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## Peripheral T-cell Lymphoma Unspecified (PTCL-U): a new prognostic model from a retrospective multicentric clinical study.

Short title: PTCL-U, prognostic model.

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Clinical Observations

## Abstract

**Objectives:** in order to assess the prognosis of Peripheral T-Cell Lymphoma-Unspecified, we retrospectively analyzed 385 cases fulfilling the criteria defined by the WHO classification.

**Results:** factors associated with a worst overall survival (OS) in a univariate analysis were: age > 60 ( $p=0.0002$ ),  $\geq 2$  ENS ( $p=0.0002$ ), LDH  $\geq$  normal levels ( $p<0.0001$ ), PS  $\geq 2$  ( $p<=0.0001$ ), stage  $\geq$  III ( $p=0.0001$ ), bone marrow involvement ( $p=0.0001$ ). Multivariate analysis showed that age (relative risk 1.732, 95% C.I. 1.300-2.309,  $p<0.0001$ ), PS (relative risk 1.719, 95% C.I. 1.269-2.327,  $p<0.0001$ ), LDH (relative risk 1.905, 95% C.I. 1.415-2.564,  $p<0.0001$ ) and bone marrow involvement (relative risk 1.454, 95% C.I. 1.045-2.023,  $p=0.026$ ) were factors independently predictive for survival. Using these four variables we constructed a new prognostic model which singled out 4 groups at different risk; group 1: no adverse factors, with 5-year and 10-year OS of 62.3% and 54.9%, respectively; group 2: 1 factor, with a 5-year and 10-year OS of 52.9% and 38.8%, respectively; group 3: 2 factors, with 5-year and 10-year OS of 32.9% and 18.0%, respectively; group 4: 3 or 4 factors, with a 5-year and 10-year OS of 18.3 and 12.6%, respectively ( $p=0.0000$ , log rank 66.79).

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## INTRODUCTION

In western countries peripheral T-cell non-Hodgkin lymphomas (PTCL) account for 15-20% of aggressive lymphomas (1) and for 7-10% of all the non-Hodgkin lymphomas (NHL) (2-3). They usually occur in middle-aged to elderly patients, and presenting features are characterized by a disseminated disease in 68% of the patients, with systemic symptoms in nearly half of them (45%), bone marrow involvement in a quarter (25.8%) and extra-nodal disease in a third (37%). Despite aggressive therapy, the prognosis is dismal, with more than half the patients dying of their disease (2).

The influence of the immunophenotype on the outcome of aggressive NHL has long been questioned (4-5); in the more recent literature, however, most authors agree on the adverse prognostic meaning of the T-cell phenotype *per se* (3, 6-9), irrespectively of other well defined clinical prognostic indexes such as the International Prognostic Index (IPI) (10).

In the past a number of definite entities corresponding to recognizable subtypes of T-cell neoplasm, such as Lennert lymphoma, T-zone lymphoma, pleiomorphic T-cell lymphoma, small and medium-sized, and large cell T-cell lymphoma and T-immunoblastic lymphoma have been described (11), but evidence that these correspond to distinctive clinicopathological entities is still lacking (12, 2, 8, 9). For this reason the recent WHO classification of the haematopoietic and lymphoid neoplasm has collected these under the single broad category of "peripheral T-cell lymphoma, unspecified – PTCL-U (17). The natural history of PTCL seems to be unchanged by the use of second- and third-generation chemotherapy regimens (8) and 5-year overall survival still remains between 25% and 47% (2-3, 6-11). Although high-dose sequential chemotherapy (HDS) followed by autologous hematopoietic stem cell transplant (ASCT) has been successfully performed in two small series of patients (13-14), others (15-16) in a large cohort of high-risk NHL treated with HDS followed by ASCT, have definitely demonstrated no benefit of autologous bone marrow transplantation in the subset of T-cell lymphomas (13).

In order to better define the clinical outcome of T-cell lymphomas grouped within the broad category of PTCL-U as a single entity, and to assess a prognostic model specifically devised for patients with this uncommon disease, the Intergruppo Italiano Linfomi (IIL) promoted a large, retrospective, collaborative study. Here we report the results of this study, performed on 385 newly diagnosed patients followed at participating institutions between January 1989 and December 2001.

## PATIENTS AND METHODS

Among 10.315 cases of lymphoma recorded through June 2002 at the IIL Lymphoma Registro we selected all cases of PTCL diagnosed between January 1989 and December 2001. A preliminary working file containing information on 512 cases, fulfilling all the characteristics of “Peripheral T-Cell Lymphoma, Unspecified” was created.

