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Definitions and use of tumor bulk in phase 3 lymphoma trials: a comprehensive literature review

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Key Points

- In phase 3 lymphoma randomized trials, definitions of bulk and its use in the design vary significantly across and within disease subtypes.
- Of 87 trials, 32 analyzed bulk as a prognostic marker in their study design with only 5 demonstrating association with survival outcomes.

Tumor "bulk" has historically been considered an important prognostic marker and a clinical tool to guide treatment in patients with lymphoma. However, its use and definitions in trial designs vary significantly, and it is unclear how this has influenced the relevance of bulk in contemporary practice. This comprehensive literature review evaluated the definitions, applications, and prognostic impact of bulk in phase 3 randomized trials in 4 major lymphoma subtypes. Overall, 87 studies were identified across follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), peripheral T-cell lymphoma (PTCL), and Hodgkin lymphoma (HL) with a wide range of bulk thresholds used (5 cm, 6 cm, 7 cm, 7.5 cm, 10 cm, and >1/3 mediastinal mass ratio [MMR]). The most common threshold was as follows: FL, 7 cm (58%); DLBCL, 7.5 cm and 10 cm (44% each); PTCL, 7.5 cm (66%); and HL, one-third MMR (91%). Bulk threshold was used by trials to determine eligibility (66%), stratification (24%), as a prognostic risk factor (37%), and as a decision tool for risk-adapted treatment, for example, radiotherapy (29%); however, bulk definitions used for these varied both between, and within, lymphoma subtypes and even within single trials in 25%. Furthermore, 32 studies incorporated bulk in prognostic analyses with only 5 showing significance for differential survival outcomes. Our analysis demonstrates high inconsistency in thresholds defining tumor bulk and use of bulk in phase 3 lymphoma trials across eligibility, stratification, therapeutic risk adaptation, and prognostication. This highlights an urgent need for international consensus on definitions of bulk within trials to improve its prognostic and predictive values and refine its application in clinical practice.

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All data sets generated and/or analyzed during this study were retrieved from the primary publications referenced in this article and the data supplement. The extracted data used in this review are available on request from LaRDR (Lymphoma and Related Diseases Registry) at sphpm-lymphoma@monash.edu.

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

Introduction

In previous eras, when localized cancer management, such as surgical excision or radiotherapy, was the sole treatment for lymphoma, tumor bulk correlated strongly with outcomes.[1-3] As lymphoma staging techniques have become more sophisticated, accuracy has improved in identifying sites of bulk and the presence of clinically occult distant disease. In parallel, systemic curative therapies have been developed and, more recently, imaging incorporating molecular activity of tumors, such as positron emission tomography, has become routine in staging and assessing response.[4-6] Thus, the role of tumor bulk in predicting prognosis and guiding treatment decisions has become more complicated and uncertain.

In modern lymphoma trials, measurement of largest "bulk" sites of disease still focuses most often on unidimensional length from anatomical imaging, such as computed tomography scanning. The presence of disease bulk in lymphoma has been variably used to define prognosis, determine the need for treatment, and delineate eligibility both for clinical trials and risk-adapted treatment decisions, such as chemotherapy dose intensity, duration, or addition of consolidative radiotherapy. Bulk is also identified as a risk factor for tumor lysis syndrome in chronic lymphocytic leukaemia[7,8] and more aggressive lymphomas, such as Burkitt lymphoma.[8]

The challenges of using bulk in these many clinical scenarios are that the definition, method of measurement, and use vary widely across lymphoma subtypes but also within specific diseases across trials recruiting similar populations. Furthermore, the measurement of bulk does not incorporate tumor metabolic activity, total tumor burden, or symptomatology or use uniform methods of measurement. In Hodgkin lymphoma (HL), for example, bulk can be defined as a single mass >10 cm or a single mediastinal mass that is more than one-third of the thoracic diameter depending on the trial design.[6] Moreover, these definitions are used to stratify patients into risk categories or groups with associated differences in outcome and determine treatment paradigms. In early stage (Ann Arbor I-II) HL, the German Hodgkin Study Group used bulk as an element of clinical division between "favorable" and "unfavorable" disease, enrolling these 2 subgroups into different trials, with different treatment paradigms.[9-11] In advanced disease, the presence of bulk is incorporated into prognostic scores that estimate outcomes of any 1 risk stratum.[12]

