# Long-term outcome of localized high-grade non-Hodgkin's lymphoma treated with high dose CHOP regimen and involved field radiotherapy: results of a GOELAMS study

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Background and Objectives. Most patients with localized high-grade non-Hodgkin's lymphoma (NHL) can be cured with or without adjuvant radiotherapy. However few data are available on the long-term outcome of these patients. Here we report the results of a prospective study, started in 1984, which was conducted to evaluate the long-term outcome of patients with localized high-grade NHL.

Design and Methods. In this multicenter, prospective study by the GOELAMS group, 253 patients with localized high-grade NHL were treated with 3 cycles of vindesine, cyclophosphamide, adriamycin and prednisone (VCAP, a high-dose CHOP regimen) followed by involved field radiotherapy (40 Gy).

Results. After completion of chemotherapy, 213 patients (84%) entered complete remission (CR) and 30 (12%) obtained a partial remission. Treatment failed in 6 patients (2.5%) and there were 4 toxic deaths (1.5%). Following radiotherapy, 239 (94%) of all patients were in CR. With a median follow-up of 88 months, overall survival and disease-free survival rates were 84% and 85% respectively at five years, and 78% and 82% respectively at ten years. The response to chemotherapy was decisive to survival. We observed 43 relapses (17%) at a median time of 20 months after CR, and 9 patients relapsed after five years. Eleven patients (3%) developed another malignancy in the follow-up period.

Intterpretations and Conclusions. High-dose CHOP followed by locoregional radiotherapy is a feasible treatment for localized high-grade NHL. It has very few complications, a good CR rate and the OS is 78% at 10 years.

Key words: localized non Hodgkin's lymphoma.

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The majority of patients with localized high-grade non-Hodgkin's lymphomas (NHL) can be cured with chemotherapy with or without adjuvant radiotherapy.[1-5] Until recently, the best therapeutic approach was based on a combination of a short course of adriamycin-containing chemotherapy and involved field radiation therapy.[6-7] Most of the studies using this therapeutic approach report a 5-year survival rate of more than 70%.

Whichever strategy is adopted, few data are available on the long-term outcome of patients treated for localized high-grade NHL, the incidence of late relapse, and the impact of the International Prognostic Index (IPI) on clinical results. Recently, Shenkier *et al.* published the long-term results of a cohort of 308 patients with a median age of 64 years, treated with different CHOP-like regimens followed by radiotherapy.[8] With a median follow-up of 86 months, these authors reported overall survival (OS) and progression-free survival (PFS) rates of 63% and 74%, respectively. They observed late relapses occurring more than 10 years after complete remission (CR). Fifty-five patients out of 247 had a relapse within 6 to 181 months (median 25 months) after CR. They emphasized the impact of the age-adjusted IPI on survival. It thus appears that long-term follow-up is needed to draw final conclusions on the curability of localized NHL. Here, we present the long-term results of a prospective study conducted by the GOELAMS group over 12 years, starting in 1984, in which 253 patients with localized NHL were treated with a high-dose CHOP regimen followed by locoregional irradiation.

## Design and Methods

### Patients

From 1984 to 1996, a series of 253 patients aged from 18 to 60 years old were enrolled in a prospective multicenter study for primary treatment of localized stage I/II nodal and extranodal high-grade NHL. The diagnosis was confirmed in all

patients on an excision biopsy. Histological analysis was performed according to the Working Formulation criteria. The histological distribution was as follows: group F (mixed small- and large cell) n=39 (15%), group G (large cell) n=159 (63%), and group H (immunoblastic cell) n=43 (17%). Patients who presented with primary central nervous system, gastro-intestinal or cutaneous lymphoma or human immunodeficiency virus infection were excluded. No patient had a history of cardiac disease or another cancer. Immunophenotyping performed on fixed sections was available for 173 patients (68%) and revealed 145 cases (86%) of B-cell lymphoma and 28 cases (14%) of T-cell lymphoma.

