Prognostic significance of maximum tumour (bulk) diameter in young patients with good-prognosis diffuse large-B-cell lymphoma treated with CHOP-like chemotherapy with or without rituximab: an exploratory analysis of the MabThera International Trial Group (MInT) study

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Summary

Background The definition and role of bulky disease in young patients (ie, aged 18–60 years) with good-prognosis diffuse large-B-cell lymphoma (DLBCL), who have been treated with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone)-like chemotherapy with or without rituximab, remain controversial. We aimed to assess the effect of maximum tumour diameter (MTD) in these patients.

Methods Patients from the MInT (Mabthera International Trial Group) study were eligible. We analysed event-free (EFS) and overall survival (OS) after CHOP-like chemotherapy with or without rituximab, according to MTD, by Martingale residual analyses and Cox regression models. Radiotherapy was given to sites of primary bulky disease according to national standards, and to primary extranodal disease at physician discretion. The primary endpoint was EFS and the secondary endpoint was OS. Analyses were by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT 00064116.

Findings Of the 824 patients enrolled in the MInT study, the informed-consent form of one patient was missing, leaving 823 patients evaluable for intention-to-treat analysis. Data on MTD of involved sites were available for 802 patients. Martingale residual analysis showed an adverse prognostic effect of MTD on EFS and OS, which increased linearly. In a multivariable analysis with MTD as a linear regression variable, the effect of MTD was significant after CHOP-like treatment alone for EFS (hazard ratio 1·090 [95% CI 1·051–1·130], p<0·0001) and OS (1·119 [1·057–1·184], p=0·0001), and after CHOP-like treatment and rituximab for OS (1·089 [1·003–1·183], p=0·043), but not for EFS (1·044 [0·991–1·099], p=0·103). For CHOP-like treatment alone, 3-year EFS ranged from 78·2% (MTD <5·0 cm, 95% CI 68·3–85·4) to 41·3% (MTD ≥10·0 cm, 31·8–50·4). For CHOP-like treatment and rituximab, 3-year EFS ranged from 83·2% (MTD <5·0 cm, 72·8–89·9) to 72·7% (MTD ≥10·0 cm, 63·8–79·7). With CHOP-like treatment alone, 3-year OS decreased from 92·9% (MTD <5·0 cm, 84·9–96·8) to 73·5% (MTD ≥10·0 cm, 63·9–81·0); for CHOP-like treatment and rituximab, 3-year OS decreased from 98·0% (MTD <5·0 cm, 92·2–99·5) to 85·2% (MTD ≥10·0 cm, 77·0–90·6). For CHOP-like treatment, any cut-off point between 5·0 cm and 10·0 cm separated two populations with a significant EFS difference (p<0·0001 for all log-rank tests) and OS difference (p≤0·003 for all log-rank tests). For CHOP-like treatment and rituximab, only a cut-off point of 10·0 cm separated two populations with a significant EFS difference (log-rank p=0·047), but any cut-off point of 6·0 cm or more separated two populations with a significant OS difference (log-rank p values 0·0009–0·037).

Interpretation Rituximab decreased, but did not eliminate the adverse prognostic effect of MTD in young patients with good-prognosis DLBCL. Due to the linear prognostic effect of MTD on outcome, arbitrary cut-off points for bulky disease can be set between 5·0 cm and 10·0 cm, depending on clinical considerations. Based on this study, a cut-off point of 10·0 cm might be a suitable margin in the rituximab era to delineate those patients with bulky disease.

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Introduction

In the MInT (MabThera International Trial Group) study,[1] 823 young patients (ie, age 18–60 years) from 18 countries with good-prognosis (none or one risk factor according to the age-adjusted International Prognostic Index [aaIPI], stages II–IV or stage I with bulky disease) diffuse large-B-cell lymphoma (DLBCL) were randomly assigned to six cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone)-like chemotherapy with or without rituximab. After a median observation time of 34 months, event-free survival (3-year EFS; 79% *vs* 59%, p<0·0001) and overall survival (3-year OS; 93% *vs* 84%,

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p=0·0001) were significantly better after treatment with CHOP-like chemotherapy plus rituximab compared with CHOP-like chemotherapy alone. A multivariable analysis showed that EFS was independently affected by treatment arm, bulky disease (HR compared with no bulky disease 1·57 [95% CI 1·20–2·05], p=0·001) and the presence of at least one aaIPI risk factor. Because bulky disease was not identified as an independent risk factor in the International Prognostic Index,[2] we analysed the effect of the maximum tumour diameter (MTD) on outcome of young patients with DLBCL who had good prognosis and who were randomly assigned to chemotherapy with or without rituximab.

Methods

Patients

Patients and procedures of the MInT study have been reported in detail elsewhere.[1] Briefly, patients aged 18–60 years with untreated CD20-positive diffuse large-B-cell lymphoma according to WHO,[3] with none or one risk factor according to the aaIPI in stages II–IV or stage I with bulky disease with an Eastern Cooperative Oncology Group performance status of 0–3 were eligible. Exclusion criteria were: transformed or secondary lymphoma after previous chemotherapy or radiotherapy for other disease; primary CNS lymphoma or gastrointestinal mucosa-associated lymphoid tissue (MALT) lymphoma as assessed by the local pathologist; known allergic reactions against foreign proteins as assessed by medical history; significant dysfunction of major organs; known HIV; or active chronic hepatitis B or C infection as assessed by medical history. The stage of lymphoma and maximum diameter of involved sites were documented by the referring physician by physical examination, laboratory parameters, computed tomography of the neck, chest, and abdomen, bone-marrow biopsy, and other investigational procedures depending on clinical symptoms. Patients were randomly assigned to six cycles of CHOP-like chemotherapy (CHOP-21, CHOEP-21, MACOP-B, and PMitCEBO) or CHOP-like chemotherapy plus rituximab, as described in more detail in the original publication of the MInT study.[1] 375 mg/m² rituximab (Roche, Basel, Switzerland) was planned intravenously for days 1, 22, 43, 64, 85, and 106 of the chemotherapy regimens. Radiotherapy (30–40 Gy, according to national standards) was given to sites of primary bulky disease. Tumour masses (single lymph nodes or conglomerates) with a diameter (ie, MTD) of more than or equal to 5·0 cm, more than or equal to 7·5 cm, or more than or equal to 10·0 cm, were defined as bulky disease according to the cut-off point predefined by each cooperative group. Radiotherapy to primary extranodal disease was given to 52 patients at the physician's discretion. Response was assessed on day 155 after starting treatment, according to the International Workshop criteria.[4]

