their narratives: i) communication; ii) discomfort; and iii) coping and support.

Several aspects of the treatment process confused or unsettled participants. Appointment letters referring to pre-treatment scans meant little to lay readers. ‘Review’ appointments turned out to be routine blood tests rather than clinical discussion where patients pre-emptively had worried that they might be discussing their response to treatment. Timelines for post-SABR follow-up and subsequent discussions pertaining to their outcomes were vague. Such ambiguities caused anxiety even in otherwise stoic patients, suggesting that plainer language and additional briefings could address concerns. When staff explanations were clear, patients felt more comfortable tolerating what was

demanded of them; when information was unclear, they used personal coping strategies and trust in their healthcare professionals to bridge the gap. Integrating this information into targeted fixes to the clinical workflow was readily suggested by the participants. PPIE work should continue to address these needs.

Although side-effects were not the focus of this study, reported toxicities were fatigue, a sense of awareness of treatment to their liver, occasional gas, and one mild transient contrast reaction. Most distress arose not from the radiotherapy, but from the physical demands of SABR setup that are essential to enable accurate and precise tumour targeting:

- Breath-hold – particularly regarding repeated exhale breath-holds being requested whilst the patient was inside the MRI bore. Patients wanted to understand more why these were being done and felt a sense of failure if they couldn't achieve them satisfactorily. Breath holds were also challenging when audio prompts were faint or not clear. Multiple patients reported that a countdown would be helpful, not just for breath-hold procedures, but also for treatment too.
- Arm / shoulder positioning – arms raised overhead for up to 45 minutes caused some patients aching and pain, with a minority being advised to take analgesia and one, an adapted position for treatment.
- Compression arch – although broadly accepted as part of the treatment, patients perceived this device as tight, restrictive and, for two patients, made breathing much harder.
- MRI – the environment felt claustrophobic and noisy for four patients, in contrast to the more open CT bore and linac rooms, the latter which were a relief for patients when they realised that was what they would have to endure. This also pointed towards a lack of understanding of the procedures.

Although these issues did not prevent treatment for these patients, these pressures negatively impacted their experience. These findings align with previous radiotherapy studies highlighting the need for improved positioning devices or more flexible immobilisation strategies [349,359]. Patients repeatedly suggested real-time timers and additional arm support. Short

coaching sessions for breath-hold might also be of benefit for some patients to avoid confusion and which led to longer scan times in MRI and CT.

Interviewees lent on stoicism, counting during procedures, family, and trust in their radiotherapy team. Patients were keen to express their trust in healthcare professionals, often following divulgence of accounts where communication or understanding was sub-optimal. This adds further support to similar findings in other healthcare research studies [182,354-356]. Additionally, some patients highlighted that their relatives found the process more distressing than the patients themselves, potentially suggesting a parallel need for caregiver support.

For most liver SABR patients, the mechanical demands of immobilisation and breathing-control were more memorable and suggested a need to address procedural burdens. Patients suggested multiple areas of the liver SABR process that could be improved, including:

- replacing jargon like ‘day zero’ with more relatable terms and some substituted them with their own language, such as ‘a dress rehearsal’,
- displaying or talking through a countdown timer or visual clue during breath-holds or other procedures, especially in MRI,
- improved personalisation with regards to immobilisation support for shoulders and arms,
- and alternative delivery of information rather than a long leaflet provided at treatment consent.

Regarding this latter point, ongoing PPIE work has suggested the creation of a ‘patient roadmap’ comprising a simple one-page summary of the procedures and brief lay explanations. With engaged patients, keen to improve the process for others, this study reinforces recent calls for more personalised and patient-adapted motion management approaches, supported by clearer communication, enhanced patient coaching, and tailored comfort interventions, i.e. patient-centred personalisation [19,21,57], that could enhance the lived experience of liver SABR patients without compromising treatment precision.

6.3.3 Proof-of-concept NMOC study

In Chapter 5, a proof-of-concept evaluation of NMOCs was performed, with MRI acquisition conducted during various breathing states (free-breathing, inhale

breath hold, and exhale breath hold) as part of the second work package of the MICROCHIPS study. This study is currently in an early stage of the R-IDEAL framework. The study aimed to determine if readily available, inexpensive, and naturally derived liquids could improve visualisation of upper-abdominal structures for the purpose of facilitating MR-guided liver SABR planning. The investigation followed a two-step process.

i. In vitro relaxometry on 1.5 T MR-simulator shortlisted candidates based on their intrinsic T_1 and T_2 values.
ii. An exploratory four-way randomised, within-subject crossover study exposed eight healthy volunteers to four scan conditions – no contrast, water, pineapple juice and yerba-mate tea (drink order randomised), whilst they underwent paired T_1- and T_2-weighted sequences. Images were scored in blinded method for organ conspicuity and artefact in the context of its impact on the ability to contour these structures, and each participant completed an acceptability questionnaire developed during this study.

