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Long term outcome of patients with localized aggressive non-Hodgkin lymphoma treated with PROMECE-CYTABOM plus involved-field radiation therapy: a study by the Gruppo Italiano Studio Linfomi

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Abstract

We conducted a retrospective analysis on 168 adult patients with newly diagnosed, limited-stage (I and II) diffuse large B-cell lymphoma (DLBCL) treated from 1988 to 2004 with PROMECE-CYTABOM (P-C) plus involved-field radiation therapy (IF-RT). At the end of P-C, the overall response rate was 92%. Radiotherapy (RT) was delivered to 84% of cases. With a median follow-up of 95 months, overall survival (OS), relapse free survival (RFS), and failure free survival at 5 and 10 years was 84% and 77%, 81% and 75%, 71% and 67%, respectively. Age (>60 years, $p = 0.002$), serum albumin (<3.5 g/dL; $p = 0.015$), and RT ($p < 0.001$) were independent predictors of OS. For patients in complete remission the administration of RT didn't improve both RFS and OS. This study confirms that patients with localized aggressive lymphoma have a high chance of cure with anthracycline containing regimens. Though the regimen used to treat these patients does not contain rituximab, results are considered excellent both in terms of efficacy and safety.

Keywords: *Localized lymphoma, chemotherapy, radiotherapy, outcome, toxicity, retrospective analysis*

Introduction

Aggressive non-Hodgkin lymphomas (NHL) represent 40% of all newly diagnosed NHL. Natural history of the disease is a rapid progression due to the rapid growth rate and immature nature of the neoplastic cells. Nevertheless, unlike indolent lymphoproliferative disorders, aggressive lymphomas are potentially curable. Their prognosis depends on the degree of tumor spread at diagnosis and intrinsic biological peculiarities of the disease, as well as clinical features and personal data of the patients. Biological aspects of aggressive lymphomas have been partially elucidated by molecular study of gene

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involvement in lymphoma-genesis, with genetic variations highlighting two genotypes with different degree of aggressiveness [1].

Thus far, stage has been considered one of the most important parameters for predicting patient outcome [2], determining tumor aggressiveness, and for tailoring treatment intensity. In particular, aggressive NHL are localized in about 30% of cases, presenting with stage I and II disease. Previous reports showed that in these cases, regardless of other prognostic parameters and therapeutic approaches, overall survival (OS) and disease free survival (DFS) can be very long [3–5]. Prognosis of patients with limited stage aggressive NHL can be easily predicted using stage-adjusted international prognostic index (saIPI), a modified version of international prognostic index (IPI) where stage is further subdivided into I and II: adverse prognosis is assigned to stage II. In cases with very limited disease (saIPI = 0), 5- and 10-year OS estimates exceed 90% [3].

The mainstay of treatment is combined modality treatment with chemotherapy (CT) and radiotherapy (RT). A stage specific treatment approach is therefore justified to reduce, when possible, the therapeutic load and consequent immediate and late toxicity, without worsening the clinical outcome. In contrast to advanced stage lymphoma, the use of rituximab has been investigated in only a few studies of localized disease [6,7], where its use in combination with CT was shown to improve survival [3].

In 1988, when data on rituximab were not available and when 3rd generation regimens were emerging as promising CT regimens, the GISL issued an internal guideline for the treatment of patients with limited stage aggressive NHL consisting of four to six courses of PROMECE-CYTABOM (P-C) CT followed by involved-field radiation therapy (IF-RT) managed according to response.

Here, we present the result of a retrospective analysis recently completed on patients with limited stage aggressive NHL treated by GISL centers according to group policy.

Materials and methods

Patients

The GISL registry of patient with malignant lymphoma was used to identify cases. The registry was opened in 1988 with the aim of prospectively registering cases with specific lymphoma subtypes that were diagnosed in one of the group centers according to running projects. The archive includes patients enrolled in clinical trials, prospective and retrospective studies; it collects basic data on clinical and diagnostic features at diagnosis and treatment modality for each lymphoma and currently includes 11 565 cases as of December 2004 the archive included 1583 patients with aggressive NHL. Patients suitable for the present study were identified from the main archive using the following criteria: previously untreated, biopsy-confirmed, aggressive NHL according to Revised European-American Lymphoma – WHO Classification, (F/DM, G/DL, and H/IBL with B-cell phenotype categories of the Working Formulation classification were also accepted), age older than 18 years, WHO performance status 0–3, limited Ann Arbor stage (I, IE, or non bulky II, IIE) with less than three involved nodal areas. Patients were also required to have received treatment according to GISL policy for localized aggressive NHL (see below). Study period was from 1988 to 2004. Patients with acquired immunodeficiency syndrome, a diagnosis or history of indolent lymphoma or other neoplasms, or marked impairment of cardiac, pulmonary, hepatic, or renal function were excluded.