	Patients, n (%)			
	<5·0 cm	5·0–7·4 cm	7·5–9·9 cm	≥10·0 cm
All	221/802 (28)	161/802 (20)	164/802 (20)	256/802 (32)
CHOP-like chemotherapy	112/399 (28)	80/399 (20)	90/399 (23)	117/399 (29)
CHOP-like chemotherapy plus rituximab	109/403 (27)	81/403 (20)	74/403 (18)	139/403 (34)
Waldeyer's ring, including tonsils*	29/42 (69)	11/42 (26)	2/42 (5)	0
Cervical, supraclavicular, infraclavicular, occipital, pre-auricular, submandibular, nuchal*	87/184 (47)	38/184 (21)	29/184 (16)	30/184 (16)
Axillary and pectoral*	16/42 (38)	9/42 (21)	8/42 (19)	9/42 (21)
Mediastinal and hilar*	11/179 (6)	20/179 (11)	59/179 (33)	89/179 (50)
Mesenteric, para-aortic, iliac*	38/166 (23)	24/166 (14)	30/166 (18)	74/166 (45)
Inguinal and femoral*†	19/43 (44)	10/43 (23)	6/43 (14)	8/43 (19)
Spleen*	3/19 (16)	3/19 (16)	3/19 (16)	10/19 (53)
Bone marrow*	0	0	0	0
Lung*	2/5 (40)	1/5 (20)	1/5 (20)	1/5 (20)
Liver*	1/1 (100)	0	0	0
Skeletal system*	8/28 (29)	3/28 (11)	9/28 (32)	8/28 (29)
Pleura, pericardium*	1/2 (50)	0	1/2 (50)	0
CNS*	1/4 (25)	1/4 (25)	1/4 (25)	1/4 (25)
Stomach*	2/17 (12)	5/17 (29)	6/17 (35)	4/17 (24)
Intestine*	4/30 (13)	10/30 (33)	8/30 (27)	8/30 (27)
Other extranodal region*	24/102 (24)	32/102 (31)	18/102 (18)	28/102 (27)

If a patient had multiple maximum tumour involvements at different sites, they were listed in the respective lines and columns (multiple listing). *Percentages based on patients with the maximum diameter of their tumour involvement in the respective location. †Diameters of tumour involvement, except for femoral lymph nodes, were measured by CT scan.

Table 1: **Grouping of patients according to maximum tumour diameter and tumour location (n=802)**

The study was done in accordance with the Helsinki declaration, the protocol was approved by the ethics-review committee of each participating centre, and all patients gave written informed consent.

Statistical analysis

The methods of the primary analysis of this trial have been published previously.[1] The aim of the current analysis was to assess the association of MTD with the primary endpoint, EFS, and the secondary endpoint, OS, both established according to the International Workshop criteria. MTD was defined as the maximum tumour diameter of any site involved by lymphoma as measured by the local radiologist or treating physician by CT scan, except for femoral lymph nodes, which were measured by physical examination only. Besides MTD, only stratification factors used in the randomisation process (ie, aaIPI and chemotherapy) and the treatment arm were included in the analyses as covariates, all of them being established as independent prognostic factors in the treatment of CD20-positive DLBCL.[1,5,6] Martingale residual analysis[7] of all patients was done to assess the functional form of tumour size to be used in a Cox proportional hazard model. First, a Cox regression model without the covariate of interest was fitted. Then we checked the functional shape to be used in the Cox regression model for the covariate by a smoothed Martingale residual plot. A cut-off point or another non-linear dependency should be considered if a remarkable buckling of the nonparametric regression curve can be shown.

Cox proportional hazard models were used to estimate the probability of not having an event in the EFS and OS. Hazard ratios (HRs) were used to estimate the probability of having an event. The proportional hazard assumption was tested by including time-dependent covariates in the model,[7] and the goodness-of-fit was assessed by bias-corrected Akaike's Information Criterion.[8] Two-sided p values were reported and the level of significance was 0·05. Statistical analyses included all patients with known maximum tumour size, and were done by intention to treat and with SAS (version 9.13) and SPSS (version 11.5) software. This trial is registered with ClinicalTrials.gov, number NCT 00064116.

Role of the funding source

This study was sponsored (M39045) by Roche (Basel, Switzerland). The sponsor accepted the protocol as proposed by the principal investigators of the 18 participating countries. The data were collected by monitors employed by independent clinical research organisations and was directly sent to the Clinical Study Centre (Homburg, Germany) for clinical plausibility check, and from there transferred to the Intergroup Data Centre (Leipzig, Germany) for data banking. Data analysis was done by the Intergroup Data Centre independent from the sponsor. The sponsor accepted the paper in its present version, but was not involved in the interpretation of the data and the writing of the report. MP, ML, and EK had full access to all of the data and had final responsibility for the decision to submit for publication.

