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ORIGINAL REPORT

CHOP Alone Compared With CHOP Plus Radiotherapy for Localized Aggressive Lymphoma in Elderly Patients: A Study by the Groupe d'Etude des Lymphomes de l'Adulte

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Both C.B. and G.F. contributed equally to this study.

This article is dedicated to the memory of Félix Reyes, chairman of the LNH-93 program and president of the Groupe d'Etude des Lymphomes de l'Adulte.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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ABSTRACT

Purpose
Chemoradiotherapy has been considered standard treatment for patients with limited-stage aggressive lymphoma on the basis of trials conducted before the introduction of the International Prognostic Index. To evaluate this approach in elderly patients with low-risk localized lymphoma, we conducted a trial comparing chemoradiotherapy with chemotherapy alone.

Patients and Methods
Previously untreated patients older than 60 years with localized stage I or II histologically aggressive lymphoma and no adverse prognostic factors of the International Prognostic Index were randomly assigned to receive either four cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) plus involved-field radiotherapy (299 patients) or chemotherapy alone with four cycles of CHOP (277 patients).

Results
With a median follow-up time of 7 years, event-free and overall survival did not differ between the two treatment groups ($P = .6$ and $P = .5$, respectively). The 5-year estimates of event-free survival were 61% for patients receiving chemotherapy alone and 64% for patients receiving CHOP plus radiotherapy; the 5-year estimates of overall survival were 72% and 68%, respectively. In a multivariate analysis, overall survival was affected by stage II disease ($P < .001$) and male sex ($P = .03$).

Conclusion
In this large prospective study, CHOP plus radiotherapy did not provide any advantage over CHOP alone for the treatment of low-risk localized aggressive lymphoma in elderly patients.

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INTRODUCTION

Radiation therapy, often after surgical staging, was the standard treatment for patients with limited-stage aggressive lymphoma until the late 1970s, providing rates of 5-year disease-free survival of less than 50%.[1] This approach subsequently evolved to the addition of chemotherapy to involved-field radiotherapy to avoid laparotomy, increase systemic control of disease, and reduce the size of irradiation fields.[2] Because good results were also achieved with chemotherapy alone,[3] these two strategies were used[4] until the finding by Miller et al[5] of the superiority of three cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) followed by involved-field radiotherapy compared with eight cycles of CHOP alone with regard to survival. Of note, patients enrolled onto this study were heterogeneous with regard to prognostic factors such as age and serum lactate dehydrogenase level.

To determine the role of radiotherapy, the Groupe d'Etude des Lymphomes de l'Adulte (GELA) initiated, in 1993, a prospective randomized study comparing four cycles of standard CHOP alone with four cycles of CHOP followed by involved-field radiotherapy. The study was conducted in a homogeneous population of elderly patients with localized aggressive lymphoma and no adverse prognostic factors as defined by the age-adjusted International Prognostic Index.[6] The results are presented here with a median follow-up time of 7 years.

PATIENTS AND METHODS

Patients

Patients had to be older than 60 years and were required to have newly diagnosed aggressive lymphoma

(International Working Formulation groups[7]: diffuse mixed, diffuse large-cell, and immunoblastic and updated Kiel subgroup[8]: anaplastic) and to present without any of the adverse prognostic factors of the age-adjusted International Prognostic Index[6] (eg, elevated lactate dehydrogenase level, performance status $>$ 1, and Ann Arbor stage III or IV). Exclusion criteria included positive serology for HIV and human T lymphotropic virus type I, transformation of previous indolent lymphoma, primary cerebral lymphoma, previous organ transplantation, concomitant or previous cancer (except in situ cervical carcinoma), liver or kidney failure, and cardiac contraindication to doxorubicin. Intestinal lymphoma, which could not be encompassed safely in a radiation field, was also excluded from the study.

