IMAGING ASSESSMENT OF HAEMATOPOIETIC AND LYMPHOID TUMOURS; ADVANCING METHODOLOGIES AND APPLICATIONS

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TABLE OF CONTENTS

LIST OF FIGURES AND TABLES

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GLOSSARY OF ABBREVIATIONS AND SYMBOLS

ABS	Association of Breast Surgeons
ADC	Apparent Diffusion Coefficient
AI	Artificial Intelligence
ALCL	Anaplastic Large Cell Lymphoma
ALK	Anaplastic Lymphoma Kinase
ARSAC	Administration of Radioactive Substances Advisory Committee
ASCT	Autologous Stem Cell Transplantation
BIA-ALCL	Breast Implant-Associated Anaplastic Large Cell Lymphoma
BRC	Biomedical Research Centre
BSH	British Society of Haematology
CAROUSEL	Immunotherapy Using CAR-T cells to Target CD19 for Relapsed/Refractory CD19+ Primary CNS Lymphoma
CCA	Contrast Clearance Analysis
CD	Castleman Disease
CE-MRI	Contrast Enhanced-Magnetic Resonance Imaging
CfG	Centre for Guidelines development (UK NICE)
CHL	Classic Hodgkin Lymphoma
CLL	Chronic Lymphocytic Leukaemia
CLL RT	Chronic Lymphocytic Leukaemia and Richter's Transformation
CNS	Central Nervous System
CNSL	Central Nervous System Lymphoma
CSF	Cerebrospinal Fluid
CT	Computed Tomography
CR	Complete Response
ctDNA	Circulating DNA
DEC	Direct Economic Costs
DLBCL	Diffuse Large B-Cell Lymphoma
DS	Deauville Score

DWI	Diffusion Weighted Imaging
ECR	European Congress of Radiology
EFS	Event Free Survival
EI	Edge Illumination
EJNMMI	European Journal of Nuclear Medicine and Molecular Imaging
ENMZL	Extra-Nodal Marginal Zone Lymphoma
EOT	End-of-Treatment
FCH	^{18}F-choline radiotracer
FDG	2-deoxy-2-[^{18}F]fluoro-D-glucose
FL	Follicular Lymphoma
FNA	Fine Needle Aspirate
FSL	Focal Splenic Lesions
GI	Gastrointestinal
GRADE	Grading of Recommendations, Assessment, Development and Methodology
HCL	Hairy Cell Leukaemia
HG-LPDs	High Grade-Lymphoproliferative Disorders
HGT	High Grade Transformation
HL	Hodgkin Lymphoma
HR	Hazard Ratio
HSCT	Haematopoietic Stem Cell Transplantation
ICIS	International Cancer Imaging Society
ICR	The Institute of Cancer Research
IPCG	International PCNSL (primary central nervous system lymphoma) Collaborative Group
IQR	InterQuartile Range
IR	Indeterminate Response
IRIS Centre	Interdisciplinary Centre for Implant-based Research
IVLBCL	IntraVascular Large B-Cell Lymphoma
IWG	Imaging Working Group

LyRIC	Lymphoma Response to Immunomodulatory Therapy Criteria
LETR	Linking Evidence to Recommendations
LG-LPDs	Low Grade-Lymphoproliferative Disorders
LG-NHL	Low Grade Non-Hodgkin Lymphoma
MALT	Mucosa-Associated Lymphoid Tissue
MCL	Mantle Cell Lymphoma
MDTMs	Multidisciplinary Team Meetings
MHRA	Medicines and Healthcare products Regulatory Agency
MM	Multiple Myeloma
MRD	Minimal Residual Disease
MRI	Magnetic Resonance Imaging
MZL	Marginal Zone Lymphoma
NCCN	National Comprehensive Cancer Network
NGS	Next-Generation Sequencing
NICE	National Institute for Health and Care Excellence
NHL	Non-Hodgkin Lymphoma
NHS	National Health Service
NMZL	Nodal Marginal Zone Lymphoma
NTAP	Neck, Thorax, Abdomen, Pelvis
NXCT	National X-ray Computed Tomography
OAFU	Open-Access-Follow-Up
OS	Overall Survival
PCNSL	Primary Central Nervous System Lymphoma
PET-CT	Positron Emission Tomography - Computed Tomography
PET-MRI	Positron Emission Tomography - Magnetic Resonance Imaging
PFS	Progression-Free Survival
PICO	Population, Intervention(s), Comparison, Outcomes
PMBCL	Primary Mediastinal B-Cell Lymphoma
POC	Proof of Concept

POP	Proof of Principle
PRASEAG	Plastic, Reconstructive and Aesthetic Surgery Expert Advisory Group
RECIL	Response Evaluation Criteria in Lymphoma
RMH	The Royal Marsden Hospital
R/R	Relapsed/Refractory
RS-DLBCL	Richter's Syndrome-DLBCL (diffuse large B-cell lymphoma)
RSNA	Radiological Society of North America
RT	Richter's Transformation
SCNSL	Secondary Central Nervous System Lymphoma
SE	Service Evaluation
SIHMDS	Specialist Integrated Haematological Malignancy Diagnostic Services
SIHMIR	Specialist Integrated Haematological Malignancy Imaging Reporting
SMZL	Splenic Marginal Zone Lymphoma
SUV_{max}	Standardised Uptake Value maximum
TMTV	Total Metabolic Tumour Volume
TLG	Total Lesion Glycolysis
T/NK-cell	T/Natural Killer-cell
TRAMs	Treatment Response Assessment Maps
UCLH	University College London Hospital
uCR	unconfirmed Complete Response
VGPR	Very Good Partial Response
WB-DWI	Whole Body-Diffusion Weighted Imaging
WBRT	Whole-Brain Radiotherapy
WHO	World Health Organization
XPCI	X-ray Phase-Contrast Imaging

PREFACE

The persistent challenge in oncology patient imaging data interpretation is to provide '*Conclusions as close as possible to the truth*.' To achieve this, it is vital to understand the underlying *tumour biology* and *'strengths and limitations*' of the tests employed. No single imaging investigation is a '*universal panacea*' (Sharma *et al.*, 2012).

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I am fortunate to have worked as a consultant with many recognised international experts at the Royal Marsden Hospital and the Institute of Cancer Research (ICR) (London and Sutton) for two decades. Inspiring colleagues are too numerous to list. However, principal mentors and collaborative colleagues deserve special mention. Had it not been for the recommendation by Professor Kevin Harrington, Head of Division of Radiotherapy and Imaging (ICR), that I pursue a PhD by publication, this thesis would not have occurred. I am indebted to close working colleagues: Professor David Cunningham, Director of Research (RMH/ICR), an inspirational clinical and research mentor; Professor David Linch, Chief Lymphoma Advisor to the UK Government, a privilege to work with on rare complex clinical cases in addition to 65 NICE Guidelines. Dr Joel Cunningham and Dr Thomas Millard, trainees with high future potential. Mrs Hannah Holmes, pivotal to managing the research outputs, a pleasure to work with each week.

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ABSTRACT

Haematological malignancies are a burden being the fifth most common cancer and the second leading cause of cancer mortality on a global scale. Their presentation is complex due to disparate patterns of biological behaviour and anatomical involvement. Accurate detection of disease and precise assessment of treatment response is critical for optimal patient management. However, the appropriate use of imaging tests requires awareness of their strengths and limitations and appreciation of the myriad biological behaviours of haematological malignancies. This thesis presents research undertaken to enhance the **imaging assessment of haematological malignancies.** Four key themes of concern were identified and addressed.

Firstly, general reporting of haematological malignancies lacked standardisation in staging, response, and prognostication assessment across all imaging studies: computed tomography (CT), positron emission tomography-computed tomography (PET-CT) and magnetic resonance imaging (MRI). A multimodality imaging report with a multidisciplinary team meeting (MDTM) style conclusion needs to be issued at each relevant timepoint in the patient pathway. The aim was to reduce imaging 'error' rates by using template reports, produce comparative datasets from different centres, and improve patient outcomes. Analogous to UK developments in pathology reporting, a robust and adaptable methodology, termed 'Specialist Integrated Haematological Malignancy Imaging Reporting' (SIHMIR), was formulated.

Secondly, breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) imaging guidance varied widely. There was no detailed analysis of the strengths and weaknesses of the numerous imaging tests used, and patient data was prone to misinterpretation. No comprehensive imaging guidance was available for the distinct types of BIA-ALCL, a 'cascade' of investigations being performed. An assessment of the strengths and limitations of all anatomical and functional imaging investigations in BIA-ALCL was undertaken, and patient imaging pathways were developed.

Thirdly, a prompt diagnosis of Richter's transformation (RT) from chronic lymphocytic leukaemia (CLL) was needed. The selection of a biopsy target to diagnose RT was a particular challenge in clinical practice. A PET-CT driven decision-making pathway to decide whether biopsy was required and, if so, to select a representative biopsy site in the era of novel therapies was developed.

Lastly, MRI, used for central nervous system lymphoma (CNSL) imaging, was unable to differentiate disease activity from benign post-biopsy and inflammatory change and did not provide prognostic information. Two imaging applications for this purpose were developed: (i) the theoretical concept and clinical use of contrast clearance analysis (CCA), with its ability to differentiate viable CNSL from benign enhancement, and (ii) ^{18}F-choline radiotracer (FCH) cranial PET-CT for staging, response-assessment, and prognostication.

This thesis advances the imaging assessment in haematopoietic and lymphoid tumours, most notably with a standardised reporting framework (SIHMIR), guidance in both BIA-ALCL and CLL RT, and two CNSL imaging applications.

The disease-histology specific approach to the use of imaging tests has been endorsed by the UK National Institute of Health and Care Excellence (NICE) Guidelines and UK Medicines and Healthcare products Regulatory Agency (MHRA) Guidelines. The new methodologies and tools described, particularly the two new tools for CNSL assessment, have the capacity to change global clinical and research trial practice.

Chapter 1: INTRODUCTION

The current World Health Organization (WHO) classification of haematopoietic and lymphoid tumours recognises >40 non-Hodgkin lymphoma (NHL) and five Hodgkin lymphoma (HL) categories (Campo *et al*., 2017). Optimal patient survival outcomes are contingent upon accurate and timely histopathological diagnosis, staging, prognostication and response-assessment across the patient pathway (*Non-Hodgkin's lymphoma: diagnosis management (NG52)* (NICE 2016); *Haematological cancers: improving outcomes (NG47)* (NICE 2016)).

Advances in anatomical and functional imaging techniques over more than 50 years have made a pivotal contribution to the management of haematological malignancies. However, the appropriate application of current techniques requires acknowledgement of their strengths and weaknesses and appreciation of the full diversity of lymphoid tumours. At any given point, the appropriate imaging investigation must be selected, and even then, complex imaging datasets in this myriad of biologically diverse tumours are prone to misinterpretation. In addition, there remains a significant unmet clinical need for accurate imaging tests in a multitude of low grade-lymphoproliferative disorders (LG-LPDs) and high grade-lymphoproliferative disorders (HG-LPDs), there is no universal imaging panacea (Sharma *et al.*, 2012; Cunningham *et al.*, 2017).

The thesis' publications focus on the development of new solutions for the imaging assessment of haematopoietic and lymphoid tumours. The key outcomes produced comprised: new structured template-based reporting, 'Specialist Integrated Haematological Malignancy Imaging Reporting' (SIHMIR); new patient algorithms for breast implant-associated anaplastic large cell lymphoma (BIA-ALCL); a new diagnostic algorithm for chronic lymphocytic leukaemia and Richter's transformation (CLL RT); two new imaging applications for central nervous system lymphoma (CNSL).

Before the research was undertaken, imaging reports lacked: standardisation in staging, prognostication and response data-metrics, a combined multimodal assessment, and integrated conclusions. Analogous to UK National Institute for Health and Care Excellence

(NICE) mandated developments in pathology reporting, a robust, adaptable framework applicable in clinical and research practice, SIHMIR, was developed (*Haematological cancers: improving outcomes (NG47)* (NICE 2016); National Institute for Health and Care Excellence. *Haematological Malignancies Quality Standards* (NICE 2017); Cunningham *et al.*, 2017).

Diagnostic assessment in BIA-ALCL varied widely. Issues included: no comprehensive analysis of the strengths and limitations of the numerous imaging tests used in this relatively recently recognised tumour; complex patient datasets were prone to misinterpretation; imaging algorithms were not available for the distinct types of BIA-ALCL; significant numbers of patients were being subjected to a 'cascade' of unnecessary investigations. A detailed assessment of the indications, strengths, and weaknesses of imaging investigations in this tumour was undertaken. Patient diagnostic algorithms for the different BIA-ALCL subsets were formulated (Sharma *et al.*, 2020; Mehdi *et al.*, 2021), subsequently endorsed by the UK Medicines and Healthcare products Regulatory Agency (MHRA) Guidelines (Turton *et al*., 2021).

Two to ten per cent of patients with CLL undergo high-grade transformation (HGT) into HG-LPDs, termed Richter's Transformation (RT) (Lenartova *et al*., 2019), which require different treatment regimens and have poor survival outcomes. Prompt diagnosis of RT is required to improve patient outcomes (Campo *et al.*, 2017). Detection of RT, and selection of a suitable biopsy target for diagnosis, was a significant challenge in clinical practice. A positron emission tomography-computed tomography (PET-CT) based algorithm was developed to define: (i) whether RT may be present and (ii) select a representative biopsy site in the era of novel therapies (Musanhu *et al*., 2021).

In CNSL, the gold standard neuroimaging modality recommended by international guidelines in recent decades has been contrast-enhanced magnetic resonance imaging (CE-MRI) (Abrey *et al*., 2005). However, there are important caveats concerning magnetic resonance imaging (MRI) interpretation, particularly the challenge of distinguishing viable tumour from post-biopsy haemorrhage and treatment-related effects. Therefore, the disease may be under-staged or over-staged, as appearances of active tumour on the

current standard of CE-MRI are indistinguishable from enhancing, non-tumoural change. Two imaging applications for this purpose were developed: (i) the original clinical hypothesis and use of contrast clearance analysis (CCA), with its ability to distinguish viable CNSL from benign enhancement at baseline staging and for response-assessment, and (ii) ^{18}F-choline (FCH) radiotracer cranial PET-CT for staging, response-assessment, and prognostication (Kowa *et al.*, 2021; Millard *et al.*, 2021).

In summary, this thesis advances the imaging assessment in haematological malignancies, most notably with a standardised reporting framework (SIHMIR), patient imaging algorithms in BIA-ALCL, a patient imaging algorithm in CLL RT, and two CNSL patient imaging applications.

1.1 Overview of the classification of haematopoietic and lymphoid tumours

This thesis does not evaluate the complex classification of haematopoietic and lymphoid tumours; however, the same is reviewed to provide context to this field of study. Tumours are of B-cell or T/Natural Killer (NK)-cell clonal origin, with mature and immature cells at various stages of differentiation (Campo *et al.*, 2017). Several mature B-cell tumours have characteristic genetic abnormalities that are important in determining their biological features and can be useful in the differential diagnosis (de Boer *et al.*, 1995; Kanungo *et al.*, 2006; Levine *et al.*, 1989).

Haematological malignancies are the fifth most common cancer on a global scale and the second leading cause of cancer mortality (Stewart & Wild, 2014). Mature B-cell tumours account for approximately 4% of all new global cancer cases per year. The most common lymphoma subtypes are follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL), accounting for >60% of all lymphomas (Anderson *et al.*, 1998).

The lymphomas are classified as HL or NHL, the latter being further subdivided into LG-LPDs and HG-LPDs. A 'watchful-waiting' management strategy is adopted in a proportion of patients with LG-LPDs. Some patients with LG-LPDs, e.g., a proportion of patients with FL, never require treatment (Campo *et al*., 2017). In contrast, HG-LPDs are generally aggressive tumours requiring therapy, comprising chemoimmunotherapy, chemotherapy, +/- radiotherapy, +/- transplantation, in most patients (*Non-Hodgkin's lymphoma: diagnosis management (NG52)* (NICE 2016)).

Within any given entity, a range in clinical behaviour can be seen, with histological or clinical progression often observed during a patient's clinical course. Both morphology and immunophenotype often change over time as the lymphoid tumour undergoes clonal evolution with the acquisition of additional genetic changes. LG-LPDs can undergo HGT to HG-LPDs; however, evolution over time does not necessarily lead to the development of more aggressive lymphoma. For example, patients with DLBCL, an HG-LPD, can relapse with a more indolent clonally related FL. Some of the clonal evolutions can be unexpected and

not obviously connected, such as the development of a plasmacytoma in a patient with classic Hodgkin lymphoma (CHL) (Campo *et al*.,2017).

Having sufficient tissue for pathological diagnosis is critical in lymphomas. Morphology and immunophenotype are sufficient for the diagnosis of most lymphoid tumours. The WHO classification emphasises the importance of knowledge of clinical features, both for accurate diagnosis and the definition of some diseases. The diagnosis of lymphoid tumours should not take place in a vacuum, but rather in the context of a complete clinical history (Campo *et al.*, 2017; Cunningham *et al.*, 2017).

1.2 Overview of imaging of haematopoietic and lymphoid tumours

Medical imaging has evolved over more than 120 years (Figure 1), and a multitude of anatomical imaging-based and increasingly complex functional imaging-based tests are now applicable in both clinical and research platforms (Sharma *et al.*, 2012). The three principal imaging tests used for the assessment of lymphoid tumours are computed tomography (CT), PET-CT and MRI (Cunningham *et al.*, 2017). These modalities were extensively analysed in the authors' Nature Reviews Clinical Oncology *Perspectives* (Sharma *et al.*, 2012) and are briefly reviewed herein to provide context to this field of study.

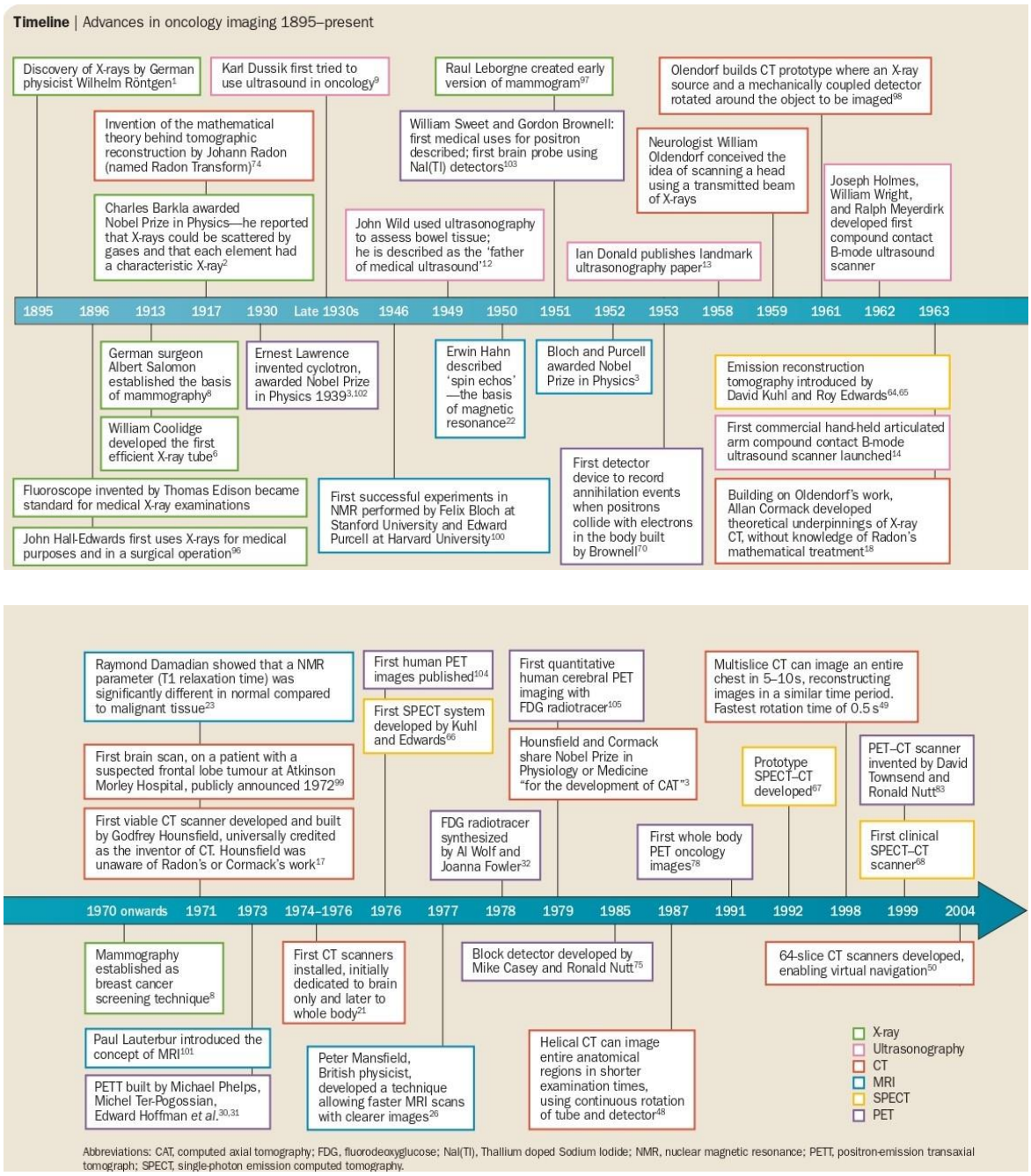

Figure 1| Timeline 1. *Advances in oncology imaging 1895 – 2004 (Sharma et al., 2012).*

CT

CT was invented in 1971 by Hounsfield (Ambrose, 1973; Hounsfield, 1973). CT uses ionising radiation, with a computer processing X-rays taken at multiple angles through the body to produce cross-sectional images (Kalender, 2011). Until the advent of CT, imaging tests available in lymphoma included chest X-rays and lymphography – the injection of

radiopaque contrast into pedal lymph vessels, with accumulation in abdominal lymph nodes, which could then be visualised with X-rays. X-rays and lymphography were crude tools used to assess thoracic and abdominal lymphadenopathy, combined with surgical staging laparotomy to assess the spleen (Carbone *et al.*, 1971; Sharma *et al.*, 2012).

CT constituted a major advance because it allowed non-invasive diagnosis of nodal and splenic disease and provided a means for response-assessment, being formally adopted into staging guidelines in 1989 (Figure 2; Lister *et al.*, 1989). However, CT was associated with limitations because it was unable to detect lymphoma in anatomically 'normal seeming' structures, including bone marrow infiltration, diffuse splenic, hepatic, or gastrointestinal disease (Cunningham *et al.*, 2017). CT is not accurate for the detection of viable lymphoma within a residual mass at 'end-of-treatment' (EOT) because inactive fibrosis and remaining viable lymphoma cannot be differentiated (Canellos, 1988).