In the first step, relaxometry validated the behaviour of yerba-mate tea and pineapple juice: relaxation times (222 / 43 ms and 341 / 68 ms) were markedly shorter than those of water, suggesting that selection of these substances could be used to highlight or suppress the gastrointestinal lumen signal depending on the chosen sequence parameters.

In the second step – the healthy volunteer study – data suggested that the overall image quality proved robust even without NMOCs (97% of the 64 image sets were deemed satisfactory for contouring). Thus, any NMOC benefit had to exceed an already demanding benchmark. Yerba mate delivered a potentially significant gain in conspicuity: on T_1-weighted images it raised the median duodenal conspicuity by one Likert point (Wilcoxon $r = 0.90$, $p = 0.023$), a difference with the potential to allow tightening of planning margins around this critical organ at risk. Water, by contrast, offered only a 0.5-point median Likert improvement in pancreatic visibility, Wilcoxon $r = -0.91$, $p = 0.046$) suggesting that signal suppression and distension on T_1-weighted sequences might aid pancreatic delineation. None of the drinks appeared to increase artefact burden; median scores stayed within 3 – 4 across all intervention conditions. It is also notable that there was one sporadic non-responder to pancreatic conspicuity,

which represents participant-level heterogeneity. This aligns with the inter-patient variability seen with the success of abdominal compression in Chapter 3 and potentially highlights a need for patient-specific verification if NMOCs become integrated into the clinical workflow.

Data on participant tolerability of the NMOCs was collected. No volunteer reported nausea, 87% of questionnaire responses were positive in sentiment, and although the smell of yerba-mate polarised opinion, its taste and texture were deemed acceptable. These findings support the continued research along the R-IDEAL framework which should progress into patient testing.

This study remains early in its R-IDEAL trajectory (Stage 1). Further research using a definitive primary endpoint – such as the Dice similarity coefficient [372] between observer contours should be obtained to add relevance in the radiotherapy context. Acknowledging that the cohort was small and healthy volunteers may not replicate the motility or comorbidities of liver-SABR patients, the *p*-values presented must therefore be viewed as exploratory.

Together however, the studies within this thesis justify continuing with the R-IDEAL approach and future a patient-based study incorporating geometric and dosimetric outcomes and provide a basis for future NMOC protocol optimisation in MR-guided liver radiotherapy.

6.4 Limitations of the thesis

6.4.1 Limitations of Chapter 2 Scoping Review

The scoping review identified a broad spectrum of literature; however, certain factors may have influenced the level of certainty in its findings. Most records were screened by one reviewer. This was intentional by design, since pragmatically this approach lessened the resource intensiveness of the process, but it did increase the risk of misclassification. An increased proportion of dual screening would have enhanced the comprehensiveness of study inclusion and robustness in reported outputs [392,393]. Six potentially eligible papers lacked an English translation and were excluded. This decision may have biased the evidence base in favour of Western dietary patterns, resulting in the underrepresentation of early studies from East Asia that were excluded. Heterogeneity amongst the articles studied was a further weakness. Field

strengths spanned experimental 0.5 T systems through to 3 T clinical scanners, whilst pulse-sequence choices and breathing instructions varied widely. While relaxometry data was only extracted and synthesised in 1.5 T contexts, all other data was grouped together. Although acknowledged, outcomes on reported signal characteristics used in the literate differed too, with many authors calling a lumen ‘bright’, ‘positive’ or ‘high signal’ without pinpointing a reference tissue, which limits extrapolation and interpretation for the frequency counts reported. Methodological appraisal was omitted in accordance with scoping-review guidelines but consequently, it could not be established whether study design influenced the 'promising' outcomes. The scoping review therefore offered a rather simplistic and broad overview rather than an in-depth analysis [284,285]. Finally, cost and workflow data were not modelled. Juices and teas are relatively cheap per litre compared to medicinal alternatives, but this cost was not quantified, and other costs added through staff time required for preparation or the provision of additional patient information was not calculated. The review did however successfully highlight potential candidate NMOCs for subsequent evaluation, but future studies could use tighter study screening criteria, improved screening methods with more than one reviewer, broader language coverage, clearer outcome definitions, direct patient-reported metrics, and an assessment of clinical feasibility that includes data on cost and resources.

