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Maximum Tumor Diameter is Associated with Relapse Risk in Limited-Stage Hodgkin Lymphoma: An International Study

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Abstract:
Tumour bulk is an established prognostic factor in Hodgkin lymphoma (HL) but most patients with limited-stage (LS) HL do not have 'bulk' by standard binary definitions. In the RAPID trial, maximum tumor diameter (MTD) was associated with risk of relapse for LS-HL patients achieving PET-negativity after ABVD chemotherapy. We aimed to externally validate these findings in the H10 trial. Patients with stage I/IIA HL, without mediastinal bulk, who achieved PET-negativity with ABVD were included. 'PET-negative' patients received 3x ABVD plus radiotherapy (n=208) or 3x ABVD alone (n=211) in RAPID, and 3-4x ABVD plus radiotherapy (n=556) or 4-6x ABVD alone (n=303) in H10. Baseline MTD was measured by CT. MTD was strongly associated with event-free survival (relapse or HL-related death) in H10 (HR=1.22, 95%CI:1.07-1.38, p=0.003), a similar effect to the RAPID trial (HR=1.19, 95%CI:1.02-1.39, p=0.02), giving an estimated 21% increase in HL-risk per centimetre MTD (HRpooled=1.21, 95%CI:1.09-1.33, p<0.001). Findings were consistent when adjusting for baseline risk stratification and chemotherapy cycles. The effect sizes were similar for patients treated with chemotherapy alone (HRpooled=1.19, 95%CI:1.01-1.35, p=0.005) and combined modality treatment (ABVD plus radiotherapy; HRpooled=1.24, 95%CI:1.05-1.46, p=0.009) with no evidence of a differential effect (pinteraction=0.97). Treatment modality and MTD were independent risk factors; patients with higher MTD receiving chemotherapy alone had the greatest risk of relapse. This international validation study confirms that MTD is strongly associated with the risk of relapse for LS-HL patients achieving PET-negativity. These findings refine assessment of risk in LS-HL and can inform clinical discussions for risk-adapted application of radiotherapy. NCT00943423 and NCT00433433

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Maximum Tumor Diameter is Associated with Relapse Risk in Limited-Stage Hodgkin Lymphoma: An International Study

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Data sharing: requests for data should be directed to the RAPID and H10 trial teams separately, or contact beth.phillips@manchester.ac.uk in the first instance

Running Head: maximum tumour diameter in limited-stage Hodgkin lymphoma

Key points:

1. Increasing maximum tumour diameter (MTD) is strongly associated with increased risk of relapse in early-stage Hodgkin lymphoma

2. MTD and omission of radiotherapy are independent risk factors; patients with high MTD who received chemotherapy alone had suboptimal EFS

Abstract

Tumour bulk is an established prognostic factor in Hodgkin lymphoma (HL) but most patients with limited-stage (LS) HL do not have 'bulk' by standard binary definitions. In the RAPID trial, maximum tumor diameter (MTD) was associated with risk of relapse for LS-HL patients achieving PET-negativity after ABVD chemotherapy. We aimed to externally validate these findings in the H10 trial. Patients with stage I/IIA HL, without mediastinal bulk, who achieved PET-negativity with ABVD were included. 'PET-negative' patients received 3x ABVD plus radiotherapy (n=208) or 3x ABVD alone (n=211) in RAPID, and 3-4x ABVD plus radiotherapy (n=556) or 4-6x ABVD alone (n=303) in H10. Baseline MTD was measured by CT. MTD was strongly associated with event-free survival (relapse or HL-related death) in H10 (HR=1.22, 95%CI:1.07-1.38, p=0.003), a similar effect to the RAPID trial (HR=1.19, 95%CI:1.02-1.39, p=0.02), giving an estimated 21% increase in HL-risk per centimetre MTD (HR_{pooled}=1.21, 95%CI:1.09-1.33, p<0.001). Findings were consistent when adjusting for baseline risk stratification and chemotherapy cycles. The effect sizes were similar for patients treated with chemotherapy alone (HR_{pooled}=1.19, 95%CI:1.01-1.35, p=0.005) and combined modality treatment (ABVD plus radiotherapy; HR_{pooled}=1.24, 95%CI:1.05-1.46, p=0.009) with no evidence of a differential effect ($p_{interaction}$=0.97). Treatment modality and MTD were independent risk factors; patients with higher MTD receiving chemotherapy alone had the

greatest risk of relapse. This international validation study confirms that MTD is strongly associated with the risk of relapse for LS-HL patients achieving PET-negativity. These findings refine assessment of risk in LS-HL and can inform clinical discussions for risk-adapted application of radiotherapy. NCT00943423 and NCT00433433

Introduction

Very high cure rates are achieved for patients with limited-stage (LS) classical Hodgkin lymphoma (HL) treated with modern combined chemo-radiotherapy approaches.(1-3) However, late toxicity from treatment is a major cause of excess morbidity and mortality in survivors, particularly increased rates of second malignancies and cardiovascular disease.(4, 5) Therefore, reducing treatment burden is a major priority in LS-HL. Risk-adapted treatment is key to achieving this, allowing de-escalation for low-risk patients whilst maintaining high cure rates, but success is dependent on accurate risk stratification.

