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ORIGINAL ARTICLE

CLIP1: A NEW PROGNOSTIC INDEX FOR INDOLENT CUTANEOUS B-CELL LYMPHOMA PROPOSED BY THE INTERNATIONAL EXTRANODAL LYMPHOMA STUDY GROUP (IELSG 11)

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ABSTRACT

Indolent primary cutaneous B-cell lymphomas (PCBCL) generally have a good prognosis, but they often relapse leading in some cases to extracutaneous disease and therefore to poor survival. We developed a prognostic model, to improve the therapeutic approach to these lymphomas.

217 patients with diagnosis of indolent PCBCL stage IE or IIE were assessed retrospectively. The prognostic model was built to fit a Cox proportional hazard model using all the covariates affecting PFS at $p < 0.1$ in the univariate analysis and the final model was selected based on the Bayes Information Criteria.

Elevated serum lactate dehydrogenase, morphology of the lesion (nodule vs. other), and >2 lesions were independent predictors for PFS. To each prognostic factor was assigned a value of 1. Patients were then stratified to three risk groups: score 0 (28%), low risk ; score 1 (55%), intermediate risk; score 2 and 3 (17%), high risk with a 5-year PFS of 91%, 64%, and 48%, respectively ($p < 0.001$).

The CLIPI is an easily applicable prognostic index and represents a promising tool for risk adapted treatment strategies. However, it needs to be addressed in prospective clinical studies.

Keywords: B-cell, CLIPI, cutaneous, lymphoma, prognostic index

INTRODUCTION

Primary cutaneous B-cell lymphomas (PCBCL) are a distinct group of B-cell non-Hodgkin lymphomas (NHL), which present exclusively in the skin and have different characteristics than their nodal counterparts[1]. They are a rare disease accounting for less than 25% of all primary cutaneous NHL and are generally associated with a good prognosis [2]. For many years the classification of these diseases was not clear since two different systems were in use, the World Health Organization (WHO) and the European Organisation for Research and Treatment of Cancer (EORTC) classifications [2,3]. In 2005 the WHO-EORTC classification for cutaneous lymphomas [1] was introduced, subdividing PCBCL in three entities: primary cutaneous marginal zone B-cell lymphoma (PCMZL), primary cutaneous follicle center lymphoma (PCFCL) and primary cutaneous large B-cell lymphoma, leg type (PCLBCL, LT). The latter are highly aggressive and lead to death in estimated 50% of the cases after 5 years [1,4], while PCFCL and PCMZL are characterized by an indolent clinical course with a 5 year overall survival (OS) \approx 95%. However, these lymphomas have a relapse rate between 20% and 60% according to different studies [5-11]. Nevertheless, since relapses are mainly confined to the skin and they do not constitute a dissemination of disease, the standard of care in patients without extensive cutaneous disease or evidences of *Borrelia burgdorferi* infection, consists of local treatments, namely surgical excision (SX) or radiotherapy (RT) [4]. However, it has been shown that extracutaneous relapses can occur in 8-10% [12], leading to a dismal outcome and therefore more aggressive treatments could be needed. Since the median age of the patients affected by PCFCL and PCMZL is below 60 years of age at time of diagnosis and the majority has a prolonged survival it is crucial to identify poor-risk patients at time of diagnosis, in order to develop risk adapted treatment strategies. Several efforts for the detection of prognostic parameters were undertaken and the most promising seems to be involvement of the lower extremities, especially in PCFCL [8,9,12-14].

However, three of these trials [14,13,8] included all PCBCL subtypes and analyses of the subgroups were not, or only partially performed. Therefore, the results were mainly focused on the poor risk of PCLBCL,LT. The international extranodal lymphoma study group (IELSG) conducted this study (IELSG-23) in order to develop a model for predicting the clinical course of patients affected by PCFCL and PCMZL.

MATERIALS & METHODS

PATIENTS

Two-hundred and seventeen patients with diagnosis of PCBCL from 28 international cancer centers were assessed through retrospective chart review. PCBCL were defined according to the WHO-EORTC classification [1] as PCFCL and PCMZL, which presented primarily as skin tumors without any involvement at other sites (stage IE or IIE). Morphology was reviewed by an expert of each participating center and all unclear cases centrally by an ad hoc expert panel. Diagnoses stated before 2005 were converted into the categories of the WHO-EORTC classification for cutaneous lymphomas. All centers contributing patients had approval of the study from the hospital's institutional review board in accordance with the declaration of Helsinki.