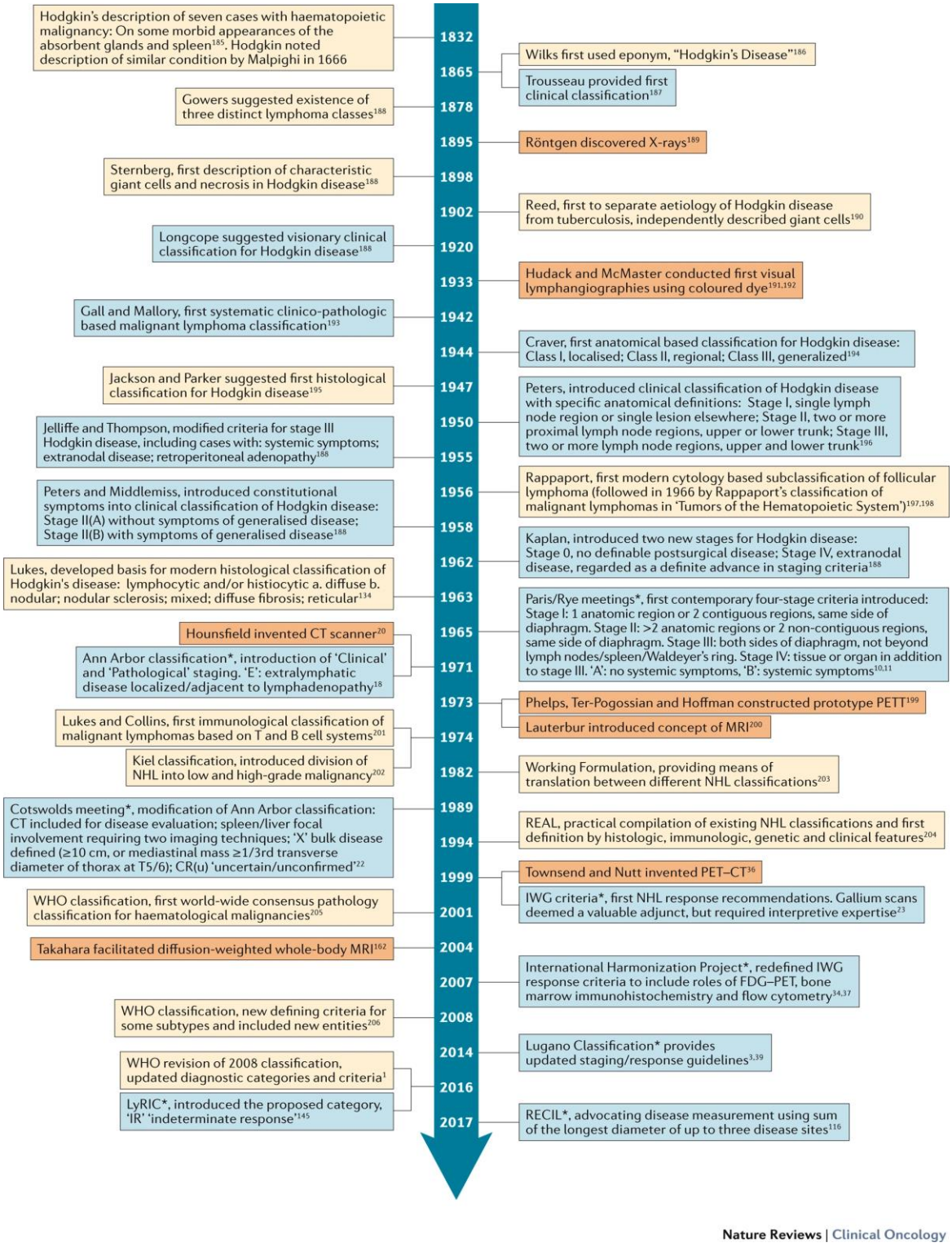

Figure 2| Timeline 2. *Timeline depicting the development of clinicopathological classifications, staging, response-assessment guidelines, and radiographic techniques in lymphoma[1] (Cunningham et al., 2017).*

[1] Developments in pathological classification systems are shown in beige, developments in clinical or radiological classification systems are shown in blue, and developments in imaging technologies are shown in orange.

Abbreviations: DLBCL, diffuse, large-B-cell lymphoma; FDG, fluorodeoxyglucose; IWG, International Working Group; LyRIC, Lymphoma Response to Immunomodulatory Therapy Criteria; MRI, magnetic resonance imaging; NHL, non-Hodgkin lymphoma; PET, positron-emission tomography; PETT, positron-emission transaxial tomography; REAL, revised European-American classification of lymphoid neoplasms; RECIL, Response Evaluation Criteria in Lymphoma; SUV, standard uptake value. *Denotes further discussion within the article. Three categories within 'timeline': development in imaging technology, pathology classification system, clinical or radiological classification/staging system.

PET-CT

PET was developed by Phelps and co-workers in 1973 (Phelps *et al.*, 1975; Ter-Pogossian *et al.*, 1975). This is a functional imaging technique; the patient is injected with a short-lived radioisotope attached to a biologically active molecule. The radiotracer overwhelmingly used in clinical practice comprises 2-deoxy-2[^{18}F]fluoro-D-glucose (FDG) (Ido *et al.*, 1978; Hoh *et al.*, 1993). The 'Warburg effect,' which describes the increased rate of glycolysis in cancer cells compared with surrounding non-malignant tissue (Warburg *et al.*, 1924), explains the theoretical basis underpinning the utility of FDG in oncology. Subsequent evidence showed FDG-PET signals could precede the detection of anatomical abnormalities associated with tumours, including haematological malignancies, and provide a sensitive staging and response-assessment tool (Strauss *et al.*, 1991; Rigo *et al.*, 1996; Spaepen *et al.*, 2003; Gatenby *et al.*, 2004; Cunningham *et al.*, 2017).

The role of PET-CT was first acknowledged within lymphoma staging and response guidelines in 2007 (Juweid *et al.*, 2007; Cheson *et al.*, 2007). Subsequently, in 2014, the Imaging Working Group (IWG) for the Lugano classification staging and response consensus recommendations embraced PET-CT as the modality of choice for disease assessment in most lymphoma categories (Cheson *et al.*, 2014; Barrington *et al.*, 2014). However, PET-CT has limitations in haematological malignancies. False-positive FDG uptake occurs with infection and inflammation (Juweid *et al.*, 2005; Buchmann *et al.*, 2001; Salaun *et al.*, 2009; Long *et al.*, 2011). FDG is not accurate at various anatomical sites, including the bone marrow, gastrointestinal tract, and central nervous system, each of which is affected by various haematological malignancies (Boellaard *et al.*, 2015). FDG accumulation can be measured on PET-CT data with the semi-quantitative 'standardised uptake value' (SUV) calculation. However, this is not accurate for differentiating most LG-LPDs from HG-LPDs (Juweid *et al.*, 2005; Cunningham *et al.*, 2017).

Rather than generically using PET-CT across the diverse spectrum of > 45 categories of haematological malignancies as advocated by the Lugano classification IWG consensus recommendations, there was a need to define the requirement or otherwise for tests in each lymphoma type (*Non-Hodgkin's lymphoma: diagnosis management (NG52)* (NICE 2016); Cunningham *et al.*, 2017).

MRI

The theoretical foundation for magnetic resonance was laid in the 1950s (Hahn, 1950), with the first MRI scans in the 1970s; Damadian, Lauterbur and Mansfield all made important contributions to the development of MRI (Lauterbur, 1973; Damadian *et al.*, 1977; Dreizen, 2004; Nobelprize.org (2012)). MRI uses the fact that most tissues in the body are abundant in hydrogen protons within water molecules. The former align in a strong magnetic field. When the magnetic pulse is turned off, the protons relax, emitting a small radiofrequency signal depending on their microenvironment (Gallagher *et al.*, 2008). MRI has several advantages over other modalities, including no patient radiation exposure and good contrast resolution (Sharma *et al.*, 2012). However, like CT, detection of viable lymphoma in anatomically normal-appearing tissue and within a residual mass is limited.

Diffusion-weighted imaging (DWI) is an MRI technique which measures the Brownian motion of water protons over microscopic distances in the extracellular space (Mansfield *et al.*, 1977; Takahara *et al.*, 2004). This is restricted in highly cellular lesions or where tissue architecture is disrupted (Padhani *et al.*, 2011). In recent years, the role of DWI in multiple myeloma has been established (*Myeloma: diagnosis management (NG35)* (NICE 2016)). Evidence for its application in other haematological malignancies is currently largely limited to studies with small populations and heterogeneous histologies (Punwani *et al.*, 2010; Mayerhoefer *et al.*, 2014; Mayerhoefer *et al.*, 2015).

The goal of the research presented in this thesis was to provide optimal, accurate disease assessment in order to improve patient survival outcomes and enable optimal use of healthcare resources.

Chapter 2: THESIS PUBLICATIONS

The publications presented in this thesis, related to the imaging assessment of haematopoietic and lymphoid tumours, and the advancement of new methodologies and applications, are illustrated in Figure 3. Six publications are included related to the four key themes of research.

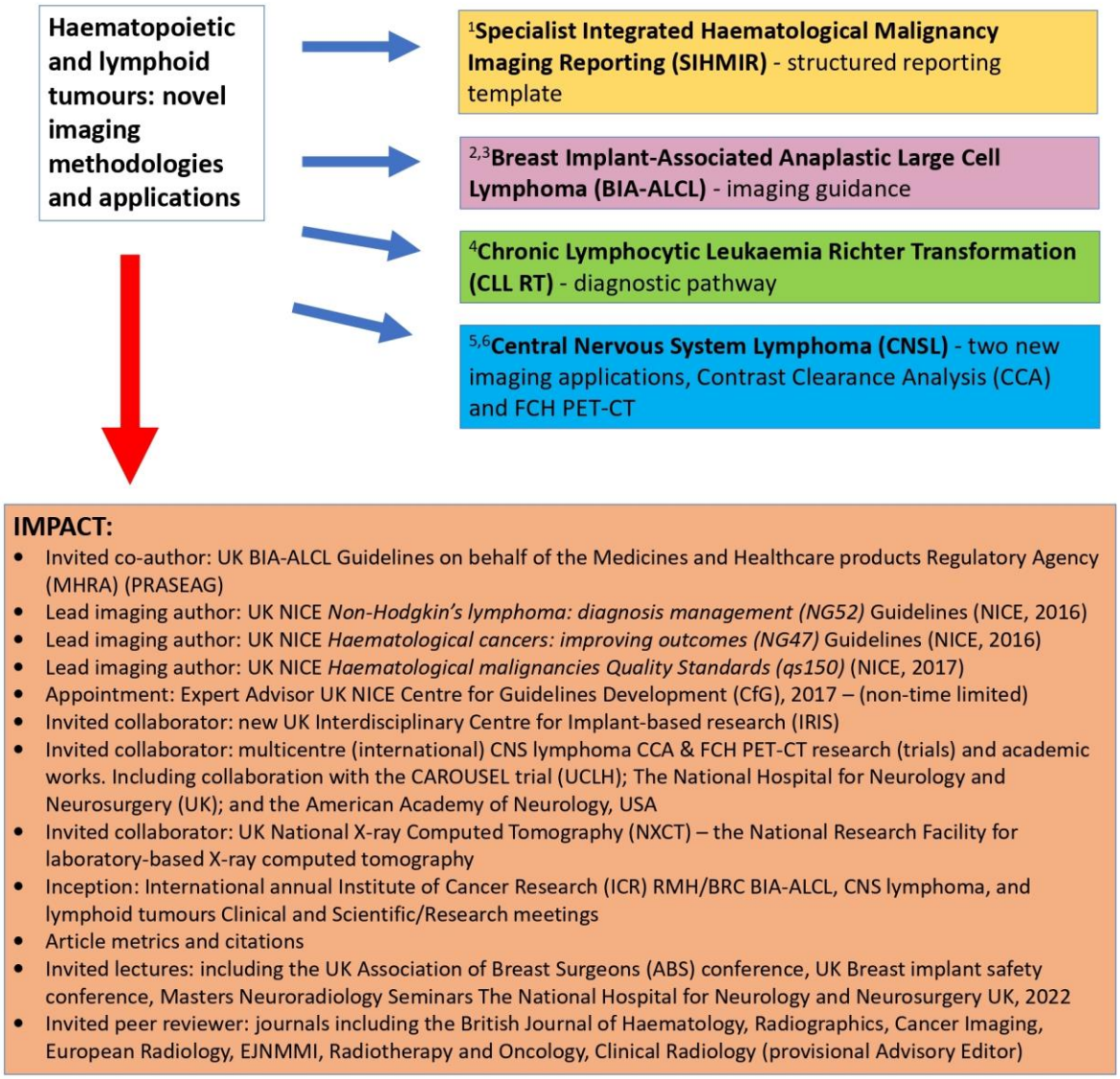

Figure 3| *A pictorial summary of thesis publications.*

Abbreviations: BRC, Biomedical Research Centre; CAROUSEL, Immunotherapy Using CAR-T cells to Target CD19 for Relapsed/Refractory CD19+ Primary CNS Lymphoma; EJNMMI, European Journal of Nuclear Medicine and Molecular Imaging; FCH, ^{18}F-choline; NHL, non-Hodgkin lymphoma; NICE, National Institute for Health and Care Excellence; PRASEAG, Plastic, Reconstructive and Aesthetic Surgery Expert Advisory Group; RMH, Royal Marsden Hospital; UCLH, University College London Hospital.

Specialist Integrated Haematological Malignancy Imaging Reporting (SIHMIR)

1. Evolution of lymphoma staging and response evaluation: current limitations and future directions. Cunningham J, Iyengar S, **Sharma B.** Nature Reviews Clinical Oncology. 2017 Oct; 14, 631 – 645. https://doi.org/10.1038/nrclinonc.2017.78 Epub 2017 Jun 13. PMID: 28607514
   Corresponding author: **Sharma B.**

Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL)

2. Breast Implant-associated Anaplastic Large Cell Lymphoma: Review and Multiparametric Imaging Paradigms. **Sharma B**, Jurgensen-Rauch A, Pace E, Attygalle AD, Sharma R, Bommier C, Wotherspoon AC, Sharma S, Iyengar S, El-Sharkawi D. Radiographics. 2020 May-Jun;40(3):609-628. https://doi.org/10.1148/rg.2020190198 Epub 2020 Apr 17. PMID: 32302264
   Corresponding author: **Sharma B.**

3. Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL): a good practice guide, pictorial review, and new perspectives. Mehdi AS, Bitar G, Sharma RK, RMH BIA-ALCL Working Group, Iyengar S, El-Sharkawi D, Tasoulis MK, Attygalle AD, Cunningham D, **Sharma B.** Clinical Radiology. 2022 Feb; 77(2): 79-87. https://doi.org/10.1016/j.crad.2021.09.002 Epub 2021 Sept 25. PMID: 34579859.
   Corresponding author: **Sharma B.**

Chronic Lymphocytic Leukaemia and Richter's Transformation (CLL RT)

4. Chronic lymphocytic leukaemia and Richter's transformation: multimodal review and new imaging paradigms. Musanhu E, Sharma RK, Attygalle A, Wotherspoon A, Chau I, Cunningham D, Dearden C, El-Sharkawi D, Iyengar S, **Sharma B**. Clinical Radiology. 2021 Nov;76(11):789-800. https://doi.org/10.1016/j.crad.2021.06.001 Epub 2021 Jun 30. PMID: 34217434. Corresponding author: **Sharma B.**

Central Nervous System Lymphoma (CNSL)

5. Are treatment response assessment maps (TRAMs) and 18 F-choline positron emission tomography the future of central nervous system lymphoma imaging? Kowa JY, Millard T, Goldman A, Sharma RK, Attygalle A, Mahalingam P, Marshall K, Welsh L, Li S, Mackinnon A, Rich P, Nicholson E, Iyengar S, El-Sharkawi D, Chau I, Cunningham D, **Sharma B**. British Journal of Haematology. 2021 Oct; 195 (1): e116-e119. https://doi.org/10.1111/bjh.17632 Epub 2021 June 9. PMID: 34109610. Corresponding author: **Sharma B.**

6. Can pre-transplant 18F-choline positron emission tomography predict relapse following autologous stem cell transplantation in primary central nervous system lymphoma? Millard T, Sammour F, Anthias C, Easdale S, Gonzalez-Arias C, Ethell M, Potter M, Iyengar S, El-Sharkawi D, Attygalle AD, Chau I, Cunningham D, Nicholson E, **Sharma B**. Can pre-transplant 18F-choline positron emission tomography predict relapse following autologous stem cell transplantation in primary central nervous system lymphoma? Bone Marrow Transplantation (*Nature).* 2022 Jan;57(1):113-115. https://doi.org/10.1038/s41409-021-01484-7 Epub 2021 Oct 5. PMID: 34611292. Corresponding author: **Sharma B.**

The next section of the thesis looks at each of the four themes in turn (SIHMIR; BIA-ALCL; CLL RT, and CNSL), providing a synopsis of the related research publications and their key original contributions.

2.1 Specialist Integrated Haematological Malignancy Imaging Reporting (SIHMIR)

Paper 1: Evolution of lymphoma staging and response evaluation: current limitations and future directions. Nature Reviews Clinical Oncology, 2017.

This [2]*Perspectives* was a critical analysis of the evolution of imaging and staging guidelines used in lymphoma (Figure 2). The strengths and limitations of clinical practice within the context of international mandates for evidence-based medicine were evaluated. The potential for novel techniques to monitor lymphoma, and changes to current clinical practice which could improve patient outcomes, were explored.

The author developed a new reporting framework termed SIHMIR. Key points are as follows.

Interpretation of multiparametric data within a haematological oncology team is fundamental to ensure the accurate and timely diagnosis and response-assessment of lymphoma. Therefore, clinicians, pathologists and imaging experts should share and discuss diagnostic results to produce robust patient management plans and improve outcomes (*Haematological cancers: improving outcomes (NG47)* (NICE 2016)). A correct histopathological diagnosis is essential in lymphoma because patient management (and survival outcomes) are primarily dependent on the lymphoma category (Dojcinov & Attanoos, 2001; Lester *et al.*, 2003). This is a complex area, with greater than 45 different lymphoma categories being recognised (Campo *et al*., 2017) and numerous different pathology diagnostic tests being used. In the UK National Health Service (NHS), 'Specialist Integrated Haematological Malignancy Diagnostic Services' (SIHMDS) have been developed as a standard of care (*Haematological cancers: improving outcomes (NG47)* (NICE 2016); *Haematological Malignancies Quality Standards* (NICE 2017)) to standardise diagnostic

[2] **Nature Reviews Clinical Oncology (NRCO) '*Perspectives*' type publications provide a forum for opinionated discussions of a topic or field, describe historical influences and foundations, and emergent research techniques and trends.**

protocols, provide patient-specific reports with clinically relevant conclusions and improve diagnostic accuracy.

Parallel issues to those in pathology diagnostic services apply in radiology. Both are increasingly complex disciplines and require the integration and correct interpretation of multiple investigations. Analogous to the development of SIHMDS in pathology, the author created the SIHMIR framework in radiology to facilitate the consistent reporting of disease burdens within multidisciplinary teams.

SIHMIR incorporates staging, prognostication, and response-assessment data from all anatomical-functional imaging tests (CT, PET-CT, MRI) within a single report, issued at each assessment point in the patient pathway. The approach is to reduce imaging 'error' rates by using standardised reporting, enable comparative datasets to be produced across different units and, therefore, improve patient outcomes.

SIHMIR involves an adaptable template-based reporting process (Figure 4), designed to ensure the analysis of all important review sites, including those which should prompt consideration of central nervous system (CNS) prophylaxis for the risk of secondary CNS lymphoma (SCNSL) and of disease or treatment-related complications. Lesion size and Deauville score data metrics are included, and consideration is given to HGT from indolent to aggressive NHL. Report conclusions are the responsibility of a single haemato-oncology imaging specialist, reflect a combined conclusion from multimodal data to provide overall stage and treatment response, and recommend the optimal test/biopsy approach for subsequent disease assessment.

Box 1 | **Specialist integrated haematological malignancy imaging reporting (SIHMIR)**

Nodal review sites

- Left/right neck
- Intraparotid
- Waldeyer's ring
- Left/right axilla
- Mediastinum: caudal extent, thymic bed involvement
- Left/right pulmonary hilum
- Retroperitoneum
- Spleen size (craniocaudal)
- Mesentery
- Left/right pelvic side wall
- Left/right inguinofemoral

Extranodal review sites

- Testes (ultrasonography)*
- Breast*
- Adrenal*
- Renal (cortical, pararenal, pelvicalyceal)*
- Bone marrow; bone (vertebral collapse)
- Paravertebral soft-tissue infiltration
- Lacrimal gland, intraorbital
- Sinonasal
- Lung; pleural; pericardial
- Liver; pancreatic; small/large bowel
- Subcutaneous; intramuscular

Toxicities/complications

- Paranasal sinuses (fungal infection)
- Venous: thromboembolism; superior vena cava obstruction
- Pulmonary: infections and drug reactions (early pneumonitis)
- CNS: hydrocephalus, spinal-cord compression
- Renal tract obstruction
- Gastrointestinal: biliary obstruction; bowel obstruction; colitis; pancreatitis

Measurements

- Anatomical largest lesions (nodal/extranodal)
- Metabolic SUV (liver and mediastinal blood pool SUV)
- Deauville score
- Possible transformation (for example, screening for Richter syndrome in patients with CLL using FDG–PET[140])

Specialist conclusions

- Bulky disease
- Number of involved nodal groups
- Number of involved extranodal sites
- Disease stage: early (I/II), advanced (III/IV) ($^{+/-}$ bone-marrow examination)
- Response: complete response, partial response, indeterminate response, stable disease, progressive disease
- Possible transformation
- Suitable biopsy sites (method)
- Optimal subsequent or response assessment scan type (CT, PET or MRI)

CLL, chronic lymphocytic leukaemia; SUV, standard-uptake value. *Lymphoma deposits in testes, breast, adrenal and renal tracts can be challenging to assess using single-modality imaging and might require additional prophylactic intrathecal therapy owing to an associated higher risk of CNS disease spread[92,102–104]. Management-focused conclusions include any further proposed investigations.

Figure 4| *Specialist integrated haematology malignancy imaging reporting (SIHMIR), an adaptable template-based imaging reporting method.*

2.2 Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL)

Paper 2: Breast Implant-Associated Anaplastic Large Cell Lymphoma: Review and Multiparametric Imaging Paradigms. Radiographics, 2020.

BIA-ALCL is a relatively newly recognised disease compared to most malignancies, first described in 1997 (Keech & Creech, 1997) and incorporated as a provisional category into the revised WHO classification of haematopoietic and lymphoid tumours in 2016 (Swerdlow *et al*., 2016). BIA-ALCL is a unique T-cell NHL, anaplastic lymphoma kinase (ALK)-negative, sharing some features of ALK-negative systemic and cutaneous anaplastic large cell lymphoma (ALCL) categories (Laurent *et al.*, 2016). The condition typically presents with a late-onset effusion, less commonly with a mass, a median of ten years following exposure to textured type breast implants (placed for oncoplastic or aesthetic indications) (Miranda *et al.*, 2014; Clemens *et al.*, 2016). The current estimated incidence varies from one in 3817 breast implant patients to one in 30,000 (de Boer *et al.*, 2018; Doren *et al.*, 2017).

Most patients with the effusion-only subtype have indolent and good prognosis disease, while those with the mass-forming subtype or advanced-stage disease have a poorer prognosis. Complete surgical removal of disease is recommended as the first line (and curative) management for most cases of BIA-ALCL. This contrasts with the wide spectrum of other lymphoma types where surgery is not indicated, systemic therapy +/- radiotherapy is used instead. Systemic combination chemotherapy is reserved for mass-forming, distant, refractory, or relapsed BIA-ALCL disease (Miranda *et al.*, 2014; Clemens *et al.*, 2016; Mehta-Shah *et al.*, 2018).

This condition is highly nuanced, principles from both haematological malignancies and solid cancers being pertinent. BIA-ALCL is not included within current international lymphoma staging and response assessment guidelines. The Lugano classification (Cheson *et al*., 2014; Barrington *et al*., 2014) and Deauville criteria (Meignan *et al*., 2009) predated the inclusion of this disease within the WHO classification. For these reasons, imaging tests are prone to misinterpretation in BIA-ALCL, leading to patient diagnostic delays and unnecessary investigations (Sharma *et al*., Radiographics 2020; Mehdi *et al*., 2021;

O'Connell *et al*., 2022). The USA [3]National Comprehensive Cancer Network (NCCN) consensus Guidelines on the diagnosis and treatment of BIA-ALCL did not include key strengths and limitations of imaging tests in BIA-ALCL and did not fully appreciate these points within the disease diagnostic algorithm (Clemens *et al*., 2019).

