

ORIGINAL ARTICLE

ACVBP versus CHOP plus Radiotherapy for Localized Aggressive Lymphoma

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ABSTRACT

BACKGROUND

Chemoradiotherapy is standard treatment for localized aggressive lymphoma. To determine the optimal therapy for nonelderly persons with low-risk localized lymphoma, we conducted a randomized trial comparing chemoradiotherapy with chemotherapy alone.

METHODS

Previously untreated patients less than 61 years old with localized stage I or II aggressive lymphoma and no adverse prognostic factors according to the International Prognostic Index were randomly assigned to three cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) plus involved-field radiotherapy (329 patients) or chemotherapy alone with dose-intensified doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone (ACVBP) plus sequential consolidation (318 patients).

RESULTS

With a median follow-up of 7.7 years, event-free and overall survival rates were significantly higher in the group given chemotherapy alone than in the group given CHOP plus radiotherapy ($P < 0.001$ and $P = 0.001$, respectively). The five-year estimates of event-free survival were 82 percent (95 percent confidence interval, 78 to 87 percent) for patients receiving chemotherapy alone and 74 percent (95 percent confidence interval, 69 to 78 percent) for those receiving chemoradiotherapy. The respective five-year estimates of overall survival were 90 percent (95 percent confidence interval, 87 to 93 percent) and 81 percent (95 percent confidence interval, 77 to 86 percent). In a multivariate analysis, event-free and overall survival rates were affected by treatment group, independently of tumor stage and the presence or absence of bulky disease.

CONCLUSIONS

In patients under 61 years of age, chemotherapy with three cycles of ACVBP followed by sequential consolidation is superior to three cycles of CHOP plus radiotherapy for the treatment of low-risk localized lymphoma.

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*Participants in the GELA study are listed in the Appendix.

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RADIODTHERAPY WAS THE STANDARD treatment for limited (stage I or II) aggressive lymphoma until 1980, although the five-year rate of disease-free survival was less than 50 percent.¹ Subsequently, chemotherapy was added to involved-field radiotherapy (chemoradiotherapy) with the goals of controlling occult systemic disease and reducing the size of irradiation fields.² Other investigators, however, advanced the idea that chemotherapy alone could cure limited aggressive lymphoma³; as a result, either chemoradiotherapy or chemotherapy alone was used for localized lymphoma⁴ until the superiority of three cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) followed by involved-field radiotherapy over eight cycles of CHOP alone was demonstrated.⁵

The Groupe d'Etude des Lymphomes de l'Adulte (GELA) has developed a chemotherapy regimen that consists of an induction phase of intensified doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone (ACVBP) followed by sequential consolidation. In a previous study of two chemotherapy regimens for intermediate or high-grade lymphoma,⁶ the estimated five-year rate of overall survival among patients with localized disease who received the ACVBP regimen was 80 percent, which is similar to results in other trials that used chemoradiotherapy. We therefore launched the present randomized study to compare the ACVBP regimen with chemoradiotherapy in patients under 61 years of age who had localized aggressive lymphoma and no adverse prognostic factors, as defined by the age-adjusted International Prognostic Index.⁷

METHODS

PATIENTS

Study patients had to be older than 15 and younger than 61 years of age, to have newly diagnosed aggressive lymphoma (diffuse mixed, diffuse large-cell, or immunoblastic according to the Working Formulation,⁸ and anaplastic according to the updated Kiel classification⁹), and to have no adverse prognostic factors according to the age-adjusted International Prognostic Index.⁷ Exclusion criteria included positive serologic tests for human immunodeficiency virus or human T-cell lymphotropic virus type 1, transformation of a previously indolent lymphoma, primary cerebral lymphoma, previous organ transplantation, concomitant or previous cancer (except in situ cervical carcinoma), liver or

kidney failure, and a cardiac contraindication to doxorubicin. Patients with intestinal lymphoma that could not be safely encompassed in a radiation field were also excluded from the study. The trial was approved by the ethics committee of Hôpital Saint-Louis, and all patients gave written informed consent.