In follicular lymphoma (FL), the most common indolent non-HL, the French Group d'Etude Lymphomes Folliculaires (GELF) developed a tool to determine tumor burden and identify patients who may benefit greater from active therapy, which relies in part on the presence or absence of "bulk" in the form of 1 site >7 cm or ≥3 sites of >3 cm each.[13] These GELF criteria have become widespread in determining eligibility for modern trials.[14,15] In diffuse large B-cell lymphoma (DLBCL), bulk has historically been used to determine the need for consolidative radiotherapy to reduce risk of local relapse,[16] including in some definitions of limited-stage disease,[17] and the size varies between individual trials of the same disease. However, in peripheral T-cell lymphoma (PTCL), the role of bulk is less certain.

Here, we systematically reviewed published phase 3 trials and validated international prognostic scores across 4 key lymphoma subtypes to identify the definitions of bulk used, how it was used, and its impact as a risk factor on prognostic outcomes in studies where it was analyzed.

Methods

Search strategy and inclusion criteria

We searched the databases MEDLINE, Cochrane, and Embase between January 2000 and January 2023 for studies involving bulky disease in FL, DLBCL, PTCL, and HL. These were used as MeSH (Medical Subject Headings) terms and combined with the keywords "bulk," "bulky," and/or "burden" in the search.

Results from Embase were filtered using a randomized controlled trial (RCT) strategy from the British Medical Journal Best Practice website, whereas a similar filter was used to narrow down the articles obtained from MEDLINE.[18]

We included phase 3 RCTs that used the presence of bulk or tumor burden in their trial design, in predominantly adult patients with FL, DLBCL, PTCL, or HL, and published in English. We excluded nonrandomized studies and early phase RCTs and trials performed predominantly in pediatric patients. Studies that involved a heterogeneous group of lymphomas, such as indolent or aggressive non-HL, were included if the predominant type was 1 of the 4 subtypes in this review.

Bulky disease was defined as a tumor mass (either single or conglomerate) greater than a certain determined threshold, frequently in the transverse plane or the longest diameter on imaging. Other definitions include a mass greater than a predefined ratio of the mediastinum.

Duplicates were removed, and both abstracts and titles of the remaining articles were screened for relevance by a single reviewer (L.W.), with discussion with a second reviewer (E.A.H.) if required. Only abstracts with full-text articles available were included, and additional articles were manually searched for in the bibliographies of these.

Where a clinical trial has published subsequent articles from the initial trial, only the original article was included in the review to avoid duplicates. Any additional prognosis data in the follow-up publications, however, were collected and included for the review.

Data extraction

The study characteristics extracted from the publications included the trial period, sample size, type of trial population (either naïve or relapsed/refractory disease), intervention arms, and disease stage (early/limited, advanced, or all stages).

Data regarding bulk collected for this review included definitions used (centimeter), methods used by individual trials of measuring bulk on imaging (either transverse/coronal plane, longest diameter, or standardized methods, including one-third mediastinal mass ratio [MMR] or GELF), its use in the trial design, and the impact of bulk on prognosis in the outcome analysis. Uses of bulk were categorized into eligibility (inclusion or exclusion criterion), randomization stratification factor, treatment decisions (radiotherapy or chemotherapy), and assessment of bulk as a prognostic variable in univariate, multivariate, or subgroup analyses. Treatment decisions regarding radiotherapy included eligibility for radiotherapy treatment arm and determining

which patients qualified for additional consolidative radiotherapy or higher doses than usual.

