行う群との比較試験が報告されているが、そこでも両群に生存で差はなかったとされている[18]。しかし、この2つの試験では、大量化学療法前の寛解導入療法のレジメンのDIが対照群と比較して十分ではなかったこと、対照群の治療レジメンが現在の標準的な治療と考えられているものとは異なっていることなどから、大量化学療法の意義を否定するものではないとも考えられている。CHOP療法を対象として大量化学療法の有用性を検討した比較試験がフランスのGroupe Ouest-Est des Leucemies et des Autres Maladies du Sangから報告されているが、そこでは統計学的な有意差こそ認められなかったものの5年全生存割合は71% vs 56%と大量化学療法群が良好であり、5年無イベント生存割合においては55% vs 37%と有意に大量化学療法群が勝っていたとされた(**図9**)[19]。しかしこの試験は、IPIのhigh risk群を「CHOP療法の適応とすることは倫理的ではない」として対象から除外している一方で、IPIのlow～low-intermediate riskという、通常では第一寛解期における大量化学療法の適応とはならないような例も対象としており(試験に登録された例の約半数がIPI low～low-intermediate riskであった。サブグループ解析においてhigh-intermediate riskでは大量化学療法群が勝っていたものの、low～low-intermediate riskでは両群の生存に差は認められなかった)、この結果をもって大量化学療法がCHOP療法に勝ると結論づけることはできないと考えられている。このように、初回

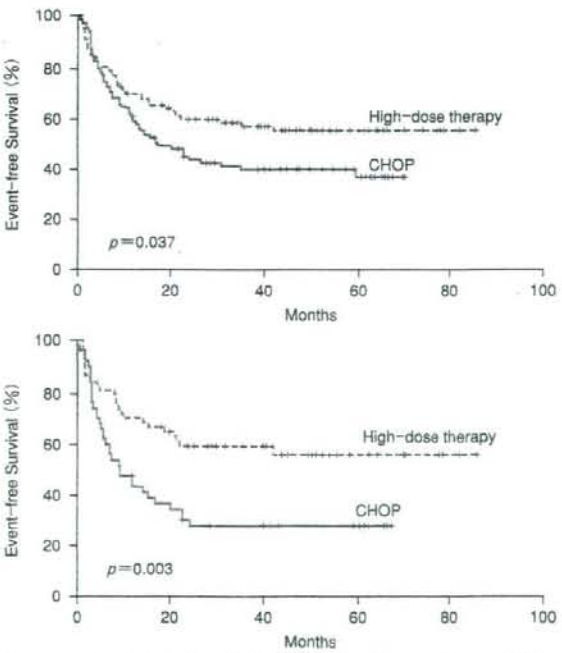

図9　CHOP療法と大量化学療法の比較試験における生存曲線
(上：全登録例における無イベント生存割合、下：IPI high-intermediate riskにおける無イベント生存割合)

治療としての大量化学療法は有望な方法であるが、現在も検討中の試験的治療なのである。なお、IPI low～low-intermediate risk に対してはCD20 陽性であるならばR-CHOP 療法で約80%以上の長期生存が期待できるため、R-CHOP 療法以外の治療を選択する理由はない。

6 高齢者に対する治療(図3)

悪性リンパ腫の発症のピークは50～60 歳であり、患者の半数以上は60 歳以上の高齢者となる。加齢に伴い年齢死亡率も増加する傾向にあるため、高齢者に対する治療の重要性はこれからも増していくであろう。IPI high risk の患者に対しては大量化学療法などのDI を高めたより強力な治療により予後が改善する可能性が見い出されてきているが、臓器機能の低下や合併症の多さなどから化学療法の毒性増強が懸念される高齢者においてはそれらの治療を行うことは困難である。それどころか、標準的な化学療法レジメンであるCHOP 療法でさえも強い毒性が認められる可能性がある。これまで高齢者に対してより毒性の弱い治療法も考案されてきたが、毒性は少なくなるも十分な効果も得られなくなり、結局はCHOP 療法を上回る利益が得られるものはなく、高齢者での標準的な治療も「通常量のCHOP 療法」とされてきた[20]。標準療法ではあるが、高齢者においてはCHOP 療法では50%弱の完全寛解割合、40%弱程度の長期生存しか得られていない。その中で、高齢者に対してもG-CSF などを併用することで、可能な限り治療のDI を高めることが予後の改善が得られるかを検討した比較試験も存在する。GELA で行われた、予後不良な61～69 歳の高齢者の中悪性度リンパ腫を対象としたACVBP 療法とCHOP 療法の比較試験では、完全寛解割合は58% vs 56%と差はなかったものの、5 年無イベント生存割合で39% vs 29%、5 年全生存割合で46% vs 38%と有意にACVBP 療法が上回っていた。しかしその一方で、治療関連死も13% vs 7%とACVBP 療法群で高率に認められたとされている[21]。ドイツのGerman High Grade non Hodgkin's Lymphoma Study Group からは、3 週ごとに行うCHOP(CHOP-21)療法、治療間隔を2 週間に短縮してDI を高めたCHOP-14 療法、それぞれにetoposide を加えたCHOEP-21 療法、CHOEP-14 療法の四群を比較した試験が報告されている。そこでは61～75 歳の中悪性度リンパ腫の患者が四群に均等に割り付けられ、完全寛解割合、3 年無イベント生存割合、5 年全生存割合のいずれもCHOP-14 が最も優れていた(**図10**)[22]。しかしこの試験では、当初は3-weeks regimen vs 2-weeks regimen とetoposide の有無を比較することが計画されており、単純に四群を比較するという試験デザインではなかったということ、60 歳以下のIPI low risk の若年者を対象とした同様の比較試験ではCHOEP-21 が勝っていたという結果などから、結果の解釈には留意する必要がある。また、わが国ではJapan Clinical Oncology Group(JCOG)でCHOP 療法とbiweekly CHOP 療法(=CHOP-14)の比較試

験が行われたが、そこでは両群でまったく差は認められていない。以上のことから、化学療法の治療の強度を高めることで予後改善が得られる可能性もあるものの、毒性などを考えるとCHOP療法に代わると断言できるほどの化学療法レジメンは存在しない。なお先述のとおり、rituximabの臨床導入以降のCD20陽性のリンパ腫に対する標準的治療はR-CHOP療法と考えられている。

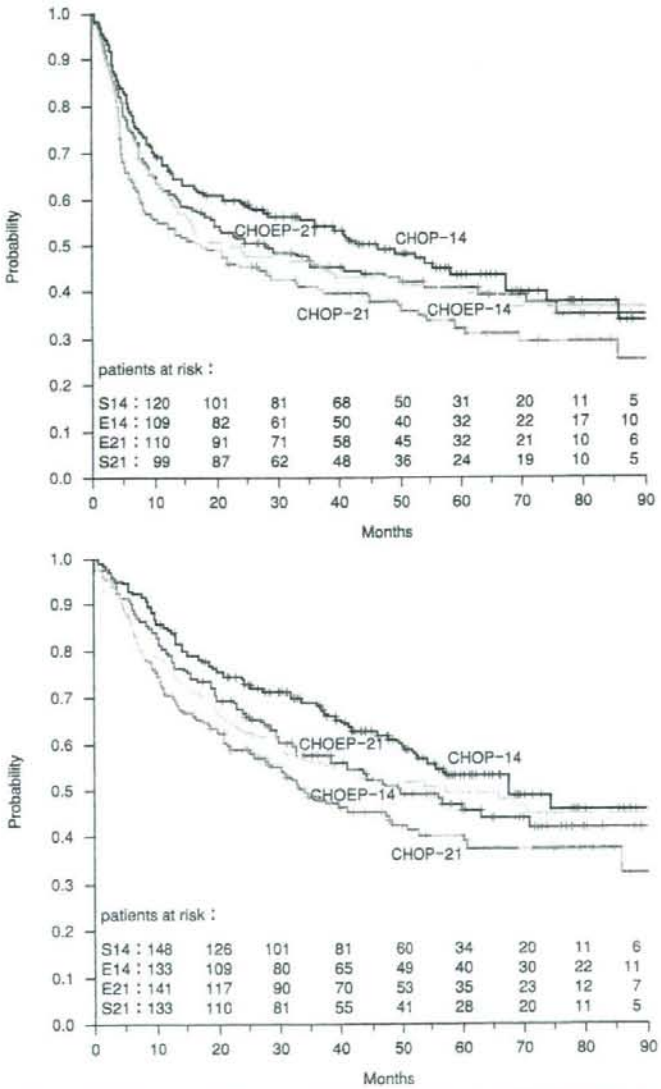

図 10　CHOP-21、CHOP-14、CHOEP-21、CHOEP-14の比較試験の生存曲線（上：無イベント生存割合、下：全生存割合）

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7 再発例に対する救援療法(図3)