An analysis of the strengths and weaknesses of all anatomical and functional imaging tests used in BIA-ALCL was published; the unique biology and natural history of BIA-ALCL contribute to false positives and false negatives (Table 1).

Table 1| *Strengths and limitations of anatomical-functional imaging tests in BIA-ALCL, including new research tools (WB-DWI).*

Table 2: Strengths and Weaknesses of Radiologic Techniques in BIA-ALCL

Imaging Finding, Purpose, or Aspect	Modality					
	US	Mammography	Breast MRI	CT	PET	Whole-Body DWI
Effusion	First-line test Accurate	Not accurate	Second-line test Accurate	Accurate	Demonstrates effusion Accurate	Demonstrates effusion Accurate
Mass component	First-line test Accurate	Not accurate	High accuracy	Accurate	Demonstrates mass Accurate	Demonstrates mass Accurate
Biopsy guidance	First-line test	Not useful	Can be used	Not routinely used	Not routinely used	Can be used
Whole-body staging	Not provided	Not provided	Not provided	Provided Second-line test	Provided First-line test	Provided Research indication
Radiation exposure	None	0.4 mSv	None	15 mSv	14–24.4 mSv*	None
Intravenous contrast material injection	None	None	Administered (unless contraindicated†)	Administered (unless contraindicated†)	Administered	None
Causes of false positives	…	…	Internal mammary chain Axillary lymphadenopathy	Internal mammary chain Axillary lymphadenopathy	Breast implant capsule uptake Internal mammary chain Axillary lymphadenopathy	Internal mammary chain Axillary lymphadenopathy
Causes of false negatives	…	Effusion Mass	…	Bone marrow	Effusion Bone marrow	Bone marrow—research application

Note.—Assessment of BIA-ALCL is nuanced, in the context of both the peri-implant effusion subtype and the mass-forming or distant disease subtype. To ensure accurate and optimal patient management, it is critical to appreciate the strengths and limitations of the panoply of imaging techniques in this unique condition. DWI = diffusion-weighted imaging.
*Dose dependent on the PET/CT technique.
†Contraindications to intravenous contrast material include patient allergy.

Abbreviations: WB-DWI, whole body-diffusion weighted imaging.

[3] **NCCN guidelines comprise the consensus standard of care for diagnosis and management of most recognised cancers in the USA. The guidelines are evidence-based where possible, expert consensus opinion being utilized in areas where evidence is lacking. The clinical practice guidelines are based on the concurrence of 27-component oncology centres, member committees being formed by over 1200 clinician volunteers.**

Based on these principles, disease algorithms with imaging guidance for both effusion-only and mass-forming subtypes were developed by the author. This included diagnosis, staging, response-assessment, and surveillance guidance, being designed to enable optimal patient management and outcomes and efficient use of healthcare resources (Figure 5).

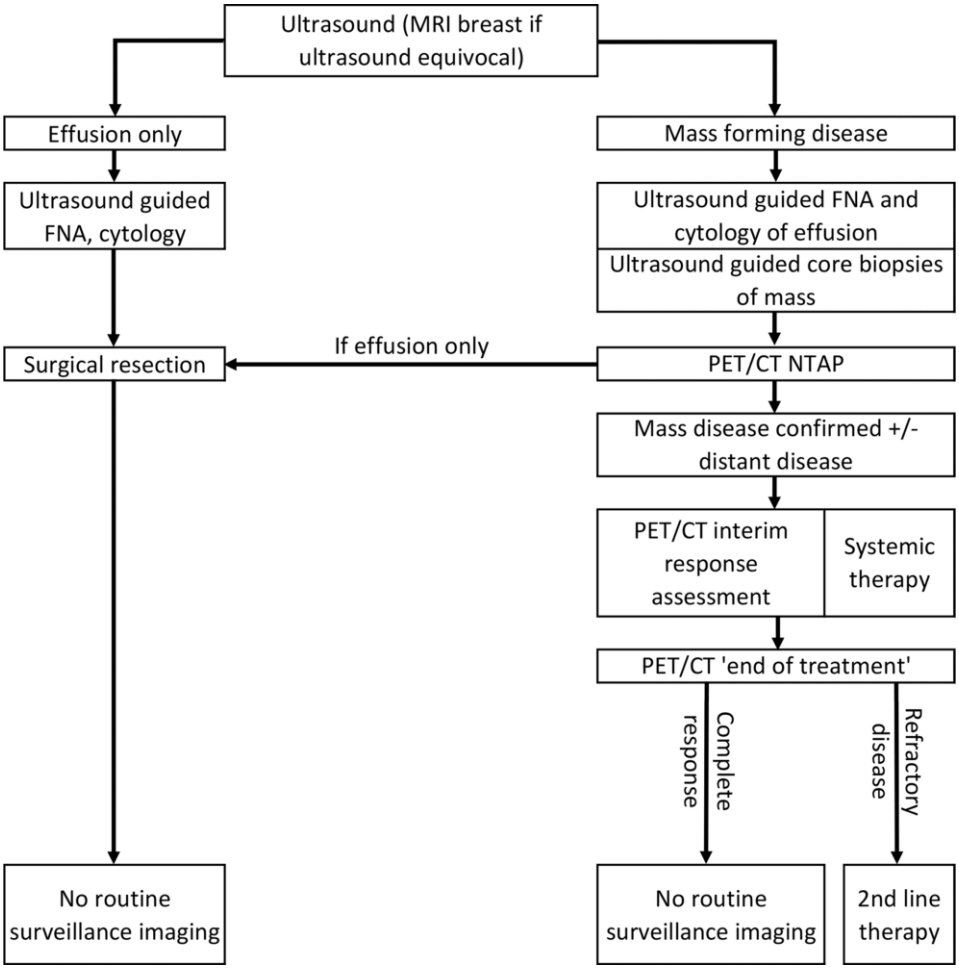

Figure 5| *Original imaging algorithms for diagnosis, staging, response-assessment, and surveillance for both 'effusion-only' and 'mass-forming' subsets of BIA-ALCL.*

NB Original pathway diagram summarizes patient management paradigms for accurate staging and response-assessment with optimal use of currently available imaging and healthcare resources. *FNA* = fine-needle aspiration; *NTAP* = neck, thorax, abdomen, pelvis.

A significant departure from the NCCN Guidelines was the new statement that routine post-treatment imaging surveillance is not required in BIA-ALCL. NCCN Guidelines had stated the role of radiographic disease surveillance is unclear, but CT or PET imaging may

be considered every six months for two years, then as clinically indicated. The rationale for the authors' statement that routine surveillance is not warranted included the following points:

- Evidence does not support routine post-treatment surveillance imaging in HL, or DLBCL patients in remission after first-line therapy; clinical follow up is crucial (*Non-Hodgkin's lymphoma: diagnosis management (NG52)* (NICE 2016)).

- Post-treatment surveillance imaging in lymphoma patients does not improve patient outcomes or overall survival (OS).

- Evidence demonstrates the detection of lymphoma relapse is not increased with routine surveillance imaging. In the lymphoma setting, most relapses present clinically and at 'different timepoints' from arbitrary imaging or clinical follow up appointment times.

- Routine imaging results in a significant rate of incidental findings and false positives, causing further tests and follow up in patients. Imaging tests also cause anxiety in a considerable proportion of patients both with hospital attendances and while waiting for scan results (Armitage, 2012; Dann *et al.*, 2014; Thompson *et al.*, 2014).

- Effusion-only disease, which comprises most BIA-ALCL patients, has a good prognosis. Surgical explantation of disease is curative in most patients (Miranda *et al*., 2014; Clemens *et al*., 2016).

- Based on the evidence in NHL above, UK NICE Guidelines 2016 (Sharma B, co-author) recommended 'routine surveillance imaging should not be offered to people in complete remission after first-line treatment with curative intent in DLBCL' *(Non-Hodgkin's lymphoma: diagnosis management (NG52) (*NICE 2016)).

- The author stated this principle, as in other lymphoma categories, also applies in BIA-ALCL. Early evidence evaluating post-treatment surveillance imaging (PET-CT) in BIA-ALCL supports this. Disease relapse has not been detected on routine

surveillance imaging in BIA-ALCL (Johnson *et al*., 2017; O'Connell *et al.,* 2021; Mehdi, *et al.*, (ASH abstract) 2021).

This publication provided: an analysis of the evidence in this emergent field; an assessment of the strengths, limitations, and indications of the panoply of radiological tests in BIA-ALCL; new patient algorithms for the management of different BIA-ALCL subtypes, including the new statement that routine surveillance imaging is not indicated; and new research perspectives (Chapter 6).

Paper 3: Breast Implant-associated anaplastic large cell lymphoma (BIA-ALCL): a good practice guide, pictorial review, and new perspectives. Clinical Radiology, 2021.

A significant unmet need remained in the published literature relating to a practical guide for specialist and general radiologists and trainees who may encounter BIA-ALCL. This publication provided a step-by-step best practice guide for patient management. The work also evolved to include new guidance statements, which the author developed in a NICE Guideline statement format.

Key original concepts within this publication included the following:

- Primary mediastinal B-cell lymphoma (PMBCL) is the archetypal lymphoma category where radiological and pathological correlation is mandatory to provide the correct diagnosis. Correlation is also required to diagnose the three types of marginal zone lymphoma (MZL): (i) splenic marginal zone lymphoma (SMZL), (ii) nodal marginal zone lymphoma (NMZL) and (iii) extra-nodal marginal zone lymphoma (ENMZL) (Campo *et al.*, 2017). This correlation is also fundamental to the correct and timely diagnosis of BIA-ALCL - a delayed diagnosis in a considerable proportion of patients. Correlation aids in ensuring appropriate volumes of cytology aspirates are obtained, appropriate biopsies of any mass-forming components are obtained, and suitable cytology work-up with BIA-ALCL markers is undertaken at an SIHMDS. The diagnosis of BIA-ALCL effusion-only subtype disease, good prognosis, and BIA-ALCL mass-forming disease, poorer prognosis, is enabled by this approach.

- Examples of detailed practical guidance for radiologists who may encounter possible BIA-ALCL patients included: the frequency of ultrasound probe to be used, methods for obtaining cytology and histology samples, the MRI sequences to be acquired.

- The clinical problem of a non-diagnostic aspirate was also addressed. In patients with effusions suspected to be due to BIA-ALCL and recurrent implant-associated effusions, 'as much of the peri-implant effusion as possible should be aspirated and analysed.' This is because small-volume aspirates and repeat aspirations are associated with higher false-negative cytology rates due to serial dilutional effects (Jones *et al.*, 2019). Pathological diagnosis at an SIHMDS is recommended prior to surgery.

- UK MHRA Plastic, Reconstructive and Aesthetic Surgery Expert Advisory Group (PRASEAG) Guidelines had been recently published (Turton *et al.*, 2021; Sharma B, co-author), and USA NCCN BIA-ALCL Guidelines had been recently updated (National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology. T-cell lymphomas. Version 1.2021.). The UK and USA Guidelines were analysed, and guidance statements, in a NICE guideline format were formulated (Table 2).

Table 2|*Imaging pathway for breast implant-associated anaplastic large cell lymphoma (BIA-ALCL): a summary of guidelines and recommendations at each step of the patient pathway, stratified by disease subtype, has been created to simplify the diagnostic imaging pathway.*

DIAGNOSIS AND STAGING	
Offer	Breast ultrasound for people with suspected BIA-ALCL.
Offer	Ultrasound-guided FNA and cytological analysis if an effusion is present.
Offer	Ultrasound-guided core biopsies if a mass is present.
Offer	Staging PET-CT (NTAP) if the mass is histologically diagnosed as BIA-ALCL.
ASSESSING RESPONSE TO TREATMENT	
Do Not	Do not routinely offer imaging after surgical resection of effusion-only disease.
Offer	PET-CT for interim response-assessment if mass-forming BIA-ALCL or distant disease.
Offer	PET-CT for 'end-of-treatment' response if mass-forming BIA-ALCL or distant disease.
PRE-SURGICAL ASSESSMENT	
Consider	MRI breast or diagnostic CT if surgery is planned as part of salvage therapy for mass-forming/refractory disease.
SURVEILLANCE	
Do Not	Do not routinely offer surveillance imaging for BIA-ALCL (effusion-only or mass-forming) disease.

- During cross-sectional imaging reporting, if a breast implant is *in situ*, this should be a routine review site and included as a data item as per SIHMIR (Cunningham *et al.*, 2017).

- The prognosis for most patients with treated BIA-ALCL is excellent, and the relapse rate is low, particularly in patients with the effusion-only disease, which comprises most patients (Miranda *et al.*, 2014; Clemens *et al.*, 2016). In line with published work in other lymphomas and practice in breast cancer, the author suggested an open-access-

follow-up (OAFU) clinic/telephone clinic policy may be applied, enabling prompt alleviation of patient concerns and efficient use of limited healthcare resources.

- The author stated current imaging practice in BIA-ALCL is an example of the 'Cascade Effect' in the clinical care of patients. In biological systems, cascade refers to a process that 'when commenced proceeds stepwise to its full inevitable conclusion.' The cascade effect also occurs in clinical care (Mold & Stein, 1986). It describes a process where a series of patient interventions take place, often catalysed by anxiety, which then becomes difficult to stop. It includes the scenario where an initial test is performed based on 'weak' evidence, resulting in incidental and false-positive findings, leading to multiple further investigations over a period, i.e., a cascade of patient interventions. Invariably the cascade effect is not recognised. This occurs in a considerable proportion of patients being investigated for BIA-ALCL, with various imaging tests being utilised at a variety of time points in the patient pathway. Data is prone to misinterpretation, together with incidental findings. This leads to further imaging investigations, including biopsies and follow-up scans, causing patient anxiety, and impacting limited healthcare resources. It is important that practitioners caring for BIA-ALCL patients, as well as healthcare professionals in general and specialist disciplines, are aware of the cascade effect.

This publication provided a practical step-by-step best practice guide for the diagnostic work-up of patients with potential BIA-ALCL, clinical practice has varied widely across the UK NHS and in developed countries. Guidance statements for the patient pathway in a NICE guideline format were first presented.

2.3 Chronic lymphocytic leukaemia and Richter's transformation

Paper 4: Chronic lymphocytic leukaemia and Richter's transformation: multimodal review and new imaging paradigms. Clinical Radiology, 2021.

CLL is the most common leukaemia in adults. The condition manifests as a diverse spectrum from indolent to aggressive disease, RT. The ability to promptly diagnose RT was a significant unmet need at the time of this work.

The WHO classification of haematopoietic and lymphoid tumours defines CLL as 'an accumulative lymphoproliferative disorder of monomorphic round B-lymphocytes involving the peripheral blood, bone marrow and lymphoid organs' (Campo *et al.*, 2017). The prognosis varies widely, with approximately one-third of patients having indolent disease not requiring treatment (Baumann *et al*., 2014).

RT is defined as the 'transformation of CLL into an aggressive lymphoma,' most commonly Richter's syndrome-DLBCL (RS-DLBCL) (Richter *et al.*, 1928; Lortholary *et al.*, 1964; Rossi *et al*., 2011). RT may develop at any time and has a poor prognosis with a median OS of 12 months - requiring different therapy from CLL (Wang *et al*., 2020; Tsimberidou *et al*., 2006).

It is clinically vital to diagnose RT rapidly to commence appropriate treatment, which may improve patient outcomes (progression-free survival (PFS) and OS) (Wang *et al.*, 2020; Tsimberidou *et al.*, 2006; Allan *et al.*, 2018).

HGT also occurs in other lymphomas. LG-LPDs such as FL, lymphoplasmacytic lymphoma and MZL also transform to DLBCL in a proportion of patients (Swerdlow *et al.*, 2017).

Regarding HGT:

- The prevailing orthodoxy had been PET-CT is useful to detect HGT. The contemporary view in clinical practice was that LG-LPDs such as FL have lower SUV_{max} levels than HG-LPDs such as DLBCL, retrospective studies suggest 'cut-off' SUV_{max} values may discriminate, e.g., a SUV_{max} of ten (Casulo *et al*., 2015; Cunningham *et al.*, 2017).

- However, studies evaluating the FDG-avidity and SUV_{max} levels of different lymphoma histological categories were of low quality by Grading of Recommendations, Assessment, Development and Methodology (GRADE) methodology (NICE 2012; http://gradeworkinggroup.org/). The number of studies was small, analyses were retrospective, with small numbers of both patients and histological categories. For example, the largest of these studies (Weiler-Sagie *et al*., 2010) reporting the FDG avidity of lesions in 766 lymphoma patients contained a diverse range of histological categories.

- FL, although an LG-LPD, paradoxically demonstrates high SUV_{max} levels (there are no good quality published studies analysing the SUV_{max} in different grades of FL). In clinical practice, there is a significant overlap in the SUV_{max} values between FL and DLBCL. PET-CT cannot accurately detect FL transformation to DLBCL (*Non-Hodgkin's lymphoma; diagnosis management (NG52)* (NICE, 2016)), a common clinical problem in lymphoma.

- Falchi *et al.* (2014) correlated PET SUV_{max} with histology in 332 CLL patients. Indolent CLL, accelerated phase CLL, and RT cohorts were assessed, finding SUV_{max} correlates with aggressiveness of the disease. From specialist lymphoma experience at the Royal Marsden Hospital (RMH) and the Institute of Cancer Research (ICR) for 2 decades, the author had also observed indolent CLL typically demonstrates extremely low SUV_{max} levels on PET imaging, whereas HG-LPDs such as DLBCL and CHL demonstrate intense FDG accumulation. Unlike the situation in most of the other currently recognised lymphomas, CLL is one indication where PET may accurately discriminate HGT. Based on these principles and the authors' prior work developing NICE NHL Guidelines, which included NHL HGT Guidelines (*Non-Hodgkin's lymphoma; diagnosis management (NG52)* (NICE, 2016)), an original

patient management pathway using PET as a decision-making tool in CLL was formulated (Figure 6).

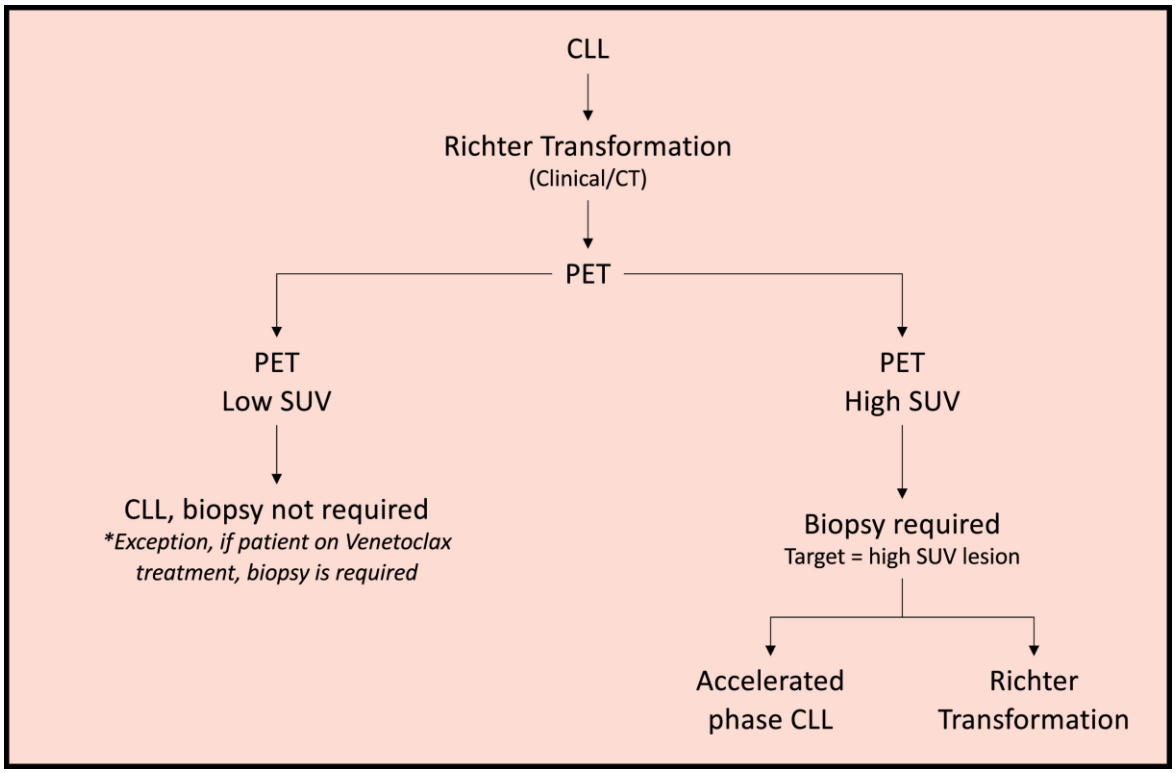

Figure 6| *A PET-CT driven decision tool for CLL patient management in the era of novel therapies, to define: i). whether biopsy for potential RT is required; ii). to select a suitable representative biopsy site.*

- This algorithm enabled two clinical decisions:

(i) Whether a biopsy should be performed for potential RT. Clinical and/or imaging features may suggest RT. The latter include a rapid size increase of lymphadenopathy, either generalised or disproportionately affecting a nodal site, and/or change in morphology (e.g., the development of central necrosis, which may be due to rapid growth). However, these features do not have high specificity for RT. PET SUV_{max} will accurately discriminate indolent CLL (low SUV_{max}) from accelerated phase CLL and RT (both demonstrate high SUV_{max}) (Falchi *et al*., 2014). Therefore, if RT is suspected either clinically or with imaging, a PET-CT study should be performed to decide whether a biopsy is required (also avoiding the common clinical problem of unnecessary biopsy in patients with indolent CLL).

(ii) Selection of a suitable representative biopsy site. In most patients with RT, a proportion of lesions reflect indolent CLL, others reflecting RT. The selection of a suitable biopsy target to diagnose RT is challenging. PET-CT enables this selection, the interventional radiologist being able to target a high SUV_{max} lesion (also avoiding the common clinical problem of patients having to undergo repeat biopsies to different lesions, with initial biopsies reflecting known indolent CLL).

Although PET SUV_{max} is an accurate non-invasive imaging biomarker tool to differentiate indolent CLL from accelerated phase CLL & RT, exceptions apply if the patient is being treated with novel agents – with false low SUV_{max} measurements in the context of BCL-2 inhibitors such as venetoclax, and false high SUVmax measurements when patients develop resistance to B-cell receptor signalling pathway inhibitors such as ibrutinib (Mato *et al*., 2019). These findings were incorporated into the algorithm.

This publication provided a comprehensive review and new perspectives for anatomical and functional imaging tests in CLL and RT diagnosis, staging and response-assessment. A PET-CT driven decision-making algorithm for the significant clinical problem of diagnosing HGT (RT) from CLL was developed.

2.4 Central Nervous System Lymphoma

Paper 5: Are treatment response assessment maps (TRAMs) and ^{18}F-choline positron emission tomography the future of central nervous system lymphoma imaging? British Journal of Haematology, 2021.

There are two classifications of CNSL. The WHO defines primary central nervous system lymphoma (PCNSL) as 'lymphoma confined to the CNS parenchyma, dura, leptomeninges, cranial nerves and spinal cord or the intraocular compartment in immunocompetent patients.' SCNSL is defined as 'lymphoma that has spread to the CNS from elsewhere in the body' (Campo *et al.*, 2017). PCNSL constitutes 2.2% of brain malignancies, with a higher incidence in older adults and the immunosuppressed. SCNSL occurs early (median 5-12 months) following diagnosis of aggressive NHL (Hill & Owen, 2006). Both are devastating conditions. OS is circa three years for PCNSL and two to several months for SCNSL (Korfel & Schlegel, 2013; Hill & Owen, 2006).