	CHOP-like chemotherapy (n=399)	CHOP-like chemotherapy plus rituximab (n=403)
Patients defined as having bulky disease, n (%)	197 (49)	205 (51)
Bulk defined as ≥5·0 cm, n (%)	20 (4)	18 (5)
Median (range), cm	10·0 (6·8–20·0)	10·0 (5·0–16·0)
Bulk defined as ≥7·5 cm, n (%)	166 (42)	173 (43)
Median (range), cm	10·0 (7·5–24·0)	10·0 (7·5–25·0)
Bulk defined as ≥10·0 cm, n (%)	11 (3)	14 (3)
Median (range), cm	12·0 (10·0–15·0)	11·0 (10·0–16·8)

Table 2: **Patients classified as having bulky disease according to the cut-off points defined by their respective (national) cooperative study group**

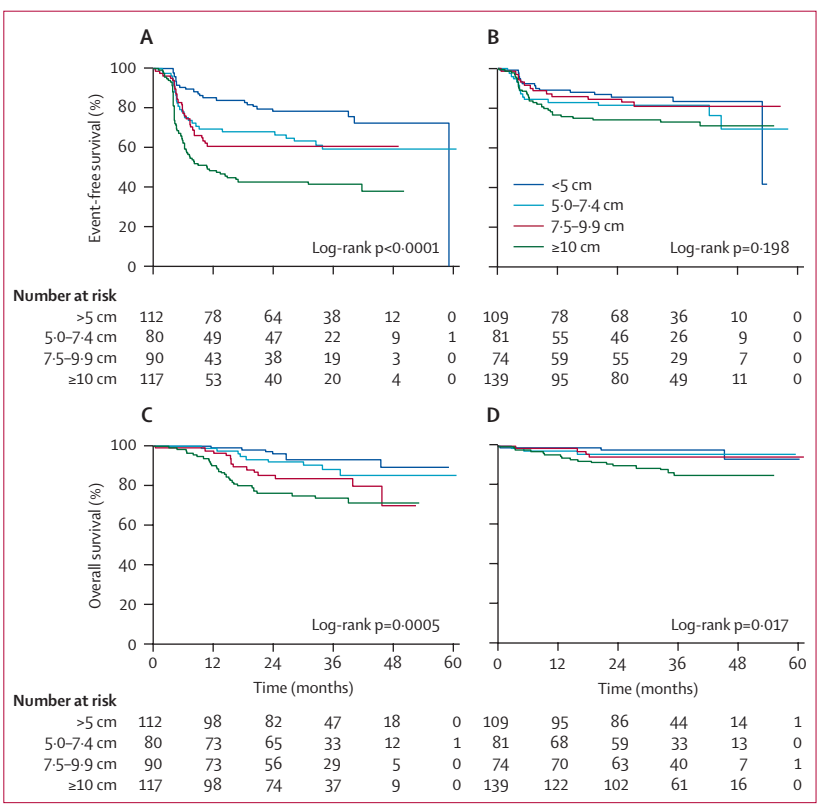

Figure 1: **Event-free and overall survival of patients grouped according to maximum tumour diameters**
Event-free survival of patients treated with six cycles of a CHOP-like chemotherapy only (A) and of patients treated with the same chemotherapy plus six applications of rituximab (B). Overall survival of patients treated with six cycles of a CHOP-like chemotherapy only (C) and of patients treated with the same chemotherapy plus six applications of rituximab (D).

Results

Of the 824 patients enrolled in the MInT study, the informed-consent form of one patient was missing, leaving 823 patients evaluable for intention-to-treat analysis. Data on MTD of involved sites were available for 802 patients