Bulk was considered a prognostic marker if it was associated with a statistically significant hazard ratio for survival end points in multivariate Cox regressional analyses performed as part of the study results reported by the authors. In subgroup analyses, bulk was considered prognostic if the treatment effect was heterogeneous but not if it was homogenous or if there was no subgroup effect. In addition, we considered whether the primary end point was met and whether the analysis was a priori or post hoc (as specified through the article itself, relevant supplemental Appendix, or study protocols).

Outcomes end points used for evaluation of bulk in prognosis included overall survival (OS), progression-free survival (PFS), event-free survival, and disease-free survival. Freedom from treatment failure, time-to-disease progression, and response rates were not included as end points.

Prognostic indices

To supplement the literature search with respect to analyses of the value of bulk in prognostication, the original published articles that developed frequently used validated prognostic indices were evaluated to identify whether bulk was (1) evaluated as a potential variable and (2) predictive of survival outcomes in their scoring systems. The indices reviewed included Follicular Lymphoma International Prognostic Index (FLIPI),[19] FLIPI-2,[20] and PRIMA-Prognostic Index[21] for FL; the revised International Prognostic Index (R-IPI)[22] and the National Comprehensive Cancer Network IPI[23] for DLBCL; the Prognostic Index for T-cell lymphoma (PIT),[24] modified PIT (mPIT),[25] and International Peripheral T-cell Lymphoma Project score (IPTCLP)[26] for PTCL; and the Hasenclever International Prognostic Score[27] and Advanced-Stage Hodgkin Lymphoma IPI[12] for HL. We scrutinized the univariable and multivariable analyses done within the pivotal papers for each of these prognostic indices to identify the contribution of bulk disease to these.

Results

Our initial search identified 1593 studies with 286 full-text studies subsequently assessed for eligibility after removal of duplicates and abstract screening (Figure 1). One article from 2004 was not included as it had been subsequently retracted in 2013.[28]

Trial details

A total of 87 studies were eligible for the analysis based on inclusion and exclusion criteria, by lymphoma subtype: 33 FL, 19 DLBCL, 3 PTCL, and 32 HL studies. The complete list of included articles is presented in the supplemental Appendix (supplemental Tables 1-4).

Details of the 87 studies are summarized in Table 1. Treatment-naïve populations were enrolled in 81 of 87 studies. The 7 of 87

Figure 1. Summary of search strategies and results.

