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Low-grade Follicular Lymphomas: Analysis of Prognosis in a Series of 281 Patients

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From 1963 to 1988, 281 patients with newly diagnosed follicular lymphomas were treated and followed at the Foundation Bergonié. Distribution of stages was: 72 I, 61 II, 83 III and 65 IV. Within stage III, two subgroups were retrospectively defined: stages III_1 (32 cases) included patients with less than 8 involved sites, only 1 or 2 above diaphragm, and no spleen or mediastinal enlargement. Stage III_2 (51 cases) included the remaining stage III cases. Median follow-up was 9 years. Complete remission (CR) rate was 82%. 10-year overall survival (OS) and time to treatment failure (TTF) rates were, respectively 38% and 29.5%. 10-year time to relapse (TTR) rate was 36%. Statistical analyses showed concordant results with two main prognostic factors: age (<60/>60) and stage (I to III_1/III_2 and IV). Age was the most important factor for OS analysis and stage for CR and TTR analysis. This leads to only three prognostic groups with different outcome. The first includes younger patients (<60 years) with limited stages ($\leq III_1$); the second, patients either older than 60 or with advanced stages; the last, elderly patients with advanced stages. CR rates of these three groups were, respectively 97%, 75% and 57%. 10-year OS were, respectively 73.5%, 27% and 0%; 10-year TTR were 54%, 22% and 0%. These results have lead to data which are easy to handle and which can help to establish a rationale for further prospective trials.
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INTRODUCTION

As demonstrated by all pathological classifications, there is a broad variety among non-Hodgkin lymphomas (NHL). This is confirmed by clinical findings. Correct definition of different groups is not easy to reach since pathological classifications are numerous [1] and not reproducible [2]. However, one large group is homogeneous: that of follicular lymphomas (FL). Indeed, the follicular pattern has 95% reproducibility [1]. However, some investigators [3] have shown some discrepancies between pathologists when classifying FL; yet molecular biology provides some arguments for grouping them together. A large majority of cases (>85%) present t[14,18] chromosomal translocation [4] which is the single most common abnormality in NHL. Molecular analyses show activation of transcription of the proto-oncogene *bcl2* [5] as a result of the translocation. The t[14, 18] chromosomal translocation is the result of a mistake of the VDJ joining enzyme at the pre-B cell stage [6]. *bcl2* will probably define a new category of oncogenes, since it appears to be involved in the mechanism of programmed cell death (apoptosis) [7]. So, although pathological difficulties persist, increasing knowledge of the molecular biology of FL led us to study them together.

Radiotherapy allows prolonged complete remissions (suggesting cure) for localised disease in large series [8, 9] whereas the treatment of choice remains unsettled in advanced follicular lymphomas [10]. It is disappointing to find there is no survival improvement with therapeutic intensification: monochemotherapy is equivalent to polychemotherapy [11]; adjunction of doxorubicin to the usual cyclophosphamide, vincristine and prednisone (CVP) [12, 13] does not add survival advantage [13], and has only given the advantage of relapse-free survival [12].

The majority of FL series study few patients. Only two have had enough patients for powerful prognostic analysis [8, 14]. However, prognostic synthesis is not easy since there are too many groups [8]: the aim of prognostic analyses is to help definition of rationale for trials and to be easy to use. Furthermore, in these series, patient selection is not always in agreement with current knowledge [8].

So, this analysis was aimed at defining prognostic factors in our series of FL patients.

PATIENTS AND METHODS

Patients

From 1 January 1963 to 30 June 1988, 281 previously untreated patients were consecutively admitted with a diagnosis of FL at the Fondation Bergonié. We did not exclude any patients even those who died within one day or older patients. All pathological diagnoses were reviewed in our institute and confirmed follicular small cleaved or mixed lymphomas according to the Working Formulation [1] or follicular centroblastic-centrocytic lymphomas according to the Kiel classification [15]. Follicular large cell lymphomas were not included since we considered and treated them as intermediate grade NHL (they were included in the treatment policies of diffuse centroblastic lymphomas).

