

Impact case study (REF3)

Institution: King's College London		
Unit of Assessment: 1		
Title of case study: Global improvement to the diagnosis and treatment of patients with lymphoma 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:
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

Lymphoma is the fifth most common cancer. More than 100,000 people are diagnosed annually with lymphomas in the UK and US alone, and many more globally. Research by King's on the application of positron emission tomography (PET) to lymphoma diagnosis and management has led to the following impacts:

- a new primary test for staging and for assessing patient response in lymphomas using a 5-point PET-CT scanning reporting scale developed at King's, now included in international guidelines ;
- patients experiencing fewer side-effects and improved cure rates for patients with advanced disease globally;
- bone marrow biopsy is now an unnecessary test in patients with Hodgkin lymphoma (HL) changing practice in the UK, Europe, Australia and US;
- substantial change in practice for the treatment of Hodgkin Lymphoma internationally, using an early PET-CT scan to stratify and guide treatment.

2. Underpinning research

Lymphomas are a major cause of morbidity and mortality worldwide. Hodgkin lymphoma (HL) is the most common cancer in teenagers and young adults but also affects older patients with 2,000 new diagnoses in the UK annually. Non-Hodgkin lymphomas mainly affects patients over 60 with 14,000 patients diagnosed annually in the UK.

There are several different treatments that are used, with varying levels of intensity and risk/side effects. Treatment can include different combinations of chemotherapy and/or radiotherapy. Some chemotherapy programmes are more intensive and more effective than others but have more side-effects e.g. those that include the drug bleomycin can cause significant lung damage in some patients. Radiotherapy may also have long term side-effects such as heart and lung disease and increased chance of developing second cancers.

Until King's work in this area, doctors have struggled to select the right treatment for each patient. This is because assessment using Computerised Tomography (CT) provides only structural information making it hard to tell whether treatment is working until it is too late and which fails to identify patients with a high risk of relapse and treatment failure.

Since 2000, academics at King's College London pioneered the use of Positron Emission Tomography (PET) imaging to solve these issues. PET gives information on tumour metabolic properties (i.e. tumour activity). In particular, a reduction in metabolic rate is a very early indicator of therapy working.

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King's led this practice-changing research in two randomised controlled trials (1,2) which established that an early PET read-out could guide and improve treatment in HL. The 'RAPID' trial, funded by Blood Cancer UK, recruited patients from 2003 to 2010, and involved 602 patients from the UK; the 'RATHL' trial, funded by Cancer Research UK, which recruited from 2008 to 2012 involved 1,204 international patients. These trials demonstrated that it was possible to reduce treatment while maintaining a successful treatment outcome after two or three months of a planned 4-6 months course of treatment, for those patients with a complete metabolic response (no evidence of the disease) on PET. We developed a new 5-point staging scale to assess initial disease, as well as a rapid readout for response to treatment (1-4).

Additionally, the RATHL trial demonstrated that PET scans were superior to CT scans and bone marrow biopsies to stage and map the extent of disease before treatment (3). This meant that patients with Hodgkin lymphoma no longer need biopsies which are invasive and painful if they have a PET scan instead. The research found a high level of agreement between PET experts, indicating that our 5-point reporting criteria was robust (3) and this has subsequently become the international standard (5,6). A recent King's analysis further refined the use of the scale and helps with stratifying treatment, by suggesting modifications to the point on the scale used by clinicians to define an inadequate response (based upon disease stage and measured effectiveness of treatment) (7).

King's have also shown that PET research-based end of treatment approaches can be applied to non-Hodgkin lymphoma. They collaborated on a third international study in non-Hodgkin lymphoma ('GALLIUM', funded by Hofman la Roche Pharmaceuticals) involving 533 patients. King's and colleagues in Europe and Australia showed that PET is superior to CT, in terms of overall patient response to treatment, when using the 5-point scale in another more indolent lymphoma type, Follicular Lymphoma (FL). Our results suggest that PET is a better imaging modality than contrast-enhanced CT for response assessment after first-line immunochemotherapy in patients with follicular lymphoma (8).