Staging procedures included complete physical examination with assessment of the performance status [15], skin biopsy or surgical excision of the lesion, and computed tomography (CT) of thorax, abdomen and pelvis. Since in the early 1980s not all centers were equipped with a CT device, ultrasonography was used in some cases. In order to exclude a stage IV disease, the majority of the patients underwent bone marrow biopsy. Stage was assessed according to the Ann Arbor classification modified by Musshoff [16]. Although all requested information was available, extent of disease was not measured

according to the recently published TNM system[17], since it combines several clinical factors such as number of lesions and diameter of disease, which could have a a different impact on progression free survival (PFS).

Patients were treated according the extent of disease, following the standards of the participating centers. Therefore patients with localized disease underwent local treatment modalities (LT), consisting of RT, SX or both, whereas cases with regional or disseminated disease underwent either chemotherapy (CHT) alone or in combination with LT. However, since the patients were assessed retrospectively in different institutions, there was no uniform treatment policy and some patients with localized disease underwent CHT.

STATISTICAL ANALYSIS

The study strove to develop of a simple prognostic scoring system easily applicable in the clinical routine without the need of extensive diagnostics.

Comparisons between clinical parameters were made by means of Fisher's exact test when appropriate or chi-square test. Response was assessed after the completion of the treatment. Complete remission (CR), partial remission (PR), stable disease (SD) and progressive disease (PD) as well as OS, progression free survival (PFS) and disease-free survival (DFS) were defined according to the criteria by Cheson et al [18]. The actuarial duration of OS, PFS and DFS were plotted as curves according to the Kaplan-Meier [19] method.

The LDH level was categorized according to the previous published threshold value. Otherwise, for continuous covariates the cut-off values were obtained by comparing distribution quartiles using the log-rank test, whereas categorical covariates were dichotomized comparing the Kaplan-Meier curves by means of log-rank test. Since we considered only patients affected by indolent PCBCL (PCFCL and PCMZL) for the development of the score and since they usually have a favorable clinical course leading

to a low death rate, the prognostic score was developed according to PFS [20], reflecting tumor growth and not being confounded by the administration of subsequent treatments. Afterwards we applied the score on OS and DFS. For determination of the most significant variables contributing to survival, univariate analysis was performed with the log-rank test [21]. Multiple test correction was not done, because this method was applied to discard parameters without a significant impact. In the next step a prognostic model was built to fit a Cox proportional hazard model [22] using all the covariates affecting PFS at $p < 0.1$ in the univariate analysis and the final model was selected based on the Bayes Information Criteria proposed by Raftery-Volinsky (BIC'), as a measure of overall fit. We chosen the model with the more negative BIC [23]. The proportionality of the risks and overall model fit were graphically checked using scaled Schoenfeld [24] and Cox-Snell residuals; overfitting (shrinkage factor) and the performance of the model were checked using Harrell's method [25]. The scoring system was confirmed with the log-rank test and the Harrell's concordance index (C-Harrell) [26]. All p-values were based on two-sided testing. A $p < 0.05$ was considered to demonstrate a moderate strength against the null hypothesis. All statistical analyses were performed with Stata Statistical Software release 8.0 (StataCorp, College Station, TX) and PASW Statistics v17.02 (SPSS, Chicago, IL, USA).

RESULTS

PATIENTS CHARACTERISTICS AND TREATMENTS

From 1980 to 2007, 217 patients with indolent PCBCL stage IE or IIE were assessed. Patient characteristics at time of diagnosis are listed in Table 1. The median age was 55 years (range, 18-91 years) and a male predominance (m:f=1.57) was observed. Less than one third of the patients presented with regional or generalized disease (66 patients, 30%), stage IIE was present in 20% (43 patients) and nodular lesions prevailed (142, 65%). No statistical significant differences were observed between FCL and MZL, except in the