再発した中悪性度リンパ腫は初回治療に用いられた薬剤に対して抵抗性となっていることが多い。それを打破するための方法として、①交差耐性をもたない薬剤を使用する、②大量の薬剤を用いる、③投与法を変更する(持続投与にする)、などがある。Etoposide、ifosphamide、mitoxantron、cytosine arabinocide、methotrexate、プラチナ製剤などを用いた併用療法が数多く存在するが、期待できる効果はどのレジメンも横並びで、second line の治療として最も推奨されているレジメンというものは存在しない。しかし、こ

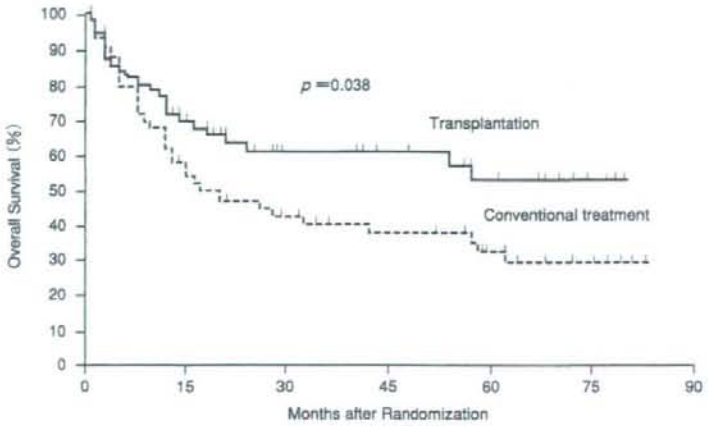

図 11 再発例に対する通常の化学療法と大量化学療法の比較試験における生存曲線

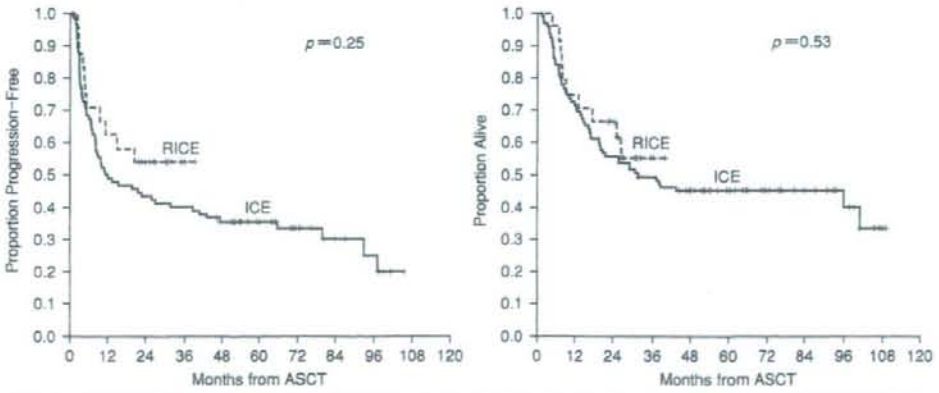

図 12 救援療法の1つである ICE 療法のデータをコントロールとした rituximab 併用 ICE(RICE)療法の生存曲線(左：無増悪生存割合、右：全生存割合)
例数および観察期間も十分でなく統計学的な差は認められていないが、生存の改善が期待される。

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れらの化学療法でPR以上の効果が得られた場合、そのまま化学療法を行うのと大量化学療法を行うのでは長期予後が期待できる可能性は大量化学療法を行った方が有意に高いことが欧米で行われた比較試験の結果から知られており(**図11**)[23]、化学療法感受性の再発例に対しては自家造血幹細胞移植併用の大量化学療法を行うことが推奨されている。さらに、CD20陽性のリンパ腫の場合にはrituximabを併用することで大量化学療法に到達できる確率、大量化学療法後の予後が改善されることも期待されており(**図12**)[24]、初回治療にrituximabが用いられていない場合には、積極的にrituximabを併用すべきであろう。しかし、CD20陽性のリンパ腫に対する現在の標準的な初回治療はR-CHOP療法であり、よほどの事情がない限りrituximabが併用されないことはない。R-CHOP療法後の再発例に対する救援療法のevidenceはまだ存在していないため、そのような場合にどのような治療を行うべきか明確な指針はない。R-CHOP療法後の再発の予後は不良であるとの意見もあり、救援療法にrituximabを併用する意義も不明である。しかしrituximabは、再投与でもそれなりに効果が期待できること、併用する抗腫瘍薬に耐性となった腫瘍細胞の薬剤感受性を回復させることも知られており、再発時のリンパ腫細胞のCD20が依然として陽性であるならば、rituximabの再投与は試みる価値があるだろう。

(大間知　謙)

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bjh research paper

Remission induction therapy containing rituximab markedly improved the outcome of untreated mature B cell lymphoma

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Summary

Many controlled clinical trials have proven that rituximab improves the clinical outcome of patients with mature B cell lymphoma. This study was conducted to assess the contribution of rituximab in the actual clinical practice. Patients with newly diagnosed mature B cell lymphoma treated at 20 National Hospital Organization hospitals from January 2000 to December 2004 were consecutively registered. Rituximab was approved in September 2002 for indolent B cell lymphoma and in September 2003 for aggressive B cell lymphoma in Japan. The patients were divided into two groups depending on whether they received induction therapy containing rituximab. The endpoint was to evaluate the rituximab benefit based on 2-year progression-free survival (PFS) and 2-year overall survival (OS). A total 1126 patients received chemotherapies. Of these, 762 were diagnosed as diffuse large B cell lymphoma (DLBCL) and 215 as follicular lymphoma (FL). PFS and OS were markedly improved in the rituximab group compared with the non-rituximab group in patients with DLBCL (both $P < 0{\cdot}001$) and in patients with FL ($P < 0{\cdot}001$ and $P = 0{\cdot}003$ respectively). Rituximab, when used for remission induction therapy, significantly improved the clinical outcome of the mature B cell lymphoma patient in actual clinical practice.

Keywords: rituximab follicular lymphoma, diffuse large B cell lymphoma, clinical practice.

Non-Hodgkin lymphoma (NHL) is one of the leading causes of cancer death, and its incidence is increasing. The majority of NHL has a B cell phenotype. Almost all B cell lymphomas express CD 20 antigen on the cell surface. Rituximab, a chimeric anti-CD20 monoclonal antibody, was developed and is now widely used to treat B cell lymphoma. Many clinical

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studies have established the effect of rituximab against B cell lymphoma (MacLaughlin *et al*, 1998; Czuczman *et al*, 1999, 2004; Coiffier *et al*, 2002; Forstpointner *et al*, 2004; Hiddemann *et al*, 2005; Lenz *et al*, 2005; Marcus *et al*, 2005; Rivas-Vera *et al*, 2005; Habermann *et al*, 2006; van Oers *et al*, 2006; Pfreundschuh *et al*, 2006, 2008; Herold *et al*, 2007). The toxicity of rituximab has been generally graded as 1 or 2, and it occurs with the first infusion (MacLaughlin *et al*, 1998); the safety of rituximab when combined with chemotherapy has been shown to be similar to that of chemotherapy alone. Randomized phase III studies have proven the survival benefits of the addition of rituximab to multi-agent chemotherapy for patients with untreated follicular lymphoma (FL) (Hiddemann *et al*, 2005; Herold *et al*, 2007) and those with untreated diffuse large B cell lymphoma (DLBCL) (Coiffier *et al*, 2002; Pfreundschuh *et al*, 2006, 2008;). A systematic review also showed the clinical impact of rituximab for low-grade B cell lymphoma (Schulz *et al*, 2007). These data demonstrated that rituximab has an indisputable benefit for patients with untreated and relapsed/refractory B cell lymphoma who were enrolled in well controlled clinical studies. One population-based retrospective analysis by the British Columbia Cancer Registry assessed the effect of rituximab in combination with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) for DLBCL and demonstrated improvement in treatment outcome (Sehn *et al*, 2005). This survey revealed that rituximab contributed to the management of DLBCL in clinical practice. However, the cases studied were restricted to those with DLBCL who received CHOP (with/without rituximab) with curative intent. Therefore, no study has reported the clinical benefit of rituximab in patients with B cell lymphoma in actual clinical practice. To address this point, a retrospective survey comparing patients with B cell lymphoma treated with and without rituximab was conducted. The results showed remarkable improvement in the survival of patients with FL and those with DLBCL, which account for the majority of mature B cell lymphoma patients, by the addition of rituximab in actual clinical practice.

