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^{18}F -FDG PET for Posttherapy Assessment of Hodgkin's Disease and Aggressive Non-Hodgkin's Lymphoma: A Systematic Review

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Although studies have shown that ^{18}F -FDG PET, when used to assess the response of malignant lymphoma after treatment, has a strong ability to predict relapse, its diagnostic accuracy in clinical practice remains unclear. The aim of this study was to systematically review the diagnostic accuracy of ^{18}F -FDG PET in detecting residual disease at the completion of first-line therapy of Hodgkin's disease (HD) and aggressive non-Hodgkin's lymphoma (NHL). **Methods:** We searched relevant articles from 1966 to July 2006 using MEDLINE, EMBASE, SCOPUS, Biological Abstracts, bibliographies, review articles, and textbooks without language restriction. One assessor (for non-English-language studies) or 2 assessors (for English-language studies) independently reviewed each article to abstract relevant study characteristics and results. Relevant individual patient data or subgroup data were provided by the investigators if they were unavailable from the publications. We estimated summary receiver operating characteristic curves and confidence regions for summary sensitivity and specificity. **Results:** Nineteen studies consisting of 474 HD and 254 aggressive NHL patients were included. These studies had heterogeneity and suboptimal methodologic quality and reporting. Reported ranges for the sensitivity and specificity of ^{18}F -FDG PET in predicting disease relapse were 0.50–1.00 and 0.67–1.00, respectively, for HD and 0.33–0.77 and 0.82–1.00, respectively, for NHL. These estimates were similar when conventional imaging tests showed a residual mass. For HD studies, the summary receiver operating characteristic curves were similar irrespective of whether a residual mass was detected by conventional tests. Factors explaining the variability of diagnostic estimates were not identified. **Conclusion:** Although currently available evidence is still limited, ^{18}F -FDG PET seems to have good diagnostic accuracy for assessing residual HD at the completion of first-line treatment. Clinical data on this use of ^{18}F -FDG PET for aggressive NHL are more limited. Prospective studies with a more rigorous research design, conduct, and reporting would more reliably reveal the clinical diagnostic accuracy of this imaging modality.

Key Words: ^{18}F -FDG PET; lymphoma; response assessment; residual disease

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Persistence of a mass after completion of first-line therapy is a common problem in assessing the response of both Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL) (1,2). Based on the likelihood of residual disease, clinicians need to proceed to further therapeutic interventions such as applying radiotherapy to the residual mass or salvage chemotherapy with or without high-dose chemotherapy followed by stem cell transplantation. Therefore, more accurate diagnostic tests to distinguish a posttherapy disease mass from fibrosis or scar tissue are needed to reduce the likelihood of unnecessary and potentially toxic therapy (3).

^{18}F -FDG PET is a promising functional imaging test for patients with malignant lymphoma and other malignancies and has gained wide use during the last decade (4). Its routine use has been recommended to assess the posttherapy response of HD, especially if CT reveals a residual mass (3). Others have also recommended its use for the same purpose on the basis of its high negative predictive value for HD and high positive predictive value for NHL (5). A recent survey of physicians caring for lymphoma patients found that intended management plans were often changed on the basis of ^{18}F -FDG PET results (6).

Recently, a systematic review explored the diagnostic accuracy of ^{18}F -FDG PET for this purpose and assessed the quality of the included studies (7). Similar to studies of diagnostic tests in other medical fields, this review revealed several methodologic problems affecting both the internal and the external validity of the published studies. The authors, however, estimated summary diagnostic accuracy without considering the effect of major methodologic variability on diagnostic tests underlying the original studies. For example, some of the studies included a mix of NHL histologies consisting of indolent, aggressive, and highly

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aggressive lymphomas, and others included a mix of patients consisting of those who received first-line therapy and those who received salvage therapy. The diagnostic accuracy estimates reported from these studies have limited external validity and cannot be directly applied to specific clinical scenarios; each distinct histologic subtype has its unique clinical profiles, such as treatment strategies, responses, and prognoses. Also, the review did not consider the different ways that the primary studies presented results (e.g., individual patient vs. each lymphoma lesion, all involved sites vs. only bulky disease, or single vs. multiple inclusions of a patient).

This study was an updated systematic review of the diagnostic accuracy of ^{18}F -FDG PET in assessing the response of HD and aggressive NHL after first-line therapy, with special emphasis on the methodologic issues discussed above.

MATERIALS AND METHODS

Study Identification

We searched MEDLINE and EMBASE from January 1966 through July 2006 without language restriction. The detailed search strategy can be found in Supplemental Table 1 (supplemental materials are available online only at <http://jnm.snmjournals.org>). This search was augmented by SCOPUS and Biological Abstracts. We also manually reviewed the reference lists of eligible studies, review articles, and textbooks.

Study Selection

Two of us reviewed the pertinent studies to determine eligibility. We included prospective or retrospective studies evaluating posttherapy response assessment by ^{18}F -FDG PET exclusively for patients with HD or aggressive NHL followed by clinical follow-up, with or without pathologic confirmation as a reference standard. We included studies that evaluated at least 10 patients. We considered aggressive NHL to be mantle cell lymphoma; follicular center lymphoma, grade III; diffuse large B-cell lymphoma (DLBCL); primary mediastinal large B-cell lymphoma; peripheral T-cell lymphoma, unspecified; angioimmunoblastic T-cell lymphoma; angiocentric lymphoma; and anaplastic large cell lymphoma, T- and null-cell type by the Revised European-American Classification of Lymphoid Neoplasms (REAL)/World Health Organization classification, or corresponding subcategories for the International Working Formulation classification, the Kiel classification, or the Rappaport classification (8). We included studies of only those patients who completed first-line chemotherapy, radiotherapy, or combined-modality therapy and underwent conventional imaging tests such as CT, ultrasonography, or MRI for posttreatment restaging just before or after undergoing PET. We focused our analysis on studies that reported individual patients as the unit of analysis irrespective of the number of relapses or of the sites of relapse or residual disease, because this is the most appropriate perspective for clinical decision making. We excluded abstracts, editorials, comments, letters, review articles, and case reports. We excluded studies enrolling patients with HIV-associated or post-transplant lymphoproliferative disorders.

Many studies did not meet all the rigorous inclusion criteria but did partially include a relevant patient population. For these studies, we contacted the authors by mail or email to ask for individual patient data or subgroup data relevant to our inclusion criteria. When there was no response within 3 wk, another correspondence was

sent. When there was no response to the third communication attempt, we considered the request rejected.

Data Abstraction

Two independent, board-certified hematologists abstracted relevant data for English-language articles. For non-English-language articles, data were extracted by a single reviewer working with a physician native speaker of the relevant language. We used an abstraction form consisting of items recommended in the Standards for Reporting of Diagnostic Accuracy (9). One nuclear medicine specialist evaluated the technical specifications and quality of the PET procedure by using recommended guidelines (10). The reviewers knew in which journals the studies had been published. Based on the enrollment of participants before PET, we categorized studies into 2 groups: "posttherapy evaluation," or studies that included patients irrespective of restaging results on conventional imaging tests, and "residual mass evaluation," or studies that evaluated only patients for whom visible residual mass lesions were shown on conventional imaging tests. In the posttherapy evaluation, we also abstracted the data on the subgroup of patients who had a residual mass shown on imaging. If the relevant data were unavailable from the published literature, we contacted the authors of the paper to request the subgroup data. Inconsistencies between reviewers were either clarified by the paper authors or resolved by consensus.

Assessment of Study Quality and Applicability

To evaluate the quality and applicability of the studies included in this review, we used an established quality rating system for diagnostic studies (11) and a recently proposed quality evaluation tool (12). In the established system, we examined 6 aspects of study quality: quality and application of the reference standard, independence of test interpretation, description of patient characteristics, cohort assembly, and sample size. We then rated each study as "a" (the highest quality), "b," "c," or "d" (the lowest quality) according to the predefined score. The recently proposed quality evaluation tool, which was designed exclusively for studies of diagnostic accuracy, comprehensively explores both methodologic quality and reporting. The tool consists of 14 items addressing patient spectrum, reference standard, disease progression bias, partial and differential verification bias, test review bias, clinical review bias, incorporation bias, test execution of both index test and reference standard, study withdrawals, and indeterminate test results.

Data Synthesis and Statistical Analysis

For each study, we constructed a 2×2 contingency table consisting of true-positive, false-positive, false-negative, and true-negative, where all patients were categorized as being PET-positive or -negative and as being positive or negative for disease according to the results determined through ^{18}F -FDG PET and the reference standard, respectively. We defined as disease-positive a patient who had biopsy-confirmed residual disease or whose disease had relapsed during clinical follow-up. We did not independently combine the sensitivity and specificity of the included studies because this approach does not take into account the interdependence of these 2 test parameters. We instead estimated summary receiver operating characteristic (ROC) curves and elliptical 95% confidence regions of summary sensitivity and specificity by the hierarchical summary ROC method (13). This model is a more sophisticated approach than the conventional linear regression model to compute summary diagnostic measures taking account of variations both within a study and between studies. We fitted the model by using maximum-

likelihood estimation implemented in the NLMIXED procedure of SAS/STAT (version 8; SAS Institute) (14). Then, we depicted the summary ROC curves and confidence regions for summary sensitivity and specificity by using Stata (version 8.2.; Stata Corp.) (15). Also, we estimated the area under the curve and the Q* statistic, the point on the curve where sensitivity equals specificity, as global measures for the summary ROC curves. We explored heterogeneity between studies by visual assessment of ROC plots for the following predetermined items: study design (prospective vs. retrospective), rates of patients with residual mass as found on conventional imaging tests, relapse rates, follow-up period, timing of PET scan after completion of therapy, and publication year. We also performed post hoc subgroup analyses for the items used for the technical specifications of PET and quality assessment.