number of lymphomas occurring on lower extremities (7% in FCL versus 16% in MZL, $p=0.003$). Patients received CHT (40/217, 18%), RT (87/217, 40%) or SX alone (37/217, 17%) or a combination of CHT and/or RT (53/217, 25%). In 66% of the cases (65/98) chemotherapy consisted of an anthracycline-containing regimen. Only two patients received rituximab. Overall, 198 patients (91%) achieved CR, 16 (8%) a PR and only 3 patients (1%) did not respond to treatment, in two cases due to PD and in another two due to SD. After a median follow up of 55 months (range 2 - 244 months) 54 patients (27%) relapsed: 37 (19%) locally, 10 (5%) at distant cutaneous sites or with a disseminated but disease confined to the skin and 7 (3%) with extracutaneous lymphoma. Notably, the majority of recurrences occurred in patients with primary localized disease (34 patients, 63%). Eight of ten distant cutaneous recurrences as well as all extranodal relapses, were observed within this subgroup of patients. The relapse rate did not differ significantly among the different treatment modalities ($p=0.058$), but the percentage of relapse was 17% in the group which underwent combined treatment modalities vs. 31% in the other. Eighteen patients died (3.7%): 11 due to disease, 2 of second tumor and 4 for other causes. The majority of lymphoma related deaths (8 cases) were observed in patients who relapsed after primary localized disease. The 5-year OS, PFS and DFS were 90% (median not reached), 68% (median 139 months), 69% (median 145 months), respectively (Fig 1). The different treatment modalities did not influence PFS significantly (data not shown), even when analyzed according to the extent of disease (Supplementary Fig 1).

DEVELOPMENT OF THE PROGNOSTIC MODEL

In order to identify the most important parameters influencing the PFS, univariate analysis was performed. Sixty events were observed: 54 relapses, 7 disease progressions (11%), two deaths in CR (3%) and one lymphoma related death (2%). Eleven variables were

analysed and six variables had a $p < 0.1$: age > 65 years ($p = 0.04$), male sex ($p = 0.156$), serum lactate dehydrogenase (LDH) $>$ upper normal limit (UNL; $p < 0.001$), morphology of lesion (nodule or not; $p < 0.001$), locoregional distribution vs. generalized disease ($p = 0.151$) and more than 2 lesions ($p = 0.004$) (Supplementary Table). Subsequently we built a prognostic model to fit a Cox proportional hazard model. We chose the model with the best overall fit in terms of BIC'. Although the hazard ratio (HR) differed among the single factors, the standard errors were approximately proportional (Table 2). Variables with independent prognostic value were LDH serum level, number of lesions and nodular lesions. Therefore, we constructed a risk score by summing the number of factors present in a single patient without weights. Risk groups were defined by comparing the relative risk of disease progression in patients with each possible number of presenting prognostic factors and combining the categories with a similar relative risk. Then, patients were stratified according to the following three risk groups: score 0 (28%), low risk (LR); score 1 (55%), intermediate risk (IR); score 2 and 3 (17%), high risk (HR) (Table 3). According to the different scores, 5-years PFS was 91%, 64%, and 48% for patients at LR, IR, and HR, respectively ($p < 0.001$). CLIPI was also highly predictive for DFS ($p < 0.001$), whereas the impact on OS was not significant ($p = 0.449$).

The CLIPI was also predictive for each of the two indolent lymphoma categories included in this study when applied to PFS and DFS. Interestingly, among MZL the ability to discriminate patients with poorer survival was not significant ($p = 0.350$), whereas among FCL the score was able to stratify the risk groups, although we did not refute the null hypothesis with enough strength ($p = 0.091$) (Supplementary Fig 2).

DISCUSSION

This retrospective multi-center study was conducted to develop a prognostic score for indolent PCBCL. It consists of elevated LDH serum level, number of cutaneous lesions and nodular lesions, and constitutes an easy and useful tool to distinguish three prognostic subgroups. The 5-yr PFS was 91%, 64% and 48% respectively for patients with low, intermediate and high risk according to the CLIPI.

The main limits of this study were the retrospective assessment of the patients, the long time period of data collection and the lack of a statistically significant impact of the score on OS. The first two limits were due to the rarity of this disease, whereas the last one could be ascribed to the generally indolent course of this PCBCL and efficient salvage treatments [4].

Baseline clinical characteristics, outcome and survival of our cohort reflected those of previously published series [13,12,1]. We observed no statistical significant differences in terms of clinical characteristics and survival between the two indolent subtypes PCMZL and PCFCL.

In univariate analysis six factors had a $p < 0.2$ and were therefore included in the development of the prognostic score. After multivariate analysis only elevated LDH, morphology of the lesion and >2 lesions constituted the CLIPI.

Already Zinzani et al [13] showed that among indolent PCBCL the presence of more than one lesion influences the DFS negatively. Of note, among the different parameters which contribute to the TNM system [17], this is the only one with an independent impact on PFS in this setting of patients.