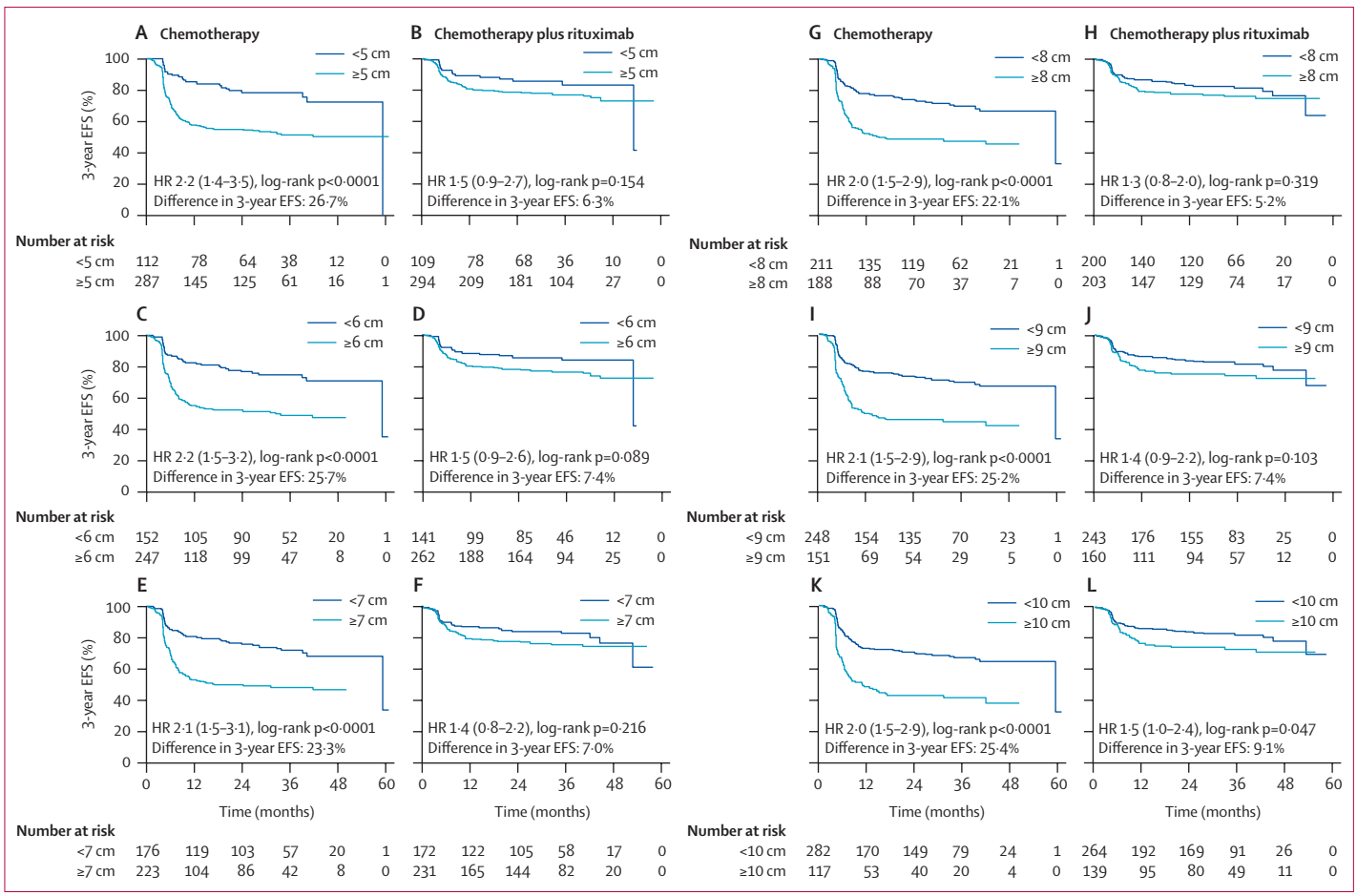

***Figure 2*: Event-free survival (EFS) of patients with and without bulky disease according to different cut-off points**
EFS=event-free survival. The differences in EFS between the bulky and non-bulky population after chemotherapy only (A, C, E, G, I, K) and after chemotherapy plus rituximab (B, D, F, H, J, L) are shown for cut-off points at 5 cm (A, B), 6 cm (C, D), 7 cm (E,F), 8 cm (G, H), 9 cm (I, J), and 10 cm (K, L).

(97%), of whom 399 patients were randomly assigned to six cycles of CHOP-like chemotherapy alone, and 403 patients were randomly assigned to the same chemotherapy plus six applications of rituximab.

Table 1 shows the grouping of patients according to MTD and the distribution of MTD according to tumour location. 221 of 802 (28%) patients had an MTD of less than 5·0 cm, 161 of 802 (20%) patients had an MTD of 5·0–7·4 cm, and 164 of 802 (20%) patients had an MTD of 7·5–9·9 cm. 256 of 802 (32%) patients had an MTD of 10·0 cm or more. The numbers of patients who had radiotherapy of bulky areas was none of 221 patients with an MTD of less than 5·0 cm, 14 of 161 (9%) patients with an MTD of 5·0–7·4 cm, 150 of 164 (91%) patients with an MTD of 7·5–9·9 cm, and 246 of 256 (96%) patients with an MTD of more than 10·0 cm.

Median MTD was 7·5 cm (IQR 4·4–10·0) for all 802 patients, 7·5 cm (4·0–10·0) for patients assigned to CHOP-like chemotherapy alone, and 7·6 cm (4·0–10·0) for those assigned to CHOP-like chemotherapy plus rituximab. 197 of 399 (49%) patients assigned to CHOP-like chemotherapy alone and 205 of 403 (51%) patients assigned to CHOP-like chemotherapy plus rituximab were defined as having bulky disease per protocol. Table 2 shows the distribution of patients with bulky disease as assigned by the different cut-off points set by each participating cooperative group.

After CHOP-like chemotherapy alone, estimated 3-year EFS decreased from 78·2% (MTD <5·0 cm, 95% CI 68·3–85·4) to 41·3% (31·8–50·4) in patients with an MTD of 10·0 cm or more (figure 1). In a multivariable analysis that adjusted for treatment arm, the type of chemotherapy received (CHOP, CHOP plus etoposide [CHOEP], or other) and the presence of at least one aaIPI risk factor, the HRs for an event were significant for patients with an MTD 7·5 cm or more. Clear differences in EFS between groups with different MTDs were recorded after CHOP-like chemotherapy alone: compared with tumours with an MTD of less than 5·0 cm, after CHOP-like chemotherapy alone, HR was 1·672 (0·960–2·912) for tumours with an MTD of 5·0–7·4 cm, 1·832 (1·056–3·179) for tumours with an MTD of 7·5–9·9 cm, and 2·946 (1·813–4·789) for tumours with