RESULTS

Study Characteristics

We included 19 studies: 9 studies (16–24) that met all eligibility criteria and 10 studies (25–34) with relevant published data or with unpublished data obtained by contacting the authors of the paper (Table 1). The detailed process by which articles were selected can be found in the Supplemental Appendix and in Supplemental Figure 1. Because one group of researchers reported a “residual therapy evaluation” for HD and aggressive NHL and a “posttherapy evaluation” exclusively for aggressive NHL—and included in both groups the data on some participants (23,29)—we separately extracted the relevant data. Another group of researchers published an updated “post-therapy evaluation” for HD, with some participants overlapping from the previous report (27,31). We contacted the principal investigator and obtained updated combined results. For 5 studies that reported both HD and aggressive NHL (25–28,30), the contacted investigators provided unpublished subgroup data for each category. As a result, we finally had for further evaluation 15 studies consisting of 474 patients with HD and 8 studies consisting of 254 patients with aggressive NHL (Table 2).

Most studies were retrospective (Table 1). Four studies exclusively evaluated patients for whom a posttherapy visual residual mass was found on conventional imaging tests (25,29,32,34). Generally, patients underwent PET 1–3 mo after completing therapy, but some underwent PET at less than 1 mo. Most studies included both adult and adolescent patients, but 3 studies also included pediatric patients (16,21,24).

For HD studies, nodular sclerosis was the leading histologic subcategory and either ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) or MOPP (nitrogen mustard, vincristine, procarbazine, prednisone) plus ABVD or ABV (doxorubicin, bleomycin, vincristine) with or without radiotherapy was the most widely reported first-line treatment (Table 2). In posttherapy evaluations, 35%–72% of patients were found to have a residual mass on conventional imaging (Supplemental Table 2). Relapse rates were similar for both posttherapy evaluations and residual mass evaluations, ranging from 4% to 55% and 0% to 50%, respectively.

For aggressive NHL studies, DLBCL was the leading histologic subcategory, and the most widely adopted first-line therapy was CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or comparable doxorubicin-containing regimens with or without radiotherapy (Table 2). In posttherapy evaluations, 26%–56% of patients were found to have a residual mass on conventional imaging (Supplemental Table 2). Relapse rates were 33%–60% for posttherapy evaluations and 33%–67% for residual mass evaluations.

Concerning imaging techniques and technologies, although their reporting was limited, the included studies generally followed the guidelines of the Society of Nuclear Medicine for performing ^{18}F -FDG PET (Supplemental Table 3). Only a single study used PET/CT (30). Most studies adopted qualitative diagnostic criteria: foci of elevated ^{18}F -FDG uptake unexplained by physiologic uptake. Two studies (32,34) also adopted quantitative diagnostic criteria: standardized uptake values (the ratio of ^{18}F -FDG uptake in tumor sites to that in normal sites). Only 2 studies clearly reported that all the included participants underwent pretherapy PET (17,23). Generally, experienced nuclear medicine physicians interpreted the results.

Sensitivity, Specificity, and Summary ROC Curves

HD studies reported widely ranging sensitivities and specificities for ^{18}F -FDG PET. For posttherapy evaluations, sensitivity ranged from 0.50 to 1.00 and specificity ranged from 0.67 to 1.00 (Supplemental Table 2; Fig. 1). For residual mass evaluations, reported estimates had a similarly wide range: 0.43–1.00 for sensitivity and 0.67–1.00 for specificity. The summary ROC curves and confidence regions for summary sensitivity and specificity for posttherapy evaluations and residual mass evaluations were similar (Fig. 2): The area under the curve for the summary ROC curve was 0.94 for posttherapy evaluations and 0.93 for residual mass evaluations, and the Q* statistic was 0.88 for posttherapy evaluations and 0.86 for residual mass evaluations.

Studies of aggressive NHL also reported a widely ranging sensitivity but a narrower high specificity. For posttherapy evaluations, sensitivity ranged from 0.33 to 0.77 and specificity ranged from 0.82 to 1.00 (Supplemental Table 2; Fig. 1). For residual mass evaluations, sensitivity ranged from 0.33 to 0.87 and specificity ranged from 0.75 to 1.00. We did not perform the metaanalysis because there were too few data points to reliably estimate the summary ROC curves and confidence regions for summary sensitivity and specificity.

Investigating Heterogeneity

We did not identify any clinical or ^{18}F -FDG PET test characteristics, or any items that assessed the quality and applicability of each study, to explain the heterogeneity of sensitivity and specificity (data not shown).

Quality Assessment of Published Studies

Overall, the quality and reporting of the included studies were limited (Supplemental Table 4), suggesting that they are subject to bias and variation limiting the internal and

TABLE 1
Studies Included in the Systematic Review

Study	Clinical indication	Study design	Time from therapy completion to PET (mo)			Follow-up (mo)			No. of patients	No. of female patients	Age (y)		Exclusion of patients with PIF or PD during treatment
			Median	Range	Median	Range	Median	Range					
HD and NHL													
de Wit et al. (25)	Residual mass	Retrospective	2	<10	13	1-26	34	NR	NR	43	21-73	NR	
Foo et al. (26)	Posttherapy	Retrospective	NR	NR	NR or 13*	3-65	24†	33%‡	33%‡	33‡	20-67	NR	
Jerusalem et al. (27)	Posttherapy	Prospective	NR	1-3	23 or 21*	NR	54	27 (50%)	27 (50%)	47	15-80	Yes	
Mikosh et al. (28)	Posttherapy§	Retrospective	NR	>1	NR	>12	93	NR	NR	NR	NR	NR	
Mikhaeel et al. (29)	Residual mass	Retrospective	NR	<1	38	16-68	32	31 (31%)	31 (31%)	NR	NR	NR	
Schaefer et al. (30)	Posttherapy†	Retrospective	3	NR	9.3#	NR	41†	38%‡	38%‡	39.6*	NR	NR	
HD													
Filmon et al. (16)	Posttherapy	Retrospective	5.2	1-87	14	6-39	32	22 (53%)	22 (53%)	30	6-65	NR	
Friedberg et al. (17)	Posttherapy	Prospective	NR	<1	24	10-32	32†	36%‡	36%‡	30‡	18-60	NR	
Guay et al. (18)	Posttherapy	Retrospective	2	0-55	15	1-60	48	25 (50%)	25 (50%)	38	17-78	NR	
Jerusalem et al. (31)	Posttherapy§	Prospective	1	NR	NR§	NR	36	23 (64%)#	23 (64%)#	28	13-71	Yes	
Keresztes et al. (32)	Residual mass	Retrospective	3#	2-5	50 or 62**	5-98	31†	42%‡	42%‡	31 or 37**	13-70	NR	
Mocikova et al. (33)	Posttherapy	Retrospective	NR	NR	25	NR	94	44 (47%)#	44 (47%)#	30	28-85	NR	
Rigacci et al. (19)	Posttherapy	Prospective	4	2-8	45	NR	28	14 (50%)	14 (50%)	30.6	16-73	NR	
Spaepen et al. (20)	Posttherapy	Retrospective	NR	1-3	30	12-48	60	33 (45%)	33 (45%)	35	11-75	NR	
Wehrauch et al. (34)	Residual mass§	Prospective	NR	<4	28	16-68	28	8 (26%)	8 (26%)	36	18-76	NR	
Wickmann et al. (21)	Posttherapy	Retrospective	NR	0-7	32	1-56	48	36	36	NR	<18	NR	
NHL													
Juwaid et al. (22)	Posttherapy	Retrospective	1	0-5	35	25-60	54	NR	NR	58	21-79	No	
Mikhaeel et al. (23)	Posttherapy	Retrospective	NR	<2	30	7-56	45†	37%‡	37%‡	NR	NR	Yes	
Spaepen et al. (24)	Posttherapy	Retrospective	NR	1-3	21	11-50	93	34 (37%)	34 (37%)	47	2-77	NR	

*Patients without or with residual mass, respectively.

†Only subset of participants who were evaluated with PET after completion of therapy.

‡Data abstracted from total participants, not limited to patients who were evaluated with PET at end of therapy.

§Some PET scans were taken at the end of salvage therapy.

||Some participants underwent PET multiple times.

¶Each lymphoma lesion was evaluated as the unit of analysis.

#Mean.

**Patients with or without bulky mass before therapy, respectively.

NR = not reported; PD = progressive disease; PIF = primary induction failure.