### Staging

In addition to clinical examination, all patients underwent a blood cell count, liver and kidney function tests and assay of lactate dehydrogenase (LDH) concentration. The staging procedure included chest X-rays, thoracic and abdominal computed tomography (CT) scans, bone marrow biopsy, and lumbar puncture for cerebrospinal fluid examination. Cervical CT scans were also performed for optimal evaluation of head and neck localization. The definitive stage was determined according to the Ann Arbor criteria. Bulky disease was defined as a tumor mass exceeding 5 cm in any diameter in the case of peripheral tumors, and 10 cm in the case of a thoracic or abdominal mass.

### Treatment protocol

The high-dose CHOP regimen (VCAP) was administered as follows: vindesine 4 mg/m$^2$ given intravenously on day 1, cyclophosphamide 1.5 g/m$^2$ given intravenously on day 2, doxorubicin 80 mg/m$^2$ given intravenously on day 2, and prednisone 80 mg/m$^2$ given orally from day 1 to day 5. A total of 3 cycles was delivered, one every 3 weeks. All patients received intrathecal methotrexate (15 mg) for each cycle. Complete or partial responders received radiation therapy to the initial tumor site after completion of chemotherapy, starting approximately one month after the last cycle of high-dose CHOP. The radiation dose was identical regardless of the tumor site: 40 Gy in 20 fractions (2 Gy/day). Granulocyte colony-stimulating factor (G-CSF) was given after each cycle of chemotherapy from 1990 to the end of the study (110 patients).

### Treatment response

Treatment response was determined by clinical and biological examination, chest X-rays and chest or abdominal CT scan depending on the initial tumor site. Complete response was defined as a complete disappearance of all clinical, biological and radiographic evidence of disease for more than one month. Partial response (PR) was defined as a tumor reduction greater than 50% lasting at least one month. Treatment failure was defined as a less than 50% reduction in tumor size. Relapse was defined as the resurgence of lymphoma after a previous CR. Deaths were recorded as lymphoma-related or non-related.

### Follow-up

Each patient was followed up for potential relapse by clinical and radiographic assessment every 6 months. The stopping date for the analysis was August 2001.

### Statistical analysis

Multivariate analysis was performed using the proportional hazards model regression analysis of survival. Patients were analyzed according to a stage-adjusted IPI using the following criteria: increased LDH level, poor performance status (PS), and stage II disease as previously proposed by Miller *et al.*[9] A risk level was assigned according to the number of adverse prognostic features as low, intermediate, and high risk defined by 0, 1 or 2 and 3 risk factors, respectively.[8-9] Overall survival (OS) time was defined as time from diagnosis to death of any cause. Disease-free survival (DFS) was defined as time from complete remission to relapse or death from any cause. Probabilities of OS and DFS were estimated by the Kaplan-Meier method. Statistical analysis of observed differences was evaluated by the log-rank test, and $p$ values were two-sided (SPSS software).

## Results

The patients' characteristics are listed in Table 1. The median age at presentation was 42.3 years (range, 18 to 60 years). There were 145 male and 108 female patients (sex ratio 1.3). The patients were assessed as having stage I (52%) or II (48%) disease according to the Ann Arbor classification. There were 59% nodal tumors and 41% extra-nodal tumors at initial presentation. The most frequently involved site was the head and neck (43% of all cases). Eleven percent of the patients had B symptoms, and 10% had a performance status equal to or higher than 2. The LDH level was above the normal value in 25% of cases. Forty-six patients had bulky disease.

### Response to treatment

Two hundred and thirteen patients (84%) entered CR after completion of chemotherapy while 30 obtained a partial response (12%). There were 6 failures (2.5%) and 4 toxic deaths (1.5%). Out of the 30