Traditionally, treatment selection in LS-HL has been based on the presence of clinical risk factors, according to EORTC or GHSG criteria. More recently, 18F-fluorodeoxyglucose positron emission tomography (PET) response to chemotherapy has consistently been associated with outcomes and become established in routine clinical practice.(6, 7) PET response-adapted treatment strategies have been increasingly adopted and may have reduced the prognostic value of pre-treatment clinical risk stratification.(6) However, attempts to de-escalate treatment and omit radiotherapy based on early PET response have met with mixed success, with an increase in relapse rates of 4-12% in patients achieving PET-negativity.(1, 2, 8) The negative predictive value of PET response is suboptimal, with more than half of relapses occurring in patients who are PET-negative, irrespective of treatment modality.(2, 3) Therefore, further improvements in predictive biomarkers are required to inform more precise application of risk-adapted therapy in LS-HL.

The size of tumor masses is a well-established prognostic factor in HL.(9-12) Tumor 'bulk' in HL was originally defined by the Cotswold report in 1989 to encompass mediastinal masses ≥1/3 of the internal transverse diameter of the thorax at the level of T5/6 on postero-anterior chest X-ray and masses ≥10 centimeters (cm) elsewhere.(13) Despite advances in lymphoma staging with PET, evolution of treatment pathways and the introduction of response-adapted therapy, the Cotswold definition is still widely used to this day.(14) In particular, the presence of mediastinal bulk is incorporated into pre-treatment clinical risk stratification in LS-HL.(8, 15) However, the majority of patients with LS-HL do not meet traditional definitions of tumour bulk.(8) Furthermore, the relevance of tumour bulk has not been evaluated in the context of PET-directed treatment.

We previously evaluated the role of tumour diameter outside of conventional definitions of bulk in LS-HL for patients receiving PET-adapted therapy in the UK NCRI RAPID trial. We demonstrated that baseline maximum tumor diameter (MTD) is independently associated with event-free survival (EFS) and progression-free survival (PFS) in LS-HL patients who had a negative PET scan after ABVD chemotherapy (doxorubicin, bleomycin, vinblastine, dacarbazine). HL-risk increased by 19% per cm increase in baseline MTD (HR=1.19, 95% CI:1.02–1.39, p=0.02).(11) The aim of the current study was to validate these findings by assessing the prognostic association of MTD in an external cohort of LS-HL patients recruited to the EORTC/FIL/LYSA H10 trial,(8) and to explore the influence of treatment modality.

Patients and Methods

Discovery cohort: RAPID trial

RAPID was a randomised controlled, phase III, non-inferiority trial comparing ABVD chemotherapy alone (*C*) with combined modality therapy (ABVD plus involved-field radiotherapy; *CMT*) in LS-HL patients achieving PET-negativity after 3 cycles of ABVD. The trial design and procedures have been published previously.(2) Briefly, eligible patients were aged 16-75 years with newly diagnosed, histologically-confirmed stage IA or IIA HL, and no mediastinal bulk (≥33% of the internal thoracic diameter at T5-T6). In total, 602 patients were recruited, of whom 571 had centrally-reviewed PET, 426 achieved PET-negativity (i.e. Deauville score 1-2) and were eligible to be randomised. Six PET-negative patients withdrew before randomisation and 1 additional patient has been excluded, where review of original diagnostic material at relapse identified a non-HL diagnosis. Therefore, 419 RAPID patients are included (211 *C*, 208 *CMT*).

Validation cohort: H10 trial

H10 was a randomised controlled, phase III, non-inferiority trial, comparing *CMT* with a PET-directed approach, whereby patients achieving PET-negativity after 2 cycles of ABVD completed further chemotherapy treatment without radiotherapy. The trial design and procedures have been published previously.(8) In brief, eligible patients were aged 15-70 years with newly diagnosed, supra-diaphragmatic stage I or II classical HL. Patients who were PET-negative by International Harmonisation Project criteria (16) received either 4-6 cycles of ABVD (540 *C*) or 3-4 cycles of ABVD plus involved-node radiotherapy (1024 *CMT*), with the duration of ABVD determined by baseline EORTC risk stratification. Randomisation was halted after an interim analysis demonstrated futility with all subsequent patients enrolled receiving *CMT*. 687 patients had mediastinal bulk and/or B symptoms and would have been ineligible for RAPID so are excluded from this validation cohort. Thus, 877 H10 patients are included in the current analysis (311 *C*, 566 *CMT*).

Assessment of clinical risk factors

For both trials, bi-dimensional baseline tumour dimensions (in cm) were evaluated by CT, reported by local radiologists, and prospectively collected at trial entry. The larger of these dimensions was taken as baseline MTD. Use of intravenous contrast was mandated in the H10 protocol, and was used according to local standards in RAPID. Data were missing for 18 RAPID-eligible patients recruited to the H10 trial. Baseline clinical risk factors were collected prospectively to allow stratification according to EORTC risk group, including age, mediastinal-thoracic ratio, B symptoms, erythocyte sedimentation rate (ESR) and number of involved nodal areas.

Statistical considerations

The primary objective of this study was to externally validate the prognostic value of MTD in LS-HL patients recruited to the H10 trial. The primary endpoint was HL-related event-free survival (EFS), defined as relapse or HL-related death; censoring deaths from treatment toxicity or causes unrelated to HL. Patients were censored at the date last seen if no event was observed. Secondary objectives included describing the association with MTD by treatment modality (i.e. *C* or *CMT*), and the association of MTD with PFS (progression or death due to any cause). There were too few events to explore associations with overall survival (RAPID: 1 HL and 10 non-HL deaths, H10: 3 HL and 5 non-HL deaths).

