

Impact case study (REF3)

Institution: King's College London		
Unit of Assessment: 12 Engineering		
Title of case study: Improved diagnosis and treatment of patients with lymphoma globally using Positron Emission Tomography (PET) imaging technology		
Period when the underpinning research was undertaken: 2000 - 2018		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Paul Marsden	Professor of PET Physics	From 15/07/1991
Sally Barrington	Professor of PET Imaging	From 01/06/1993
Lucy Pike	Senior Clinical Scientist	From 30/07/2009
Period when the claimed impact occurred: August 2013 - December 2020		
Is this case study continued from a case study submitted in 2014? N		
1. Summary of the impact (indicative maximum 100 words)		
<p>More than 100,000 people are diagnosed annually with lymphomas in the UK and US alone, and many more globally. Imaging technology research at King's College London (King's) using positron emission tomography (PET):</p> <ul style="list-style-type: none"> • has led to new international guidelines using PET-CT scanning as the primary test for staging and for assessing response in lymphomas using a 5-point reporting scale developed at King's; • has resulted in fewer side-effects and improved cure rates for patients with advanced disease globally; • has rendered bone marrow biopsy an unnecessary test in patients with Hodgkin lymphoma (HL) especially in UK, Europe, Australia and US; • has changed practice for the treatment of HL internationally, using an early PET-CT scan to guide treatment. 		
2. Underpinning research (indicative maximum 500 words)		
<p>Since the establishment of the King's PET Centre embedded in St. Thomas' Hospital, King's has been at the forefront of the development of positron emission tomography (PET) technology, with a particular strength in multi-modality imaging, combining PET with computed tomography (PET-CT) and with magnetic resonance imaging (PET-MR). Since 2000, Marsden has led pioneering PET imaging technology development at King's, notably in the areas of image registration, kinetic modelling, motion correction, multi-modality image acquisition, radiomics assessment and data-driven PET acquisition [R1-R3]. In 2016 Marsden was awarded the inaugural John Mallard Award from the International Organisation for Medical Physics (IOMP) for his contribution to the development of PET-MR.</p> <p>A strong multidisciplinary approach, combining biomedical engineering research with clinical and scientific expertise, has formed the foundation of the PET imaging technology research carried out by the King's group. This approach, exemplified in the long-standing collaboration between Marsden and Barrington [R2,R4] has fostered a culture of continuous development, a rigorous approach to analysis of clinical trial data, and ongoing detailed assessment of all methodology in the complex PET imaging process.</p> <p>King's research has adapted and comprehensively evaluated major aspects of the complex PET imaging technology for application in patient management, including production of short-lived radionuclides, tracer synthesis, data acquisition protocols and parameters, and subsequent image reconstruction and processing, facilitated by the synergy with hybrid imaging technology development, as outlined above. In 2008 Marsden was invited to be the technical lead for the National Cancer Research Institute (NCRI) PET Research Initiative,</p>		

established to ensure a coordinated expansion of PET research in the UK [F1], which was followed by the establishment of a UK national PET Imaging Core Lab at St Thomas' Hospital, co-led by Marsden and Barrington [F2]. Based on their combined expertise in performance assessment and quality control of PET-CT scanner systems [R5], the group at King's devised detailed technical standards for scanner performance and quality control for the conduct of multicentre trials, which have then been implemented throughout the UK for cancer trial imaging. Barrington subsequently received the flagship award of Research Professorship from the National Institute for Health Research (NIHR) in 2017 [F3].

The multidisciplinary engineering and clinical research at King's has led to significant advances in the role of PET imaging technology in the diagnosis, staging and treatment of lymphomas, which are cancers of the lymphatic system [R6]. Prior to the King's-led research, lymphoma disease mapping at diagnosis and response assessment at the end of treatment were carried out using CT scans (which only serve to monitor the size of lymph nodes and tumour masses), as well as invasive, often painful bone marrow biopsies (which only show the presence or absence of lymphoma in a small sample acquired from the pelvic bone).

The underpinning PET imaging research at King's led by Marsden, with Barrington as clinical imaging lead, has resulted in new international guidelines for imaging and management of patients with lymphoma. Specifically, King's research has shown that PET scans using the tracer 18F-fluorodeoxyglucose (FDG) that images glucose metabolism, which is increased in lymphomas, can more reliably assess the majority of lymphoma subtypes in the body than CT scans, including in the bone marrow, and can predict treatment response much earlier than CT does.