PATHOLOGY

The Working Formulation⁸ and the Kiel classification⁹ were used to classify lymphoma at the time of enrollment. A central review was conducted by at least two pathologists from the GELA, and tumors were then reclassified according to the classification of the World Health Organization.¹⁰

STAGING

The extent of the disease was evaluated by means of physical examination, computed tomography of the chest, abdomen, and pelvis, cerebrospinal fluid examination, bone marrow biopsy, and other investigational procedures depending on clinical symptoms. The stage of lymphoma was defined on the basis of the Ann Arbor classification: stage I was defined as the involvement of a single lymph-node region or extranodal site, and stage II as the involvement of two or more nodal regions or involvement of an extranodal site and one or more adjacent nodal 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 the serum lactate dehydrogenase level was expressed as the ratio of the maximal value to the normal value.⁷

TREATMENT

Patients were randomly assigned to treatment with chemotherapy alone or chemoradiotherapy, both delivered on an ambulatory basis. Chemotherapy alone consisted of three cycles of ACVBP⁶ (75 mg of doxorubicin per square meter of body-surface area and 1200 mg of cyclophosphamide per square meter on day 1, 2 mg of vindesine per square meter and 10 mg of bleomycin on days 1 and 5, and 60 mg of prednisone per square meter on days 1 through 5) given at two-week intervals and followed by sequential consolidation consisting of two cycles of methotrexate (3 g per square meter) plus leucovorin rescue, four cycles of etoposide (300 mg per square meter) and ifosfamide (1500 mg per square meter),

and two cycles of cytarabine (100 mg per square meter) subcutaneously for four days given at two-week intervals.⁶

Chemoradiotherapy consisted of three cycles of CHOP (50 mg of doxorubicin per square meter, 750 mg of cyclophosphamide per square meter, 1.4 mg of vincristine per square meter [up to a maximal dose of 2 mg] on day 1 and 60 mg of prednisone per square meter on days 1 through 5) repeated at 21-day intervals. Involved-field radiotherapy began one month after the last cycle of CHOP. The prescribed dose of radiation was 40 Gy in 22 fractions of 1.8 Gy, five days per week. Irradiated volumes encompassed involved nodal or extranodal sites and adjacent uninvolved nodes.

In neither group was adjustment of the dose of chemotherapy planned in response to specific adverse events, but courses were postponed until leukocyte and platelet counts increased to greater than 2000 and 100,000 per cubic millimeter, respectively. Patients could receive granulocyte colony-stimulating factor at the discretion of each investigator.

ASSESSMENT OF RESPONSE

Response was evaluated one month after the completion of treatment, according to the International Workshop criteria.¹¹ 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 percent smaller than the original abnormality. A partial response was defined as the regression of tumor volumes by more than 50 percent, and stable disease was defined as a lesser response. Progressive disease (growth of the initial lesion by more than 25 percent or the appearance of a new lesion) during treatment was considered to indicate primary treatment failure.

STATISTICAL ANALYSIS

Randomization was stratified according to center and the presence or absence of bulky disease. The main objective of the trial was to detect an absolute improvement of 10 percent with chemotherapy alone given a two-year rate of event-free survival of 75 percent in the group assigned to CHOP plus radiotherapy (with a type I error of 0.05 and a type II error of 0.10). This design required the enrollment of 400 patients over a period of four years. After a planned interim analysis performed after 200 patients had been enrolled and monitored for at least

six months, the data and safety monitoring committee recommended that the sample size be calculated on the assumption of an absolute improvement of 7 percent in the two-year rate of event-free survival and thus that the total enrollment be increased to 600 patients. Secondary end points were the rate of response and overall survival.

Analyses included all the enrolled patients and followed the intention-to-treat principle. They were also performed on patients who met the eligibility criteria, after histologic review, and after the exclusion of those with an erroneous International Prognostic Index score (Table 1). Patients' characteristics and response rates were compared by means of the chi-square and Fisher's exact tests. Event-free survival was measured from the date of randomization to primary treatment failure, relapse, or death from any cause or the stopping date, which for this analysis was February 1, 2004. Overall survival was measured from the date of randomization to the date of death from any cause or the stopping date. Data were censored on the date of the last follow-up evaluation when the stopping date was not reached. Survival rates were estimated according to the Kaplan–Meier method¹² and compared with the use of the log-rank test.¹³ Taking into account the stratification according to bulky-disease status, we used a stratified log-rank test to analyze event-free and overall survival. Multivariate analyses were performed with the use of the Cox model for survival data.¹⁴ Differences were considered significant when the two-sided P value was less than 0.05. All statistical analyses were performed with SAS software, version 8.0.

The study was designed by the GELA scientific committee. Data collected at participating centers were checked by GELA research assistants and sent to the centralized database in Creteil. One investigator analyzed the data and was the principal writer of this article.