TABLE 2
Patient Characteristics for Studies Included in the Systematic Review

Study	No. of patients*	Histologic class	Pretherapy stage†	Type of therapy
HD				
de Wit et al. (25)	5	NA	NA	Chemotherapy ± radiotherapy
Filimon et al. (16)	32	22 NS, 7 MC, 2 LP, 1 LD	NA	Chemotherapy ± radiotherapy ± surgery or autologous transplantation
Foo et al. (26)	9	7 NS, 1 MC, 1 unclassifiable	8 II, 1 III	Chemotherapy ± radiotherapy
Friedberg et al. (17)	32	20 NS, 6 MC, 3 LP, 7 unclassifiable	3 I, 23 II, 6 III, 4 IV	ABVD or MOPP + ABVD ± radiotherapy
Guay et al. (18)	48	NA	2 I, 23 II, 15 III, 8 IV	MOPP or ABVD ± radiotherapy
Jerusalem et al. (27,31)	31	27 NS, 3 MC, 1 LD	NA	Chemotherapy ± radiotherapy
Keresztes et al. (32)	26	NA	NA	C-MOPP + ABVD or C-MOPP + ABV + CEP ± radiotherapy
Mikosch et al. (28)	31	NA	NA	Chemotherapy ± radiotherapy
Mikhaeel et al. (29)	15	NA	8 I + II, 7 III + IV	ABVD ± radiotherapy
Mocikova et al. (33)	71	NA	NA	Chemotherapy ± radiotherapy
Rigacci et al. (19)	28	22 NS, 5 MC, 1 LD	21 II, 5 III, 2 IV	ABVD ± radiotherapy
Schaefer et al. (30)	18	17 NS, 1 MC	NA	NA
Spaepen et al. (24)	60	45 NS, 9 MC, 3 LP, 3 unclassifiable	25 II, 19 III, 16 IV	Stanford V or MOPP + ABV ± radiotherapy
Wehrauch et al. (34)	20	NA	1 I, 9 II, 7 III, 2 IV	ABVD, C-MOPP + ABVD, or BEACOPP ± radiotherapy‡
Wickmann et al. (21)	48	NA	NA	GPOH-HD 95§
Aggressive NHL				
de Wit et al. (25)	6	Aggressive by REAL/WHO criteria	NA	Chemotherapy ± radiotherapy
Foo et al. (26)	12	11 diffuse large, 1 PTCL	3 I, 5 II, 2 III, 2 IV	Chemotherapy ± radiotherapy
Jerusalem et al. (31)	35	27 DLBCL, 8 FL grade 3	NA	Chemotherapy ± radiotherapy
Juweid et al. (22)	54	47 diffuse large cell, 4 ALCL, 2 diffuse mixed, 1 angioimmunoblastic T-cell	19 I + II, 35 III + IV	22 CHOP, 29 R-CHOP, 2 ProMACE-CytaBOM, 1 CNOP
Mikosch et al. (28)	24	Aggressive by REAL/WHO criteria	NA	Chemotherapy ± radiotherapy
Mikhaeel et al. (23)	45	"Aggressive" (diffuse mixed, diffuse large cell, large cell immunoblastic)	30 I + II, 19 III + IV	Radiotherapy only or CHOP ± radiotherapy
Schaefer et al. (30)	5	5 DLBCL	NA	NA
Spaepen et al. (24)	73	50 DLBCL, 8 ALCL, 7 ALCL HD-like, 5 MCL, 3 PTCL	NA	Doxorubicin-containing regimen or UKCCSG protocol (pediatric cases)

*Who met inclusion criteria of this systematic review.

†According to Ann Arbor staging system.

‡Eight relapsed cases (excluded) received salvage therapy with or without high-dose therapy followed by stem-cell transplantation.

§Treatment strategy for HD in children and adolescents (35).

||Data abstracted from total participants, not limited to patients who were evaluated with PET at end of therapy.

ALCL = anaplastic large cell lymphoma; BCL = B-cell lymphoma; BEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; CEP = follicular lymphoma; LD = lymphocyte depleted; LP = lymphocyte predominance; MC = mixed cellularity; MCL = mantle cell lymphoma; NA = not available; NS = nodular sclerositis; ProMACE-CytaBOM = prednisone, cyclophosphamide, doxorubicin, etoposide, cytarabine, bleomycin, vincristine, methotrexate; PTCL = peripheral T-cell lymphoma; R-CHOP = rituximab plus CHOP; Stanford V = doxorubicin, vinblastine, mechlorethamine, vincristine, etoposide, bleomycin, cyclophosphamide, procarbazine, prednisone; UKCCSG = United Kingdom children cancer study group; WHO = World Health Organization.

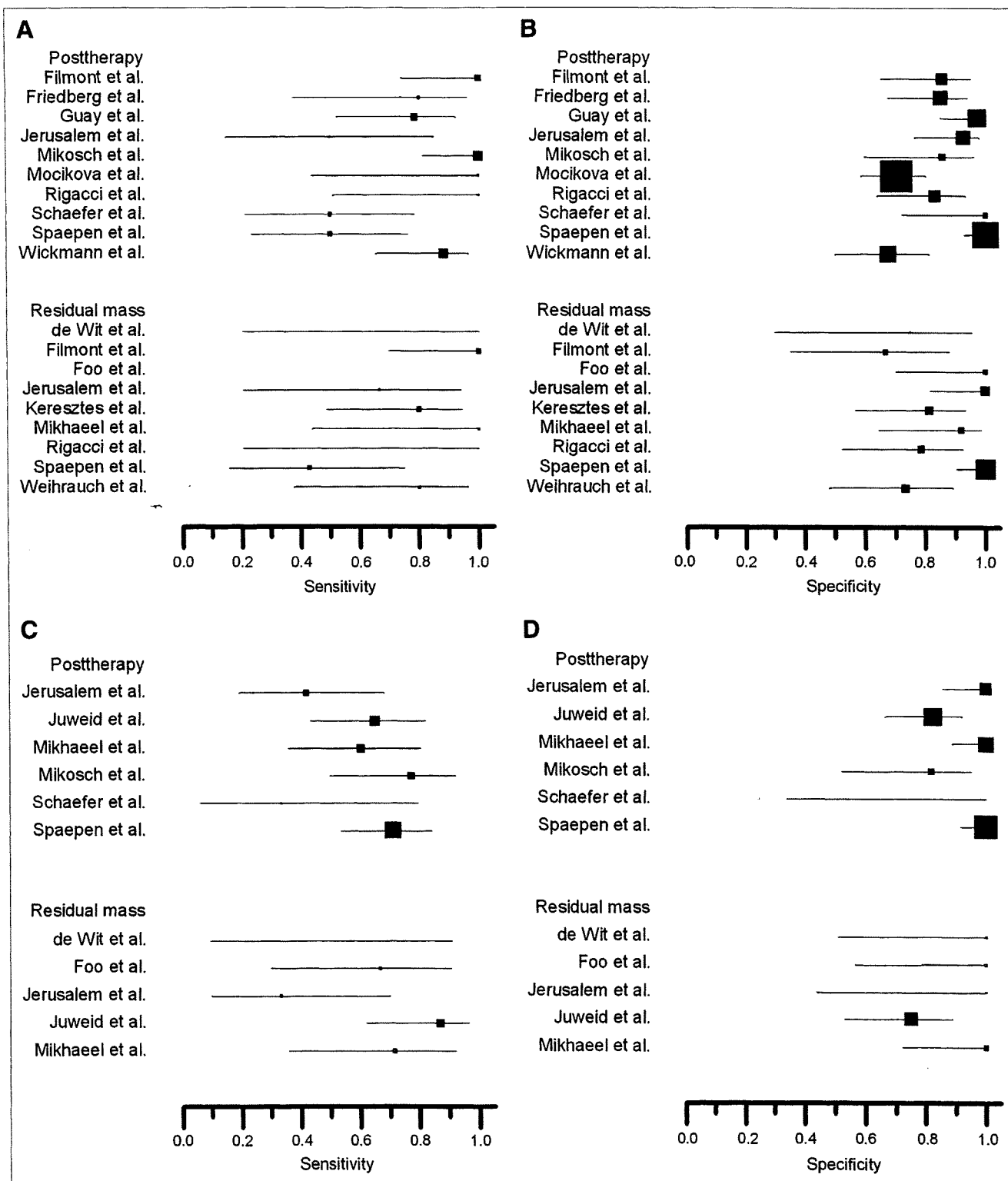


FIGURE 1. Sensitivity and specificity for HD (A and B) and aggressive NHL (C and D). Size of square plotting symbol is proportional to sample size (for sensitivity, number of patients who relapsed; for specificity, number of patients in remission) for each study. Horizontal lines are 95% confidence intervals. One study (Foo et al.) is omitted for sensitivity for HD because there were no cases of relapse.

external validities, respectively, of the test results. The detailed results of the quality assessment can be found in the Supplemental Appendix.