Staging studies always included complete blood cell counts, serum chemistries and chest X-ray. Bipedal lymphography and/or abdominal computed tomography (CT) were completed in 98% of cases (bipedal lymphography: 250 cases, 89%; abdominal CT: 81 cases, 29%). We never performed staging laparotomy; diagnostic laparotomy was done on 12 patients (4%). Bone

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Table 1. Patients' characteristics

Age (years)		
Mean	58.3	
Median (range)	60.8	(23–88)
Sex		
Male	136	(48.5%)
Female	145	(51.5%)
Architectural pattern		
Follicular	155	(55%)
Follicular and diffuse	126	(45%)
Stage		
I	72	(25.5%)
II	61	(22%)
II1/II2	27	(10%)/34(12%)
III	83	(29.5%)
III1/III2	32	(11.5%)/51(18%)
IV	65	(23%)
Involved sites*		
Mean	4.3	
Median (range)	3	(1–18)
Maximal tumour† size (cm)		
Mean	6	
Median (range)	4	(1–20)
B symptoms*	29	(10.5%)
Compressive symptoms*	33	(11.5%)
ESR‡ (mm)		
Mean	21.5	
Median (range)	11	(1–126)

*2, †46 and ‡18 missing values.

marrow status was analysed by bone marrow aspirate in 54 cases (20%) and by unilateral bone marrow biopsy in 178 cases (63.5%). All therapy was either administered or closely supervised by physicians of our institute. Patients were staged according to Ann Arbor recommendations. Stage II was divided into two groups in order to improve tumour bulk assessment. Limited stage II (II1), as previously defined by Gospodarowicz [8] included patients with contiguous involvement of only two lymph node areas or extranodal involvement. Remaining stage II constituted stage II2. In the same way, we defined limited stage III (III1) as involvement of less than eight lymph node areas with only two above the diaphragm and without spleen or mediastinal enlargement. Remaining stage III patients were called III2. For the involved sites count, we considered all supradiaphragmatic sites (mediastinal involvement was considered as one site). For subdiaphragmatic ones, we considered paraortic, iliac and inguinal nodes only.

The main features of patients are outlined in Table 1. 8 patients were older than 80 years. Compressive symptoms were defined as vascular or lymphatic compression such as vascular pelvic compression with leg oedema.

Some patients (17%) had predominant extranodal involvement: head and neck (13.5%) and gastrointestinal tract (3.5%). Pathologists defined two kinds of architectural patterns among FL: exclusively follicular or follicular and diffuse.

The cut-off date for the current analysis was 30 June 1989. Median follow-up was 9 years (range: 1–26.5). No patient was lost to follow-up.

Treatment

Localised stages (stages I and II, 133 patients). For most localised disease (113 patients, 85%), radiotherapy was given to involved areas up to 40 Gy median midplane total dose (range: 20–60 Gy) (2 Gy per day at five daily fractions per week) with either a Cobalt-60 unit or a high energy photon beam (×25 MeV). Only 7 patients (6%) received total doses of less than 35 Gy (total abdominal irradiation, 3 cases; prevailing policy at the time of treatment, 4 cases; death before completion of irradiation, 1 case). Most of them (82 cases, 72.5%) received chemotherapy as part of their treatment: one or two courses of CVP or cyclophosphamide, vincristine, doxorubicin and prednisone (CHOP) regimen before and after irradiation as described previously [9, 16]. 18 patients with stage I received no treatment after initial lymph node biopsy because of absence of residual disease.

2 patients received exclusive monochemotherapy for stage II disease since they were old.

Advanced stages (148 patients). Among stages III (83 cases), 24 patients (including 14 III1) received involved field irradation up to 40 Gy median midplane total dose (range: 20–40) preceded and followed by one to three courses of CVP or CHOP [16]. 3 patients received less than 35 Gy midplane total dose. 15 patients received combination of chemotherapy and low dose total body irradiation (two courses of irradiation of 0.75 Gy midplane delivered in five fractions over 1 week, separated by a rest period of 2 weeks) as part of a prospective trial [17].

Chemotherapy was the main treatment for the remaining 44 patients: one to three courses of CVP or CHOP followed by monochemotherapy (vincristine or cyclophosphamide) for at least 2 years. Most stage IV (38 cases) received mainly chemotherapy as described for stage III. 27 patients also received low-dose total body irradiation, as for stage III. Adjuvant BCG therapy was delivered to 52 complete responders as part of randomised trials previously published [18].

Response, survival, time to treatment failure and time to relapse

We followed Dixon's recommendations [19] who proposed a standardisation of reporting outcomes. Complete response (CR) represented disappearance of all signs and symptoms of disease as determined by clinical and radiographic evaluation. Other patients were considered non-responders. We performed restaging when clinical CR was achieved. It included always complete blood counts and chest X-rays. For patients staged by lymphangiography, we performed lymphogram controls at each follow-up. For patients staged by abdominal CT, without any lymphangiography, we performed a new CT only when the initial one was abnormal. New bone marrow biopsies were never performed at restaging. Patients were then followed quarterly for 1 year, twice a year for the next 2 years and then yearly. Each time we performed complete blood cell counts, chest X-ray and control lymphogram. When necessary, we performed CT.