**Table 1.** Patients' characteristics.

| | *No. of patients* | *%* |
|---|---|---|
| Total no. | 253 | |
| Median age (range) | 42.3 (18-60) | |
| Sex (male/female) | 145/108 | |
| Histology (Working Formulation) | | |
| F | 39 | 15% |
| G | 159 | 63% |
| H | 43 | 17% |
| I | 4 | 2% |
| Unclassified | 8 | 3% |
| Phenotype | | |
| B | 148 | 86% |
| T | 25 | 14% |
| Initial tumor site | | |
| Head and neck | 108 | 43% |
| *Nodal* | 38 | 15% |
| *Extra-nodal* | 70 | 27% |
| Cavum | 12 | 5% |
| Sinus | 5 | 2% |
| Parotid gland | 3 | 1% |
| Waldeyer's ring* | 50 | 20% |
| Thyroid | 9 | 4% |
| Axillaries | 12 | 5% |
| Mediastinum | 51 | 20% |
| Inguinal lymph node/ pelvis | 28 | 11% |
| Retroperitoneal mass | 11 | 4% |
| Bone/vertebra | 14 | 5% |
| Testis | 5 | 2% |
| Breast | 5 | 2% |
| Others | 10 | 4% |
| Extra-nodal site | 103 | 41% |
| Bulk disease | 117 | 46% |
| Stage | | |
| I | 131 | 52% |
| II | 122 | 48% |
| B symptoms | | |
| Yes | 27 | 11% |
| No | 226 | 89% |
| LDH level | | |
| normal | 161 | 75% |
| > normal | 54 | 25% |
| Performance status | | |
| 0-1 | 227 | 90% |
| 2-3 | 25 | 10% |
| IPI: (no. of risk factors) | | |
| 0 | 96 | 42% |
| 1 | 91 | 40% |
| 2 | 33 | 14% |
| 3 | 9 | 4% |

**including base of tongue, tonsil and nasal cavities.*

partial responders, 26 entered CR after radiotherapy. In the intent-to-treat analysis, 243 out of 253 patients (96%) completed the full program. Overall, 239 patients (94%) achieved CR after chemotherapy and radiotherapy. The six patients who were unresponsive to chemotherapy rapidly died of progressive disease despite four of them being administered radiotherapy (Table 2).

**Table 2.** Response rates according to treatment.

| | *After Chemotherapy* | *After Radiotherapy* | *Relapse/death* |
|---|---|---|---|
| Complete remission | 213 (84%) | 239 (94%) | 35/20 |
| Partial remission | 30 (12%) | 2 | 8/7 |
| Failure or disease progression | 6 (2%) | 8 (3%) | 6 deaths |
| Deaths | 4 | | |

*Survival and relapse*

The median follow-up was 88 months. After 5 and 10 years, the OS rates were 84% (95% confidence interval [CI] 79 to 89%) and 78% (95% CI, 72 to 84%), and DFS rates were 85% (95% CI, 80 to 90%), and 82% (95% CI, 76 to 88%) respectively (Figure 1). Forty-three patients out of 239 (18%) relapsed. Nine patients had disease relapse in the initial site and 34 outside the radiation field with disseminated disease in 21 of these latter. The median relapse time was 20 months (1-160 months) (Table 3 and Figure 2). Thirteen patients relapsed 3 years after CR, 9 after 5 years, and 3 more than 10 years after achieving CR. The onset of relapse influenced the outcome of the relapsing patients: 14 out of the 16 patients who relapsed within the first year died as compared to 13 out of 27 patients who relapsed after one year ($p$=0.01). The prognosis of relapsing patients was very poor, with a 50% survival rate at 24 months after relapse (95% CI, 34 to 66%) (Figure 3). The median OS time for patients relapsing within one year was 11 months and 43 months for those relapsing more than one year after treatment ($p$<0.0001; Figure 3B). With a median follow-up of 35 months after relapse, 27 patients (63%) died of progressive disease. Relapsing patients underwent salvage therapy. Thirty-four patients entered a second CR and 2 patients entered a second partial remission, while therapy failed in 7 patients. Thirteen received high-dose therapy (autologous bone marrow transplant: n=12, allogeneic bone marrow transplant: n=1), without any benefit as compared to the 30 patients receiving standard dose chemotherapy (Figures 3A, B). Histological analysis was available at relapse for 16 patients out of 43 (37%): 13 presented with the same subtype as the initial disease and 3 had low-grade non-Hodgkin's lymphoma. Finally, there were 52 deaths.