6.4.2 Limitations of Chapter 3 Motion management in liver SABR – motion of compression

The retrospective evaluation of liver motion is the largest single-centre assessment of a rigid abdominal compression arch in liver SABR to date but possesses many limitations. Its retrospective, unpaired design delivered a practical convenience and large sample size, but it also introduced a selection imbalance and an unavoidable single-institution bias. Motion was captured from two extreme phases of one planning scan, a snapshot that omits hysteresis, inter-fraction or day-to-day variability, and tumour-specific deformation. The use of Hausdorff distance offered a simple worst-case metric, however its clinical relevance in this context of motion measurement has yet to be validated in the literature, in phantom work or correlated with dose. Given some level of distension appears to have positively impacted organ observer-rated conspicuity, it is unknown what, (if any) potential dosimetrical consequences

exist from NMOC ingestion. Important covariates such as fibrosis, ascites, pulmonary limitation, and compression plate position were absent. Although the literature has previously reported responders to compression [111,112,135], this author is unaware of any evidence that links arbitrary figures, such as the 5mm used to define excessive motion, with treatment outcomes. Of note, nearly half the cohort still exceeded that target despite compression. In the absence of paired data, it was not possible to determine which individuals might benefit from compression. Like most other UK departments [113], since breath-hold or real-time gating are not currently offered treatment options in the host institution, a comparable cohort in an institution that does offer multiple techniques would provide a more thorough analysis and potential links to outcomes. Finally, the study was limited to determining motion metrics not dosimetry. Although clinically the arch's average 4 mm reduction in SI motion can translate into materially smaller internal target volumes, any translation of tighter margins was deemed outside of the scope of this study. Therefore, this work could not demonstrate whether the observed displacement changes translated into smaller margins, lower organ doses, or better tumour control. This could be potentially calculated using this dataset, although challenges regarding how to handle multiple tumour volumes would need to be handled robustly. These caveats do not negate the value of the dataset. The purpose of the evaluation was to establish a local baseline against which the new MR-compatible belt required for both clinical treatments and the subsequent stages of the MICROCHIPS study could be compared and determine if patient personalisation based on quantifiable body habitus metrics was possible. The evaluation also successfully demonstrated a practical python-based pipeline for large-scale motion analysis using readily available clinically approved contours that could be expanded to evaluate motion in other institutions using the recent creation of 'ProKnow' [306]. However, a more thorough evaluation would require prospective, paired designs, improved covariate data collection, intra- and inter-fractional motion tracking, and a clear link between motion, dose, and patient outcomes.

6.4.3 Limitations of Chapter 4 Patient experience of liver SABR

The qualitative study undertaken offered the first in-depth look at how people perceive and live through the procedures involved in liver SABR, providing rich

detail on communication gaps, discomfort, and coping strategies. The main strength of this work lies in the depth of the interviews. Patients were interviewed at or near the end of their treatment, when they could reflect on the full pathway. However, several design features limit the generalisability of its findings. The study's small, male-dominated (9:1 male: female) sample from a single hospital in Northern England limited participant diversity, and the interviewer's close familiarity with local processes could have reduced critical perspectives that an independent interviewer could have elicited. Although most interviews were conducted towards the end of the treatment schedule, specific timing of this interview varied according to participant availability, inviting recall distortion. Furthermore, the study leant on only one data source from a single institution and could have been conducted across multiple radiotherapy centres. The use of an a priori analytic framework delivered structure, and although it was iteratively modified for analysis as themes emerged, this may have reduced the opportunity for discovery of unexpected concerns when compared with more open-ended methods. These factors could have limited the generalisability and therefore the utility to inform modification of pathways and workflows of liver SABR elsewhere. Future work would benefit from larger, more diverse samples, multiple centres, mixed data streamsand explicit member checking to ground the insights more firmly in the broader liver SABR population.

6.4.4 Limitations of Chapter 5 Non-medicinal oral contrasts in liver SABR

Finally, the evidence presented in Chapter 5 exploring the potential of NMOCs in the liver SABR context has provided an encouraging first glimpse that everyday drinks might enhance MR visibility of abdominal organs, yet the evidence is at an early R-IDEAL proof-of-concept stage. Although there was an equal distribution of females to males, this does not reflect the demographics of the general UK liver SABR population. Seven of eight volunteers identified as White British. Taste preference, and tolerability might vary by culture and diet, thus acceptability data may not translate to the wider population. The study data was designed to provide proof-of-concept data to justify further research, and with only eight participants, is under-powered for meaningful statistical analysis, whilst the reliance on volunteers who are younger and healthier than future