The associations of baseline MTD with EFS and PFS were described using the Kaplan-Meier method, analysed using multivariable Cox regression analyses and model assumptions of proportional hazards and linearity of MTD were checked. Firstly, associations with MTD were assessed adjusting for treatment arm, to account for differences in trial design including number of ABVD cycles, and then also adjusting for baseline risk stratification by EORTC criteria (missing for 51 RAPID patients) in multivariable analyses. Finally, after independent validation was confirmed, data from RAPID and H10 were pooled to provide more precise estimates for the associations with MTD, adjusting for trial population and treatment arm to account for trial design. These associations were also investigated within treatment group (i.e. *C* or *CMT*), and via tests of interaction. In exploratory analyses, MTD was dichotomised using increasing 1cm intervals to investigate the utility of different MTD thresholds by assessing effect sizes and performance via time-dependent receiver operating characteristic curves.

Data analyses were performed using SAS software, version 9.4 (SAS Institute), and GraphPad Prism, version 9.3.1 for Windows (www.graphpad.com).

RAPID was approved by the UK Multicentre Research Ethics Committee H10 was approved by national ethics committees in all participating countries (France, Belgium, Italy, Netherlands)

Results

External validation of MTD

The baseline characteristics for patients achieving PET-negativity on RAPID and H10 (without B symptoms or mediastinal bulk) are shown by trial arm in Table 1. Generally, MTD was higher in H10 than RAPID (median 3.9 versus 3.0 cm, respectively). Also, patients were marginally younger (median 32 vs. 34 years), with a higher proportion of stage II disease (71.4 vs. 66.8%), ESR >50 (14.3 vs. 11.9%) and extra-nodal disease (2.7 vs. 0.2%) in H10 than RAPID. Baseline EORTC risk groups were similar in the two trials (66.8 vs. 65.2% favourable, respectively).

After a median follow-up of 4.5 years in the H10 validation cohort of RAPID-eligible patients, 38 HL relapse events (27 *C*, 11 *CMT*), 3 HL-related deaths (3 *C*, 0 *CMT*) and 5 non-HL deaths (2 *C*, 3 *CMT*) have been observed. Non-HL deaths were censored in the primary analysis of EFS but included as events for secondary analysis of PFS.

For H10 patients that were RAPID-eligible, we found a clear association between MTD in cm and EFS (n=859; HR=1.22, 95% CI: 1.07-1.38, p=0.003; Table 2), similar to that observed in RAPID (n=419; HR=1.19, 95% CI: 1.02-1.39, p=0.02). Results in the H10 validation cohort were consistent when adjusted for number of chemotherapy cycles (HR=1.24, 95% CI: 1.09-1.42, p=0.001) and EORTC risk stratification (HR=1.22, 95% CI: 1.07-1.39, p=0.003) in multivariable analyses. There was no evidence of an association between MTD in cm and EFS for RAPID-ineligible H10 patients (i.e. B symptoms and/or mediastinal bulk present) with available MTD data (n=672; HR=1.03, 95% CI: 0.96-1.11, p=0.37).

Similar results were observed when including the 5 non-HL deaths in analyses of PFS, as expected given the small number of these events (Supplementary Table). There was a clear association between MTD in cm and PFS (n=859; HR=1.22, 95% CI: 1.08-1.37, p=0.001), as well as when adjusted for number of chemotherapy cycles (HR=1.24, 95% CI: 1.10-1.41, p=0.001) and EORTC risk stratification (HR=1.21, 95% CI: 1.08-1.37, p=0.002).

MTD and Treatment Modality

For RAPID-eligible H10 patients receiving chemotherapy alone, we again found a similar association between MTD in cm and EFS (n=303; HR=1.19, 95% CI: 1.01-1.40, p=0.03), as observed in RAPID (n=211; HR=1.20, 95% CI: 0.99-1.44, p=0.06). Results were consistent when adjusted for number of chemotherapy cycles and EORTC risk stratification in multivariable analyses, and similar associations were observed for PFS.

For RAPID-eligible H10 patients receiving *CMT*, there was also an association between MTD in cm and EFS, although only 11 HL events were observed (n=556; HR=1.27, 95% CI: 1.04-1.56, p=0.02). There were only 9 HL events in RAPID patients receiving *CMT* but a similar association with EFS was observed (n=208; HR=1.19, 95% CI: 0.92–1.55, p=0.19), although this was not statistically significant. Again, results were consistent when adjusted for number of chemotherapy cycles and EORTC risk stratification, and in analyses of PFS.

Pooled analyses of RAPID and H10 data

Given the observed consistency in results between the RAPID discovery cohort and the H10 validation cohort, a pooled analysis was carried out to provide more precise estimates on the role of MTD with a larger number of events (Figure 2 and Table 2). For all RAPID-eligible patients (*C* and *CMT*), adjusting for trial cohort and treatment group in multivariable analyses, we found a 21% increase in HL relapse risk per cm increase in MTD at baseline (n=1278; pooled HR=1.21, 95% CI: 1.09-1.33, p<0.001).

In patients receiving chemotherapy alone, we found a 19% increase in HL relapse risk per cm increase in MTD at baseline (n=514; pooled HR=1.19, 95% CI: 1.01-1.35, p=0.005), with no clear MTD threshold above which we could identify a marked difference in EFS. An MTD threshold of 5cm (AUC=60.0%) performed marginally better than MTD thresholds of 4cm, 3cm and 6cm (AUC's=59.2%, 58.5% and 56.7%, respectively) in time-dependent receiver operating characteristic curve analyses (Table 3 & Supplementary Figure). Five-year EFS rates

for patients receiving chemotherapy alone with MTD <5cm and MTD ≥5cm were 92.4% (95% CI: 89.1-94.7) and 82.3% (95% CI: 73.8-88.2), respectively.