### Prognostic factors for survival and relapse

In univariate analysis, increased LDH level, poor performance status (≥2), B symptoms, bulky tumor, absence of CR after chemotherapy, and age-adjusted

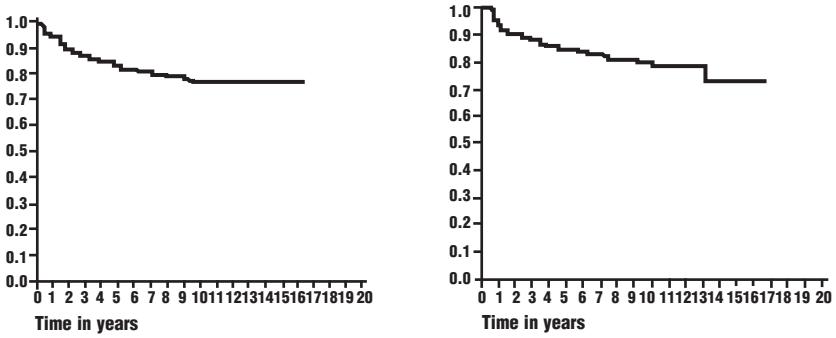


**Figure 1.** Overall survival (OS) and disease-free survival (DFS) of 253 patients treated with 3 courses of high-dose CHOP and involved-field irradiation. (median follow-up: 88 months)

**Table 3.** Characteristics of relapse (n=43).

| *Date of relapse (time from diagnosis)* | *No. of pts.* | *Outcome* | |
|---|---|---|---|
| | | *Dead* | *Alive* |
| < 1 year | 16 | 14 | 2 |
| Between 1 and 3 years | 14 | 6 | 8 |
| Between 3 and 5 years | 4 | 1 | 3 |
| > 5 years | 9 | 6 | 3 |
| Site of relapse | | | |
| Localized | | | |
| Initial site | 9 | | |
| Other site | 13 | | |
| Disseminated | 21 | | |

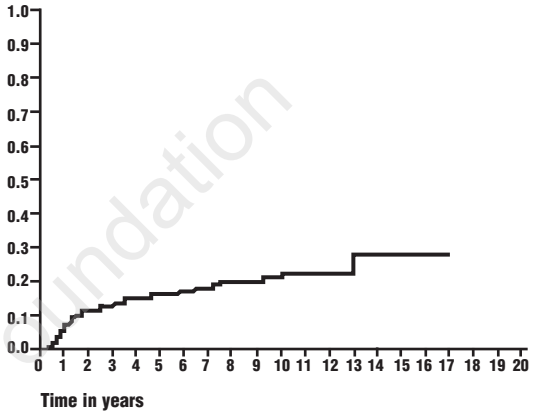


**Figure 2.** Incidence of relapse among the 253 patients receiving 3 courses of high-dose CHOP and radiotherapy.

IPI (Figures 4A, B) were significant adverse prognostic factors for survival (Table 5). For patients with a low IPI (IPI=0/1), OS at 5 years was 87% (95% CI, 83 to 91%) whereas it was 64% for those with a high IPI (IPI=2/3) (95% CI, 50 to 78%). Among the 36 patients who had only a partial response or no response to chemotherapy and despite 27 of them achieving CR after radiotherapy, 13 died of progressive disease (36%) whereas there were 20 relapses (9%) in the 213 patients in CR after chemotherapy ($p$<0.001). Overall survival at 5 years for CR patients was 89% (95% CI, 85 to 93%) as compared to 54% for patients with partial remission (95% CI, 38 to 70%). T-cell subtype was not a worse prognostic factor than B-cell phenotype, nor was extra-nodal involvement or Ann Arbor staging. It must be underlined that 8 patients had anaplastic T-cell NHL (34% out of the 25 patients with T-cell NHL) which is recognized to have a better prognosis. The Cox model multivariate analysis showed that poor PS ($p$=0.009) and failure after chemotherapy ($p$=0.026) were the two factors associated with shorter survival (Figures 4 C,D). Overall survival at 5 years for patients with good PS (0) was 86% (95% CI, 82 to 90%) as compared to 60% for patients with PS ≥1 (95% CI, 40 to 80%).

