

# Maximum tumor diameter is associated with event-free survival in PET-negative patients with stage I/IIA Hodgkin lymphoma

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## Key Points

- Baseline maximum tumor diameter is an important predictor of relapse for patients with ES-HL achieving complete metabolic remission.
- Patients with baseline tumor size  $\geq 5$  cm have worse outcomes with ABVD alone and are likely to benefit from consolidation radiotherapy.

## Introduction

The high cure rates achieved in early-stage (ES) Hodgkin lymphoma (HL) are one of the great successes of hemato-oncology, but late treatment-related toxicity undermines long-term survival. Improving overall survival and quality of life further will require maintaining disease control while potentially de-escalating chemotherapy and/or omitting radiotherapy to reduce late toxicity. Accurate stratification of patients is required to facilitate individualized treatment approaches. Response assessment using <sup>18</sup>F-fluorodeoxyglucose positron emission tomography (PET) is a powerful predictor of outcome in HL,<sup>1,2</sup> and has been used in multiple studies, including the United Kingdom National Cancer Research Institute Randomised Phase III Trial to Determine the Role of FDG–PET Imaging in Clinical Stages IA/IIA Hodgkin's Disease (UK NCRI RAPID) trial, to investigate whether patients achieving complete metabolic remission (CMR) can be treated with chemotherapy alone.<sup>3–5</sup> These PET-adapted trials have demonstrated that omitting radiotherapy results in higher relapse rates, but without compromising overall survival.<sup>3–5</sup>

For the 75% of patients who achieved CMR in RAPID, neither baseline clinical risk stratification (favorable/unfavorable) nor PET (Deauville score 1/2) predicted disease relapse; additional biomarkers are needed.<sup>1</sup> Tumor bulk has long been recognized as prognostic in HL,<sup>1,6</sup> but there remains uncertainty about the significance and definition of bulk in the era of PET-adapted treatment.<sup>7</sup> We performed a subsidiary analysis of RAPID to assess the prognostic value of baseline maximum tumor dimension (MTD) in patients achieving CMR.

## Methods

We have previously reported the RAPID trial design, primary results, and outcomes according to pretreatment risk stratification and PET score.<sup>1,3</sup> Patients were aged 16 to 75 years with untreated ES-HL and without B-symptoms or mediastinal bulk (mass  $> 1/3$  internal mediastinal diameter at T5/6).<sup>6</sup> Metabolic response after 3 cycles of ABVD chemotherapy (doxorubicin, bleomycin, vinblastine, and dacarbazine) was centrally assessed using PET (N = 562). Patients with CMR (ie, Deauville score 1–2) were randomly assigned to receive involved field radiotherapy (IFRT; n = 208) or no further therapy (NFT; n = 211). PET-positive patients (score, 3–5; n = 143) received a fourth cycle of ABVD and IFRT.

Baseline disease assessment was performed by computed tomography, and bidimensional target lesion measurements were reported by local radiologists in millimeters. The association of baseline MTD with HL-related event-free survival (EFS: progression or HL-related death) and progression-free survival

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All data requests relating to the RAPID patient population should be submitted for consideration to the sponsor of RAPID via the Chief Investigator (John Radford; e-mail: [john.radford@manchester.ac.uk](mailto:john.radford@manchester.ac.uk)).

The full-text version of this article contains a data supplement.

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**Table 1. Association between increasing maximum tumor dimension (MTD) thresholds and event-free survival in PET-negative patients randomly assigned to receive no further therapy (N = 211)**

MTD threshold, mm*	<MTD threshold		≥MTD threshold		HR ≥threshold	95% CI	P
	n	Events	n	Events			
10	20	2	191	19	0.97	0.23-4.19	.97
20	51	4	160	17	1.35	0.45-4.01	.59
30	103	6	108	15	2.43	0.94-6.27	.07
40	151	11	60	10	2.38	1.01-5.61	.05
<b>50</b>	<b>172</b>	<b>12</b>	<b>39</b>	<b>9</b>	<b>3.78</b>	<b>1.59-9.02</b>	<b>.003</b>
60	187	17	24	4	2.00	0.67-5.95	.21
70	198	19	13	2	1.60	0.37-6.88	.53
80	205	19	6	2	3.36	0.77-14.64	.11
90	209	20	2	1	5.56	0.74-41.64	.09
100	210	21	1	0	—	—	—

Bold text indicates chosen MTD threshold.

\*Small numbers of patients and events across some groups.

(PFS) (progression or any-cause death) was assessed using Kaplan-Meier and Cox regression analyses. Non-HL deaths were either related to primary treatment toxicity or occurred in HL remission.<sup>1</sup>

United Kingdom ethical approval for the RAPID trial was via the UK Multicentre Research ethics committee.