A complete dataset was then defined and data were collected for eligible patients. The dataset was built to collect data on demographics, disease extent, laboratory tests, treatment, response to treatment, and follow-up. Bulky disease was defined as any mass with a diameter of more than 10 cm or a mediastinal mass with a maximal diameter exceeding one third of maximal chest diameter on chest X-ray. The following clinical and laboratory data were considered for the clinical and prognostic evaluation: age, sex, stage, performance status (PS), extranodal sites (ES), serum lactate dehydrogenase (LDH), B symptoms, bulk, erythrocyte sedimentation rate (ESR), serum albumin (SA) level, hemoglobin (Hb) level, white blood cell (WBC) count, platelets (PLT) count.

Therapy

The GISL guideline for treatment of patients with localized stage aggressive NHL consisted of 4–6 cycles of P-C followed by IF-RT. The P-C regimen consisted of: cyclophosphamide 650 mg/m^2 day 1, epidoxorubicin 30 mg/m^2 day 1, VP 16 120 mg/m^2 day 1, prednisone 60 mg/m^2 days 1–14, Ara-C 300 mg/m^2 day 8, bleomicine 5 mg/m^2 day 8, vincristine 1.4 mg/m^2 day 8, methotrexate 120 mg/m^2 day 8, and leucovorin 10 mg/m^2 every 6 h for five times and 24 h after methotrexate infusion. Cycle were to be delivered with a 21 days interval according to the original design [8]. Patients achieving complete remission (CR) within the fourth cycle were to be treated immediately with RT. Patients not achieving CR within cycle 4 received the full six courses of P-C before starting RT.

Treatment was to be interrupted in case of disease progression, patient's refusal to continue with therapy, or in case of severe concomitant illness or adverse events at the physicians' discretion.

After CT, all patients had to receive RT (36 Gy) to the area of initial disease presentation, irrespective of the result of CT.

Tumor response evaluation

For the purposes of this study the response was retrospectively assessed and was defined as follows: CR was defined as the disappearance of all clinical evidence of disease and the normalization of previously abnormal laboratory tests and radiographs. Partial remission (PR) was defined as greater than 50% reduction in the largest dimension of each anatomic site of measurable disease for at least 1 month. No response (NR) was defined as less than 50% regression or stable or progressive disease.

Variables analyzed

The study endpoints were overall response rate (ORR), OS, relapse free survival (RFS), failure free survival (FFS), and treatment related toxicity. ORR was defined as percentage of patients with CR and PR, respectively. OS was defined as time from diagnosis to death from any cause. RFS was defined as the time from CR or unconfirmed CR to relapse. FFS was calculated as time from diagnosis to NR, progression, relapse, or death from any cause.

Statistical analysis

Proportions were compared with Chi_2 or Fisher's exact test for categorical variables and with Kruskall-Wallis test for parametric variables. Survival curves were plotted according to Kaplan–Meier method [9] and compared with Log rank test. The adjustment for prognostic factors for DFS and OS was performed using Cox regression analysis [10]. The level of statistical significance was set at a two-sided $p < 0.05$.

Toxicity was coded on a 0 to 4 scale according to the National Cancer Institute Common Toxicity Criteria (CTC), version 2. Cumulative incidence of second tumor was estimated in the competing risk model with death from any causes considered a competing event [11].

Results

From 1988 to 2004, 185 cases with limited stage aggressive lymphomas were identified from GISL archives that were treated according to the group guidelines for limited stage aggressive lymphoma. Of these, 12 were excluded because they were classified as Mantle Cell lymphoma (one case) and Follicular lymphoma (11); and five cases were not considered due to missing data. The remaining 168 were considered fully eligible for the present analysis. Patients were registered from 27 Italian GISL centers throughout the national territory. Characteristics of eligible patients are listed in Table I.