DISCUSSION

This systematic review showed that the reported sensitivities and specificities of ¹⁸F-FDG PET to assess residual

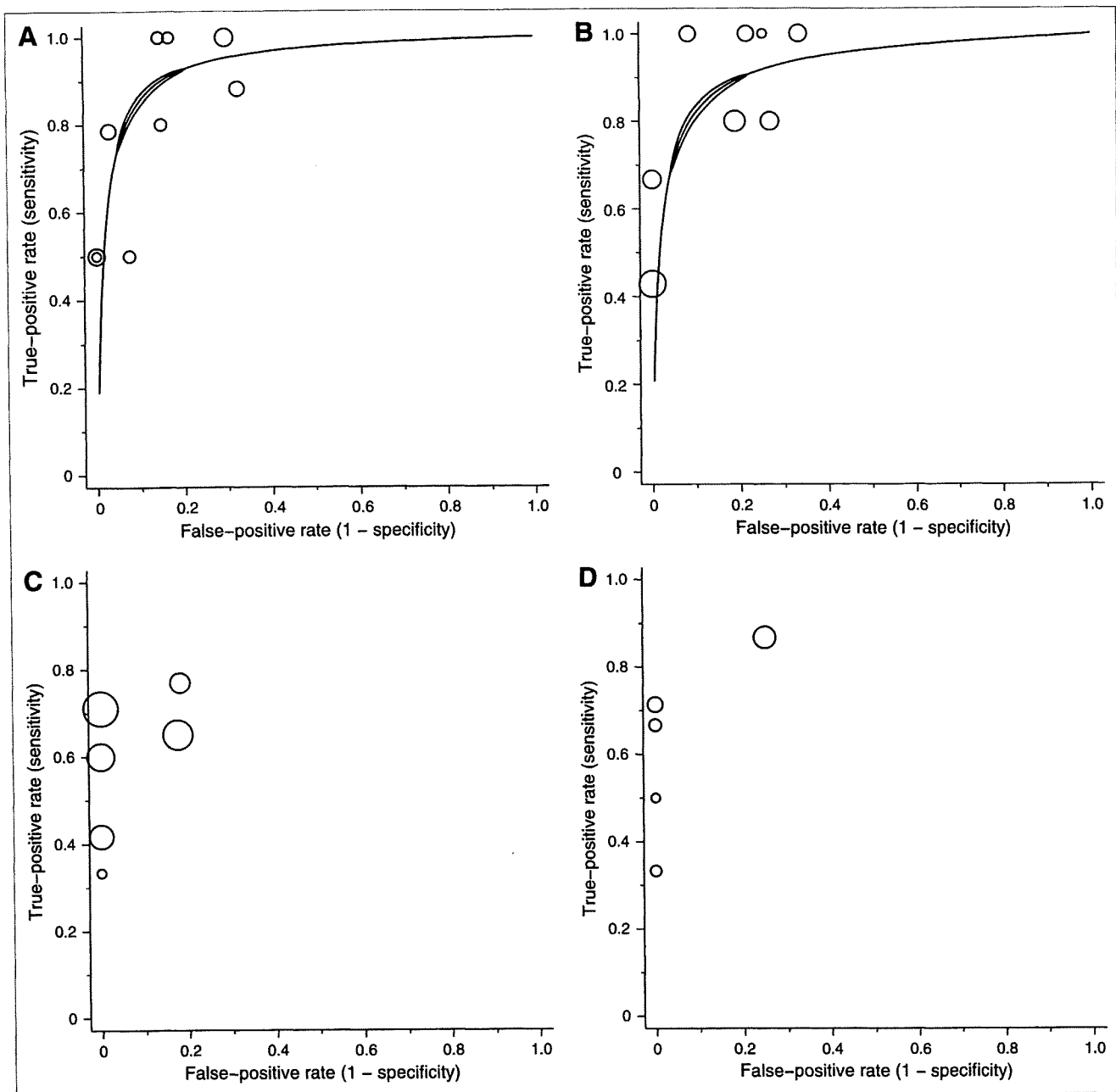


FIGURE 2. ROC plotting and summary ROC curve of ^{18}F -FDG PET for HD and aggressive NHL. Individual study estimates of sensitivity and $1 - \text{specificity}$ are shown for posttherapy evaluation and residual mass evaluation of HD (A and B) and aggressive NHL (C and D). Size of each circle is proportional to sample size for each study (all study participants). Solid crescent boundary represents 95% confidence region for summary sensitivity and specificity.

disease for patients with HD who completed first-line chemo- or chemoradiotherapy had large between-study heterogeneity. In addition, the summary ROC curves and confidence regions for sensitivity and specificity showed similar and good overall diagnostic accuracy irrespective of the presence of a visible residual mass on conventional imaging modalities such as CT or MRI. For aggressive NHL, although our review showed a relatively stable high specificity and variable sensitivity, there were too few studies to calculate a reliable overall diagnostic accuracy.

Many potential factors may explain the heterogeneity. For test characteristics, differences in the type of PET scanner, in the timing of PET after the completion of therapy, in positive test criteria, and in the clinical experience of the interpreters are relevant. For patient characteristics, several differences should be considered: in the type of histology, especially for aggressive NHL (e.g., DLBCL vs. other aggressive NHLs); in therapeutic strategy (e.g., chemotherapy vs. combined-modality therapy); in the presence or absence of a visible residual mass on conventional imaging tests; and in relapse

risk groups, such as the international prognostic score for advanced-stage HD (36) or the international prognostic index for aggressive NHL (8). For study characteristics, differences such as method of patient selection (e.g., prospective vs. retrospective), type and application of a reference standard, and patient follow-up have been reported to affect the variability of sensitivity and specificity (9,37). Because the available data were limited, we could not identify specific factors that explain the heterogeneity, which should be further addressed in future studies. Although the reported positive PET criteria appeared almost identical in all HD studies, the large crescent shape of the confidence regions implies a negative correlation between sensitivity and specificity across the included studies, suggesting that a variation in threshold may partially explain the between-study heterogeneity.

Our study had several important limitations. Because we selected only those studies for which pertinent data were available, several important investigations (some of which were included in the previous metaanalysis) may have been excluded. Also, because most data were derived from retrospective studies with poor-quality design and reporting, our conclusions are subject to the bias and variations in the original studies (37). In addition, our review included only a single study in which patients with DLBCL received rituximab in addition to CHOP (22). Because the combination of rituximab with CHOP is a current standard therapy (38), our results may be less applicable to clinical practice. Further, we included only a single study (30) that used a relatively new and promising additional technique—PET/CT—that may overcome the current technical limitations of PET (39).

In the recently revised consensus recommendations, ^{18}F -FDG PET has become an important component of posttherapy response assessments in clinical trials for HD and DLBCL (40). Although the currently available data have limitations, our systematic review would probably support the clinical relevance of the response criteria for high-risk HD; incomplete response defined by positive PET findings would have an excellent ability to predict relapse irrespective of whether a residual tumor mass is found on conventional imaging. For favorable-risk HD, patients labeled as incomplete responders after first-line therapy should still have a moderate possibility of long-term remission. Thus, clinical investigators adopting the recommendations into therapeutic efficacy trials would need to decide how to manage patients in this category before implementing the trials. For DLBCL and other aggressive NHLs, our results based on the limited clinical evidence would not suffice to support the criteria, and further research is necessary to validate them.

Our review shows that currently available data do not suffice to answer the phase 3 question of diagnostic accuracy studies: What is the diagnostic accuracy of ^{18}F -FDG PET for posttherapy response assessment of malignant lymphoma? (41). Reliable clinical evidence is especially limited for aggressive NHL. Further investigation should include prospective diagnostic accuracy studies (phase 3) of PET or

PET/CT that adopt a more rigorous research methodology. We propose that, ideally, diagnostic accuracy studies should accompany prospective clinical trials to answer efficacy questions. Data on additional therapy, such as involved-field radiotherapy or high-dose chemotherapy with autotransplantation, for posttherapy PET-positive patients are limited. Before the routine clinical implementation of a treatment strategy based on posttherapy PET findings, randomized studies should assess the impact on patients' clinical outcomes, if appropriate (phase 4) (41). Also, determination of the cost-effectiveness of treatment strategies adopting PET is necessary to allow a better understanding of the role of posttherapy PET.

CONCLUSION

The currently available data show that ^{18}F -FDG PET has good overall accuracy in detecting residual disease in patients with HD who have completed first-line therapy. The current literature has methodologic weaknesses that may overestimate accuracy. Because data from original studies are limited, our review could not find robust evidence to answer the question of whether clinicians should routinely use PET to assess the posttherapeutic response, suggesting that they should be cautious about making clinical decisions based solely on a PET result.