Thereafter we considered eligible for the study all patients with:

1. Histologically confirmed diagnosis of PTCL-U, according to the WHO Classification (17). Distinctive entities, formerly classified as PTCL and characterized by a definite clinical picture (such as angioimmunoblastic T-cell lymphoma, Anaplastic Large-Cell Lymphoma (ALCL), enteropathy associated T-cell lymphoma, nasal type T-cell lymphoma, or primary cutaneous T-cell lymphoma), were excluded from the analysis. No cases of T-prolymphocytic leukaemia, adult T-cell leukaemia/lymphoma, or primary hepatosplenic T-cell lymphoma were recorded.
2. Proven T-cell phenotype either by immunohistochemistry, flow cytometry or rearrangement of T-cell receptor.

Additional criteria for inclusion were:

3. Availability of a complete set of clinical data for an accurate clinical staging, including diagnostic biopsy with immunohistochemistry and/or flow cytometry, complete blood count, biochemistry, whole body TC scan and/or <sup>67</sup>Gallium scintigraphy, bone marrow trephine biopsy.
4. A minimum follow-up of one year, with the last observation recorded no more than six months before data collection.

Out of 512 cases retrieved from the Registro for the primary working file we excluded 127 patients for the following reasons: 23 exhibited clinical characteristics and a histological description of “nasal type” T-cell lymphoma, 47 for incomplete clinical data, 21 for unproven T-cell phenotype, and 36 for inadequate follow-up. The participating centers were asked for a simple set of clinical data including: age, sex, complete blood count, ESR, LDH, serum beta<sub>2</sub>microglobulin. Ann Arbor stage, IPI, number and sites of extranodal disease, BM involvement, systemic symptoms, bulky disease, PS, date of diagnosis, type of treatment, response to therapy, date of assessment of response, date of relapse, date of last follow-up, status (alive or deceased), and, if deceased, date and cause of death. Bulky disease was defined as a mass with the largest diameter greater or equal to 10 cm. or, for the mediastinum only, a mass larger than one third of the chest diameter. Systemic symptoms were defined, according to Ann Arbor criteria, as recurrent fever (more than 38 °C), or night sweats, or loss of a more than 10% of body weight.

Response to treatment was assessed one month after the end of induction therapy by performing all the examinations with pathologic values at baseline, which concurred to define the stage. Complete remission (CR) was defined as the disappearance of all clinical evidence of the disease and the normalization of all laboratory values and radiological findings that had been considered abnormal before starting therapy. Partial remission (PR) was defined as a greater than 50% reduction, for at least one month, of the largest dimension of each measurable anatomical site of disease localization. Non-response (NR) was defined as a less than 50% regression of tumor size, or stable/progressive disease. All the deaths occurring because of disease progression or related to treatment toxicity were considered as treatment failures, and the patients were included in the NR group.

### Histological findings

Table 1 lists the different histological subtypes conforming to PTCL-U diagnosis.

Table 1 - Histological PTCL-U subtypes.

Description	N	% of the cases
PTCL-U NOS	162	42.0
Large cell	71	18.4
Large + medium sized cell	64	16.6
Pleomorphic cell	31	8.0
Small cell	23	5.9
Lymphoepitelioid	19	4.9
T-zone	15	3.8

The most frequent subtype (189/385: 49.1%) was characterized by a simple cytological description of the tumor, and included a number of sub-entities (large cell, large and medium sized cell, pleomorphic cell, small cell) differing in cell size and the relative proportion of large or small cells. Other categories were PTCL-U Not Otherwise Specified (PTCL-U NOS), T-zone lymphoma, lymphoepitelioid lymphoma (or Lennert lymphoma). In 290 cases the T-phenotype was proven on immunoistochemical grounds, in 73 cases by cytofluorimetric assay of a fresh cellular suspension, and in 22 cases by rearrangement of T-cell receptor.

### Treatment strategies

Patients were grouped in four main categories (see Table 2), according to the treatment strategy adopted: a) only supportive care, 7/385 (2%); b) non-anthracyclin chemotherapy, 32/385 (8%); c) anthracyclin-based chemotherapy, 302/378 (78%) d) autologous or allogeneic bone marrow transplantation as part of a primary treatment 44/385 (12%).