Histology and Immunophenotype

Central review was conducted by at least two pathologists from GELA, and the International Working Formulation[7] and Kiel grouping[8] used at the time of entering patients onto the study was then reclassified according to the WHO classification.[9]

Staging

The extent of the disease was evaluated by physical examination; computed tomography of the chest, abdomen, and pelvis; CSF examination; bone marrow biopsy; and other investigational procedures depending on the clinical symptoms. Patients were staged on the basis of Ann Arbor classification. Stage I was defined as an involvement of a single lymph node region or extranodal site, and stage II included involvement of two or more node regions or involvement of an extranodal site and one or more adjacent node regions on the same side of the diaphragm. Tumor measurements were obtained before biopsy, and bulky disease was defined as any mass 10 cm or more in maximal diameter. Performance status was assessed according to the Eastern Cooperative Oncology Group scale, and lactate dehydrogenase level was expressed as the maximum to normal value ratio.[6]

Treatment

Patients were randomly assigned to treatment with either chemotherapy alone or combined chemoradiotherapy. The chemotherapy-alone arm consisted of four cycles of the CHOP regimen (doxorubicin 50 mg/m^2, cyclophosphamide 750 mg/m^2, vincristine 1.4 mg/m^2 [up to a maximum dose of 2 mg] on day 1, and prednisone 60 mg/m^2 on days 1 to 5) repeated at 21-day intervals. The combined arm consisted of four cycles of CHOP repeated at 21-day intervals, followed in patients with complete or partial response by involved-field radiotherapy beginning 1 month after the last cycle of CHOP.

The prescribed dose of radiation was 40 Gy in 22 fractions of 1.8 Gy 5 days per week. Irradiated volumes encompassed involved nodal or extranodal sites and adjacent uninvolved nodes. For example, the iliac or the supraclavicular nodes were included if inguinal or cervical nodes were initially involved, respectively. The whole Waldeyer's ring or stomach had to be irradiated if any part was involved, and irradiation of the uninvolved adjacent regional nodes was recommended. Specific technical factors, such as optimal balistic combination of photons and/or electrons or energy, were determined by the treating radiation oncologist. Dosimetric calculations were recommended at least bidimensionally on the central axis and in two other in-field clinically relevant areas. Radiotherapy data were prospectively reported in a specific case record form and centrally reviewed for identification of protocol deviations.

In both arms, no dose adjustment of chemotherapy was planned according to toxicity, but courses were postponed until leukocyte and platelet counts increased to greater than 2,000 and 100,000/μL, respectively. Patients could receive granulocyte colony-stimulating factor at the discretion of each investigator.

Assessment of Response

Response was evaluated 1 month after the completion of treatment, according to the International Workshop criteria.[10] A complete response was defined as the disappearance of all clinical evidence of disease and of radiologic abnormalities observed at diagnosis. An unconfirmed complete response was defined as a complete response with some persisting radiologic abnormalities, which in the aggregate had to be at least 75% smaller than the original abnormality. A partial response was defined as the regression of tumor volumes by more than 50%, and stable disease was defined as a lower response. Progressive disease (growth of the initial lesion by $>$ 25% or the appearance of a new lesion) during treatment was considered to indicate primary failure.

Statistical Analysis

Random assignment was stratified according to participating center and the presence or absence of bulky disease. The primary end point was event-free survival; the secondary end points were the response rate and overall survival. Calculation of sample size was based on the primary end point. To detect a change at 2 years of 10% (null hypothesis: 60%; alternative hypothesis: 70%), we calculated that 650 patients (330 events) would be required to provide the trial with 90% power at an overall 5% significance level. The trial began in March 1993. After 500 patients had been enrolled, the data and safety monitoring committee undertook the planned interim analysis, which was completed in December 2001. Results indicated no significant difference in 5-year event-free survival (chemotherapy alone, 67% *v* chemoradiotherapy, 62%; $P > .05$). Because, at that time, there was growing evidence that rituximab might dramatically improve chemotherapy efficacy in elderly patients with aggressive lymphoma, the data and safety monitoring committee recommended that the study be stopped. A total of 576 patients had been randomly assigned and were observed to assess event-free survival. The revised power of the study with 576 patients is 0.85.

Analyses included all of the enrolled patients and followed the intent-to-treat principle. Patient characteristics and response rates were compared using χ^2 and Fisher's exact tests. Event-free survival was measured from the date of random assignment to primary failure, relapse, or death from any cause. Overall survival was measured from the date of random assignment to the date of death from any cause. Survival functions were estimated using the Kaplan-Meier method[11] and compared by log-rank test.[12] Multivariate analyses were performed using the Cox model for survival data.[13]

Differences between the results of comparative tests were considered significant if the two-sided $P < .05$. All statistical analyses were performed using SAS 9.1 software (SAS Institute, Cary, NC).