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Clinicopathological features of pyothorax-associated lymphoma; a retrospective survey involving 98 patients

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To investigate clinicopathological features of pyothorax-associated lymphoma (PAL), we examined medical records of 98 patients (88 males and 10 females) with PAL at a median age of 70 years (range 51–86). Seventy-nine patients had a history of artificial pneumothorax. Median interval between diagnosis and artificial pneumothorax was 43 years (range 19–64). At diagnosis, performance status (PS) was 0–1 ($n = 56$) and 2–4 ($n = 42$). Clinical stages were I ($n = 42$), II ($n = 26$), III ($n = 8$) and IV ($n = 22$). Pathological diagnosis comprised diffuse large-B-cell ($n = 78$) and peripheral T-cell lymphoma ($n = 1$). Seventeen were treated supportively. The other 81 received aggressive treatments; chemotherapy ($n = 52$), radiotherapy ($n = 7$), surgery ($n = 4$) and combination ($n = 18$). Five-year overall survival (OS) was 0.35 (95% confidence interval, 24% to 45%). Causes of deaths were PAL ($n = 39$), respiratory failure ($n = 13$) and others ($n = 12$). Multivariate analysis identified prognostic factors for OS; lactate dehydrogenase levels [hazard ratio (HR) = 2.36; $P = 0.013$], sex (female versus male) (HR = 0.15; $P = 0.01$), PS (2–4 versus 0–1) (HR = 2.20; $P = 0.02$), clinical stages (III/IV versus I/II) (HR = 1.95; $P = 0.037$) and chemotherapy (HR = 0.31; $P = 0.01$). Most patients with PAL are elderly and have comorbidities, while some of them achieve durable remission with appropriate treatments. These findings prompt us to establish an optimal treatment strategy on the basis of risk stratification of individual patients.

Key words: artificial pneumothorax, diffuse large B-cell lymphoma, Epstein–Barr virus, malignant lymphoma, tuberculosis

introduction

Pyothorax-associated lymphoma (PAL) is a lymphoproliferative disorder developing in the pleural cavity after a long-standing history of pyothorax. While the pathogenesis, clinical features and optimal treatment have not been clarified, PAL represents an entity distinct from other malignant lymphomas [1]. PAL usually develops in patients who have undergone artificial pneumothorax for the treatment of pulmonary tuberculosis, and the interval between the operation and development of PAL has been reported to be 22–55 years [1–7]. Most studies on PAL are reported from Japan, but occasionally from other Asian [8]

and Western countries [9] in the recent literature. Artificial pneumothorax, as a form of surgical treatment of lung tuberculosis, had been more widely carried out in Japan than in the Western countries, especially in the 1930s to 1950s [10]. Artificial pneumothorax is the most significant risk factor for development of PAL [10]. Approximately 2% of patients with chronic pyothorax develop PAL [7]. In the majority of these patients, the lymphoma cells are classified as large atypical B cells, and they express latent gene products of Epstein–Barr virus (EBV) [11, 12].

Optimal management of PAL is unclear. In Japan, ~70% of patients with PAL receive chemotherapy and/or radiotherapy [1]. Recent studies showed that PAL is responsive to chemotherapy [6] and radiotherapy, but the overall prognosis is poor, with a 5-year survival of 21.6% [6]. Some case series

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indicated that surgical interventions including open-window thoracostomy and pleuropneumectomy are beneficial for the treatment of PAL [1]; however, their studies are too small to make a definite conclusion. Since most patients with PAL are elderly and/or have comorbidities, invasive approaches are not feasible options in these patients. Treatment strategy of PAL must be established on the basis of the risk stratification of individual patients. We reviewed 98 cases of patients with PAL to investigate its clinicopathological features, treatment outcomes and prognostic factors.

patients and methods

patient selection and clinical records

We collected data from a total of 139 cases of PAL from 88 collaborating institutions. Clinical, pathological, immunophenotypic and karyotypic data were obtained from patients' records, autopsy request forms and pathological reports in 98 patients. Four cases were reported previously in the nationwide retrospective analysis in Japan [2, 6]. All the patients were diagnosed from November 1980 to May 2001. Performance status (PS) was evaluated by using Eastern Cooperative Oncology Group (ECOG) PS [13]. International Prognostic Index was evaluated as previously described [14].

Histological diagnosis was done on the basis of institutional diagnosis. Discrepancies in nomenclature among centers were resolved according to the synonyms in the World Health Organisation classification [15].

diagnostic criteria of PAL

PAL was defined as lymphoma developing in the pyothorax with or without involvement of regional lymph nodes or other visceral tissues [6]. Diagnosis of PAL was made by pathological examination of biopsy specimens obtained from the lesion in the pleural cavity or autopsy. Diagnosis of PAL was not established in patients without lesions in the pleural cavity or those without a history of pyothorax. Clinical stages were evaluated according to the proposed criteria [16].

end points and statistical analysis

The end points of this study are to (i) describe clinicopathological features of PAL, (ii) clarify its prognostic factors and (iii) investigate its optimal treatment. The probability of survival was calculated as a function of time with the Kaplan–Meier method. The estimated survival was calculated as of 31 July 2001. A log-rank test was applied to assess the impact by the factor of interest when appropriate. Uni- and multivariate Cox proportional hazard models were applied to assess the impact of potential prognostic factors. Multivariate model was built with forward/backward stepwise method using threshold *P* value for removal and adding in the model as 0.20 and 0.10, respectively. We applied *P* value <0.05 as statistical significance. All the analyses were conducted by STATA version 9.2 (STATA Corp., College Station, TX).

results

patients' characteristics

Patients' characteristics at the diagnosis of PAL are shown in Table 1. There were 88 males and 10 females, and their median age was 70 years (range 51–86). Seventy-nine patients (81%) had a history of artificial pneumothorax, and median interval between diagnosis of PAL and artificial pneumothorax was 43 years (range 19–64). At the diagnosis of PAL, PS was 0–1 (*n* = 56) and 2–4 (*n* = 42), and 49 patients (50%) had B

Table 1. Patient characteristics at the diagnosis of PAL

Variables	
Patient background	
Number of patients	98
Median age (range), years	70 (51–86)
Sex (male/female)	88/10
Artificial pneumothorax ^a	79
Median age at the onset of pyothorax (range), years	30 (14–50)
Side of pyothorax (right/left/unknown)	40/57/1
Interval between pyothorax and development of PAL, median (range), years	43 (19–64)
Clinical stage (I/II/III/IV)	42 ^b /26/8/22
B symptoms (present/absent)	49/49
LDH, median (range), IU/l	523 (109–3100)
IPI (low risk/low-intermediate risk/high-intermediate risk/high risk)	5/21/33/39
ECOG PS (0/1/2/3/4)	21/35/20/15/7
Immunohistochemical characteristics of lymphoma cell	
CD3 (positive/negative)	0/43
CD4 (positive/negative)	0/6
CD5 (positive/negative)	1/6
CD8 (positive/negative)	0/6
CD10 (positive/negative)	1/6
CD20 (positive/negative)	41/2
CD30 (positive/negative)	3/8
CD33 (positive/negative)	0/8
CD34 (positive/negative)	0/7
CD43 (positive/negative)	4/5
CD56 (positive/negative)	0/6
CD79a (positive/negative)	14/1

^aInformation was not available in one patient.

^bAll are classified as stage IE.

ECOG: Eastern Cooperative Oncology Group; IPI: International Prognostic Index; LDH: lactate dehydrogenase; PAL: pyothorax-associated lymphoma; PS: performance status.

symptoms. Clinical stages were I (*n* = 42), II (*n* = 26), III (*n* = 8) and IV (*n* = 22).

pathological examination

In situ hybridization using a probe for EBV-encoded RNA-1 demonstrated the presence of the EBV genome in the nucleus of tumor cells in 28 of 29 (88%) patients. Immunohistochemical studies revealed that 12 of 14 (86%) and 11 of 17 (65%) patients were positive for Epstein–Barr virus nuclear antigen (EBNA)-2 and latent membrane protein (LMP)-1, respectively. Immunohistochemical analysis for human herpes virus (HHV)-8 detection in lymphoma cells was not conducted.

Information on pathological diagnosis was available in 79 patients. The diagnosis included diffuse large B-cell lymphoma (*n* = 78) and peripheral T-cell lymphoma (*n* = 1). Immunohistochemical characteristics of lymphoma cells are shown in Table 1. Information on cytogenetic analysis was obtained in seven patients. Two patients had a normal karyotype. One patient had the abnormality of dicentric

(15;18)(p11:p11). The remaining four patients had a complex karyotype, including 56-64, XX, -X, add(1)(q11), add(4)(q31) ($n=1$), add(3)(p11), -18, +mar ($n=1$) and hyperdiploid with abnormality of 3p, 8q, 15p ($n=1$). The information was not available in one patient.

treatment and outcomes

Seventeen patients (17%) were treated supportively, and the other 81 patients (83%) received aggressive treatments

Table 2. Clinical stage and outcome

Variables	Stage I	Stage II	Stage III-IV
Number of patients	42	26	30
ECOG PS (0/1/2/3/4)	14/18/8/1/1	4/12/4/5/1	3/5/8/9/5
Treatment of PAL			
Aggressive therapy ^a			
Chemotherapy	15 ^b	18 ^c	19 ^d
Irradiation	4	2	1
Surgery	4	0	0
Chemotherapy and irradiation	10	2	0
Chemotherapy and surgery	4	0	1
Chemotherapy, irradiation and surgery	1	0	0
Response rate of aggressive therapy	76%	76%	32%
Palliative therapy	4	4	9
Alive/dead at last follow-up	18/24	10/16	6/24
Median survival (months)	51.8	12.2	7.5
Cause of death			
PAL	15	11	13
Respiratory failure	7 ^e	2 ^f	4 ^g
Sepsis	0	0	3
Hemorrhage	0	0	2
Renal failure	1	0	0
Multiple organ failure	0	1	1
Heart failure	0	1	0
Others ^h	1	1	1
Death with PAL in remission	3	1	0
Death within 1 year after onset of PAL	9	12	19

^aNo patient received rituximab.