In an exploratory pooled analysis of RAPID-eligible patients treated with *CMT*, MTD in cm was associated with EFS (n=764; HR=1.24, 95% CI: 1.05-1.46, p=0.009); with only 20 events in this group, it was not possible to fully evaluate MTD thresholds. However, EFS rates were high irrespective of MTD; using a median split in the *CMT* group, 5-year EFS rates were 96.3% with MTD <3.6cm and 97.7% with MTD ≥3.6.cm respectively.

There was no evidence of a differential effect for MTD between treatment modalities (interaction p=0.97), and the confidence intervals for each include the overall effect estimate for MTD in cm. Kaplan-Meier plots of EFS according to MTD and treatment modality are shown in Figure 3.

Discussion

This international validation study confirms the association between baseline MTD in cm and relapse risk for LS-HL patients, without B symptoms or mediastinal bulk, in an external independent cohort. Results were consistent between the RAPID cohort and the external H10 validation cohort across all analyses, with remarkably similar observed effect sizes. Although the association between conventional tumour 'bulk' expressed as a binary variable and outcomes in HL is well established,(9, 12, 17) the largest prior study of MTD in LS-HL was a single-centre, retrospective study (N=185) with a heterogeneously-treated cohort.(10) Our study is unique in two major respects. First, it uses prospective clinical data from two large, highly cited, phase III clinical trials featuring contemporary PET-adapted treatment. Second, the findings are applicable to the modern era for a favourable-risk, low-tumour-burden LS-HL population, where few patients meet conventional definitions of 'bulk'.

A key finding was that increasing MTD correlated with higher risk of relapse as a continuous variable. Importantly, there was no step-wise threshold beyond which the relapse risk markedly increased. For patients treated with chemotherapy alone in this low-tumour-burden LS-HL population (without B symptoms or mediastinal bulk), a threshold of 5cm performed marginally better than others based on the highest AUC value, although a similar effect size was seen using thresholds between 3cm and 6cm in this patient group. Another study of MTD in stage I/II HL that included patients with higher tumour burden (i.e. patients with mediastinal bulk and B symptoms) suggested a higher threshold of 7cm.(10) This indicates a continuum of increased risk with increasing MTD. If a binary cut off is required for risk stratification, the optimal threshold will vary according to the patient population and the proposed intervention being investigated. A threshold of 5cm is currently being evaluated for risk stratification in LS-HL in the RAFTING (NCT04866654) clinical trial. In the future, a more nuanced approach would be to incorporate MTD values with other risk factors to create a personalised risk calculation capable of informing discussions about the comparative risks

and benefits of using radiotherapy in addition to chemotherapy treatment approaches in LS-HL. Such developments are beyond the scope of this study, but will be essential in realising the ultimate goal of achieving optimal tumor control with primary treatment whilst minimising late consequences such as cardiovascular disease and second cancers.

By combining data from randomised trials comparing chemotherapy alone versus chemotherapy and radiotherapy, this study provides unique insights into the relevance of treatment modality. Both treatment modality (*C versus CMT)* and MTD were independently associated with risk of relapse in multivariable analyses, but there was no evidence of a differential effect for MTD between the two treatment groups. EFS rates for patients with both risk factors (i.e. higher MTD and receipt of chemotherapy alone) were suboptimal. Whilst radiotherapy reduces this risk, it does not eliminate the impact of MTD, although the absolute difference in EFS rates for those with high versus low MTD for patients receiving CMT is small. Ongoing studies are evaluating whether MTD can be used to guide use of radiotherapy in LS-HL, including the RADAR clinical trial (NCT04685616) where, at investigator discretion, radiotherapy is permitted for those with who become PET negative after chemotherapy if their baseline MTD was ≥5cm. An advantage of using a 5cm threshold in this patient group is that it limits the use of radiotherapy and its associated risk of late effects (e.g. second malignancies, cardiovascular disease) to a relatively small proportion of higher-risk patients. Outside of clinical trials, radiotherapy consolidation should be considered for patients with higher MTD where the risk of late toxicity is not unacceptably high. A threshold lower than 5cm can be considered where the risks of radiotherapy toxicity are low.

There was no association between MTD and EFS in H10 patients who would not have been eligible for RAPID (i.e. those with B symptoms and/or mediastinal bulk). This is unexpected given that the association between bulk and outcomes in HL has been observed in multiple studies, and mediastinal bulk is a well-validated adverse prognostic factor.(9, 10) Noting that these findings require validation, one consideration is that mediastinal bulk can be heterogeneous, comprising a large solitary mass or multiple smaller or conglomerate nodes, so may not be reported consistently by trial sites, nor always correlate with MTD. The majority of these patients also have more widespread disease, therefore the influence of a single dominant lesion may be less important. These findings mirror experience in advanced-stage HL, where 'bulk' is associated with higher rates of early PET-positivity but is not an independent prognostic factor when considered alongside PET response.(18-20)

In this validation study, we did not receive data on outcomes for PET-positive patients in the H10 trial and therefore cannot comment on the association of MTD with EFS for the trial population as a whole. However, there was no association between MTD and EFS for PET-positive patients in the RAPID trial.(11) It is important to note that the definition of 'PET-negativity' in these trials did not encompass patients with a Deauville score of 3, who would now be considered to have achieved complete metabolic response by modern criteria.(14) Another limitation of this analysis is a lack of centralised radiology review and therefore we cannot guarantee that MTD was evaluated in coronal or sagittal as well as axial planes in all

cases. However, we demonstrate that our findings are applicable to 'real world' radiology reporting and clinical practice, and are highly reproducible.