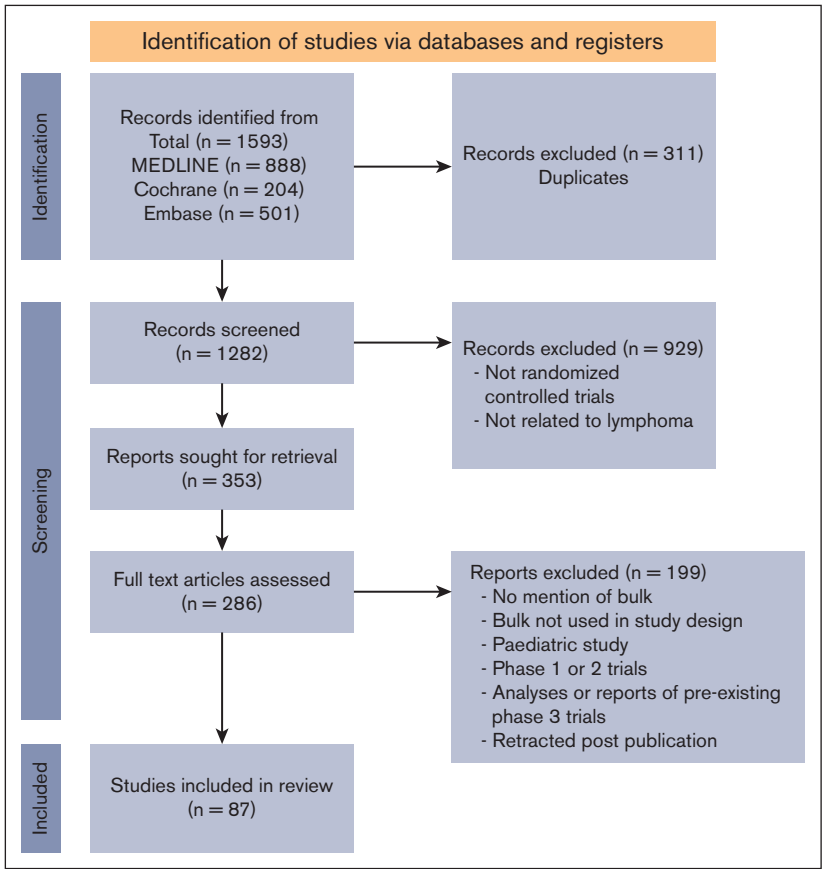

Table 1. Phase 3 RCT details according to lymphoma subtype

	All studies	FL	DLBCL	PTCL	HL
N	87	33	19	3	32
Trial population					
Treatment naïve	81	28*	19	3	31
Relapsed/refractory	7	6*	0	0	1
Disease stages					
Early/limited stage	19	1	2	0	16
Advanced stage	48	25	7	1	15
All stages	20	7	10	2	1
Trial period, y	2002-2022	2002-2022	2002-2022	2010-2021	2002-2021
Trial participants					
Median	468	358	602	103	815.5
Range	2114 (68-2182)	1074 (128-1202)	1156 (258-1414)	28 (88-116)	2114 (68-2182)
Age range of participants, y	14-89	20-89	18-89	17-71	14-87

*Taverna et al[1] included both naïve and relapsing/refractory FL.

trials enrolling relapsed and/or refractory disease populations comprised 6 FL and 1 HL.[29] The 6 relapsed FL RCTs varied in previous treatment eligibility requirements: 2 enrolled rituximab or CD20 monoclonal antibody-refractory populations[30,31]; 1 enrolled both relapsed and treatment-naïve diseases[32]; 1 excluded previous anthracycline, rituximab, or stem cell transplant use[33]; and 1 was completed in rituximab-naïve disease.[34]

Bulk definition and measurement

The definitions of bulk in the trials included 5 cm, 6 cm, 7 cm, 7.5 cm, 10 cm, and one-third of the mediastinal mass-to-thoracic ratio (1/3 MMR or 0.35 MMR; Figure 2). FL trials used 5 different definitions, both DLBCL and HL 4, and PTCL 2. Of 87 studies, 22 (25%) used multiple definitions of bulk within their trial design, including 5 FL, 1 DLBCL, and 16 HL. Seven of these had different uses for each of their definitions.[11,35-40]

In FL, the most common threshold was 7 cm, found in 19 of 33 studies (58%); 15 studies specifically referenced the GELF criteria as the rationale for this cutoff. One study used 7 cm (GELF) to determine trial eligibility but 10 cm for the subgroup analysis.[35] Another study used 5 cm for stratification and 7 cm (GELF) for subgroup analysis.[41]

In DLBCL, 7.5 cm and 10 cm were the most common definitions, found in 8 of 19 studies (42%) each. One study did not list a specific threshold of bulk,[42] and 1 study allowed 3 different definitions (5 cm, 7.5 cm, and 10 cm) with discretion up to the local investigator group (7.5 cm was most often used in 84% of all participants this study).[40]

In PTCL, the bulk threshold definition was either 5 cm or 7.5 cm across 3 studies, with 7.5 cm being the most common in 2 of 3 studies (67%).

In HL, 5 studies used different definitions of bulk for different purposes. All 5 used one-third MMR and 5 cm, with the former definition only used for eligibility while the latter was used for stratification in 3,[11,36,38] determining additional radiotherapy in 1,[39] and subgroup analysis in another.[37]

With respect to method of measuring bulk across 87 studies, defining it at its longest or maximal diameter was the most frequently found in 36 studies. In FL, the GELF criteria were the most common found in 15 studies, whereas 12 used longest diameter in length, 2 used one-third MMR, and 2 specified a transverse or horizontal plane (centimeter).[43,44] In 19 DLBCL studies, 11 studies used maximal diameter in any plane and 8 did not specify. Of 3 studies in PTCL, 1 study specified maximal diameter, whereas 2 did not list a method. In HL, one-third MMR was the most frequently found in 29 studies and use of longest diameter (centimeter) in 12.