The study was designed by the GELA scientific committee and monitored by the GELA coordinating center, which issued treatment allocation by fax after confirmation of the patient eligibility. Case report forms collected at participating centers were sent to the GELA centralized database and keyed in twice for verification. Outliers and erroneous values were checked routinely. Queries and onsite monitoring were used for final validation.

The trial was approved by the local committee on human investigations and was conducted in accordance with a written assurance approved by the local Department of Health and Human Services. All of the patients included had to give informed consent to participate.

RESULTS

Patient Characteristics

Between March 1993 and June 2002, 576 patients were enrolled at 65 participating centers; 277 were assigned to chemotherapy alone, and 299 were assigned to CHOP plus radiotherapy. The characteristics of the patients did not differ between the two treatment groups; entire clinical data were available in 96% of the enrolled patients, and histologic central review was performed in 89% of patients (Table 1). Median age was 68 years (range, 60 to 85 years). Bulky disease was present at random assignment in 49 patients (8%). Sixty-five percent of the patients had stage I disease. Extranodal involvement was found in half of the patients. Diffuse large B-cell lymphoma was the most common subtype, occurring in 80% of the patients.

Response to Treatment

A complete or unconfirmed complete response was observed in 89% of the patients treated with chemotherapy alone and in 91% of

Table 1. Patient Characteristics

Characteristic	CHOP		CHOP Plus Radiotherapy	
	No. of Patients	%	No. of Patients	%
Total No. of patients	277		299	
Median age, years	69		68	
Male sex	148	53	151	50
Bulky disease at random assignment	21	8	28	9
Clinical characteristics				
Information available	266	96	289	97
Stage				
I	172	65	186	65
II	87	32	99	34
IV*	7	3	4	1
Lactate dehydrogenase				
Normal	261	98	281	97
Elevated*	5	2	8	3
Performance status				
0	191	72	211	73
1	74	27	75	26
2*	1	< 1	3	1
Age-adjusted International Prognostic Index scores				
0	253	95	274	95
1*	13	5	15	5
Extranodal involvement	139	52	135	46
Organ involved				
Waldeyer's ring and sinus	53	20	72	25
Stomach	29	11	18	6
Bone	11	4	10	3
Skin	9	3	7	2
Other†	37	14	28	10
Histologic findings				
Centrally reviewed‡	242	87	269	90
Eligible histology	218/242	90	250/269	93
Diffuse large B-cell lymphoma	187	77	223/269	83
Anaplastic large-cell lymphoma	8	3	7	3
Nonanaplastic T/NK-cell lymphoma	13	6	12	4
Unclassified aggressive lymphoma	10	4	8	3
Inappropriate histology*	24	10	19	7
Small lymphocytic lymphoma	5	2	1	< 1
Marginal zone lymphoma	2	< 1	0	0
Follicular lymphoma	5	2	6	2
Mantle cell lymphoma	5	2	2	< 1
Lymphoblastic lymphoma	1	< 1	1	< 1
Burkitt's lymphoma	1	< 1	2	< 1
Hodgkin's lymphoma	2	< 1	4	1
Carcinoma	2	< 1	1	< 1
Nonmalignant	1	< 1	2	< 1

Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; NK, natural killer.
*This was an exclusion criterion.
†Other categories include: breast, thyroid, testis, orbit, kidney, pancreas, adrenal gland.
‡The classification of the WHO was used.

Table 2. Response to Treatment in the Assessable Patients*

Outcome	CHOP Alone (n = 273)		CHOP Plus Radiotherapy (n = 295)	
	No. of Patients	%	No. of Patients	%
Complete or unconfirmed complete response	244	89	270	91
Partial response	8†	3	1	< 1
Stable disease	8	3	4	1
Primary failure	9	3	17	6
Death	4	1	3	1

Abbreviation: CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone.
*Response was assessed 1 month after completion of treatment. Because of missing data, response could not be assessed in four patients from the CHOP-alone group and in four patients from the CHOP plus radiotherapy group.
†Protocol violation occurred in six patients with partial response who were given additional radiotherapy by their physician.

patients treated with chemoradiotherapy (Table 2). In each treatment group, 94% of the patients received at least 80% of the theoretical dose-intensity of doxorubicin and cyclophosphamide.