patients limit generalisability. Liver SABR patients are generally older, may have ascites, altered anatomy from surgery, diabetes-related gastroparesis, or compromised liver function. These factors can affect gastrointestinal motility and might affect the contrast effect observed to date in the healthy volunteers. Type II errors are possible, and any significant *p*-values are questionable since a multiplicity correction was not required by the protocol. Although this was by design and is a supported methodology used for exploratory studies, firmer conclusions cannot be made until study accrual. Although the volunteers were asked to fast for four hours before scanning and were scanned twenty minutes after drinking, the gastric and bowel volumes have not yet been measured, and fluid distribution was not tracked over time to reproducibly acquire anatomically comparable data. Without these data it has currently not been determined whether conspicuity gains stem from true signal change or simply from differences in luminal filling. Buscopan was also administered to provide consistent image quality and reduce artefacts from bowel motion. However, since Buscopan is currently not used in current liver SABR planning imaging protocols, its use might result in large improvements to image quality compared to the standard image protocol, regardless of whether NMOCs are used or not. Despite patients reporting in the qualitative study that consuming small volumes of fruit juices would be permissible for those with diabetes, it is also unknown if the sugar or caffeine content of the NMOCs currently studied might impact patients with diabetes or ascites. The MRI slices in this study were five millimetres thick, but clinical planning sequences typically use 1 – 2 mm slice thicknesses, and any subtle benefits might only emerge under a higher resolution. A major limitation is the lack of a ‘gold-standard’ for organ conspicuity. Findings were therefore based on subjective, albeit done by paired consensus, judgements. Two radiographer observers graded images on a four-point Likert scale, but because these were graded by consensus and not independently, inter-rater reliability statistics cannot be provided, calling into question the validity of the Likert scoring system, and leaving it potentially open to observer bias. Given the high baseline rating of the control cases where no NMOC was administered, it is possible the scoring system was also not sensitive enough to detect certain effects. The study did not provide any other data other than visual scores. It has not yet attempted to correlate if contouring could be made more reproducible across multiple radiographers, nor if

improved conspicuity translates into tighter margins, lower organ doses, or reduced segmentation time. Until other data that more closely relates to the context of liver SABR contouring practice such as a Dice similarity coefficient [372] comparison-based contour study and a dosimetric analyses are acquired in a patient cohort, the practical value of the contrast agents remains hypothetical. These limitations are, however, characteristic of early-stage R-IDEAL studies, where sample sizes are limited and the exploratory nature each stage can inform the next phase [202,378,394]. These limitations should however not detract the novelty of using biphasic liquids or seeking patient views to provide improvements to clinical practice. It is important to acknowledge that many technical, statistical, and translational steps lie between this preliminary proof-of-concept emerging evidence and a protocol that will genuinely tighten margins in future liver SABR treatments.

6.4.5 Synthesis of limitations

Across this thesis. there was a consistent application of pragmatic study designs, where the selected methods were feasible but chosen over more ambitious prospective controlled designs with definitive endpoints in patient cohorts. This was, however, intentional. The justification of this approach was that the studies in this thesis were conducted in accordance with the R-IDEAL framework and aimed to generate early predicate evidence without adding unnecessary burden to patients.

A second recurring limitation is that of transferability. The single-centre context, sampling, or protocol specific factors such as abdominal compression mean results are foundational and limit generalisability.

A third limitation across the chapters relates to outcome measures. The relationship between motion surrogates, although established in a novel way from the 4DCT contour extremes, or the Likert conspicuity scores, obtained to evaluate the NMOCs, lack an established clinically meaningful correlation.

Reflexively, as a therapeutic radiographer, the author’s professional lens places an emphasis on deliverability, workflow feasibility and patient burden. This strengthened the translational focus of the thesis and was the purpose of the research questions. However, this may have resulted in more of a procedural framing in the qualitative analysis.

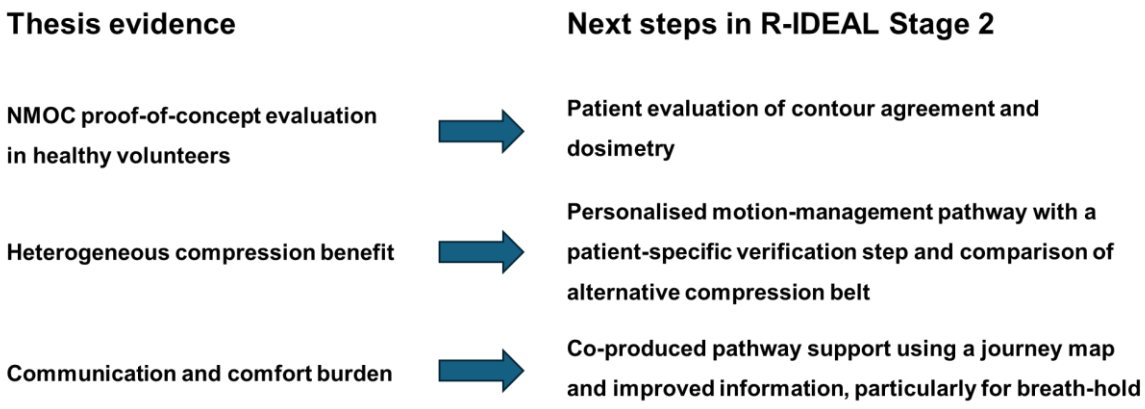
Overall, these limitations do, however, highlight what is required in terms of future directions for this programme of work – patient studies with clear outcomes that link complex intervention changes to both clinical and experiential benefit.