For recent decades, CE-MRI has been the standard imaging approach for CNSL, as per International PCNSL Collaborative Group (IPCG) consensus guidelines (Abrey *et al.*, 2005). Enhancing intracranial abnormalities are designated active disease. However, it is important to appreciate that CE-MRI has significant limitations. CE-MRI does not reliably distinguish viable tumour from iatrogenic causes of enhancement, e.g., biopsy, chemotherapy-induced inflammation, infarcts and radionecrosis (Wen *et al.*, 2010). Additionally, both radiotherapy treatment and novel anti-lymphoma immunotherapy are associated with pseudoprogression: an atypical response with new/enlarging enhancement in the absence of true disease progression (Cheson *et al.*, 2016). Equivocal CE-MRI findings may lead to patients receiving inadequate treatment.

Furthermore, the prognostic value (for PFS and OS) of early complete response by IPCG MRI criteria has produced contradictory results (Tabouret *et al.*, 2017). The disparity compared to imaging advances in CHL over the last two decades is striking: FDG PET-CT has proven to have high accuracy in staging, response-assessment, and prognostication across the entire

CHL patient pathway, contributing significantly to improved survival outcomes (Cunningham *et al.*, 2017).

To address these challenges, inspiration was taken from imaging in solid cancers. Two novel CNSL imaging techniques were piloted by the author at the RMH tertiary specialist referral centre: CCA, formerly known as treatment response assessment maps (TRAMs) and ^{18}F-choline (FCH) PET-CT.

CCA is an MRI-based approach whereby CE-MRI images are acquired at 5 and 60-105 minutes after contrast injection, a subtraction map derived and displayed as a colour scale, high contrast clearance (due to 'disruption' of the blood-brain barrier) is depicted in blue and low clearance (due to an 'intact' blood-brain barrier) in red; the contrast clearing blue areas considered to reflect active disease. At the time of this work there was limited published literature describing this technique in primary cranial tumours (gliomas) and CNS metastases from solid cancers (Zach *et al.*, 2014), and there were no publications in relation to either the concept or use of CCA in CNSL.

PET-CT imaging to date has overwhelmingly used FDG as a radiotracer in clinical practice (Sharma *et al.*, 2012). However, accurate CNS assessment with FDG is precluded due to high physiological levels of FDG uptake by grey and white matter (Cunningham *et al.*, 2017). The FCH radiotracer had been utilised in high-grade-gliomas (Lam *et al.*, 2011). Activated choline metabolism is associated with oncogenesis (Glunde *et al*., 2011), and in PCNSL is thought in part to be due to MYC overexpression (a potent oncogene related to several aggressive lymphoma subtypes) (Xiong *et al*., 2017; Campo *et al.*, 2017).

Unlike FDG in the CNS, FCH provides a high 'tumour-to-normal-tissue' uptake ratio (Rice *et al.*, 2011). The published literature for FCH PET-CT in lymphoma had been extremely limited, e.g., comprising single patient case reports of histology proven CNSL in a cranial tumour series (Utriainen *et al*., 2003) and incidental systemic lymphoma detected during prostate cancer imaging (FCH is a radiotracer used for prostate cancer imaging) (De Leiris *et al.*, 2018). Following UK Administration of Radioactive Substances Advisory Committee

(ARSAC) licence approval in 2011, it was possible for the author to lead the novel implementation of radiotracer FCH PET-CT imaging alongside conventional CE-MRI imaging for staging and response-assessment of CNSL patients at the RMH.

Findings demonstrated that CCA appears efficacious for the clinical problem of differentiating active CNSL from benign post-biopsy change, in line with work suggesting utility for this indication in other tumour types (Zach *et al*., 2014). This publication was the first report on the use of CCA and FCH PET-CT to differentiate viable remaining lymphoma from post-biopsy benign change (Figure 7).

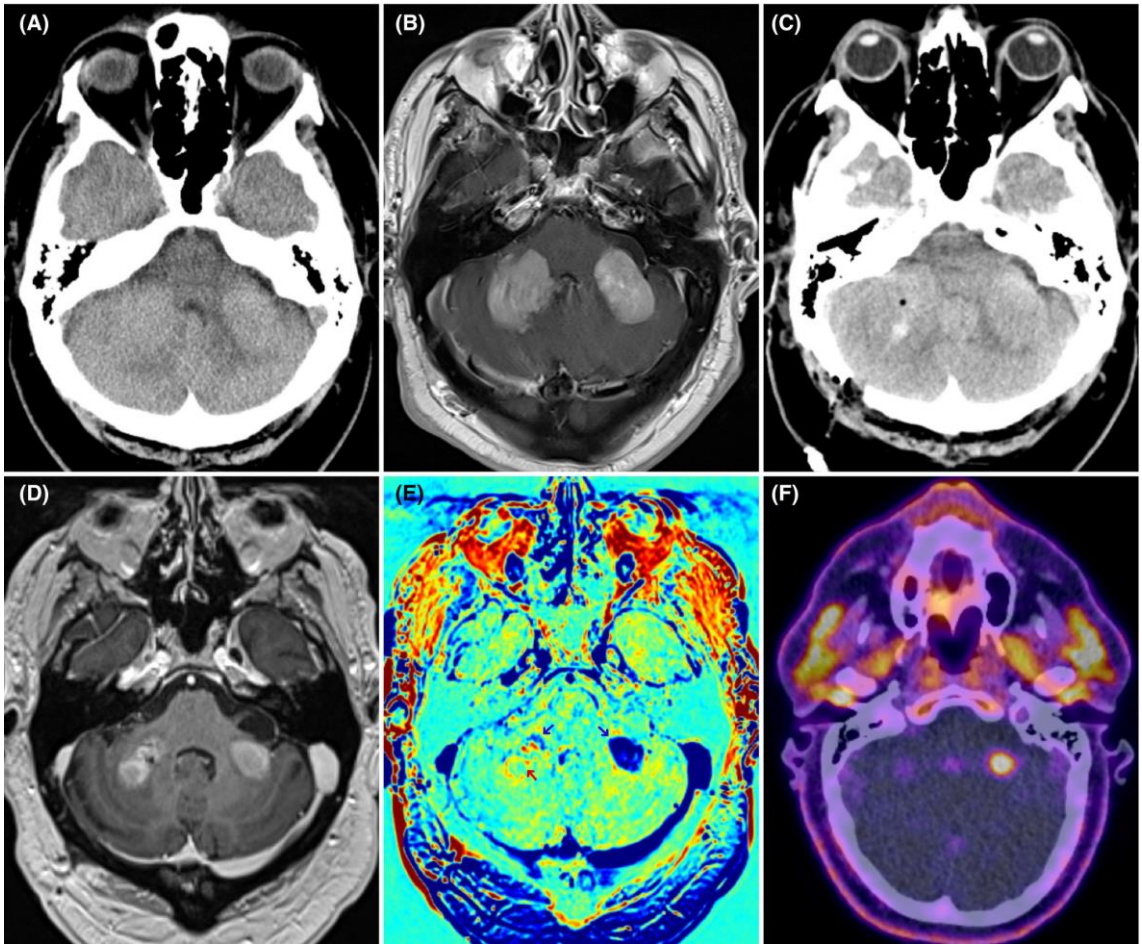

Figure 7| *The efficacy of two novel applications of (i) contrast clearance analysis (CCA) and (ii) FCH PET-CT to differentiate viable lymphoma from post-surgical biopsy benign change in central nervous system lymphoma (an unmet clinical need).*

N.B A patient with diffuse large B-cell lymphoma presenting with bilateral cerebellar lesions seen initially on CT (A) with subsequent CE-MRI (B). The patient went on to have a biopsy of the right cerebellar lesion with CT following (C). A short interval follow-up CE-MRI after starting

dexamethasone (D) found reduced size bilateral cerebellar lesions. TRAMs at this time (E) demonstrated only small volume active disease (blue arrows) in the right biopsied lesion with the remainder of the right sided CE-MRI enhancement (D) unrelated to active disease (red arrow). FCH PET-CT supported these findings (F). CE-MRI, contrast-enhanced-magnetic resonance imaging; CT, computed tomography; FCH, ^{18}F-choline; TRAMs, treatment response assessment maps; PET, positron emission tomography.

CCA and FCH PET-CT may have greater accuracy than CE-MRI for interim and EOT responses because these imaging applications provide information beyond that of CE-MRI. Patient cases where CCA and FCH PET-CT were both more accurate (for predicting PFS) than CE-MRI at EOT were also described in this work. In each case, CE-MRI showed persistent enhancement (false-positive) whereby CCA and FCH PET-CT demonstrated Complete Response (CR), avoiding the need for further treatment (including radiotherapy, with its associated toxicity profile, in one of the described cases).

Further original points in this publication included: FCH PET-CT can be clinically utilised in patients who are unable to undergo MRI imaging (e.g. due to contraindications, including non-MRI compatible pacemakers and *in situ* metal prosthesis); FCH PET-CT may also reduce the overall patient dose of MRI gadolinium-based intravenous contrast agents, an area where there have been safety concerns (including nephrogenic systemic fibrosis and organ deposition) (Young *et al*., 2019; McDonald *et al.*, 2015; European Medicines Agency 2017).

This publication described early work with a small number of patients and was the first to describe two novel imaging applications of CCA and FCH PET-CT in CNSL.

Paper 6: Can pre-transplant 18F-choline positron emission tomography predict relapse following autologous stem cell transplantation in primary central nervous system lymphoma? Bone Marrow Transplantation, 2021.

PCNSL has poor patient survival outcomes. Following first-line treatment, consolidation therapy is therefore used. In responding transplant-eligible patients, this comprises autologous stem cell transplantation (ASCT), whilst transplant-ineligible patients are recommended to undergo whole- brain radiotherapy (WBRT) (Prica *et al.* 2012; Korfel & Schlegel 2013; Ferreri *et al.*,2017; Fox *et al.*, 2019). Of concern, and unlike the clinical situation in both CHL and systemic DLBCL, there is a lack of prognostic tools in PCNSL prior to transplant, particularly to predict early post-transplant relapse.

The disease may be over-staged with CE-MRI, as appearances of active tumour on the current standard of MRI are indistinguishable from enhancing, non-tumoural change. It was hypothesized that enhancing lesions on CE-MRI, but without significant activity on FCH PET-CT, do not reflect active disease. If FCH PET-CT can distinguish between benign enhancement on CE-MRI and active disease, it would be expected to provide a more accurate assessment of disease status.

Following institutional approval, retrospective consecutive patient-series data at our specialist centre were analysed. Between 2015 and 2019, eleven PCNSL patients underwent ASCT. Nine patients had FCH PET-CT and CE-MRI prior to ASCT. Two of these nine patients subsequently clinically relapsed following ASCT. Both had residual disease on pre-ASCT FCH PET-CT. The seven patients who did not clinically relapse had a reported CR on FCH PET-CT (Figure 8). With pre-ASCT MRI, five cases of residual disease (enhancement) were observed. This included the two patients who clinically relapsed but also three patients who did not (follow up 1.8-3.3 years post-ASCT).

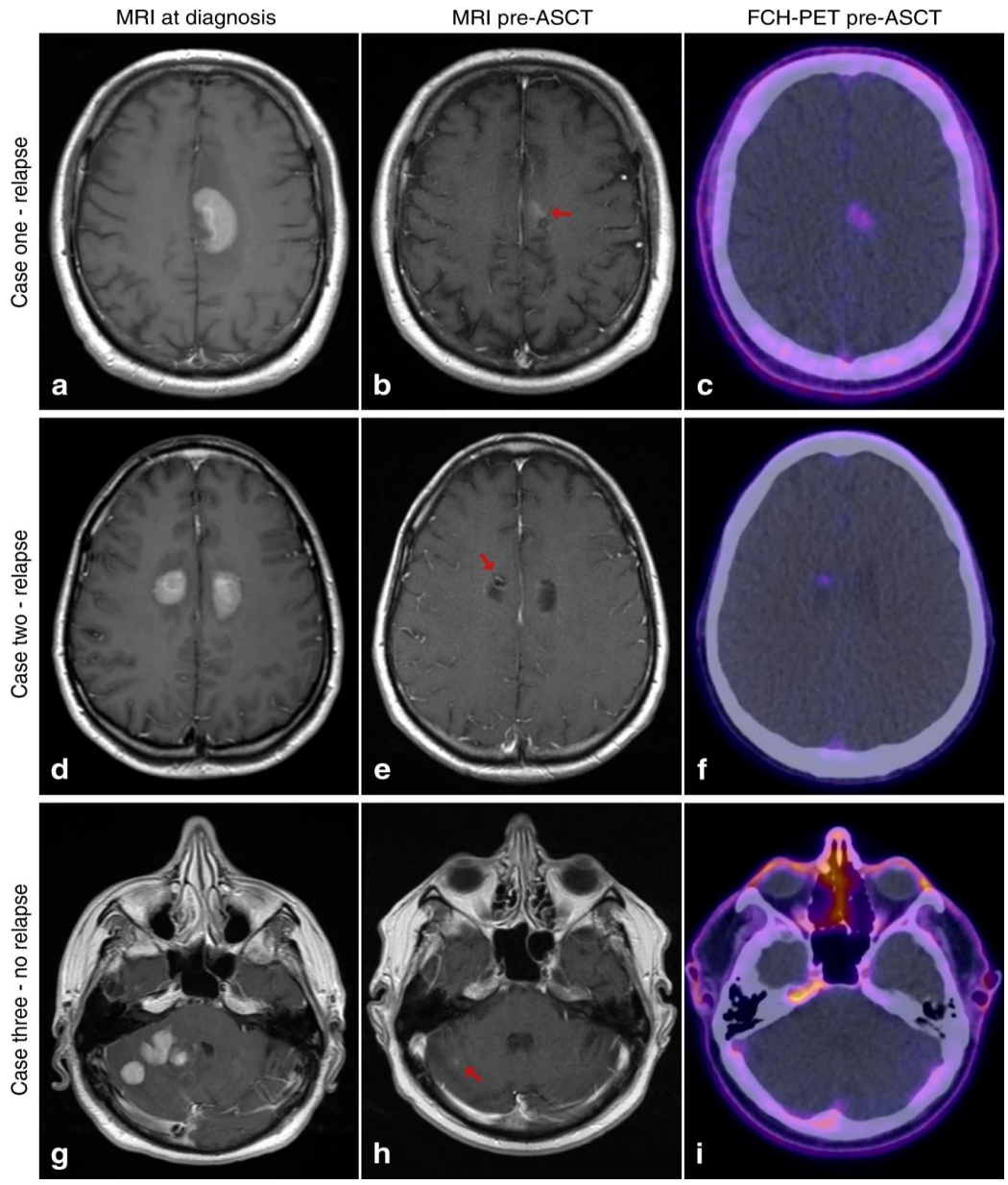

Figure 8| *Original data from three cases. FCH PET-CT and CE-MRI findings pre-autologous stem cell transplantation (ASCT), prognostic value for patient clinical outcomes post-ASCT.*

NB Case one shows a left callosal lesion (a) with residual enhancement on pre-ASCT MRI (b–red arrow) and activity on the pre-ASCT FCH-PET (c); the patient went on to relapse. Case two shows bilateral callosal lesions (d) with residual enhancement in the right lesion (e–red arrow) pre-ASCT. Subtle activity was present on the pre-ASCT FCH-PET images (f); the patient went on to relapse. In case three the patient had cerebellar lesions (g), with residual enhancement on MRI pre-ASCT (h–red arrow) but no activity on FCH-PET (i). This patient is 3 years post-ASCT without clinical relapse.

This comprised an important early observation suggesting FCH PET-CT may have prognostic value in PCNSL. If this could be proven, it would constitute a significant advance in disease assessment and a major advance in PCNSL management.

2.5 Summary of Original Contributions to global literature in all PhD by publication outputs

Original contributions to the global literature within this PhD by publication are summarised within Table 3. below.

Table 3| *Summary of Original Contributions to the global literature in PhD by publication.*

Article (with link)	**Original Contribution to Global Literature**
SIHMIR	
Evolution of lymphoma staging and response evaluation: current limitations and future directions.	The first publication of the novel reporting framework, 'Specialist Integrated Haematological Malignancy Imaging Reporting' (SIHMIR); a comprehensive adaptable method for patient assessment in clinical and research practice. An original multidisciplinary Timeline illustrating the evolution of clinicopathological criteria, staging and response-assessment criteria, and imaging tests in haematological malignancies from 1832 to 2017. Only one published retrospective study had suggested coronal *'vertical'* measurement analysis, in addition to axial measurement analysis, to detect bulky (high-risk) disease (Kumar *et al*., 2016). I advocated prospective research to assess the value of maximal lesion length measurement '*in any plane,'* this being more representative of pathological assessment. Imaging assessment in the diverse array of haematological malignancies is complex, and the development of a radiological sub-speciality of haemato-oncological imaging was suggested. A new radiogenomics based paradigm, utilising novel macroscopic and microscopic parameters, including diffusion weighted imaging (DWI), minimal residual disease (MRD) and circulating DNA (ctDNA), to stage and monitor patients, enabling a more accurate assessment of depth and quality of response, was presented. Future new applications of novel techniques such as DWI, MRD, ctDNA, and novel PET radiotracers in haematological malignancies were discussed. The first data demonstrating the performance of novel FCH radiotracer PET-CT for staging, prognostication, and response-assessment in CNSL relative to standard of care CE-MRI was presented.
BIA-ALCL	
Breast Implant-associated Anaplastic Large Cell Lymphoma: Review and Multiparametric Imaging Paradigms	Comparative analyses of BIA-ALCL, a nuanced, relatively recently recognised tumour, and other low grade (LG) and high grade (HG) lymphomas were first summarily presented regarding the diagnostic method, staging, response-assessment, and treatment. A detailed analysis of the strengths and limitations of the wide array of anatomical and functional imaging tests used in BIA-ALCL was first presented, including the application of novel DWI. Recognition that internal

	mammary chain lymph nodes may be a 'false-positive' on multimodal imaging in this condition was highlighted, and a management strategy was provided of interval repeat imaging. New patient imaging paradigms for diagnosis, staging, response-assessment, and surveillance in the different subsets of BIA-ALCL were first published. Surveillance imaging was not recommended in BIA-ALCL, this being new guidance differing from USA NCCN consensus guidelines (Clemens *et al.*, 2019). Discussion of patient management in both breast and lymphoma unit multidisciplinary team meetings (MDTMs) was first recommended - prior USA National Comprehensive Cancer Network (NCCN) guidelines not having explicitly recommended discussion at both specialist MDTMs (Clemens *et al.*, 2019). A novel research paradigm for the use of DWI for staging and response-assessment in BIA-ALCL was first published. New research applications of PET-MRI, novel PET radiotracers, MRD and ctDNA in BIA-ALCL were first detailed.
Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL): a good practice guide, pictorial review, and new perspectives	The first publication in the radiological literature with practical step-by-step guidance for clinical radiologists for the management of BIA-ALCL. The first published comparison of updated USA NCCN and new UK BIA-ALCL guidelines (National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology. Version 1.2021 (2020); Turton *et al.*, 2021). Introduction of the concept that radiological-pathological correlation is important for correct diagnosis of BIA-ALCL. NICE guideline-style guidance statements, with the *'Offer'*, *'Do not offer'* and *'Consider'* nomenclature, for the management of BIA-ALCL patients were first published. USA NCCN guidelines had suggested PET-CT provides a surgical roadmap in BIA-ALCL (Clemens *et al.*, 2019). Contrary to this, this publication detailed MRI as a more accurate modality for this purpose, partly due to false-positive uptake by FDG PET-CT. First published guidance was provided for the clinical problem of peri-implant effusions of uncertain significance, recommending repeat aspirations of the largest fluid-volume possible for cytological analysis, and cytological diagnosis being required before surgical intervention. Breast implants were recommended as a routine review site during routine cross-sectional imaging reporting and as part of the SIHMIR framework. Post-treatment, an open-access follow-up (OAFU) approach/telephone clinics was first recommended for use in BIA-ALCL. The 'cascade effect' (Mold *et al.*, 1986), where tests performed in the absence of suitable evidence may lead to unexpected findings causing a series (cascade) of further interventions, was first described in the context of BIA-ALCL.
CLL RT	
Chronic lymphocytic leukaemia and Richter's transformation: multimodal review and new imaging paradigms	Comprehensive anatomical-functional imaging features for the recognition of potential RT in CLL were first described. An original two-step PET-CT based decision-making patient paradigm to (i) define whether RT may be present, and biopsy required and, if so, (ii) to select a representative biopsy site in the era of novel CLL therapies was first published. Measurement of the single largest node in three planes including the longest length in any plane was first recommended, following on from early work assessing bulk disease in an axial and coronal plane in early-stage Hodgkin

	lymphoma (Kumar *et al.*, 2016). Future research directions in CLL, including novel PET radiotracers, WB-DWI, radiomics, nanoparticle contrast agents, PET-MRI and ctDNA, were first published.
CNS Lymphoma	
Are treatment response assessment maps (TRAMs) and 18 F-choline positron emission tomography the future of central nervous system lymphoma imaging?	This was the first publication describing two new tests of CCA (TRAMs) and FCH PET-CT in CNSL. This publication was the first global publication describing both the theoretical concept for CCA in CNSL and the application of CCA in a small series of patients. The potential roles, with patient examples, of CCA and FCH PET-CT at baseline staging, interim response-assessment, 'end-of-treatment' (EOT) response-assessment, and as a therapy decision-making tool was described. FCH PET-CT was described as a tool which may be used in patients where MRI is contraindicated and a modality which can reduce the need for gadolinium-based MRI contrast agents with potential associated adverse effects. Further original research was recommended to investigate the potential for a new paradigm utilising CCA, FCH PET-CT and ctDNA for CNSL patient management.
Can pre-transplant 18F-choline positron emission tomography predict relapse following autologous stem cell transplantation in primary central nervous system lymphoma?	The first publication which compared the prognostic value of pre-transplant FCH PET-CT against standard of care CE-MRI for relapse post-ASCT. This publication was the first to describe the theoretical concept for the use of the new test of FCH PET-CT as a prognostic indicator for this purpose, and the first published patient data, comprising nine patients in a retrospective consecutive series. This publication was the first analysis to show that FCH PET-CT may have a greater prognostic value than CE-MRI for post-ASCT relapse. Future research was recommended with larger prospective series of this early work, together with original research of epitope-specific radiotracers for CNSL, such as CD20 labelled PET-CT imaging (England *et al.*, 2017).

Chapter 3: Authorship Contributions to Publications

It is confirmed that the publications in this thesis have not been previously submitted to an institute for a Higher Education award either Nationally or Internationally (form RD12a, Appendix B). Author contributions to thesis publications are summarised in Table 4. below (attribution confirmation letters from co-authors, Appendix B).

Table 4| *Attribution table: Estimation of contribution of the candidate to each publication.*

ARTICLE TITLE (with a clickable link)	First/Last Author Yes/No, Joint?	Conception and Design %	Data Acquisition, Analysis, Interpretation %	Original Concepts within Manuscript %	Manuscript Draft, Revision, Approval %, Corresponding Author?
SIHMIR					
Evolution of lymphoma staging and response evaluation: current limitations and future directions.	Last Author	50%	50%	95%	50% Corresponding Author
BIA-ALCL					
Breast Implant-associated Anaplastic Large Cell Lymphoma: Review and Multiparametric Imaging Paradigms.	First Author	100%	100%	100%	60% draft 100% revision, approval Corresponding Author
Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL): a good practice guide, pictorial review, and new perspectives	Last Author	95%	50%	100%	50% Corresponding Author
CLL RT					
Chronic lymphocytic leukaemia and Richter's transformation: multimodal review and	Last Author	95%	50%	100%	50% Corresponding Author

new imaging paradigms					
CNSL					
Are treatment response assessment maps (TRAMs) and 18 F-choline positron emission tomography the future of central nervous system lymphoma imaging?	Last Author	95%	50%	100%	50% Corresponding Author
Can pre-transplant 18F-choline positron emission tomography predict relapse following autologous stem cell transplantation in primary central nervous system lymphoma?	Last Author	95%	80%	100%	60% Corresponding Author

Chapter 4: Research Methodology

Summary of Methodology used in PhD by publication outputs

The methodology used in the PhD *by prior publication* papers is summarised in Table 5. below.