In the CHOP plus radiotherapy group, the median time from the last cycle of chemotherapy to the beginning of radiotherapy was 35 days; 5% of patients started irradiation before 21 days, and 5% started after 59 days. Ninety-six percent of the irradiated patients received a dose of 36 to 44 Gy, and 77% received the recommended dose of 40 Gy. Thirty-five of the 299 allocated patients did not receive the planned radiotherapy as a result of poor response (n = 9) or death after CHOP chemotherapy (n = 3), medical decision (n = 10), and refusal (n = 13).

Among the seven deaths that occurred during treatment (Table 2), five resulted from toxicity secondary to chemotherapy, and two resulted from lymphoma progression. No life-threatening acute toxicity of radiotherapy was reported. Eight episodes (3%) of grade 3 infection were reported in the CHOP-alone group compared with 10 episodes (3%) of grade 3 and two episodes of grade 4 infection in the chemoradiotherapy group.

Outcome

With a median follow-up time of 7 years, 252 events (primary failure, relapse, or death) were observed (125 in the chemotherapy-alone group and 127 in the chemoradiotherapy group). Event-free survival did not differ between the groups ($P = .6$), with 5-year estimates of 61% (95% CI, 55% to 66%) in the chemotherapy-alone group and 64% (95% CI, 58% to 69%) in the chemoradiotherapy group (Fig 1).

There were 145 relapses, 79 in the chemotherapy-alone group and 66 in chemoradiotherapy group; median times to relapse were 14 and 17 months, respectively. In the chemotherapy-alone group, disease recurred in the initial site in 47% of patients who experienced relapse, at a distant site in 37% of patients, and at both initial and distant sites in 16% of patients. In the CHOP plus radiotherapy group, disease recurred in the irradiation field in 21% of patients who experienced relapse, out of field in 66% of patients, and both in and out of field in 13% of patients.

There were 215 deaths, 101 in the chemotherapy-alone group and 114 in the CHOP plus radiotherapy group. Overall survival did not significantly differ between the groups ($P = .5$), with 5-year estimates of 72% (95% CI, 66% to 77%) in the chemotherapy-alone group and 68% (95% CI, 63% to 74%) in the chemoradiotherapy group (Fig 2). In the subgroup of 247 patients older than 70 years, the 5-year overall survival rate was higher in patients treated with

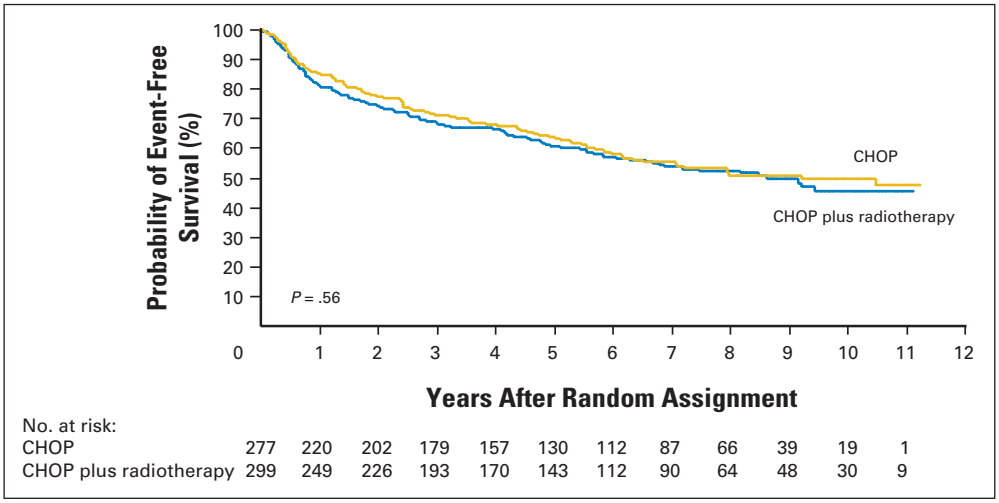

Fig 1. Event-free survival among 576 patients assigned to either chemotherapy alone with four cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or four cycles of CHOP plus involved-field radiotherapy.

chemotherapy alone (69% *v* 58% in patients receiving chemoradiotherapy), but this trend did not reach significance ($P = .2$).