RESULTS

PATIENTS' CHARACTERISTICS

Between March 1993 and June 2000, 647 patients were enrolled at 86 participating centers; 318 were assigned to chemotherapy alone with ACVBP and 329 to chemoradiotherapy consisting of CHOP plus involved-field radiotherapy. The main characteristics of the patients were similar in the two groups (Table 1). Diffuse large B-cell lymphoma was the most common subtype of lymphoma. Extranodal involvement was found in 49 percent of

Table 1. Characteristics of the 647 Patients.*

Characteristic	ACVBP (N=318)	CHOP plus Radiotherapy (N=329)
Median age — yr	46	47
Male sex — no. (%)	190 (60)	211 (64)
Bulky disease at randomization — no. (%)	32 (10)	41 (12)
HIV positive — no. (%)†	1 (<1)	0
Stage‡		
I	209 (67)	215 (66)
II	100 (32)	104 (32)
IV†	3 (1)	7 (2)
Lactate dehydrogenase level — no. (%)‡		
Normal	302 (97)	317 (97)
Elevated†	10 (3)	9 (3)
Performance status — no. (%)‡		
0	252 (81)	251 (77)
1	59 (19)	74 (23)
2†	1 (<1)	1 (<1)
Age-adjusted International Prognostic Index scores — no. (%)‡		
0	298 (96)	310 (95)
1†	14 (4)	16 (5)
Extranodal involvement — no. (%)‡	148 (47)	169 (52)
With regional-node involvement	52 (17)	52 (16)
Without regional-node involvement	96 (31)	117 (36)
Organ involved — no. (%)		
Waldeyer's ring and sinus	74 (24)	85 (26)
Stomach	19 (6)	20 (6)
Bone	11 (4)	12 (4)
Skin	5 (2)	16 (5)
Breast	9 (3)	7 (2)
Thyroid	6 (2)	5 (2)
Other§	24 (8)	24 (7)
Histologic findings not centrally reviewed — no. (%)	35 (11)	28 (9)
Histologic findings centrally reviewed — no./total no. (%)¶	283/318 (89)	301/329 (91)
Eligible	261/283 (92)	275/301 (91)
Diffuse large-B-cell lymphoma	235/283 (83)	239/301 (79)
Anaplastic large-cell lymphoma	11/283 (4)	18/301 (6)
Nonanaplastic T-cell or NK-cell lymphoma	8/283 (3)	15/301 (5)
Unclassified aggressive lymphoma	7/283 (2)	3/301 (1)
Inappropriate†	22/283 (8)	26/301 (9)
Small lymphocytic lymphoma	1/283 (<1)	0
Marginal-zone lymphoma	1/283 (<1)	4/301 (1)
Follicular lymphoma	7/283 (2)	8/301 (3)
Mantle-cell lymphoma	1/283 (<1)	1/301 (<1)
Lymphoblastic lymphoma	1/283 (<1)	1/301 (<1)
Burkitt's lymphoma	3/283 (1)	3/301 (1)
Hodgkin's lymphoma	4/283 (1)	4/301 (1)
Nonmalignant	4/283 (1)	5/301 (2)

* Results are given on an intention-to-treat basis. HIV denotes human immunodeficiency virus, and NK natural killer.

† This was an exclusion criterion.

‡ Information was available for 638 patients (99 percent): 312 in the ACVBP group and 326 in the group given CHOP plus radiotherapy.

§ Other categories include muscle, testis, orbit, kidney, pancreas, and adrenal gland.

¶ The classification of the World Health Organization was used.

the patients. Bulky disease was present at randomization in 73 patients; mediastinal and abdominal involvement accounted for 34 percent and 16 percent of these cases, respectively.

RESPONSE TO TREATMENT

A complete or unconfirmed complete response occurred in 93 percent of the patients treated with chemotherapy alone and 92 percent of those treated with chemoradiotherapy (Table 2). Eighty percent of the patients in the ACVBP group received at least 80 percent of the planned dose of doxorubicin and cyclophosphamide, and 98 percent did so in the group given CHOP plus radiotherapy. In the latter group, 26 patients did not receive the planned radiotherapy, as a result of a lack of response to CHOP in 15, medical decision in 6, and refusal in 5. Among the remaining patients, 93 percent received a dose of 36 to 40 Gy.

There were no treatment-related deaths. Thirty-four episodes of grade 3 infection (11 percent of patients) and two episodes of grade 4 infection (1 percent) occurred in the chemotherapy group, as compared with four episodes of grade 3 infection in the chemoradiotherapy group (1 percent). No life-threatening acute adverse effects of radiotherapy were reported.