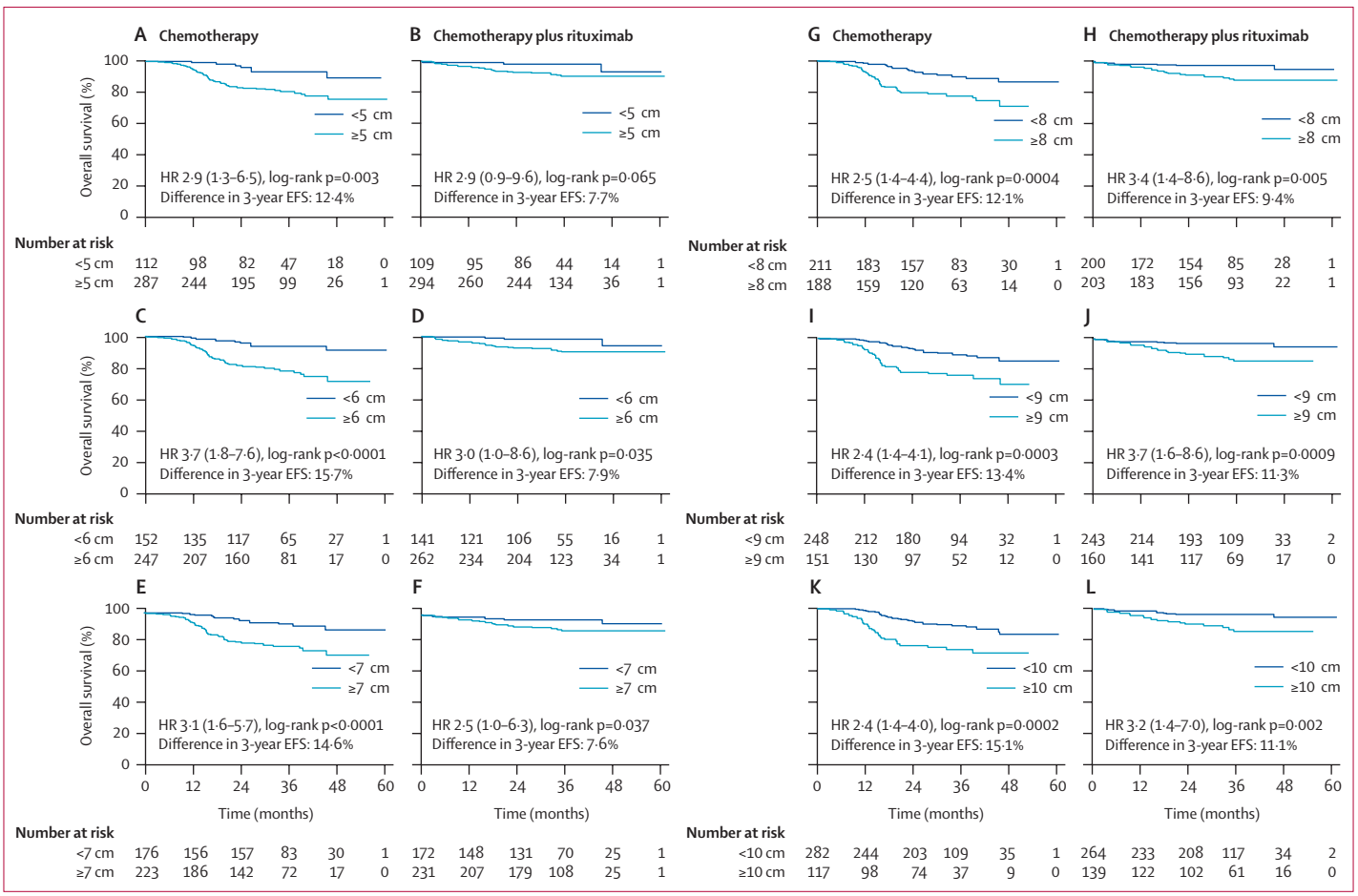

***Figure 3*: Overall survival of patients without bulky disease according to different cut-off points**
The differences in overall survival between the bulky and non-bulky population after chemotherapy only (A, C, E, G, I, K) and after chemotherapy plus rituximab (B, D, F, H, J, L) are shown for cut-off points at 5 cm (A, B), 6 cm (C, D), 7 cm (E,F), 8 cm (G, H), 9 cm (I, J), and 10 cm (K, L).

an MTD of 10·0 cm or more. EFS estimates after CHOP-like chemotherapy plus rituximab ranged between 83·2% (MTD <5·0 cm, 72·8–89·9) and 72·7% (63·8–79·7) in patients with an MTD of 10·0 cm or larger (figure 1). Compared with tumours that measured less than 5·0 cm in diameter, the HRs for EFS in the multivariable analysis for those assigned to chemotherapy plus rituximab were not significant, even for tumours of 10·0 cm or larger in diameter. Compared with tumours with an MTD of less than 5·0 cm, after CHOP-like chemotherapy plus rituximab, HR was 1·399 (0·682–2·871) for tumours with an MTD of 5·0–7·4 cm, 1·183 (0·558–2·508) for tumours with an MTD of 7·5–9·9 cm, and 1·769 (0·955–3·276, p=0·070) for tumours with an MTD of 10·0 cm or more. These findings suggest that rituximab diminishes the adverse effect of tumour size. A Cox regression model adjusted for treatment arm, chemotherapy regimen, and aaIPI confirmed this observation (HR for EFS per cm increase MTD 1·096 [1·058–1·136], p<0·0001; HR for interaction between MTD and rituximab 0·939 [0·883–0·998], p=0·044). We recorded similar findings for OS as for EFS: compared with tumours with an MTD of less than 5·0 cm, patients with tumours with an MTD of 7·5 cm or more had significantly worse OS after CHOP-like chemotherapy alone, whereas after CHOP-like chemotherapy plus rituximab, OS was significantly worse only for those with tumours with an MTD of 10·0 cm or more (HR 4·336 [1·251–15·032], p=0·021).

3-year OS after CHOP-like chemotherapy alone decreased from 92·9% (84·9–96·8%) in patients with tumours with an MTD of less than 5·0 cm to 73·5% (63·9–81·0) for those with tumours with an MTD of 10·0 cm or more (figure 1). This effect on OS was significant for tumours with MTDs of 7·5 cm or more (HR 2·863 [1·150–7·127], p=0·024) and 10·0 cm or more (4·100 [1·772–9·482], p=0·001), but not for tumours with an MTD of less than 7·5 cm compared with tumours with an MTD of less than 5·0 cm. After CHOP-like chemotherapy plus rituximab (figure 1), OS decreased from 98·0% (MTD <5·0 cm, 92·2–99·5) to 85·2% (MTD ≥10·0 cm, 77·0–90·6). In a multivariable analysis, only patients with tumours with an MTD of 10·0 cm or more