The prognostic role of the morphology of the lesion (nodular or not), has not been evaluated yet in previous trials. Nevertheless, already in univariate analysis it emerged as one of the most important factors influencing the PFS of indolent PCBCL. As shown in Supplementary Fig 3, the PFS of patients with nodular lesions is highly influenced by the type of treatment and only anthracycline-containing chemotherapy was able to improve the

outcome. This suggests that, albeit these NHL have a tendency to remain localized to a limited area of the skin [7], neoplastic cells could infiltrate the surrounding tissue deeply, leading to a higher relapse rate.

Despite the CLIPI was developed according to PFS, we demonstrated that it is applicable to DFS; when applied to OS no statistical significance was observed, although there seems to be a slight impact in FCL. The majority of relapses occurred in patients with primary localized disease, leading to a lymphoma related death in 8 cases. Certainly the relapse rate and the severity of the recurrences observed in this study might be underestimated since 40% of the patients with localized disease underwent CHT, which in 80% contained anthracyclines. Nevertheless, our results suggest that probably, mostly due to the rather indolent course of this NHLs, their aggressiveness gets underestimated in some cases, causing not only recurrence of disease, but also a dismal survival. Indeed, a large trial of 153 patients affected by PCBCL and solely treated with RT, it has been shown that, despite indolent PCBCL being considered as highly radiosensitive (CR rate of 100%), the relapse rate is rather high and extranodal disease can occur[10]. Since the CLIPI is able to identify poor-risk patients at time of diagnosis, it constitutes a useful tool to provide risk adapted treatment strategies and to avoid unnecessary toxicity. Therefore, in patients with high-risk CLIPI, even if they have primary localized disease, alternative treatment modalities should be considered.

In conclusion, the IELSG-23 trial confirms that indolent PCBCL have a significant rate of distant relapses which can be reliably predicted by several clinical features, and these can be assembled together to provide a strong prognostic index. The CLIPI is able to discriminate patients with low, intermediate and high risk disease allowing the development of risk adapted treatments. This prognostic model does not require extensive diagnostics and is therefore easy to use in clinical practice. However, prospective studies are warranted to validate the clinical role of CLIPI in patients with indolent PCBCL.

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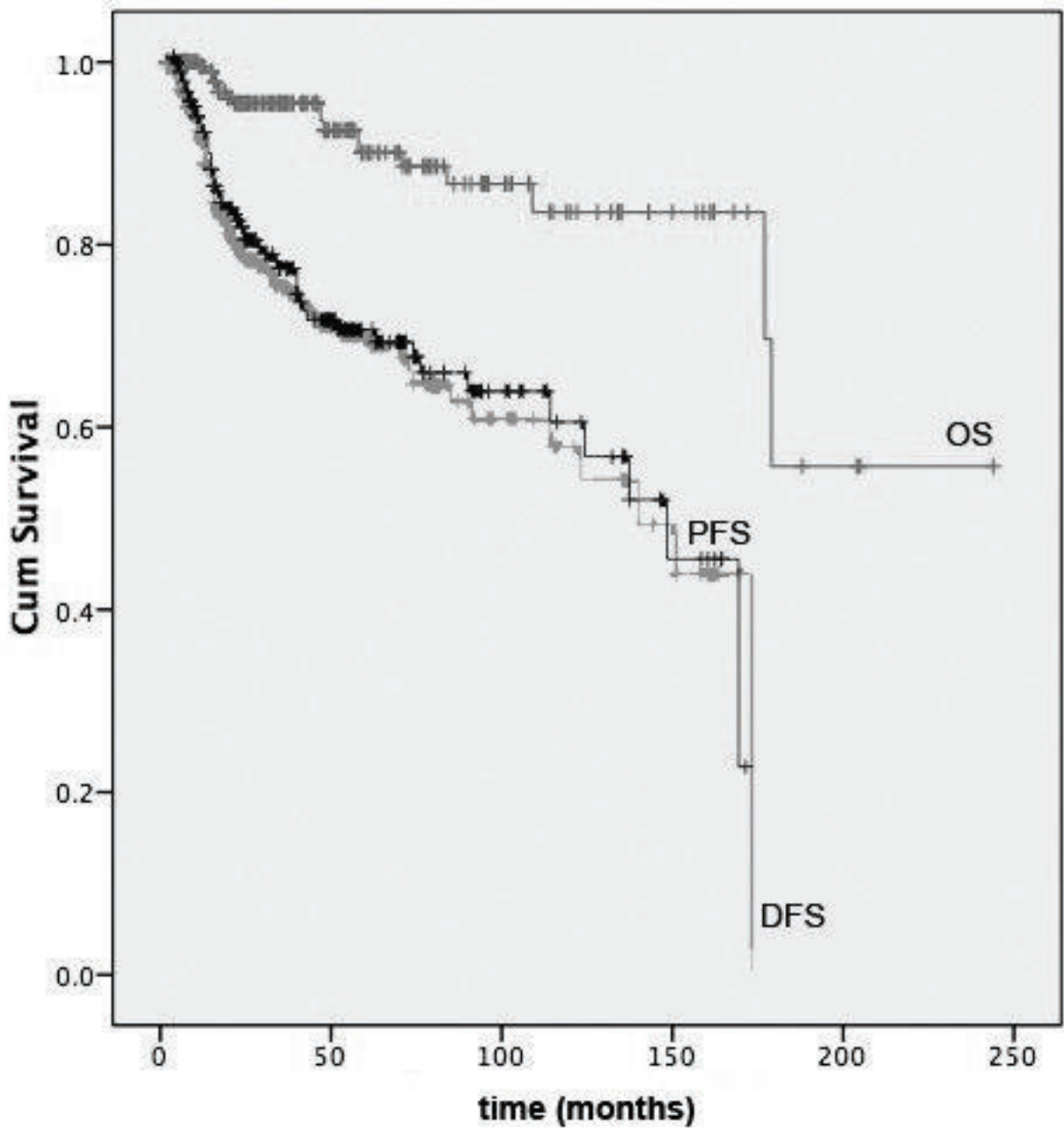
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FIGURE LEGENDS