^bThose patients who received CHOP or its related regimen.

^cThose patients who included CHOP or its related regimen ($n = 17$) and ProMACE-CytaBOM ($n = 1$).

^dThose patients who included CHOP or its related regimen ($n = 18$) and MACOP-B ($n = 1$).

^eCaused by pneumonia ($n = 2$), pulmonary tuberculosis ($n = 1$), pyothorax ($n = 1$) and bronchopleural fistula ($n = 1$). The information was not available in remaining two patients.

^fCaused by pulmonary emphysema ($n = 1$) and pneumonia ($n = 1$).

^gCaused by pneumonia ($n = 3$) and pyothorax ($n = 1$).

^hIncluded suicide ($n = 1$) and unknown ($n = 2$).

CHOP, combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone; ECOG, Eastern Cooperative Oncology Group; PAL, pyothorax-associated lymphoma; PS, performance status.

ProMACE-CytaBOM, the combination chemotherapy with cyclophosphamide, doxorubicin, etoposide, prednisone, cytarabine, bleomycin, vincristine, methotrexate and leucovorin.

(Table 2). Response rates to chemotherapy, radiotherapy and chemoradiotherapy were 56%, 71% and 83%, respectively. Since assessable lesions were completely removed by surgery, response was not assessable in the remaining 10 patients who received it. Clinical characteristics and outcomes according to clinical stages are shown in Table 2.

Sixty-four patients died during their clinical courses. Their causes of deaths included PAL ($n = 39$), respiratory failure ($n = 13$) and others ($n = 12$) (Table 2). Four patients died without recurrence of PAL. Autopsy was conducted in 22 patients. Either ante-mortem or post-mortem examination revealed multiorgan involvement of PAL in 69 patients (70%). These organs included lymph nodes ($n = 32$), liver ($n = 12$), bone ($n = 9$), bone marrow ($n = 8$), contralateral lung ($n = 13$), gastrointestinal tract ($n = 9$), central nervous system ($n = 8$), spleen ($n = 6$), diaphragm ($n = 4$), pancreas ($n = 5$), skin ($n = 8$), kidney ($n = 5$), heart ($n = 3$), bladder ($n = 2$), prostate ($n = 2$) and testis ($n = 2$).

Median follow-up of the surviving patients was 33 months (range 1–241 months). The 5-year overall survival (OS) rate was 0.35 [95% confidence interval (CI) 0.24–0.45] (Figure 1). The 5-year OS rate was 0.47 (95% CI 0.30–0.63), 0.35 (95% CI 0.16–0.54) and 0.15 (95% CI 0.04–0.33) in patients with stages I, II and I–IV disease, respectively (Figure 2). Of the 41 patients with stage I disease, four received surgery alone as a primary treatment. Two patients died at 8 and 47 months after the diagnosis of PAL due to progression of underlying disease and respiratory failure, respectively. The remaining two patients are alive 32 and 62 months after the diagnosis of PAL.

prognostic factors of PAL

Prognostic factors of PAL are shown in Table 3. Multivariate analysis identified several prognostic factors for OS; lactate dehydrogenase (LDH) levels [hazard ratio (HR) = 2.36;

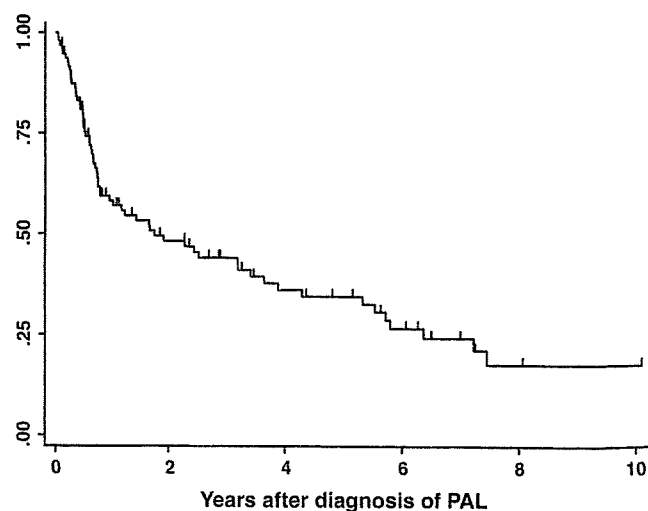


Figure 1. Overall survival (OS) of patients with pyothorax-associated lymphoma. The 5-year OS rate was 0.35 (95% confidence interval 0.24–0.45). PAL indicates pyothorax-associated lymphoma.

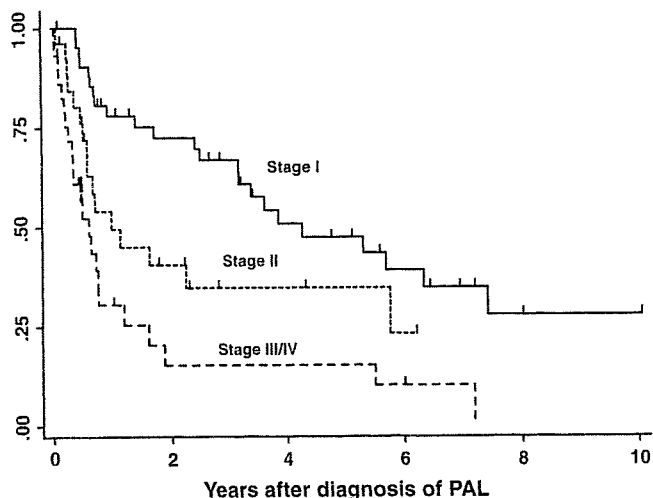


Figure 2. Overall survival (OS) of the patients with stage I, II and III/IV diseases. The 5-year OS rates were 0.47 [95% confidence interval (CI) 0.30–0.63], 0.35 (95% CI 0.16–0.54) and 0.15 (95% CI 0.04–0.33) in patients with stages I, II and I–IV disease, respectively. OS is different among the three groups ($P < 0.0001$). PAL indicates pyothorax-associated lymphoma.

Table 3. Prognostic factors of overall survival

	Hazard ratio	95% CI	P value
Univariate factors			
Age	1.00	0.97–1.04	0.94
Sex (female versus male)	0.18	0.04–0.74	0.02
Interval between onset of pyothorax and PAL	1.00	0.99–1.02	0.63
Side of pyothorax (right versus left)	0.77	0.46–1.29	0.32
LDH (elevated versus normal)	1.06	0.86–1.30	0.58
B symptoms	1.63	0.99–2.70	0.06
History of artificial pneumothorax	0.88	0.47–1.66	0.70
Clinical stage (stage III/IV versus I/II)	2.89	1.70–4.89	<0.001
Irradiation	0.86	0.49–1.51	0.60
Chemotherapy	0.67	0.37–1.22	0.19
Operation	0.40	0.14–1.09	0.07
ECOG PS (2–4 versus 0–1)	3.38	1.98–5.77	<0.001
Multivariate factors			
Age	1.01	0.97–1.05	0.72
LDH (elevated versus normal)	2.36	1.20–4.65	0.01
B symptoms	1.65	0.95–2.87	0.08
Clinical stage (stage III/IV versus I/II)	1.95	1.04–3.65	0.04
Sex (female versus male)	0.15	0.03–0.64	0.01
Irradiation	0.49	0.22–1.10	0.09
Chemotherapy	0.31	0.13–0.75	0.01
Operation	0.31	0.09–1.08	0.07
ECOG PS (2–4 versus 0–1)	2.20	1.15–4.20	0.02

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; PAL, pyothorax-associated lymphoma; PS, performance status; LDH, lactate dehydrogenase.

$P = 0.013$], sex (female versus male) (HR = 0.15; $P = 0.01$), PS (2–4 versus 0–1) (HR = 2.20; $P = 0.02$), clinical stages (III/IV versus I/II) (HR = 1.95; $P = 0.037$) and chemotherapy (HR = 0.31; $P = 0.01$).

discussion

Clinical features of PAL shown in the present study are comparable to previous reports [2, 6, 7, 17]. PAL develops in elderly patients with a history of artificial pneumothorax, and median interval between artificial pneumothorax and the diagnosis of PAL was 43 years (range 19–64). Approximately two thirds of patients had localized diseases, whereas the PS was poor even in patients with early-stage disease. The present nationwide study showed that the ECOG PS was ≥ 3 in 43% of the patients with PAL, while the patients with good general conditions were reported in a previous small-sized case report from Japan [18].