3. References to the research (indicative maximum of six references)

R1. Marsden PK, Strul D, Keevil SF, Williams SC, Cash D (2002). Simultaneous PET and NMR. *British Journal of Radiology* 75(suppl_9):S53 - S59. DOI: [10.1259/bjr.75.suppl_9.750053](https://doi.org/10.1259/bjr.75.suppl_9.750053)

R2. Schleyer PJ, O'Doherty MJ, Barrington SF, Marsden, PK (2009). Retrospective data-driven respiratory gating for PET/CT. *Physics in Medicine and Biology* 54(7):1935-1950 DOI: [10.1088/0031-9155/54/7/005](https://doi.org/10.1088/0031-9155/54/7/005)

R3. Chicklore S, Goh V, Siddique M, Roy A, Marsden PK, Cook GJR (2013). Quantifying tumour heterogeneity in 18F-FDG PET/CT imaging by texture analysis. *European Journal of Nuclear Medicine and Molecular Imaging* 40(1):133-140. DOI: [10.1007/s00259-012-2247-0](https://doi.org/10.1007/s00259-012-2247-0)

R4. Barrington SF, MacKewn JE, Schleyer P, Marsden PK, Mikhaeel NG, Qian W, Mouncey P, Patrick P, Popova B, Johnson P, Radford J, O'Doherty MJ (2011). Establishment of a UK-wide network to facilitate the acquisition of quality assured FDG-PET data for clinical trials in lymphoma. *Annals of Oncology* 22(3):739-745. DOI: [10.1093/annonc/mdq428](https://doi.org/10.1093/annonc/mdq428)

R5. Pike L, Julyan P, Marsden PK, Waddington W (2013). *Quality Assurance of PET and PET/CT Systems*. IPEM Report 108, ISBN: 978 1 903613 54 2.

R6. Barrington SF, Mikhaeel NG, Kostakoglu L, Meignan M, Hutchings M, Müller S, Schwartz LH, Zucca E, Fisher RI, Trotman J, Hoekstra OS, Hicks RJ, O'Doherty MJ, Hustinx R, Biggi A, Cheson BD (2014). Role of imaging in the staging and response assessment of lymphoma: consensus of the ICML Imaging Working Group. *J Clin Oncol*, 32:3048–58. DOI: [10.1200/JCO.2013.53.5229](https://doi.org/10.1200/JCO.2013.53.5229)

Research funding:

F1. Marsden, PK, NCRI: PET research network, Cancer Research UK. GBP318,726, 1/05/2009-31/07/2012

F2. Barrington S, Marsden, PK, NCRI: PET Core Lab, Cancer Research UK. GBP401,176, 1/08/2012-31/03/2017

F3. Barrington S. Using PET Imaging to improve survival and reduce side-effects of treatment for patients with cancer, NIHR (RP-2016-07-001). GBP1,567,064, 1/12/2017-30/11/2022

4. Details of the impact (indicative maximum 750 words)

Research at King's on the standardised use of FDG-PET scans to inform lymphoma treatment has led to the development of new international guidelines, shaped professional practice and treatment and helped improve patient diagnosis, management and outcomes internationally. Over 100,000 people are diagnosed annually with lymphomas in the UK and US alone, and many more globally.

Background: PET-Directed Therapy for Lymphoma

Hodgkin lymphoma (HL) is the commonest cancer in teenagers and young adults, but also affects older patients, with 2,000 new diagnoses in the UK and over 8,000 new diagnoses in the US annually. Non-Hodgkin lymphomas mainly affect patients over 60, with 14,000 patients diagnosed annually in the UK and 77,240 in the US with many more affected globally.

The PET imaging quality assurance and standardisation procedures established by the UK PET Core Lab (<http://www.ncri-pet.org.uk>) co-led by Marsden and Barrington [F2], and the preceding work on which they are based [R1-R4], ensure that accurate radiotracer uptake values are obtained, which is critical for conducting multicentre trials where quantitative data from all sites need to be pooled in combined analysis to maximise the statistical power of the study. Barrington led the clinical imaging working group that developed the international guidance on imaging stage and response assessment for patient management [R6] and led the use of quality-assured PET imaging scans to guide treatment in the clinical trials RAPID [S1] and RATHL [S2,S3]. The quality assurance and standardisation procedures developed at King's and documented [R5] contributed to obtaining statistically significant results of these studies, and their high clinical impact.

The 'RAPID' trial, funded by Blood Cancer UK, recruited patients from 2003 to 2010, involved 602 patients from the UK and the 'RATHL' trial, funded by Cancer Research UK (Grant reference: CRUK/07/033), which recruited from 2008 to 2012, involved 1,204 international patients. These trials demonstrated that it was safe to reduce treatment when patients have a satisfactory (complete metabolic) response on PET after two or three months of planned 4-6 months treatment, with fewer side-effects for patients with advanced disease, while patients with inadequate early response lived longer if more intensive chemotherapy was given. This approach also reduces the need for high-dose chemotherapy and bone marrow transplant in non-responding patients [S1,S2,S3].