After 3–4 cycles of CT, 109 patients were in CR (65%), 8 in PR (5%), and 3 in SD/PD (1.8%). At the end of CT (six cycles), an additional 33 CR and 4 PR were achieved. Therefore at the end of CT program, a total of 142 CRs (85%) and 12 PR (7%) were obtained. Overall 14 patients did not complete the treatment program and were recorded as treatment failures (1 stable disease, 2 progressive disease, 11 early withdrawals).

RT after CT was performed in 141 cases (84%), of which 133 were in CR or PR. In 82 patients, RT was carried out at the initial site of the disease, while in 16 cases it was extended to a larger area. In 35 patients, the area of irradiation was not indicated. The patients received RT in the range of 26 to 54 Gy with a median radiation dose of 36 Gy; 80% of patients received RT dose between 32 and 44 Gy. At the end of radio- CT, 151 (90%) patients were in CR and 3 (2%) in PR (Figure 1). This corresponds to an ORR of 92%.

At time of current analysis, the median follow-up for living patients is 95 months (range 7–213). During follow up, 25 of 151 responder patients relapsed. Moreover, 32 patients died. Cause of death was relapse/progression in 20 patients (62%), second

Table I. Baseline characteristics of the 168 patients included in our retrospective analyses.

	Population ($n = 168$)	
Characteristic	*n*	%
Age, years ≥60 years	67	40
Male gender	107	64
Ann Arbor stage		
I	121	72
II	47	28
Extranodal involvement 2+	3	2
ECOG performance status 2–4	1	<1
Elevated LDH	29	17
International prognostic index M		
0	68	40
1	57	34
2–3	43	26
B symptoms	8	5
Bulky disease	9	5

ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; IPI M, modified International Prognostic Index applied to early-stage NHL (IPI with stage I = 0 and stage II = 1).

malignancies in 3 (10%), infection in 2 (6%), heart failure in 2 (6%), and treatment toxicity in 2 (6%). Cause of death was not known in three patients (10%).

At the end of the retrospective analyses, 120 patients (71%) were in CR.

After 5- and 10- year follow-up, OS was 84% (CI95% 77–89) and 77% (CI95% 68–83), respectively. Five- and 10-year FFS was 71% (CI95% 63–77) and 67% (CI95% 59–74), respectively. Five- and 10-year RFS was 81% (CI95% 73–87) and 75% (CI95% 65–83), respectively [Figures 2(a) and 2(b)]. For patients who achieved CR after CT $\pm$ RT, the cumulative risk of relapse or death of any causes was calculated at 12.4% (95% CI 7.7%–19%), 21% (14.2%–31%), and 28% (18.6%–42%) at 3, 5, and 10 years, respectively.

When univariate analysis for OS was performed the following parameters were significantly related to survival: age > 60 ($p < 0.001$), LDH > normal value ($p = 0.002$), SA < 3.5g/dL: $p = 0.042$) and ESR (>30; $p = 0.046$). The administration of RT also predicted survival ($p < 0.001$). The performance of stage adjusted IPI (saIPI) score was also tested and was statistically significant for OS ($p = 0.007$) (Table II); however, significance was only found comparing patients without risk factors *versus* patients with two or three factors. saIPI was also predictive of outcome when tested for FFS and RFS.

When multivariate analysis was performed for OS, statistically significant factors were age > 60, SA < 3.5 g/dL, and RT (Table III). However, the role of RT as an independent predictor of OS was not maintained when a multivariate analysis for OS was performed only for patients achieving CR at treatment completion. In this latter analysis, only age and elevated LDH were confirmed to be

Table II. Five and ten years overall survival evaluated according to modified IPI.

IPI M	IPI M%	5 yr OS (%)	10 yr OS (%)
0	40	92 (CI95% 82–97)	90 (CI95% 78–95)
1	34	82 (CI95% 69–90)	77 (CI95% 63–86)
2–3	26	73 (CI95% 57–84)	57 (CI95% 35–73)

OS, overall survival; IPI M, IPI M, modified International Prognostic Index.