OUTCOME

During a median follow-up of 7.7 years, there were 168 events (primary treatment failure, relapse, or death): 61 in the chemotherapy group and 107 in the chemoradiotherapy group. Event-free survival differed significantly between the groups ($P < 0.001$), with five-year estimates of 82 percent in the chemotherapy group (95 percent confidence interval, 78 to 87 percent) and 74 percent in the chemoradiotherapy group (95 percent confidence interval, 69 to 78 percent) (Fig. 1). The difference remained significant in separate analyses of the 574 patients without bulky disease (Fig. 2) and the 73 patients with bulky disease ($P = 0.002$ and $P = 0.04$, respectively). In a multivariate analysis of the 647 patients, event-free survival was independently affected by the presence of bulky disease ($P < 0.001$; risk ratio, 2.5; 95 percent confidence interval, 1.7 to 3.7), treatment with chemoradiotherapy ($P < 0.001$; risk ratio, 1.8; 95 percent confidence interval, 1.3 to 2.5), and the presence of stage II disease ($P = 0.03$; risk ratio, 1.4; 95 percent confidence interval, 1 to 1.9).

There were 120 relapses, 42 in the chemotherapy group and 78 in the chemoradiotherapy group. In the former group, the median time to relapse

Table 2. Outcome of Treatment at One Month in the 630 Patients Who Could Be Evaluated.*

Outcome	ACVBP (N=309)	CHOP plus Radiotherapy (N=321)
	<i>no. of patients (%)</i>	
Complete or unconfirmed complete response	288 (93)	294 (92)
Partial response	6 (2)	4 (1)
Stable disease	4 (1)	6 (2)
Primary treatment failure	11 (4)	17 (5)
Death	0	0

* Response was assessed one month after the completion of treatment. Response could not be assessed in nine patients in the ACVBP group and eight patients in the group given CHOP plus radiotherapy (data were missing for six and three patients, respectively, and treatment was stopped by the investigator without evaluation of the tumor in three and five patients, respectively).

was 21 months and relapses involved the initial site of disease in 41 percent of patients, a distant site in 38 percent, and both initial and distant sites in 21 percent. In the chemoradiotherapy group, the median time to relapse was 15 months and relapses occurred in the irradiation field in 23 percent of the patients, outside the field in 72 percent, and both within and outside the field in 5 percent.

There were 115 deaths, 40 in the chemotherapy group and 75 in the chemoradiotherapy group. Overall survival differed significantly ($P = 0.001$), with five-year estimates of 90 percent in the chemotherapy group (95 percent confidence interval, 87 to 93 percent) and 81 percent in the chemoradiotherapy group (95 percent confidence interval, 77 to 86 percent) (Fig. 3). The difference remained significant when the patients without bulky disease ($P = 0.01$) (Fig. 4) and those with bulky disease ($P = 0.03$) were analyzed separately. In a multivariate analysis of the 647 patients, survival was adversely affected by the presence of bulky disease ($P < 0.001$; risk ratio, 3.0; 95 percent confidence interval, 2.0 to 4.8) and treatment with chemoradiotherapy ($P = 0.002$; risk ratio, 1.8; 95 percent confidence interval, 1.3 to 2.7), but not by the presence of stage II disease ($P = 0.2$; risk ratio, 1.3; 95 percent confidence interval, 0.9 to 1.9).

The influence of chemotherapy alone remained significant with respect to both event-free and overall survival when multivariate analysis was restricted to the patients who met eligibility criteria (Table 1) ($P = 0.001$ and $P = 0.004$, respectively), as well as to those with diffuse large-B-cell lymphoma ($P = 0.004$ and $P = 0.03$, respectively).