Fig 1. Overall survival, progression free survival and disease free survival of 217 patients used for Cutaneous B-cell lymphoma International Prognostic Index development.

Fig 2. PFS (A), DFS (B) and OS (C) of 217 patients according to CLIPi: low risk, score 0; intermediate risk, score 1; high risk, score 2-3.



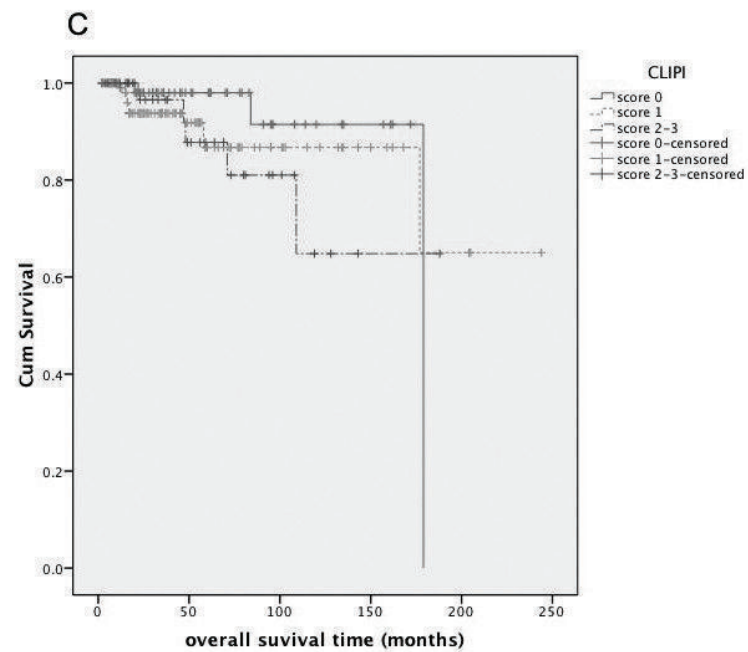
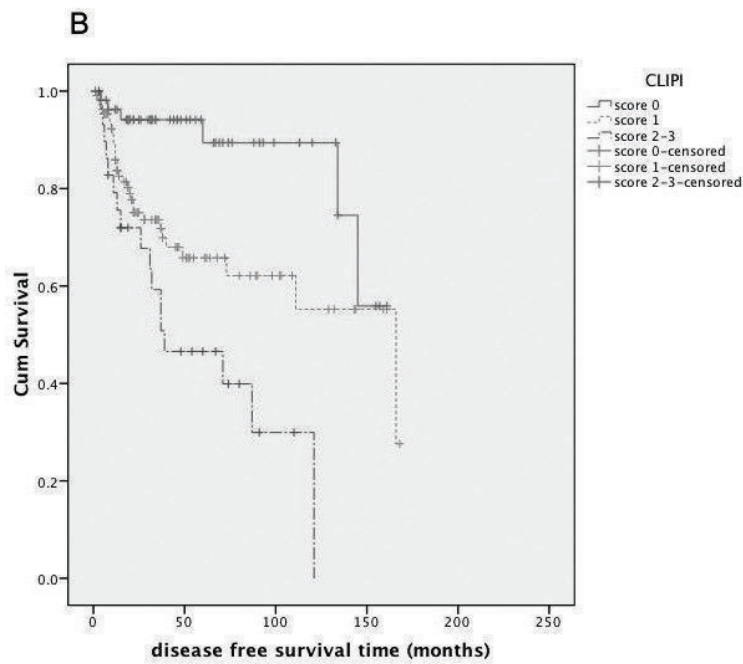
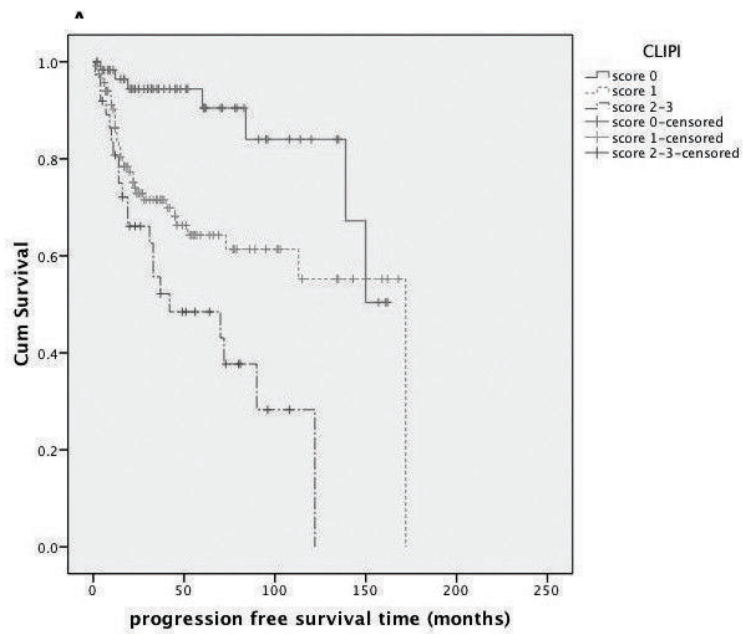