Table 5| *Summary of Methodology used in PhD by prior publication.*

Article (with a link)	**Methodology**
SIHMIR	
Evolution of lymphoma staging and response evaluation: current limitations and future directions.	**Critical literature review.** Two hundred and six articles (predominantly original) sourced from PubMed, Google Scholar, The British Library, foreign institutions, including The Washington Armed Services Institute (USA) via institutional access at the ICR. Critical evidence appraisal using Grading of Recommendations, Assessment, Development and Evaluation (GRADE) principles. **Paradigm building:** (i) novel SIHMIR reporting framework; (ii) novel multimodal staging, prognostication, response-assessment, and surveillance patient clinical algorithm using novel imaging and molecular tools. Population, Intervention(s), Comparison, Outcomes (PICO) framework. Linking evidence to recommendations (LETR) principles. **Research recommendations.**
BIA-ALCL	
Breast Implant-associated Anaplastic Large Cell Lymphoma: Review and Multiparametric Imaging Paradigms.	**Critical literature review.** Eighty-five articles sourced from PubMed, Google Scholar, and via the ICR. Critical evidence appraisal (GRADE principles). **Paradigm building**: (i) novel clinical multiparametric imaging paradigm for the management of the peri-implant effusion only, mass-forming, and advanced disease subtypes; (ii) novel research model of multimodal assessment using novel imaging. PICO framework. LETR principles. **Research recommendations.**

Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL): a good practice guide, pictorial review, and new perspectives	**Critical literature review.** Thirty-two articles sourced from PubMed, Google Scholar, and via the ICR. Critical evidence appraisal (GRADE principles). **Paradigm building**: best practice guidance statements formulated. NICE Guideline Development principles used to develop guidance, the wording utilised denoting the certainty and evidence-base with which statements are made. 'Offer', 'do not offer' and 'consider' guidance formulated. PICO framework. LETR principles. **Research recommendations.**
CLL RT	
Chronic lymphocytic leukaemia and Richter's transformation: multimodal review and new imaging paradigms	**Critical literature review.** Eight-two articles sourced from PubMed, Google Scholar, and via the ICR. Critical evidence appraisal (GRADE principles). **Paradigm building**: (i) novel clinical PET-CT based 2-step clinical decision-making algorithm to (i) detect whether potential RT is present in a CLL patient and therefore biopsy is required and if so, (ii) select a suitable representative biopsy target. PICO framework. LETR principles. **Research recommendations.**
CNS Lymphoma	
Are treatment response assessment maps (TRAMs) and 18 F-choline positron emission tomography the future of central nervous system lymphoma imaging?	**Critical literature review.** Articles sourced from PubMed, Google Scholar, and via the ICR. Critical evidence appraisal (GRADE principles). **Theory building**: novel proof of concept (POC) & proof of principle (POP) study, short retrospective patient case series analysis (n=3) to illustrate the theoretical utility of two new test applications in CNSL, CCA and FCH PET-CT. Institutional service evaluation (SE) approval received prior to study commencement (SE782; Appendix C). PICO framework. LETR principles. **Research recommendations.**
Can pre-transplant 18F-choline positron emission tomography predict relapse following autologous stem cell transplantation in primary central nervous system lymphoma?	**Critical literature review.** Articles sourced from PubMed, Google Scholar, and via the ICR. Critical evidence appraisal (GRADE principles). **Theory building**: novel POC & POP short retrospective consecutive patient case series (n=11) to evaluate efficacy of FCH PET-CT to predict relapse post-ASCT in PCNSL. Institutional service evaluation (SE) approval

	received prior to study commencement (SE782; Appendix C). PICO framework. LETR principles. **Research recommendations.**

The methodology used for paradigm and theory building in the authors' thesis publications was based on UK NICE guideline development principles, as follows.

- Areas of current unmet clinical need were analysed. This included (i) areas with diverse variation in practice or uncertainty regarding best practice; (ii) areas with potential unsafe practice; (iii) uncertainty regarding optimal algorithms for patient care; (iv) a lack of high-quality evidence; (v) where new evidence suggests current clinical practice may not be optimal.

- The scope specified the key clinical issues to be covered by the paradigm.

- Rationale. An explanation of why the topic is important from a clinical +/- research perspective.

- The paradigms were based on the best available evidence of clinical and cost-effectiveness, following a critical and comprehensive literature review, and critical appraisal of the evidence.

- Paradigms were developed based on the Population, Intervention(s), Comparison, Outcomes (PICO) framework principles (National Institute for Health and Care Excellence. The guidelines manual [Internet] London, UK, 2012). This approach includes consideration of four aspects: (i) the population for inclusion; (ii) the intervention(s), what is being done; (iii) the comparison, the other main test, or management options; (iv) the outcomes, measures of the intervention(s) effectiveness.

- The quality of evidence used following critical appraisal of the published literature was based on GRADE (Grading of Recommendations, Assessment, Development and Evaluation) principles (NICE 2012. http://gradeworkinggroup.org/). The four

quality levels in GRADE comprise: High, further research is very unlikely to change the confidence in the estimate of effect; Moderate, further research may change the estimate of effect; Low, further research is likely to change the estimate of effect; Very Low, the real effect is very likely to be different from the reported effect. High-quality evidence (e.g., prospective randomised controlled trials) was used wherever available to underpin paradigms. Moderate and lower quality evidence was subjected to critical analysis. Very low-quality data, which included Indirectness bias (differences in the study population) and Imprecision bias (relatively few patients and few events, thus wide confidence intervals around the effect estimate), was not included in the paradigm, and theory building, works.

- Guidance was worded in a NICE guideline style, the wording exemplifying the certainty of guidance. A concise statement was formulated. The quality of evidence underpinning the statement was considered, all guidance was based on an analysis of the benefits and harms of an intervention and effective use of health care resources. The terms used, as per NICE guidelines, included: (i) 'Offer', for most patients, the benefit is greater than potential harm; (ii) 'Do not offer', the intervention will not benefit most patients; (iii) 'Consider', the benefit is less certain, the intervention will be more beneficial than harmful for most patients, the options should be discussed with the patient.

- Linking evidence to recommendations (LETR) principles were used for paradigm, and theory building works, with a section describing how evidence was used accompanying all algorithms and guidance statements (National Institute of Health and Care Excellence. *Non-Hodgkin's lymphoma: diagnosis management (NG52)* (NICE, 2016)). Key principles in LETR included the following points: (i) the relative value of the outcomes; (ii) the strength of evidence for benefits and harms of an intervention; (iii) costs, cost-effectiveness and healthcare resource implications; (iv) quality of evidence (GRADE).

- Recommendations for future research were included in all works. Key considerations for areas of future work included the potential impact of the research on patient survival outcomes and the feasibility of the studies.

Chapter 5: Impact

The most significant impact of the works undertaken includes the authors' development of **UK National Guidelines**, as per publications 1-6 below (other author thesis-related publications are summarised in Appendix D).

1. National Institute for Health and Care Excellence. Non-Hodgkin's lymphoma: diagnosis management (NG52). NICE non-Hodgkin Lymphoma Clinical Guideline Committee (inc. **Sharma B**). [online] https://www.nice.org.uk/guidance/ng52 (NICE, 2016). **Sharma B, Lead PET-CT NICE sub-committee**.

2. National Institute for Health and Care Excellence. Haematological cancers: improving outcomes (NG47). NICE non-Hodgkin Lymphoma Clinical Guideline Committee (inc. **Sharma B**). [online] https://www.nice.org.uk/guidance/ng47 (NICE, 2016).

3. National Institute for Health and Care Excellence. Haematological Malignancies Quality Standards. NICE non-Hodgkin Lymphoma Clinical Quality Standard Committee (inc. **Sharma B**). National Institute for Health and Care Excellence. *Haematological Malignancies Quality Standards* [online]. https://www.nice.org.uk/guidance/qs150 (NICE, 2017).

4. UK Guidelines on the Diagnosis and Treatment of Breast Implant-Associated Anaplastic Large Cell Lymphoma on behalf of the Medicines and Healthcare products Regulatory Agency Plastic, Reconstructive and Aesthetic Surgery Expert Advisory Group. Turton P, El-Sharkawi D, Lyburn I, **Sharma B**, Mahalingam P, Turner SD, MacNeill F, Johnson L, Hamilton S, Burton C, Mercer N. Br J Haematol. 2021 Feb;192(3):444-458. https://doi.org/10.1111/bjh.17194 Epub 2020 Nov 22. PMID: 33222158; PMCID: PMC7894347.

   Sharma B. *invited UK imaging expert by MHRA PRASEAG committee. RMH Press Communications (2021).*

5. UK Guidelines on the Diagnosis and Treatment of Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL) on behalf of the Medicines and Healthcare products Regulatory Agency (MHRA) Plastic, Reconstructive and Aesthetic Surgery Expert Advisory Group (PRASEAG). Turton P, El-Sharkawi D, Lyburn I, **Sharma B**, Mahalingam P, Turner SD, MacNeill F, Johnson L, Hamilton S, Burton C, Mercer N. Eur J Surg Oncol. 2021 Feb;47(2):199-210. https://doi.org/10.1016/j.ejso.2020.07.043 Epub 2020 Dec 18. PMID: 33358076.

6. UK Guidelines on the Diagnosis and Treatment of Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL) on behalf of the Medicines and Healthcare products Regulatory Agency (MHRA) Plastic, Reconstructive and Aesthetic Surgery Expert Advisory Group (PRASEAG). Turton P, El-Sharkawi D, Lyburn I, **Sharma B**, Mahalingam P, Turner SD, MacNeill F, Johnson L, Hamilton S, Burton C, Mercer N. J Plast Reconstr Aesthet Surg. 2021 Jan;74(1):13-29. https://doi.org/10.1016/j.bjps.2020.10.064 Epub 2020 Nov 12. PMID: 33483089.

The authors' approach of an LPD *'histology-specific'* and *'stage-specific'* use of PET-CT for staging, prognostication, and response-assessment was published in UK NICE NHL Guidelines (*Non-Hodgkin's lymphoma: diagnosis management (NG52)* (NICE, 2016). Prior to these guidelines, a generic application of PET-CT across the wide spectrum of different lymphomas had been recommended by international Lugano classification consensus guidelines (Cheson *et al*., 2014; Barrington *et al*., 2014). Key factors underpinning NICE guideline development included systematic evidence review (GRADE methodology), evidence the test may improve patient survival outcomes, and efficient use of healthcare resources (Sharma B, PET-CT lead author, NICE guideline development committee).

SIHMDS was developed as a standard of care (National Institute for Health and Care Excellence. *Haematological cancers: improving outcomes (NG47)* (NICE, 2016); Sharma B, NICE guideline committee member and co-author) in the UK NHS to improve the accuracy of patient diagnosis, which is the most critical step in the haematological malignancies' patient pathway, enabling appropriate management and improved survival outcomes

(Cunningham *et al*., 2017). The guideline was subsequently also mandated as one of five NICE Quality Standards (National Institute for Health and Care Excellence. *Haematological Malignancies Quality Standards* (NICE, 2017); Sharma B, NICE Quality Standards committee member and SIHMDS quality standard author). NICE quality standards differ from NICE guidelines, being considered as key measures which are clinically applicable, highly likely to improve patient outcomes, and suitable for annual audit.

The authors' original BIA-ALCL imaging algorithms (Sharma *et al*., 2020) have been endorsed by UK MHRA PRASEAG Guidelines (Turton *et al*., 2021; Sharma B., invited co-author), updated USA NCCN BIA-ALCL Guidelines (National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology. T-cell lymphomas. Version 1.2021.) now also being more aligned with this approach.

UK NICE clinical guidelines and UK MHRA PRASEAG guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances, produced to help healthcare professionals and patients make informed choices about appropriate healthcare in areas where advice is most needed. For example, this includes (i) uncertainty regarding best practice or unacceptable variation in practice; (ii) unsafe practice; (iii) uncertainty regarding optimal service configuration; (iv) a lack of high-quality evidence; (v) where the current practice may not be optimal, based on new evidence. Guidelines avoid making recommendations on areas where there is already agreed practice and assist the practice of healthcare professionals; they do not replace their knowledge and skills (National Institute of Health and Care Excellence. *Non-Hodgkin's lymphoma: diagnosis management (NG52)* NICE 2016)). The impact of clinical guidelines and quality standards is to change clinical practice in areas of uncertainty and variable practice, as detailed above, application of guidelines and quality standards being auditable nationally.

The two new tools of FCH-PET and CCA have the potential to transform clinical and research trial practice in CNSL. CE-MRI has limitations for staging, prognostication, and response-assessment in CNSL. The more accurate differentiation of active from inactive lymphoma at specific time points in the patient pathway with these new tools enables more optimal therapeutic decision-making, contributing to reduced patient treatment-

related morbidity and improved survival outcomes. The two new tools are being incorporated as primary and secondary exploratory endpoints in CNSL trials (Kowa *et al*., 2021; Millard *et al*., 2021).

The SIHMIR methodology has the capacity to change routine clinical reporting and research practice in haematological malignancy. The analogous concept of SIHMDS has changed practice in pathology services. SIHMIR provides for template-based radiological assessment, providing all data items and conclusions required for patient management, a currently unmet clinical need (Mahalingam *et al.*, 2019). Comprehensive and accurate radiological information regarding the patient status enables timely and appropriate clinical management decision-making, contributing to improved morbidity and mortality outcomes. The SIHMIR methodology also facilitates retrospective and prospective research analyses, all relevant data items having been captured (Cunningham *et al.*, 2017).

The innovative use of PET as a decision-making tool in CLL to detect RT has the capability of changing clinical practice in CLL patient management. The algorithm is a decision-making tool utilising PET-CT to decide (i) whether a biopsy for potential RT is required in CLL patients and, if so, (ii) to select a representative biopsy site. This will: reduce the number of unnecessary biopsies undertaken in CLL, i.e., in indolent CLL patients who have not undergone RT; reduce the number of repeat biopsies in patients, as a site representative of RT will have been targeted; enable the timelier diagnosis of RT, enabling suitable patient therapy, and thereby contributing towards improving patient outcomes (Musanhu *et al*., 2021).

Chapter 6: Critical Reflections and Future Work

Critical Reflections

Critical reflections on the research work included: (i) the adoption of the SIHMIR structured reporting template in clinical practice; (ii) the understanding of BIA-ALCL guidance in routine clinical practice; (iii) the utilisation of CCA and FCH PET-CT in the management of CNSL patients.

(i) SIHMIR

- SIHMIR is a novel template-based reporting methodology designed to provide all imaging data items necessary for optimal patient management in a comprehensive and timely manner (Cunningham *et al*., 2017). The construct is based on an analogous rationale and principles to those underpinning the development of SIHMDS in pathology reporting, which in recent years has been NICE mandated in the UK NHS (National Institute of Health and Care Excellence. *Haematological cancers: improving outcomes* (NG47) (NICE, 2016); National Institute of Health and Care Excellence. *Haematological Malignancies Quality Standards* (NICE, 2017)).

- Evidence underpinning the SIHMDS concept comprised discrepancy rates of 20 – 48% between primary diagnosis and central expert haematopathologist review diagnosis in haematological malignancies (Bird *et al.*, 1984; Dick *et al*., 1987; Youngson *et al*., 1995; Dojcinov & Attanoos, 2001). Subsequent analysis by the All Wales Lymphoma Panel demonstrated a significant proportion of cases (46 of 99; 46%) had a change in management due to central review (Lester *et al.*, 2003).

- To apply SIHMIR in clinical imaging practice, similar evidence to that in pathology is required. Initial retrospective consecutive analysis by the author's group in 40 patients with HL and DLBCL demonstrated a significant proportion of imaging

reports did not include key data items required for patient management, with some key variables missing in 90% of reports (Mahalingam *et al.*, 2019; [4]ASH abstract).

- The authors' ASH publication (Mahalingam *et al.*, 2019) comprised a single-centre retrospective analysis. To provide further data to highlight this problem in *'real world'* imaging reporting, a multicentre larger retrospective consecutive patient series study is required with a central expert review of imaging reports to evaluate whether mandatory data items required for optimal patient management are included (according to national and international guidelines). Further, a feasibility study to evaluate the use of SIHMIR in routine clinical practice is required.

- Software application of the SIHMIR template, adapted to individual lymphoma categories, together with artificial intelligence applications to analyse a proportion of data-metrics from imaging studies, may then be envisaged (Zafar *et al.*, 2021).

(ii) BIA-ALCL

- The authors' guidance algorithms for the spectrum of BIA-ALCL types (Sharma *et al*., 2020) have been endorsed by UK BIA-ALCL Guidelines (Turton *et al*., 2021), and guidance statements in a NICE guideline format have been published by the author (Mehdi *et al*., 2021).

- However, a significant clinical requirement remains for education and training in BIA-ALCL, the condition being highly nuanced and multimodal imaging and pathology data prone to misinterpretation (Mehdi *et al*., 2021). Early works by the authors' group reflect this, including a retrospective consecutive analysis of 11 patients demonstrating significant unnecessary surveillance imaging, leading to a

[4] **The American Society of Haematology (ASH) meeting is considered the premier annual global conference for haematology. The Society's primary mission statement is to improve the understanding and management of haematological conditions by promoting research and education. Meeting abstracts are published as supplements in *Blood*.**

cascade of further investigations and a health-economics impact (Mehdi *et al*. 2021 (ASH abstract); O'Connell *et al.*, 2021 ([5]ASCO abstract); O'Connell *et al.*, 2021).

These quantitative works are retrospective and single-institution and with small patient numbers, larger series requiring multi-centre analysis in this rare tumour.

- A UK quantitative questionnaire to evaluate the confidence and knowledge-base regarding BIA-ALCL across healthcare professionals who may manage BIA-ALCL has been formulated by co-workers and the author in collaborative works as part of the new UK Interdisciplinary Centre for Implant-based Research (IRIS Centre). To capture the wide spectrum and tiers of relevant healthcare professionals, following ethics approval, this has been circulated to breast and lymphoma unit multidisciplinary team meetings (MDTMs) across the UK NHS, and professional bodies such as the Association of Breast Surgeons (ABS, UK) and the British Society of Haematology (BSH). International application is also envisaged, including with USA collaborators.

- National/international training and education workshops regarding BIA-ALCL, including the complex multimodal nuances pertaining to imaging and pathology, are necessary. In this context, the author has developed a training and educational clinical and research BIA-ALCL programme – the international ICR/RMH/Biomedical Research Centre (BRC) annual BIA-ALCL clinical and research meeting (Appendix E).

(iii) CNSL

- Early works by the author have introduced two new imaging test applications for staging, prognostication, and response-assessment in CNSL, FCH PET-CT and CCA (Kowa *et al*., 2021; Millard *et al*., 2021). However, these series are retrospective, single-centre, and with small patient numbers, studies requiring a multicentre design to recruit larger patient numbers in this relatively rare malignancy.

[5] **The American Society of Clinical Oncology (ASCO) is considered the world's premier organization for professionals caring for oncology patients, hosting the world's leading annual cancer meeting.**

- An international multicentre prospective blinded trial is required comparing two new tests of FCH PET-CT and CCA with the current standard of care CE-MRI in primary and secondary CNSL. Staging, response-assessment, prognostication, and surveillance timepoints in the patient pathway would need analysis. Macroscopic imaging assessments should be correlated with the minimal residual disease (MRD) approach of novel circulating DNA (ctDNA) biomarker quantification, a histology specific subcohort analysis also being required. The prognostic value of the three macroscopic imaging tests and ctDNA for survival outcomes, including PFS and OS, would be assessed. This would provide the highest quality evidence for the application of these new tests in CNSL. New patient paradigms incorporating FCH PET-CT, CCA and ctDNA can be envisaged (Cunningham *et al.*, 2017; Kowa *et al.*, 2021; Millard *et al.*, 2021).

Future Work

Areas for future research endeavour include: (i) Virtual histology in haematological malignancies, (ii) A prospective trial to compare the accuracy of CCA and FCH PET-CT with CE-MRI for staging, prognostication, and response-assessment in CNSL (iii) Novel epitope-specific PET radiotracers, ctDNA, MRD and DWI applications (author ongoing works also included in Appendix E).

(i) Virtual histology in haematological malignancies

Incorrect diagnosis of the lymphoma subtype remains a problem, despite the advent of SIHMDS. Specialist centralised review of pathology diagnostic samples is vital to address this issue, with sample morphology analysis a critical step (*Haematological Malignancies Quality Standards* (NICE 2017); Campo *et al*., 2017). The ability to rapidly create a high-resolution 3D image of a biopsy sample, non-destructively and without processing, which can be viewed remotely via computer, may be significantly beneficial. It would enable representation of the whole sample stored, which could be rapidly shared with other

expert pathologists, nationally and internationally. Further sequential pathology testing could then be decided from this scan.

The concept described above is a technically challenging problem due to the high spatial and contrast resolution required and the small sample size. Various methods have been investigated for this purpose, and all have limitations. A conventional nano/microfocus x-ray CT is limited by contrast resolution and optical methods by sample size. X-ray phase-contrast imaging (XPCI) CT techniques may be a suitable solution, significant development having occurred since the mid-90s (Olivo, 2021). Several such applications are under active development in solid cancers and for intra-operative use, with some promising preliminary results for virtual histology (Figure 9) (Zdora *et al.*, 2020; Massimi *et al*., 2021; Ecclestone *et al*., 2021; Wolfson *et al.*, 2021; Twengstrom *et al*., 2022). Research is required to evaluate the utility of a standard x-ray tube with standard laboratory equipment for this purpose.

To the authors' knowledge, there are no current publications for virtual histology in haematological malignancies. This original concept is under active development by the author and co-workers as a significant body of research in collaboration with the UK National X-ray Computed Tomography (NXCT) centre, the National Research Facility for laboratory-based X-ray computed tomography. The Edge-illumination (EI) XPCI method will be evaluated in haematological malignancies (Olivo, 2021).

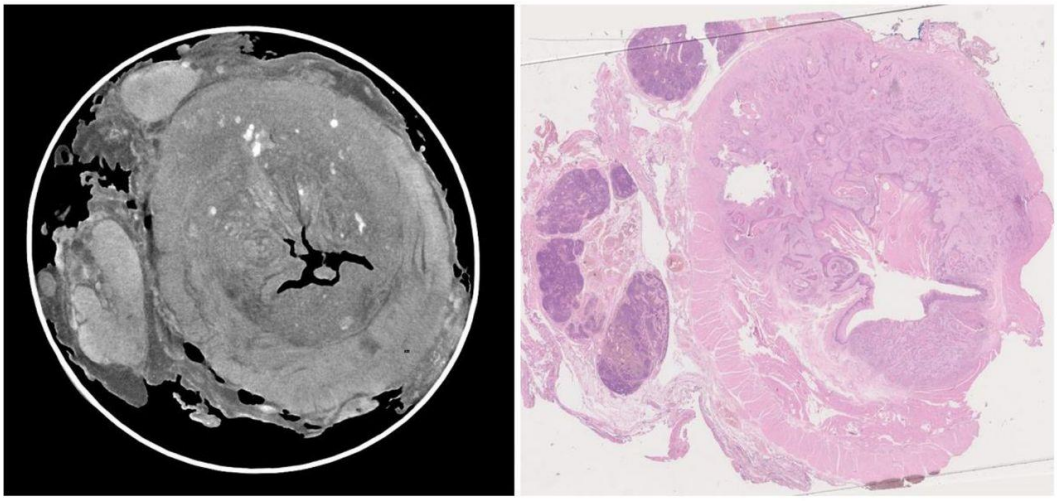

Figure 9| The concept of Virtual Histology in solid cancers. XPCI image (left) showing oesophageal tumour with matched histology section (right).