Of the 115 deaths, 89 were related to progres-

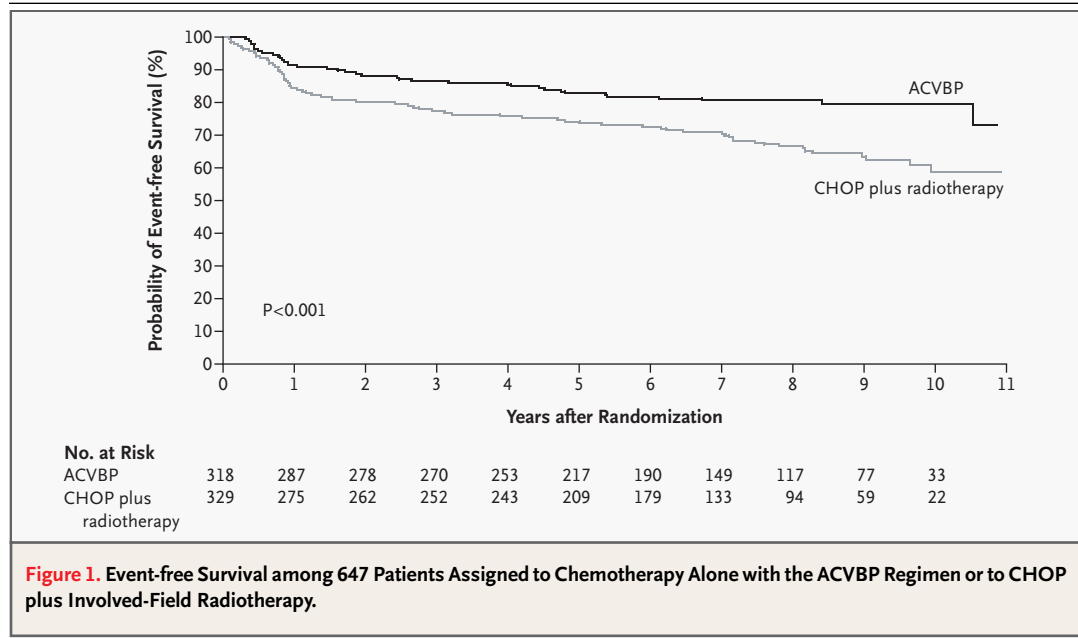


Figure 1. Event-free Survival among 647 Patients Assigned to Chemotherapy Alone with the ACVBP Regimen or to CHOP plus Involved-Field Radiotherapy.

sive lymphoma, 29 in the chemotherapy group and 60 in the chemoradiotherapy group. Sixteen deaths occurred as a result of a second cancer that developed after enrollment: seven of these were in the chemotherapy group, including one acute myelogenous leukemia; nine occurred in the chemoradiotherapy group, including two cases of myelodysplasia and one pancreatic cancer within the irradiation field. At the time of death, 15 of these 16 patients with a second cancer were in a primary remission from their lymphoma and 1 was in a secondary remission. Death was related to salvage treatment for relapsed lymphoma in four patients. Other causes of death in patients in a primary remission included suicide in two, a car accident in one, myocardial infarction in one (outside the irradiation field), and stroke in one; one patient in secondary remission died from peritonitis.

Nonfatal late effects of radiotherapy included persistent xerostomia in 6 percent of patients with Waldeyer's-ring lymphoma, hypothyroidism (five cases), carotid stenosis (two cases), gastritis (three cases), and vertebral fracture (two cases). No episodes of congestive heart failure were reported in either treatment group.

DISCUSSION

This randomized trial, which enrolled 647 patients with low-risk aggressive lymphoma in stage I or II who were younger than 61 years of age, compared

chemotherapy alone (three cycles of ACVBP followed by sequential consolidation) with three cycles of CHOP followed by involved-field radiotherapy. The latter has been considered standard therapy for localized lymphoma since Miller et al. reported the results of a randomized study of 400 patients, with a median follow-up of 4.4 years.⁵ After a median follow-up of 7.7 years, we found superior event-free and overall survival rates among patients treated with chemotherapy alone.

The ACVBP regimen consists of an induction phase with higher doses of doxorubicin and cyclophosphamide than those used in CHOP and a consolidation phase consisting of treatment with drugs not used during induction. The ACVBP regimen improves survival among elderly patients with poor-risk aggressive lymphoma, as compared with eight cycles of standard CHOP.¹⁵ Two other studies have suggested that the efficacy of CHOP can be improved by increasing the doses of doxorubicin and cyclophosphamide.^{16,17} In the present trial, the increased doses and reduced intervals between the three courses of ACVBP increased the theoretical dose intensity of doxorubicin and cyclophosphamide by a factor of 2.25 and 2.4, respectively, as compared with three cycles of CHOP. As a consequence, in 95 percent of the patients in the chemotherapy group, the theoretical dose intensity was at least 150 percent of that delivered by three cycles of CHOP.

We defined our study population of patients younger than 61 years with localized lymphoma on