Patients and methods

This was a retrospective cohort study that examined the clinical outcome of all untreated patients with B cell lymphoma who visited the haematological department of 20 hospitals belonging to the National Hospital Organization (NHO), a major, nationwide hospital group in Japan, from January 2000 to December 2004. This research group was founded for the purpose of creating and generalizing clinical evidence in the haematological field by NHO and is called the Clinical Hematology Group of NHO (CHG–NHO). In Japan, rituximab was approved by the Ministry of Health and Labour for the treatment of low-grade B cell lymphoma in September 2002 and for the treatment of aggressive B cell lymphoma in September 2003. The patients with B cell lymphomas were divided into two groups (the rituximab group and the non-rituximab group) based on whether they had received induction therapy containing rituximab in order to determine the benefit of rituximab as part of first remission induction therapy. This study received approval by the responsible ethics committee.

Patients

The patients included in this study were older than 15 years and were newly diagnosed as having mature B cell lymphoma with CD 20 expression by pathological or cytological examination during the period of the study. The pathological diagnosis of each institution was used. Both limited and advanced stage patients based on the Ann-Arbor classification were included (Carbone *et al*, 1971). Patients were excluded if they were human immunodeficiency virus (HIV)-positive or had central nervous system involvement at the time of presentation. All patients fitting the above criteria were serially enrolled. Final statistical analysis was performed for patients who received systemic chemotherapy, whether or not the intention was curative.

Clinical characteristics of the patients included in this survey

All patients' pathological diagnoses were done based on the WHO classification. Age, Eastern Cooperative Oncology Group (ECOG) performance status (PS), lactate dehydrogenase (LDH) levels, clinical staging (Ann-Arbor classification), number of extra-nodal lesions (0, 1 vs. ≥2) were also collected and used to calculate the International Prognostic Index (IPI) (The International Non-Hodgkin's Lymphoma Prognostic Factors Project, 1993) and the revised IPI (R-IPI; Sehn *et al*, 2007). The primary remission induction therapy regimen of all enrolled patents was determined. Usage of rituximab was the focus of this investigation. The kinds of chemotherapy were divided into two groups: those containing anthracyclin and those not containing anthracyclin.

A complete response to treatment was defined as the disappearance of all clinical evidence of disease. Progression-free survival (PFS) was defined as the interval from the diagnosis to the first recurrence of disease (progression or relapse), death from any cause, or the date of the last follow-up in patients who had no relapse. Overall survival (OS) was defined as the interval from diagnosis to death from any cause. Systemic therapy was initiated promptly after diagnosis for almost all of the patients (usually within 1 month).

Statistical analysis

The patients' clinical characteristics and treatment outcomes were compared between patient groups who received systemic chemotherapy with and without rituximab for first induction therapy. The primary endpoint of this study was to confirm the benefit of rituximab for patients with B cell lymphoma when used in remission induction by evaluating the 2-year PFS and

2-year OS. PFS and OS were assessed using the Kaplan–Meier method, and the groups were compared using the log-rank test. A multivariate Cox regression analysis was performed to assess the effects of treatment and the various baseline prognostic factors on PFS and OS. The heterogeneity of treatment effect on the survival outcomes was also examined across the different risk groups based on the R-IPI. The patients with B cell lymphoma were analysed according to pathological diagnosis; therefore, the variables for patients with DLBCL and those with FL were also assessed separately. The analysis is based on follow-up until January 2007. The prognostic variables were compared between the groups using the Mann–Whitney *U*-test for continuous variables and the chi-squared test for categorical variables. All *P* values are two-tailed. Statistical analysis was performed using STATA 8.1 (StataCorp. LP, College Station, TX, USA) and Review Manager (REVMAN; version 5.0. Copenhagen Denmark: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008). *P* values < 0·05 were considered significant.

Results

All B cell lymphoma patients

A total of 1229 patients with newly diagnosed mature B cell lymphoma were enrolled in the study. Of these, 1126 patients (91·6%) received systemic chemotherapies. Patients given rituximab alone for induction were also included. Patients who received systemic therapies were the subject of this analysis, so that patients given radiation alone or eradication of *Helicobacter pylori* alone for induction were excluded. The pathological classifications are listed in Table I. The breakdown of the pathological classification was significantly different between the groups with and without rituximab for induction therapy (Table I). The ratio of patients with FL was higher in the rituximab group. This was caused by the different approval dates of rituximab for indolent B cell lymphoma and aggressive B cell lymphoma. Therefore, direct comparison of the clinical outcomes between these two groups was not considered appropriate, and the analyses were performed separately for each pathological group. Overall, 762 (67·7%) of these patients were diagnosed as having DLBCL, and 215 (19·1%) were diagnosed with FL. Thus, 86·8% (977/1126) of the patients were classified as having DLBCL or FL, so that these two diseases represented the majority of mature B cell lymphoma.

Table I. Pathological subtype of patients (n = 1126).

Histology at diagnosis	Rituximab group (n = 348)	Non-rituximab group (n = 778)	Total (n = 1126) %
DLBCL	184	578	762 (67·7)
Burkitt lymphoma	1	17	18 (1·6)
Follicular lymphoma	111	104	215 (19·1)
Small lymphocytic lymphoma	1	9	10 (0·9)
Lymphoplasmacytic lymphoma	5	8	13 (1·2)
Splenic marginal zone lymhoma	0	3	3 (0·3)
MALT-lymphoma	14	20	34 (3·0)
Nodal marginal zone B cell lymphoma	9	0	9 (0·8)
Mantle cell lymphoma	18	26	44 (3·9)
Others	5	13	18 (0·7)

DLBCL, diffuse large B-cell lymphoma; MALT-lymphoma, extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue.

DLBCL

A total of 762 DLBCL patients were enrolled. Of these, 184 patients received rituximab as part of the first-line treatment in combination with chemotherapy (rituximab group), and 578 patients were treated by chemotherapy alone (non-rituximab group). This difference in patient number was caused by the date of rituximab approval (September 2003 for aggressive B cell lymphoma) and the time period of the study (from January 2000 to December 2004). After approval, almost all DLBCL patients were treated with rituximab, but rituximab was available for only 1 year and 4 months of the 5-year study period. The patients' characteristics are listed in Table II. The ratio of cases receiving anthracyclin containing regimens in each group was not significantly different (rituximab group, 183/184; non-rituximab group, 560/578; P = 0·057). The prognostic variables (IPI and IPI subgroup) were not different between the rituximab group and the non-rituximab group (Table II). The median follow-up time for living patients was 22 months for the non-rituximab group (range, 1–50 months) and 22 months for the rituximab group (range, 1–84 months). PFS was markedly improved in the rituximab group compared with the non-rituximab group [hazard ratio (HR), 0·58; 95% confidence interval (CI), 0·44–0·77; P < 0·001, Fig 1]. The 2-year estimated PFS was 64·4% (95% CI, 56·41–71·3%) in the rituximab group and 48·7% (95% CI, 44·4–52·9%) in the non-rituximab group. OS was also improved in the rituximab group compared with the non-rituximab group (HR, 0·52; 95% CI, 0·37–0·73; P < 0·001, Fig 1). The 2-year estimated OS was 78·0% (95% CI, 70·5–83·7%) in the rituximab group and 61·7% (95% CI, 57·42–65·7%) in the non-rituximab group. Looking only at the patients who received an anthracyclin-containing regimen (CHOP or a CHOP-like regimen), the PFS and OS were compared between the rituximab group and the non-rituximab group in each R-IPI risk group. R-IPI is the revised prognostic model for DLBCL in patients receiving R-CHOP; it identifies three distinct prognostic groups (very good, good and poor). Among DLBCL patients receiving an anthracyclin-containing regimen, the ratio of these risk groups in the rituximab group and the non-rituximab group was not significantly different (Table II). For the R-IPI very good risk

Table II. Characteristics of DLBCL patients (n = 762).