(ii) CCA and FCH PET-CT in CNSL

High-quality evidence for the accuracy of CCA and FCH PET-CT in CNSL would require a prospective blinded trial comparing these two novel imaging applications with the current standard of care CE-MRI. PCNSL and SCNSL require assessment, including the different histological categories of SCNSL. The study would need to be designed to compare the three imaging tools' sensitivity, specificity, and prognostic value.

Each time point in the patient pathway requires assessment: baseline staging, including post-biopsy; early, interim and EOT response; pre- and post-transplantation; pre- and post-radiotherapy, including the differentiation of pseudoprogression from true progression. Response assessment in novel therapies, including immunotherapy, also requires analysis. Due to the condition's rarity, a multicentre trial would be needed to provide sufficient case numbers. Difficulties with this study include the limited possibility for histological tissue correlation of CNS lesions. To address this ctDNA, may be utilised as an exploratory biomarker at all time points, with evaluation of ctDNA in the cerebrospinal fluid (CSF) with samples obtained via lumbar puncture, together with ctDNA on blood-serum analysis in the context of SCNSL (Cunningham *et al*., 2017; Bobillo *et al*., 2021).

The above is another significant body of research by the author, Team Leader for the 'Lymphoproliferative disorders: new methodologies and applications' group at ICR/RMH. Works include author collaboration with the CAROUSEL trial, Immunotherapy Using CAR-T cells to Target CD19 for Relapsed/Refractory CD19+ Primary CNS Lymphoma, at University College London Hospital (UCLH) (ClinicalTrials.gov Identifier NCT04443829). CCA and FCH PET-CT have been incorporated as exploratory end-points pre- and post- CAR-T cell therapy, with comparison with standard of care CE-MRI, and correlation with ctDNA. Collaboration is also underway with multiple other leading global centres, including the National Hospital for Neurology and Neurosurgery, London, UK and the American Academy of Neurology, USA.

(iii) Minimal residual disease, ctDNA, epitope-specific PET radiotracers, DWI

Algorithms, where MRD, ctDNA, epitope-specific PET radiotracers and DWI may be included into the patient pathway, are depicted in Figures 10 and 11 (Cunningham *et al.*, 2017; Sharma *et al*., 2020). Systematic research evaluating these microscopic and functional approaches is needed in each lymphoma type.

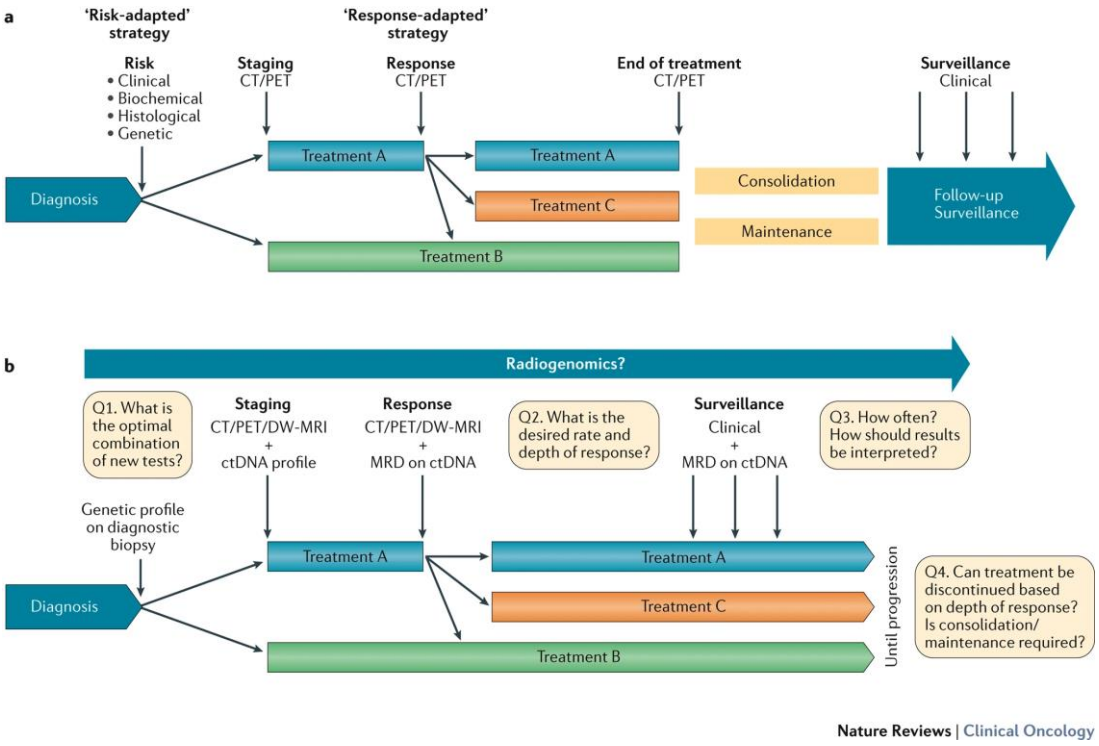

Figure 10| *Risk-adapted and response-adapted strategies, staging, response-assessment and surveillance a) Pathway diagram summarizing current practice in assigning patients to receive conventional chemotherapies. b) A template for future practice in assigning patients to receive novel agents/long term therapies.*

The yellow boxes highlight some of the key questions that are best answered using prospective clinical trials (Cunningham et al., 2017). **Q1.** Combined-modality imaging using contrast-enhanced CT, diffusion-weighted (DW)–MRI and/or PET–CT, depending on lymphoma subtype, might facilitate the more-accurate measurement of tumour volume and provide data that enables radiogenomic approaches. Genetic profiling of diagnostic biopsy samples and analysis of circulating tumour DNA (ctDNA) could define a genetic signature that enables non-invasive disease monitoring in the majority of patients. An integrated Specialist Integrated Haematological Malignancy Diagnostic Services (SIHMDS)/ Specialist Integrated Haematological Malignancy Imaging Reporting (SIHMIR) document should ideally contain the diagnosis, stage, risk category and genetic profile for tailoring treatment, recommended imaging modality and genetic signature for ctDNA monitoring. **Q2.** This is perhaps the most challenging aspect of patient management with novel therapies, and is likely to depend on tumour type and therapy used. Clinical response and treatment tolerability, rather than imaging findings, are more likely to guide the initial approach to therapy for treatments associated with 'tumour flare'. Clinical trials should attempt to define the critical time points for assessing refractoriness to individual agents using imaging and/or based on the emergence of resistance mutations. The latter is likely to be more informative in terms of selection of the next line of therapy. **Q3.** Two cohorts of patients requiring surveillance exist: those 'with' and those 'without' measurable residual disease, whether or not they continue on therapy. The former cohort should be monitored more frequently compared with the latter, with the intervals defined based on lymphoma histology and therapy. Surveillance with ctDNA is preferable to avoid exposure to radiation, with scans repeated if clinically indicated by evidence of progression according to ctDNA or disappearance of ctDNA (to confirm lymphoma clearance). Patients with 'low risk, curable' lymphomas who have completed treatment could receive only clinical surveillance. **Q4.** Clinical trials should be conducted to evaluate the possibility of discontinuation of therapy in patients with undetectable MRD. Randomized trials should also be undertaken to evaluate the role of consolidation or maintenance strategies in the setting of undetectable MRD, particularly in patients with high-risk disease.

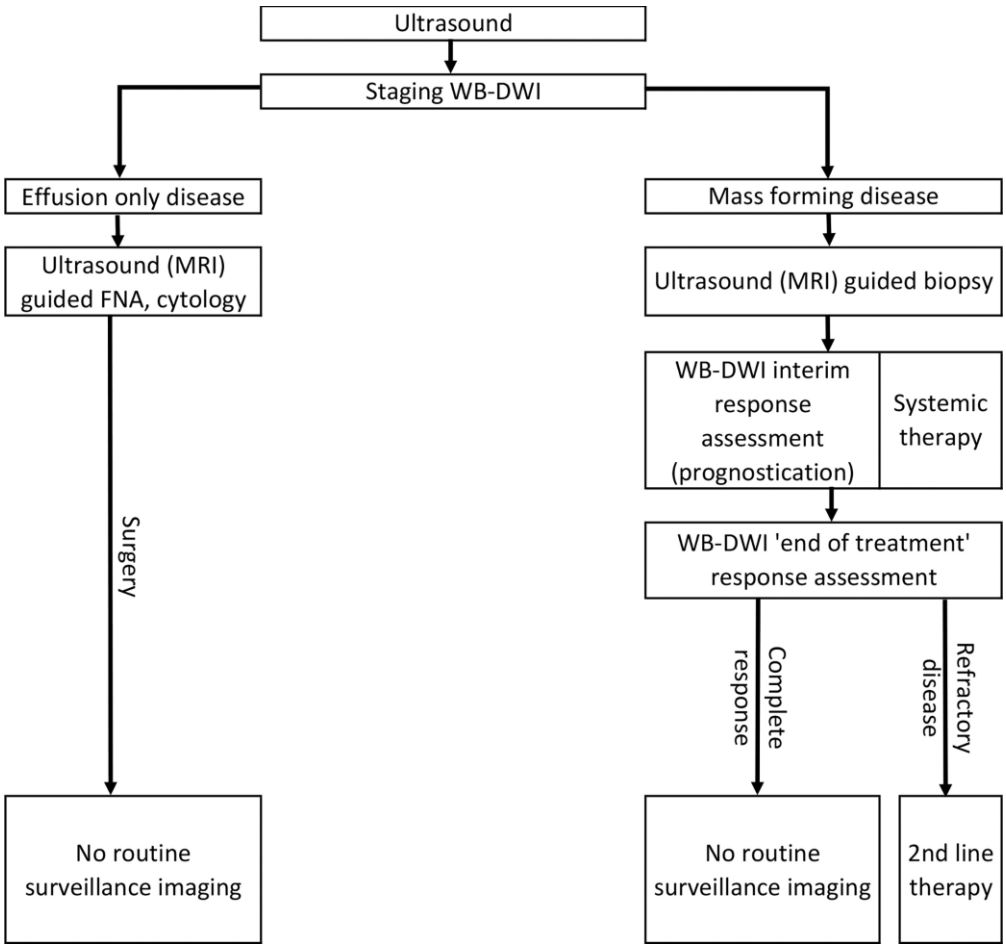

Figure 11| *Research paradigm for diagnosis, staging, response-assessment, and surveillance strategies for the peri-implant effusion and mass-forming or distant disease subtypes of BIA-ALCL.*

NB Original pathway diagram for future practice shows use of whole-body *(WB)* DWI for staging and response-assessment. This potential approach requires research validation. *FNA* = fine-needle aspiration.

Reliable detection and elimination of MRD is an important goal to improve cancer outcomes. In mantle cell lymphoma (MCL), FL and CLL, MRD negativity is an accurate predictor of more prolonged remission than the presence of MRD (Bottcher *et al.*, 2012; Thompson & Wierda, 2015; Galimberti *et al*., 2014; Pott *et al*., 2010). Next-generation sequencing (NGS) approaches can be utilised for MRD detection (Ladetto *et al*., 2014). NGS of ctDNA from liquid biopsies in patients with DLBCL has detected relapse nine months earlier than clinical or PET-CT evidence (Roschewski *et al*., 2015; Kurtz *et al*., 2015). Liquid

biopsies can provide information on risk stratification, response-assessment and tailoring of therapy.

FDG is not a tumour specific ligand. Radiotracers targeted for different cell surface proteins/receptors in the lymphoid tumours provide more accurate imaging, for example targeting CD20 (DLBCL) or CD30 (England *et al*., 2017; Sharma *et al*., 2012; Cunningham *et al*., 2017).

The high-acid, low-oxygen milieu of a tumour provides a low-diffusion environment for disease detection using DWI (Gatenby & Gillies, 2004). DWI is quantifiable with the apparent diffusion coefficient (ADC) calculation (Takahara *et al.*, 2004; Sharma *et al.*, 2012). The technique has rapidly translated from 'bench-to-bedside' and has an established role in the management of multiple myeloma (*Myeloma: diagnosis management (NG35)* (NICE, 2016)).

Small cells in multiple myeloma are tightly packed. DWI may also have efficacy in other lymphoid tumour categories with small cells, including FL and CLL. The author plans prospective studies comparing DWI with 'standard of care' in lymphoid tumours such as MCL, ENMZL, and CLL (Research protocol: Appendix E). These diseases infiltrate extra-nodal sites such as the gastrointestinal tract, bone marrow and liver, anatomical sites beyond the accurate resolution of current imaging techniques and DWI may provide a detectable signal for disease.

In CNSL, for example, a combination of clinical parameters, multimodal imaging including CCA and novel CD20-labelled PET-CT, and ctDNA (CSF and blood) may form a powerful future paradigm - for staging, response-assessment, prognostication, and surveillance (Kowa *et al*., 2021; Millard *et al*., 2021).

Chapter 7: Conclusions

A diverse range of greater than 40 NHL and five HL categories are currently recognised, with disparate patterns of biological behaviour. Imaging tests are an established cornerstone for disease evaluation, accurate disease detection being critical for optimal patient management. However, the appropriate application of these tests requires acknowledging their strengths and limitations, and it is crucial to develop solutions for currently unmet clinical needs.

A summary of the contributions from the published works include:

1) Parallel challenges apply in haemato-oncology radiology reporting as those in pathology. Both require the interpretation and integration of multiple complex datasets. In pathology, SIHMDS has been developed as a standard of care (*Haematological cancers: improving outcomes (NG47)* (NICE 2016); *Haematological Malignancies Quality Standards* (NICE 2017)). An original analogous methodology, SIHMIR, has been formulated for radiology.

2) SIHMIR involves a standardised template-based imaging reporting process designed to ensure the assessment of all essential review sites and inclusion of all data items required for staging, prognostication, and response-assessment throughout the patient pathway. An integrated clinically relevant conclusion from multimodal data is detailed. This adaptable methodology is widely applicable across clinical and research platforms.

3) Clinical imaging practice in BIA-ALCL varied widely. Imaging datasets in this nuanced condition were prone to misinterpretation, and significant numbers of patients underwent a 'cascade' of unnecessary investigations. A detailed assessment of all imaging tests' indications, strengths, and limitations in this relatively recently recognised tumour was performed. Original diagnostic algorithms for the different

BIA-ALCL subsets were formulated, including that routine surveillance imaging is not required; subsequently endorsed by UK MHRA BIA-ALCL Guidelines.

4) Detection of RT and selection of a suitable biopsy target for diagnosis were significant challenges in clinical practice. An original PET-CT based patient management algorithm to define (i) whether RT may be present and (ii) select a representative biopsy site in the era of novel therapies was formulated.

5) In CNSL, the current standard of care CE-MRI does not differentiate disease activity from benign post-biopsy and inflammatory changes. Two novel imaging applications for this purpose were developed: (i) the original theoretical concept and practical use of CCA and (ii) FCH PET-CT.

6) The publications provide the first CCA and FCH PET-CT data illustrating the differentiation of viable lymphoma from benign enhancing MRI change in the post-biopsy setting, a current significant unmet clinical need.

7) Early data suggesting FCH PET-CT and CCA may have higher prognostic value for response outcome than CE-MRI was first published. If this could be proven in more extensive studies, it would constitute a significant advance in disease assessment and CNSL management. In addition, original data showing FCH PET-CT is an alternative clinical test suitable for patients unable to undergo MRI (due to contraindications), was published.

8) In the future, multimodal disease assessment with radiological and pathological tests (including CCA (for CNSL), DWI, novel PET radiotracers, ctDNA and virtual histology) have potential to improve the accuracy of diagnosis, response-assessment, and detection of MRD.

In summary, haematopoietic, and lymphoid tumours account for significant global morbidity and mortality. There have been dramatic technological advances in imaging tests for this broad spectrum of malignancies, particularly over 50 years. However, there remains significant unmet clinical need for the accurate detection of disease.

The thesis publications focus on: a novel structured reporting framework, 'Specialist Integrated Haematological Malignancy Imaging Reporting'; original patient management algorithms for breast implant-associated anaplastic large cell lymphoma; an original diagnostic algorithm for Richter's transformation in chronic lymphocytic leukaemia; and two novel imaging applications of contrast clearance analysis and ^{18}F-choline positron emission tomography-computed tomography, providing new practice-changing perspectives. The persistent challenge in tumour imaging is to provide an assessment which is '*as close as possible to the truth*' to enable optimal patient management and improve patient outcomes.

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Zdora, M.C., Thibault, P., Kuo, W., *et al*. (2020). 'X-ray phase tomography with near-field speckles for three-dimensional virtual histology.' *Optica*, 7(9), pp.1221-1227. https://doi.org/10.1364/OPTICA.399421

Appendices A-C removed for privacy and copyright reasons

Appendix D - Other thesis-related author publications/published conference abstracts

Other works related to PhD by publication*;* [6]senior author publications by Sharma B.

	Reference under thesis-related group	Brief Descriptive
	SIHMIR	
	Publications:	
1.	Zafar, S., Sharma, R.K., Cunningham, J., Mahalingam, P., Attygalle, A.D., Khan, N., Cunningham, D., El-Sharkawi, D., Iyengar, S., **Sharma, B.** (2021). **'Current and future best practice in imaging, staging, and response assessment for Non-Hodgkin's lymphomas: the Specialist Integrated Haematological Malignancy Imaging Reporting (SIHMIR) paradigm shift.'** *Clinical Radiology*, 76(5), pp.391.e1–391.e18. https://doi.org/10.1016/j.crad.2020.12.022 PMID: 33579517. **Corresponding author: Sharma B.**	The original SIHMIR framework, a comprehensive template-data driven methodology to enable 'best-practice' in imaging data assessment, a potential paradigm shift in clinical and research practice, was described for the first time in the radiological literature. The publication described the persistent challenge at all patient timepoints in the >45 lymphoma categories recognised by the latest revised WHO classification of lymphoid tumours as to provide an assessment '*as close as possible to the truth*.' An exhaustive analysis of NHL imaging aspects pertinent to daily clinical practice, and research, to aid multiparametric imaging (CT, PET-CT, MRI, DWI) data assessment was detailed. The concept of '*disease tempo,*' often not included in imaging reports, was highlighted. New criteria including RECIL and LyRIC were described. Future research directions including the concepts of: disease quantification, total metabolic tumour volume (TMTV) and total lesion glycolysis (TLG); MRD; WB-DWI; novel PET radiotracers; radiogenomics; and artificial intelligence, were explored.
	Publications: New applications and anatomical-functional multimodal data interpretation:	
2.	Kafaei, L., Millard, T., Wotherspoon, A., Attygalle, A.D., Cunningham, D., **Sharma, B**. (2022). '**Follicular dendritic cell sarcoma in the setting of Castleman disease.'** *British Journal of Haematology*. Advanced online publication. https://doi.org/10.1111/bjh.18097 PMID: 35303313 **Corresponding author: Sharma B.**	This publication highlighted the importance of the assessment of the CT contrast enhancement characteristics of lesions for accurate data interpretation.

[6] 45 senior author publications (first/last author); three third author publications.

3.	Din, F., Mellor, F., Millard, T., Pace, E., Khan, N., Attygalle, A.D., Cunningham, D., Zafar, S., **Sharma, B**. (2022). **'Radiology of Castleman disease: the pivotal role of imaging in diagnosis, staging, and response assessment of this rare entity.'** *Clinical Radiology*, 77(6), pp.399–408. https://doi.org/10.1016/j.crad.2022.01.045 PMID: 35177229 **Corresponding author: Sharma B**	This publication provided a comprehensive review of anatomical-functional imaging in Castleman disease (CD) and new perspectives, including research directions with DWI and novel PET radiotracers.
4.	Renn, A., Wotherspoon, A., Attygalle, A.D., Vroobel, K., Cunningham, D., **Sharma, B**. (2021). **'Discordance between positron emission tomography standard uptake value and proliferation index in mantle cell lymphoma: An initial communication.'** *eJHaem*, 3(1), pp.249–250. https://doi.org/10.1002/jha2.348 **Corresponding author: Sharma B**.	The first publication in the literature analysing the correlation between PET SUV_{max} and ki67 proliferation index in mantle cell lymphoma (MCL). MCL comprises a biological spectrum ranging from indolent disease, where a 'watchful-waiting' approach (without active treatment) is adopted, through to aggressive disease, warranting therapy, with poor clinical outcomes. The cell proliferation index in MCL, measured by the ki67 index, is a measure of aggressiveness, a high ki67 is >30% (Campo *et al.*, 2017). No prior data analysing the correlation between PET SUV_{max} and ki67 had been published. In this early work, discordance between the two measures appeared to be present. An accurate imaging biomarker for proliferation index in MCL would be clinically useful, providing a non-invasive prognostic tool enabling stratification of patients into 'need-for-treatment' groups; further research to explore whether a correlation exists was recommended. A further original point in this publication was the hypothesis that DWI with quantitative ADC measurement may have the potential to assess ki67 in MCL, with research evaluation being endorsed.
5.	Bitar, G., Wotherspoon, A., Attygalle, A.D., Cunningham, D., **Sharma, B**. (2021). **'Intravascular large B-cell lymphoma treated with polatuzumab-based salvage therapy: A rare case.'** *eJHaem*, 2(4), pp.887–888. https://doi.org/10.1002/jha2.301 **Corresponding author: Sharma B**.	This publication included a description of the critical Deauville 'X' score ('activity which may be unrelated to active lymphoma'), which is significantly under-recognised both in lymphoma clinical and lymphoma research/trial practice; the false-positive PET-CT activity in this patient was considered due to COVID-19 vaccination. The publication was the second literature description of the use of polatuzumab-based therapy in intravascular large B-cell lymphoma (IVLBCL).
6.	Phillips, C., Attygalle, A.D., Iyengar, S., Wotherspoon, A., Cunningham, D., **Sharma, B**. (2021). **'Pulmonary manifestations of**	This publication illustrated the strengths and limitations of anatomical-functional imaging tests for pulmonary lesion

	grade III lymphomatoid granulomatosis complicated by haemophagocytic lymphohistiocytosis: Rare disorders.' *eJHaem*, 2(3), pp.669–670. https://doi.org/10.1002/jha2.240 **Corresponding author: Sharma B.**	assessment in the context of haematological malignancies, the limitations of PET-CT for response assessment in this context and the importance of recognising the Deauville 'X' score. In addition to the lack of accuracy of the FDG radiotracer for lung lesion assessment (which is under-appreciated in clinical practice), the publication also highlighted that FDG PET-CT is not prognostic for outcome in the context of lung lesion assessment in haematological malignancies.
7.	Algudkar, A., El-Sharkawi, D., Cross, M., Tunariu, N., Attygalle, A.D., **Sharma, B**. (2021). **'Whole body-diffusion weighted imaging for the assessment of treatment response in hairy cell leukaemia: A positive first step.'** *eJHaem*, 2(2), pp.311–312. https://doi.org/10.1002/jha2.158	The first theoretical, and practical literature description of whole-body diffusion-weighted imaging (WB-DWI) in hairy cell leukaemia (HCL). The incidence of bone lesions in HCL is estimated at 3% (Campo *et al.*, 2017). Commonly lytic, prior work by the authors' group demonstrated bone lesions could be associated with high tumour burden and aggressive poor-prognosis disease (Cross *et al.*, 2019). Lytic bone lesions are challenging to assess for response. Conventional radiologic techniques such as CT and MRI are not accurate for this purpose (*Eisenhauer et al.*, 2009), with systemic therapy-related FDG uptake confounding bone response assessment with PET-CT. The author postulated WB-DWI might have utility for this unmet clinical need – WB-DWI being efficacious in multiple myeloma (MM) for lytic bone lesion response-assessment (*Myeloma: diagnosis management (NG35)* (NICE 2016)). From first principles HCL has similar tumour biology to MM with tightly packed small cells (i.e., hypercellularity, which can be analysed with DWI). In the presented case data, WB-DWI appeared to discriminate responding lytic bone disease from persistent active disease. This differentiation was not possible with other available imaging tools at the time. Further research to evaluate this new application of WB-DWI in HCL for staging, prognostication, and response-assessment, was advocated.
8.	Bitar, G.G., O'Connor, S., Attygalle, A.D., El-Sharkawi, D., Iyengar, S., **Sharma, B**. (2021). '**A case of neurolymphomatosis: A rare complication of diffuse large B-cell lymphoma.'** *eJHaem*, 2(2), pp.305–306. https://doi.org/10.1002/jha2.141 **Corresponding author: Sharma B.**	This publication illustrated the importance of different anatomical-functional imaging tests in haematological malignancies (disease categories which are challenging to assess accurately) and the importance of understanding the strengths and limitations of these tests.