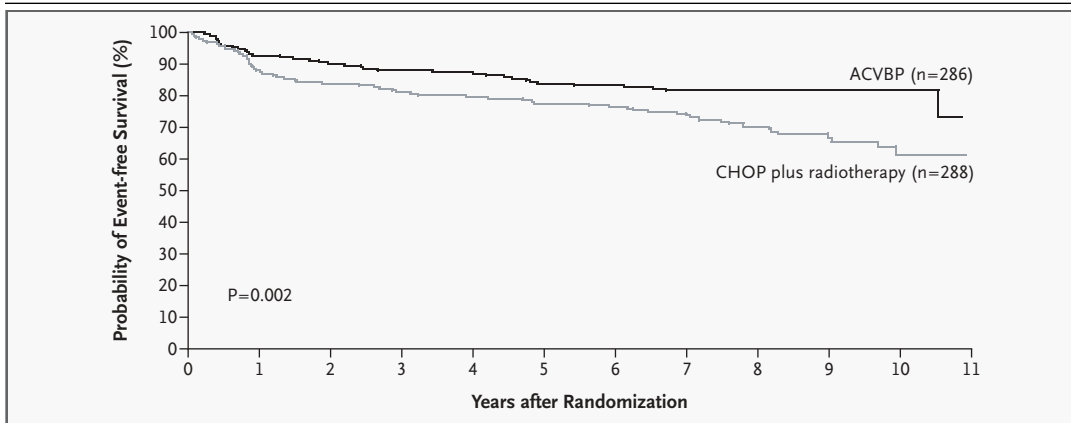


Figure 2. Event-free Survival among 574 Patients without Bulky Tumor Assigned to Chemotherapy Alone with the ACVBP Regimen or to CHOP plus Involved-Field Radiotherapy.

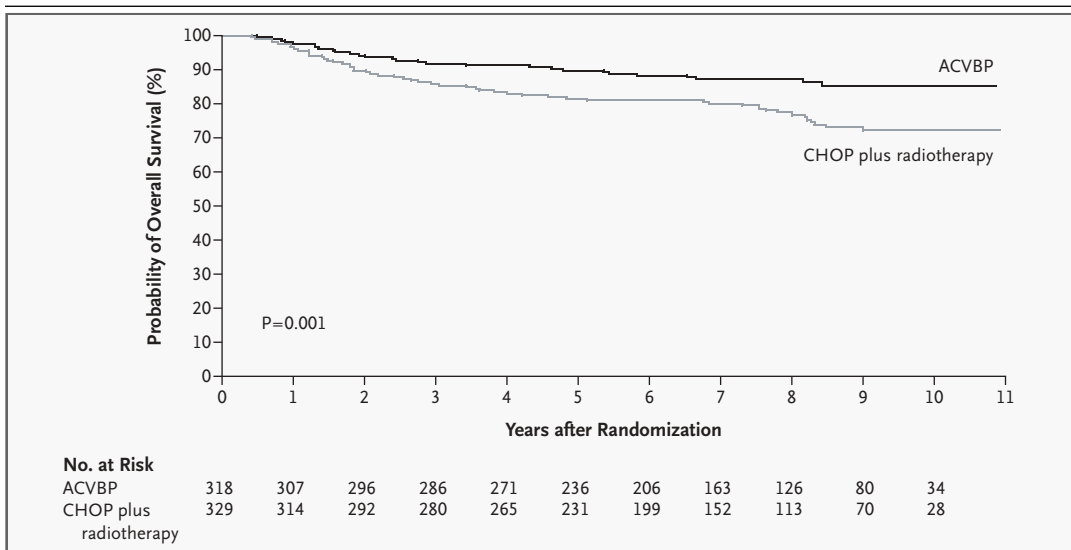
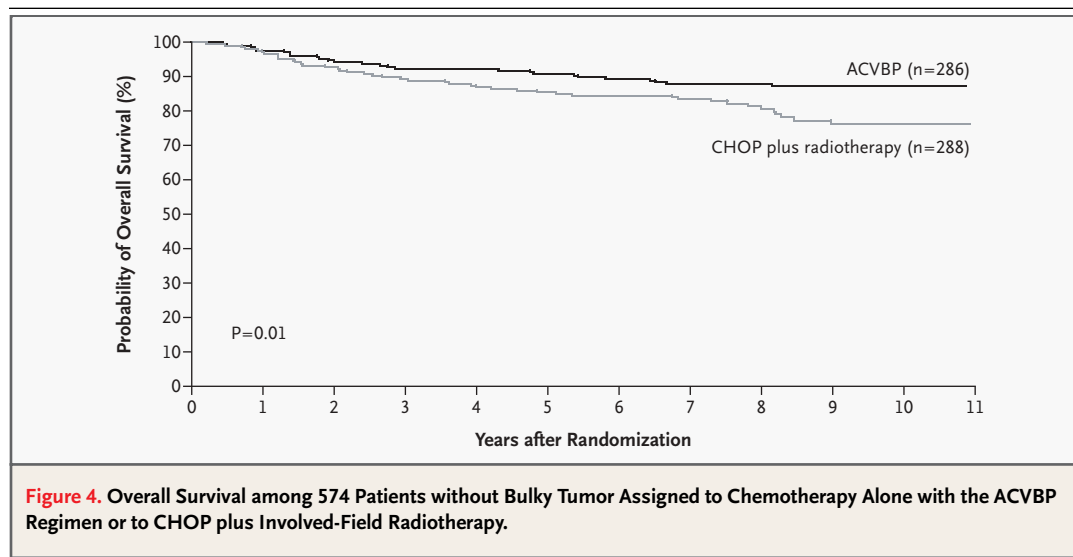


