Predicted Risks of Cardiovascular Disease Following Chemotherapy and Radiotherapy in the UK NCRI RAPID Trial of Positron Emission Tomography–Directed Therapy for Early-Stage Hodgkin Lymphoma

David J. Cutter, MD, DPhil1,2; Johanna Ramroth, DPhil1; Patricia Diez, MSc3; Andy Buckle, MSc2; Georgios Ntentas, DPhil1,4; Bilyana Popova, MSc5; Laura Clifton-Hadley, PhD5; Peter J. Hoskin, MD3,6; Sarah C. Darby, PhD1; John Radford, MD6; and Tim Illidge, MD, PhD6

PURPOSE The contemporary management of early-stage Hodgkin lymphoma (ES-HL) involves balancing the risk of late adverse effects of radiotherapy against the increased risk of relapse if radiotherapy is omitted. This study provides information on the risk of radiation-related cardiovascular disease to help personalize the delivery of radiotherapy in ES-HL.

METHODS We predicted 30-year absolute cardiovascular risk from chemotherapy and involved field radiotherapy in patients who were positron emission tomography (PET)–negative following three cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine chemotherapy within a UK randomized trial of PET-directed therapy for ES-HL. Cardiac and carotid radiation doses and chemotherapy exposure were combined with established dose-response relationships and population-based mortality and incidence rates.

RESULTS Average mean heart dose was 4.0 Gy (range 0.1-24.0 Gy) and average bilateral common carotid artery dose was 21.5 Gy (range 0.6-38.1 Gy), based on individualized cardiovascular dosimetry for 144 PET-negative patients receiving involved field radiotherapy. The average predicted 30-year radiation-related absolute excess overall cardiovascular mortality was 0.56% (range 0.01%-6.79%; 0.5% in 67% of patients and >1% in 15%), whereas average predicted 30-year excess incidence was 6.24% (range 0.31%-31.09%; 5% in 58% of patients and >10% in 24%). For cardiac disease, the average predicted 30-year radiation-related absolute excess mortality was 0.42% (0.79% with mediastinal involvement and 0.05% without) and for stroke, it was 0.14%.

CONCLUSION Predicted excess cardiovascular risk is small for most patients, so radiotherapy may provide net benefit. However, for a minority of patients receiving high doses of radiation to cardiovascular structures, it may be preferable to consider advanced radiotherapy techniques to reduce doses or to omit radiotherapy and accept the increased relapse risk. Individual assessment of cardiovascular and other risks before treatment would allow personalized decision making about radiotherapy in ES-HL.

INTRODUCTION Over recent decades, the standard management of early-stage Hodgkin lymphoma (ES-HL) has been combined modality treatment including chemotherapy and radiotherapy. For favorable ES-HL, this is currently two cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) chemotherapy and 20 Gy involved field radiotherapy (IFRT), giving excellent 5-year survival (>90% relapse-free and >95% overall).1 Attention is now focused on reducing late toxicity. In the past, extended-field radiotherapy and higher radiation doses provided good disease control but incurred substantial risks of second cancers and cardiovascular disease (CVD).2,3 More recently, randomized controlled trials (RCTs) have combined clinical risk factors and positron emission tomography (PET)—a radiologic biomarker of response—to identify patients for whom initial treatment can be less intensive, hopefully reducing long-term toxicity without compromising cure.4,5,6

The UK National Cancer Research Institute Lymphoma Study Group RAPID trial was an RCT in ES-HL designed to test the omission of radiotherapy following a complete metabolic response on fluorodeoxyglucose-PET scans after three cycles of
CONTEXT

Key Objective
To predict 30-year absolute excess risks of radiation-related cardiovascular disease for positron emission tomography-negative patients given radiotherapy in the UK RAPID trial of early-stage Hodgkin lymphoma using novel methodology that combines individual radiation dosimetry and epidemiologic data.

Knowledge Generated
Mean heart dose was < 1 Gy for more than half the patients and < 5 Gy for more than two thirds, whereas mean bilateral common carotid dose was 21 Gy. If radiotherapy were given selectively to the 50% of patients with the lowest predicted risks, then their average predicted 30-year absolute excess risks of radiation-related cardiovascular disease would be 0.11% for mortality and 1.79% for incidence.

Relevance
For the majority of positron emission tomography-negative patients in the RAPID trial, the predicted cardiovascular risks are small. These risks should be even lower with the most modern radiotherapy techniques. The decision to give radiotherapy for early-stage Hodgkin lymphoma should be patient-specific, based on individualized risk predictions of dose to critical structures and of all the late effects of these exposures.

METHODS

Patients and Treatment
Six hundred two patients were enrolled into the trial during 2003-2010 (median age, 34 years; range, 16-75 years). Five hundred seventy-one received three cycles of ABVD followed by fluorodeoxyglucose-PET. Among PET-negative individuals (Deauville score 1-2, n = 426), 209 were randomly assigned to IFRT and 183 received it. Among PET-positive individuals (Deauville score 3-5, n = 145), 129 received IFRT (Data Supplement, online only).