Survival was computed from date of pathological diagnosis. For overall survival (OS), all causes of deaths were considered as events. Time to treatment failure (TTF) was measured from date of pathological diagnosis until relapse, disease progression, death due to treatment, withdrawal or date last known alive. Relapse was considered as soon as its first symptom. Relapse, progression, treatment-related deaths and withdrawals were considered as events. Time to relapse (TTR) was computed from date of pathological diagnosis until relapse or date last known free of disease, including only complete responders and

counting only relapses as events. Survival curves were computed by the method of Kaplan and Meier. Comparisons of features among groups were made using the Student's test for quantitative factors, χ^2 tests for qualitative factors and complete remission rates, and using log rank tests for curves (OS, TTF, TTR). For correlations, we used the Kendall's non-parametric test.

Prognostic analysis

Eight pretreatment variables were studied to evaluate their influence on OS, TTR and CR. These were age (5 categories: 45, 50, 55, 60, 65 years), sex, stage of disease (6 substages: I, II1, II2, III1, III2, IV), involved sites count (1 to 7), B symptoms, compressive symptoms, architectural pattern (follicular versus follicular and diffuse) and erythrocyte sedimentation rate (ESR) (20 and 50 mm). Maximal tumour diameter was excluded from all statistical analyses since most of the missing values were not randomly distributed: most of them were included in stage I (27 among 46: 54%). Therefore, this variable was not representative of the whole population. Lactate dehydrogenase (LDH) and β_2-microglobulin levels had been included in the routine pretreatment work-up for only 3 years. Consequently, we could not analyse their prognostic value.

We also compared OS of complete responders and non-responders. Since numerous parameters were studied, significant factors were considered in the univariate analysis only when P was less than 0.01.

Conditional annual probability of relapse was computed using the life table method: $P = Ev/(Exp - 0.5\ Cd)$, where P = conditional annual probability of relapse, Ev = count of relapses during interval, Exp = patients exposed to risk at the beginning of the interval and Cd = patients censored during interval.

Three kinds of analyses were successively performed: OS and CR prediction for all patients and TTR of complete responders. We first performed univariate analysis. Then, all factors were included in a regression model as dichotomous variables (choosing the most significant cutpoint defined by the univariate analysis). Finally, in order to ensure the validity of these models, we performed other regression analyses including all interval variables as continuous variables. This second model was considered more related to reality, but less easy to handle for clinicians. For OS and TTR analyses, we used the Cox regression model and for response rate, the logistic model. All statistical results were obtained with Medlog and BMDP (2L and LR programs) softwares.

RESULTS

Treatment results

At the time of analysis, 138 patients were alive (116 with no evidence of disease and 22 with relapse) and 143 were dead (102 from lymphoma, 3 from treatment-related cause, 13 from second cancer, 20 from intercurrent disease and 5 from undetermined reasons). The 3 treatment-related deaths occured during second-line treatment of one non-responder and 2 relapses.

CR rate was 82% (231 patients): 97% stage I, 95% stage II, 78% stage III1, 71% stage III2 and 63% stage IV. 117 patients relapsed. The annual relapse probability is outlined in Fig. 1.

5, 10 and 15-year OS were, respectively 62.5%, 38% and 24% (Fig. 2); TTF, 39.7%, 29.4% and 27.3% (Fig. 2); and TTR (CR) 49%, 36% and 33%.

Other cancers

29 patients presented another malignancy before or after FL. 12 patients were treated for another cancer, at least 6 months

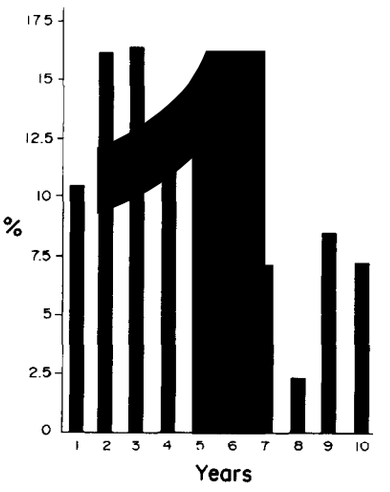

Fig. 1. Conditional annuals probability of relapse (complete responders = 231 cases).