Threshold definitions of bulk used in RCTs within different subtypes did not alter over time from 2000 to 2023 (supplemental Figure 1).

Use of bulk in study design and protocol therapy

The uses of bulk across the phase 3 RCTs along with thresholds used are found in Table 2. Bulk was used for >1 purpose in the study designs of 38 of 87 trials (44%). Eligibility was the most common use of bulk across all trials, found in 58 of 87 trials (67%).

Of the 25 studies where bulk was used to guide protocol-driven therapy, 23 of 25 (92%) involved the use of radiotherapy with consolidation being the most common specific use, found in 18 of 23 (78%). Other uses of radiotherapy included need for additional or high doses for bulky disease (2/23)[43,45] and as a specific part of a trial treatment arm (3/23).[38,46,47]

Two studies used the presence of bulky disease to guide chemotherapy with 1 involving additional cycles of rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in DLBCL[48] and the other determining need for cytoreductive prephase cyclophosphamide to patients with FL.[49]

Impact of bulky disease on prognosis

Of the 32 studies (37%) that assessed bulk as a prognostic factor either in multivariate analysis (MVA) or subgroup analysis, 13 were in FL (including 4 that used modified GELF specifically), 12 DLBCL, 1 PTCL, and 6 HL. Furthermore, 20 studies prespecified the analysis of bulk as a prognostic factor, but it was post hoc in 9, and 5 did not specify (in 2 studies, the analysis of bulk was