Baseline PET assessment was not mandatory in either RAPID or H10. Advanced PET metrics offer an alternative method of measuring tumour 'bulk'. The most widely studied has been metabolic tumour volume (MTV), which provides a measure of overall tumour burden. MTV is associated with PFS in HL, including in LS-HL patients recruited to the H10 trial.(7) Progress is being made towards standardisation of MTV measurement which should inform optimal thresholds for specific patient populations in the near future.(21) Whether measurement of overall tumour burden by MTV has a stronger association with prognosis than the diameter of the largest single lesion in LS-HL remains unclear and is currently under further investigation. For now, MTD is easily measured in routine clinical practice without the need for calibration of measurement against a benchmark, as for MTV.(22) The ongoing RADAR trial is evaluating MTD alongside MTV and other PET metrics simultaneously in a LS-HL population.

In conclusion, this international validation study confirms that increasing MTD is associated with shorter EFS in patients with LS-HL, without mediastinal bulk or B symptoms, who achieve PET-negativity. Furthermore, MTD was an independent risk factor for disease relapse in this favourable-risk HL group. These findings can inform clinical discussions of risk for a personalised application of radiotherapy in LS-HL, particularly for patients not meeting classical bulk criteria, as well as the design of future clinical trials. Finally, we propose moving away from binary definitions of 'bulk' to consideration of maximum tumor size as a continuous variable that confers greater risk of relapse as MTD increases, with integration of this into clinical decision making.

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Contributions:

E.H.P, N.C. and J.R. designed the research, analyzed data and wrote the paper. All authors performed research and approved the final manuscript.

Disclosures

The authors declare no conflicts of interests related to this study

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Table 1: Baseline characteristics for patients achieving PET-negativity in RAPID and H10 subset (excluding Stage III/IV, B symptoms & mediastinal bulk)

Baseline characteristic	RAPID PET-*CMT* group (N=208)	RAPID PET-*C* group (N=211)	*RAPID* PET-*Total* *(N=419)*	H10 PET-*CMT* group (N=566)	H10 PET-*C* group (N=311)	*H10* PET-*Total* *(N=877)*
Maximum Tumour Diameter in cm, median (interquartile range)	3.0 (1.8-4.5)	3.0 (2.0-4.0)	*3.0 (1.9-4.3)*	3.9 (2.9-5.2) [10 missing]	3.8 (2.7-5.0) [8 missing]	*3.9 (2.8-5.1) [18 missing]*
Age in years, median (interquartile range)	34 (25-48)	34 (25-47)	*34 (25-47)*	32 (24-44)	31 (24-44)	*32 (24-44)*
Age in years, n (%)						
<50 years	160 (76.9%)	166 (78.7%)	*326 (77.8%)*	475 (83.9%)	264 (84.9%)	*739 (84.3%)*
50+ years	48 (23.1%)	45 (21.3%)	*93 (22.2%)*	91 (16.1%)	47 (15.1%)	*138 (11.7%)*
Sex, n (%)						
Female	106 (51.0%)	104 (49.3%)	*210 (50.1%)*	282 (49.8%)	160 (51.4%)	*442 (50.4%)*
Male	102 (49.0%)	107 (50.7%)	*209 (49.9%)*	284 (50.2%)	151 (48.6%)	*435 (49.6%)*
Stage, n (%)						
I	69 (33.2%)	70 (33.2%)	139 (33.2%)	154 (27.2%)	97 (31.2%)	*251 (28.6%)*
II	139 (66.8%)	141 (66.8%)	280 (66.8%)	412 (72.8%)	214 (68.8%)	*626 (71.4%)*
ESR >50, n (%)	20 (11.8%)	22 (12.1%)	*53 (11.9%)*	89 (15.7%)	36 (11.6%)	*125 (14.3%)*
Extranodal disease, n (%)	0 (0.0%)	1 (0.5%)	*1 (0.2%)*	15 (2.7%) [14 missing]	8 (2.6%) [6 missing]	*23 (2.7%) [20 missing]*
No. of nodal areas, n (%)						
≥3 involved	64 (30.8%)	61 (28.9%)	*125 (29.8%)*	190 (33.6%)	89 (28.6%)	*279 (31.8%)*
≥4 involved	19 (9.1%)	22 (10.4%)	*41 (9.8%)*	39 (6.9%)	20 (6.4%)	*59 (6.7%)*
EORTC criteria, n (%)						
favourable	118 (64.5%)	122 (65.9%)	*240 (65.2%)*	371 (65.5%)	215 (69.1%)	*586 (66.8%)*
unfavourable	65 (35.5%)	63 (34.1%)	*128 (34.8%)*	195 (34.5%)	96 (30.9%)	*291 (33.2%)*

Abbreviations: centimeter (cm); chemotherapy alone (C); combined modality therapy (CMT); erythocyte sedimentation rate (ESR); European Organisation for Research and Treatment of Cancer (EORTC); maximum tumor diameter (MTD).