IFRT comprised treating the extent of disease detected by computed tomography (CT) before chemotherapy. There was no intention to treat uninvolved contiguous nodal areas, or entire nodal regions. The recommended field-edge margins were 5 cm up-and-down involved nodal chains with 1.5-2.0 cm lateral margins around the postchemotherapy volume of disease within the mediastinum.11 The dose specified was 30 Gy in 1.8-2.0 Gy fractions, treated in the supine position, by opposed anterior and posterior 5-8 MV beams, both delivered daily.

Cardiovascular Radiation Dosimetry
Radiotherapy departments supplied details of the IFRT administered to the National Radiotherapy Trials Quality Assurance team. Where CT planning was used (72%), the original data sets were requested. If the CT did not cover the entire heart, regression was used to estimate the volume missing to calculate heart dose and to estimate doses to cardiac substructures. Where x-ray simulation was used (28%), copies of films were requested and substitute CTs were used to estimate dosimetry. Further details are in the Data Supplement. Treatment data collection and subsequent analysis were approved by the appropriate Research Ethics Committee.

Prediction of Cardiovascular Risks
Predictions of 30-year cardiovascular mortality were based on individual radiation doses to the whole heart, left ventricle, heart valves, and common carotid arteries, and the
administered anthracycline dose. They were derived using the estimated percentage increases in mortality rate per unit dose obtained from long-term studies of cardiac disease\textsuperscript{12-14} and stroke\textsuperscript{15} following HL treatment, combined with 5-year age- and sex-specific death rates from CVD in the general UK population. Deaths from all causes other than CVD in the general population were competing risks. The 30-year risk of incident CVD was estimated in a similar fashion, using age- and sex-specific first CVD incidence rates from a representative UK cohort\textsuperscript{16} (details are in the Data Supplement).

RESULTS

Patients Included in the Analysis

Of the 183 PET-negative patients who received IFRT, data sufficient to complete dosimetry were available for 144 (78.7\%, Data Supplement). Of the 129 PET-positive patients who received IFRT, data sufficient to complete dosimetry were available for 103 (79.8\%). The baseline characteristics of patients for whom dosimetry was and was not completed were similar (Data Supplement).

Doses Received by the Heart, Cardiac Substructures, and Carotid Arteries

For PET-negative patients, the average MHD was 4.0 Gy: 0.3 Gy for those without and 7.8 Gy for those with mediastinal involvement (Table 1). For almost all patients without mediastinal involvement, the MHD was < 1 Gy (72/73, 98.6\%), whereas for those with mediastinal involvement, the MHD ranged widely (0.8-24.0 Gy, Table 1 and Fig 1A). Considering all PET-negative patients, MHD was < 1 Gy for more than half (76/144, 52.8\%) and < 5 Gy for more than two thirds (100/144, 69.4\%). The most superior cardiac substructures, such as the pulmonary valve and sinoatrial node, received the highest mean radiation doses (Table 1). The mean radiation dose to the common carotid arteries averaged over 20 Gy but varied widely with peaks for patients receiving unilateral and bilateral neck irradiation (Fig 1B). Dose distributions for PET-positive patients receiving IFRT were similar to those with PET-negative disease (Data Supplement).

Predicted 30-Year Risks of Cardiovascular Mortality

Mortality from heart disease or stroke. The average predicted 30-year cardiovascular mortality risk for PET-negative patients who received IFRT after ABVD was 5.02\% (range over individuals 0.30\%-19.37\%), and comprised 3.52\% expected risk from general population rates plus 0.94\% absolute excess risk because of anthracycline chemotherapy and a further 0.56\% because of IFRT (Fig 2A). The absolute excess risk because of IFRT was dominated by ischemic heart disease (0.36\%) and stroke (0.14\%; Fig 2B). Considering the radiation-related risk to individual patients, the predicted 30-year absolute excess was < 0.5\% in 67\% of patients, whereas the