6.5 Future directions

Based on initial data indicating proof-of-concept, future research in the MICROCHIPS study should proceed to the developmental R-IDEAL Stage 2 stage. No unacceptable tolerability or safety concerns were observed and there was no systematic reduction in image quality or increase in artefacts. The next stage will include evaluating efficacy in clinical settings with patient participants using clinically meaningful endpoints (contour agreement and dosimetry). Progression toward implementation into routine practice would be contingent on demonstrating benefit without unacceptable patient burden.

The proposed next steps derived directly from the findings of this thesis are illustrated in Figure 33.

Figure 33 From thesis evidence to the next stage of MICROCHIPS. The figure summarises how the main findings of this thesis will shape future work.



Stage 2 will test NMOCs and personalised motion control in 15 liver-SABR patients, providing enhancements to information provision, timing of sequence acquisition, breathing management and immobilisation. Rapid scout scans may be used to confirm duodenal distension before the planning protocol sequence is acquired. Following Stage 2, if successful, further study might be warranted to establish early indications of clinical effectiveness and safety in a multi-institutional setting. This could involve a small multicentre cohort or

stepped-wedge feasibility study comparing MR-NMOC planning with standard care, tracking imaging metrics, acute toxicities and patient-reported outcomes. If feasible, subsequent study would quantify margin reduction and normal-tissue sparing. The aim at that stage would be to evaluate for meaningful improvements – perhaps reducing inter-observer variability enough to lower treatment margins. However, it has previously been acknowledged that radiotherapy, a complex intervention involving rapid and continuous development of technology causes insufficient equipoise and does not fit a lengthy traditional trial framework [201,202]. This coupled with the high-dependence on staff and their training; an alternative option could be to take inspiration from the RAPID-RT programme and conduct a continuous improvement method study [395]. Routinely collecting plans and outcomes data could feed iterative plan-do-study-act cycles, enabling practice to evolve whilst evidence accrues in real time [395]. This could result in a more rapid translation of this new protocol to clinical use where it is continually refined whilst simultaneously generating evidence on effectiveness and safety. Margin reduction might correlate with reduced normal liver dose and or better sparing of critical structures such as bowel and patient reported outcomes measures. In addition, it would also be important to assess if the patient experience remains positive when the protocol is deployed in the real-world setting. Accordingly, quality of life and patient-reported outcome measures should be included in these studies, building on the questionnaire and interviews from this thesis to monitor how patients feel about the process when it is part of standard care.

Working with technology providers and clinical guidelines bodies to formalise the approach could also be advantageous to provide greater impact for future patients. Treatment planning systems could incorporate tools to account for the different contrast in MRI to facilitate easier segmentation on NMOC enhanced scans or, perhaps with the aid of alternative relaxometry sequences [97,308], to provide further training for deep-learning based auto-contouring algorithms to identify NMOCs or functional hepatocytes and delineate these as OAR tissues. The inclusion of MR-based planning and coaching for breath-hold into radiographer training and quality assurance could be included to improve robustness. The use of an NMOC protocol might fit well with the emerging platform of the MR-linac to aid online adaptive radiotherapy. Whilst the current

study was firmly limited to the SABR planning phase, the ultimate translation might be to facilitate real-time adaptive treatments, where each fraction on an MR-linac benefits from reduced motion (using breath-hold gating or abdominal compression or free breathing dependent on patient-level assessment if achievable) and improved organ visibility with an ingested NMOC prior to each fraction.

This thesis provides evidence that not all patients benefit from the same approach and there are numerous opportunities to explore the facets of personalised medicine based on these findings. Data from Chapter 3 demonstrated that some patients, when compressed, have more motion than those uncompressed and could potentially benefit from breath-holding. Since the motion of different segments (and tumours located within them) has been show to vary [90], subsequent study could leverage image-registration techniques to investigate the significance of liver tumour positioning with regards to liver-segment location in attempt to derive segment-specific ITV margins, personalising planning rather than applying the same ITV margins for all. This could also feed into a decision algorithm to tailor the motion mitigation strategy to each patient personally. The use of cine MR data or 4D MRI sequences, currently in development, could form part of this, especially in cases where abdominal compression proves ineffective. Future research should also capture data on inhale and exhale breath-hold as alternative methods. This data could indicate if these approaches can be integrated into the next phase of the protocol for evaluation in patients. The qualitative data can inform this personalisation further. For example, if a patient expresses high anxiety about holding their breath, an alternative method might provide a better experience, even if the motion reduction is slightly less. The patient could have input into this decision.