### *Toxicity and long-term effects*

There were 4 fatal infections due to septic shock during neutropenia. These occurred after the first course of high-dose CHOP in patients not receiving G-CSF (n=143, before 1990). Two other patients developed severe infections. Eleven patients (3%) presented a secondary malignancy which developed at a median of 36 months after ending treatment (range, 0 to 109 months). Five patients died of leukemia (n=2), melanoma (n=1), or rectal cancer (n=2). Three patients died of unrelated causes. There were 3 cases of thyroid dysfunction, occurring in patients receiving cervical irradiation, and 3 cases of heart failure, possibly due to anthracycline toxicity (Table 4).

## Discussion

We report the long-term results of a series of 253 patients under 60 years old suffering from localized large cell NHL all treated with combined chemo-radiotherapy. The value of our study mainly lies in the long follow-up period which enabled us to assess the incidence of long-term relapse and toxicity, and

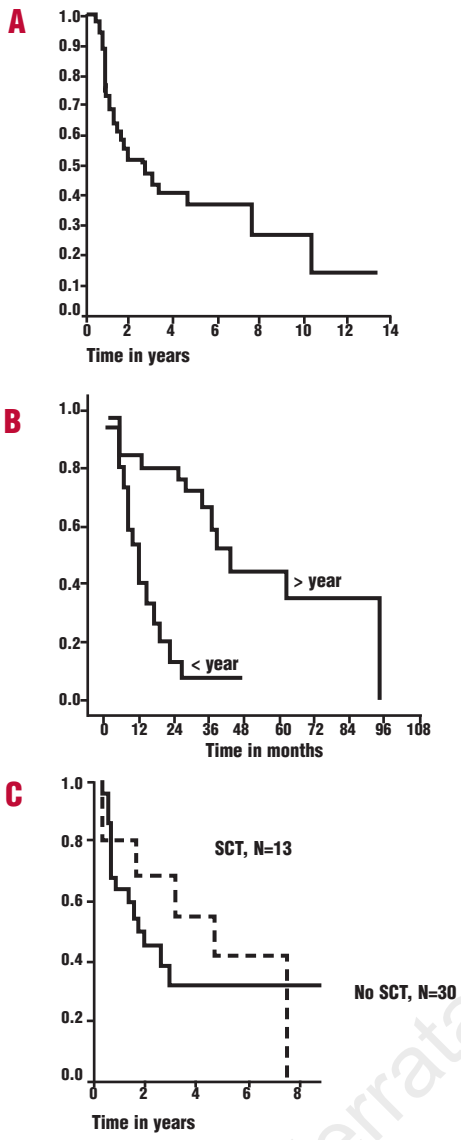


**Figure 3.** Overall survival according to the age-adjusted IPI (including LDH level, performance status, and stage (A), to IPI 0/1 vs. 2/3 (B), and according to the response after 3 courses of chemotherapy (C), and PS at diagnosis (D).

**Table 4.** Toxicity and long-term adverse effects of 3 courses of high-dose CHOP + radiotherapy.

| *Type of Complications* | *Number* |
|---|---|
| Infections (n = 8) | |
| Fatal infections (septic shock) | 4 |
| Hepatitis | 2 |
| Other infections | 2 |
| Neoplasia (n = 11) | |
| Acute leukemia | 2 |
| Melanoma | 1 |
| Rectal carcinoma | 2 |
| Lung carcinoma | 1 |
| Breast cancer | 2 |
| Head and neck cancer | 3 |
| Hyperthyroidism (n = 3) | |
| Hashimoto thyroiditis | 2 |
| Grave's disease | 1 |
| Cardiac and coronary disease (n = 3) | 3 |
| Unrelated deaths (n = 3) | |
| Car crash | 1 |
| Suicide | 1 |
| Drowning | 1 |