Table - 2: Treatment strategies

Treatment	N° cases	Percent
No therapy	7	2%
Non-anthracyclin CT	32	8%
CT with anthracyclin	302	78%
HDS plus ASCT	44	12%

### Statistical analysis

All data were analyzed with the Statistical Package for the Social Sciences (SPSS) (18). OS and Relapse-Free Survival (RFS) curves were calculated according to the Kaplan and Meier method (19). OS was calculated from the date of diagnosis until death from any cause or date of last contact for living patients. For patients in CR, RFS was calculated from the date of diagnosis to the first evidence of relapsing disease. The association between clinical factors and the probability of attaining CR was evaluated by likelihood ratio  $\chi^2$  test. In cases where the date of the therapy onset was not available the survival was calculated from the date of the diagnosis until the date of the last follow-up or death. RFS was applied only in patients attaining CR, and was calculated from the end of first-line therapy to relapse. The univariate association between individual clinical features and overall survival were determined with the log-rank test (20). Factors independently associated with OS were identified in multivariate analysis by the Cox proportional hazards regression model (21).

The limit of significance for all analyses was defined as  $p = .05$ . Two-sided tests were used in all calculations.

## RESULTS

The characteristics of the 385 patients fulfilling the inclusion criteria and entered into the study are summarized in Table 3.

Table 3 - Clinical and biologic characteristics of the patients.

Characteristics	N° of patients	Available	%
Age (yrs)		385	
< or =60	234		60.8
> 60	151		39.2
Men	249	385	64.7
Women	136		35.3
PS (ECOG)		383	
0-1	274		71.2
2-4	109		28.3
Stage (Ann Arbor)		385	
I-II	92		23.9
III-IV	293		76.1
Systemic symptoms		385	
yes	175		45.4
no	210		54.6
Bulky disease (> 10 cm)		385	
yes	58		15.0
no	327		85.0
Number of extranodal sites		385	
0-1	224		58.2
> 2	161		41.8
BM		368	
involved	118		32.1
uninvolved	250		67.9
LDH		350	
normal	191		54.6
> than normal	159		45.4
IPI		346	
1-2	189		54.6
3-4	157		45.4
Hb level		352	
<12 g/dL (men) or <10g/dL (women)	78		22.1
>12 g/dL (men) or >10g/dL (women)	278		78.9

The median age was 54 years (range 15-96), and there was a male preponderance, with a male to female ratio of 1.83. Disease extension and frequency of extra-nodal sites were suggestive of an aggressive onset: three quarters (291/385: 76.1%) were in stage III or IV, and nearly half (192/385: 49.9%) in stage IV; more than two thirds (281/385: 73%) presented organ involvement. Table 4

shows the extra-nodal spread of the disease, with bone marrow being the most frequent site (118/385: 32.2%), followed by spleen (95/385: 24.6%), liver (50/385: 12.9%), Waldeyer ring (42/385: 10.9%) and skin (39/385).

Table 4 - Sites involved in 281 patients with extra-nodal involvement

Site	Number of cases	% of cases	% of all extra nodal sites
Bone marrow	118	30.6	41.9
Spleen	95	24.6	33.8
Liver	50	12.9	17.7
Waldeyer	42	10.9	14.9
Skin	39	10.1	13.8
Lung + pleura	38	9.8	13.5
Gut	35	9.0	12.4
Bone	18	4.6	6.4
Soft tissues	5	1.2	1.7
Others	54	14.02	19.2

Bulky disease was present in a minority of the patients (58/385 pts: 15.1%); mean hemoglobin value was 12.35 gr./dl; (range 6-17); mean absolute neutrophils count was 5,362/ $\mu$ l (range 238 – 35,520), mean lymphocytes count 2,323/ $\mu$ l (range 165-75,072) and mean platelet count 235,345/ $\mu$ l (range 3000 – 613,000). Nearly half the patients presented with systemic symptoms (175/385: 45.5%), while two thirds showed an ambulatory performance status ( P.S. ECOG 0-1: 274/385: 71.2%); LDH was elevated in one third of the cases (> 1 x normal values 159/350: 45.4%).

IPI scoring was available in 346/385 (89.9% of the patients); accordingly 98 (28.3%) patients were classified as low risk (0-1), 91 (26.3%) as intermediate-low (2) ; 93 (26.9%) as intermediate-high (3) and 64 (18.5%) as high risk (4-5).