Taken together, this research means that we can now personalise lymphoma therapy: clinicians can assess very rapidly which patients are responding well to therapy, and which are not (and therefore need to be switched immediately to an intensive regime). This ultimately means that more lymphoma patients survive, and fewer patients experience long-term damage from treatment. King's method has transformed the approach to lymphoma treatment worldwide, as evidenced in various guidelines.

3. References to the research

1. Radford J, Illidge T, Counsell N, Hancock B, Pettengell R, Johnson P, Wimperis J, Culligan D, Popova B, Smith P, McMillan A, Brownell A, Kruger A, Lister A, Hoskin P, O'Doherty M, **Barrington S**. Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. N Engl J Med. 2015 Apr 23;372(17):1598-607. doi: 10.1056/NEJMoa1408648 (RAPID trial)
2. Johnson PWM, Federico M, Kirkwood AA, Fossa A, Berkahn L, Carella AM, D'Amore F, Enblad G, Franceschetto A, Fulham M, Luminari S, O'Doherty M, Patrick P, Roberts T, Sidra G, Stevens L, Smith P, Trotman J, Viney Z, Radford JA, **Barrington SF**. Adapted treatment guided by interim PET-CT scan in advanced Hodgkin lymphoma. N Engl J Med 2016; 374:2419-2429 DOI: 10.1056/NEJMoa1510093 (RATHL trial)
3. **Barrington SF**, Kirkwood AA, Franceschetto A, Fulham MJ, Roberts TH, Almquist H, Brun E, Hjorthaug K, Viney ZN, Pike LC, Federico M, Luminari S, Radford J, Trotman J, Fosså A, Berkahn L, Molin D, D'Amore F, Sinclair DA, Smith P, O'Doherty MJ, Stevens L, Johnson PW. PET-CT for Staging & Early Response: Results from 'Response Adapted Therapy in Advanced Hodgkin Lymphoma' (RATHL) (CRUK/07/033) Blood 2016 Mar 24;127(12):1531-8
4. Gallamini A, **Barrington SF**, Biggi A, Chauvie S, Kostakoglu L, Gregianin M, Meignan M, Mikhaeel GN, Loft A, Zaucha JM, Seymour JF, Hofman MS, Rigacci L, Pulsoni A, Coleman M, Dann EJ, Trentin L, Casasnovas O, Rusconi C, Brice P, Bolis S, Viviani S, Salvi F, Luminari S, Hutchings M. The predictive role of Positron Emission Tomography on Hodgkin Lymphoma

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Treatment outcome is confirmed using the 5-point scale interpretation criteria. *Haematologica* 2014 Jun;99(6):1107-13.

5. SF Barrington, NG Mikhaeel, L Kostakoglu, M Meignan, M Hutchings, S Müller, LH Schwartz, E Zucca, RI Fisher, J Trotman, OS Hoekstra, RJ Hicks, MJ O'Doherty, R Hustinx, A Biggi and BD Cheson. The role of imaging in the staging and response assessment of lymphoma: consensus of the ICML Imaging Working Group *Journal Clinical Oncology* 2014 32:3048-3058.

6. BD Cheson, RI Fisher, **SF Barrington**, F Cavalli, LH Schwartz, E Zucca, TA Lister. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. *Journal Clinical Oncology* 2014:32: 3059-3067

7. Barrington SF, Phillips EH, Counsell N, Hancock B, Pettengell R, Johnson P, Townsend W, Culligan D, Popova B, Clifton-Hadley L, McMillan A, Hoskin P, O'Doherty MJ, Illidge T, Radford J. PET score has greater prognostic significance than pre-treatment risk stratification in early-stage Hodgkin lymphoma in the UK NCRI RAPID study. *J Clin Oncol* 2019 37(20): 1732-41.

8. Trotman J, **Barrington SF**, Belada D, et al. Prognostic value of end-of-induction PET response after first-line immunochemotherapy for follicular lymphoma (GALLIUM): Secondary analysis of a randomised, phase 3 trial. *Lancet Oncol.* 2018;19:1530-1542.

4. Details of the impact

Research at King's on the approach to management of lymphoma using PET scanning has led to the development of new international guidelines and shaped professional practice and treatment around the world. This work has ultimately improved patient diagnosis, management and outcomes nationally and internationally for those diagnosed with lymphomas.

