Institution: The University of Manchester		
Unit of Assessment: 1 (Clinical Medicine)		
Title of case study: Improving survival and reducing treatment damage in Hodgkin lymphoma.		
Period when the underpinning research was undertaken: January 2001 – December 2020		
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:**
John Radford	Professor of Medical Oncology Honorary Professor	2007 – present 2001 – 2007
Tim Illidge	Professor of Targeted Therapy & Oncology	2004 – present
Period when the claimed impact occurred: 1 August 2013 – 31 December 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

University of Manchester (UoM) research has led to fundamental treatment changes in Hodgkin lymphoma (HL):

- Individualising treatment, leading to fewer treatment-related second cancers and less heart disease for early stage HL patients, and less lung damage in advanced HL.
- Changing clinical guidelines on radiotherapy treatment, reducing dose and field size, decreasing patient risk.
- Introduction of Brentuximab Vedotin in Europe and US for advanced HL, the first new treatment option and change to clinical practice in over 40 years.
- Creation of national Breast Screening after Radiotherapy (BARD) dataset, which identifies women at risk of radiotherapy-induced breast cancer following HL treatment, and its introduction into Public Health England policy.

2. Underpinning research

Context

Hodgkin Lymphoma (HL), typically a young adult disease, is usually curable. However, undesirable late treatment consequences (second cancers, lung and heart disease) are a major cause of future illness and premature death. UoM research has focused on maximising cure and minimising negative treatment impacts as follows:

1. PET Imaging Research

From 2003 to 2010, the UK RAPID trial for patients with early stage HL designed and led by Radford, performed positron emission tomography (PET) scans after 3 chemotherapy cycles. PET-negative patients were randomly allocated to “no further treatment” or “standard radiotherapy”. 3-year, disease-free survival was similar in both groups, showing that the 70% of patients who become PET-negative after chemotherapy could be spared the risks of radiotherapy-induced second cancers and heart disease [1].

The international phase III RATHL trial (2008 to 2012) in advanced stage HL (Radford senior Trial Management Group member) showed that for the 75% of patients with a “negative” PET scan after 2 cycles of chemotherapy, Bleomycin could be dropped from subsequent cycles without any reduction in survival rates. This reduced Bleomycin exposure by approximately 66%, minimising Bleomycin-related lung damage [2]. Together, RAPID and RATHL confirmed the value of PET-adapted therapy in HL treatment, and identified the UK as international leader in this field.

2. Reducing radiotherapy fields

Radiotherapy is an important component of curative lymphoma treatment. Late side-effects (e.g. second cancers) result in premature death. Illidge, with members of the International

Lymphoma Radiation Oncology Group (ILROG), contributed to modernising radiotherapy by defining smaller yet still effective radiation fields (Involved Field, then Involved Site Radiotherapy), reducing late radiation toxicity. Smaller radiotherapy volumes are now administered in fewer fractions and doses are better shaped to the tumour resulting in reduced side-effects and improved patient outcomes [3].

3. Brentuximab Vedotin (BV): Evaluating an effective new drug for HL

In 2010-11, an investigator-led study initiated by Radford showed that BV was effective in patients with recurrent HL [4] (overall response rate 72%, complete response rate 17%). Results showed BV could provide a bridge to allogeneic transplantation in 25% of patients unresponsive to other treatments [4]. Subsequently, from 2012 to 2016, the ECHELON-1 trial (Radford chief investigator outside North America) compared chemotherapy alone with chemotherapy plus BV in untreated advanced HL [5]. The addition of BV improved the proportion of patients alive and disease-free at two years. Two year modified progression free survival with treatment was 82.1%, a 4.9% lower risk of progression, death or non-complete response at 2 years [5]. (*NB 5-year results presented to American Society of Hematology (December 2020) confirm BV efficacy with improved disease-free survival p=0.002 over chemotherapy alone, with the same low rate of secondary malignancies and no impact on successful pregnancies/births*.)