Characteristic	Rituximab group (n = 184)	Non-rituximab group (n = 578)	P
Age (years), median (range)	67 (20–96)	68 (16–95)	0·947*
Gender male/female	100/84	300/278	0·563†
PS at diagnosis			
0	58	182	0·309*
1	74	195	
2	26	100	
3	22	75	
4	4	26	
LDH > normal	101	346	0·233†
Extranodal site > 1	42	130	0·925†
Clinical stage			
I	30	92	0·797*
II	60	176	
III	32	118	
IV	62	192	
IPI			
L	66	174	0·141*
LI	41	138	
HI	37	115	
H	40	151	
Receiving anthracyclin-containing regimen	183	560	0·057†
R-IPI			
Very good	26	60	0·251*
Good	80	244	
Poor	77	256	

PS, ECOG performance status; LDH, lactate dehydrogenase; IPI, International Prognostic Index (L, low; LI, low-intermediate; HI, high-intermediate; H, high); R-IPI, Revised International Prognostic Index.
*Mann–Whitney U-test.
†Chi-squared test.

group, the PFS and OS of the rituximab group were not statistically different from those of the non-rituximab group (HR, 1·38; 95% CI, 0·40–4·72; P = 0·61, HR, 1·89; 95% CI, 0·42–8·49; P = 0·40 respectively) (Fig 2). However, for the R-IPI higher risk groups (good and poor), PFS was significantly improved by the addition of rituximab (HR, 0·58; 95% CI, 0·35–0·96; P = 0·035, HR, 0·54; 95% CI, 0·38–0·76; P < 0·001 respectively) (Figs 3 and 4). OS was also improved in the R-IPI poor risk group (HR, 0·48; 95% CI, 0·32–0·72; P < 0·001), and an improvement in the R-IPI good risk group was also noted, but it was not statistically significant (HR, 0·52; 95% CI, 0·26–1·05; P = 0·069). We also performed a forest plot to explore the heterogeneity between these subgroups. There was no evidence of substantial heterogeneity in the relative treatment effect on PFS and OS between different risk groups based on the R-IPI (The P value for heterogeneity was 0·35 and 0·23 respectively) (Fig 5). These results suggest that rituximab improved the clinical outcome of all DLBCL patients.

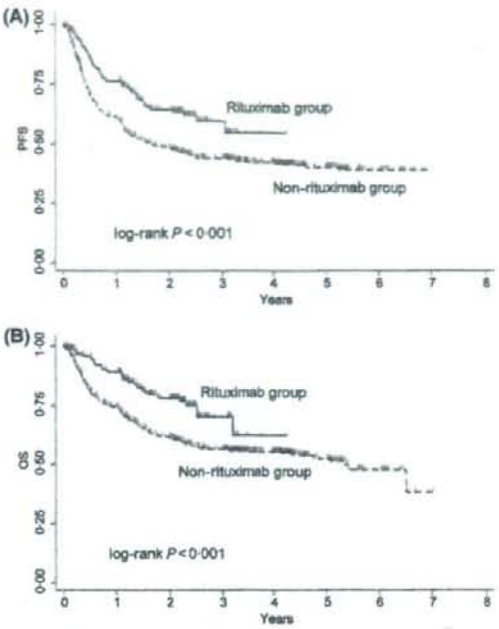

Fig 1. Progression-free survival (A) and overall survival (B) of 762 DLBCL patients. The rituximab group received rituximab in addition to systemic chemotherapy as first remission induction. The non-rituximab group received systemic chemotherapy alone as first remission induction.

Follicular lymphoma

A total of 215 FL patients were enrolled. Of these, 111 patients were in the rituximab group, and the other 104 were in the non-rituximab group. The patient number in each group was almost equal because of the date of rituximab approval (September 2002 for indolent B cell lymphoma) and the time period of the study (from January 2000 to December 2004). After approval, almost all FL cases were treated with rituximab, so that rituximab was available for 2 years and 4 months of the 5-year study period. The patients' characteristics are listed in Table III. The ratio of cases receiving an anthracyclin-containing regimen in each group was not significantly different (rituximab group, 104/111; non-rituximab group, 91/104; P = 0·159). Only three (age, LDH level, Ann-Arbor clinical stage) of the five prognostic variables that make up the FLIPI could be evaluated. These variables were not different between the rituximab group and the non-rituximab group (Table III). The median follow-up time for living patients was 37 months for the non-rituximab group (range, 1–72 month) and 41 months for the rituximab group (range, 1–80 months). PFS was markedly improved in the rituximab group compared with the non-rituximab group (HR, 0·45; 95% CI, 0·30–0·69; P < 0·001, Fig 6). The 2-year estimated PFS was 77·6% (95% CI, 68·1–84·5%) in the rituximab group and 56·3% (95% CI,

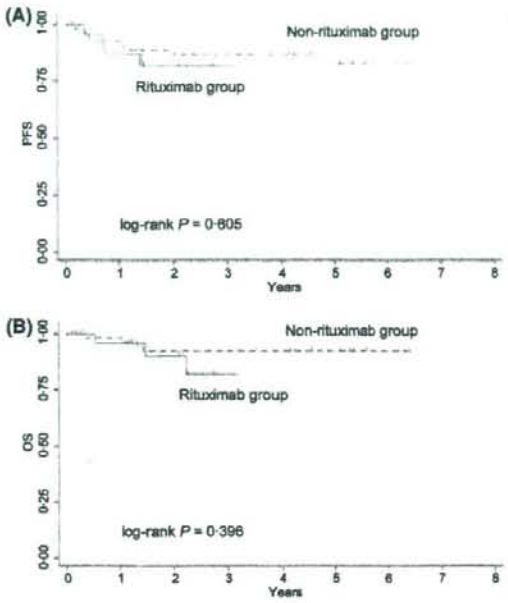

Fig 2. Progression-free survival (A) and overall survival (B) of 86 DLBCL patients (R-IPI very good risk). The rituximab group received rituximab in addition to systemic chemotherapy as first remission induction. The non-rituximab group received systemic chemotherapy alone as first remission induction.

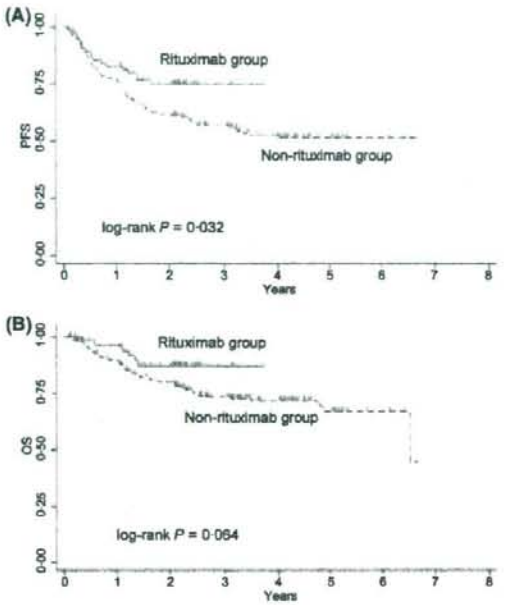

Fig 3. Progression-free survival (A) and overall survival (B) of 324 DLBCL patients (R-IPI good risk). The rituximab group received rituximab in addition to systemic chemotherapy as first remission induction. The non-rituximab group received systemic chemotherapy alone as first remission induction.

45·9–65·5%) in the non-rituximab group. OS was also improved in the rituximab group compared with the non-rituximab group (HR, 0·35; 95% CI, 0·17–0·72; $P = 0·003$, Fig 5). The 2-year estimated OS was 94·3% (95% CI, 87·8–97·4%) in the rituximab group and 81·7% (95% CI, 72·5–88·0%) in the non-rituximab group.

A multivariate analysis was performed to assess the effect of rituximab on clinical outcome after controlling for prognostic variables. After controlling for the prognostic variables included in R-IPI and IPI itself, rituximab remained an independent prognostic predictor of both PFS (risk ratio, 0·56; 95% CI, 0·43–0·74; $P < 0·001$) and OS (risk ratio, 0·50; 95% CI, 0·36–0·70; $P < 0·001$) in DLBCL. In FL, rituximab was also an independent prognostic predictor of both PFS (risk ratio, 0·49; 95% CI, 0·32–0·74; $P = 0·001$) and OS (risk ratio, 0·44; 95% CI, 0·21–0·92; $P = 0·028$) after adjustment for prognostic variables (age, LDH level and clinical stage).

Discussion

This retrospective survey showed that the addition of rituximab significantly improved PFS and OS in patients with FL and DLBCL when used as part of first remission induction therapy. This survey was carried out among 20 hospitals belonging to CHG–NHO. The clinical data of all patients diagnosed with NHL during this study were accumulated, and the PFS and OS of B cell lymphoma patients receiving systemic chemotherapies with and without rituximab were analysed. Rituximab was approved in September 2002 for indolent B cell lymphoma and in September 2003 for aggressive B cell lymphoma in Japan. The period of this survey was from January 2000 to December 2004 (5 years); therefore, differences in clinical outcomes could be compared between the rituximab group and the non-rituximab group. NHL patients were enrolled without regard to the chemotherapeutic regimen. During the study period, 1229 mature B cell lymphoma patients were newly diagnosed, and 1126 (92%) received systemic chemotherapy. Of the 1126 patients, 977 were diagnosed with DLBCL or FL, so that these cases accounted for 86·8% of the 1126 cases of mature B cell lymphoma receiving systemic chemotherapy. Thus, the clinical outcomes of these subjects reflect those of almost the entire mature B cell lymphoma population in clinical practice.