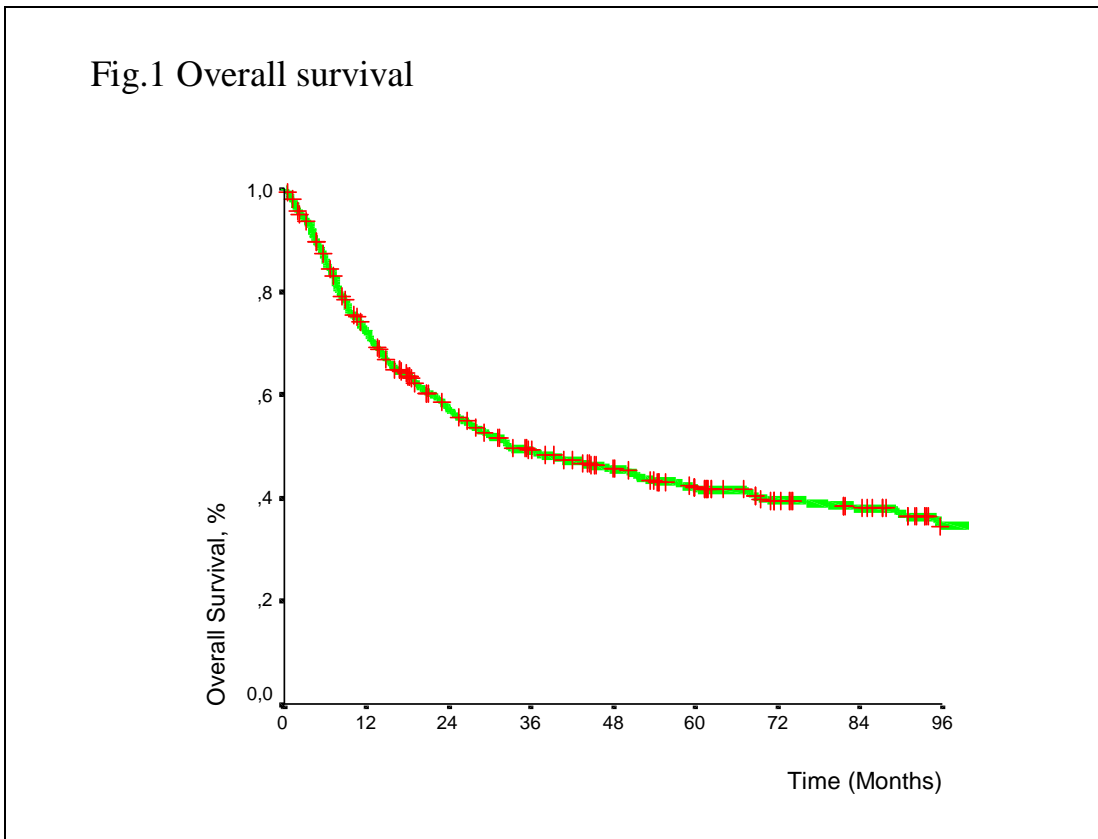
#### *Analysis of response*

In 6 out of 385 patients the response to therapy was not recorded and in 7 no therapy was given; therefore there were 372 patients available for treatment response. Overall, the CR rate was 53.2% (198/372); partial responses were observed in 20.7% (77/372) and failures in 26.1 % (97/372). In univariate analysis the factors associated with a lower probability of achieving CR were advanced stage (III-IV) (o.r. = 2.781; 95% C.I. 1.656-4.671; p<0.0001), the presence of extra nodal sites (o.r. = 2.577; 95% C.I. 1.688-3.935; p<0.0001), bone marrow involvement (o.r. = 2.501; 95% C.I. 1.580-3.959; p<0.0001), poor performance status (o.r. = 2.213; 95% C.I. 1.393-3.517; p=0.001), high LDH levels (o.r. = 2.158; 95% C.I. 1.397-3.334; p= 0.001), age greater than 60 (o.r. = 1.719; 95% C.I. 1.129-2.618; p=0.012) and low hemoglobin level (o.r. = 1.708; 95% C.I. 1.018-2.865; p=0.042). IPI proved to be of highly significant prognostic value (p<0.0001).

The five characteristics that remained independently significant in multivariate analysis were: poor performance status (o.r. = 2.381; 95% C.I. 1.141-4.968; p=0.021), the presence of extra nodal sites (o.r. = 2.112 ; 95% C.I. 1.106-4.032; p=0.023), age greater than 60 (o.r. = 2.144; 95% C.I. 1.101-4.176; p=0.025), bone marrow involvement (o.r. = 2.169; 95% C.I. 1.038-4.532; p=0.039) and high LDH levels (o.r. = 2.127; 95% C.I. 1.018-4.441; p = 0.045).

#### *Analysis of survival*

After a mean follow up of 43.2 months, 229/385 (59.4%) patients had died, and the cumulative probability of survival at 5 years (Fig. 1) was 43.0%.



Forty-four percent of the deaths occurred in the first 12 months and an additional 23% occurred in the following year. The 5-year and 10-year RFS among patients who achieved CR were 49.5% and 42.9%, respectively. Factors significantly associated with prolonged response duration were early stage ( $p=0.00004$ ), absence of bone marrow involvement ( $p=0.0011$ ), normal serum LDH levels ( $p=0.0150$ ), good performance status ( $p=0.0232$ ) and female gender ( $p=0.0215$ ).