When analysis was restricted to patients who met eligible histologic criteria, 5-year estimates of event-free and overall survivals were identical for both treatment arms. Event-free survival estimates were 62% for CHOP alone compared with 63% for chemoradiotherapy ($P = .8$), and the overall survival estimates were 71% for CHOP alone compared with 68% for chemoradiotherapy ($P = .6$).

In a multivariate analysis of the 576 patients, overall survival was affected by stage II disease ($P < .001$; risk ratio, 1.9; 95% CI, 1.4 to 2.5) and male sex ($P = .03$; risk ratio, 1.4; 95% CI, 1.0 to 1.8) but not by bulky disease ($P = .3$); event-free survival was affected only by stage II disease ($P < .001$; risk ratio, 1.8; 95% CI, 1.4 to 2.3). Of note, among the 576 patients, 5-year event-free and overall survival rates were 70% and 76% for patients with stage I disease, respectively, and 49% and 58% for patients with stage II disease, respectively.

Among the 215 deaths, the cause could be documented in 212 patients (99 patients in the chemotherapy-alone group and 113 patients in the chemoradiotherapy group). Among the 212 documented deaths, 135 (64%) were related to lymphoma progression (65 in the CHOP alone group and 70 in the chemoradiotherapy group). Twenty-nine deaths (14%) occurred as a result of a second cancer that developed in patients after their entry onto the study. Nine of these second cancers were observed in the CHOP-alone group, including one myelodysplasia; 20 occurred in the chemoradiotherapy group, including one acute myelogenous leukemia and three cancers within the irradiation field. At the time of death, these 29 patients with second cancer were in remission from their lymphoma. In the aggregate, 8 patients died from toxicity that occurred during or after primary treatment, and three additional patients died from toxicity related to salvage treatment for lymphoma relapse. Other causes of death in patients with lymphoma in primary or secondary remission included cardiovascular disease in 32 patients (16 patients in each treatment group), infection in two patients, suicide in two patients, and hypereosinophilic syndrome in one patient. Of note, nonfatal late effects of radiotherapy included persistent xerostomia in 36% of patients with Waldeyer's ring lymphoma and other events such as gastritis (three patients) and ileitis (two patients).

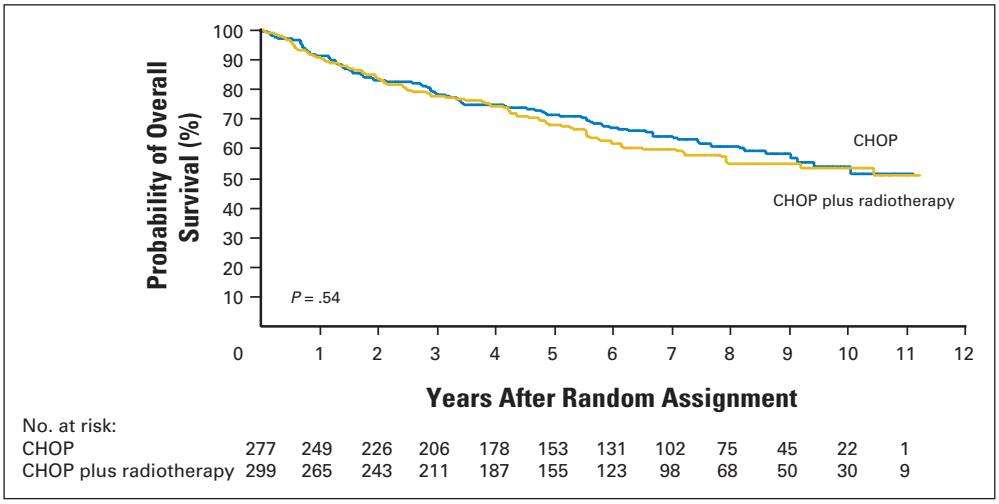

Fig 2. Overall survival among 576 patients assigned to either chemotherapy alone with four cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or four cycles of CHOP plus involved-field radiotherapy.