So far, many clinical studies have shown the benefits of rituximab in the treatment of B cell lymphoma. In 1999, a single arm phase II study of a combination of rituximab and CHOP for untreated indolent B cell lymphoma was reported (Czuczman *et al*, 1999). The response rate was 95% (38 of 40), and long-term remissions were observed (Czuczman *et al*, 2004). Several randomized phase III studies have demonstrated

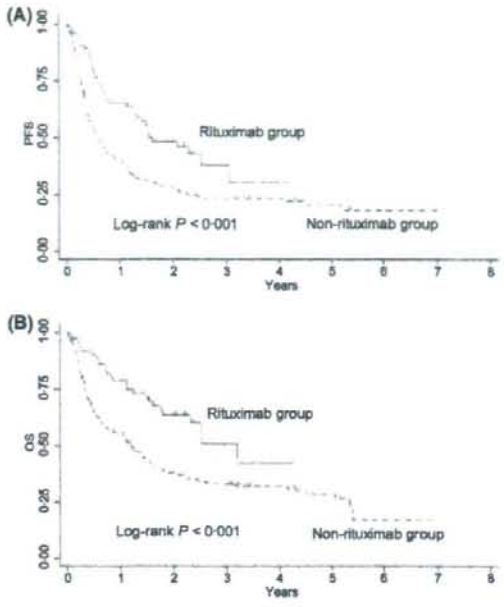

Fig 4. Progression-free survival (A) and overall survival (B) of 333 DLBCL patients (R-IPI poor risk). The rituximab group received rituximab in addition to systemic chemotherapy as first remission induction. The non-rituximab group received systemic chemotherapy alone as first remission induction.

the advantages of the addition of rituximab to chemotherapy, both in previously untreated patients, as well as in relapsed/refractory indolent B cell lymphoma patients (Forstpointner *et al*, 2004; Hiddemann *et al*, 2005; Lenz *et al*, 2005; Marcus *et al*, 2005; Rivas-Vera *et al*, 2005; van Oers *et al*, 2006; Herold *et al*, 2007; Schulz *et al*, 2007). The German Low-Grade Lymphoma Study Group (GLSG) conducted a phase III study comparing CHOP combined with rituximab to CHOP alone, and they showed significant improvements in remission rates, PFS and OS in the combination group (Hiddemann *et al*, 2005). Other studies also showed that chemotherapy with rituximab provided a better PFS than chemotherapy alone. Recently, the Cochrane Hematological Malignancies Group performed a comprehensive systematic review and meta-analysis to compare the efficacy of chemotherapy with rituximab to the identical chemotherapy alone in patients with indolent B cell lymphoma or mantle cell lymphoma (Schulz *et al*, 2007). This analysis included seven well-controlled, randomized studies comparing rituximab–chemotherapy combination therapy with chemotherapy alone, and indicated that the rituximab–chemotherapy combination provided superior OS to chemotherapy alone.

For DLBCL, many phase III studies have proven the benefits of the addition of rituximab to chemotherapy. The Groupe d'Etude des Lymphomes de l'Adulte study showed superiority of CHOP and rituximab to CHOP alone in elderly, advanced, previously untreated, DLBCL patients with respect to PFS and OS (Coiffier *et al*, 2002). The advantage of rituximab in

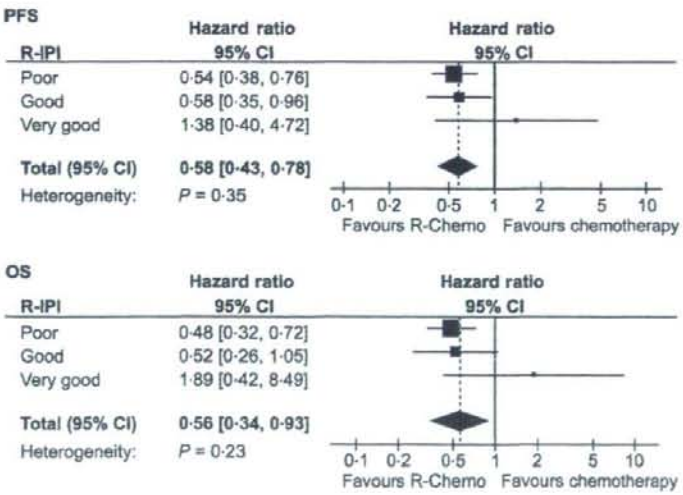

Fig 5. Disease control for DLBCL in each R-IPI risk group receiving rituximab with chemotherapy (R-chemo) or chemotherapy alone. Disease control is shown as the hazard ratio (HR) for a disease event (progression or death). Solid squares represent risk estimates for the each R-IPI risk group. The size of squares represents the weight assigned to each R-IPI risk group and is proportional to inverse variance of the estimate. Horizontal lines indicate 95% confidence intervals (CIs). The diamond indicates the 95% CIs for the overall HR. Values less than 1·0 indicate HRs that favour R-chemo.

Table III. Characteristics of follicular lymphoma patients (n = 215).

Characteristics	Rituximab group (n = 111)	Non-rituximab group (n = 104)	P
Age (years), median (range)	56 (26–83)	57 (23–91)	0·497*
Gender male/female	49/62	48/56	0·767†
PS at diagnosis			
0	60	53	0·395*
1	38	31	
2	8	13	
3	4	6	
4	1	1	
LDH > normal	42	47	0·274†
Clinical stage			
I	4	7	0·065*
II	28	15	
III	41	32	
IV	38	50	
Receiving anthracyclin-containing regimen	104	91	0·159†

PS, ECOG performance status; LDH, lactate dehydrogenase.
*Mann–Whitney U-test.
†Chi-squared test.

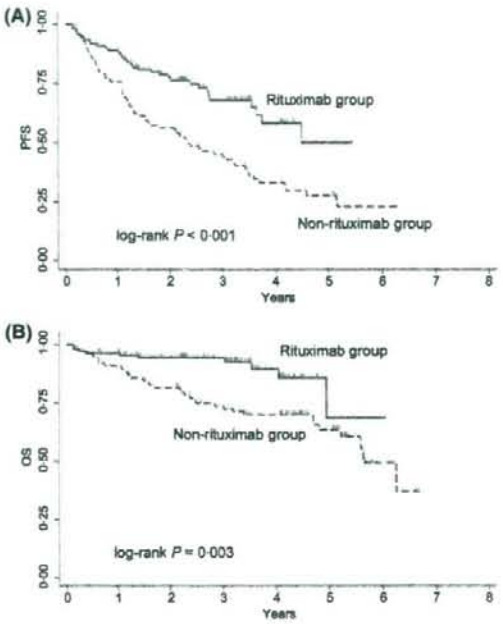

Fig 6. Progression-free survival (A) and overall survival (B) of 215 follicular lymphoma patients. The rituximab group received rituximab in addition to systemic chemotherapy as first remission induction. The non-rituximab group received systemic chemotherapy alone as first remission induction.

combination with a CHOP-like regimen for the younger DLBCL population was indicated by the intergroup cooperative study (MInT study) (Pfreundschuh *et al*, 2006). Therefore, the clinical merits of the use of rituximab in the induction treatment of mature B cell lymphoma have now been established by these well controlled, phase III studies, but the actual benefits of rituximab benefits in clinical practice have not been addressed. Prospective clinical trials for treatment have critical inclusion and exclusion criteria, and patients with poor PS or organ dysfunction are usually excluded. One population-based retrospective analysis, by the British Columbia Cancer Registry, assessed the effect of rituximab in combination with CHOP for DLBCL and demonstrated improvement in treatment outcome in clinical practice (Sehn *et al*, 2005). However, this study was limited to patients who were treated with curative intent. The present study serially enrolled all patients with mature B cell lymphoma who were newly diagnosed, and all patients receiving systemic chemotherapy, whether or not the intent was curative, were included in the analysis to evaluate the effect of rituximab. This approach reflects the actual state of management of mature B cell lymphoma patients in clinical practice.

In DLBCL, PFS and OS were better in the rituximab group than in the non-rituximab group. When DLBCL was classified by R-IPI, the benefit of rituximab was statistically identified in the good and poor risk group but not in the very good risk group. The favourable effect of rituximab seemed to be restricted in higher risk patients, but the significant heterogeneity between these subgroups was not identified by the forest plot (Fig 5). This finding might be a result of small patient numbers in the very good risk group. To clarify whether rituximab contributes to the clinical outcomes of the very good risk group or not, more cases need to be analysed.

In conclusion, this retrospective analysis showed that the use of rituximab for remission induction therapy significantly improved OS and PFS in patients with FL or DLBCL, who constitute the majority of mature B cell lymphoma patients. This study was planned to elucidate the state of NHL management in clinical practice and found that rituximab appeared to dramatically improve clinical outcomes in patients with mature B cell lymphoma.