## Results and discussion

Baseline patient characteristics have been previously described.<sup>1</sup> Median age was 34 years (range, 16-75 years); 184 (37.4%) of 492 patients had unfavorable risk by European Organisation for Research and Treatment of Cancer criteria, and 155 (32.3%) of 480 by German Hodgkin Study Group criteria. Median MTD for patients achieving CMR was 3.0 cm (interquartile range, 2.0-4.0 cm) and 3.0 cm (interquartile range, 1.8-4.5 cm) in the NFT and IFRT groups, respectively, whereas PET-positive patients had a median MTD of 3.9 cm (interquartile range, 2.8-5.1 cm). After a median follow-up of 61.6 m, 44 HL progression events occurred: 21 NFT, 9 IFRT and 14 PET-positive. No patient received salvage treatment without documented progression. Only 5 HL-related deaths occurred (1 IFRT, 4 PET-positive), and 12 non-HL deaths (4 NFT, 6 IFRT, 2 PET-positive).<sup>1</sup>

For patients with CMR (N = 419), there was a strong association between MTD and EFS (hazard ratio [HR], 1.19; 95% confidence interval [CI], 1.02-1.39; *P* = .02), adjusting for treatment group, with an approximate 19% increase in HL risk per centimeter increase in MTD. The association was similar in both treatment groups (NFT HR, 1.20 [95% CI, 0.99-1.44; *P* = .06]; IFRT HR, 1.19 [95% CI, 0.92-1.55; *P* = .19]). The observed effect sizes did not markedly change after adjusting for baseline clinical risk factors, and similar results were observed for PFS (supplemental Table 1). In contrast, for PET-positive patients, there was no association between MTD and EFS (HR, 0.88; 95% CI, 0.70-1.11; *P* = .29) or PFS (HR, 0.87; 95% CI, 0.70-1.08; *P* = .21).

In an exploratory analysis within the NFT group, MTD was dichotomized using increasing 1-cm intervals to investigate the relationship between MTD thresholds and EFS. The largest effect size was observed with an MTD threshold of ≥5 cm (Table 1). Similar results were observed for PFS; this threshold also performed best

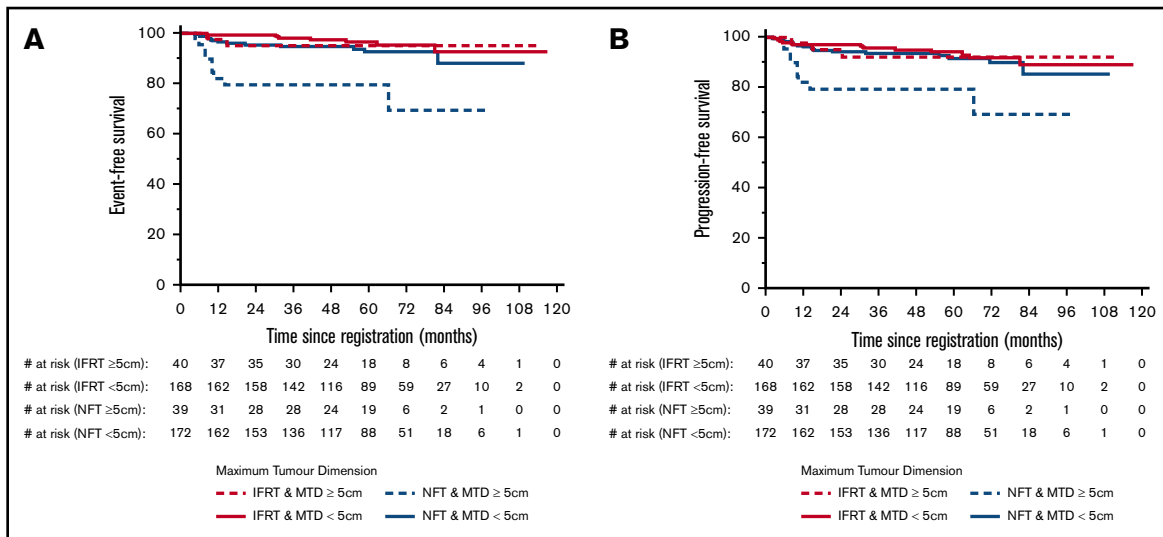
in time-dependent receiver operating characteristic curve analyses. It was not possible to assess MTD thresholds in the IFRT group with only 9 events. Among all randomized patients, 79 (18.9%) had MTD of ≥5 cm, the majority with mediastinal (n = 43), supraclavicular (n = 17), or cervical (n = 16) locations. Five-year EFS for patients with MTD of ≥5 cm randomly assigned to NFT and IFRT was 79.3% (n = 39; 95% CI, 66.6%-92.0%) and 94.9% (n = 40; 95% CI, 88.0%-100%), respectively (*P* = .03; Figure 1).

This subsidiary analysis of a large, prospective, randomized trial reinforces the prognostic relevance of tumor size with PET-adapted treatment. We found a clear association between MTD and EFS for patients achieving CMR after ABVD that was most evident for those randomly assigned to NFT, principally as a result of the higher number of events in this group. A threshold of 5 cm best stratified risk in RAPID patients receiving chemotherapy alone, acknowledging the small number of events and a need for validation.