4. Establishment of national Breast screening after Radiotherapy Dataset (BARD)

Women who receive chest radiotherapy for HL under age 36 run a one-in-seven chance of developing breast cancer and national breast screening guidelines are in place to facilitate its early detection. UoM research showed that this screening detects breast cancer at an early and highly curable stage, but population take-up was poor and many women missed opportunities for curative treatment [6]. The UoM established the Breast Screening after Radiotherapy Dataset (BARD), a national English database of 6,500 women at high risk of breast cancer after radiotherapy below age 36, and devised a mechanism for timely screening using Cancer Registry and Radiotherapy Centre data, without the need for individual referrals by their oncologist or GP.

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. *New England Journal of Medicine.* 2015 Apr 23;372(17):1598-607. DOI: 10.1056/NEJMoa1408648

2. 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 and early response: results from the Response-Adapted Therapy in Advanced Hodgkin Lymphoma study. *Blood*. 2016 Mar 24;127(12):1531-8. DOI: 10.1182/blood-2015-11-679407

3. Specht L, Yahalom J, **Illidge T**, Berthelsen AK, Constine LS, Eich HT, Girinsky T, Hoppe RT, Mauch P, Mikhaeel NG, Ng A; ILROG. Modern radiation therapy for Hodgkin lymphoma: field and dose guidelines from the international lymphoma radiation oncology group (ILROG). *International Journal of Radiation Oncolology, Biology, Physics*. 2014 Jul 15;89(4):854-62. DOI: 10.1016/j.ijrobp.2013.05.005

   Illidge was one of 3 lead international authors. This paper is the most highly cited manuscript in this area with >400 citations in an area where primary research is very difficult or impossible to do and has changed clinical practice.

4. Gibb A, Jones C, Bloor A, Kulkarni S, **Illidge T**, Linton K, **Radford J**. Brentuximab vedotin in refractory CD30+ lymphomas: a bridge to allogeneic transplantation in approximately one quarter of patients treated on a Named Patient Programme at a single UK center. *Haematologica.* 2013 Apr;98(4):611-4. DOI: 10.3324/haematol.2012.069393

5. Connors JM, Jurczak W, Straus DJ, Ansell SM, Kim WS, Gallamini A, Younes A, Alekseev S, Illés Á, Picardi M, Lech-Maranda E, Oki Y, Feldman T, Smolewski P, Savage KJ, Bartlett NL, Walewski J, Chen R, Ramchandren R, Zinzani PL, Cunningham D, Rosta A, Josephson NC, Song E, Sachs J, Liu R, Jolin HA, Huebner D, **Radford J**; ECHELON-1 Study Group. Brentuximab Vedotin with Chemotherapy for Stage III or IV Hodgkin's Lymphoma. *New England Journal of Medicine*. 2018 Jan 25;378(4):331-344. Erratum in: *New England Journal of Medicine*. 2018 Mar 1;378(9):878.: DOI: 10.1056/NEJMoa1708984

6. Howell SJ, Searle C, Goode V, Gardener T, Linton K, Cowan RA, Harris MA, Hopwood P, Swindell R, Norman A, Kennedy J, Howell A, Wardley AM, **Radford J**. The UK national breast cancer screening programme for survivors of Hodgkin lymphoma detects breast cancer at an early stage. *British Journal of Cancer*. 2009 Aug 18;101(4):582-8. DOI: 10.1038/sj.bjc.6605215

4. Details of the impact

Approximately 2,100 people, mostly young adults, develop HL annually in the UK. Long-term chemotherapy and radiotherapy toxicities causing ill health and premature death are of particular concern. A more individualised approach to treatment maximises cure and minimises late treatment toxicities.

Reduced risk of second cancers and heart disease for Early Stage HL

Previously, everyone with early stage HL received chemotherapy and radiotherapy and was at risk of radiotherapy-induced second cancers and heart disease. As a result of UoM research (RAPID), the European Society for Medical Oncology (ESMO) guidelines now state that for Early Stage HL, radiotherapy may be omitted following an interim PET scan for "*individual patients when the late risk of delivering RT* (radiotherapy) *is thought to outweigh the short-term benefit of improved disease control*" [A,1].