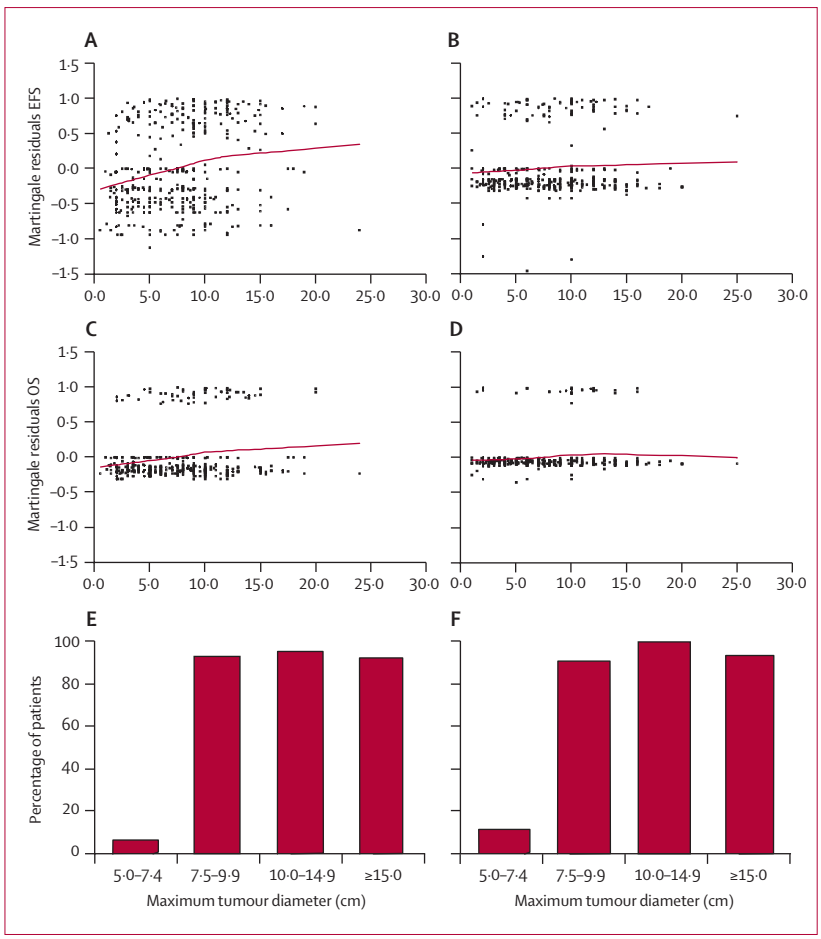

***Figure 4*: Martingale residual analysis**

Plots of Martingale residuals versus maximum tumour diameter and smoothed nonparametric regression curve (A–D) and proportion of patients (chemotherapy only: E; chemotherapy plus rituximab: F) assigned to additional radiotherapy to bulky areas according to the cut-off point predefined for bulky disease by the respective cooperative group. Dots represent maximum tumour diameter for patients assigned to chemotherapy only (n=399) and patients assigned to chemotherapy plus rituximab (n=403). Martingale residuals were obtained by Cox regression modelling for event-free (chemotherapy only: A; chemotherapy plus rituximab: B) and overall survival (chemotherapy only: C; chemotherapy plus rituximab: D) adjusted for chemotherapy and age-adjusted International Prognostic Index. The smoothed regression curves are linear up to 12 cm tumour diameter. Red columns (E, F) represent the percentage of patients assigned to additional radiotherapy to bulky areas according to the cut-off point predefined for bulky disease by the respective cooperative group.

had a significantly worse OS compared with patients with an MTD of less than 5·0 cm (HR 4·336 [1·251–15·032], p=0·021).

The differences in EFS between patients with and without bulky disease were similar, irrespective of where the cut-off point was defined, and were smaller after CHOP-like chemotherapy plus rituximab than after CHOP-like chemotherapy alone. In patients assigned to CHOP-like chemotherapy alone, differences in EFS ranged between 22·1% and 26·7% (figure 2). Therefore, at any cut-off point for bulky disease defined between 5·0 cm and 10·0 cm, the differences in EFS would exceed 20% between patients with bulky and non-bulky assigned to CHOP-like chemotherapy alone, and any cut-off point would separate two populations with a significantly different EFS.

For patients assigned to CHOP-like chemotherapy plus rituximab, the differences of EFS estimates between patients with and without bulky disease for any cut-off point between 5·0 cm and 10·0 cm ranged between 5·2% and 9·1% (figure 2), and only the 10-cm cut-off point separated a bulky and non-bulky population with a significantly different EFS (log-rank p=0·047).

The differences in the estimated OS for patients assigned to CHOP-like chemotherapy alone (figure 3) ranged between 12·1% with a cut-off point of 8·0 cm to 15·7% with a cut-off point at 6·0 cm, and any cut-off point could separate two populations with a significantly different OS. For patients assigned to CHOP-like chemotherapy plus rituximab, the respective OS differences (figure 3) ranged between 7·6% and 11·3%, and any cut-off point of 6·0 cm or more separated two populations with a significantly different OS.

Martingale residual analysis[7] was done to assess the functional form of tumour size to be used in a Cox proportional hazard model. The findings of this analysis showed that the adverse prognostic effect of MTD on EFS and OS fits into a linear model, showing that the risk of having an event increases in a linear fashion with increasing MTD (figure 4). Similar findings (ie, linear dependence between MTD and EFS or OS) were obtained when data for three different regions (infradiaphragmatic, mediastinal-hilar, and supradiaphragmatic-extrathoracic lymph nodes) were analysed separately (data not shown). Since Martingale residual analysis[7] did not show any relevant non-linearity between 5·0 cm and 10·0 cm, there is no cut-off point associated with an abrupt increase in the hazard for an event, neither for EFS nor OS. Therefore, cut-off points for "bulky" disease can be set arbitrarily between 5·0 cm and 10·0 cm, depending on clinical considerations.

In Cox regression models that adjusted for treatment arm, aaIPI, and chemotherapy regimen, the HRs were 1·072 (1·041–1·105, p<0·0001) for EFS and 1·105 (1·055–1·158, p<0·0001) for OS per cm increase of MTD. Further analyses showed interaction between treatment arm and MTD. We therefore estimated the regression coefficients stratified by treatment arm. The regression coefficients were 1·090 (1·051–1·130, p<0·0001) for EFS and 1·119 (1·057–1·184, p=0·0001) for OS per cm increase of MTD for patients assigned CHOP-like chemotherapy alone. For patients assigned CHOP-like chemotherapy plus rituximab, the regression coefficients were decreased compared with patients assigned to CHOP-like chemotherapy alone, and were 1·044 (0·991–1·099, p=0·103) for EFS and 1·089 (1·003–1·183, p=0·043) for OS. Based on these stratified models, we calculated predicted 3-year EFS and OS for patients with specific tumour diameters to show the increasing risk of an event. Table 3 shows the differences between the predicted outcomes of different subpopulations of patients—eg, with none or one aaIPI risk factor, or for different MTD with or without rituximab.