**Table 5.** Prognostic factors for survival.

| | Univariate | Multivariate |
|---|---|---|
| LDH> normal | 0.0036 | ns |
| PS >1 | <0.00001 | 0.009 |
| Stage I/II | 0.11 | ns |
| B symptoms | 0.0035 | ns |
| Phenotype | 0.34 | ns |
| Extra-nodal | 0.36 | ns |
| Bulky disease | 0.0003 | ns |
| Failure after 3 courses of chemotherapy | <0.00001 | 0.026 |
| IPI 0/1 vs. 2/3 | 0.0001 | ns |

the results of dose intensity since the chemotherapy was calculated on the basis of 3 courses of a high dose CHOP regimen. Our results confirm that a high CR rate may be obtained with anthracycline-based chemotherapy followed by involved field radiotherapy.[1-5,10-14] We observed a 94% CR rate after completion of treatment, which compares well with other series, reporting CR rates of 75% to 99%. With a median follow-up of 88 months (which is the longest ever reported in such patients), OS at 10 years was 78%. However, relapse occurred in 43 patients (18%). Nine relapses (27%) occurred after 5 years, 3 of which after 10 years. This means that even in a context of localized NHL in young patients, it is difficult to reach a plateau and that very late relapses may be observed. Reported relapse rates have varied from 10 to 27%.[1-5,8-9,10-14] However, the median follow-up time was generally relatively short, being less than 5 years in most series, which means that the relapse rate is possibly underestimated. Our data confirm the results of studies by Shenkier *et al.* and Velasquez *et al.* who reported late relapses up to ten years after CR.[10,15] This finding emphasizes the need for long-term observation even for patients with localized NHL. In our study, 34 relapses (79%) occurred outside the irradiated field and 9 (21%) in the initial field, matching previous reports in different series.[8,10] The