Figure 3. Overall Survival among 647 Patients Assigned to Chemotherapy Alone with the ACVBP Regimen or to CHOP plus Involved-Field Radiotherapy.

the basis of the age-adjusted International Prognostic Index, the most widely used system to stratify tumors before therapy,⁷ thus providing a relatively homogeneous cohort of patients with regard to principal prognostic factors: age, lactate dehydrogenase level, and performance status. By contrast, in the study by Miller et al.,⁵ half the patients were over 60 years of age and 20 percent had an elevated lactate dehydrogenase level. An update of that study with a longer follow-up showed convergence of survival curves as a result of an excess of relapses and deaths from lymphoma in the group given CHOP plus radiotherapy.¹⁸

In our patients with limited disease, the influence of treatment group was independent of classic prognostic factors such as stage II disease⁵ and a large tumor burden.¹⁹ Thus, the advantage of chemotherapy alone over chemoradiotherapy applied to the entire population of patients — not only to the patients with bulky disease, a condition in which adjuvant radiotherapy is believed to result in optimal control of local disease,^{20,21} but also to patients without a bulky tumor. In our population of patients younger than 61 years, the ACVBP regimen could be given on an ambulatory basis. As a consequence of the high dose intensity of ACVBP,



neutropenia was more frequent than with CHOP, but in our patients, we observed only two grade 4 life-threatening infections among 309 patients and no treatment-related deaths. In our previous study of 2210 patients who received ACVBP, an age of more than 60 years, elevated lactate dehydrogenase levels, and an Eastern Cooperative Oncology Group score of more than 1 predicted early treatment-related deaths.²²

After a median follow-up of 7.7 years, there were a similar number of fatal second cancers in each group. There were nine cases in the chemoradiotherapy group, which is in keeping with other reports of a moderate risk of second cancer after brief CHOP chemotherapy plus involved-field radiotherapy.^{23,24} A longer follow-up may, however, reveal additional late solid tumors related to radiotherapy.²⁵ There were seven cases of fatal second cancers in the ACVBP group, a number consistent with our retrospective analysis of 2837 patients treated with the ACVBP regimen in consecutive GELA trials.²⁶

Thus, moving from CHOP plus radiotherapy to intensified chemotherapy alone did not increase the number of deaths from second cancers.

In conclusion, chemotherapy with ACVBP alone significantly improved event-free and overall survival among persons younger than 61 years with newly diagnosed, low-risk, localized aggressive lymphoma, as compared with the standard treatment with CHOP plus radiotherapy. Efforts are now needed to further improve event-free survival among such patients. Given the benefit of the combination of rituximab and chemotherapy,²⁷ the GELA has undertaken a trial of rituximab plus the ACVBP regimen in young adults with localized low-risk aggressive lymphoma.

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APPENDIX

The following persons and study centers participated in the GELA study (all in France, unless otherwise specified): Hôpital Saint-Antoine, Paris — M. Aoudjane; Clinique du Mail, Grenoble — D. Assouline; Hôpital Pasteur, Colmar — B. Audhuy; Centre Hospitalier de Saint Germain, Saint Germain en Laye — M. Azagury; Hôpital de Bayonne, Bayonne — F. Bauduer; Centre Medico-Chirurgical de Foch, Suresnes — E. Baumelou; Centre Hospitalier de Montluçon, Montluçon — M.A. Bichoffe; Centre Léon Berard, Lyon — P. Biron; Centre Hospitalier de Chambéry, Chambéry — M. Blanc; Hôpital Dupuytren, Limoges — D. Bordessoulle; Cliniques Universitaires de Mont Godinne, Yvoir, Belgium — A. Bosly; Institut Paoli Calmette, Marseille — R. Bouabdallah; Centre Hospitalier de Saint Brieuc, Saint Brieuc — P. Bourquard; Hôpital Saint-Louis, Paris — P. Brice, N. Mounier, D. Simon, C. Gisselbrecht, H. Dombret; Hôpital Beaujon, Clichy — J. Brière; Centre Hospitalo-Universitaire de Dijon, Dijon — D. Caillot, O. Casasnovas, M. Flesch, B. Chauffert; Centre Hospitalo-Universitaire de Nice, Nice — G.P. Cassuto; Hôpital André Mignot, Le Chesnay — S. Castaigne; Hôpital Bon Secours, Metz — B. Christian; Hôpital Lyon-Sud, Pierre-Bénite — B. Coiffier, G. Salles; Polyclinique de Courlancy, Reims — P. Colin and G. Pinon-Netter; Centre A. Vautrin, Vandoeuvre lès Nancy — T. Conroy; Centre Jean Perrin, Clermont-Ferrand — H. Curé; Hôpital Hôtel-Dieu, Paris — A. Delmer; Hôpital Jean Bernard, Poitiers — V. Delwail; Centre Hospitalier de Corbeil, Corbeil Essonnes — A. Devidas; Hôpital Cochin, Paris — F. Dreyfus; Clinique de Chaumont, Chaumont — G. Dupont; Centre Hospitalier E. Muller, Mulhouse — J.C. Eisenmann; Centre Val d'Aurelle, Montpellier — M. Fabbro; Centre de Bligny, Briis sous Forges — C. Fermé; Centre Hospitalo-Universitaire de Liège, Liège, Belgium — G. Fillet; Hôpital J. Monod, Le Havre — C. Fru-