| Cardiovascular Structure                  | Med+ (n = 71) | Med− (n = 73) | All (n = 144) |
|------------------------------------------|--------------|--------------|--------------|
|                                         | Ave  | Range       | SD | Ave  | Range  | SD | Ave  | Range  | SD |
| Whole heart                              | 7.8  | 0.8-24.0    | 5.4 | 0.3  | 0.1-1.4  | 0.2 | 4.0  | 0.1-24.0  | 5.3 |
| Left coronary artery                     | 8.6  | 0.6-23.9    | 6.0 | 0.3  | 0.21-2.2  | 0.3 | 4.4  | 0.1-23.9  | 5.9 |
| Right coronary artery                    | 7.3  | 0.5-27.9    | 6.5 | 0.2  | 0.0-0.7  | 0.2 | 3.7  | 0.0-27.9  | 5.8 |
| Circumflex coronary artery               | 12.4 | 0.8-32.5    | 9.1 | 0.4  | 0.1-2.4  | 0.4 | 6.3  | 0.1-32.5  | 8.7 |
| Aortic valve                             | 16.1 | 0.9-34.0    | 11.2 | 0.5  | 0.1-1.5  | 0.3 | 8.2  | 0.1-34.0  | 11.1 |
| Mitral valve                             | 8.7  | 0.6-32.7    | 9.7 | 0.3  | 0.0-1.8  | 0.3 | 4.5  | 0.0-32.7  | 8.0 |
| Tricuspid valve                          | 6.2  | 0.4-31.9    | 8.0 | 0.2  | 0.0-0.7  | 0.2 | 3.2  | 0.0-31.9  | 6.3 |
| Pulmonary valve                          | 22.3 | 1.8-34.5    | 9.2 | 0.7  | 0.1-2.6  | 0.5 | 11.4 | 0.1-34.5  | 12.6 |
| Left ventricle                           | 3.3  | 0.3-20.5    | 3.9 | 0.2  | 0.0-2.1  | 0.3 | 1.7  | 0.0-20.5  | 3.2 |
| Right ventricle                          | 4.8  | 0.4-26.9    | 5.5 | 0.2  | 0.0-1.0  | 0.2 | 2.5  | 0.0-26.9  | 4.5 |
| Left atrium                              | 15.8 | 1.5-32.8    | 8.8 | 0.5  | 0.1-1.4  | 0.3 | 8.0  | 0.1-32.8  | 9.9 |
| Right atrium                             | 9.9  | 0.8-27.7    | 8.1 | 0.3  | 0.0-1.1  | 0.2 | 5.0  | 0.0-27.7  | 7.4 |
| Sinoatrial node                          | 21.7 | 1.3-34.9    | 9.9 | 0.6  | 0.1-2.2  | 0.4 | 11.0 | 0.1-34.9  | 12.7 |
| Atrioventricular node                    | 8.8  | 0.6-32.0    | 10.5 | 0.3  | 0.0-0.9  | 0.2 | 4.5  | 0.0-32.0  | 8.5 |
| Left carotid artery                      | 28.3 | 8.7-38.4    | 5.1 | 15.4 | 0.3-34.6  | 12.3 | 21.8 | 0.3-38.4  | 11.5 |
| Right carotid artery                     | 28.2 | 12.2-37.8  | 5.0 | 14.3 | 0.7-30.7  | 10.8 | 21.1 | 0.7-37.8  | 10.9 |

Abbreviations: Ave, average of mean doses; PET, positron emission tomography; range, range of mean doses; SD, standard deviation of mean doses.
median risk (ie, the average of patients ranked 72 and 73 out of 144) was 0.26%. The range across individuals was 0.01%-6.79% (Fig 3A) and the risk was 1% in 15% of patients. If IFRT were given selectively to the 50% of PET-negative patients with the lowest predicted radiation-related risks, then the average predicted 30-year absolute excess radiation-related cardiovascular risk for these patients would be 0.11% (Fig 3B).

**Mortality from heart disease.** When the PET-negative patients were subdivided into five categories of MHD, the average predicted 30-year absolute excess risk of radiation-related mortality from heart disease ranged from 0.03% for those receiving < 0.5 Gy MHD to 2.20% for those receiving 10+ Gy (Fig 2C). For individuals, the radiation-related risk ranged from 0.002% to 6.55%. The average was 0.42%; 0.79% for those with mediastinal involvement and 0.05% without. The main determinant of MHD, and hence of cardiac risk, was the inferior border of the radiotherapy field (Data Supplement). Average MHD was higher for females than for males (5.4 v 2.7 Gy) because of a higher proportion with mediastinal involvement (59% v 41%) and, on average, a lower inferior border to the mediastinal radiation field (median level seventh thoracic vertebra in females v sixth in males). Consequently, the predicted proportional increase in mortality from heart disease was on average higher for females. However, as men have higher cardiac mortality rates in the general population, the estimated 30-year absolute excess mortality risk from treatment-related heart disease (chemotherapy and radiotherapy combined) was actually lower for females (1.2% for females and 1.5% for males, Data Supplement).

**Mortality from stroke.** When the PET-negative patients were grouped into four categories of mean bilateral carotid artery dose, the predicted 30-year average absolute excess radiation-related risk of mortality from stroke varied from 0.05% in those receiving < 10 Gy to 0.24% in those receiving 30+ Gy (Fig 2D). For individual patients, the radiation-related risk ranged from 0.008% to 1.12%, with an average of 0.14%.