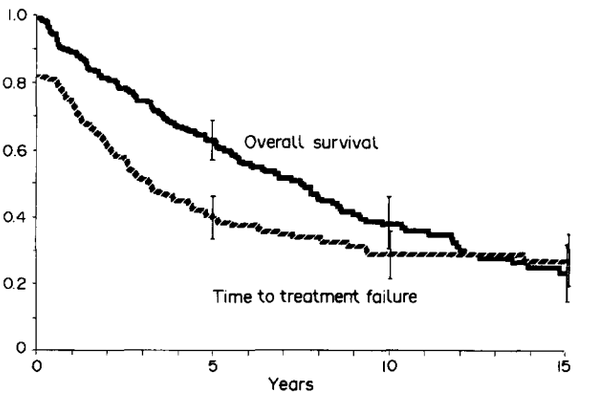

Fig. 2. Overall survival and time to treatment failure of the 281 patients.

before FL diagnosis. These were 10 breast cancers, 1 bladder cancer and 1 testicular seminoma. All of these patients achieved CR. However, 2 patients died from metastatic relapse of their breast cancer 1 and 2 years after completion of FL treatment.

For 17 patients, we diagnosed second malignancy during follow-up. These were 15 solid tumours: 7 gastrointestinal cancers (stomach 1, colon 3, rectum 2), 2 breast cancers, 3 pelvic cancers (endometrial 1, ovary 1, vagina 1) and 3 other cancers (kidney 1, lung 1, melanoma 1). 9 patients died from this second malignancy.

We observed 2 secondary acute non-lymphoblastic leukaemias. Both patients previously received prolonged chemotherapy (5.5 and 9 years of treatment) with high total doses of cyclophosphamide (76 and 120 g). These 2 patients died.

OS analysis

After univariate analysis, six variables were significant (Table 2): CR occurrence (Fig. 3), age (<60/>60), involved sites count (≤4, >4), stage (≤III1/>III1), B symptoms, ESR (≤20/>20 mm) and compressive symptoms. CR occurence was excluded from multivariate analysis since it is a post-treatment factor. All other factors, including non-significant ones, were included in a Cox model as dichotomous variables. The most

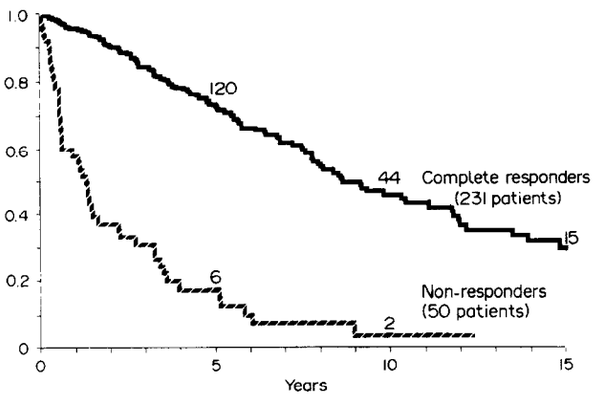

Fig. 3. Overall survival: treatment response. $P < 10^{-28}$.

Table 2. Overall survival: unifactorial analysis

Factor*		OS (years) 5	10	15	P
Complete response					
Yes	(231)	73.5(120)	46 (44)	30 (15)	$<1.10^{-28}$
No	(50)	17.5 (8)	3.5 (2)	—	
Age					
<60	(133)	74 (80)	57 (42)	40 (15)	6.10^{-10}
>60	(148)	52.5 (48)	12 (4)	—	
Involved sites					
≤4	(176)	71 (84)	48 (34)	35 (13)	8.10^{-8}
>4	(103)	50 (43)	22 (11)	8.5 (3)	
Stage					
I–III1	(165)	70 (79)	51 (35)	34.5(13)	3.10^{-7}
III2–IV	(116)	53 (49)	21.5(11)	9.5 (3)	
B symptoms					
No	(250)	66 (117)	40 (41)	27.5(14)	6.10^{-4}
Yes	(29)	42 (10)	21 (4)	7 (2)	
ESR (mm)					
≤20	(165)	68.5 (81)	43.5(30)	31 (11)	2.10^{-3}
>20	(98)	52.5 (37)	29 (11)	14 (3)	
Compressive symptoms					
No	(246)	65 (115)	38.5(39)	25 (14)	4.10^{-2}
Yes	(33)	40 (9)	19 (4)	19 (2)	
Pathology					
Follicular	(155)	64 (75)	44 (34)	29.5(14)	9.10^{-2}
Follicular and diffuse	(126)	62 (53)	29 (12)	10.5 (2)	
Sex					
Male	(136)	64 (62)	36.5(24)	23.5 (6)	0.81
Female	(145)	62.5 (66)	40 (22)	26 (10)	

Percentage (number of patients exposed).
*Only the most significant category is outlined.

significant cutpoint of each one, according to the results of the univariate analysis, was selected. The results are presented in Table 3. We observed three significant parameters: age, stage and compressive symptoms.