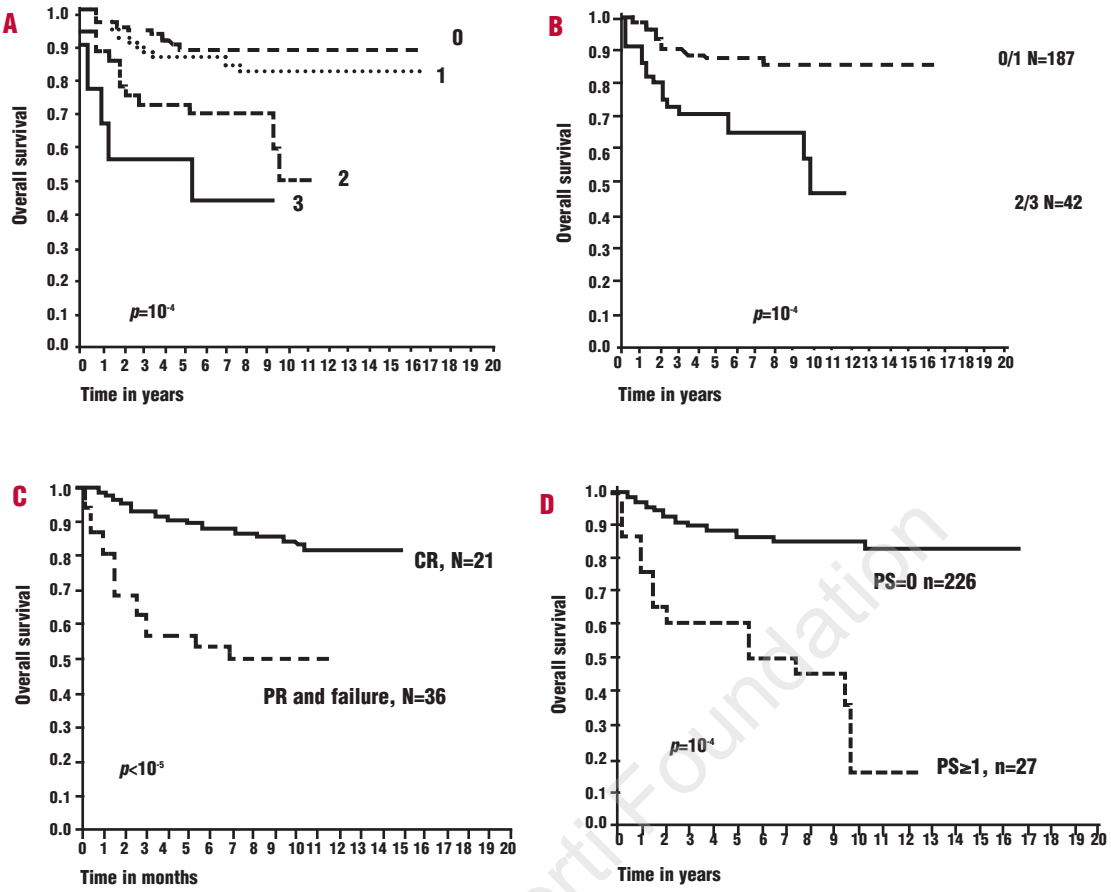


**Figure 4.** Overall survival according to the age-adjusted IPI, including LDH level, performance status, and stage (A and B) and according to the response after 3 courses of chemotherapy (C), and PS at diagnosis (D).



prognosis of relapsing patients was very poor, particularly for those who had an early relapse (within the first year after the end of initial treatment). In a univariate analysis, we observed that 187 patients with 0 or 1 risk factor had a significantly better OS at 5 years (87%) than the 42 patients with 2 or 3 factors (63%, $p$=0.0001). Two major studies reported the clinical impact of IPI on survival.[8-9] These studies examined four factors: age, LDH level, stage, and PS. In the series reported by Miller *et al.*, the progression-free survival was 77% for patients with 0 or 1 risk factor, and 34% for patients with 3 risk factors.[9] Shenkier *et al.* identified 3 groups of patients according to the IPI.[8] Two groups of patients, representing 90% of the series, defined by the presence of 0 to 2 factors had a good prognosis, with a 10-year OS of 95% and 81%, while a small group of 31 patients (10%) with 3 or 4 risk factors had a less favorable outcome with a 10-year OS of 61%. These data clearly indicated the potential impact of IPI on OS in localized NHL. In multivariate analysis, only poor PS and absence of CR after chemotherapy were of significant value in predicting OS in our series. Our study highlights the poor clinical outcome of patients who do not reach CR after chemotherapy. For these patients, although radiotherapy may lead to a clinical CR, the rate of relapse or disease progression is high. The high-dose CHOP regimen was well tolerated in this series of patients under 60 years old. We observed 4 toxic deaths due to severe infections at the beginning of the study when G-CSF was not available and not routinely administered (before 1990, n=143 patients). Using G-CSF support, the duration of absolute neutropenia (< $0.5\times10^9$ neutrophils/L) was less than 4 days in the 110 patients treated after 1990. There were 12 unrelated deaths, 5 due to leukemia or cancers. This incidence is much lower than that observed in the study by Shenkier, who reported 57 (19%) secondary malignancies: this difference can probably be explained by a median age of 64 years in Shenkier's series, as compared to 42 years in our study.[8]

The optimal therapeutic strategy for localized high-grade lymphoma is still much debated. There are two main issues: (i) should patients with localized NHL receive local irradiation ? and (ii) should they, at least those under 60 years old, receive more intensive chemotherapy ? As far as concerns the first issue, two

**Table 6. Summary of the 4 randomized studies published on stage I-II intermediate and/or high-grade NHL treated with combined adriamycin-containing chemotherapy and radiotherapy (RT) or CT alone.**