TABLE LEGENDS

Table 1. Baseline characteristics of the assessable patients (n=217).

Abbreviations: m, male; f, female; UNL, upper normal limit; RT, radiotherapy; SX, surgery; CHT, chemotherapy.

Table 2. Multivariate analysis of progression free survival (PFS). Slope shrinkage and c-Harrel obtained after 250 bootstrap replications. Abbreviations: HR, hazard ratio; SE, standard error.

Table 3. CLIP score performance in progression free survival (PFS).

TABLES

Characteristic	No.	%
Median age, years	55	
Range	18-91	
≤65 years	161	74
>65 years	56	26
Gender (m:f)	131:83	62:38
Site of disease		
Head and neck	65	30
Trunk, upper extremities	121	56
Lower extremities	16	7
Generalized skin disease	15	7
Extent of cutaneous involvement		
Local	151	70
Regional or generalized	66	30
Morphology of the lesion		
Nodular	142	65
Other (plaque, macule etc)	75	35
No. of lesions		
Median (range)	1(1-80)	
1-2	170	78
>2	47	22
Ann Arbour stage		
I E	174	80
II E	43	20
ECOG PS		
0-1	178	82
>1	39	18
Serum LDH		
≤UNL	209	96
>UNL	8	4
B-Symptoms		
No	209	96
Yes	8	4
Treatment modalities		
RT	87	40
SX	36	17
CHT	40	18
CHT + (RT or SX)	54	25

Table 1.

Covariate	Adverse Factor	Patients (%)	5yr PFS (%)	Final Model (N=217)			Slope shrinkage
				HR	SE	p	
LDH	>UNL	4	12	3.40	1.42	0.003	0.913
# Lesion	>2	22	55	1.76	0.48	0.038	0.939
Nodular lesion	positive	55	59	2.63	0.89	0.004	0.914
Model							0.914
c-Harrel							0.662

Table 2.

Score	Patients		5yr PFS (%)
	N	%	
0	61	28	91
1	119	55	64
2-3	37	17	48
Log-rank			<0.001
c-Harrel			0.648

Table 3.