In order to assess the validity of the cutpoints selected, we performed another Cox model including all interval variables as continuous ones (age, stage, involved sites count and ESR). The

Table 3. Overall survival analysis: stepwise Cox model

Variable	Coefficient	P
Age		
<60/>60	0.926	$<1.10^{-4}$
Stage		
I–II–III1/III2–IV	0.768	5.10^{-4}
Compressive symptoms		
No/yes	0.516	5.10^{-2}
Pathology		
Follicular/follicular and diffuse	0.237	0.21
B symptoms		
No/yes	0.301	0.25
ESR		
≤20/>20	0.194	0.30
Sex		
Male/female	0.01	0.58
Involved sites		
≤4/>4	0.115	0.61

Number of cases studied = 258, missing = 23, number of events = 135, global $\chi^2 = 67.33$.

results are consistent with the first model with the same three significant factors: age ($P < 0.0001$), stage ($P = 0.02$) and compressive symptoms ($P = 0.06$). The other factors are not significant ($P > 0.20$).

Prognostic data were summarized in survival groups (Fig. 4) with the two main prognostic variables: age and stage. Group I included patients younger than 60 with localised disease (I to III1), group III patients older than 60 with advanced disease (III2 and IV) and group II, patients either old or with advanced stages.

CR prediction

Five factors were significant after univariate analysis (Table 4), including stage (≤III1/>III1, $P = 4.10^{-11}$) involved sites count (≤4/>4), 9.10^{-11}) and B symptoms ($P = 1.10^{-6}$). All factors were included in a logistic regression analysis (Table 5) using the most significant category according to univariate analysis. Three factors remained significant: stage, involved sites count and B symptoms. In order to confirm the validity

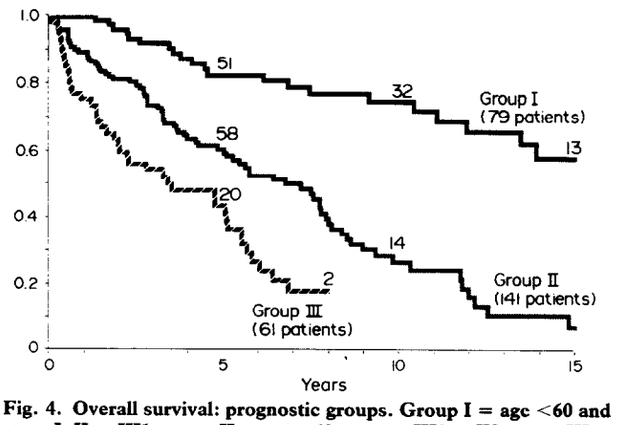

Fig. 4. Overall survival: prognostic groups. Group I = age <60 and stage I, II or III1, group II = age >60 or stage III2 or IV, group III = age >60 and stage III2 or IV.

Table 4. Complete remission prediction univariate analysis

Factor	Patients exposed	CR rate (%)	*P*
Stage			
I–III1	165	95	4.10^{-11}
III2, IV	116	64	
Involved sites			
≤4	176	94	9.10^{-11}
>4	103	62	
B symptoms			
No	250	86.5	1.10^{-6}
Yes	29	48	
Age			
<60	133	87	1.10^{-3}
>60	148	78	
ESR (mm)			
≤20	165	87	8.10^{-3}
>20	98	73.5	
Compressive symptoms			
No	246	84	3.10^{-2}
Yes	33	67	
Pathology			
Follicular	155	84	0.51
Follicular and diffuse	126	80	
Sex			
Male	136	82	0.93
Female	145	82	

of these categories, we performed another regression analysis including all interval variables as continuous. We observed three significant factors: stage ($P = 6.10^{-3}$), B symptoms ($P = 2.10^{-2}$) and age ($P = 4.10^{-2}$).