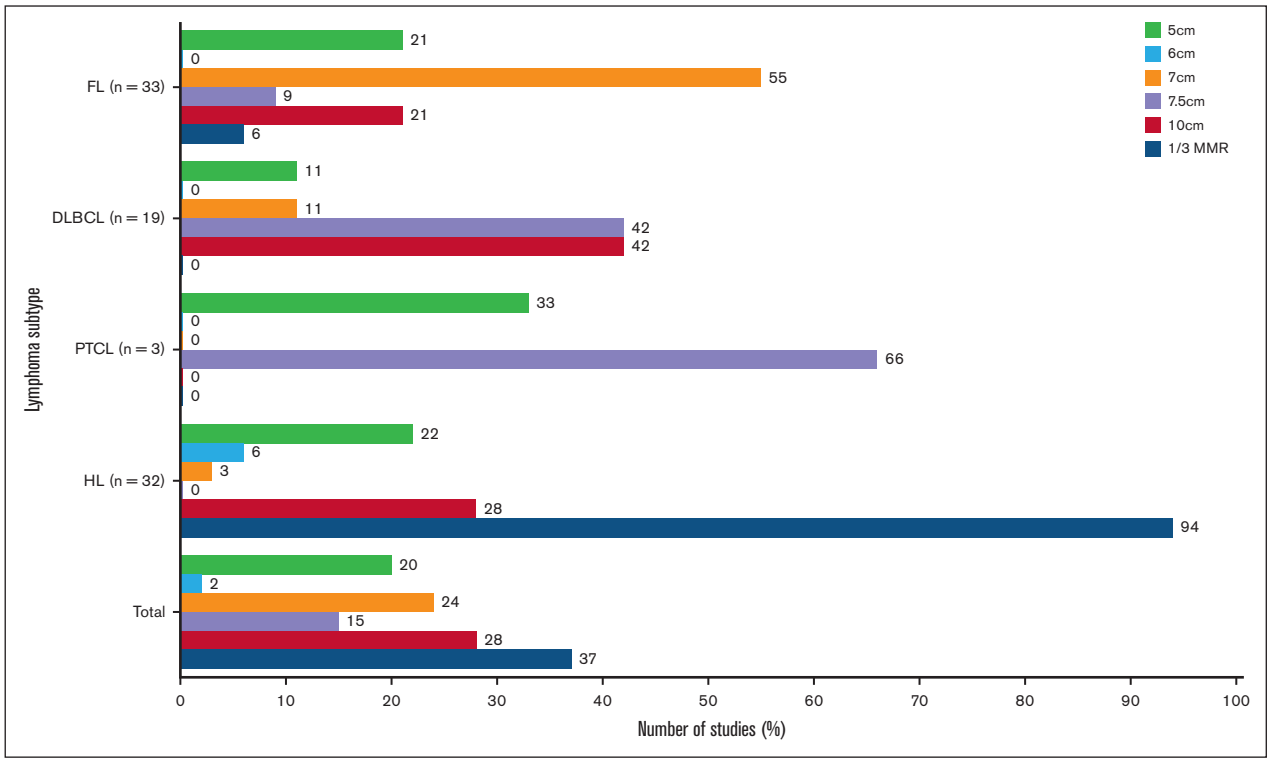

Figure 2. Threshold definitions of bulk used according to lymphoma diagnosis. The data labels indicate the percentage of studies using each definition within the subtypes of lymphoma.

preplanned in MVA but post hoc in subgroup analysis[11,50]). The most common end point assessed was PFS (26/32 studies; Table 2). Only 5 studies demonstrated statistical significance of bulk in end points on MVA with 2 of these in FL[47] (1 of which used modified GELF[34]) and 1 each in DLBCL,[40] PTCL,[51] and HL,[52] noting all 5 preplanned the analysis of bulky disease or high tumor burden in their study design.

No study identified a differential treatment effect according to the presence of bulk disease in subgroup analyses (Table 2).[11,31,40,44,48,50,52-59] Of the 14 subgroup analyses, 8 were preplanned, 4 post hoc, and 2 not specified.

Moreover, 9 studies assessed bulk in univariate analyses (3 DLBCL,[42,48,60] 4 FL,[14,43,61,62] and 2 HL[37,52]) with 5 demonstrating an association with prognostic outcomes including disease-free survival,[48] PFS,[37,42,52] and OS[61] but only 1 retaining significance on subsequent MVA.[52]

Prognostic indices

The type of analysis, the thresholds of bulk, and the variables included in the final model are summarized in Table 3. Bulk was assessed in all prognostic indices reviewed except FLIPI and R-IPI. It was considered in FLIPI but unable to be analyzed due to lack of consensus on threshold for "bulk," and therefore, the number of nodal sites (>4 sites) was used.[19] This was replaced in FLIPI2 by a simpler surrogate marker, the longest diameter of largest involved node > 6 cm.[20] R-IPI did not formally assess bulk as it was based on the original IPI in 1993 where bulk was found to be statistically significant in univariate analysis but not in MVA performed by the authors of this study and therefore excluded from the model.[22]

In PTCL, bulk was not statistically significant both on univariate analysis and MVA in the development of the 2 PTCL prognostic scores, PIT and mPIT, respectively.[24,25] Bulky disease was predictive of OS in step-wise MVA in the IPTCLP for clinical factors only but no longer predictive when accounting for both clinical and pathological factors.[26]

Hasenclever International Prognostic Score did not find MMR to have a strong prognostic effect in advanced-stage HL unless the MMR was >0.45, which was found in a very few patients.[27]

Discussion

Unique to the current literature, our comprehensive review serves to describe the variations in both definition and utility of bulk used by these practice-influencing studies and prognostic indices of 4 common lymphoma subtypes. Across the 87 studies identified, the most frequently used definitions of bulk differed between the 4 different disease subtypes, but also within each disease with 5 different definitions used for FL, 4 for DLBCL and HL, respectively, and 2 in only 3 studies for PTCL. Furthermore 22 of 87 studies (25%) applied multiple definitions of bulk within the study, 16 of which were found in HL and 7 of these used the multiple definitions of bulk for different uses within their study design. When looking specifically at the 25 studies using bulk for treatment decision-making, 92% related to radiotherapy delivery. However, the thresholds used for protocolized radiotherapy delivery were also highly variable between and within lymphoma subtypes, particularly in DLBCL and FL. One DLBCL study allowed for investigator discretion, and therefore, 3 different definitions were all used within the 1 trial. These findings significantly affect the potential implementation and value of bulk as a useful tool in clinical practice.