9.	Bitar, G., Chau, I., Wotherspoon, A., El-Sharkawi, D., Iyengar, S., **Sharma, B**. (2020). '**A very rare complication of subdural haematoma: fibrin-associated diffuse large B-cell lymphoma.'** *British Journal of Haematology*, 192(6), pp.947–947. https://doi.org/10.1111/bjh.17239 PMID: 33336795 **Corresponding author: Sharma B.**	This publication illustrated the importance of radiological-pathological correlation to achieve the correct diagnosis of haematological malignancies.
10.	Kumar, R., Hujairi, N., Mohammed, K., Attygalle, A., Alexander, E., Chau, I., Cunningham, D., Iyengar, S., El-Sharkawi, D., **Sharma, B**. (2020). **'Early interval and serial positron emission tomography-computed tomography (PET-CT) after an indeterminate response defined by a PET scored 4 on the Deauville scale in lymphoma.'** *British Journal of Haematology*, 190(6), e357-e362. https://doi.org/10.1111/bjh.16919 PMID: 32643153	This retrospective analysis of 30 patients with high-grade lymphoma was the first publication assessing the value of early interval PET-CTs in patients with indeterminate 'end-of-treatment' studies (Deauville score (DS) 4) as a surrogate for histology confirmation or refutation of refractory disease where confirmation biopsy is not feasible. In addition, the concept of the Deauville score of 'X' ('activity which may not reflect high-grade lymphoma'), significantly under-recognised in both clinical and research practice, was highlighted. The hypothesis for this study was that early interval PET-CTs can improve the specificity of indeterminate EOT PET-CT scans by decreasing the rate of 'false-positives'. This study demonstrated that in 63 per cent of patient's early interval PET-CT demonstrated CR, maintained in the majority; hence EOT PET DS 4 had been a false-positive. This was an important concept, not included within most trial designs, e.g., the ECHELON-1 trial in Advanced Stage HL (Connors *et al.*, 2018) where modified PFS (defined as DS 3,4 or 5, followed by anticancer therapy) was a primary endpoint (without histological confirmation) – a proportion of these patients will likely to have been false-positive on PET-CT (i.e., a DS of 'X').
11.	Lee, A.T.J., Attygale, A.D., Sharma, R.K., Iyengar, S., El-Sharkawi, D., Chau, I., Vroobel, K.M., Fotiadis, N., Khan, N., Butterfield, N., Wotherspoon, A., Cunningham, D., **Sharma, B**. (2020). **'LyRIC indeterminate response and Immune-mediated pseudoprogression of diffuse large B-cell lymphoma following polatuzumab-based salvage therapy.'** *British Journal of Haematology*, 189(6). e248-251. https://doi.org/10.1111/bjh.16679 PMID: 32342503 **Corresponding author: Sharma B.**	The first published description for confirmed pseudoprogression and subsequent metabolic complete response of refractory diffuse large B-cell lymphoma (DLBCL) to polatuzumab-vedotin based salvage therapy. The importance of recognising the limitations of imaging science and data interpretation was highlighted with the concept of the 'Indeterminate Response (IR)' category, newly proposed by the 'lymphoma response to immunomodulatory therapy criteria' (LyRIC) (Cheson *et al.*, 2016). In addition, the importance of the Deauville Classification score of 'X', significantly under-recognised in both clinical and

		research/trial publication practice in the lymphomas, was described.
12.	Mir, F., Wilding, C., Mcaddy, N., Butterfield, N., Sena, L., Thompson, S., Mitra, I., Mohammed, K., Vroobel, K., Attygalle, A., Chau, I., Cunningham, D., Dearden, C., El-Sharkawi, D., Fotiadis, N., Wotherspoon, A., **Sharma, B**., *et al*. (2020). **'Focal splenic lesions in indolent B-NHL: association with high grade transformation and safe percutaneous biopsy.'** *British Journal of Haematology*, 189(4), e157-e160. https://doi.org/10.1111/bjh.16580 PMID: 32196643.	The aims of this single-centre retrospective consecutive patient analysis were: -to study the histology of splenectomy specimens from patients with indolent B-cell NHL on whom splenic abnormalities, either focal or diffuse, had been detected by CT or PET-CT (n=72). -to compare survival outcomes in FL patients with focal splenic lesions (FSL) treated with anthracycline based chemotherapy against those treated with non-anthracycline containing regimens (n=39). -to analyse the safety and utility of percutaneous plugged biopsy for FSL (n=13). Of 15 high-grade lymphomas diagnosed on splenic histology, 14 (93%) had FSL on imaging, whereas only 7/57 (12%) low grade lymphomas demonstrated FSL. The *p*-value for the hypothesis that FSL indicate potential high-grade lymphoma was significant through the McNemar test, p=0.034. There was a significant event free survival (EFS) benefit in FL patients with FSL treated with anthracycline based chemotherapy (p=0.040). Cox proportional hazard regression analysis demonstrated a longer EFS in the patient cohort treated with anthracycline, hazard ratio (HR) 0.47 (95% CI: 0.22-0.98); p=0.043. For splenic plugged biopsies, 1-6 cores (18G or 16G) were taken per patient, diagnostic in 11/13 cases, with HGT diagnosed in 3/13. In all cases the tract was 'plugged' with haemostatic material (gelfoam). No complications, early or late, were observed. FSL observed on anatomical or functional imaging should raise the suspicion of HGT in FL. Splenic plugged core biopsy, a safe technique, should be considered in these patients as it may identify a proportion of patients who may benefit from anthracycline-based chemotherapy.
13.	Martin, A.V., Cunningham, D., **Sharma, B**. (2013). **'Positron emission tomography/CT in the management of lymphoma.'** *Imaging*, 22(1), p.20110086. https://doi.org/10.1259/imaging.20110086	This was a comprehensive review for the clinical use of anatomical-functional imaging tests in lymphomas, highlighting the importance of recognising the Deauville 'X' score.

14.	**Sharma, B**., & Martin, A. (2013). '**Picture quiz: Recurrent FDG-uptake in the anterior mediastinum of a young man previously treated for Hodgkin lymphoma.'** *Imaging*, 22(1), p.20120013. https://doi.org/10.1259/imaging.20120013 **Corresponding author: Sharma B.**	The first literature publication describing DWI as a problem-solving tool to distinguish thymic hyperplasia from lymphoma, which was an unmet clinical need.
	Conference Abstracts/Poster Presentations:	
15.	Zafar, S., Din, F., Sharma, R.K., Chau, I., Musanhu, E.M., El-Sharkawi, D., Nicholson, E., Attygalle, A.D., Cunningham, D., **Sharma B**. (2021). **Standardized reporting in lymphoma radiology (CT, PET-CT, MRI): SIHMIR, a paradigm shift.** Radiological Society of North America (RSNA) conference, December 2021.	The Radiological Society of North America (RSNA) represents 31 radiological specialities from 145 countries and hosts the largest annual global radiology conference. Supplements are published in *Radiographics*, one of the five top peer-reviewed radiology journals. The authors' original SIHMIR paradigm, for application in both clinical and research practice in haematological malignancies, was presented via this forum. Artificial intelligence (AI) applications for SIHMIR were also explored.
16.	Musanhu, E., **Sharma B.** (2021). '**Renal Involvement in Lymphoma; extranodal high risk lymphoma sites for secondary CNS lymphoma and the SIHMIR tool. Proceedings of the International Cancer Imaging Society Meeting and 20th Annual Teaching Course (ICIS), September 2021.'** *Cancer Imaging*, 21(suppl.1), 53; P13. https://doi.org/10.1186/s40644-021-00422-6	The International Cancer Imaging Society (ICIS) aims to promote education and research in oncological imaging. This publication was to introduce the authors' new paradigm of SIHMIR via this forum. This publication also provided an educational update regarding extranodal sites of lymphoma involvement and their significance, including the three principal patterns of renal involvement – under-recognised in clinical practice (Cunningham *et al.*, 2017; Mahalingam *et al.*, 2019).
17.	Cordell S., **Sharma B**. (2021). '**Extra-nodal risk sites for CNS lymphoma; review, good practice guide and the new SIHMIR paradigm shift.'** Royal College of Radiologists (RCR) Learning Live 21. 4-23 Oct 2021.	This educational abstract described the extranodal risk sites for secondary CNS lymphoma, which are important to recognise on imaging, and introduced the authors new paradigm of SIHMIR via this forum.
18.	Mahalingam, P., Iyengar, S., El-Sharkawi, D., **Sharma B.** (2019). '**Implementing a specialist integrated haematological malignancy imaging reporting paradigm to lymphoma radiology assessment can significantly improve the quality of data for patient management and clinical research'.** American Society of Haematology, ASH. Dec 2019. *Blood*, 134 (Suppl_1), pp.5835-5835 https://doi.org/10.1182/blood-2019-126155	This ASH publication was an original retrospective consecutive patient analysis (n=40) to analyse whether key data items required for patient management (staging, response-assessment, prognostication) were included within imaging reports. The analysis demonstrated key data items were missing from a large percentage of reports, with some data-items missing in 90 per cent of 'real-world' clinical imaging reports. The SIHMIR paradigm was suggested as a solution for this.

19.	Pendower, L., Kelly-Morland, C., Cunningham, D., **Sharma B.** (2022). '**Imaging Concepts and New Horizons in the Lymphomas – PET/MRI, DWI, MRI Treatment Response Assessment Maps (TRAMs): review and new perspectives.'** Abstract number: 13946**.** European Congress of Radiology Conference (ECR), July 2022.	The European Congress of Radiology (ECR) is one of the leading annual international global events in radiology, is one of the largest medical meetings in Europe and the second-largest global radiological meeting. This publication comprised a review of the use of the new modality of positron emission tomography-magnetic resonance imaging (PET-MRI) in haematological malignancies and new perspectives for the use of this tool in areas of current unmet clinical imaging need. In addition, the new tool of CCA (TRAMs) in CNSL was described.
20.	Musanhu, E., Cunningham, D., **Sharma B.** (2022). **'Patterns of splenic involvement in low-grade and high-grade non-Hodgkin lymphoma's: significance, evaluation (PET/CT/MRI/DWI) and diagnosis (biopsy).'** European Congress of Radiology Conference (ECR), July 2022.	There is a significant unmet clinical need for diagnostic radiologists, interventional radiologists, and nuclear medicine physicians to be aware of the natural history of the vast histological spectrum of lymphoid neoplasms. This is necessary to enable optimal assessment *and* interpretation of imaging datasets and therefore to contribute toward improved patient outcomes (Cunningham *et al.*, 2017; Zafar *et al.*, 2021). HGT of lymphoma is a clinically significant diagnosis, which can be nuanced on imaging. This abstract was the first conference publication of original work by the authors' group (Mir *et al.*, 2020) comprising retrospective analysis of 72 patients which demonstrated (i) focal splenic lesions in patients with LG NHL reflect HGT in a significant proportion of patients (not recognised in clinical practice at the time); and are (ii) amenable to safe percutaneous plugged splenic biopsy (not considered or undertaken in most centres at the time).
21.	Musanhu, E., Cunningham, D., **Sharma B.** (2022). **'Multimodal imaging of extra-nodal lymphoma: key points on PET/CT/MRI, diagnostic pitfalls, a pictorial review.'** European Congress of Radiology Conference (ECR), July 2022.	Detection and correct data interpretation of extra-nodal sites of lymphoma involvement are essential, particularly in categories such as DLBCL, where SCNSL risk is informed partly by the number of involved extranodal sites. This publication provided an educational overview of this complex area.
22.	Bitar, G., Cunningham, D., **Sharma B.** (2022). **'Peripheral neurolymphomatosis: challenges of staging and response assessment, anatofunctional imaging with PET/CT, MRI, DWI'.** European Congress of Radiology Conference (ECR), July 2022.	This publication assessed anatomical and functional imaging data assessment nuances in this challenging condition.
23.	Din, F., Zafar, S., Millard, T., Cunningham, D., **Sharma B.** (2022). **'An insight into imaging of**	This publication was a review and included new perspectives for anatomical-functional imaging in Castleman disease (CD).

	Castleman disease.' European Congress of Radiology Conference (ECR), July 2022.	
24.	Zafar, S., Din, F., Sharma, R.K., Khan, N., Chau, I., Musanhu, E.M., El-Sharkawi, D., Nicholson, E., Attygalle, A.D., Cunningham, D., **Sharma B.** (2021). '**Treatment response assessment in lymphoma radiology: utility of PET-CT, Deauville classification, the new RECIL and LyRIC criteria'.** Control no:3644. Radiological Society of North America (RSNA) conference, December 2021.	An educational update publication regarding new response evaluation criteria in haematological malignancies, as addressed in the author's NRCO 2017 publication (Cunningham *et al.*, 2017). The simplified new RECIL methodology, including the new category of 'minor response' was detailed (Younes *et al.*, 2017), with case-based examples of application. The new LyRIC modification of the Lugano Classification, with 3 'indeterminate response' (IR) categories of IR1, IR2, IR3 (Cheson *et al.*, 2016), was highlighted. Both new criteria were under-recognised in clinical and research practice at the time.
25.	Musanhu, E., & **Sharma B.** (2021). '**Extranodal risk sites for secondary CNS lymphoma – prognostication.'** Proceedings of the International Cancer Imaging Society meeting and 20th annual teaching course (ICIS). *Cancer Imaging*, 21,53;p18, (2021). https://doi.org/10.1186/s40644-021-00422-6	An educational update following prior published works (Cunningham *et al.*, 2017). Extranodal sites of lymphoma involvement are under-recognised and prone to misinterpretation (Mahalingam *et al.*, 2019). Therefore, it is essential to evaluate these sites, prophylactic CNS treatment requirement being decided by this data.
26.	Kowa, J., Gabriel, J., Iyengar, S., El-Sharkawi, D., Vroobel, K., Attygalle, A., Wotherspoon, A., **Sharma B.** (2020). **'Gastric MALT lymphoma – current concepts in diagnosis and management.'** 31st European Society of Gastrointestinal and Abdominal Radiology (ESGAR). *Insights into Imaging*, 11 (Suppl 3). https://doi.org/10.1186/s13244-020-00873-8 PMID: 32419107.	The imaging assessment of extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) lymphoma is challenging. This publication reviewed this NHL category and detailed the strengths and limitations of anatomical-functional imaging techniques for disease detection. New imaging perspectives were also explored.
27.	Kowa, J.Y., Gabriel, J., Attygalle, A., El-Sharkawi, D., Vroobel, K., Wotherspoon, A., Iyengar, S., **Sharma B.** (2020). **'Non-Hodgkin lymphomas of the gastrointestinal tract: a primer for the diagnostic radiologist.'** 22nd British Society of Gastrointestinal & Abdominal Radiology (BSGAR). Clinical Radiology Journal. Feb 2020. 75.	Various lymphoma categories can involve the gastrointestinal (GI) tract with varying incidence, mantle cell lymphoma and MALT can typically involve the GI tract and are very difficult to detect with current imaging tools. This abstract comprised a review of NHL involvement of the GI tract, with new perspectives including DWI research directions.
28.	Pace, E., Wotherspoon, A., Attygalle, A., Iyengar, S., **Sharma B.** (2018). '**Castleman's disease: the challenging mimic.'** European Congress of Radiology (ECR) Feb 2018. https://dx.doi.org/10.1594/ecr2018/C-2955	Castleman disease (CD) is a challenging condition to diagnose, being a delayed diagnosis in a significant proportion of CD patients. This abstract provided a detailed review of CD including anatomical-functional imaging manifestations.
29.	Kumar, R., Iyengar, S., **Sharma B.** (2017). **'6-week interval PET-CT in predicting end of treatment response in high grade lymphoma.'** European Congress of Radiology (ECR), Mar 2017. https://dx.doi.org/10.1594/ecr2017/C-1008	This was an original retrospective consecutive patient analysis (n=30) assessing the utility for short interval PET-CT studies to evaluate indeterminate 'end-of-treatment' PET findings in HGL.

30.	Lown, R.N., Constantinidou, A., Ebdon, C., Mohammed, K., Ethell, M., Chau, I., Cunningham, D., Potter, M., **Sharma, B.** (2014). **'Successful long-term outcomes in patients with lymphoma achieving only partial response on [^{18}F]FDG-PET prior to allogeneic transplant.'** American Society of Hematology (ASH), Dec 2014. *Blood,* 124(21), pp. 1249-1249. https://doi.org/10.1182/blood.V124.21.1249.1249	Allogeneic haematopoietic stem cell transplantation (HSCT) is a treatment option in patients with relapsed/refractory (R/R) lymphoma. Consensus remained to be reached on the prognostic value of [^{18}F]FDG PET-CT prior to HSCT. A single-centre retrospective analysis of 44 patients undergoing HSCT, with pre-HSCT PET-CT, between 2004 and 2013 was performed, with Kaplan-Meier analysis to assess the impact of categorical variable on patient outcome. Patients included Hodgkin and non-Hodgkin lymphoma categories. Patients with less than CR on pre-HSCT PET-CT showed a trend towards inferior PFS (48% versus 24% at 3 years, p=0.092), but there was no impact on OS. This analysis showed although a CR on PET-CT is desirable prior to HSCT, patient showing a partial response to prior therapies may still have a successful long-term outcome.
31.	Lown, R.N., Constantinidou, A., Ebdon, C., Mohammed, K., Ethell, M., Chau, I., Cunningham, D., Potter, M., **Sharma B.** (2014). **'Residual disease on FDG-PET and multiple lines of prior therapy predict poorer outcomes following autologous hematopoietic stem cell transplantation for lymphoma.'** American Society of Hematology (ASH), Dec 2014. *Blood*,124(21), pp. 3971-3971. https://doi.org/10.1182/blood.V124.21.3971.3971	The utility of [^{18}F]FDG PET-CT pre autologous haematopoietic stem cell transplantation (HSCT) was performed in a single-centre retrospective review of 104 patients with Hodgkin and non-Hodgkin lymphomas between 2004 and 2013. Kaplan-Meier and Cox regression analyses assessed univariate and multivariate analysis of disease outcomes. Predictors of inferior PFS on multivariate analysis included 4 or more lines of prior therapy (hazard ratio (HR) 3.36, p=0.009), and patients with PR on pre-HSCT PET-CT (HR 2.93, p=0.007). In this large single-centre cohort, patients with less than very good partial response (VGPR) and those who had undergone four or more prior lines of prior treatment had significantly poorer outcomes.
32.	Kumar, R., & **Sharma B.** (2014). '**Multi-parametric imaging in haematological malignancy: PET, CT, whole body-diffusion weighted imaging. Staging, response evaluation (early) and prognostication.'** United Kingdom Radiological Congress (UKRC) 2014.	This educational abstract provided a review of anatomical-functional imaging in haematological malignancies and explored new research perspectives including the potential application of WB-DWI.
	BIA-ALCL	
	Publications:	
33.	O'Connell, R.L., **Sharma, B.**, Van Kerckhoven, L., *et al.* (2022). **'Cost and clinical benefit of imaging surveillance after treatment for breast implant-associated anaplastic large cell lymphoma (BIA-ALCL).'** *European Journal*	Recent UK guidelines (Turton *et al.* 2021) had recommended post-treatment surveillance imaging should not routinely be performed for BIA-ALCL patients unless clinically indicated. This single-centre

	of Surgical Oncology, 48(4), pp.748–751. https://doi.org/10.1016/j.ejso.2021.12.463 PMID: 34974948	retrospective consecutive analysis of 11 patients quantified the direct economic costs (DEC) associated with post-treatment routine radiological surveillance prior to guideline adoption. There were no cases of disease relapse [median follow-up 38 months (interquartile range, IQR, 12-47)]. The total cost of imaging was £10,396 with a median cost of £1953 per patient (IQR £526-2029). This cost could have been saved based on new guidelines recommending 'no routine surveillance imaging for asymptomatic patients.'
34.	Davies, O., ***Sharma, B.**, Pace, E., MacNeill, F. (2019). '**Breast implant associated anaplastic large cell lymphoma.'** *BMJ*. 366, p.l4302. https://doi.org/10.1136/bmj.l4302 ***Sharma B, senior author, listed 2nd in *The BMJ* publication.**	This publication provided an educational review of BIA-ALCL to a wide readership via the BMJ; there being a need for education and training regarding this relatively recently recognised condition across a wide range of health-care disciplines.
	Conference Abstracts/Poster Presentations:	
35.	Musanhu, E., Cunningham, D., **Sharma, B.** (2022). '**Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL), a newly recognised WHO lymphoma category: Practical Diagnostics guide for Radiologists, and new perspectives.'** European Congress of Radiology (ECR), July 2022.	This publication provided step-by-step guidance for imaging investigations along the BIA-ALCL patient pathway. The clinical problem of accurate assessment of internal mammary chain lymph nodes, demonstrated in a significant proportion of patients with breast implants, was detailed. These nodes often present as reactive benign nodes related to implants. The nodes 'wax-and-wane' on anatomical and functional imaging tests over a chronic time. The accurate differentiation of benign reactive from lymphoma involved nodes is challenging (Sharma *et al.*, 2020). The original concept of DWI as a new research application to characterise these nodes was advanced.
36.	Mehdi, A., O'Connell, R., Potter, M., Marshall, C., Van Kerckhoven, L., Iyengar, S., Nicholson, E., El-Sharkawi, D., Tasoulis, M., Cunningham, D., **Sharma B**. (2021). '**Breast Implant-associated Anaplastic Large Cell Lymphoma: A cost evaluation study of management and surveillance, and review of the recent USA and UK guidelines.'** American Society of Haematology (ASH), December 2021. *Blood*, 138 (Supplement 1), pp.4014-4014 https://doi.org/10.1182/blood-2021-153675	An original retrospective analysis of 11 consecutive BIA-ALCL patients with the primary aim to analyse the pattern of surveillance imaging and quantify the direct and indirect economic costs of surveillance imaging performed compared to compliance with UK guidelines. The secondary aim was to highlight and raise awareness of USA NCCN and UK guidelines and promote practice standardisation. A highly variable surveillance practice pattern was demonstrated, numerous tests being performed, leading to additional tests and clinic appointments, with an associated health care resource and cost implication. However, no recurrence was detected in the BIA-ALCL cohort

		undergoing surveillance imaging. This built upon earlier work by the authors' group evaluating the direct economic costs of surveillance imaging (O'Connell *et al.*, 2021 (ASCO abstract); O'Connell *et al.*, 2021). This publication also recommended developing global consensus guidelines for BIA-ALCL patient investigation and management and a global patient registry (the incidence of BIA-ALCL is difficult to assess accurately due to a lack of global registry data, including for the denominator of the population with breast implants).
37.	Mehdi, A.M., Bitar, G., Sharma, R., Cunningham, D., **Sharma B.** (2021). **'BIA-ALCL: a review of the recent national/international guidance and best practice guide**.' Control number: 16123. Radiological Society of North America (RSNA), December 2021.	The aim of this publication in the RSNA forum was to raise awareness and provide education for BIA-ALCL. This comprised a 'best-practice' guidance publication, including detailed analyses of the nuances of multimodal imaging in BIA-ALCL, and the first conference presentation of 'NICE guideline style' BIA-ALCL imaging guidance statements for the entire patient pathway.
38.	Adejolu, M., Gagliardi, T., **Sharma B**. (2021). '**Breast Implant-Associated Anaplastic Large Cell Lymphoma: current diagnostic and management guidelines in the UK and USA. Proceedings of the International Cancer Imaging Society Meeting and 20th Annual Teaching Course (ICIS), September 2021.'** *Cancer Imaging* 21, 53; P6 (2021). https://doi.org/10.1186/s40644-021-00422-6	The intention of this abstract was to raise awareness of BIA-ALCL via this forum. By the time of this work, the author had recognised a specific subset of patients in clinical practice with the dilemma of implant-associated effusions of unknown diagnostic significance. These effusions also tend to be recurrent. New detailed guidance for this specific situation was therefore included in this publication, as follows. This subset of patients should be managed via the MDTM setting. Surgery without a pathological diagnosis is not recommended. All differential diagnoses for an effusion/seroma need to be considered, including aspirate analysis for infection (microbiology). It is vital to persevere to obtain a definitive diagnosis before any significant surgical intervention, with the repeated aspiration of the largest possible fluid volume at interval re-accumulation. The sample needs to be assessed by a specialist lymphoma/BIA-ALCL hematopathologist, including for a cell block and immunohistochemistry tests, at a SIHMDS. Other imaging such as breast MRI should be considered if the patient has only been imaged with ultrasound, to evaluate whether mass forming disease is present and if other benign implant complications may be responsible for the effusion – for example implant rupture.