The clinical parameters associated with reduced survival in univariate analysis are listed in table 5: age greater than 60 years ( $p=0.0002$ ),  $\geq 2$  extra nodal sites ( $p=0.0002$ ), LDH  $\geq$  normal values ( $p<0.0001$ ), P.S.  $\geq 2$  ( $p<0.0001$ ), advanced disease (stage  $\geq$  III;  $p=0.0001$ ), bone marrow involvement ( $p=0.0001$ ),  $\beta_2$ microglobulin level (available in 109/385 pts.)  $> 2.7$  ng/ml ( $p=0.0231$ ), less than complete response to the therapy ( $p<0.0001$ ) and IPI ( $p<0.0001$ ). Systemic symptoms and bulky disease were non-significant factors.

Table 5 - Clinical parameters influencing survival in univariate analysis

Parameter	Cut-off value	p value
Age	$> 60$ y.	0.0002
Performance Status (ECOG)	$\geq 2$	$< 0.0001$
Stage	$\geq$ III	0.0001
LDH	$> 1x$ normal value	$< 0.0001$
E.N.S.	$\geq 2$	0.0002
IPI	L, I-L, I-H, H	$< 0.0001$
BOM	Infiltrated	0.0001

Response to CT	CR vs. PR vs. NR	< 0.0001
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Excluding  $\beta_2$ microglobulin, the eight above mentioned prognostic factors available in the majority of the patients (324/385), were significantly associated with prognosis in univariate analysis. All these cases were selected for developing a prognostic model.

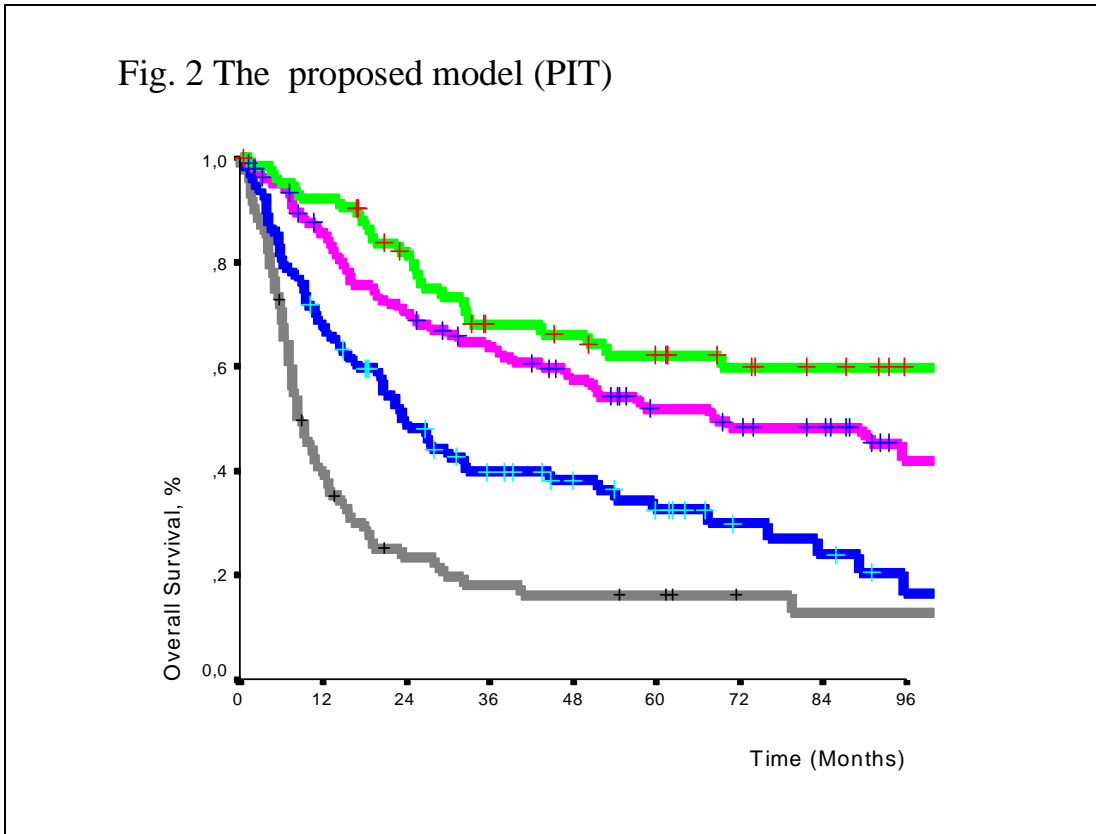
*Prognostic model*

In multivariate analysis the factors that turned out to correlate significantly with survival were age (p<0.0001; relative risk 1.732, 95% C.I. =1.300-2.309), performance status (p<0.0001; relative risk 1.719, 95% C.I. = 1.269-2.327), LDH (p<0.0001; relative risk 1.905, 95% C.I.= 1.415-2.564) and bone marrow involvement (p= 0.026; relative risk 1.454, 95% C.I.= 1.045-2.023) (Table 6).