	Maximum tumour diameter					
	5 cm	6 cm	7 cm	8 cm	9 cm	10 cm
Predicted 3-year event-free survival, % (95% CI)†						
CHOP, IPI=0	69·9 (61·6–79·2)	67·6 (59·2–77·3)	65·3 (56·6–75·3)	62·9 (53·9–73·3)	60·3 (50·9–71·3)	57·6 (47·8–69·4)
CHOP, IPI=1	54·2 (44·6–65·9)	51·3 (42·1–62·6)	48·3 (39·4–59·3)	45·3 (36·6–56·1)	42·2 (33·7–52·8)	39·0 (30·6–49·7)
CHOEP, IPI=0	77·5 (70·6–85·0)	75·7 (68·6–83·6)	73·9 (66·3–82·3)	71·9 (63·9–80·9)	69·8 (61·3–79·5)	67·6 (58·4–78·1)
CHOEP, IPI=1	64·7 (56·4–74·3)	62·2 (53·9–71·8)	59·6 (51·3–69·3)	56·9 (48·5–66·8)	54·1 (45·5–64·4)	51·2 (42·3–62·0)
R-CHOP, IPI=0	86·4 (80·3–92·9)	85·8 (79·7–92·4)	85·3 (79·1–92·0)	84·7 (78·3–91·6)	84·1 (77·4–91·2)	83·4 (76·5–91·0)
R-CHOP, IPI=1	82·1 (74·8–90·1)	81·4 (74·3–89·2)	80·7 (73·7–88·3)	79·9 (72·9–87·5)	79·1 (72·1–86·8)	78·3 (71·1–86·2)
R-CHOEP, IPI=0	84·3 (77·8–91·4)	83·7 (77·1–90·9)	83·0 (76·3–90·4)	82·4 (75·3–90·0)	81·7 (74·3–89·8)	80·9 (73·2–89·6)
R-CHOEP, IPI=1	79·5 (71·9–87·8)	78·7 (71·3–86·8)	77·8 (70·6–85·8)	77·0 (69·7–85·0)	76·1 (68·7–84·3)	75·2 (67·5–83·7)
Predicted 3-year overall survival, % (95% CI)†						
CHOP, IPI=0	89·1 (83·6–94·9)	87·9 (82·1–94·1)	86·5 (80·3–93·2)	85·0 (78·4–92·3)	83·4 (76·1–91·4)	81·6 (73·6–90·5)
CHOP, IPI=1	87·1 (81·0–93·8)	85·7 (79·4–92·6)	84·2 (77·6–91·3)	82·5 (75·7–89·9)	80·6 (73·5–88·4)	78·6 (71·0–86·9)
CHOEP, IPI=0	89·6 (84·4–95·2)	88·5 (82·8–94·5)	87·2 (81·1–93·7)	85·8 (79·1–93·0)	84·2 (76·9–92·3)	82·5 (74·3–91·6)
CHOEP, IPI=1	87·8 (82·1–93·8)	86·4 (80·5–92·7)	84·9 (78·8–91·6)	83·3 (76·8–90·3)	81·5 (74·6–89·1)	79·6 (72·1–87·8)
R-CHOP, IPI=0	96·5 (93·4–99·7)	96·1 (92·9–99·5)	95·8 (92·4–99·4)	95·4 (91·8–99·3)	95·0 (91·1–99·2)	94·6 (90·3–99·1)
R-CHOP, IPI=1	94·3 (90·0–98·8)	93·8 (89·4–98·5)	93·3 (88·7–98·0)	92·7 (88·0–97·6)	92·1 (87·2–97·2)	91·4 (86·2–96·9)
R-CHOEP, IPI=0	96·0 (92·6–99·5)	95·6 (92·1–99·3)	95·3 (91·5–99·2)	94·8 (90·8–99·1)	94·4 (90·0–99·0)	93·9 (89·1–99·0)
R-CHOEP, IPI=1	93·5 (88·9–98·4)	93·0 (88·3–98·0)	92·4 (87·5–97·5)	91·7 (86·7–97·1)	91·0 (85·8–96·6)	90·3 (84·7–96·3)

CHOEP=CHOP plus etoposide. R=rituximab.†Prediction based on Cox regression model for event-free or overall survival, adjusted for treatment regimen, type of chemotherapy received, presence of ≥1 age-adjusted International Prognostic Index risk factor, and maximum tumour diameter modelled continuously.

***Table 3*: Predicted 3-year event-free survival and overall survival according to maximum tumour diameter**

Discussion

This analysis of the MInT study shows a linear prognostic effect of MTD on outcome, which is decreased, but not eliminated by the addition of rituximab to CHOP chemotherapy in young patients with good-prognosis DLBCL.

Since the first report that the addition of rituximab to CHOP significantly improves the outcome of elderly patients with DLBCL,[9] rituximab plus CHOP has been readily adopted as standard treatment for DLBCL, and was shown to achieve a significant improvement in the prognosis of patients with DLBCL in a population-based study.[10] In patients with limited (stage I and non-bulky stage II) disease, the addition of rituximab also improved outcome, both after full-cycle chemotherapy[1] and after abbreviated chemotherapy (ie, only three cycles of CHOP) followed by involved-field radiotherapy.[11,12] However, to the best of our knowledge, the role of bulky disease for the treatment of DLBCL in the rituximab era has not been analysed so far.

In the pre-rituximab era, many researchers,[6,8,13–39] but not all[2,40–43] reported a prognostic effect of bulky disease on outcome of aggressive lymphomas and DLBCL. The reasons for these divergent observations are manifold: different subpopulations were studied (all patients, limited-stage only, or advanced stage only) receiving various treatment approaches (radiotherapy, chemotherapy, or combined modality) and different cut-off points were defined arbitrarily, ranging from 5·0 cm to 10·0 cm. To our knowledge, a systematic analysis—that includes a Martingale residual analysis—of the role of a range of MTD on outcome has never been published.

So far, MInT is the largest prospective trial in young patients with good-prognosis DLBCL, and because MTD was known for 802 patients, a detailed analysis of the effect of MTD was possible. MInT enrolled young patients (aged 18–60 years) with good-prognosis DLBCL (aaIPI=0 or 1; stages II–IV; stage I only with bulky disease), and represents a typical young population with good-prognosis DLBCL (low and low-intermediate risk according to the aaIPI) with a bias towards a higher proportion of patients with bulky disease because the best prognostic subgroup (non-bulky stage I patients) had been excluded. This, however, does not bias our analysis because the inclusion of patients with stage I DLBCL without bulky disease would have only better powered the population with MTD of less than 5·0 cm. A caveat of this analysis might be that no central review of the computer scans was done; however, the large number of patients might compensate for possible interindividual differences and represent real clinical life. Bulky disease, defined as the presence of tumours with an MTD of 5·0 cm or more, 7·5 cm or more, or 10·0 cm or more according to the cut-off point predefined by every cooperative group participating in the MInT trial, was a stratification variable and evolved as a highly significant and independent prognostic factor in MInT.