39.	O'Connell, R.L., **Sharma, B.**, Van Kerckhoven, L., *et al*. (2021). '**Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL): Quantifying the direct economic costs of post-treatment radiological surveillance.'** American Society of Clinical Oncology (ASCO), June 2021. *Journal of Clinical Oncology*, 39(15_suppl), pp.e19574–e19574. doi:10.1200/jco.2021.39.15_suppl.e19574.	Recent UK guidelines (Turton *et al.* 2021) had recommended post-treatment surveillance imaging should not routinely be performed for BIA-ALCL patients unless clinically indicated. This single-centre retrospective consecutive analysis of 11 patients quantified the direct economic costs (DEC) associated with post-treatment routine radiological surveillance prior to guideline adoption. There were no cases of disease relapse [median follow-up 38 months (interquartile range, IQR, 12-47)]. The total cost of imaging was £10,396 with a median cost of £1953 per patient (IQR £526-2029). This cost could have been saved based on new guidelines recommending 'no routine surveillance imaging for asymptomatic patients.'
40.	Pace, E., Wotherspoon, A., Attygalle, A., Iyengar, S., **Sharma, B.** (2018). '**Breast Implant Associated Lymphoma: what a radiologist should know.'** European Congress of Radiology (ECR), 2018. https://dx.doi.org/10.1594/ecr2018/C-3245 PMID: 29450851	Multimodal imaging data in BIA-ALCL is prone to misinterpretation. This publication comprised an educational review for radiologists regarding anatomical-functional imaging data-interpretation in this nuanced condition.
	CLL RT	
	Conference Abstracts/Poster Presentations:	
41.	Musanhu, E., & **Sharma B.** (2021). **'Chronic lymphocytic leukemia and Richter transformation, an overview of multiparametric imaging principles, diagnosis, and pitfalls. Proceedings of the International Cancer Imaging Society meeting and 20th annual teaching course (ICIS).'** *Cancer Imaging* 21,53; p14, (2021). https://doi.org/10.1186/s40644-021-00422-6	This publication comprised an educational overview and new perspectives relating to CLL and RT, including the nuances of multimodal imaging. In addition, the authors' original PET-CT driven decision-making paradigm, to define (i) whether a biopsy is needed in CLL for possible RT and (ii) a suitable representative biopsy site, was presented for the first time in the conference literature.
	CNSL	
	Publications:	
42.	Millard, T., Chau, I., Iyengar, S., El-Sharkawi, D., Cunningham, D., **Sharma, B**. (2022). **'Treatment Response Assessment Maps (TRAMs), a new tool for CNS lymphoma.'** *eJHaem*, 3(1), pp.247–248. https://doi.org/10.1002/jha2.346 **Corresponding author: Sharma B.**	One of the first global publications (all from the authors' group) which described the theoretical concept and clinical application of CCA (TRAMs) in CNS lymphoma. CCA enables MRI contrast-enhancing regions to be stratified into areas of viable lymphoma and benign enhancement, increasing the accuracy of staging and response-assessment used to guide patient management decisions.
43.	Millard, T., Chau, I., Iyengar, S., El-Sharkawi, D., Cunningham, D., **Sharma, B**. (2021). **'^{18} F-choline radiotracer positron emission tomography as a new means to monitor central nervous system lymphoma.'** *British*	The first published description of FCH PET-CT to monitor CNS lymphoma. The successful application highlighted the potential of FCH PET-CT as a new monitoring tool for CNSL.

	Journal of Haematology, 193(6), pp.1026–1026. https://doi.org/10.1111/bjh.17374 PMID: 33690883 Corresponding author: **Sharma B.**	
44.	Marshall, K., **Sharma, B**., Millard, T., *et al*. (2021). **[18F]Fluoromethylcholine PET/CT for CNS lymphoma assessment: a new tool.'** *F1000Research* Published [version 1; peer review: 1 approved with reservations], 10, p.1137. https://doi.org/10.12688/f1000research.73232.1	A single-centre retrospective consecutive patient analysis of 40 patients between 2011 and 2019 analysing the concordance of response rates between exploratory FCH PET-CT and standard of care CE-MRI post induction chemotherapy (EOT) for CNS lymphoma, with analysis of survival according to response rate. EOT FCH PET-CT and CE-MRI had a concordance rate of 65%. PFS for the whole cohort was 78% at 100-days and 51.2% at 2-years, OS was 61%. There was no difference in OS (p=0.29) between the groups. To the authors knowledge this was the first publication comparing the new tool of FCH PET-CT with CE-MRI for EOT response in CNSL.
	Conference Abstracts/Poster Presentations:	
45.	DuPreez, M., Meintjes, M., Summers, S., **Sharma B.** (2022)**. 'F18 choline, a novel radiotracer for central nervous system lymphoma: Technical report and original clinical perspectives.'** Society of Nuclear Medicine and Molecular Imaging (SNMMI), 2022.	The author's institution is the only global specialist lymphoma centre routinely performing FCH PET-CT imaging (> 86 patients scanned by the time of this work). A technical report was provided, with practical step-by-step protocol guidance for this new test, and some clinical perspectives.
46.	Bitar, G., Kowa, J.Y., Goldman, A., Rich, P., Mackinnon, A., Chau, I., Cunningham, D., **Sharma B.** (2021). **'A new global tool for CNS lymphoma imaging: Treatment Response Assessment Maps (TRAMs).'** Radiological Society of North America (RSNA), Chicago, USA, 2021.	One of the authors' early original publications describing clinical applications and new perspectives for the use of CCA (TRAMs) in CNSL.
47.	Bitar, G., Sharma, R.K., Chau, I., Cunningham, D., **Sharma, B.** (2021). **'A new tool: 18-FCH PET/CT in primary CNS lymphoma.'** Radiological Society of North America (RSNA), Chicago, USA, 2021.	One of the authors early original publications describing clinical applications and new perspectives for the use of FCH PET-CT in CNSL.
48.	Li, S., Chau, I., Rich, P., Benjamin, P., Mackinnon, A., Cunningham, D., **Sharma B.** (2021). **'18F-choline positron emission tomography and treatment response assessment maps (TRAMs) are potential novel imaging modalities in primary and secondary central nervous system (CNS) lymphoma.'** British Society of Neuroradiologists Annual Meeting, November 2021.	This publication detailed original points for CCA (TRAMs) and FCH PET-CT in CNSL, including aspects as follows. Delineating the quality of response in CNSL with CE-MRI remains a clinical dilemma in patients due to uncertainty regarding the nature of persisting contrast enhancement (CE). Unconfirmed complete response (uCR) may be attributed to patients with residual persisting CE if appearances are stable on subsequent scans, suggesting CE is not due to viable residual lymphoma. However, this can be challenging to apply. Clinical

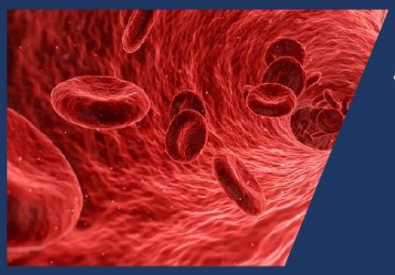
		examples of the utility of the two new tests of CCA and FCH PET-CT were detailed. (A). In a case where CE-MRI appeared to demonstrate a very good response; however, both CCA and FCH PET-CT identified that this lesion remained at risk of progression (i.e., further therapy being indicated). This was confirmed on short interval follow up CE-MRI. (B). In a case where CE-MRI demonstrated a persistent enhancing lesion; however, CCA and FCH PET-CT suggested this was low risk (i.e., not requiring further therapy). This was supported clinically with the patient demonstrating a sustained remission without further treatment. Validation for CCA and FCH PET-CT was recommended within clinical trials.
49.	Sammour, F., Nicholson, E., Anthias, C., Arias, C., Easdale, S., Ethell, M., Potter, M., Iyengar, S., Attygalle, A.D., El-Sharkawi, D., Chau, I., Cunningham, D., **Sharma B.** (2021). **'18Fluoromethylcholine PET/CT to predict outcomes of patients pre and post autologous stem cell transplantation (ASCT) for CNS lymphoma – a new CNS lymphoma imaging tool.'** European Society for Blood and Marrow Transplantation (EBMT) 47th annual meeting, March 2021.	This original retrospective analysis evaluated the prognostic value of pre-transplant FCH PET-CT versus standard of care CE-MRI to predict post-transplant relapse in CNSL (n = 9 patients). This early work suggested that FCH PET-CT may have a higher prognostic value than CE-MRI for this purpose. Prospective blinded research analysis with a more extensive series was recommended.
50.	Marshall, K., Du, Y., Zerizer, I., Chhabda, S., Sheikh, F., Guilhem, E., Chau, I., Cunningham, D., Iyengar, S., **Sharma B**., El-Sharkawi, D. (2020). **'18Fluoromethylcholine-positron emission tomography computed tomography is not inferior to gadolinium-enhanced magnetic resonance imaging in central nervous system lymphoma imaging.'** British Society of Haematology (BSH), virtual meeting November 2020. *British Journal of Haematology*, 189 (Suppl.1), pp. 4-294. https://doi.org/10.1111/bjh.16638	A single-centre retrospective consecutive patient analysis of 40 patients between 2011 and 2019 analysing the concordance of response rates between exploratory FCH PET-CT and standard of care CE-MRI post induction chemotherapy (EOT) for CNS lymphoma, with analysis of survival according to response rate. EOT FCH PET-CT and CE-MRI had a concordance rate of 65%. PFS for the whole cohort was 78% at 100-days and 51.2% at 2-years, OS was 61%. There was no difference in OS (p=0.29) between the groups. To the authors knowledge this was the first abstract publication comparing the new tool of FCH PET-CT with CE-MRI for EOT response in CNSL.

Appendix E - Ongoing and Future Works

1. Haemato-oncology Transplant & Cellular Therapy ICR/RMH/BRC clinical & research meeting.

The ROYAL MARSDEN
NHS Foundation Trust

ICR The Institute of Cancer Research



The ICR and RMH / BRC

Haemato-Oncology Transplant and Cellular Therapy Meeting

Monday 14th November, 2022
Institute of Cancer Research,
London. UK

Free of charge
CPD Accredited

Target Audience: *All levels from Professorial to Junior. Haematologists, Oncologists, Pathologists, Radiologists, Clinical Scientists, AMPs, Clinical Nurse Specialists, Pharmacists, Stem Cell Lab Specialists.*

Programme

How to register: *We are fortunately able to offer this course **'free of charge'** and places are on a first come, first served basis. To register, please complete the form on the next page and email it to Hannah.holmes@rmh.nhs.uk. We would ask for a £100 cheque deposit to secure your place which will be destroyed upon attendance of the course.*

AM Chair: Dr Bhupinder Sharma		
9.15am	Opening Address: Clinical and Research Directions in Transplant Lymphoma.	*Professor David Cunningham* *Consultant Medical Oncologist, Royal Marsden NHSFT*
9.30am	Haemato-oncological transplant imaging: pearls and pitfalls, X and IR categories, new imaging tools (f-choline, CCA, DWI).	*Dr Bhupinder Sharma* *Consultant Radiologist, Royal Marsden NHSFT, Honorary Faculty, ICR*
10.10am	Cardiac complications of chemo and targeted therapy and optimization of patients prior to CAR-T and Transplant.	*Dr Alexander Lyon* *Senior Lecturer & Consultant Cardiologist, Royal Brompton Hospital, London.*
10.50am	Coffee	
11.10am	Allogeneic CAR-T cells	*Dr Reuben Benjamin* *Consultant Haematologist, King's College Hospital NHSFT*
11.50am	CAR-T cells for Mantle Cell Lymphoma	*Dr Claire Roddie* *Consultant Haematologist, UCLH*
12.30pm	Lunch	
PM Chair: Dr Emma Nicholson		
1.30pm	Relapsed/Refactory ALL and role of CAR-T vs HSCT	*Dr Rachel Hough* *Consultant Haematologist, UCLH*
2.10pm	MRD monitoring pre and post HSCT for AML	*Professor Sylvie Freeman* *Professor of ImmunoHaematology, University Hospitals Birmingham NHSFT*
2.50pm	Coffee	
3.10pm	Alternative Donor HSCT	*Dr Chloe Anthias* *Consultant Haematologist, Royal Marsden Hospital NHSFT*
3.50pm	Haem-onc transplant MDM (60 mins) -Difficult transplant cases/difficult diagnostic challenges or management in transplant. OR Sequencing of novel therapies and Transplant in DLBCL – Emma/Sandra/Carlos/Sunil	*Dr Emma Nicholson, Dr Sandra Easdale, Dr Carlos Gonzalez Arias, Dr Sunil Iyengar.* *Royal Marsden Hospital NHSFT*
4.50pm	Take home message	*Dr Emma Nicholson*
5pm	Close	*Dr Bhupinder Sharma*

Exclusive Networking Event 5.30pm–8pm – see next page for further info.

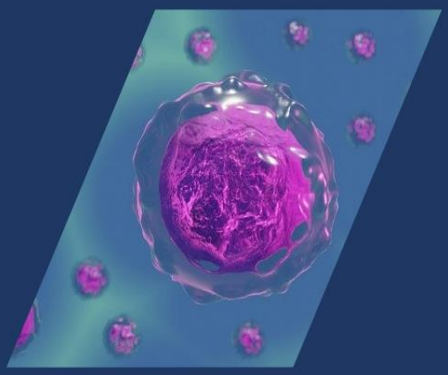
Organising Committee: Dr Bhupinder Sharma, Mrs Hannah Holmes, Dr Emma Nicholson, Dr Sandra Easdale, Dr Chloe Anthias, Dr Carlos Gonzalez Arias, Dr Preethika Mahalingam

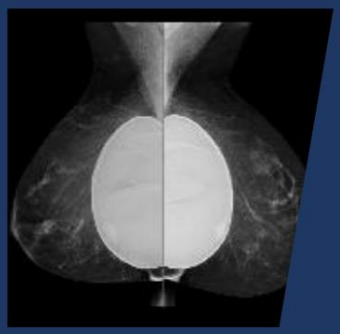
Faculty: Dr Bhupinder Sharma, Dr Emma Nicholson, Dr Chole Anthias, Professor David Cunningham, Dr Sandra Easdale, Dr Carlos Gonzalez Arias, Dr Sandra Easdale

2. BIA-ALCL ICR/RMH/BRC clinical & research meeting.

The ROYAL MARSDEN
NHS Foundation Trust

ICR The Institute of Cancer Research





The ICR and RMH / BRC

BIA-ALCL International Annual Clinical, Research and Scientific Meeting

Tuesday 15th November, 2022
Institute of Cancer Research,
London. UK

Free of charge
CPD Accredited

Target Audience: *All levels from Professorial to Junior. Haematologists, Oncologists, Pathologists, Radiologists, Clinical Scientists, AMPs, Clinical Nurse Specialists*

Programme

How to register: *We are fortunately able to offer this course **'free of charge'** and places are on a first come, first served basis. To register, please complete the form on the next page and email it to Hannah.holmes@rmh.nhs.uk. We would ask for a £100 cheque deposit to secure your place which will be destroyed upon attendance of the course.*

AM Chair: Dr Bhupinder Sharma		
9.00am	Introduction: BIA-ALCL clinical & research perspectives.	*Professor David Cunningham* *Consultant Medical Oncologist, Royal Marsden NHSFT*
9.20am	Pathogenesis, genetics, molecular biology.	*Professor Suzanne Turner* *Consultant Pathologist, Addenbrooke's Hospital*
10.00am	Pathology diagnosis - pearls & pitfalls.	*Dr Ayoma Attygalle* *Consultant Histopathologist, Royal Marsden NHSFT*
10.30am	Imaging tests. Data misinterpretation, pathways.	*Dr Bhupinder Sharma* *Consultant Radiologist, Royal Marsden NHSFT*
10.50am	Coffee	
11.20am	Recent national & international guidelines (USA NCCN & UK).	*Tbc*
12.00pm	Plenary session: BIA-ALCL, the MSKCC / USA experience & perspectives. International invited speaker: tbc	*Tbc*
12.40pm	Lunch	
PM Chair: Mr Marios Tasoulis		
1.40pm	Surgical management - key points.	*Mr Marios Tasoulis* *Consultant Surgeon, Royal Marsden NHSFT*
2.20pm	Systemic therapy - mass forming, advanced stage, relapsed / refractory disease.	*Tbc*
2.50pm	Coffee	
3.10pm	BIA-ALCL Psychology - clinical & research perspectives.	*Professor Georgina Jones* *Professor of Health Psychology, UK Interdisciplinary Centre for Implant-based research (IRIS)*
3.50pm	BIA-ALCL MDTM	*Dr Bhupinder Sharma, Dr Ayoma Attygalle, Mr Marious Tasoulis, Dr Tom Millard* *Royal Marsden Hospital NHSFT*
4.50pm	Closing remarks	*Dr Bhupinder Sharma*

Exclusive Networking Event 5.30pm–8pm – see next page for further info.

Organising Committee: Dr Bhupinder Sharma, Mr Marious Tasoulis, Hannah Holmes, Dr Tom Millard

Faculty: RMH BIA-ALCL Working Group; RMH Lymphoma MDTM

3. Research proposal_DWI_CLL_Sharma B, 2022.

Title.

Whole-body diffusion weighted imaging (WB-DWI) for treatment response assessment in CLL in the context of chemo-immunotherapy and novel agents.

Investigators.

Principal Investigator: Sharma B.

Co-investigators: Iyengar S, Cunningham D.

Hypothesis.

In patients with chronic lymphocytic leukaemia (CLL), whole-body diffusion weighted imaging (WB-DWI) MRI may be useful to assess bone marrow changes induced by treatment and to evaluate treatment response.

Aims.

1. To identify qualitative and quantitative WB-DWI MRI parameters in CLL patients responding and refractory to treatment.

2. To evaluate the use of WB-DWI MRI as an imaging biomarker of response in CLL.

Background.

CLL is the most common adult leukaemia with a reported incidence of 5.1/100,000 in the US, generally affecting an older patient population (Hallek *et al.*, 2015; Teras *et al.*, 2016). A feature of the disease is the accumulation of mature B-lymphocytes in blood, bone marrow and lymphoid tissue. Diagnosis can be made on peripheral blood samples based on blood counts, blood smears and B-lymphocyte immunophenotyping (Campo *et al.*, 2017).

In the majority of patient's, a 'watchful-waiting' policy can be used until the disease becomes active/symptomatic, unless patients are at intermediate or high risk at presentation in which case treatment is usually immediately initiated. Standard treatment comprises chemoimmunotherapy, although substantial progress has been made in drug development for CLL in recent years. This has resulted in the emergence of promising new agents targeting different tumour pathways, such as B-cell receptor (BCR) inhibitors (e.g., Ibrutinib) and BCl2-inhibitors (e.g., Venetoclax) (Robak *et al.*, 2016). These new agents can induce a 'fast and deep partial response', although bone marrow disease is often still present, and can remain undetected by standard analysis of blood samples. This, so called minimal residual disease (MRD), is an important and independent predictor of patient survival (Thompson *et al.* 2016) and can be accurately determined in peripheral blood three months after the end of therapy. Before this time point, MRD evaluation in peripheral blood is unreliable and bone marrow should be assessed instead (Hallek *et al.*, 2015). However, bone marrow biopsy is an invasive technique, while geographical variations may result in sampling errors leading to false negative results (Campo *et al.*, 2017).

Whole-body diffusion weighted imaging (WB-DWI) is an magnetic resonance imaging (MRI) technique which is established in the oncological setting, quantifiable with the apparent diffusion coefficient (ADC) (Padhani *et al.* 2011). In the context of haematological malignancies, DWI has proven to be very useful to detect bone lesions in smouldering multiple myeloma (MM) and solitary bone plasmacytoma's and has become part of patient work-up as recommended by UK National Institute for Health and Care Excellence (NICE) Guidelines (*Myeloma: diagnosis management (NG35)* (NICE 2016)). Analogous to plasma cells in MM, in CLL monoclonal B-lymphocytes accumulate in the bone marrow, with small cells which are tightly packed (Campo *et al.*, 2017). Therefore, we hypothesise WB-DWI MRI may have potential to assess bone marrow disease burden and evaluate treatment response in CLL, a current unmet clinical imaging need (Sharma *et al.*, 2012; Cunningham *et al.*, 2017).

Study design.

Inclusion criteria.

- Patients with a proven diagnosis of relapsed or refractory CLL.

- Patients included before the initiation of standard immunochemotherapy or novel agents such as B-cell receptor (BCR) inhibitors (Ibrutinib) and BCl2-inhibitors (Venetoclax).

Exclusion criteria.

- General contra-indications to MRI (including pacemaker, claustrophobia).
- Concomitant haematological or other malignancies.
- Concomitant haematological, metabolic, or musculoskeletal disorders.

End points.

Primary endpoint. To identify visual and quantitative WB-DWI MRI parameters that can discriminate responding and non-responding patients.

Secondary endpoint. To correlate WB-DWI MRI findings with patient PFS and OS outcomes in the context of standard treatment and novel agents.

Methodology.

A single centre prospective pilot study, including a target population of 20 patients with relapsed or refractory CLL. A standard WB-DWI MRI examination, including conventional T2 and T1 imaging, and a WB-DWI sequence, will be performed before treatment, for treatment response at nine months, and six months post treatment completion. Images will be assessed visually and quantitatively by two Consultant Radiologists (experienced experts in WB-DWI), blinded to each other. Discrepant analysis between the 2 readers will be adjudicated by a third expert reader.

WB-DWI MRI findings will be correlated with the results of blood samples and trephine biopsies and clinical disease course following treatment.

Statistical analysis.

Statistical analysis will consist of assessment of inter observer variability between baseline and follow-up WB-DWI MRI assessment.

Mann-Whitney U test will be performed to detect significant WB-DWI MRI differences between responding and non-responding lesions. To correlate WB-DWI MRI findings with outcome, Kaplan-Meier survival analysis will be performed with progression-free-survival (PFS) and overall survival (OS) as outcomes.

Ethics permission.

Institutional permission will be obtained for this study prior to commencement. Each patient will provide written consent prior to inclusion. All data will be anonymised before analysis. Data will be stored securely at RMH/ICR as per institutional policy.

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