Table 2: Association between maximum tumor diameter (MTD, per centimeter) and event-free survival (EFS) for patients achieving PET-negativity – H10 subset and pooled analysis of H10 subset with RAPID

Association between MTD and EFS in multivariable analyses	HR (95% CI), p-value
H10 PET-, all patients* (N=859, 18 missing MTD)	
adjusting for treatment group (i.e. *C* or *CMT*)	1.22 (95% CI: 1.07-1.38), p=0.003
adjusting for treatment arm (i.e. *C* or *CMT* & cycles)	1.24 (95% CI: 1.09-1.42), p=0.001
adjusting for treatment group and EORTC risk group	1.22 (95% CI: 1.07-1.39), p=0.003
H10 PET-, *C* group† (N=303, 8 missing MTD)	
unadjusted	1.19 (95% CI: 1.01-1.40), p=0.03
adjusting for treatment arm (i.e. cycles)	1.22 (95% CI: 1.03-1.45), p=0.02
adjusting for EORTC risk group	1.21 (95% CI: 1.02-1.44), p=0.03
H10 PET-, *CMT* group‡ (N=556, 10 missing MTD)	
unadjusted	1.27 (95% CI: 1.04-1.56), p=0.02
adjusting for treatment arm (i.e. cycles)	1.29 (95% CI: 1.04-1.59), p=0.02
adjusting for EORTC risk group	1.28 (95% CI: 1.04-1.57), p=0.02
Pooled PET-, all patients** (N=1278)	
adjusting for trial and treatment group (i.e. *C* or *CMT*)	1.21 (95% CI: 1.09-1.33), p<0.001
adjusting for trial and treatment arm (i.e. *C* or *CMT* & cycles)	1.22 (95% CI: 1.10-1.35), p<0.001
adjusting for trial, treatment group and EORTC risk group***	1.18 (95% CI: 1.06-1.30), p=0.002
Pooled PET-, *C* group†† (N=514)	
adjusting for trial	1.19 (95% CI: 1.01-1.35), p=0.005
adjusting for trial and treatment arm (i.e. cycles)	1.21 (95% CI: 1.06-1.37), p=0.004
adjusting for trial and EORTC risk group***	1.15 (95% CI: 1.01-1.32), p=0.040
Pooled PET-, *CMT* group‡‡ (N=764)	
adjusting for trial	1.24 (95% CI: 1.05-1.46), p=0.009
adjusting for trial and treatment arm (i.e. cycles)	1.25 (95% CI: 1.06-1.47), p=0.009
adjusting for trial and EORTC risk group***	1.25 (95% CI: 1.06-1.47), p=0.007

*41 EFS events in total: †30 in the *C* group and ‡11 in the *CMT* group

**71 EFS events in total: ††51 in the *C* group and ‡‡20 in the *CMT* group

***51 RAPID patients missing EORTC risk group: 26 in the *C* group and 25 in the *CMT* group

Abbreviations: centimeter (cm); chemotherapy alone (C); combined modality therapy (CMT); confidence interval (CI); European Organisation for Research and Treatment of Cancer (EORTC); event-free survival (EFS); hazard ratio (HR); maximum tumor diameter (MTD).

Table 3: Association between increasing maximum tumor diameter (MTD) thresholds and event-free survival (EFS) for patients achieving PET-negativity treated with chemotherapy alone – pooled analysis of H10 subset with RAPID (N=514)

MTD (cm) Threshold*	< MTD Threshold		≥ MTD Threshold		Effect ≥ MTD Threshold
	N	Events	N	Events	HR (95% CI)†, p-value
1	20	2	494	49	0.98 (0.24-4.05), p=0.977
2	74	5	440	46	1.61 (0.63-4.13), p=0.319
3	191	10	323	41	2.63 (1.31-5.31), p=0.007
4	309	20	205	31	2.55 (1.43-4.52), p=0.001
5	399	30	115	21	2.65 (1.51-4.64), p<0.001
6	441	38	73	13	2.27 (1.21-4.28), p=0.011
7	477	46	37	5	1.45 (0.57-3.64), p=0.435
8	497	48	17	3	1.79 (0.56-5.77), p=0.329
9	506	50	8	1	1.22 (0.17-8.84), p=0.847
10	512	51	2	0	*not estimable*
11	513	51	1	0	*not estimable*
12	513	51	1	0	*not estimable*
13	514	51	0	0	*not estimable*

*N.B. small numbers of patients and events across some groups
†adjusted for trial cohort

Abbreviations: centimeter (cm); confidence interval (CI); event-free survival (EFS); hazard ratio (HR); maximum tumor diameter (MTD).