Cox regression models adjusted for treatment arm, chemotherapy regimen, and aaIPI showed a greater HR per cm increase of MTD in patients assigned to CHOP-like

chemotherapy alone than in those assigned to CHOP-like chemotherapy plus rituximab, which again shows the stronger prognostic effect of increasing MTD in patients receiving CHOP-like chemotherapy alone than in those receiving CHOP-like chemotherapy plus rituximab, both in terms of EFS and OS. The reason why the effect of bulky disease is greater on OS than on EFS is unclear; one explanation could be that patients with bulky disease are more difficult to salvage after treatment failure or relapse.

To establish the best cut-off point for separating a non-bulky from a bulky population with the most significantly different prognosis, we assessed the discriminating power of different cut-off points. After CHOP-like chemotherapy alone, any cut-off point of 5·0 cm or more separated a bulky from a non-bulky population with a significant ($p<0·0001$) difference in the estimated 3-year EFS of over 20% (figure 2), whereas after CHOP-like chemotherapy plus rituximab, no cut-off point separated two populations with a 3-year EFS difference of more 10%, and only the cut-off point at 10 cm would distinguish between two populations with a significantly different EFS (log-rank $p=0·047$, 3-year difference 9·1%; figure 2). After CHOP-like chemotherapy plus rituximab, the 3-year OS differences between the bulky and non-bulky population were also compressed compared with after CHOP-like chemotherapy alone, ranging between 7·6% to 11·3%, depending on the respective cut-off point, and were significant for cut-off points of 6·0 cm or more (figure 3). Comparing the effects of MTD on 3-year EFS and OS suggests that the effect of tumour size might be greater on OS than on EFS.

To our knowledge, three studies[1,9,44] so far have compared chemotherapy alone with chemotherapy plus rituximab in patients with DLBCL. Whereas tumour size was not reported in the US Intergroup trial,[44] bulky disease measuring 10·0 cm or more did not evolve as a prognostic factor in the Groupe d'Etude des Lymphomes de l'Adulte (GELA) study.[9] Two reasons might explain the absence of significance of bulky disease in the GELA study: first, the numbers of patients were too small to render this parameter significant; second, the GELA study included patients with advanced-stage cancer and therefore with high tumour burden. It is conceivable that the relative effect of MTD might be smaller in advanced disease than it is in limited disease where a single bulky tumour might confer a considerable proportion of the total tumour burden. The analysis of bulky disease in the rituximab with CHOP over age 60 years (RICOVER-60) trial[45] by the German High-Grade Non-Hodgkin Lymphoma Study Group (Deutsche Studiengruppe Hochmaligne Lymphome; DSHNHL) in 1240 elderly patients with DLBCL which compared six and eight cycles of CHOP-14, both with and without rituximab, will show whether the effect of MTD in the rituximab era is confined to young good-prognosis patients or can be extended to other subpopulations.

A Martingale residual analysis confirmed that the adverse prognostic effect of MTD increased in a linear fashion. This was true when all MTD were analysed together, and when mediastinal or hilar, infradiaphragmatic, and supradiaphragmatic-extrathoracic involvements were analysed separately, implying that there is no ideal cut-off point, ie, a cut-off point with an abrupt increase of risk. The steeper slope of the Martingale residuals derived from patients assigned to treatment without rituximab (figure 4) compared with patients who were assigned to rituximab shows the stronger effect of MTD on outcome of patients who were not assigned to rituximab. Based on this study, a cut-off point of 10·0 cm might be an appropriate margin in the rituximab era to delineate patients with bulky disease.

The fact that patients with bulky disease received additional radiotherapy to the respective area in MInT suggests that the effect of MTD might be even more pronounced if additional radiotherapy were not given, because radiotherapy should have had a positive—if any—effect on outcome, since there were no events or deaths due to the radiotherapy given and adherence to the chemotherapy protocol was the same in patients who received radiotherapy or not. The adherence to the protocol with regard to radiotherapy was good: in the 823 evaluable patients, 74 (41 patients assigned to CHOP-like chemotherapy; 33 patients assigned to CHOP-like chemotherapy plus ritiximab) did not receive the planned radiotherapy, while 29 (15 patients assigned to CHOP-like chemotherapy; 14 patients assigned to CHOP-like chemotherapy plus ritiximab) received additional (unplanned) radiotherapy. The fact that the Martingale residual analysis showed a linearity throughout MTD ranges between 5 cm or more and less than 10 cm, even though only 9% of the patients with an MTD of 5·0–7·4 cm, but 91% of the patients with an MTD of 7·5–9·9 cm were assigned to additional radiotherapy, suggests that radiotherapy for bulky disease might not have a relevant effect on outcome in the MInT study, which is in contrast to a study in stage IV patients from the pre-rituximab era.[46] Nonetheless, our current analysis does not allow for definite conclusions as to the usefulness of radiotherapy in this approach, but underlines the need for additional clinical studies. Only a randomised trial like the ongoing UNFOLDER (UNFavOrable young Low-risk patients treated with DEnsification of R-chemo regimens) study by the DSHNHL, which specifically addresses this question, will show whether the benefit of additional radiotherapy for these patients studied in the pre-rituximab era[47] can be confirmed if rituximab is part of the therapeutic approach.

Contributors

MP, ML, and EK wrote the report. The other authors were the major patient recruiters and contributed to the discussion of the report. Study coordination, data safety, and monitoring committee, members of the reference pathology panel, participating cooperative study groups and statisticians, national principal investigators, participating centres, and recruiting physicians are listed in the original publication[1].

Conflicts of interest

MP, RP, and JW have received honoraria and travel grants from Roche (Basel, Switzerland). MP received an unrestricted grant from Roche in 2004. All other authors declared no conflicts of interest.

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