Critically, future development must continue to involve patients. PPIE will continue to guide and reflect on the design of future studies, ensuring trial protocols, patient information and the conduct of the study align with patient priorities. One outcome from the qualitative interview study and PPIE follow-up work should be to co-create a liver SABR ‘roadmap’, explaining the various procedures and timelines in a single page, as these were frequently raised as

an area of uncertainty. By integrating such feedback, it is hoped high levels of acceptability can be maintained or perhaps even improved.

Finally, an important future direction is the dissemination of the findings of this work and working with clinical leaders to consider implementation pathways if the technique proves worthwhile. Health technology assessment might become relevant and the cost and resource implications of adding NMOCs to MRI for liver SABR planning should be confirmed. With improvements to MR-planning protocols, costs might be offset by better initial imaging if the need for re-scans is reduced.

In summary, the future work will hopefully transition this innovation from a proof-of-concept evaluation into a tested, refined and scalable clinical method. Each subsequent stage should build on the foundation laid by this thesis. By adhering to the R-IDEAL framework, the evidence can be gathered systematically and ethically, balancing innovation with patient safety. The information on current practice, patient experience, and early proof-of-concept but encouraging results on the use of NMOCs in liver SABR covered by this thesis provide a momentum and justification to carry this programme of research forward.

6.6 Summary

This thesis has examined several aspects of the liver SABR pathway using a methodology supported by the R-IDEAL framework, including scoping review evidence synthesis, quantitative motion evaluation, qualitative enquiry and novel proof-of-concept testing of NMOCs in MR-planning for liver SABR. It is hoped that further research will ultimately contribute to improvements in the therapeutic ratio for patients receiving liver SABR.

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Appendix A Research database ethical approval

The Leeds Teaching Hospitals NHS Trust

UNIVERSITY OF LEEDS

Research Database: Leeds Cancer Centre Computer Aided Theragnostics (LeedsCAT)
v2.0
REC reference: 19/YH/0143
IRAS project ID: 342888

Radiotherapy Research Department
Level 4 Offices, Bexley Wing
Leeds Teaching Hospitals NHS Trust
Leeds
LS97TF

10/12/24

Dear Matt

RE project:

Study Quantifying Use of Abdominal breathing Suppression for Hepatic motion Equipment Development (SQUASHED)

Your project has been considered by the LeedsCAT Governance board in November 2024. The LeedsCAT Governance board consists of representatives from Research and Innovation, Information Governance, PPI and experts in Radiotherapy.

A favourable decision was made, and we can confirm that we are able to approve your project within the scope of the LeedsCAT research database ethical approval.

Terms:

- In order to comply with the NHS national data opt out policy (in effect from 31st July 2022) if you are responsible for the patient list needed for your research, you need to ensure that the data you plan to use does not come from those that have opted out. To check this please email your NHS numbers list to jack.baldwin@nhs.net.
- With respect to the use of data we expect that you will comply with GDPR, Caldicott guidance, Information Governance procedures and all Trust policies
- If there are any significant changes to the project, including change in the list of people who will access project data, you will need to notify the LeedsCAT project manager
- When the project has ended you will take the necessary steps to ensure the data is deleted or archived correctly.

Regards,

John Lilley
on behalf of the LeedsCAT Governance Board

LEEDS RADIOTHERAPY RESEARCH

Appendix B HRA ethical approval

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Mr Matthew Beasley
Radiotherapy Research Group
Bexley Wing
Leeds Teaching Hospitals NHS Trust
LS9 7TFN

Email: approvals@hra.nhs.uk

16 May 2023

Dear Mr Beasley

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**MRI scans with respiratory Immobilisation to Contour Radiotherapy Organs at riskusing oral Contrast of Hypo or hyper intense fluids Including the Patient perSpective:The MICROCHIPS study.**
IRAS project ID:	**305442**
Protocol number:	**N/A**
REC reference:	**23/WM/0070**
Sponsor	**Leeds Teaching Hospitals NHS Trust**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report

(including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **305442**. Please quote this on all correspondence.

Yours sincerely,
Michelle Ahmed

Approvals Specialist

Email: approvals@hra.nhs.uk

Copy to: *Ms Sarah Hall*

Appendix C Normality and variance tests of motion

Table 26 Body habitus metrics and associated Shapiro-Wilk's test form normality by compression group and Levene's test for homogeneity of variance.
Assumptions were violated if $p < 0.05$.