**Predicted 30-Year Risks of Incident CVD**

**Incidence of heart disease or stroke.** The average predicted 30-year risk of developing CVD for the PET-negative patients receiving IFRT after ABVD was 35.8% (range over individuals 7.7%-86.8%). This comprised 22.9% expected risk from general population rates plus 6.7% absolute excess risk because of anthracycline chemotherapy and a further 6.2% because of IFRT (Fig 4A). The absolute excess risk because of IFRT was dominated by ischemic heart disease (3.28%) and stroke (2.31%; Fig 4B). Considering the radiation-related risk to individual patients, the predicted 30-year absolute excess risk was < 5% in 58% of patients, whereas the median individual risk was 3.61%. The range across individuals was 0.31%-31.09% (Fig 3A) and the risk was > 10% in 24% of patients. If IFRT were given selectively to the 50% of PET-negative patients with the lowest predicted radiation-related cardiovascular risks, then the average predicted 30-year excess absolute radiation-related incidence risk for these patients would be 1.79% (Fig 3B).

**Incidence of heart disease.** When individuals were grouped into five categories of MHD, the average predicted 30-year
Absolute excess risk of developing radiation-related heart disease ranged from 0.21% for those receiving < 0.5 Gy MHD to 16.33% for those receiving 10+ Gy (Fig 4C). For individuals, the radiation-related risk ranged from 0.03% to 27.88%. The average was 3.93%; 7.66% for those with mediastinal involvement and 0.31% without.
Incidence of stroke. When individuals were grouped into four categories of mean bilateral carotid artery dose, the predicted 30-year absolute excess risk of incident stroke ranged from 0.66% in those receiving 10 Gy to 3.42% in those receiving $30\,\text{Gy}$ (Fig 4D). For individuals, the radiation-related risk ranged from 0.09% to 5.35%, with an average of 2.31%.

**DISCUSSION**

This study reports the cardiovascular radiation doses received by ES-HL patients treated with IFRT within the RAPID trial and uses them to predict 30-year radiation-related cardiovascular risks for patients who were PET-negative after initial chemotherapy. Because of the varied distribution of disease, the doses received varied widely between individuals and so, therefore, did the predicted radiation-related risks. For 67% of patients, the predicted radiation-related 30-year absolute excess cardiovascular mortality risk was < 0.5% and for 58%, the incidence risk was < 5%. Although these risks are low, they are clinically relevant when considered in the context of an expected 5-year relapse-free survival of > 95% for ES-HL. At the other end of the scale, for 15% of patients, the mortality risk was > 1% and for 24%, the incidence risk was > 10%. For all patients, individualized late toxicity risks should be balanced against the 6%-12% absolute benefit in PFS from consolidation radiotherapy observed in three large RCTs.

Our study gives a representative picture of cardiovascular risk from IFRT for all patients in the RAPID trial who were PET-negative after initial chemotherapy. Previous dosimetry studies have concentrated largely on patients with more extensive mediastinal involvement and reported techniques to reduce cardiac exposure. In this study, radiotherapy did not include the mediastinum for more than half the patients and we confirm previous findings that the level of mediastinal involvement is a critical determinant of cardiac dose, largely independent of the radiation techniques used. With our methods, the minority of patients receiving the highest radiation doses to the heart and carotid arteries have predicted risks of CVD similar to those seen for historical forms of radiotherapy (Table 2) and consistent with results observed from large cohort studies with prolonged follow-up. In sharp contrast are the 35% who received only unilateral neck irradiation in the RAPID trial for whom the doses to cardiovascular structures, and consequently the predicted risks, are much lower.

Anthracycline-based chemotherapy approximately doubles the risk of cardiac disease from mediastinal irradiation,

**FIG 3.** Predicted 30-year absolute excess risk of radiation-related heart disease or stroke for PET-negative patients who received radiotherapy and for whom dosimetry was completed ($n = 144$). Mortality is indicated by orange lines and incidence by black lines. (A) Individual absolute excess risks. Dotted line corresponds to the median excess risk (ie, average of patients ranked 72 and 73 of 144), which was 0.26% for mortality and 3.61% for incidence. (B) Population average absolute excess risks. Dotted line corresponds to population average for irradiated patients if 50% of PET-negative patients with the lowest predicted risks were irradiated. This group of irradiated patients has 0.11% average excess risk for mortality and 1.79% for incidence. PET, positron emission tomography.
even in the presence of lower cardiac radiation doses, and it increases cardiac mortality risk even in the absence of radiotherapy. Anthracycline exposure was therefore included in the models used to predict treatment-related cardiac disease. It is important to recognize that the cardiac risk from chemotherapy in many patients is equal to, or