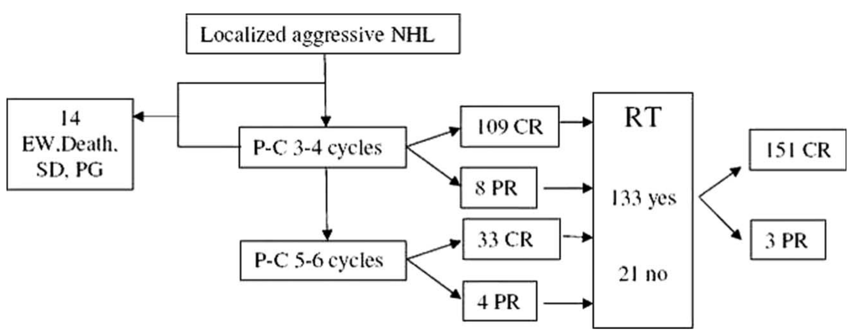

Figure 1. Study flow chart.

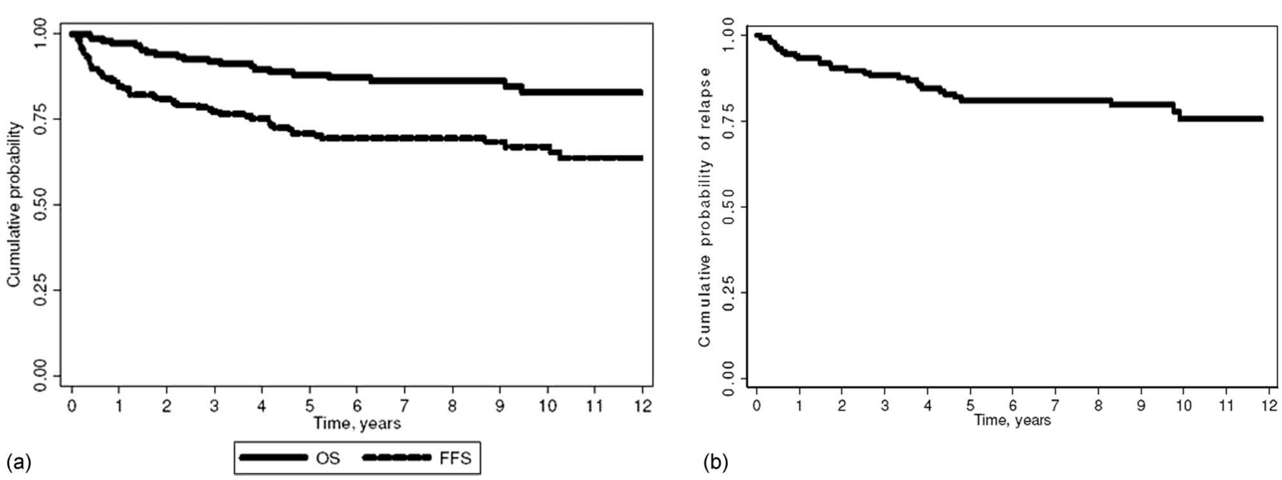

Figure 2. (a) Overall survival and failure free survival of 168 patients treated following GISL guidelines from 1988 to 2004. (b) Relapse free survival of 168 patients treated following GISL guidelines from 1988 to 2004.

independently correlated with OS. The same results were obtained for multivariate analysis of RFS (Table IV).

Toxicity

Acute toxicity was primarily hematological. In total, 25 patients (14%) experienced grade III and IV (WHO) toxicity: four cases of anemia (2%), 11 neutropenia (7%), 2 thrombocytopenia (1%), and 8 infections (4%). Fatal toxicity consisted of severe infections (two cases).

Late toxicity, documented throughout follow up, appears quite mild. A second neoplasm was diagnosed in six patients: one prostatic carcinoma (+48 months), one lung cancer (+72 months), one myelodysplastic syndrome (+98 months), one laryngeal cancer (+101 months), and two colorectal cancers (+72, +108 months). One patient developed lung fibrosis and *cor pulmonale* at 36 months and another patient had an acute myocardial infarction at month 108. Cumulative incidence of developing a second malignancy after 5- and 10-year follow-up is calculated at 0.7% and 7%, respectively.

Discussion

The present retrospective analysis aimed to evaluate the role of CT followed by RT in the treatment of aggressive, early stage NHL. The median follow up time in our series allowed evaluation of long-term outcome.

Some early studies on patients with stage I and II disease receiving a variable number of CHOP cycles with and without consolidation RT showed that short course CT followed by IF-RT was effective [12–14]. Following these reports and based on the results of a phase III randomized study, the standard approach to patients with localized aggressive NHL has been a brief course of CT followed by IF-RT [3].