Figure 1: CONSORT flow diagram

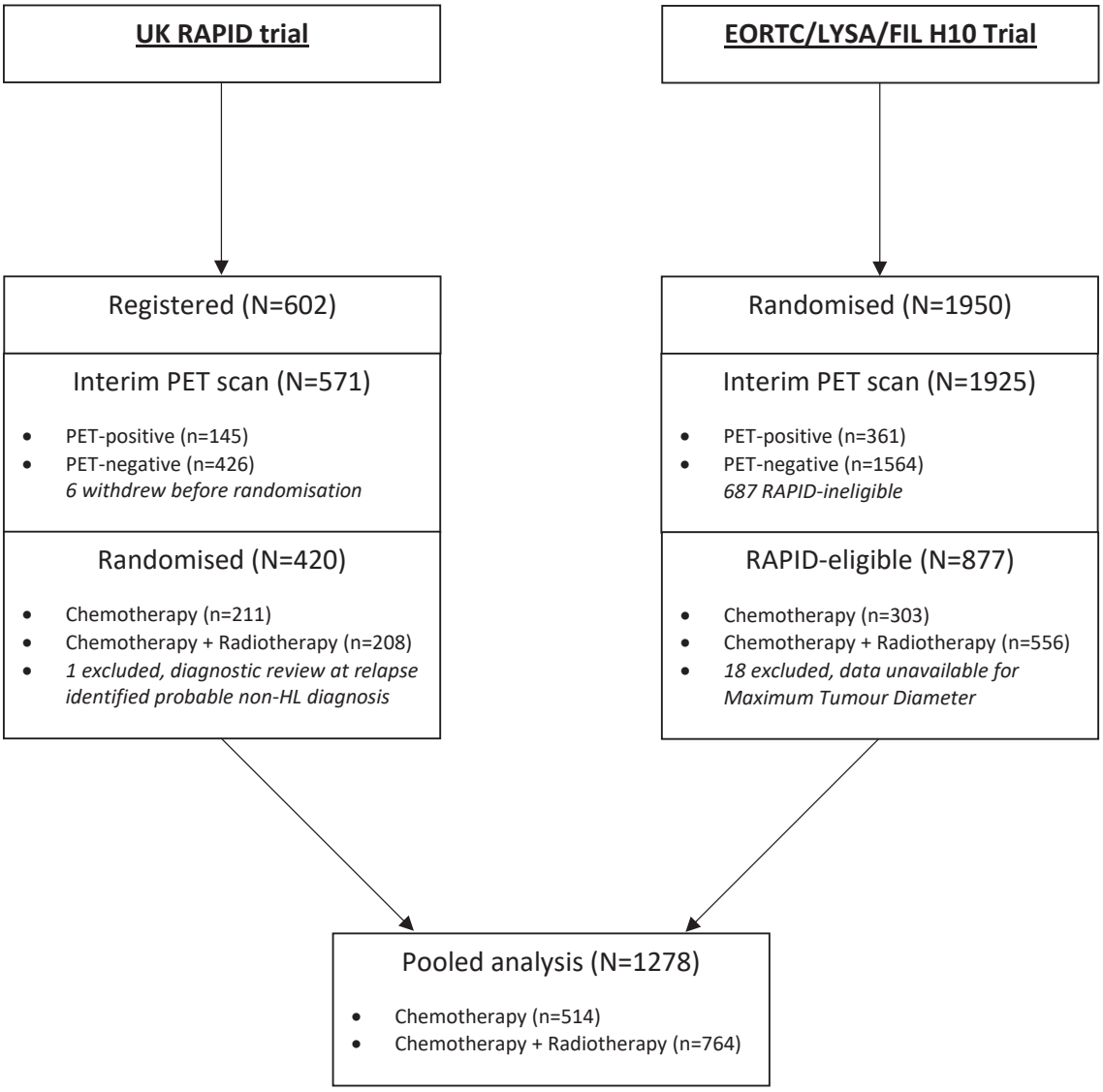
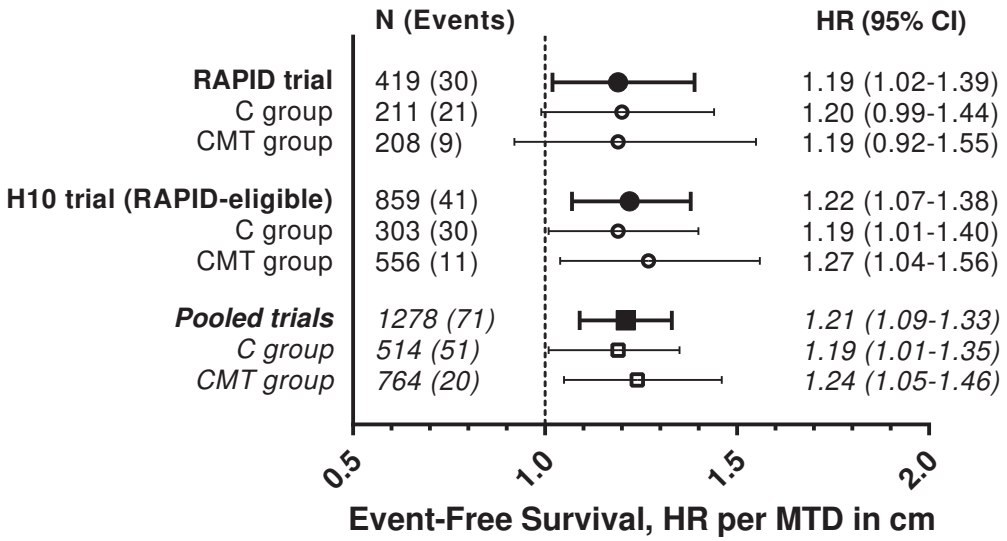


Figure 2

Figure 2. Forest plot showing the association between maximum tumor diameter (MTD, per centimeter) and event-free survival (EFS) for patients achieving PET-negativity