Body habitus metric	Compression	Shapiro-Wilk's *p*	Normality in both compression groups?	Levene's *p*	Variances equal?	Test selected
AP 95% (mm)	Uncompressed	0.068	No (compressed failed)	<0.001	No	Mann-Whitney U
	Compressed	0.021				
LAT 95% (mm)	Uncompressed	0.074	Yes	0.003	No	Welch's t test
	Compressed	0.509				
Maximum area (mm^2)	Uncompressed	0.104	No (compressed failed)	0.146	Yes	Mann-Whitney U
	Compressed	<0.001				
Body-fat fraction	Uncompressed	0.089	No (compressed failed)	0.063	No (borderline)	Mann Whitney U
	Compressed	0.012				

Appendix D Normality and variance tests of the body habitus

Table 27 Motion metrics and associated Shapiro-Wilk's test form normality by compression group and Levene's test for homogeneity of variance.

Assumptions were violated if $p < 0.05$.

Motion metric	Compression	Shapiro-Wilk's *p*	Normality in both compression groups?	Levene's *p*	Variances equal?	Test selected
Left-Right	Uncompressed	<0.001	No	0.306	Yes	Mann-Whitney U
	Compressed	<0.00				
Anterior-Posterior	Uncompressed	0.115	No (compressed failed)	0.139	Yes	Mann-Whitney U
	Compressed	0.007				
Superior-Inferior	Uncompressed	0.349	No (compressed failed)	0.023	No	Mann-Whitney U
	Compressed	<0.001				
Hausdorff distance	Uncompressed	0.051	No (compressed failed)	0.527	Yes	Mann-Whitney U
	Compressed	<0.001				

Appendix E Covariate metric analyses

Table 28 Sex differences in body-habitus metrics: Welch t-tests and effect sizes (female – male).

Metric	t (Welch)	p	Cohen's d (95 % CI)	Magnitude
AP 95	–4.82	< 0.001	–1.22 (–1.64 to –0.79)	Large (0.8)
LAT 95	–2.30	0.027	–0.55 (–0.95 to –0.14)	Medium (0.5)
Maximum area	–2.14	0.039	–0.52 (–0.93 to –0.11)	Medium (0.5)
Fat fraction	–0.38	0.703	–0.09 (–0.49 to 0.31)	None

Table 29 Spearman's rho correlations across covariates.

**Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed).

			AP	LAT	Area	Fat Fraction	LR (mm)	AP (mm)	SI (mm)	Hausdorff (mm)
Spearman's rho	**AP**	Correlation Coefficient		.747**	.822**	.587**	0.004	0.162	0.069	.175*
		Sig. (2-tailed)		0.000	0.000	0.000	0.964	0.062	0.428	0.043
		N		134	134	134	134	134	134	134
	LAT	Correlation Coefficient	.747**		.818**	.670**	0.017	0.160	0.066	.187*
		Sig. (2-tailed)	0.000		0.000	0.000	0.849	0.065	0.452	0.031
		N	134		134	134	134	134	134	134
	Area	Correlation Coefficient	.822**	.818**		.606**	0.017	.185*	0.102	0.153
		Sig. (2-tailed)	0.000	0.000		0.000	0.849	0.032	0.240	0.078
		N	134	134		134	134	134	134	134
	Fat Fraction	Correlation Coefficient	.587**	.670**	.606**		-0.068	.194*	0.109	0.005
		Sig. (2-tailed)	0.000	0.000	0.000		0.434	0.025	0.210	0.955
		N	134	134	134		134	134	134	134

			AP	LAT	Area	Fat Fraction	LR (mm)	AP (mm)	SI (mm)	Hausdorff (mm)
	LR_mm	Correlation Coefficient	0.004	0.017	0.017	-0.068		0.087	.175*	0.157
		Sig. (2-tailed)	0.964	0.849	0.849	0.434		0.316	0.044	0.070
		N	134	134	134	134		134	134	134
	AP_mm	Correlation Coefficient	0.162	0.160	.185*	.194*	0.087		.503**	.323**
		Sig. (2-tailed)	0.062	0.065	0.032	0.025	0.316		0.000	0.000
		N	134	134	134	134	134		134	134
	SI_mm	Correlation Coefficient	0.069	0.066	0.102	0.109	.175*	.503**		.375**
		Sig. (2-tailed)	0.428	0.452	0.240	0.210	0.044	0.000		0.000
		N	134	134	134	134	134	134		134
	Hausdorff_mm	Correlation Coefficient	.175*	.187*	0.153	0.005	0.157	.323**	.375**	
		Sig. (2-tailed)	0.043	0.031	0.078	0.955	0.070	0.000	0.000	
		N	134	134	134	134	134	134	134	

Table 30 Collinearity statistics for the selected body habitus metrics
The variance inflation factor (VIF) is shown in the final column.