Table 6 - Clinical parameters influencing survival in multivariate analysis

Parameter	Significance (p)	Odd ratio (exp.B)	95% C.I. – low	95% C.I. high
Age	.000	1.732	1.300	2.309
Performance status	.000	1.719	1.269	2.327
LDH	.000	1.905	1.415	2.564
BM attainment	.026	1.454	1.405	2.023

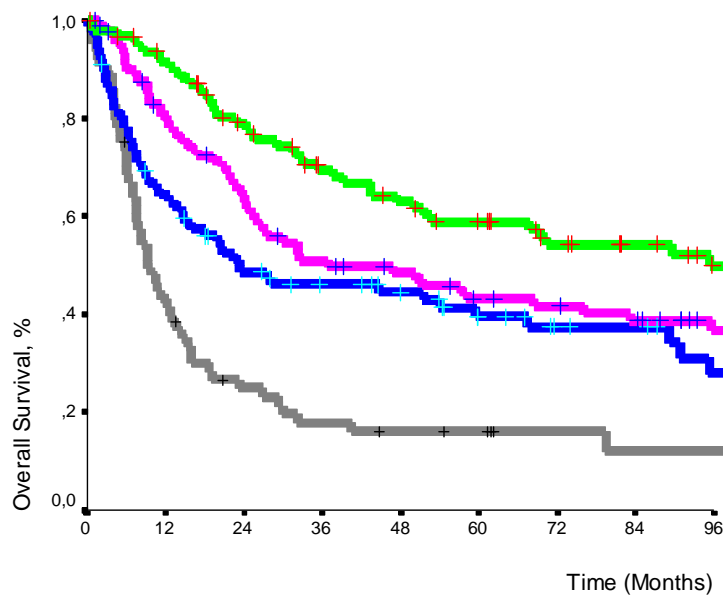
Since the relative risk associated with each of the 4 factors was comparable, we constructed a new prognostic model by combining these prognostic variables in the following way: Group 1: no adverse factor, Group 2: one factor, Group 3: 2 factors, Group 4: 3 or 4 factors. This novel Prognostic Index for PTCL-U (PIT) model was able to efficiently identify 4 groups of patients with different outcomes (Fig. 2) ( $p= 0.0000$ ; log rank 66.79).



For the 64 patients in Group 1 the 5-year and 10-year survival rates were 62.3% and 54.9% respectively; for the 108 patients in Group 2, 52.9% and 38.8%; for the 83 patients in Group 3, 32.9% and 18.0%; and for the 67 patients in Group 4, 18.3% and 12.6%.

In the same cohort of 324 patients, the IPI predictive model, developed for aggressive B-cell non Hodgkin's lymphoma, was able to identify four categories of patients with different prognoses: low in 91 patients, intermediate-low in 86 patients, intermediate-high in 85 patients and high in 62 patients. The 5-year and 10-year survival rates were 58.94% and 50.0% respectively, in the low risk group; 45.6% and 32.3% in the intermediate-low risk group; 39.7% and 29.8% in the intermediate-high risk group; 18.3% and 9.15% in the high risk group ( $p= 0.0000$ , log rank 53.80) (Fig. 3).

**Fig. 3: International Prognostic Index (IPI)**



Considering a simplified two-class model both for IPI and PIT we found that 278/322 patients (86.3%) were allocated in the same risk group using both indexes; the latter however showed a superior predictive power (log rank 47.48 versus 28.91, fig. 4).

## DISCUSSION

Peripheral T-cell lymphomas are an heterogeneous group of neoplasm presenting as advanced disease, and characterized by widespread dissemination, aggressive behavior and a very poor outcome. In the literature so far published the 5-year overall survival ranges between 25% and 45% (2, 3, 7-10, 13, 22). However, the meta-analysis of the prognosis of these neoplasms from the retrospective clinical reviews is somewhat cumbersome, due to the differences of the histological subtypes accrued and of different follow-up times. Moreover, in 1994 the REAL classification and in 1997 the WHO classification introduced a substantial modification in the classification of these disorders. A number of different T-cell peripheral lymphomas, once considered as distinctive entities are now collectively referred to as PTCL-U. Conversely, other lymphoma subtypes such as ALCL, formerly classified as peripheral T-cell lymphoma and characterized by a relatively good prognosis, were singled out, and considered separately. For example, in the largest series published so far on the prognosis of PTCL-U, Gisselbrecht et al. (8) report a 5-year OS for “peripheral T-cell lymphoma” of 41%, but this value drops to 31% upon withdrawal from the analysis of ALCL.