![Graphs showing predicted cardiovascular disease incidence](image-url)
TABLE 2. Predicted 30-Year Excess Absolute Risks for Mortality and Incidence of Cardiovascular Diseases for Two Examples of 30 Gy IFRT in Patients of Median Age (34 years) Within the RAPID Trial Cohort, and for an Historical 36 Gy Mantle Field Radiotherapy

| Dose               | Unilateral Neck (40% of patients) | Bilateral Neck and Low Mediastinum | Mantle |
|--------------------|-----------------------------------|------------------------------------|--------|
| Prescribed dose    | 30 Gy                             | 30 Gy                              | 36 Gy  |
| Mean heart dose    | 0.3 Gy                            | 15 Gy                              | 18 Gy  |
| Mean carotid dose  | 13.8 Gy                           | 30 Gy                              | 36 Gy  |

| Disease            | Male          | Female         | Male          | Female         | Male          | Female         |
|--------------------|---------------|----------------|---------------|----------------|---------------|----------------|
| Mortality          |               |                |               |                |               |                |
| Cardiac            | 0.05          | 0.01           | 2.68          | 0.79           | 3.29          | 1.00           |
| Stroke             | 0.06          | 0.03           | 0.13          | 0.08           | 0.15          | 0.09           |
| All cardiovascular | 0.11          | 0.05           | 2.80          | 0.87           | 3.44          | 1.09           |
| Incidence          |               |                |               |                |               |                |
| Cardiac            | 0.44          | 0.25           | 25.02         | 16.17          | 32.31         | 21.96          |
| Stroke             | 1.62          | 1.38           | 3.51          | 3.01           | 4.22          | 3.61           |
| All cardiovascular | 2.06          | 1.64           | 28.53         | 19.18          | 36.53         | 25.57          |

Abbreviations: IFRT, involved field radiotherapy; PET, positron emission tomography; RT, radiotherapy.

*60% of PET-negative patients who were treated with RT within RAPID received IFRT of greater extent than unilateral neck.

*49% of PET-negative patients who were treated with RT within RAPID received IFRT including part of the mediastinum; however, < 5% received extensive mediastinal radiation with a cardiac dose of $ \geq 15 $ Gy, such as in the example given above.

*Mantle RT included treatment of the axillae bilaterally, which increases the radiation dose received by the breasts and lungs, but not to the heart. A higher prescribed dose was also often used, such as in the example above. Only 8% of PET-negative patients in RAPID received axillary RT as part of IFRT.
greater than, the risk from radiotherapy. Indeed, we estimate that in the RAPID cohort, the cardiovascular risk from anthracycline exposure exceeded that from radiotherapy in 65% of individuals.

A strength of this study is the number of individuals (n = 247, 144 PET-negative) for whom dosimetry was completed, which is considerably greater than in the largest previous study reporting cardiac doses from IFRT (n = 41).9 Dosimetry was completed on a high proportion of patients receiving radiotherapy within the trial (79%), and comparison of baseline characteristics suggests that this sample is representative of the entire cohort. The study includes patients from 42 radiotherapy centers across the United Kingdom (87.5% of departments within the trial). It is therefore a representative sample of UK practice at the time.

There are, however, some limitations to this study. First, not all dosimetry was based on individual anatomy, as substitute CT data sets and data interpolation were used to calculate doses for a minority of patients (28%). This is unlikely to affect the average cardiovascular doses and predicted risks substantially, as demonstrated in a recent study.29 Second, the method used to predict radiation-related CVD has not been prospectively validated, as 20 additional years of follow-up would be required to assess the accuracy of the predictions. Our method is, however, based on the best available epidemiologic evidence regarding the magnitude of the long-term risks of radiation and anthracycline chemotherapy in HL survivors, together with current mortality and incidence rates in the general population. Third, we cannot provide separate risks for patients with pre-existing cardiovascular risk factors such as smoking and diabetes. In the future, adjustments to the model could use individual data on cardiovascular risk factors, but such information was not available for this study. Fourth, we did not attempt to model the possible impact of HL relapse in a small proportion of patients or the cardiotoxicity of subsequent treatments, so it is likely that we are underestimating the net benefit of initial radiotherapy. Finally, although we used the dose metrics from the best epidemiologic evidence currently available12-15 as the basis for our methods, we recognize the ongoing uncertainty over the radiation dose metric that may best predict the risks of radiation-related cardiac disease and stroke.29,30

The challenge of a personalized approach in ES-HL is to balance the risk of late adverse effects from radiotherapy against the omission of radiotherapy, which in turn increases risk of relapse and necessitates further therapy, perhaps including autologous stem-cell transplantation. If, rather than giving radiotherapy to all patients (or to none) regardless of their individual risk of late effects, radiotherapy were given just to patients predicted to be at lower risk of radiation-related CVD, then a substantial proportion of the benefit in terms of recurrence reduction would remain while fewer radiation-related cardiovascular complications would occur. For example, if the 50% of PET-negative patients at lowest risk of cardiovascular complications received radiotherapy, around 50% of the recurrences that would occur by withholding radiotherapy would be prevented, but only one fifth of the excess cardiovascular mortality from irradiating the whole cohort would be incurred (0.11%, Figs 3B, of the total 0.56%, Fig 2A). No individual patient's 30-year excess absolute cardiovascular mortality risk from IFRT would exceed 0.26% (Fig 3A) and the therapeutic ratio of the treatment would be improved. Current efforts to identify which individuals have greatest reduction in relapse risk from upfront radiotherapy (eg, using maximal tumor dimension at diagnosis31) may also help to identify patients who would benefit most from combined modality treatment.