Underlying chronic pyothorax or respiratory failure, which is probably associated with the poor PS, can be an obstacle to the treatment of PAL. Male predominance has been demonstrated in reports on PAL, and most researchers discussed that it is attributable to the male dominance of tuberculosis [2, 6, 7, 17]. The male : female ratio in the present study and in the previous study from Japan [19] was 9 : 1 and 12.3 : 1, respectively. While these are not comparable, these are remarkably higher than the ratio of 2 : 1 in the Japanese patients with tuberculosis [20]. It is reasonable to assume that genetical and/or environmental factors other than tuberculosis might be involved in the male dominance of PAL and that these might be associated with the pathogenesis of PAL. In consideration of future clinical significance of PAL, it should be noted that 20% of the patients have not received artificial pneumothorax in the present study. Artificial pneumothorax is now rarely conducted in Japan; however, the present study indicates the possibility that PAL can occur in patients with structural lung diseases, genetic abnormalities, and disorders of innate or acquired immunity [21]. PAL remains an important clinical entity, and further investigations are awaited on PAL without a history of artificial pneumothorax. Immunohistochemical analyses for HHV-8 detection in lymphoma cells were required in those patients to exclude the possibility of HHV-8-associated primary effusion lymphoma, which has been reported in elderly patients without immune deficiency [22].

The present study showed that the clinical stage of PAL is an important variable in the therapeutic decision making for PAL. Advanced PAL has a poor prognosis; the 5-year survival rate was 15% in patients with PAL at stage 3–4. Approximately 30% of these patients were treated with supportive measures due to advanced ages and/or comorbidities, while the remaining 70% of the patients received aggressive treatments. These findings indicate that it is difficult to control advanced PAL with the current therapeutic procedures on the basis of combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP). Considering that no patients were given either rituximab or ibritumomab in the present study, clinical significance of these molecular agents warrant further investigation.

In contrast, some patients with PAL at an early stage achieved durable remission in the present study. PAL at an early stage can be cured with the current therapeutic measures. Development of PAL is associated with chronic inflammation, and these situations are similar with malignant lymphoma of mucosa-associated lymphoid tissue and that of thyroid gland, in which

Helicobacter pylori-induced gastritis and Hashimoto's thyroiditis contribute to their pathogenesis [23, 24]. Surgery generally plays a limited role in the treatment of malignant lymphoma, while surgical resections of lymphoma lesions are frequently curative in these lymphomas [25–27]. Four patients with PAL at stage 1–2 were treated with surgery alone in the present study, and two achieved durable remission. Surgical resection might be curative for early-stage PAL. Further studies are warranted to investigate its role in the treatment of PAL. On the other hand, one patient died of recurrence of PAL, and distant lesions of PAL can be overlooked using the current diagnostic procedures. Since PAL occasionally involves the extra nodal organs [28], precise evaluation of clinical stage is essential to establish optimal treatments for PAL. Novel diagnostic modalities, such as magnetic resonance imaging and positron emission tomography, may be useful for making an accurate staging of PAL [29].

Immunohistochemical examination of PAL cells in the present study has shown the same expression pattern as reported previously [1, 6, 7, 30–32]. PAL cells expressed some EBV-associated antigens; EBNA-2 and LMP-1 in 12 of 14 and 11 of 17 patients, respectively. These antigens are targets of the cytotoxic T lymphocytes [33], and the expression pattern of EBV-associated antigens in PAL is categorized as latency III, which is same as the pattern of malignant lymphomas developing in immunocompromised patients. These findings raise the possibility of underlying immune defects in PAL; however, a majority of the patients with PAL are immunocompetent. It remains unknown how PAL evades the immune system in immunocompetent patients, but it is to be noted that PAL develops in the lung abscess and that it sometimes stays there without any nodal involvement. In the present study, 66 of the 98 patients with PAL had not presented nodal involvement through their clinical courses. Since the immune system cannot work well in the space of abscess [30], PAL may be able to survive in the lung abscess even in immunocompetent patients. Nodal involvement rarely occurs until progression of PAL, and some genetic events such as loss of tumor suppressor genes may be required for the dissemination of PAL. Clinicopathological studies using molecular [34, 35] and immunological techniques [36] are warranted to clarify the mechanism of immune escape and progression of PAL.

Identification of prognostic factors of PAL is important to establish an optimal treatment strategy, considering that some patients with PAL at early stage can be cured with adequate treatments and that approximately two thirds of the patients were at stage 1–2 when the diagnosis of PAL was established. The present study has demonstrated that sex is significantly associated with survivals as well as conventional prognostic factors including serum levels of LDH, clinical stage and PS [37]. Interestingly, none of the 10 female patients died of disease progression (data not shown). The prognosis is more favorable in females than in males. These observations will provide an important clue to investigate the pathogenesis of PAL. Sex hormones *per se* might play a role in the development and progression of PAL. Alternatively, some factors associated with sex might be involved in the lymphomagenesis and progression of PAL. Previous epidemiological studies have identified several risk factors of malignant lymphoma, and some of them are

associated with sex. These included pregnancy [38], smoking history [39] and alcohol consumption [40]. Further studies are warranted to investigate the association between sex and PAL.

While the present study provided novel information on PAL, it has some limitations to be discussed. Firstly, this is a retrospective study, involving a small number of patients. It might have been influenced by unrecognized bias. Secondly, the present study provided little information on morphological, immunohistochemical, karyotypic and genetic findings of PAL. More detailed information on these findings has to be investigated. The more detailed macroscopic findings, such as size of lesions and the depth of the invasion of pleura, are also needed. Thirdly, clinical features of PAL, which is not associated with pneumothorax, are not clarified, while these kinds of PAL may become a significant problem in the future. Fourthly, information of the type and the degree of comorbidities is limited in the present study although these comorbidities have an impact on response rate and survival in the elderly patients. Lastly, optimal treatments for PAL have not been established. These findings prompt us to conduct further large-scale prospective studies.

appendix

This study was conducted at the following institutions under the auspices of the following investigators in Japan: M. Kami and M. Kawabata (Toranomon Hospital, Tokyo); Y. Tanaka and A. Yamazaki (Tokyo University Hospital, Tokyo); K. Mori (Juntendo University Hospital, Tokyo); M. Mori (Tokyo Metropolitan Geriatric Hospital, Tokyo); S. Sunaga (Hitachi General Hospital, Hitachi); J. Kojima and S. Komastumoto (Dokkyo Medical University School of Medicine, Tochigi and Ashikaga Red Cross Hospital, Ashikaga); S. Miyata (Toyama Prefectural Central Hospital, Toyama); T. Hashizume (National Hospital Organization Kanagawa Hospital, Hatano); M. Fukase (Shonai Hospital, Tsuruoka); S. Okamoto (Keio University School of Medicine, Tokyo); Y. Irie (Saga Prefectural Hospital Koseikan, Saga); T. Miki and Y. Hashimoto (Himeji Brain and Heart Center, Himeji); K. Nakayama (Nihon University School of Medicine, Tokyo); Y. Atsuta and T. Nishida (Nagoya First Red Cross Hospital); A. Hirasawa (Yokohama Rosai Hospital, Yokohama); A. Taguchi (Yokohama City University Hospital, Yokohama); M. Yagita (Kitano Hospital, Osaka); T. Kumagai and Y. Adachi (NTT Kanto Medical Center, Tokyo); K. Tanaka (Kurume University Hospital, Kurume); M. Takagawa (Ishinomaki Red Cross Hospital, Ishinomaki); H. Yanai (Hiroshima City Hospital, Hiroshima); S. Hara (Kurashiki Daiichi Hospital, Kurashiki); S. Taniguchi (Hamanomachi Hospital, Fukuoka); J. Suzumiya (Fukuoka University Hospital, Fukuoka); T. Ishibashi (Shizuoka Hospital, Shizuoka); H. Ishihara (Yamanashi University Hospital, Yamanashi); S. Fukuda (Okayama Medical Center, Okayama); M. Kurosawa (Sapporo Kosei Hospital, Sapporo); A. Wakita (Nagoya City University Hospital, Nagoya); H. Saito (Nagano Red Cross Hospital, Nagano); K. Tsukazaki (Nagasaki University Hospital, Nagasaki); F. Nagamura (Institute of Medical Science, University of Tokyo, Tokyo); K. Suga (Saga Medical University Hospital, Saga); Y. Hasegawa (Tsukuba University Hospital, Tsukuba); H. Mizuno (Chukyo Hospital, Nagoya); A. Oyama

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4. Antibody Therapy for Malignant Lymphoma

Kensei Tobinai

Abstract

Rituximab, a genetically engineered, chimeric anti-CD20 monoclonal antibody, induces the apoptosis of B-lymphoma cells, in addition to the lyses by complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC), as shown in Fig. 1 (1). A Japanese phase I study of rituximab in relapsed or refractory patients with B-cell non-Hodgkin's lymphoma (B-NHL) showed an overall response rate (ORR) of 64% (7/11) with minimal toxicities. Elimination half-life ($T_{1/2}$) of serum rituximab was 445 ± 361 hours, and the serum rituximab was detectable at three months. In the subsequent phase II study, 90 relapsed or refractory patients with indolent B-NHL or mantle cell lymphoma (MCL) were treated with rituximab at $375 \text{ mg/m}^2 \times 4$ weekly infusions. ORRs in indolent B-NHL and MCL were 61% (37/61) and 46% (6/13), respectively. In this presentation, the results of clinical trials of antibody therapy of malignant lymphoma are summarized, focusing on the two recent Japanese multicenter trials of rituximab and a Japanese feasibility study of anti-CD20 radioimmunotherapy with yttrium-90-labeled ibritumomab tiuxetan (2).