For these reasons we undertook a large, multicenter, retrospective analysis with the main end point of studying the prognosis of PTCL-U patients who were enrolled in the IIL clinical trials during a period of more than a decade. This is, as far as we know, the largest clinical retrospective review on the prognosis of this lymphoma subset. After withdrawal of cases not fulfilling the inclusion criteria, we were able to enroll 385 patients affected by PTCL-U, as defined by the WHO classification (17). According to authors, PTCL-U category is an “empty basket” containing several histological subtypes, characterized by a prevalent nodal presentation and an aggressive but non-

specific clinical behavior. Even if not all cases underwent a systematic histological review, we believe that the detailed histopathologic picture, the concurrent immunophenotype and the exclusion of a number of well-defined clinico-pathologic entities, could have further reduced the inclusion of non PTCL-U lymphomas in our series.

The 5-year and the 10-year overall survival of the patients enrolled in the present study (43.03% and 33.50%) fit in the upper limit of the range reported in the literature. This may be because of the median age, up to 10 years younger than the one reported in other series (8-10, 22), and the large predominance of patients with ambulatory performance status (performance status 0-1: 274/382 = 71.7%). Both differences could partially reflect a selection of the patients fitting the inclusion criteria for entering into the clinical trials. Finally, unlike other retrospective studies, the present doesn't encompass subsets of T-cell lymphomas with a very poor prognosis such as nasal-type T-cell lymphoma, and enteropathy-associated T-cell lymphoma.

At this writing 229 out of 385 patients have died, mostly because of disease progression or relapse. The risk of death was higher in the first two years since diagnosis, and decreased over time; although a true plateau was never reached, 44.1% and 67.2% (23.1%) of the deaths were recorded within the first 12 and 24 months, respectively. This pattern of the survival curve (Fig.1) seems also to demonstrate that the therapy was unable to change the course of the disease whatever the strategy chosen; however, the survival of patients attaining CR was significantly longer. High-dose chemotherapy followed by autologous bone marrow transplantation was performed in 44/372 patients (11.8%) and failed to show any advantage over standard therapy in prolonging survival ( $p=0.2$ , data not shown) This result, in keeping with Rodriguez data (16), is not surprising, if one takes into account the low overall response rate to therapy (53.2%) that we observed in our study, without statistical differences among the three therapeutic strategies ( $p=0.6$ ), and the very aggressive behavior of these neoplasms. However, we are fully aware that no definite conclusions regarding the role of the therapy can be drawn from a retrospective clinical trial with an accrual time spanning more than a decade.

Several studies have been made in order to assess the contributions of a number of clinical factors to the prognosis. IPI seems to work as well in peripheral T-cell lymphomas as in diffuse large-cell lymphomas (8-10, 13); however, besides IPI, systemic symptoms and bone marrow infiltration have been found to correlate with prognosis in a single study (9).