It should be noted that developments in radiotherapy techniques since the RAPID trial, including smaller target volumes,32 the use of deep-inspiration breath-hold techniques,33 optimized intensity-modulated radiotherapy,34 and proton beam therapy,35 have reduced irradiated volumes and radiation doses to normal tissues, especially when combined with a 20 Gy prescribed dose for favorable ES-HL.35 Radiation-related CVD is not the only late side effect that may be reduced by the omission of radiotherapy. Risks of second cancers and other radiation-related late toxicities such as xerostomia and hypothyroidism, which would also be reduced by a chemotherap-only approach, are also likely to be lower with contemporary radiotherapy, but a comprehensive assessment of late toxicities goes beyond the scope of this study. Consideration of all the important toxicities of alternative treatment strategies including the toxicity of treating possible HL relapse would likely suggest that an optimal approach will involve irradiating those ES-HL patients who are at lower risk of RT-related toxicity, rather than a strategy advising radiotherapy for all or none, based only on PET response.

In conclusion, IFRT for ES-HL as given in RAPID is likely to produce a small increase in the long-term risk of CVD. However, the magnitude of the risk varies widely and, for a majority of patients, the benefit of reduced HL relapse substantially outweighs the risk of CVD. With more modern radiotherapy techniques, the cardiovascular radiation doses achieved35 would result in even lower predicted risks than those seen for the RAPID cohort. As the sites of disease and degree of mediastinal involvement are known at diagnosis, the radiation doses to cardiovascular organs, and hence the risk of radiation-related CVD, can be estimated when the initial treatment strategy is decided. Such an approach could identify high-risk patients who, because of their predicted radiation-related cardiovascular risk, should be considered for treatment with chemotherapy alone as well as for novel radiation techniques, such as deep-inspiration breath-hold techniques and proton beam therapy, that can minimize cardiac exposure.18,39 As knowledge increases, a personalized assessment including all relevant risks would be helpful in determining the optimal strategy for individual patients.
AFFILIATIONS
1 Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom
2 Oxford Cancer and Haematology Centre, Oxford University Hospitals NHS Foundation Trust, Churchill Hospital, Oxford, United Kingdom
3 National Radiotherapy Trials Quality Assurance Group, Mount Vernon Cancer Centre, Northwood, United Kingdom
4 Department of Medical Physics, Guy’s and St Thomas’ NHS Foundation Trust, London, United Kingdom
5 Cancer Research UK, UCL Cancer Trials Centre, London, United Kingdom
6 Manchester Academic Health Science Centre, Manchester Cancer Research Centre, University of Manchester, The Christie NHS Foundation Trust, Manchester, United Kingdom

CORRESPONDING AUTHOR
David J. Cutter, MD, DPhil, Nuffield Department of Population Health, University of Oxford, Richard Doll Building, Old Road Campus, Roosevelt Dr, Headington, Oxford OX3 7LF, United Kingdom; e-mail: david.cutter@ndph.ox.ac.uk.

EQUAL CONTRIBUTION
D.J.C. and J. Ramroth contributed equally to this work as first authors. J. Radford and T.I. contributed equally to this work as last authors.

PRIOR PRESENTATION
Presented at the ISHL-11, Cologne, Germany, October 27-29, 2018.

SUPPORT
Supported by Cancer Research UK grant (C8225/A21133) and by the British Heart Foundation Centre for Research Excellence, Oxford (grants RE/08/04 and RE/13/1/30181). T.I. and P.H. are supported by the Manchester NIHR Biomedical Research Centre. Funding for the RAPID trial (ClinicalTrials.gov identifier, NCT00943423) was provided by the Leukaemia and Lymphoma Research (now Blood Cancer UK), the Lymphoma Research Trust, Teenage Cancer Trust, and the UK Department of Health. The RAPID trial was run by the Cancer Research UK and University College London Cancer Trials Centre.

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.21.00408.

DATA SHARING STATEMENT
All data requests relating to the RAPID trial should be submitted for consideration to the trial sponsor via the Chief Investigator (john.radford@manchester.ac.uk). All data requests relating to the dosimetric and risk prediction analysis should be submitted to the corresponding author (david.cutter@ndph.ox.ac.uk). All information necessary to reproduce the calculation of cardiovascular risks is provided or referenced in the Data Supplement.

AUTHOR CONTRIBUTIONS
Conception and design: David J. Cutter, Patricia Diez, John Radford, Tim Illidge
Administrative support: Bilyana Popova, Laura Clifton-Hadley
Provision of study materials or patients: Patricia Diez, Bilyana Popova, John Radford
Collection and assembly of data: David J. Cutter, Johanna Ramroth, Patricia Diez, Andy Buckle, Bilyana Popova
Data analysis and interpretation: David J. Cutter, Johanna Ramroth, Georgios Ntenta, Peter J. Hoskin, Sarah C. Darby, Tim Illidge
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT
The authors thank the investigators, PET centers, and patients from all parts of the United Kingdom for their support.