King's research has changed international guidelines. The methods developed in the King's-led RATHL and RAPID trials (**1-3**) have contributed to the harmonisation of practices across PET imaging centres worldwide, stratification of patients and management of the disease. Specifically, King's research led to changes to international guidelines for management of lymphoma from the European Society of Medical Oncology (ESMO) and the US National Comprehensive Cancer Network (**A, B**); and contributed to European guidelines for performing quality-assured PET imaging from the European Association of Nuclear Medicine (EANM) (**C**). The 5-point scale developed at King's (**5**) has become the international standard also known as the 'Deauville criteria' and has been adopted in multiple countries since 2014. Previously, there was no agreed common method to perform and report PET scans in lymphoma.

King's research has influenced clinical practice and health services internationally. The approaches tested in these trials using PET have become the new standards-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 professional material (**H**), and patient booklets (**I**). This is also confirmed by the Head of Department of Haematology at Concord Hospital, the University of Sydney (**Australia**) and 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*" (**J**).

The continuous influence King's researchers have had in professional practice can also be evidenced by (1) Prof Barrington's Research Professorship flagship award from the National Institute for Health Research (NIHR) in 2017 and (2) her four-year membership of the European Lymphoma Institute's scientific committee for international clinical workshops on PET and lymphoma (2010-2018) (**D**). The Scientific Advisor at Lymphoma Research Foundation (**USA**) attested to the clinical significance of her work: "*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*" (**E**).

King's research has improved outcomes for lymphoma patients. The adoption of international best-practice guidelines resulting from King's research has ensured that PET-CT is now the

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standard imaging test at diagnosis of HL worldwide **(A, B)**, allowing patients to avoid painful and invasive bone marrow biopsies, as documented by patient-advocates in the UK charity Lymphoma Action Booklet **(F)**.

Moreover, the quality assured PET reporting led to improved outcomes for HL patients treated with ABVD chemotherapy with inadequate early response to initial treatment in the RATHL trial. These patients received more intensive treatment following this PET assessment and as a result 67% of them were alive and free of lymphoma 3 years after treatment **(2,3)**. 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 trials **(1-3)** who received less toxic treatment as a consequence of the quality-assured PET reporting were alive without lymphoma three years after treatment.

The Chair of the **UK** National Cancer Research Institute's Hodgkin Lymphoma Research Group has said: *"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"* **(G)**.

Research by King's has informed the work of cancer charities in the UK. Lymphoma Action is the UK's only charity dedicated to lymphoma and has provided in-depth, evidence-based information for over 30 years, helping thousands of people affected by lymphoma. In 2016, their website, which had over 1,000,000 unique website users, reported on the RATHL trial conducted on HL at King's **(K)**. In 2018, at their National Patient and Carer conference, they highlighted the benefits of using PET to guide treatment demonstrated in RAPID and RATHL **(L, 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 **(M)**.

5. Sources to corroborate the impact

A. Eichenauer DA et al. (on behalf of the ESMO Guidelines Committee), (2018). European Society 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) [PDF]

B. 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) [PDF]

C. 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) [PDF]

D. European Lymphoma Institute's scientific committee for international clinical workshops on PET and lymphoma [Website](#) [PDF]

E. Testimonial email from the Scientific Advisor at Lymphoma Research Foundation (USA), 17th June 2020 [PDF]

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

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G. Testimonial email from the Chair of the National Cancer Research Institute's Hodgkin Lymphoma Research Group, 17th June 2020 [PDF]

H. You tube video from New England Journal of Medicine describing outcomes from the RATHL trial with 27,401 views last accessed 18/01/2021 [PDF]

I. 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. [PDF]

J. Testimonial from the Head of Department of Haematology at Concord Hospital, University of Sydney 27th January 2021 [PDF]

K. Sources corroborating King's influence on Lymphoma Action's work: **L.1** Lymphoma Action website - comments on RATHL trial 'Reducing serious side effects and improving outcomes'; **L.2** Lymphoma Action 2016 Annual report and accounts (p.7) [PDF]

L. 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 [PDF]

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