DISCUSSION

This study of 576 patients is the only randomized trial comparing brief chemotherapy alone consisting of four cycles of CHOP with the same chemotherapy followed by consolidative involved-field radiotherapy. The latter approach has been considered standard therapy for localized disease[14] since the study of Miller et al[5] based on 400 patients with 4.4 years of median follow-up time. In the present study of patients older than 60 years with low-risk stage I or II aggressive lymphoma and with a median follow-up time of 7 years, we found that event-free and overall survival estimates among patients treated with chemotherapy alone did not differ from those observed among patients treated with chemoradiotherapy. Of note, we observed a lack of difference in outcome for the 49 patients with bulky disease, a condition in which adjuvant radiotherapy is believed to optimally control local disease[15,16]; however, this must be interpreted cautiously because of the small size of this subset of patients.

We selected our study population of elderly patients using the age-adjusted International Prognostic Index, the widely used system to stratify patients before therapy,[6] thus providing a homogeneous cohort of patients with regard to main prognostic parameters such as age, lactate dehydrogenase level, and performance status. By contrast, the patient sample in the study by Miller et al[5] included half of patients younger than 61 years and 20% of patients with an elevated lactate dehydrogenase level. Of note, an update of this study with a longer follow-up showed that survival curves ultimately converged as a result of an excess of lymphoma relapses in the CHOP plus radiotherapy group.[17] Horning et al[18] recently reported the results of a study with a median follow-up of 12 years in which patients with limited-stage aggressive lymphoma received consolidative radiotherapy after eight cycles of CHOP; as in the study by Miller et al,[5] the study population was heterogeneous because it included young adult and elderly patients and possibly varying lactate dehydrogenase levels (not available at diagnosis). Of note, radiotherapy did not affect survival despite some marginal improvement in event-free survival. As commented by the authors,[18] radiotherapy provided good local control, but systemic relapses remained the major cause of treatment failure. This is confirmed in our study because, although the majority of patients had stage I disease, belonging to the very limited category described by Miller,[19] consolidative radiotherapy altered the pattern of localization of relapses but did not decrease their overall rate compared with CHOP alone.

With a median follow-up time of 7 years, we observed, as have others,[14] that second malignancies and cardiovascular disease remained a significant cause of subsequent death in elderly patients with lymphoma. Twenty-nine second cancers developed after patient enrollment onto the study. Nine second cancers were in the CHOP-alone group, including one myelodysplasia; 20 occurred in the chemoradiotherapy group but included only one acute myelogenous leukemia and three cancers within the irradiation field. This is in keeping with existing reports of a moderate risk of second malignancy after brief CHOP chemotherapy plus involved-field radiotherapy.[14,20]

Our study demonstrates that chemotherapy with four cycles of CHOP followed by consolidative radiotherapy, as administered in a large-scale trial, is not superior to four cycles of CHOP alone in elderly patients with low-risk localized aggressive lymphoma. Taking also into account the results of our previous study in young adult patients that showed an advantage of chemotherapy alone over chemoradiotherapy,[21] the GELA decided to abandon radiotherapy as first-line treatment of localized aggressive lymphoma, with the advantage of avoiding its late effects, especially in the frequently involved cervical and Waldeyer's ring regions.

To improve survival over the 72% 5-year rate observed in the present study, a result which is in keeping with that of earlier cited studies,[5,18] it is reasonable to propose that such elderly patients with localized B-cell aggressive lymphoma should be treated with a combination of CHOP and rituximab. This recommendation is based on the results of the previous GELA study in elderly patients[22] and of its recent update[23] in which the 5-year survival rate of patients with low-risk stage II disease is estimated at more than 80% after eight cycles of CHOP plus rituximab. Alternatively, a shorter immunochemotherapy regimen followed by radiolabeled antibodies might be a potential approach that deserves to be investigated.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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Manuscript writing: Georges Fillet, Hervé Tilly, Félix Reyes
Other: Georges Fillet, Félix Reyes

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).