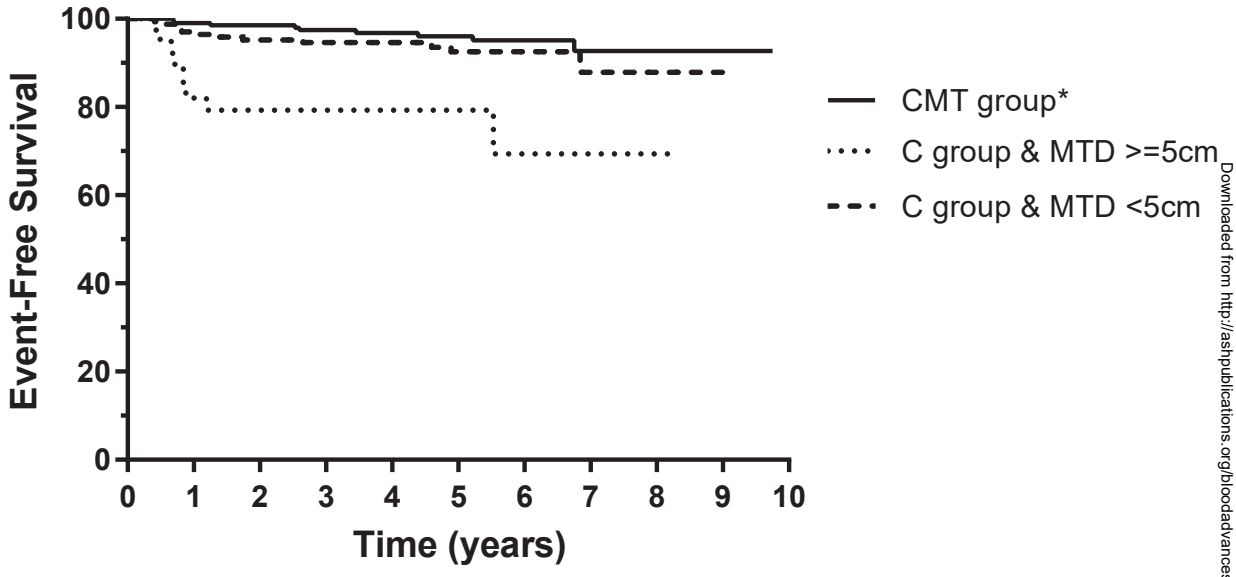


Abbreviations: centimeter (cm); chemotherapy alone (C); combined modality therapy (CMT); confidence interval (CI); event-free survival (EFS); hazard ratio (HR); maximum tumor diameter (MTD).

Figure 3

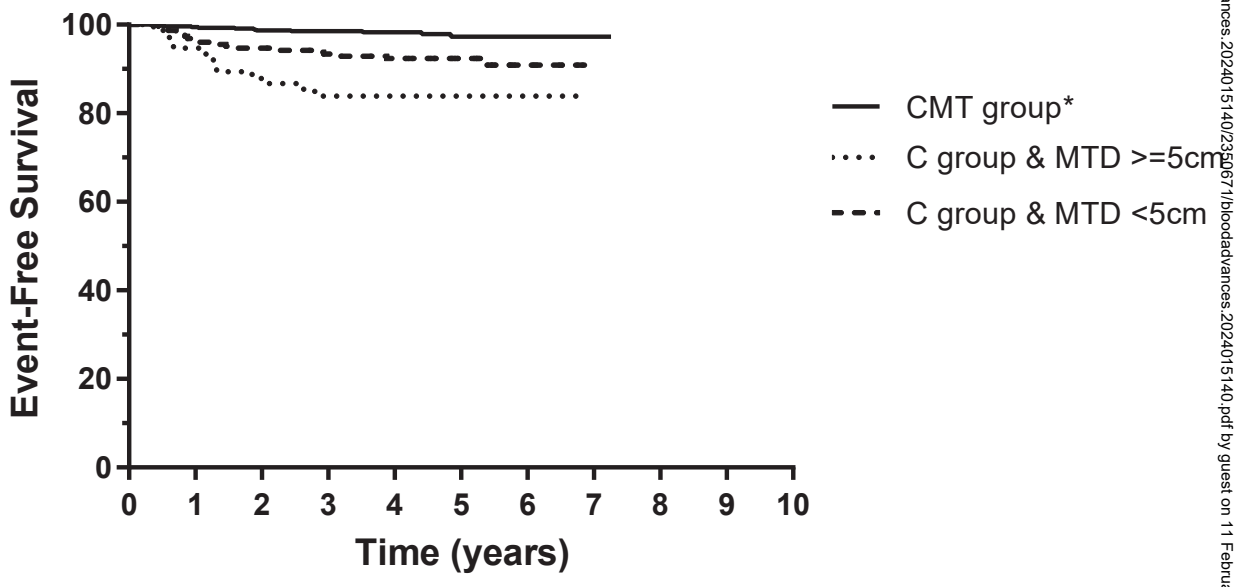
Figure 3. Kaplan-Meier plots of event-free survival (EFS) by treatment group and maximum tumor diameter (MTD) for patients achieving PET-negativity in A) RAPID and B) H10 subset

A)



# at risk (CMT*):	208	199	193	172	140	107	68	33	14	3	0
# at risk (C ³ 5cm):	39	31	28	28	24	19	6	2	1	0	0
# at risk (C <5cm):	172	162	153	136	117	88	51	18	6	1	0

B)



# at risk (CMT*):	556	548	533	465	301	158	41	4	0	0	0
# at risk (C ³ 5cm):	76	72	65	58	53	34	9	0	0	0	0
# at risk (C <5cm):	227	219	212	203	183	108	27	1	0	0	0

**evaluation of MTD thresholds was not possible in the CMT group due to low number of events*

Abbreviations: centimeter (cm); chemotherapy alone (C); combined modality therapy (CMT); event-free survival (EFS); maximum tumor diameter (MTD).