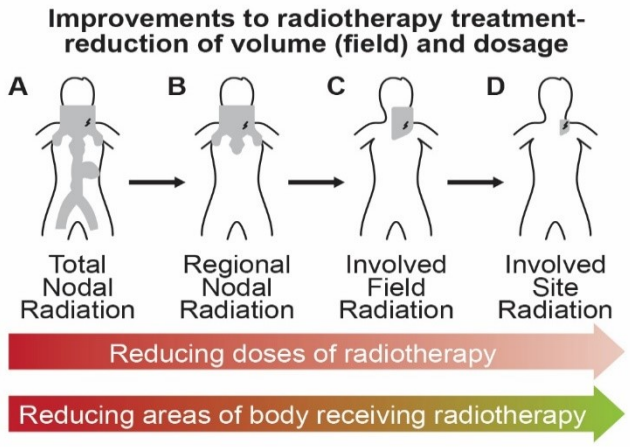
National Comprehensive Cancer Network® (NCCN®) is an alliance of 30 leading US cancer centres. There are >1,200,000 registered users of NCCN Guidelines® globally and they have been downloaded in >180 countries. NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®) for Hodgkin Lymphoma cite the RAPID trial and state interim PET scans "*may also be useful to identify a subgroup of patients with early…stage disease that can be treated with chemotherapy alone*" [B,1].

Reduced risk of lung damage in Advanced Stage HL

Standard treatment for advanced HL includes Bleomycin, a drug causing lung damage and, in 1-2%, death due to respiratory failure. The RATHL treatment approach [2] reduces Bleomycin exposure by 75%. For advanced HL treatment, NCCN Guidelines® now state, "*If reduced exposure to Bleomycin is desired, the panel recommends omitting Bleomycin from ABVD (chemotherapy) per the RATHL trial*" [B].

Changing radiotherapy fields to reduce patient risk

Illidge, with ILROG partners, led the introduction of smaller doses of radiotherapy given to smaller areas (fields) of the body. ILROG international guidelines [3] have profoundly affected clinical practice and changed radiotherapy delivery in lymphoma (see illustration). These changes (now employed routinely in international HL treatment) have fewer late consequences without a reduction in disease control. Their importance is demonstrated by adoption of involved-site radiotherapy (ISRT) in clinical



guidelines. NCCN Guidelines® confirm ISRT as an alternative to involved-field radiotherapy (IFRT) *"in an effort to restrict the size of the RT fields and to further minimize the radiation exposure to adjacent uninvolved organs and the potential long term toxicities associate with radiation exposure*" [B,3] and states "*ISRT is recommended as the appropriate field for Hodgkin Lymphoma*" [B]. European ESMO HL Clinical Guidelines recommend ISRT instead of IFRT after chemotherapy in limited and intermediate disease stages [A,3].

New drug treatment - patient health benefits and impact on clinical guidance

For the 10-15% of patients with recurrent and refractory HL, there were previously few therapeutic options and little prospect of cure. In 2016, Radford provided 'real world' evidence to the National Institute for Health and Care Excellence (NICE) committee from an analysis of Manchester patients: *"8 of 25 patients eligible for allogeneic transplantation proceeded to transplant after BV alone and 5 (20%) are alive and disease-free after a median follow-up of 25.3 months"* [Ci]. In 2017, NICE recommended BV for use within the Cancer Drugs Fund as an option for recurrent HL after two previous therapies [Cii]. A Public Health England (PHE) report, based on a questionnaire created with input from Radford, formed part of NICE's review. The report assessed 219 'real life' patients treated between 2013 and 2016: 36% who received BV to bridge to stem cell transplant were able to have the transplant without needing salvage chemotherapy [Ciii]. In June 2018, NICE recommended routine BV commissioning [Civ,4]. Takeda who market BV as Adcetris, estimate it is now prescribed to 190-200 patients per year in the UK for this indication [D].

In advanced HL, the US Food and Drug Administration (FDA) approved first line BV treatment in combination with chemotherapy in March 2018, based on ECHELON-1 [E,5]. The FDA said BV approval represented "*an improvement in the initial treatment regimens of advanced HL that were introduced into clinical practice more than 40 years ago*" [E]. In February 2019, EMA approved this indication based on ECHELON-1 [F,5]. Treatment with BV and chemotherapy is also recommended in NCCN Guidelines® for stage III-IV disease [B].