Coefficients	VIF
Compression	1.102
Sex	1.504
AP (mm)	2.368
Fat fraction	1.865

Table 31 Binary logistic regression results

Predictor	B (log-odds)	SE	Wald	*p*	Odds ratio (Exp B)	95% CI
Sex	1.107	0.593	3.49	0.062	3.03	0.95 – 9.67
AP diameter (mm)	-0.010	0.01	1.18	0.278	0.99	0.97 – 1.01
Fat fraction	-5.240	3.643	2.07	0.15	0.005	0.00 – 6.69
Intercept	5.862	1.956	8.98	0.003	351.6	-

Appendix F Interview topic guide

Version 1.0 **Date: 27/02/2023** **IRAS: 305442**

MICROCHIPS semi-structured interview topic guide

The following topic guide is divided into two sections: the first describes the key topic areas and themes; and the second provides example questions and potential probes to steer the interview. Following best practice, the topic guide will be used as a flexible tool and is not prescriptive. The order of questions may change, and questions or probes may be adapted to each interview situation and respondent. It may be amended as interviews continue, since new experiences of interviewees emerge which may need exploring in subsequent interviews.

Topic areas:

- Personal journey
- Radiotherapy planning and treatment
  - CT planning
  - MRI planning
  - Radiotherapy treatments
- Development
  - Equipment
  - Information
  - Breathing
  - Drinking oral contrast
- Messages for others

Potential questions and prompts in semi-structured interviews

Topic	Guiding questions	Possible follow-up question prompts/probes
Introduction	[Housekeeping] [Note taking] [Recording] [Data use, anoymisation, transcript] [Consent confirmation] Do you have any questions or comments for me before we begin?	
Narrative	Would you talk me through your history leading up to where you are now in your radiotherapy treatment?	You mentioned... can you tell me more about that? I'd like to move on to discuss...

Topic	Guiding questions	Possible follow-up question prompts/probes
CT planning scan	I'm interested in your experience of the CT scan. [Show Figure 1 picture as a reminder] Can you tell me about that?	Did you feel prepared for the scan? What did the radiographers ask you to do at your CT scan? Were you asked to drink anything beforehand? Were you asked to hold your breath? How did it make you feel?
MRI planning scan	Can you tell me about your experience in the MRI planning scan? [Show Figure 2 picture of an MRI scanner] How did it compare to the CT scan?	Did you feel prepared for the scan? Were you asked to drink anything beforehand? What did the radiographers ask you to do at your MRI scan? Were you asked to hold your breath? How did it make you feel?
Radiotherapy treatments	Can you tell me about your experience of your radiotherapy treatments? (Show Figure 3 picture of linac as a reminder). How did the treatment compare to the MRI and CT planning scans?	Did you feel prepared for treatments? Were you asked to drink anything beforehand? What did the radiographers ask you to do at your treatment(s)? How did it make you feel?
Development	What might have helped to make it a better experience for you?	Was anything challenging?

Topic	Guiding questions	Possible follow-up question prompts/probes
	[Thank you voucher]	

Figure 1 CT Simulator scanner.

Topic	Guiding questions	Possible follow-up question prompts/probes
	What do you think about the information you were given?	Did you discuss any procedures with staff? How did that make you feel?
	Can you tell me about any of the equipment we used? [Show Figure 4 picture of abdominal compression and vac bag immobilisation equipment]	
	I am interested in asking people to drink different amounts of fluid or different fluids like juice or milk. Do you have any thoughts about that?	
	I'm interested in exploring how people hold their breath for the scans. Do you have any thoughts about that?	
Messages to others	Do you have any advice for other patients going through radiotherapy?	
Opportunity to discuss other topics	Is there anything at all you haven't had the opportunity to talk about today that you want to?	
Closing	[Thank them for their time.] [Availability and details to contact a member of the study team and/or additional support.] [Option to provide outcomes with appropriate permission]	

Figure 2 MRI Simulator scanner [note this is to be replaced once supplied with new Leeds photo once the MRI Sim installation at LTHT is completed]

Figure 3 Radiotherapy machine (linear accelerator or 'linac')

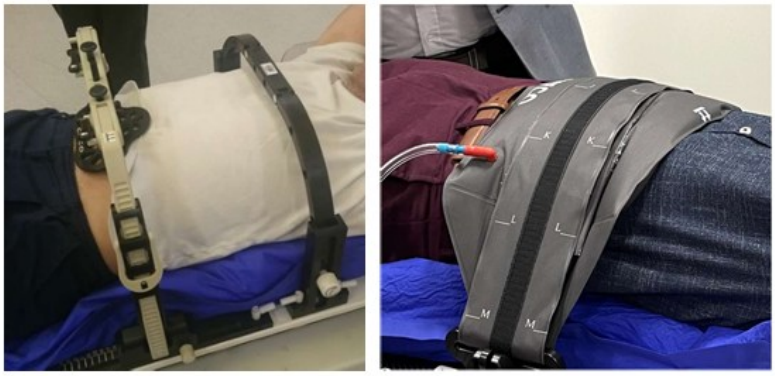

Figure 4 Abdominal compression equipment and vac bag immobilisation equipment