Our findings are consistent with large, pre-PET studies in ES-HL<sup>8</sup> and relapsed HL,<sup>9</sup> in which MTD of ≥5 cm was an adverse prognostic factor. This is a more conservative risk threshold than conventional definitions of bulk,<sup>10</sup> and a recently proposed threshold of 7 cm for ES-HL.<sup>7</sup> Because of the exclusion of patients with B symptoms and mediastinal bulk, few patients had MTD of above 7 cm in RAPID, with a limited number of events to assess the significance of higher MTD cutoffs, although there was evidence of an association between risk and increasing MTD as a continuous variable.

Because of the small number of events in the IFRT group, it remains unclear whether radiotherapy can overcome the prognostic influence of MTD. However, excellent outcomes were achieved for patients in CMR with MTD of ≥5 cm who received IFRT. PET positivity as an indicator of chemotherapy resistance may override the earlier influence of baseline MTD on EFS and explain the lack of association between MTD and EFS in PET-positive patients.

Although omitting radiotherapy in ES-HL is accompanied by a small increase in early relapse, data from randomized trials are too immature to assess whether this is compensated for by a reduction in late toxicity or long-term survival difference.<sup>3-5</sup> Therefore, it remains contentious whether radiotherapy should be omitted in selected patients. This study



**Figure 1. EFS and progression-free survival according to MTD in patients with CMR.** (A) Event-free survival. (B) Progression-free survival.

demonstrates that patients with CMR can be risk-stratified by MTD to identify a group of patients for whom chemotherapy alone may be insufficient. We hypothesize that targeted use of radiotherapy for patients with CMR and baseline MTD of  $\geq 5$  cm may improve outcomes, which requires validation in prospective studies.

Personalized treatment approaches will require assessment of potential radiation toxicity, considering age, sex, and disease site. Of note, only 43 (54.4%) of 79 disease sites  $\geq 5$  cm were mediastinal, where radiation toxicity is considered to be higher. Meanwhile, selected patients with MTD smaller than 5 cm and very low risk for radiation toxicity may benefit from RT.<sup>11</sup>

The main limitation of this study is that computed tomography scans were not centrally reviewed. As with most prospective trials, data were not collected on which image planes were examined. Therefore, this study provides a real-world assessment of MTD.

In summary, our study demonstrates a striking association between increasing MTD and relapse risk for patients with ES-HL achieving CMR. For RAPID patients receiving ABVD alone, a cutoff of  $\geq 5$  cm best stratified those at highest risk for relapse. These findings will help inform discussions about the personalized application of RT, where benefits of radiotherapy are balanced against potential risks. These findings have informed the design of our follow-on trial to RAPID, which will prospectively allow involved-site RT consolidation for patients in CMR with baseline MTD of  $\geq 5$  cm.

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## Authorship

Contribution: T.M.I., E.H.P., N.C., and J.R. designed this study, analyzed/interpreted the data, and wrote the manuscript; T.M.I., R.P., P.W.M.J., D.J.C., A.M., P.H., and J.R. recruited patients and provided clinical data; B.P. and L.C.-H. coordinated central trial management and data collection; S.F.B. conducted the central PET review; and all authors reviewed and approved the final version of this manuscript

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## References

- Barrington SF, Phillips EH, Counsell N, et al. Positron emission tomography score has greater prognostic significance than pretreatment risk stratification in early-stage Hodgkin lymphoma in the UK RAPID Study. *J Clin Oncol*. 2019;37(20):1732-1741.

2. Cottreau AS, Versari A, Loft A, et al. Prognostic value of baseline metabolic tumor volume in early-stage Hodgkin lymphoma in the standard arm of the H10 trial. *Blood*. 2018;131(13):1456-1463.
3. 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*. 2015;372(17):1598-1607.
4. André MPE, Girinsky 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/LYSA/FIL H10 trial. *J Clin Oncol*. 2017;35(16):1786-1794.
5. Fuchs M, Goergen H, Kobe C, et al. PET-guided treatment of early-stage favorable Hodgkin lymphoma: final results of the international, randomized phase 3 trial HD16 by the German Hodgkin Study Group. *Blood*. 2018;132(Suppl 1):925-925.
6. Lister TA, Crowther D, Sutcliffe SB, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. *J Clin Oncol*. 1989;7(11):1630-1636.
7. Kumar A, Burger IA, Zhang Z, et al. Definition of bulky disease in early stage Hodgkin lymphoma in computed tomography era: prognostic significance of measurements in the coronal and transverse planes. *Haematologica*. 2016;101(10):1237-1243.
8. Klimm B, Goergen H, Fuchs M, et al. Impact of risk factors on outcomes in early-stage Hodgkin's lymphoma: an analysis of international staging definitions. *Ann Oncol*. 2013;24(12):3070-3076.
9. Bröckelmann PJ, Müller H, Casasnovas O, et al. Risk factors and a prognostic score for survival after autologous stem-cell transplantation for relapsed or refractory Hodgkin lymphoma. *Ann Oncol*. 2017;28(6):1352-1358.
10. Cheson BD, Fisher RI, Barrington SF, et al; United Kingdom National Cancer Research Institute. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014;32(27):3059-3068.
11. Maraldo MV, Illidge TM. How do we move towards a personalised approach in the treatment of Early Hodgkin lymphoma? *Br J Haematol*. 2018;182(2):163-164.