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JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Fluorine-18-Fluorodeoxyglucose Positron Emission Tomography for Interim Response Assessment of Advanced-Stage Hodgkin's Lymphoma and Diffuse Large B-Cell Lymphoma: A Systematic Review

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ABSTRACT

Purpose
To systematically review the prognostic accuracy of fluorine-18-fluorodeoxyglucose positron emission tomography (FDG-PET) for interim response assessment of patients with untreated advanced-stage Hodgkin's lymphoma (HL) or diffuse large B-cell lymphoma (DLBCL).

Methods
MEDLINE, EMBASE, SCOPUS, and Biologic Abstracts were searched for relevant studies. Two assessors independently reviewed studies for inclusion and extracted data. Relevant unpublished data were requested from the investigators if unavailable from publications. A meta-analysis of the prognostic accuracy was performed.

Results
Thirteen studies involving 360 advanced-stage HL patients and 311 DLBCL patients met our inclusion criteria. Advanced-stage HL studies included few unfavorable-risk patients. DLBCL studies were heterogeneous. FDG-PET had an overall sensitivity of 0.81 (95% CI, 0.72 to 0.89) and a specificity of 0.97 (95% CI, 0.94 to 0.99) for advanced-stage HL, and a sensitivity of 0.78 (95% CI, 0.64 to 0.87) and a specificity of 0.87 (95% CI, 0.75 to 0.93) for DLBCL. Meta-regression and subgroup analyses did not identify factors that affect prognostic accuracy.

Conclusion
For low- to intermediate-risk advanced-stage HL, FDG-PET performed after a few cycles of standard chemotherapy seems to be a reliable prognostic test to identify poor responders, warranting prospective studies to assess PET-based treatment strategies. For DLBCL, no reliable conclusions can be drawn due to heterogeneity. Interim PET remains an unproven test for routine clinical practice. Its use should be reserved for research settings where treatment regimens and imaging conditions are standardized.

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INTRODUCTION

Malignant lymphoma is the fifth most commonly diagnosed cancer in the United States.[1] With advances in treatments, Hodgkin's lymphoma (HL) and diffuse large B-cell lymphoma (DLBCL) are potentially curable lymphomas.[2,3] However, challenges remain especially in the treatment for high-risk patients,[4,5] since more than half of these patients do not achieve long-term survival with currently available standard first-line chemotherapy. A possible treatment involves intensive and toxic polychemotherapy for advanced-stage HL[6] or first-line high-dose chemotherapy with stem-cell support for DLBCL,[7] depending on individual risk of treatment failure. Therefore, better identification of poor responders to first-line therapy is important to advance risk-adapted treatment strategies.

Fluorine-18-fluorodeoxyglucose positron emission tomography (FDG-PET) is a functional imaging test that has become widely used in the management of both HL and non-Hodgkin's lymphoma (NHL).[8] Studies that assessed FDG-PET as a prognostic tool performed during chemotherapy have reported the ability to predict poor outcomes.[8] However, the studies used different design, conduct, and reporting, making interpretation of the results difficult. In particular, inclusion of heterogeneous populations with different categories of disease (eg, limited-stage *v* advanced-stage HL or DLBCL

Table 1. Studies of PET for Interim Response Assessment of Malignant Lymphoma Included in the Systematic Review

Study	Year	Country	Study Design	No. of Involved Institutions	Start of Follow-Up Period	Follow-Up (months)		Pretherapy Scan to Confirm FDG Avidity (%)
						Median	Range	
Advanced-stage HL + DLBCL								
Kostakoglu et al[32]	2006	USA	Retrospective	1	Start of therapy	21†	3-47	100
Advanced-stage HL								
Friedberg et al[33]	2004	USA	Prospective	3	Pre-therapy PET	24†	10-32	100
Hutchings et al[37]	2005	UK	Retrospective	1	Diagnosis of lymphoma	40†	6-125	100
Gallamini et al[30]	2006	Italy	Prospective	11	Diagnosis of lymphoma	20‖	2-46	100
Hutchings et al[13]	2006	Denmark	Prospective	3	Diagnosis of lymphoma	22	6-40	100
Zinzani et al[14]	2006	Italy	Prospective	1	NR	18	12-27	100
Gallamini et al[29]	2007	Italy + Denmark	Prospective	14	Diagnosis of lymphoma	26†	4-62	100
DLBCL								
Spaepen et al[34]	2002	Belgium	Prospective	1	End of therapy	36††	18-51	97†
Haioun et al[31]	2005	France	Prospective	4	Study enrollment	24†	NR	100
Mikhaeel et al[12]	2005	UK	Retrospective	1	Diagnosis of lymphoma	24†	NR	100
Fruchart et al[35]	2006	France	Prospective	1	Start of therapy	19	2-35	100
Quereliou et al[36]	2006	France	Retrospective	1	Start of therapy	15†¶	9-28	100
Ng et al[26]	2007	Australia	Retrospective	1	Start of therapy	28	2-81	Partial

(continued on following page)

v other aggressive NHLs) clearly affects the clinical applicability of the study results because each category has different clinical profiles (eg, treatment strategies, response, and prognosis). In this systematic review, we assessed the prognostic accuracy of FDG-PET performed during first-line therapy to predict disease progression or relapse in patients with advanced-stage HL and DLBCL, paying particular attention to the clinical applicability of the reported results.

METHODS

Data Sources and Searches

We searched Ovid MEDLINE and EMBASE from 1966 through July 2006,[9] and PubMed from August 2006 through July 2007 without language restriction. The search strategy can be found in online-only Appendix Table A1. This search was augmented by searches of SCOPUS and Biologic Abstracts. We also examined the reference lists of eligible studies, review articles, and textbooks.

Study Selection

Two reviewers (T.T., H.N.) screened abstracts and determined eligibility. Full-text articles were reviewed when abstracts did not provide sufficient information for determination. We included studies that evaluated FDG-PET performed between the first and the fourth cycle of first-line chemotherapy for patients with advanced-stage HL or DLBCL. We included both prospective and retrospective studies, and we considered clinical follow-up with or without pathologic confirmation to be a reference standard. We included studies that evaluated at least 10 patients and included at least five patients who progressed during chemotherapy or relapsed through clinical follow-up. We accepted studies in which patients received high-dose chemotherapy followed by autologous stem cell transplantation as long as it was administered as a part of primary therapy or consolidation therapy after standard induction chemotherapy. We excluded abstracts, editorials, comments, letters, and review articles. We excluded studies that enrolled patients with HIV-associated or post-transplant lymphoproliferative disorders.

Many studies did not meet all the inclusion criteria, but did partially include a relevant patient population. For these studies, we contacted the authors for relevant individual patient or subgroup data. When there was no response after 4 weeks, another correspondence was sent. When there was no response after the third communication attempt, we considered the request rejected.

Data Extraction and Quality Assessment

Two independent, board-certified hematologists (T.T., H.N.) abstracted relevant data. We extracted patients' demographic and clinical characteristics including the International Prognostic Scores (IPS) for advanced-stage HL[4] or the International Prognostic Indexes (IPI) for DLBCL,[5] therapeutic interventions, interim PET results, and final clinical outcomes. We subdivided the treatment failures into three categories based on the relative timing to the completion of first-line therapy: during therapy, after 1 year from diagnosis or the start of therapy, and in between. When the timing of completion of first-line therapy was unclear, we arbitrarily considered the treatment period to be 6 months. We also extracted the number of cases in remission but censored from follow-up within 1 year from the start of therapy (early censoring). One nuclear medicine specialist (T.N.) evaluated the technical specification and quality of PET procedures using recommended guidelines.[10] Reviewers were not blinded to the name of the journal. Inconsistencies between reviewers were either clarified by the authors or resolved by consensus.

To evaluate the quality, applicability, and reporting of the studies, we used QUADAS, a recently proposed tool to assess the quality of studies of diagnostic accuracy included in a systematic review.[11] Details on how we scored each item can be found in online-only Appendix Table A2. We assessed only published data and did not use unpublished data because the latter was not available from all the studies.