The GISL adopted P-C as the CT regimen of choice, a protocol that has subsequently been abandoned based on the results of a large randomized trial. Though questionable, the choice of third generation combination CT (P-C) as recommended treatment was based on extensive experience within the GISL in the treatment of aggressive advanced stage lymphoma [15–18] and the lack of comparative data concerning CHOP when this protocol was defined in 1988.

Our results show that the P-C regimen followed by RT provides high response rates and excellent survival: in particular, the 92% response rate and the 77% 10-year OS compare favourably with the outcome of previous reports, which were 70% and 90% in stage modified IPI > 0 and IPI = 0, respectively (Table V). The prolonged follow-up of our series allowed accurate analysis of late events. Overall, observed adverse events are very few and in line with previously reported experience on the same patients' subset. Non oncological events were rare and in only one case they were likely to be related to CT (lung fibrosis at +3 years). A second solid cancer was diagnosed in five patients after a median follow-up of 6 years and without a predominant histology; the only young patient who developed a second tumor (laryngeal carcinoma) was a heavy smoker. Non solid cancer only occurred in one patient who experienced MDS after 8 years. These data confirm the long term safety of P-C CT [20]. Finally, among 168 cases only one had a CNS involvement at relapse (0.6%: data not shown); though most patients considered in our study were at low risk. This observation favourably compares with the expected 2.2–2.8% risk of CNS relapse described for aggressive lymphomas [21,22].

Interestingly, these positive results were obtained with the combination of P-C CT and IF-RT by modulating the number of CT courses based on initial response to treatment. Briefly, patients in CR after the first three to four cycles were immediately treated with RT. Patients not achieving CR after the initial four cycles had to complete six full courses of CT before RT. Overall adherence to the treatment plan was satisfactory with the majority of patients (109/168) achieving a CR early, within four courses of CT. The addition of two more cycles in 37 patients achieved an additional 33 CRs. These results suggest the importance of monitoring response early during treatment, also if assessment is by CT scan only, and confirm results obtained with a similar

Table III. Multivariable analysis for OS carried out on all analyzable patients.

Covariate	HR	SE	*p*
Age > 60	3.31	1.30	0.002
Alb < 3.5 g/dL	3.45	1.69	0.015
RT no	4.20	1.75	< 0.001

OS, overall survival; HR, hazard ratio; SE, standard error; Alb, albumin; RT, radiotherapy.

Table IV. Multivariable analysis for OS and RFS, carried out on patients who achieved CR at the end of the therapeutic protocol.

Covariate	OS		RFS	
	HR	*p*	HR	*p*
Age > 60	3.34	0.019	2.66	0.004
Elevated LDH	3.03	0.020	2.55	0.008

OS, overall survival; RFS, relapse free survival; HR, hazard ratio; LDH, lactate dehydrogenase.

Table V. Results of clinical trials on treatment of patients with limited stage aggressive B cell lymphoma.

	CT only		CT + RT				CT + Rituximab + RT
	Swog 8736 [3]	GELA [4]	Swog 8736 [3]	BCCA [5]	GELA [4]	GISL	Swog 0014 [19]
N	201	318	200	308	329	168	60
Age (median)	59	46	59	64	47	39	69
CT	8 × CHOP	3 × ACVBP	3 × CHOP	3 × ADM-based CT	3 × CHOP	4–6 × P-C	R + 3 × CHOP
Stage I	67%	67%	68%	61%	66%	72%	57%
RT	NA	NA	IF-RT	IRRT	IF-RT	IF-RT	IF-RT
Time	5 years	5 years	5 years	5 years	5 years	5 years	4 years
OS	72%	90%	82%	81%	81%	84%	92%
PFS	64%	82% (EFS)	77%	80%	74% (EFS)	81% (RFS)	88%
Incl/excl	stage I and II non bulky	stage I and II, bulky admitted, aa-IPI = 0	stage I and II non bulky	no bulky (10 cm), T-NHL 12%, ENL (66%)	stage I and II, bulky admitted, aa-IPI = 0	bulky admitted, treatment length based on response	stage I and II non bulky, SmIPI > 0