| *Patients* | *Treatment* | *Median age* | *Median follow-up (months)* | *CR (%)* | *FFS (%)* | *5-yr OS (%)* | *DFS (%)* | *ref* |
|---|---|---|---|---|---|---|---|---|
| 345 | 8 CHOP + RT | | | 89 | 73 | 84 | 73 | |
| | vs. | 59 | 72 | *nd* | *p*<0.04 | *p*=0.06 | *p*=0.03 | 14 |
| | 8 CHOP | | | 61 | 58 | 70 | 58 | |
| 401* | 3 CHOP + RT | | | 75 | 77 | 82 | | |
| | vs. | 59 | 53 | ns | *p*=0.0.3 | *p*=0.02 | nd | 9 |
| | 8 CHOP | | | 73 | 64 | 72 | | |
| | | | | *5 yr- EFS (%)* | | | | |
| 631 | 3 ACVBP + prolonged CT* | | | 93 | 82 | 90 | | |
| | vs | 47 | 92 | ns | *p*<0.001 | *p*=0.001 | nd | 12 |
| | 3 CHOP +RT | | | 92 | 74 | 81 | | |
| 518 | 4 CHOP | | | 89 | 66 | 76 | | |
| | vs. | 68 | 49 | ns | *p*=0.6 | *p*=0.1° | nd | 13 |
| | 4 CHOP + RT | | | 91 | 61 | 67 | | |

**Maintenance chemotherapy; °for patients > 60 years old, OS was better in the 4 CHOP arm (p<0.02); nd: not done.*



ranndomized studies clearly underlined the benefit of administering radiotherapy after completion of chemotherapy.[9-14] This can help to shorten the number of cycles of chemotherapy with less toxic effects and decrease the incidence of relapse, especially at the initial tumor sites. Conversely, a more provocative strategy raised the question of the utility of radiotherapy. In a randomized trial in elderly patients, the GELA group showed that 4 courses of CHOP alone gave identical results to the same regimen followed by local irradiation.[13] Furthermore, in patients over 69 years old, OS was better for those who did not receive radiotherapy.

With regards to the second issue, in our study patients received a high-dose CHOP regimen but the results, in terms of CR rate and OS, were identical to those of previous studies in which patients received a standard CHOP regimen (Table 6). In the recently published GELA study, including younger patients (< 60 years), an intensified cytostatic regimen followed by a prolonged maintenance chemotherapy regimen without irradiation was compared to 3 courses of CHOP + radiotherapy. With a median follow-up of 92 months, OS at 5 years was statistically superior in the chemotherapy group.[12] However, longer follow-up is needed to assess the incidence of secondary malignancies which could be increased by prolonged chemotherapy.

It is possible that these results could be improved by optimizing the chemo-radiotherapy regimen or by better identification of the poor prognosis subgroup. The former strategy has been tested successfully by a combination of rituximab with chemotherapy in advanced high-grade B-cell NHL.[17] This strategy is also beneficial for localized NHL as demonstrated by the recent MINT trial in which rituximab was combined with CHOP in low risk patients (including stage II) with advanced B-cell NHL.[18] Dose intensity has been proven to optimize the results in large B-cell NHL. Administration of CHOP twice monthly (CHOP-14) instead of every 3 weeks increased CR rate and survival in a German trial.[19] This strategy should also be tested for localized NHL. As regards identification of the poor prognosis subgroup, positron emission tomography (PET) could help to identify non-responders better. It has been recently shown that a persistent positive PET in patients after front-line chemotherapy had a very high impact on OS in patients with advanced aggressive NHL.[15-16] This point should be analyzed in patients with localized NHL.

Gene expression profiling has confirmed the heterogeneity of diffuse large B-cell lymphomas and identified patients with different prognoses.[20] The germinal-center B-cell-like subgroup has a high level expression of germinal-center B-cell signature genes and these patients have a higher rate of overall survival.[21-22] However, it has recently been shown that long term relapses preferentially present features from the germinal-center B-cell-like subgroup with bcl-2 and CD10 expression.[23] Therefore, gene expression profiles in localized NHL could be helpful in characterizing high-risk patients.

Finally, our study demonstrated that high-dose CHOP followed by radiotherapy in localized intermediate or high-grade NHL is feasible with very few com-

plications, a good CR rate, and 78% OS at 10 years. The majority of patients with very limited stage NHL (low IPI and non bulky) may be cured by 3 courses of a doxorubicin-based regimen followed by involved field radiotherapy. Nevertheless, late relapses do occur. Patients with more advanced disease (IPI >1, stage II and bulky) should be offered adapted therapy including rituximab and intensive chemotherapy.

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*The order of authorship is in accordance with the number of patients included per center. The authors declare that they have no potential conflicts of interest.*

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