Table 2. Uses of bulk in lymphoma RCTs

Use of bulk[§]	Total studies	FL	DLBCL	PTCL	HL
Eligibility	**58**	**18**	**10**	**2**	**28**
Inclusion	46	14	8	2	22
Exclusion	12	4	2	0	6
Definitions used					
5 cm	6	2*	1*	–	3*
7 cm	14	13	1	–	–
7.5 cm	10	3*	5*	2	–
10 cm	12	1*	5*	–	6*
1/3 MMR	29	2*	–	–	27*
Stratification	**21**	**6**	**6**	**1**	**8**
Definitions used					
5 cm	7	2	2*	–	3
7 cm	3	2	1	–	–
7.5 cm	5	–	4*	1	–
10 cm	4	2	1*	–	1*
1/3 MMR	5	–	–	–	5*
Protocol-directed therapy	**25**	**5**	**9**	**1**	**10**
Radiotherapy	23	4	8†	1	10
Chemotherapy	2	1	1	0	0
Definitions used					
5 cm	10	2	1*	1	6
7 cm	3	–	1	–	2
7.5 cm	5	–	5*	–	–
10 cm	8	3‡	3*,‡	–	2*
1/3 MMR	3	–	–	–	3*
Prognostic analyses	**32**	**13**	**12**	**1**	**6**
MVA	22	10	7†	1	4
Statistical significance, n (%)	5 (23)	2 (20)	1 (14)	1 (100)	1 (25)
Subgroup analysis	14	3	7	0	4
Significant treatment effect, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Definitions used					
5 cm	7	3	2*	–	2*
7 cm	8	6	1	–	1*
7.5 cm	5	–	4*	1	–
10 cm	13	4	6*	–	3*
1/3 MMR	5	–	–	–	5*
Survival outcomes assessed					
OS	14	5	8	1	–
PFS	26	10	9	1	6
EFS	10	5	3	1	1
DFS	2	1	1	–	–

DFS, disease-free survival; EFS, event-free survival.
*In which a study or studies has used multiple definitions.
†Xu et al[42] used bulk for radiotherapy and prognostic analyses but did not provide a definition.
‡Definition used for additional chemotherapy.
§Uses of bulk in trials are presented in bold with numbers reflecting the total under each lymphoma subcategory.

As highlighted in our results, bulk is frequently used to guide risk-adapted treatment, particularly with respect to radiotherapy delivery. Our analysis identified cohorts defined by bulk that would have been irradiated in certain trials but would not have been in others. The wide range of bulk definitions used in phase 3 RCTs has direct implications on toxicity and efficacy for patients being treated with

Table 3. Analysis of bulk in published prognostic indices

	Bulk assessed	Analysis	Statistical significance	Threshold	Included	Stage	Validated variables in final model
FL							
FLIPI	N	NA	NA	NA	N	All	Age, >4 nodal sites, LDH, Hb
FLIPI-2	Y	MVA	Y	6 cm	Y	All	Age, LoDLIN, BM involvement, β2m
PRIMA-PI	Y	MVA	N	6 cm	N	All	BM involvement, β2m
DLBCL							
R-IPI	N	NA	NA	NA	N	All	Age, PS, LDH, extranodal site, stage
NCCN-IPI	Y	UVA MVA	Y N	10 cm	N	All	Age, ECOG, LDH, extranodal sites, stage
PTCL							
PIT	Y	UVA	N	10 cm, >1/3 MMR	N	All	Age, PS, LDH, BM involvement
mPIT	Y	UVA MVA	Y N	10 cm	N	All	Age, PS, LDH, Ki67%
IPTCLP	Y	MVA	Y	10 cm	N	All	Age, PS, platelet count
HL							
Hasenclever IPS	Y	MVA	N	>1/3 MMR	N	AS	Age, sex, albumin, Hb, stage, leukocytosis, lymphopenia
A-HIPI	Y	MVA	Y (OS not PFS)	Not provided	Y	AS	Sex, albumin, Hb, stage, any bulk, lymphocyte count