Key words: antibody therapy, malignant lymphoma, CD20, rituximab, radioimmunotherapy

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1. Chimeric Anti-CD20 Antibody, Rituximab

1) Phase II study of rituximab in relapsed or refractory aggressive B-NHL

To evaluate the efficacy and feasibility of rituximab monotherapy in Japanese patients with relapsed or refractory aggressive B-NHL, a multicenter phase II study was conducted (3). Sixty-eight patients were enrolled and treated with rituximab at 375 mg/m^2 by eight consecutive weekly infusions. The ORRs of the 68 enrolled patients and of the 57 eligible patients were 35% and 37%, respectively. The median progression-free survival (PFS) of the 53 evaluable patients was 52 days, whereas the time to progression of the 21 eligible responders was 245 days. Elevated serum lactate dehydrogenase (LDH) and refractoriness to prior chemotherapy unfavorably affected ORR and PFS ($P < 0.01$). Serum trough levels of rituximab and the area-under-the-curve (AUC) for responders were higher than for non-responders ($P < 0.05$). In conclusion, treatment with eight weekly infusions of rituximab has significant anti-lymphoma activity for relapsed or refractory aggressive B-NHL (3).

2) Randomized phase II study of rituximab plus CHOP (R-CHOP) in untreated indolent B-NHL

To explore the more promising administration schedule of R-CHOP for indolent B-NHL for further investigations, this randomized phase II study was conducted (4). Untreated patients with advanced, indolent B-NHL were randomized to receive either six courses of CHOP concurrently with rituximab (Arm C) or sequential six courses of CHOP followed by six courses of weekly rituximab (Arm S). The primary endpoint was ORR. Sixty-nine patients were randomized to Arm C ($n=34$) and Arm S ($n=35$). ORR with Arm C was 94% (95% confidence interval [CI], 79-99%) including 66% of complete response (CR) compared with 97% (95% CI, 85-100%) including 68% of CR with Arm S. Patients with Arm C experienced more grade 4 hematologic toxicities (85% vs. 70%) and grade 3 or 4 non-hematologic toxicities (15% vs. 9%) as compared with Arm S. Both arms were well tolerated. With a median follow-up time of 28.2 months, the median PFS time was 1,026 days in Arm C, and has not been reached in Arm S ($P=0.227$). IgH/Bcl-2 copy numbers, especially in peripheral blood, decreased more rapidly in Arm C than in Arm S. In conclusion, R-CHOP is highly effective for untreated indolent B-NHL either by concurrent or sequential combination. The time to

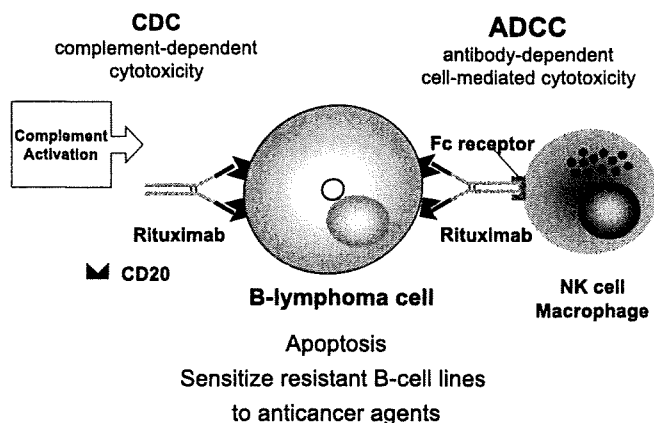


Figure 1. Putative Mechanism of Action of Rituximab.

response was more prompt with the concurrent combination, whereas PFS appears to be longer with the sequential combination. Minimal residual disease (MRD) can be effectively eradicated either by the concurrent or sequential combination; however, rapid clearance of MRD by the concurrent combination may not lead to the prolongation of PFS.

2. Radioimmunotherapy of B-cell NHL with Yttrium-90-labeled, Murine Anti-CD20 Antibody, Ibritumomab Tiuxetan

Ibritumomab is a murine anti-CD20 monoclonal antibody that was engineered to form rituximab. Tiuxetan is a MX-DTPA linker chelator that is attached to ibritumomab to form ibritumomab tiuxetan (ZevalinTM). The ibritumomab tiuxetan is radiolabeled with either ¹¹¹In (¹¹¹In-ZevalinTM) for imaging or dosimetry studies or with ⁹⁰Y (⁹⁰Y-ZevalinTM) for

therapy of B-NHL (5). Between 2002 and 2003, a phase I and feasibility study of ibritumomab tiuxetan was conducted for Japanese patients with B-NHL at the National Cancer Center. In this study, ten patients had relapsed or refractory B-NHL, including nine with follicular lymphoma and one with mantle cell lymphoma, and eight of them had been treated with rituximab. The encountered toxicities were primarily hematologic. None of the three patients in the 0.3 mCi/kg cohort developed critical toxicities, whereas two of the six patients in the 0.4 mCi/kg cohort developed critical toxicities, including one patient who developed long-lasting neutropenia and thrombocytopenia. Among the ten enrolled patients, seven showed objective responses, including five patients achieving CR and two patients achieving partial response (PR). Based on these results, we concluded that yttrium-90-labeled, murine anti-CD20 antibody, ibritumomab tiuxetan is highly effective for relapsed or refractory patients with indolent B-NHL with acceptable toxicities, and that the recommended phase II dose was 0.4 mCi/kg. Subsequently, we conducted a pivotal multicenter phase II study of ibritumomab tiuxetan for relapsed or refractory indolent B-NHL.

Summary

Rituximab, a chimeric anti-CD20 antibody, was approved for indolent B-NHL in Japan in 2001, and was approved for aggressive B-NHL in 2003. French, US and German phase III studies indicated that rituximab plus CHOP is a new standard therapy for aggressive B-NHL. A Japanese phase I study of an anti-CD20 radioimmunoconjugate, ibritumomab tiuxetan, showed high efficacy with acceptable toxicities, and a pivotal phase II study was completed. Monoclonal antibody therapies will have significant roles in the treatment of malignant lymphoma.

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Revised Response Criteria for Malignant Lymphoma

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A B S T R A C T

Purpose

Standardized response criteria are needed to interpret and compare clinical trials and for approval of new therapeutic agents by regulatory agencies.

Methods

The International Working Group response criteria (Cheson et al, *J Clin Oncol* 17:1244, 1999) were widely adopted, but required reassessment because of identified limitations and the increased use of [¹⁸F]fluorodeoxyglucose-positron emission tomography (PET), immunohistochemistry (IHC), and flow cytometry. The International Harmonization Project was convened to provide updated recommendations.

Results

New guidelines are presented incorporating PET, IHC, and flow cytometry for definitions of response in non-Hodgkin's and Hodgkin's lymphoma. Standardized definitions of end points are provided.

Conclusion

We hope that these guidelines will be adopted widely by study groups, pharmaceutical and biotechnology companies, and regulatory agencies to facilitate the development of new and more effective therapies to improve the outcome of patients with lymphoma.

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INTRODUCTION

Standardized response criteria provide uniform end points for clinical trials, allowing for comparisons among studies, facilitating the identification of more effective therapies, and aiding the approval process for new agents by regulatory agencies. Before 1999, response criteria for malignant lymphomas varied widely among study groups and cancer centers with respect to the size of a normal lymph node, the frequency of assessment and the time point the response assessment was made, the methods used to assess response, whether response was assessed prospectively or retrospectively, the percentage increase required for disease progression, and many other factors.¹ Even relatively minor differences in the definition of normal size of a lymph node can have a major influence on response rates.²

In 1999, an international working group (IWG) of clinicians, radiologists, and pathologists with expertise in the evaluation and management of patients with non-Hodgkin's lymphoma (NHL) published guidelines for response assessment and outcomes measurement.¹ These recommendations were adopted rapidly

and widely by clinicians and regulatory agencies, and were used in the approval process for a number of new agents. However, they were subject to considerable inter- and intraobserver variation and recommended technologies, such as gallium scans, are no longer considered state-of-the-art. Several points were subject to misinterpretation, notably the application of the complete remission/unconfirmed (CRu), and the recommendations did not include assessment of extranodal disease. The widespread use of positron emission tomography (PET) scans and immunohistochemistry warranted a reassessment of the prior response criteria. Since the Hodgkin's lymphoma study groups had adopted these IWG criteria, any new recommendations needed to account for those patients as well. As a result, an International Harmonization Project was initiated by the German Competence Network Malignant Lymphoma to develop recommendations that were consistent across study groups.³ Subcommittees were organized on Response criteria, End Points for Clinical Trials, Imaging, Clinical Features, and Pathology/Biology, and the recommendations are reflected in this report.

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