Data Synthesis and Statistical Analysis

For each study, we constructed a 2×2 contingency table consisting of true positive (TP), false positive (FP), false negative (FN), and true negative (TN), where all patients were categorized according to whether they were PET positive or negative, and whether they experienced treatment failure. In the main analysis, we employed the entire clinical follow-up as the reference standard. In sensitivity analysis, we categorized patients using shorter clinical follow-up as the alternative reference standard to focus on very early treatment failures (only during therapy or < 6 months), or early treatment failures (< 12 months). We counted patients in remission during the specified follow-up period as no treatment failure even if they eventually experienced treatment failure thereafter. We counted early censorings as no treatment failure in the main analysis. In sensitivity analysis to explore a worst-case scenario, early censorings were excluded from the analysis, and then counted as FP if they had negative PET results and were lost to follow-up early without treatment

Table 1. Studies of PET for Interim Response Assessment of Malignant Lymphoma Included in the Systematic Review (continued)

Study	No. of Chemotherapy Cycles Before PET Scan	Duration Between Chemotherapy and PET Scan (days)	No. of Total Participants*	Women		Age (years)	
				No.	%	Median	Range
Advanced-stage HL + DLBCL							
Kostakoglu et al[32]	1	8-15 for HL, 15-22‡ for DLBCL	34§	23†	49	48.21‖	18-76
Advanced-stage HL							
Friedberg et al[33]	3¶	NR	22	NR†	36	NR†	18-60
Hutchings et al[37]	2 or 3	8-15	28	42†	49	36.7†	15-73
Gallamini et al[30]	2	11.6‖	108	57	53	32.8‖	14-78
Hutchings et al[13]	2	8-15	46	28†	36	36	18-74
Zinzani et al[14]	2	NR	40	21	53	32	14-48
Gallamini et al[29]	2	NR	106#	127†	49	32†	14-79
DLBCL							
Spaepen et al[34]	3 or 4#	14†† or 21‡	47	18†	26	40†	3-78
Haioun et al[31]	2	13-14†† or 20-21‡	83	34†	38	53†	17-78
Mikhaeel et al[12]	2 or 3	NR	57	58†	46	55†	20-84
Fruchart et al[35]	2 or 3	12†† or 18‡	35	13†	33	56†	24-77
Querellou et al[36]	2, 3, or 4¶‡‡	15-21‡	21	NR†	33	NR†	17-75
Ng et al[28]	2, 3, or 4§§	12-14†† or 19-21‡	44	21	48	60	27-83

Abbreviations: FDG, fluorodeoxyglucose; ACVBP, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; DLBCL, diffuse large B-cell lymphoma; HL, Hodgkin's lymphoma; NR, not reported; PET, positron emission tomography; R, rituximab.

*Only advanced-stage HL or DLBCL patients were included in this systematic review.

†Data abstracted from total participants of original report, not exclusively for relevant patient population.

‡For tri-weekly cycle chemotherapy [eg, (R-)CHOP].

§Including 10 advanced-stage HL patients and 24 DLBCL patients.

‖Mean.

¶Patients underwent PET at the midpoint of the whole chemotherapy cycles (the end of the second cycle for 4-cycle chemotherapy regimens, the third cycle for 6-cycle regimens, and the fourth cycle for 8-cycle regimens).

#Only patients not included in the previous reports[13,30] were left.

**Only patients in long-term remission.

††For bi-weekly cycle chemotherapy [eg, (R-)ACVBP].

‡‡Eleven patients underwent PET at the end of the fourth cycle.

§§Eleven patients underwent PET at the end of the fourth cycle.

failure. Three studies reported intermediate PET results as minimal residual uptake (MRU).[13–14] We considered this category negative scan in the main analysis because this was how investigators analyzed the results. In sensitivity analyses, MRU results were excluded from analysis, considered positive, considered positive in the case of treatment failure and negative in the case of continuing remission (best-case scenario), and considered negative in the case of treatment failure and positive in the case of continuing remission (worst-case scenario).

We calculated sensitivity, specificity, and likelihood ratios (LRs) for each study. For the estimation of 95% CI, we used the binominal Wilson method for sensitivity and specificity, and normal approximation for LRs. Then we combined summary statistics, 95% confidence regions of summary sensitivity and specificity, and summary receiver operating characteristic (ROC) curves by the hierarchical SROC method,[15] which takes into account both within-study and between-studies variation. We fitted the model by using maximum likelihood estimation implemented in the GLLAMM algorithm[16] in STATA (version 9.2; Stata Corp, College Station, TX), and depicted the summary ROC curves and confidence regions for summary sensitivity and specificity.[17] We estimated the Q^* statistic,[15] the point on the curve where sensitivity equals specificity, as global measures for the summary ROC.

To explore heterogeneity, we performed subgroup analyses by visual assessment of ROC plots and univariate meta-regression analyses. In the meta-regression, we incorporated study design or clinical characteristics as covariates into the bivariate model using Meta-Analyst (Tufts Medical Center, Boston, MA). Our preplanned analyses included characteristics of study design (prospective *v* retrospective), whether studies included more than 10 patients with treatment failure, rates of treatment failure, adoption of combined FDG-PET and computed tomography (FDG-PET/CT), the mean number of chemotherapy cycles before PET, timing of PET scan after the administration of chemotherapy, percentage of high or high-intermediate risk for DLBCL, and percentage of rituximab (R) use for DLBCL. We also performed posthoc analyses on the use of high-dose chemotherapy. Two-sided *P* values lower than .05 were considered to be statistically significant.

RESULTS

Search Results

Online-only Appendix Figure A1 summarizes the search results. We retrieved 23 full reports for further review and contacted nine authors for additional data. We excluded three studies that presented the same participants as previous reports,[18–20] three studies that did not provide information to calculate prognostic accuracy,[21–23] two studies that adopted nondedicated PET scanner,[24,25] one study with fewer than 10 relevant participants,[26] one study with fewer than five patients who progressed or relapsed,[27] and one study that evaluated patients during salvage therapy.[28] One study[29] presented updated results combining previous reports from two independent groups[13,30] together with 106 newly evaluated patients from both groups. In this report, we included only the added subpopulation as an independent study. Three studies reported FDG-PET results at completion of second cycle and fourth cycle of chemotherapy.[13,14,31] We abstracted data only on the second cycle in these studies. One study evaluated

Table 2. Patient Characteristics of Studies of Positron Emission Tomography for Interim Response Assessment of Malignant Lymphoma

Study	Year	No. of Participants Included	Clinical Staging*	Staging Before Therapy (No.)	Standard Prognostic Scores (No.)	Therapy	Use of Rituximab (%)
Advanced-stage HL			Inclusion criteria of advanced-stage		International Prognostic Scores		
Friedberg et al[33]	2004	22	IIB-IVB, any stage with bulky disease		NR	ABVD × 6 or MOPP/ABVD × 6 ± radiotherapy	—
Hutchings et al[37]	2005	28	IIB-IVB, any stage with bulky disease		NR	ABVD × 6 to 8 ± radiotherapy	—
Gallamini et al[30]	2006	108	IIB-IVB, IIA with adverse prognostic factors†		0 pts: 28, 1 pt: 34, 2 pts: 29, 3 pts: 10, 4 pts: 3, ≥ 5 pts: 4	ABVD × 6 or COPP/EBV/CAD × 6 ± radiotherapy	—
Hutchings et al[13]	2006	46	IIB-IVB		Median 3 pts	ABVD × 6 to 8 or comparable anthracycline-containing regimen ± radiotherapy	—
Kostakoglu et al[32]	2006	10	III-IV, any stage with bulky disease‡		0 pts: 3, 1 pt: 2, 2 pts: 4, 4 pts: 1	ABVD × 6	—
Zinzani et al[14]	2006	40	IIB-IVB		NR	ABVD × 6	—
Gallamini et al[29]	2007	106	IIB-IVB, IIA with adverse prognostic factors†		0 pts: 38, 1 pt: 70, 2 pts: 87, 3 pts: 42, 4 pts: 13, ≥ 5 pts: 10§	ABVD × 6, ABVD-like regimen × 6, or COPP/EBV/CAD × 6 ± radiotherapy	—
DLBCL					International Prognostic Indexes		
Spaepen et al[34]	2002	47		IA: 1, IIA: 15, IIB: 6, IIIA: 14, IIIB: 2, IVA: 14, IVB: 20§	L: 26, L-I: 22, H-I: 17, H: 17§	CHOP × 8, biweekly CHOP × 6, CHVmPBV × 8, or COP/COPADM/CYM × 6‖	0
Haioun et al[31]	2005	83		I-II: 8, III-IV: 82§	L: 14, L-I: 23, H-I: 30, H: 23§	(R-)CHOP × 8, R-ACVBP × 4¶, or ACVBP × 4 or ACE × 4#	45
Mikhaeel et al[12]	2005	57		I: 21, II: 14, III: 9, IV: 13	NR	(R-)CHOP × 6 or PMitCEBO × 6**	16
Fruchart et al[35]	2006	35		I-II: 13, III-IV: 27§	L: 13, L-I: 2, H-I or H: 15§	(R-)CHOP × 8 or (R-)ACVBP × 4††	74
Kostakoglu et al[32]	2006	24		I: 2, II: 11, III: 10, IV: 1	L: 16, L-I: 8	R-CHOP × 6 to 8	100
Querellou et al[36]	2006	21		I: 3, II: 2, III: 4, IV: 15§	L: 8, L-I: 5, H-I: 6, H: 5§	(R-)CHOP × 8, R-COP × 6, or (R-)CEEP × 4‡‡	90
Ng et al[38]	2007	44		I: 16, II: 9, III: 5, IV: 14	L: 17, L-I: 9, H-I: 12, H: 1, NA: 5	(R-)CHOP or CHOP-like regimen × 6 to 8, (R-)Hyper-CVAD × 8, or biweekly (R-) CHOP × 6 ± radiotherapy§§	40