Changes to international guidelines and influence on professional practice

The methods developed in the King's-led trials for performing and reporting quality-assured, standardised PET imaging [S1,S2,S3] have contributed to harmonisation of practices across PET imaging centres worldwide. Specifically, King's research led to changes to international guidelines for management of lymphoma [S4,S5] and contributed to European guidelines for performing quality-assured PET imaging [S6]. The 5-point scale developed at King's has become the international standard also known as the 'Deauville criteria' and was adopted on 20 September 2014 [R6]. Previously, there was no agreed common method to perform and report PET scans in lymphoma. Barrington has continued to influence professional practice amongst haematologists and radiologists as a member of the European Lymphoma Institute's scientific committee for international workshops on PET and lymphoma (September 2014 till October 2018) [S7].

Impact on diagnosis, patient management and outcome

Research from the PET Core lab, applied to the RATHL trial [S2], directly contributed to PET-CT imaging effectively replacing CT and bone marrow biopsy as the standard-of-care for diagnosis and staging of HL [S3]. Guidelines resulting from King's research indicate PET-CT is now the standard imaging test at diagnosis of HL since 2017 [S4,S5], allowing patients to avoid painful and invasive bone marrow biopsies, as documented in patient material [S8].

The research and associated trials effected a change of practice for the treatment of HL since 2017 using early PET scans to guide current treatment, with fewer side-effects and improved survival for patients with advanced disease. In the RATHL trial [S2], early PET scans were

used for treatment adjustments. Furthermore, PET-CT has also become the standard-of-care for monitoring response in patients with follicular lymphoma (FL), the second most common type of non-Hodgkin lymphoma, receiving chemoimmunotherapy after research conducted in the international collaborative study 'GALLIUM' [S9,S10]. In this study (funded by Hofman la Roche Pharmaceuticals) involving 533 patients, Barrington and colleagues in Europe and Australia showed PET to be superior to CT for response adopting the 5-point scale previously developed for HL, and, importantly, a surrogate for overall survival (which is typically more than 10 years) for testing of novel agents in this disease [S10].

Patient outcome has been positively impacted since 2016.

Quality assured PET reporting led to improved outcomes for HL patients with inadequate early response in the RATHL trial. These patients received more intensive treatment and 67% of them were alive and free of lymphoma 3 years after treatment [S2,S3]. This is in contrast to previous reports where only 20% of patients with adverse early PET scan findings survived using the then standard-of-care. More than 85% of patients in the RAPID and RATHL [S1, S2, S3] trials who received less toxic treatment as a consequence of the quality-assured PET reporting were alive without lymphoma three years after treatment. The approaches tested in these trials using PET have become a new standard-of-care amongst the haematology and oncology community and are widely used in the UK, USA, and parts of Europe and Australia. This is evidenced by inclusion in international guidance [S4,S5], professional material [S11], and patient booklets [S7,S12]. Bleomycin is a drug that was previously given to patients for six months with advanced HL. Since RATHL, over 80% of patients with advanced HL need only take this drug for two months [S4,S5,S11].

As Dr. Graham Collins, Chair of the **UK** National Cancer Research Institute's Hodgkin Lymphoma Research Group, says, *"Professor Barrington has led the core PET laboratory at King's which has resulted in practice changing research that has directly improved the care for patients with lymphoma. PET adapted therapy is [now] routinely practised worldwide for Hodgkin lymphoma and Professor Barrington pioneered this approach by leading the PET component of the RAPID and RATHL international studies. The resulting practice change has limited acute and late toxicities of treatments for patients and improved the cure rate for advanced stage disease"* [S13].

In the words of Professor Judith Trotman, Head of Department of Haematology at Concord Hospital, the University of Sydney (**Australia**) and as past Lymphoma Chair of the Australian Lymphoma and Leukaemia Group, *"The PET guided approaches tested in RATHL and RAPID have shaped the management of patients treated in Australia, which is reflected in guidelines that will be published in Feb 2021"* [S14].

As Professor Bruce Cheson, Scientific Advisor at Lymphoma Research Foundation (**USA**), says, *"Dr. Barrington's practice changing research now allows physicians to alter treatment in high risk patients resulting in improved outcomes, and reduce the amount of therapy for those at low risk, with a reduction in toxicities"* [S15].