REFERENCES
1. Engert A, Pletschow A, Eich HT, et al: Reduced treatment intensity in patients with early-stage Hodgkin’s lymphoma. N Engl J Med 363:640-652, 2010
2. Aleman BM, van den Belt-Dusebout AW, Klokman WJ, et al: Long-term cause-specific mortality of patients treated for Hodgkin’s disease. J Clin Oncol 21: 3431–3439, 2003
3. Meyer RM, Gospodarowicz MK, Connors JM, et al: ABVD alone versus radiation-based therapy in limited-stage Hodgkin’s lymphoma. N Engl J Med 366: 399-408, 2012
4. Andre MPE, Grinsky T, Federico M, et al: Early positron emission tomography response-adapted treatment in stage I and II Hodgkin lymphoma: Final results of the randomized EORTC/LSA/FIL H10 trial. J Clin Oncol 35:1786-1794, 2017
5. Radford J, Illidge T, Counsell N, et al: Results of a trial of PET-directed therapy for early-stage Hodgkin’s lymphoma. N Engl J Med 375:1598-1607, 2017
6. Fuchs M, Goergen H, Kobe C, et al: Positron emission tomography-guided treatment in early-stage favorable Hodgkin lymphoma: Final results of the international, randomized phase III HD16 trial by the German Hodgkin Study Group. J Clin Oncol 37:2835-2845, 2019
7. Barrington SF, Mackewn JE, Schleyer P, et al: Establishment of a UK-wide network to facilitate the acquisition of quality assured FDG-PET data for clinical trials in lymphoma. Ann Oncol 22:739-745, 2011
8. Ng AK, Bernardo MP, Weller E, et al: Long-term survival and competing causes of death in patients with early-stage Hodgkin’s disease treated at age 50 or younger. J Clin Oncol 20:2101-2108, 2002
9. Koh ES, Tran TH, Heydarian M, et al: A comparison of mantle versus involved-field radiotherapy for Hodgkin’s lymphoma: Reduction in normal tissue dose and second cancer risk. Radiat Oncol 2:13, 2007
10. Maraldo MV, Lundemann M, Vogelius IR, et al: A new method to estimate doses to the normal tissues after past extended and involved field radiotherapy for Hodgkin lymphoma. Radiat Oncol 11:206-211, 2015
11. Yahalom J, Mauch P: The involved field is back: Issues in delineating the radiation field in Hodgkin’s disease. Ann Oncol 13(suppl 1):79-83, 2002
12. Cutter DJ, Schapvoet M, Darby SC, et al: Risk of valvular heart disease after treatment for Hodgkin lymphoma. J Natl Cancer Inst 107:djv008, 2015.
13. van Nimwegen FA, Schapvoet M, Cutter DJ, et al: Radiation dose-response relationship for risk of coronary heart disease in survivors of Hodgkin lymphoma. J Clin Oncol 34:235-243, 2016
14. van Nimwegen FA, Ntenta G, Darby SC, et al: Risk of heart failure in survivors of Hodgkin lymphoma: Effects of cardiac exposure to radiation and anthracyclines. Blood 129:2257-2265, 2017
15. De Bruin ML, Dorresteijn LD, van’t Veer MB, et al: Increased risk of stroke and transient ischemic attack in 5-year survivors of Hodgkin lymphoma. J Natl Cancer Inst 101:928-937, 2009
16. George J, Rapsomaniki E, Pujades-Rodriguez M, et al: How does cardiovascular disease first present in women and men? Incidence of 12 cardiovascular diseases in a contemporary cohort of 1,937,360 people. Circulation 132:1320-1328, 2015

17. Maraldo MV, Brodin NP, Vogelius IR, et al: Risk of developing cardiovascular disease after involved node radiotherapy versus mantle field for Hodgkin lymphoma. Int J Radiat Oncol Biol Phys 83:1232-1237, 2012

18. Hoppe BS, Flamport S, Su Z, et al: Effective dose reduction to cardiac structures using protons compared with 3DCRT and IMRT in mediastinal Hodgkin lymphoma. Int J Radiat Oncol Biol Phys 84:449-455, 2012

19. Campbell BA, Hornby C, Cunningham J, et al: Minimising critical organ irradiation in limited stage Hodgkin lymphoma: A dosimetric study of the benefit of involved node radiotherapy. Ann Oncol 23:1259-1266, 2012

20. Koeck J, Abo-Madyan Y, Lohr F, et al: Radiotherapy for early mediastinal Hodgkin lymphoma according to the German Hodgkin study group (GHSG): The roles of intensity-modulated radiotherapy and involved-node radiotherapy. Int J Radiat Oncol Biol Phys 83:268-276, 2012