CT, chemotherapy; RT, radiotherapy; OS, overall survival; PFS, progression free survival; Incl/excl, inclusion and exclusion criteria; IF-RT, involved-field radiation therapy; IRRT, involved region radiotherapy; EFS, event free survival; aa-IPI, age-adjusted International Prognostic Index; ENL, extranodal lymphoma; SmIPI, stage-modified International Prognostic Index; GISL, Gruppo Italiano Studio Linfomi; RFS, relapse free survival; SWOG, Southwest Oncology Group; GELA, Groupe d'Etude des Lymphomes de l'Adulte; BCCA, British Columbia Cancer Agency; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; ADM, Adriamycin; ACVBP, doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone; T-NHL, T-cell non-Hodgkin lymphomas; NA, not administered.

approach used in patients with Hodgkin lymphoma [23]. Since both a correct definition of limited disease and a reliable assessment of early complete response play a key role in the treatment of localized, aggressive lymphoma, the recently introduced PET technology is potentially valuable in this subset of patients with NHL. In fact, PET scan may represent a powerful tool for accurate staging, to evaluate the presence of active disease in residual lesions at the end of therapy, and, at least in Hodgkin lymphoma, to evaluate neoplastic cell chemosensitivity *in vivo*. Thus, PET can be useful in treatment optimization, in terms of providing maximal efficacy and minimal toxicity [24–26].

One of the major and controversial issues with the treatment of localized aggressive lymphomas is the role of RT [27–32]. Our study cannot be used to assess the role of RT as this was not a randomized trial and RT was planned for all patients, regardless of response. Nonetheless, the results show that not all patients received consolidation RT, even in some patients that achieved CR after CT, apparently as guideline deviation. We attempted to evaluate the use of RT in the univariate and multivariate analysis of survival. In a first multivariate analysis of OS, the administration of RT was confirmed as an independent prognostic factor, along with patients' age and SA. However, this result could have been biased by the fact that the decision to avoid RT in patients with more aggressive disease may have been based on unsatisfactory results with CT program or with early relapses. We then decided to perform additional multivariate analyses on RFS and on OS, but only for patients achieving CR after treatment. As a result, the administration of RT was not confirmed as an independent prognostic factor; only age and LDH were identified as independent predictors of outcome. Our results favor the hypothesis that if patients with early stage aggressive lymphoma achieve CR with initial CT, RT may be avoided, thus reducing unwanted toxicity.

In the years considered by our analyses, rituximab monoclonal antibody was not used for the treatment of B-cell NHL. Subsequently, the efficacy of rituximab in advanced high grade NHL has been widely documented, both in elderly [33] and in young patients [34]. However, the very good outcome of early stage aggressive NHL with short conventional CT plus RT makes it more difficult to demonstrate efficacy and suggest the systematic use of rituximab in this subset of NHL.

To date, few reports are dealing with the use of rituximab in early stage aggressive NHL [19]. According to the 0014 Study from Southwest Oncology Group, the impact of rituximab in limited-stage diffuse large B-cell lymphoma (DLBCL) appears to be smaller than in advanced-disease setting and when compared with results achieved with combined modality therapy. The Mabthera International Trial (MInT) was conducted to investigate the role of rituximab in young patients with low risk DLCBL [35]. Though all stages were included, the admission of patients with an IPI of 0 and 1 resulted in the inclusion of a majority of patients with limited stage disease. The overall results of the study showed that the addition of rituximab to CHOP regimen improves patients' survival. In particular, in patients with mediastinal B-cell lymphoma the addition of rituximab to CHOP therapy improved the outcome [36]. However, in this same setting of patients with mediastinal lymphoma, data have been published demonstrating that the effect of rituximab on survival improvement may be reduced by the adoption of weekly regimens [37]. One single standard treatment for patients with limited stage aggressive lymphoma is thus far from clear. As summarized in Table V, similar excellent results can be achieved with different strategies, including intensive CT regimens without RT [4] or short course of CT (CHOP, CHOP like, or third generation regimens) $\pm$ rituximab followed by RT. Considering the excellent activity with each of these regimen, identification of the best option must be based on additional considerations, i.e. long term safety is considered the most important option.

In conclusion, the long-term outcome of patients included in the present analyses confirms that anthracycline containing CT with IF-RT represents the backbone of treatment for patients with localized aggressive NHL, and that the role of RT in patients achieving a CR is questionable. The possible improvements deriving from the systematic use of PET scan and by addition of rituximab to the treatment regimen remain open questions. Well designed studies addressing both of these issues are strongly warranted.

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