chart; Hôpital de la Pitié-Salpêtrière, Paris — J. Gabarre; Hôpital du Creusot, Le Creusot — M. Gabez; Centre Hospitalier de Juvisy, Juvisy sur Orge — M. Gautier; Hôpital Henri Mondor, Créteil — C. Haioun, M. Diviné, K. Belhadj, F. Reyes; Hôpital de Haute-pierre, Strasbourg — R. Herbrecht; Hôpital Necker, Paris — O. Hermine, B. Varet; Centre René Huguenin, Saint-Cloud — M. Janvier; Centre Hospitalo-Universitaire de Nîmes, Nîmes — E. Jourdan; Hôpital de l'Ouest Parisien, Trappes — D. Kamioner; Centre Hospitalier René Dubos, Pontoise — Y. Kerneis, F. Morvan; Centre Hospitalo-Universitaire Brabois, Vandoeuvre lès Nancy — P. Lederlin; Centre Hospitalier de Brives, Brives La Gaillarde — S. Lefort; Centre Hospitalier de la Durance, Avignon — G. Lepeu; Hôpital Tenon, Paris — J.P. Lotz, C. Bouleuc; Hôpital Paul Brousse, Villejuif — D. Machover; Hôpital de Chaneaux, Macon — F. Marechal; Centre F. Magendie, Bordeaux — G. Marit; Centre Hospitalier d'Annecy, Annecy — C. Martin; Centre Hospitalier d'Esch sur Azette, Esch sur Azette, Luxembourg — S. Meyer; Centre Hospitalier de Lens, Lens — P. Morel, B. Dupriez; Institut Gustave Roussy, Villejuif — J.N. Munck, C. Fermé, P. Carde; Hôpital Universitaire de Gent, Ghent, Belgium — E. Offner; Centre Hospitalier de Troyes, Troyes — J.M. Pavlovitch; Hôpital V. Provo, Roubaix — I. Plantier; Hôpital de Fleury, Bourg en Bresse — H. Orfeuvre; Hôpital de Valence, Valence — P.Y. Péaud, D. Dramais; Centre François Baclesse, Caen — A.M. Peny; Hôpital de Thionville, Thionville — C. Platini; Hôpital Victor Dupuy, Argenteuil — M. Pullik; Centre Hospitalo-Universitaire de Lille, Lille — B. Quesnel, F. Morschauser; Centre Hospitalo-Universitaire de Caen, Caen — O. Reman, M. Leporrier; Centre Hospitalier Saint-Vincent, Lille — C. Rose; Centre Hospitalier de Blois, Blois — P. Rodon; Centre Hospitalo-Universitaire de Montpellier, Montpellier — J.F. Rossi; Hôpital de Chalons, Chalons sur Saône — B. Salles; Hôpital de Purpan, Toulouse — D. Schlaifer, F. Huguet, A. Huyn; Hôpital Edouard Herriot, Lyon — C. Sebban; Centre Hospitalier de Valenciennes, Valenciennes — M. Simon; Clinique Victor Hugo, Le Mans — P. Solal-Céligny; Centre Hospitalo-Universitaire de Grenoble, Grenoble — J.J. Sotto; Centre Hospitalier de Meaux, Meaux — C. Soussain, C. Allard; Hôpital Bicêtre, Paris — G. Tertian; Centre H. Becquerel, Rouen — H. Tilly; Centre A. Lacassagne, Nice — A. Thyss; Centre Hospitalo-Universitaire d'Amiens, Amiens — C. Traulle; Hôpital Hotel-Dieu, Clermont-Ferrand — P. Travade; Academisch Ziekenhuis Sint-Jan, Bruges, Belgium — A. Van Hoof; Hôpital Lariboisière, Paris — J.M. Zini; Pathologists — J. Brière, J. Diebold, B. Fabiani, P. Gaulard, C. Guettier, T. Molina, T. Petrella.

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