Informing the work of Lymphoma Action and Blood Cancer UK

Lymphoma Action is the UK's only charity dedicated to lymphoma (5th most common cancer) and have been providing in-depth, expert information for over 30 years, helping thousands of people affected by lymphoma. In 2016, their website reported on the RATHL trial conducted on HL at King's [S16], and in 2018, in a Lymphoma Action Meeting at their National patient and carer conference, the benefits of using PET to guide treatment demonstrated in RAPID and RATHL was highlighted [S17, p.17-23]. Blood Cancer UK, a charity dedicated to beating blood cancer since 1960 reported how findings from the RAPID trial conducted on HL at King's were changing practice worldwide *"making Hodgkin lymphoma treatment kinder"* by offering less intensive treatment to patients with fewer side-effects which can include secondary cancer and heart disease [S18].

5. Sources to corroborate the impact (indicative maximum of 10 references)

S1. Radford et al., (2015). Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. *N Engl J Med*, 372(17):1598–607. DOI: [10.1056/NEJMoa1408648](https://doi.org/10.1056/NEJMoa1408648)

S2. Johnson PWM et al., (2016). Adapted treatment guided by interim PET-CT scan in advanced Hodgkin's lymphoma. *N Engl J Med*, 374:2419–29. DOI: [10.1056/NEJMoa1510093](https://doi.org/10.1056/NEJMoa1510093) (RATHL trial) editorial: *NEJM* 2016 June 23; 374(25): 2490–1

S3. Barrington SF et al., (2016). PET-CT for staging & early response: Results from 'Response Adapted Therapy in Advanced Hodgkin Lymphoma'. *Blood*, 127(12):1531–8. DOI: [10.1182/blood-2015-11-679407](https://doi.org/10.1182/blood-2015-11-679407).

S4. Eichenauer DA et al. (on behalf of the ESMO Guidelines Committee), (2018). European Society of Medical Oncology of Medical Oncology Guidelines for Hodgkin lymphoma. Hodgkin Lymphoma: ESMO Clinical Practice Guidelines. *Ann Oncol.*, 29 (Suppl 4): iv19–iv29. DOI: [10.1093/annonc/mdy080](https://doi.org/10.1093/annonc/mdy080)

S5. Hoppe RT et al., (2017). US National Comprehensive Cancer Network Guidelines for Hodgkin Lymphoma, Hodgkin Lymphoma Version 1, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw.*, 15(5):608–38 DOI: [10.6004/jnccn.2017.0064](https://doi.org/10.6004/jnccn.2017.0064)

S6. Boellaard R et al., (2015). European Association of Nuclear Medicine guidelines for performing PET-CT tumour imaging, FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0., *Eur J Nucl Med Mol Imaging*, 42(2):328–54, DOI: [10.1007/s00259-014-2961-x](https://doi.org/10.1007/s00259-014-2961-x)

S7. [International workshops](#) on PET in Lymphoma

S8. Lymphoma Action - A Young person's guide to Hodgkin Lymphoma Booklet. 6th edition: January 2017 ISBN: 978-0-9929362-9-7

S9. [Website of Medpage Today, a medical online media company for health professionals](#)

S10. GALLIUM trial: Trotman et al., (2018) *Lancet Oncol*, 19:1530–42 doi: [10.1016/S1470-2045\(18\)30618-1](https://doi.org/10.1016/S1470-2045(18)30618-1)

S11. [You tube video from New England Journal of Medicine](#) describing outcomes from the RATHL trial with 27,401 views last accessed 18/01/2021 -Patient booklets published by Lymphoma Action a UK charity dedicated to lymphoma:

S12. [Hodgkin Lymphoma](#): - Pages 50,53 refer to treatment approach tested in RAPID trial and pages 53,55; page 52 refers to RATHL trial now in routine clinical practice. Last accessed 18/01/2021.

S13. Testimonial email from Graham Collins, Chair of the National Cancer Research Institute's Hodgkin Lymphoma Research Group, 17th June 2020

S14. Testimonial quote from Judith Trotman, Head of Department of Haematology at Concord Hospital, University of Sydney 27th January 2021

S15. Testimonial email from Bruce Cheson, Scientific Advisor at Lymphoma Research Foundation (USA), 17th June 2020

S16. [Lymphoma Action website](#) (charity and patient support group dedicated to supporting people with lymphoma) comments on RATHL trial 'Reducing serious side effects and improving outcomes'

S17. [Lymphoma Action Patient Conference](#) presentation by Dr MacKay from University of Glasgow discussing RAPID and RATHL and how they are used in clinical practice slides, 15-23 September 2018. Last accessed 18/01/2021

S18. [Blood Cancer UK website](#) (charity and community dedicated to beating blood cancer) comments on RAPID trial 'Making Hodgkin lymphoma treatment kinder'