Policy impact of new nationwide breast screening

Before BARD, screening of patients at high risk of breast cancer following radiotherapy for HL depended on individual patient referral. National guidelines existed but referrals were sporadic. Radford initiated and established BARD in collaboration with PHE to optimise screening and ensure those at risk were informed of screening options at the appropriate time. BARD has been implemented nationwide as a method of referral for women eligible for very high risk screening, and is included in PHE's guidelines [Gi] and NHS service specifications for the Breast Screening programme 2019-20 [Gii]. BARD's impact was highlighted in PHE Cancer Blogs [Hi] and Cancer Stories [Hii], which Radford was asked to contribute to, as part of PHE public dissemination. At the BARD Launch Meeting in September 2018, PHE's Director of Screening described BARD as, "*the model for cancer surveillance in high risk populations*" [I] and recently confirmed "*UK CMOs* (Chief Medical Officers) *are currently exploring policy making in relation to a broader range of screening programmes*" and confirmed Radford's work on BARD "*has been very useful to guide this new policy direction*" [J].

5. Sources to corroborate the impact

A. Hodgkin lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Eichenauer DA, Aleman BMP, André M, Federico M, Hutchings M, **Illidge T**, Engert A, Ladetto M; European Society for Medical Oncology (ESMO) Guidelines Committee. Ann Oncol. 2018 Oct 1;29. - ***cites the RAPID trial UoM reference 1 and UoM reference 3.***

B. NCCN Guidelines® for Hodgkin Lymphoma ***cites UoM references 1,2,3 and 5.*** Referenced with permission from the NCCN Guidelines® for Hodgkin Lymphoma V.2.2020 © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed [July 15, 2020]. To view the most recent and complete version of the guideline, go online to www.NCCN.org. NCCN makes no warranties of any kind

whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

C. NICE Technology Appraisals: Brentuximab vedotin for treating CD30-positive Hodgkin's lymphoma
   i. Single Technology Appraisal Committee Papers 30 August 2016 – ***Radford provided expert opinion and real world evidence.***
   ii. Brentuximab Vedotin for treating CD-30 positive Hodgkin Lymphoma Technology Appraisal Guidance TA446 28 June 2017 ***BV use as bridging treatment recommended as part of cancer drugs fund.***
   iii. Single Technology Appraisal Committee Papers 4 May 2018 - ***Committee report cites UoM reference 4 and contains PHE report with real world patient impacts.***
   iv. Brentuximab Vedotin for treating CD-30 positive Hodgkin Lymphoma Technology Appraisal Guidance 13 June 2018 – ***BV use as bridging treatment recommended.***

D. Email from Takeda Oncology Country Head - UK & Ireland, 6 November 2020 – ***confirming estimated number of UK prescriptions for BV in Relapsed/Refractory HL indication***.

E. FDA press release, 20 March 2018- ***confirming approval of Brentuximab Vedotin to treat adult patients with previously untreated stage III or IV classical Hodgkin Lymphoma in combination with chemotherapy – based on ECHELON-1 trial (UoM reference 5).***

F. Takeda press release, 11 February 2019 - ***confirming EMA extend marketing authorization of BV to include treatment of adult patients with previously untreated CD30+ Stage IV Hodgkin lymphoma in combination with AVD (chemotherapy) – based on ECHELON-1 trial (UOM reference 5).***

G. Public Health England Guidance
   i. Protocols for surveillance of women at very high risk of developing breast cancer. Updated 23 September 2020 - ***confirming process of referrals by BARD.***
   ii. NHS public health functions agreement 2019-20. Service specification No.24. NHS Breast Screening Programme - ***confirming BARD as a method of referral for women eligible for very high risk screening.***

H. Dissemination of BARD screening - ***Radford was asked to contribute to PHE publications for dissemination of BARD screening***
   i. Public Health England screening blog 'Breast screening after radiotherapy (BARD) new dataset' (26 July 2019).
   ii. Cancer story Patient data is helping to improve care for breast cancer patients' (published for Breast Cancer Awareness month- October 2019).

I. Greater Manchester Cancer Annual Report 2018 including quote from Director of Screening Public Health England - ***confirming BARD as 'the model for cancer surveillance in high risk populations'.***

J. Testimonial from Director of Screening Public Health England 5 November 2020 - ***confirming importance of UoM work in guiding policy direction.***