21. Plowman PN: Radiotherapy considerations in patients with Hodgkin’s disease who receive mediastinal radiotherapy and anthracycline-containing chemotherapy. Clin Oncol (R Coll Radiol) 10:384-391, 1998

22. Ntentas G, Dedeckova K, Andrlik M, et al: Clinical intensity modulated proton therapy for Hodgkin lymphoma: Which patients benefit the most? Pract Radiat Oncol 9:179-187, 2019

23. van Nimmegen FA, Schaapveld M, Janus CP, et al: Cardiovascular disease after Hodgkin lymphoma treatment: 40-year disease risk. JAMA Intern Med 175:1007-1017, 2015

24. Aleman BM, van den Belt-Dusebout AW, De Bruin ML, et al: Late cardiotoxicity after treatment for Hodgkin lymphoma. Blood 109:1878-1886, 2007

25. Myrehauge S, Pintilie M, Tsang R, et al: Cardiac morbidity following modern treatment for Hodgkin lymphoma: Supra-additive cardiotoxicity of doxorubicin and radiation therapy. Leuk Lymphoma 49:1486-1493, 2008

26. Pihkala J, Saarinen UM, Lundström U, et al: Myocardial function in children and adolescents after therapy with anthracyclines and chest irradiation. Eur J Cancer 32A:97-103, 1996

27. Swerdlow AJ, Higgins CD, Smith P, et al: Myocardial infarction mortality risk after treatment for Hodgkin disease: A Collaborative British Cohort Study. J Natl Cancer Inst 99:206-214, 2007

28. Ntentas G, Darby SC, Aznar MC, et al: Dose-response relationships for radiation-related heart disease: Impact of uncertainties in cardiac dose reconstruction. Radiother Oncol 153:155-162, 2020

29. Vordermark D, Seufert I, Schwab F, et al: Cardiac toxicity of mediastinal radiotherapy: Which are the critical structures? J Clin Oncol 23:3634-3636, 2005; author reply 3636

30. Hopkins BS, Bates JE, Mendenhall NP, et al: The meaningless meaning of mean heart dose in mediastinal lymphoma in the modern radiation therapy era. Pract Radiat Oncol 10:e147-e154, 2020

31. Illidge TM, Phillips EH, Counsell N, et al: Maximum tumor diameter is associated with event-free survival in PET-negative patients with stage I/IIA Hodgkin lymphoma. Blood Adv 4:209-206, 2020

32. Specht L, Yahalom J, Illidge T, et al: Modern radiation therapy for Hodgkin lymphoma: Field and dose guidelines from the International Lymphoma Radiation Oncology Group (ILROG). Int J Radiat Oncol Biol Phys 89:854-862, 2014

33. Pommier A, Ghahafian M, Gilmore J, et al: Dosimetric benefits of intensity-modulated radiotherapy combined with the deep-inspiration breath-hold technique in patients with mediastinal Hodgkin’s lymphoma. Int J Radiat Oncol Biol Phys 82:1522-1527, 2012

34. Starke A, Bowden J, Lynn R, et al: Comparison of butterfly volumetric modulated arc therapy to full arc with or without deep inspiration breath hold for the treatment of mediastinal lymphoma. Radiother Oncol 129:449-455, 2018

35. Pinnix CC, Gunther JR, Fang P, et al: Assessment of radiation doses delivered to organs at risk among patients with early-stage favorable Hodgkin lymphoma treated with contemporary radiation therapy. JAMA Netw Open 3:e2013935, 2020
AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Predicted Risks of Cardiovascular Disease Following Chemotherapy and Radiotherapy in the UK NCRI RAPID Trial of Positron Emission Tomography–Directed Therapy for Early-Stage Hodgkin Lymphoma

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/fwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Johanna Ramroth
Employment: Gilead Sciences (I)

Stock and Other Ownership Interests: Gilead Sciences

Laura Clifton-Hadley
Research Funding: Various pharmaceutical companies

Peter J. Hoskin
Research Funding: Varian Medical Systems, Astellas Pharma, Bayer, Roche, Pfizer, Elekta

John Radford
Stock and Other Ownership Interests: AstraZeneca, ADC Therapeutics

Honoraria: Takeda, ADC Therapeutics

Consulting or Advisory Role: Takeda, Seattle Genetics, Novartis

Speakers’ Bureau: Takeda, Seattle Genetics, Novartis

Research Funding: Takeda

Travel, Accommodations, Expenses: Takeda, ADC Therapeutics

Tim Illidge
Consulting or Advisory Role: Takeda, Nordic Nanovector

Speakers’ Bureau: Takeda, Bristol Myers Squibb, Roche

Research Funding: AstraZeneca/MedImmune, MSD Oncology

Travel, Accommodations, Expenses: Roche

No other potential conflicts of interest were reported.