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ACE, doxorubicin, cyclophosphamide, etoposide; ACVBP, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone; pts, patients; CAD, lomustine, doxorubicin, vindesine; CEEP, cyclophosphamide, epirubicin, vindesine, prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CHVmPBV, cyclophosphamide, doxorubicin, teniposide, prednisone, bleomycin, vincristine; COP, cyclophosphamide, vincristine, prednisone; COPADM, cyclophosphamide, vincristine, prednisolone, doxorubicin, high-dose methotrexate; COPP, cyclophosphamide, vincristine, procarbazine, prednisone; CVAD, cyclophosphamide, vincristine, doxorubicin, dexamethasone; CYM, cytrabine, high-dose methotrexate; DLBCL, diffuse large B-cell lymphoma; EBV, epirubicin, bleomycin, vinblastine; H, high risk; H-I, high-intermediate risk; HL, Hodgkin's lymphoma; L, low risk; L-I, low-intermediate risk; MOPP, nitrogen mustard, vincristine, procarbazine, prednizone; NR, not reported; PMitCEBO, cyclophosphamide, mitoxantrone, etoposide, prednisolone, vincristine, bleomycin; R, rituximab.

*According to the Ann Arbor staging system.

†> 3 nodal cites, subdiaphragmatic involvement, bulky disease, erythrocyte sedimentation rate > 40 mm/hour.

‡Selected post hoc because of no information on B symptoms.

§Abstracted from total participants of original report, not exclusively for relevant patient population.

‖Some underwent high-dose chemotherapy followed by autologous stem-cell transplantation as consolidation therapy.

¶All received an eight-cycle biweekly consolidation therapy consisting high-dose methotrexate, etoposide, ifosfamide, and cytarabine after the ACVBP regimen.

#All underwent high-dose chemotherapy followed by autologous stem-cell transplantation with or without rituximab maintenance therapy.

**A portion of patients (n = 16) with limited-stage disease underwent 2 to 4 cycles of (R-)CHOP followed by involved field radiation therapy instead of full course (R-)CHOP.

††Patents with one age-adjusted international prognostic risk factor received an eight-cycle consolidation therapy, and patients with two or three factors underwent high-dose chemotherapy followed by autologous stem-cell transplantation.

‡‡All underwent high-dose chemotherapy followed by autologous stem-cell transplantation.

§§A portion of patients (n = 13) with limited-stage disease underwent 2 to 4 cycles of (R-)CHOP or similar regimens followed by involved field radiation therapy instead of full-cycle chemotherapy.

PET at varied timing ranging from the first to fifth cycle.[36] We contacted the investigators for individual patient data, and excluded one patient who underwent PET at the fifth cycle. We found one study[14] through hand searching of the reference lists. As a result, we included 13 studies: eight studies[13,14,29,30,32-35] that met all eligibility criteria and five studies[12,31,36-38] with unpublished data available through contacting the authors (Table 1).[12-14,29-36,38]

Study Characteristics

Thirteen included studies had 360 advanced-stage HL patients and 311 DLBCL patients (Table 1). Eight reports were prospective single- or multi-institutional studies enrolling adults or adolescents. Only one study evaluated both adults and children.[34] Most of the patients in the HL studies underwent PET after receiving two cycles of first-line chemotherapy, while the number of cycles before the PET scan varied in DLBCL studies. In three DLBCL studies, 25% to 52% of included patients underwent PET after the fourth cycle.[34,36,38] One study evaluated PET after one cycle.[32] In general, participants underwent PET during the second week of intended chemotherapy cycle for biweekly chemotherapies (eg, doxorubicin, bleomycin, vinblastine, dacarbazine [ABVD] or (R-) doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone [ACVBP]) and during the third week for triweekly regimens (eg, (R-) cyclophosphamide, doxorubicin, vincristine, prednisone [CHOP]). Four studies performed CT for a portion of patients at the same timing as interim PET but they did not perform direct comparison between the two tests.[13,30,36,38]

For advanced-stage HL studies, fewer than 10% of included patients had unfavorable risk by standard prognostic tool (IPS > 3 points; Table 2). Progression or relapse rates were between 20% and 30% except for one study of 50%.[32] All studies adopted currently available standard first-line chemotherapy: six to eight cycles of ABVD or comparable regimens with or without radiotherapy. For DLBCL studies, the percentage of patients with unfavorable prognosis (high-intermediate to high risk by IPI) ranged from 0% to 59%, with progression or relapse rates of 27% to 47%. Full course (R-) CHOP and (R-) ACVBP were the two most widely adopted regimens. Two studies employed abbreviated course of (R-) CHOP or comparable regimens followed by involved-field radiation for patients with limited-stage disease.[12,36] No patients received rituximab in one study.[34] In four studies, some patients received consolidation auto-transplant after induction chemotherapy.[31,34,35,38]

Concerning imaging techniques and technologies, included studies generally followed guidelines by the Society of Nuclear Medicine (Table 3). One study exclusively adopted combined PET/CT scanner.[38] In five studies, some patients underwent combined PET/CT while the others were evaluated with stand-alone dedicated PET scanner.[13,29,30,32,36] All but one study[34] adopted attenuation correction for image reconstruction.

In general, multiple experienced nuclear medicine physicians interpreted PET results with pretherapy baseline scan as reference. All studies adopted qualitative positive and negative diagnostic criteria with various definitions (online-only Appendix Table A3). Only two studies clearly reported the referential backgrounds to define positive lesion. Five studies defined MRU criterion,[12-14,29,37] which was eventually reported as negative in three studies.[13,14,29] No study reported between-observer variability.

Quality Assessment of Published Studies

Only two studies[13,35] reported all items of the QUADAS tool (online-only Appendix Table A4). Reporting was especially limited in

Table 3. Technical Specification of PET for Interim Response Assessment of Malignant Lymphoma

Study	Year	Preparation: Measurement of Blood Glucose	Procedure: Type of PET Scanner	Procedure: Time of Scan After Injection (minutes)	Procedure: Attenuation Correction	Procedure: Image Reconstruction Method	Procedure: Administered Activity (MBq)
Advanced-stage HL + DLBCL							
Kostakoglu et al[32]	2006	Yes	PET-CT or dedicated	60	Yes	OSEM	370-444
Advanced-stage HL							
Friedberg et al[33]	2004	Yes	Dedicated	50	Yes	OSEM	370
Hutchings et al[37]	2005	Yes	Dedicated	60	Yes	NR	350
Gallamini et al[30]	2006	Yes	PET-CT or dedicated	60	Yes	OSEM or RAMLA	370/70, 259/70, 2*
Hutchings et al[13]	2006	NR	PET-CT or dedicated	45-90	Yes	OSEM	400
Zinzani et al[14]	2006	NR	Dedicated	70-90	Yes	NR	6†
Gallamini et al[29]	2007	Yes	PET-CT or dedicated	60	Yes	OSEM or RAMLA	370/70, 259/70, 2*
DLBCL							
Spaepen et al[34]	2002	Yes	Dedicated	60	No	OSEM	370-555
Haioun et al[31]	2005	Yes	Dedicated	60	Yes	OSEM	2†
Mikhaeel et al[12]	2005	NR	Dedicated	60	Yes	NR	350
Fruchart et al[38]	2006	NR	Dedicated	60	Yes	OSEM	2.5†
Querellou et al[35]	2006	Yes	PET-CT	73 ± 15‡	Yes	OSEM	5.0-7.6†
Ng et al[36]	2007	Yes	PET-CT or dedicated	60-70	Yes	OSEM	5†

Abbreviations: CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; HL, Hodgkin's lymphoma; NR, not reported; OSEM, ordered subsets expectation maximization; PET, positron emission tomography; RAMLA, row-action maximum likelihood algorithm; SUV, standard uptake value.

*Three hundred seventy MBq/70 kg at the centers that used a GE scanner, 259 MBq/70 kg at the centers that used a Philips scanner, and 2 MBq/body weight kg at the centers that used a C-PET scanner.

†Administred activity was reported as the amount per body weight MBq/kg; eg, 360 MBq was administered to a 60 kg patient for 6 MBq/kg).

‡Mean ± standard deviation.