Table 5. Complete remission prediction: stepwise logistic regression

Variable	Coefficient	Coefficient/S.E.	*P*
	4.49	5.22	
Stage			
I–II–III1/III2–IV	−1.80	−3.33	9.10^{-4}
Involved sites count			
≤4/>4	−1.00	−2.00	5.10^{-2}
B symptoms			
No/yes	−0.98	−1.93	5.10^{-2}
ESR			
≤20/>20	−0.74	−1.81	7.10^{-2}
Compressive symptoms			
No/yes	−0.84	−1.58	0.12
Age			
<60/>60	−1.52	−1.25	0.21
Pathology			
Follicular/follicular and diffuse	−0.32	−0.78	0.43
Sex			
Male/female	−0.18	−0.45	0.65

Number of cases studied = 258, missing = 23, number of events = 212.

Table 6. Time to relapse: complete responders univariate analysis

Factor		Time to relapse (years) 5	10	15	*P*
Stage					
I–III1	(157)	53 (53)	44 (23)	41 (9)	1.10^{-3}
III2–IV	(74)	40 (21)	13 (3)		
Involved sites					
≤2	(115)	59 (39)	52.5(18)	47 (7)	1.10^{-3}
>2	(114)	41 (35)	20.5 (8)	20.5(3)	
Age					
<60	(116)	57 (48)	43.5(24)	40 (9)	1.10^{-2}
>60	(115)	40 (26)	26 (2)		
Compressive symptoms					
No	(207)	48 (64)	37 (22)	34 (8)	0.48
Yes	(22)	60 (9)	28 (4)	28 (2)	
ESR (mm)					
≤50	(195)	48.5(58)	37.5(22)	34.5(8)	0.71
>50	(21)	61 (11)	27 (2)		
B symptoms					
No	(216)	49 (68)	37 (25)	34.5(9)	0.83
Yes	(14)	51 (6)	20 (1)		
Pathology					
Follicular	(130)	52 (44)	37 (18)	33 (8)	0.90
Follicular and diffuse	(101)	45 (30)	33 (8)	33 (2)	
Sex					
Male	(112)	49 (34)	34 (13)	34 (2)	0.99
Female	(119)	49 (40)	37 (13)	34 (8)	

Percentages (number of patients exposed).

TTR analysis (CR)

231 patients achieved CR. Univariate analysis showed three significant parameters (Table 6); two of them remained significant in the Cox model (Table 7): stage and age. As previously, a second Cox model with continuous variables was performed and showed the same result: stage ($P = 1.10^{-2}$) and age ($P = 6.10^{-2}$).

DISCUSSION

This is a large series of FL, treated and followed up in the same institution over a long period (median follow-up: 9 years) without any patient lost to follow-up. As previously shown, survival expectation was high and comparable to other large series [8, 14] with approximately 45% 10-year OS and 25% 10-year TTF.

Our pretreatment work-up is not as complete as that used by other teams, who performed two percutaneous bone marrow biopsies (BMB) and/or staging laparotomies. Indeed, bone marrow involvement, as currently assessed by BMB has no significant impact on prognosis in low-grade lymphomas [20]. If we add to the pretreatment work-up bilateral BMB, staging laparotomy and even analysis by the polymerase chain reaction for detection of abnormal cells in peripheral blood or bone marrow [36], we will certainly find a large majority of stage IV. However, since no systemic treatment is currently available to cure low-grade lymphomas, this will probably not have any significant impact on survival. Consequently, we decided to limit the pretreatment work-up. However, this attitude should be reconsidered in case of prospective randomised trial. Since

Table 7. Time to relapse: complete responders Cox model

Variable	Coefficient	*P*
Stage		
I–II–III1/III2–IV	0.810	4.10^{-3}
Age		
<60/>60	0.453	3.10^{-2}
Involved sites		
≤2/>2	0.279	0.46
Compressive symptoms		
No/yes	0.076	0.82
ESR		
≤20/>20	0.037	0.86
B symptoms		
No/yes	0.069	0.86
Pathology		
Follicular/follicular diffuse	0.007	0.97
Sex		
Male/female	0.004	0.98

Number of cases studied = 212, missing = 19, number of events = 107, global $\chi^2 = 15.81$.

numerous patients were studied, the prognostic analysis was powerful. Three factors had a significant influence on OS after Cox model analysis; these were age, stage and compressive symptoms. For stage, the discrimination between III1 and III2 appears to be the best. Since the categorisation of continuous variables (according to univariate analysis) could have influenced the results, we performed another Cox analysis with all variables as continuous. We found the same prognostic variables in the same order, confirming the validity of the first model. Comparing our results to the literature, most previous series found a great importance for age [8, 21, 22]. Stein [23] found no influence of it; however, his study concerned advanced disease and excluded patients older than 75. Gallagher [14] also found no influence of age on OS.