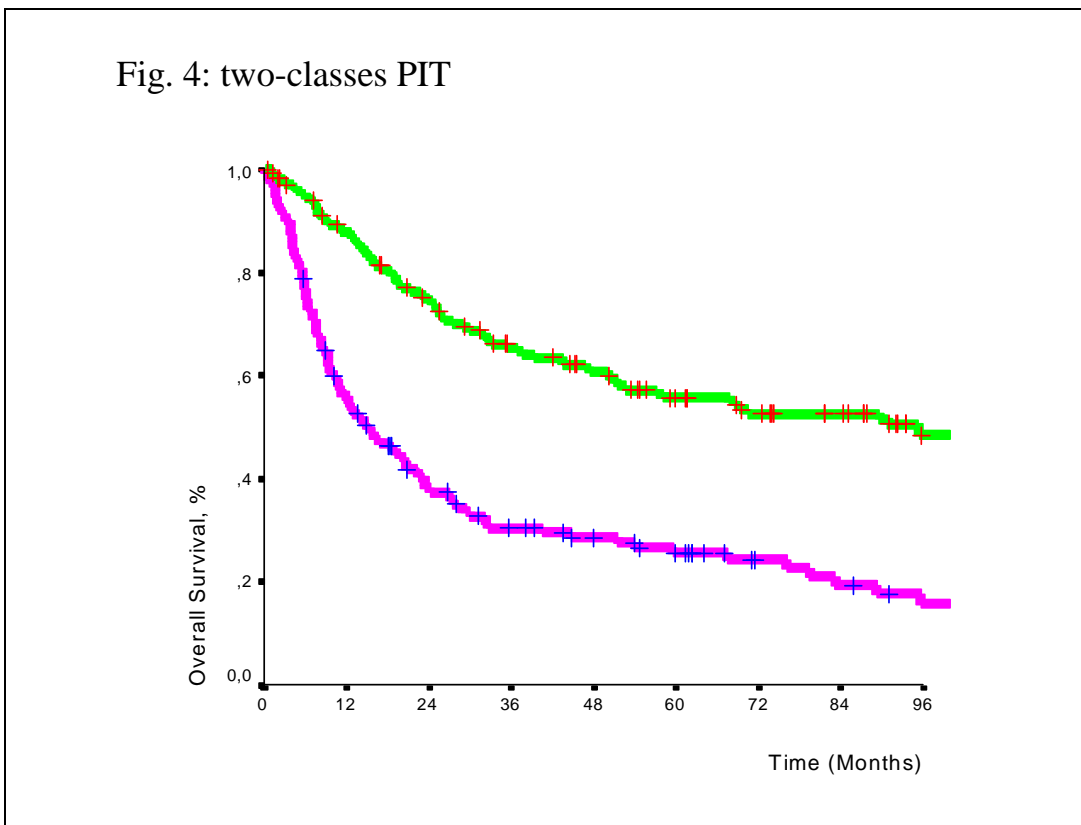
The cytology of the neoplastic cell has long been debated as a prognostic factor. In the REAL classification three morphological variants have been proposed: medium-sized cells, mixed medium and large cells, and large cells (12), but because of lack of reproducibility these provisional entities were no longer recognized in the WHO classification. Applying the updated Kiel Classification (25), Ascani et al. (2) and Noorduyt et al. (23) were unable to find any survival difference between low- and high-grade histological forms, while Rudiger et al. (22) found that the number of transformed blasts in ten random high-power fields was prognostically relevant.

Another aim of this study was to check the value of the pre-existing prognostic models, and to eventually propose a new system to evaluate the outcome of PTCL-U. As in other aggressive lymphomas IPI proved to be able to identify subsets of patients with different prognoses but in multivariate analysis, only three out of five parameters retained their prognostic significance in our study. The extension of the disease (staging) and the presence of extra nodal sites were no longer significant, probably because the disease *per se* is characterized, in more than two thirds of the patients, by a presentation in advanced stage and in two or more extra nodal sites. Bone marrow involvement has been associated with a poor response to therapy and a shorter survival in diffuse large cell B-lymphomas (25, 26); in PTCL-U it occurs in 20-40% of the cases (27) and seems to worsen the prognosis (2). In the present study we observed a bone marrow involvement in a similar proportion of cases, and we confirmed the resulting negative impact on survival. This effect occurred independently from other IPI prognostic factors, probably because of a more pronounced tendency of the tumor to spread. Of the remaining three factors prognostically significant in

multivariate analysis, two are host-related (age, performance status) and the third (elevated LDH levels) has been considered a marker of increased cell turnover (28).

On the basis of these findings we propose a new prognostic model for PTCL-U, that we have called PIT (Prognostic Index for PTCL-U), based on these four simple clinical variables: age, performance status, LDH and bone marrow involvement. PIT seems to differ from IPI because in the former the two IPI factor based on the extension of the disease (stage and extra nodal sites) do not seem to work with same efficacy. Conversely, of the two PIT factors related to the biology of the tumor (bone marrow involvement and LDH), only one (LDH) has a prognostic role in IPI.

The PIT model was able to identify four classes of patients with different outcomes, with an overall superior predictive capacity as compared to IPI (log rank 66.79 versus 55.94). The same holds true considering a simplified two-class model obtained by grouping the four prognostic classes of IPI and PIT in two risk categories: the first containing class 1 and 2 and the second containing class 3 and 4. Simplified two-class PIT fared better than simplified two-class IPI (log rank 49.36 versus 30.23) (Fig. 4).



In conclusion, in addition to better defining risk classification in respect to IPI, the proposed model has shown that nearly half of the patients affected by PTCL-U, (classified in Groups 3 and 4) had a very dismal prognosis, with a 5-year survival probability of only 26.81%. For these patients a new therapeutic strategy (e.g. monoclonal antibodies associated with ASCT or allo-BMT) should be explored.

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