A-HIPI, Advanced-Stage Hodgkin Lymphoma IPI; AS, advanced stage; BM, bone marrow; ECOG, Eastern Cooperative Oncology Group; Hb, hemoglobin; IPS, International Prognostic Score; IPTCLP, International Peripheral T-cell Lymphoma Project score; LDH, lactate dehydrogenase; LoDLIN, longest diameter of the largest involved node; mPIT, modified Prognostic Index for T-cell lymphoma; N, no; NCCN-IPI, National Comprehensive Cancer Network IPI; PRIMA-PI, PRIMA-Prognostic Index; PS, performance status; UVA, univariate analysis; Y, yes; β2m, beta-2-microglobulin.

these protocols in routine care, particularly with respect to the balance of lymphoma outcomes with the risks of radiotherapy side effects, such as secondary malignancy and cardiovascular toxicity.[11,36,63] Therefore, establishing standardized definitions of bulk would lead to better application of anatomical bulk in radiotherapy-related decision-making to improve the risk-benefit balance of this strategy.[64]

The prognostic value of baseline bulk is not well established in phase 3 lymphoma RCTs, reflected in a few studies from our review analyzing bulk for this purpose and even fewer demonstrating any associations with survival or differential treatment effects according to bulk.[31] The challenge of using bulk for prognostication is also highlighted in our assessment of 10 frequently used international prognostic indices with only 2 of 10 able to include bulk in their final models despite 9 of 10 exploring it.[12,20] A common theme was the problematic wide variety of institutional definitions and techniques to measure bulk, supported by our literature review results.[19,20] These results challenge the routine incorporation of bulk disease in future prognostic evaluations.

The main limitation in our study is the heterogeneity encountered when reviewing a broad range of studies with variation in enrolled populations (treatment-naïve and relapsed populations, early and advanced stages), treatment arms used (chemotherapy, radiotherapy, stem cell transplant, use of nonchemotherapy agents), and primary outcomes. In addition, we could not accurately analyze studies that have been published in abstract form due to the details required for our evaluation, meaning many contemporary trials are excluded. However, the deliberate inclusion of different disease subtypes and studies published in full offers detailed information on the use of bulk across a spectrum of diseases within lymphoma for clinicians treating this cohort of patients.

In conclusion, definitions and use of single-dimension tumor "bulk" in international phase 3 lymphoma RCTs are highly variable both between lymphoma subtypes and within individual diseases affecting eligibility, treatment decisions, and prognostication. This heterogeneity creates significant challenges in implementing bulk as a reliable tool in modern clinical practice. International consensus guidelines that standardize the definition of bulk in lymphoma trials are needed to overcome the variation. Establishing standard size criteria is essential to progress. On the basis of our analysis, using definitions such as those that appear to be independently associated with outcomes (eg, 10 cm in DLBCL or the GELF definition of 7 cm in FL) or the most often used (eg, 1/3 MMR for HL) seems the logical conclusion; however, international agreement on this is required. Further work from our Australasian National Lymphoma Registry to analyze the optimal cutoffs in the standard of care of patients is ongoing. Such harmonization in future trial eligibility, stratification, therapeutic decisions, and prognostication will enhance application of RCT results in clinical practice and lay robust foundations for incorporation of novel markers in improving risk stratification such as positron emission tomography radiomics, including metabolic tumor volume assessment, which provides significantly enhanced accuracy in tumor burden measurement, molecular classification, and circulating tumor DNA quantification.

Authorship

Contribution: L.W., E.C., C.W., Z.K.M., and E.A.H. designed the study analysis; L.W., E.C., and E.A.H. collected the data; L.W., E.C., C.W., and E.A.H. wrote the manuscript; A.B., B.A.C., G.C., P.R.D.C., G.P.G., G.H., A.M.J., C.T., S.O., E.M.W., and Z.K.M. contributed to editing of the draft manuscript and data analysis; and all authors approved the final manuscript.

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