Almost all series found stage to be important [8, 21, 22] as were B symptoms [8, 14, 21–23]. Gallagher's series [14] is interesting because of the high proportion of stage IV patients (55%): this could explain the lack of statistical significance of stage and the relative importance of B symptoms, hepatomegaly, anaemia and abnormal liver function tests in this study.

After multivariate analysis, three factors appeared to be predictive of CR. These were stage, involved sites count and B symptoms. For stage, the distinction between III1 and III2 confirmed its prognostic value. The second model with continuous variables showed the same predominance of stage for CR prediction, but no further influence of the involved sites count and only a slight influence of age. Indeed, stage and involved sites count were highly correlated (Kendall non-parametric test: $P < 0.001$). Finally, three factors remained important: mainly stage, but also B symptoms and age.

Only Cabanillas *et al.* [12] studied factors affecting CR occurrence. They found three significant favourable variables: chemotherapy with a doxorubicin-containing regimen, absence of bulky disease and no exposure to prior chemotherapy. The last factor was not studied in our series since no patient had received any treatment before. We did not study the influence of doxorubicin since its importance can only be questioned in randomised trials. Like Cabanillas *et al.*, we noted the importance of tumour volume.

Our results show 97% CR rate for patients of the first group (age <60 and stage ≤III1). Patients of the second (age >60 or stage >III1) had 75% CR probability. They could be divided into two groups according to age: patients older than 60 (with stages I, II or III1) whose CR rate was 92%, and those younger than 60 (with advanced disease) whose CR rate was only 70.5%. Finally, only 57% of patients of the third group (age >60 and stage >III1) achieved CR.

So, since there are great differences between those groups regarding CR rate, we have to consider this data both for curative and palliative treatment policy.

TTR analysis showed 2 significant parameters: stage and age (with the same distinction for stage between III1 and III2). We did not find any TTR analysis of complete responders in the literature. Our results confirm the main importance of tumour volume represented by stage.

We did not analyse influence of LDH or β_2-microglobulin levels on prognosis. Indeed, they have been routinely measured for only 3 years, so they are not suitable for this analysis. However, their relative importance must be assessed in future analyses since it appears to be of high value for high-grade lymphomas [24].

Finally, only two factors influenced prognosis of FL: stage and age, age being the main one for OS, and of some value for CR and TTR prediction. However, we have to consider that age probably influenced treatment modalities for the older patients and, also, possibly the outcome.

Stage was the most important prognostic factor for CR and TTR prediction. The distinction within stage III appeared to be the most significant. We previously defined two subgroups among stage III [25]. A similar partition into two subgroups of different outcome was previously performed [26]. It becomes evident that prognosis of limited stage III is closer to localised stages than advanced ones. This questions the validity of the Ann Arbor classification in FL.

Two other factors added some information to prognosis prediction: compressive symptoms for OS and B symptoms for CR prediction. However they represented only a small subset of patients (about 10% each).

Thus we can simplify prognostic data while considering only two factors: stage and age for their most significant cutpoint. This leads to the three groups defined in OS and CR analyses. The results are outlined in Table 8.

With such a long life expectancy, FL is slightly different from other cancers. Even old patients with advanced disease, the poorest prognostic group, have 44% 5-year OS and 37% 5-year RFS. This is important when defining treatment schemes: life-threatening treatment must be used cautiously.

Treatment of localised disease is well defined: involved field irradiation up to 40 Gy. With this treatment, more than 98% of patients are locally controlled for a long time [14]. Many authors agree that radiotherapy ensures prolonged CR in nearly half of patients with stages I and II [8, 9]. These results associated with flattening of survival curves argue for curability of approximately half of the patients with localised disease. This could be satisfying in old patients but not in young ones. In the latter, one could suggest treatment intensification but previous randomised trials demonstrated the lack of survival advantage when chemotherapy was added to radiotherapy in localised disease [27, 28]. Finally, treatment results are satisfying for half of localised stages, i.e. for only 20% of patients.

Table 8. Prognostic synthesis

	Group		
	I	II	III
Proportion of patients	28	50	22
OS probability (281 patients)			
5 years	81	61	44
10 years	73.5	27	/*
15 years	57	7	/*
CR probability	97	75	57
TTR probability (231 patients)			
5 years	64	41.5	37
10 years	54	22	/*
15 years	49	/*	/*

Percentages.
Group I = <60 years old and stage I, II or III1; Group II = >60 years old or stage III2 or IV; and Group III = >60 years old and stage III2 or IV.
*No patient at risk.

CR achievement is the most important prognostic factor in numerous series [12, 14, 21, 29]. However, it is currently impossible to conclude its real value: does it select patients with a good prognosis, or is it an independent prognostic variable? Can we increase survival while increasing CR rate? There are divergent opinions about this subject: some authors argue for therapeutic intensification [19, 29, 30] and others for moderate chemotherapy or no initial therapy [10, 31–33]. We tend to be of the second opinion, since for advanced stages, Stanford studies has shown the equivalence of monochemotherapy, polychemotherapy and low dose total body irradiation [11]. Furthermore, doxorubicin neither adds OS advantage nor causes plateauing [12, 13] although it allows more and longer CR. This does not argue for the potential value of high-risk chemotherapies.

The three prognostic groups obtained contribute to define a treatment scheme. For the patients of the first group, high CR rate, long life expectancy and almost 50% prolonged CR, justify the treatment used, that is involved field irradiation up to 40 Gy.

The second group has to be split into two groups by age. In our study, older patients with localised disease had a high CR rate but shorter life expectancy. About one third died from intercurrent disease: we cannot use high-risk treatments and so, the treatment of choice remains involved field irradiation up to 40 Gy. Younger patients with advanced disease might be included in prospective trials. Indeed, only 16% of complete responders are free of lymphoma 10 years after diagnosis. The treatment of choice remains unsettled.

However, one series [34] showed prolonged initial remissions in advanced stages nodular mixed lymphomas with chemotherapy. Yet this is a retrospective series with heterogeneous treatment and median follow-up of 7 years, which is insufficient for late relapses (Fig. 1). Furthermore, four randomised trials failed to demonstrate any survival advantage with addition of chemotherapy in localised stages. Finally, if usual chemotherapy regimens have any potential cure rate, it probably concerns only a small subset of patients. Hence, young patients with advanced disease must be included in prospective trials.

Patients of the last group are old and have advanced disease. They have the poorest prognosis and treatment must be adjusted for their age [35]. However, some of them (younger ones) can probably be included in trials. The remaining patients must be treated in a palliative way, namely "watch and wait" for asymptomatic patients [32] and monochemotherapy when disease becomes symptomatic.

In conclusion, no systemic treatment currently demonstrates its curative potential in FL. New trials are certainly warranted but only in patients with poor prognosis. New tools such as the polymerase chain reaction to detect minimal residual disease [36] will probably be available soon, and may help clinicians in treatment evaluation.

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Haemodynamic Effects of Recombinant Interleukin-2 Administered by Constant Infusion

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Adoptive immunotherapy with recombinant interleukin-2 (rhIL-2) has been reported to induce tumour regression in some patients with refractory cancer. However, the cardiovascular toxicity of bolus therapy requires invasive monitoring of patients in the intensive care unit (ICU). In an effort to examine the haemodynamic alterations caused by a constant infusion of IL-2, as opposed to bolus therapy, we studied the haemodynamic variables of 10 patients, with no evidence of heart disease, receiving 3 × 10^6 IU/m^2 per day of rhIL-2 as a continuous infusion for 5 days. Measured and derived haemodynamic variables were obtained immediately prior to, at 2, 24, and 48 h during, and upon termination of the infusion. There was no evidence of clinical haemodynamic instability in these patients. Except for development of fever and tachycardia, there were no clinically significant differences in any measured or derived haemodynamic parameter. Moreover, continuous electrocadiographic monitoring of these patients during the infusion did not reveal any abnormalities. Invasive haemodynamic monitoring in an ICU is not necessary in carefully selected patients receiving constant infusion rhIL-2, at the described dose and schedule.
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INTRODUCTION

ADOPTIVE IMMUNOTHERAPY with recombinant human interleukin-2 (rhIL-2) is currently being investigated for a number of malignancies. Responses have been seen in refractory cancers, such as malignant melanoma and renal cell carcinoma [1–4]. Severe cardiovascular toxicity requiring intensive care unit (ICU) management may limit its clinical application when administered on an intermittent high dose bolus schedule [1–14]. Recent investigations suggest that dose-limiting haemodynamic instability may be attenuated when rhIL-2 is administered by constant infusion [4, 15–21]. This report describes the cardiovascular responses to high dose rhIL-2 administered by constant infusion in 10 patients.

PATIENTS AND METHODS

10 patients with advanced cancer were studied. The eligibility criteria for the trial included: age 18–70 years; metastatic or unresectable melanoma or renal cell carcinoma; expected survival of greater than 16 weeks; Karnofsky performance status 80% or higher; serum creatinine 2.0 mg/dl or less, adequate