Primary Cutaneous Lymphoma: Local Control and Survival in Patients Treated with Radiotherapy

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Abstract. *Background: The treatment of primary cutaneous lymphoma is still ongoing and the role of radiotherapy, as exclusive or combined modality, is not yet clear. Materials and Methods: From 1994 to June 2004, 29 patients with cutaneous B-cell lymphoma and 9 patients with cutaneous T-cell lymphoma were treated by radiotherapy (median dose of 3900 cGy, range 600-4600 cGy). Eight patients had previously received chemotherapy. Results: The complete response rate was 94.7% with progressive disease in two patients (5%). Sixteen (42.1%) patients relapsed, with the relapse occurring only in the skin site as single episode (9 patients) and more than two episodes (7 patients). The 5-year overall survival and event-free survival were 94% and 53%, respectively. Conclusion: Radiotherapy offers a substantial local control of primary cutaneous lymphoma, both as exclusive or combined approach. The patients with wide-spread or multiple lesions, usually candidates for radiotherapy and chemotherapy, are amenable to radiotherapy alone.*

Primary cutaneous lymphomas (PCL) are a heterogeneous group of extranodal lymphoma with a clinical behaviour and prognosis quite different from a secondary skin involvement by a systemic lymphoma, regardless of histological subtype. Until recently there was no consensus regarding the optimal treatment schedule with therapeutic approach planned on the basis of experience of single institutions. In 1997, the EORTC group presented a classification for primary cutaneous lymphomas in which primary cutaneous lymphoma was defined as a distinct clinical entity (1, 2). This classification was recently updated by WHO/EORTC consensus group on the basis of histological, immunophenotypical, molecular and clinical criteria (3). Thereafter many efforts have been made for a definition of histological (and/or immunophenotypical, molecular) or clinical behaviours (*i.e.,* skin site, number of localizations, age) as risk factors (4-6). In fact, actually the main goal is the definition of a therapeuthic alghorytm based on risk-categories, in whom a loco-regional (*i.e.,* surgery and/or radiotherapy or others) or a systemic approach (chemotherapy as exclusive or combined setting) was chosen when appropriate. Although never confirmed by randomized studies, the radiotherapy still represents a suitable treatment modality with very high local control rate (80-100%) and favourable outcome, especially in several subsets of PCL (6-8). In the present report, our experience in 38 patients with diagnosis of PCL (B-cell and T-cell lymphoma) treated at Department of Radiotherapy and Department of Haematology of the University of Rome "La Sapienza", Rome, Italy, is presented.

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Patients and Methods

From January 1994 to June 2004, 38 patients were diagnosed as having PCL. There were 25 males and 13 females, aged from 18 to 92 years, median age 53 years. The main patient characteristics are listed in Table I. This study group included 29 patients with cutaneous B-cell lymphoma and 9 patients with cutaneous T-cell lymphoma. Histologically, regarding the B-cell lymphoma, there were 20 follicle center-cell lymphoma (PCFCCL), 8 marginal zone B-cell lymphoma (PCMZL), 1 diffuse large B-cell lymphoma-leg type. Only 5/9 patients with diagnosis of T-cell lymphoma were assessed for CD30 exhibiting CD30+ in 2 patients and CD30- in 3 patients. Thirty-two patients (84%) presented single lesions and 6 patients (16%) presented multiple lesions, hence requiring more than one radiotherapy field.

All skin biopsy specimens were evaluated by an expert hematopathologist. All biopsies were classified according to the WHO-EORTC classification (3). Staging procedures included: physical examination, routine blood analysis with lactate dehydrogenase (LDH), chest X-ray, chest abdominal and pelvic computed tomography, ultrasonic examination of liver and spleen and bilateral bone marrow biopsy . All patients were restaged at the end both of therapies by repeating those tests that had been

Table I. *Clinical features of all 38 patients.*

Clinical Parameter	Value
Age	
Median age	53 years
Range	18-92
Gender	
Male	25
Female	13
Initial skin site	
Head and neck	8
Trunk	20
Arms	9
Legs	1
Histological type	
B-cell lymphoma	29
T-cell lymphoma	9

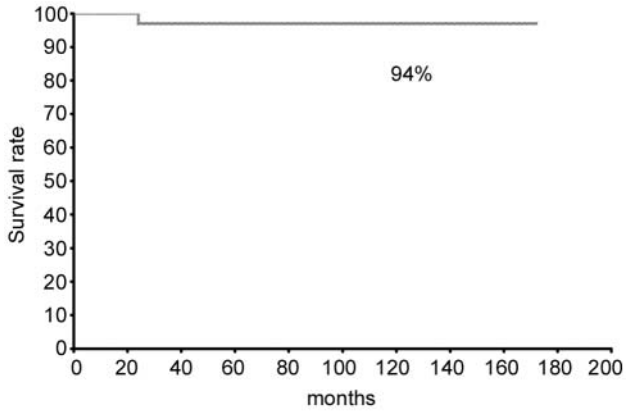

Figure 1. *Overall survival of the 38 patients with primary cutaneous lymphomas.*

abnormal during the staging evaluation. Complete remission (CR) was defined as the disappearance of all clinical (or radiographic) evidence of lymphoma, and partial remission (PR) was defined as a reduction ≥50% of the largest dimension of each measurable anatomical site of disease localization, for at least 1 month. Patients with less than 50% reduction of lesions or with disease progression during treatment were regarded as non-responders (NR). Relapse was defined as the reappearance of disease in patients who had been in CR for a period of at least four weeks. All patients considered as CR or PR after therapy were considered for follow-up. Radiation therapy, when appropriate, was started approximately 4-6 weeks following the complete resolution of surgical scar. Patients were irradiated with 7-9 MeV electron beam or ^{60}Co with a median dose of 3900 cGy (range 600-4600 cGy) with a conventional fractionation (five fractions of 200 cGy daily/week) in most cases. All doses were prescribed along the central axis of beam according to ICRU guidelines (7). In all patients the radiation fields showed clinical evidence of cutaneous lesion (or a surgical scar) and comprised a margin of 2 cm of healthy skin in all radial directions. In multiple localizations, a single field was used if the lesions were adjacent or, if the lesions were distant from one another, we preferred to treat them with individual radiation field. Overall survival (OS) and event-free survival (EFS) curves were calculated according to the Kaplan-Meier method (8). In particular, the OS was calculated as the time from diagnosis to death and EFS from diagnosis to date of progression, relapse or death. Patients in CR who died later of causes unrelated to lymphoma or its treatment were considered to have unrelated deaths and were evaluated in OS analysis. Prognostic factors such as histology (B-cell *vs.* T-cell), skin site (favourable=head-and neck, upper arms; unfavourable=trunk, leg, disseminate disease) and therapy (surgery *vs.* chemotherapy plus radiotherapy *vs.* radiotherapy) were considered to allow a statistical analysis for the survival end-points considered. In particular for B-cell histology and skin sites our stratification was based on the Prognostic Index by Smith *et al.* (5). The survival was computed using the Kaplan-Meier method and the differences between the curves were analyzed with a log-rank test when appropriate. All *p*-values were two-tailed. The Student's *t*-test was computed when appropriate. Multivariate analysis of prognostic factors was performed using the Cox regression model. All patients were observed every 3 months during the first year of follow-up, and every six months during following years.

Results

The median follow-up of all 38 patients was of 71 months (range 21-195 months) with an actuarial overall survival rate at 5 years of 94% (Figure 1). Two patients died; a male died of leg skin lymphoma progression, and a female after a systemic progression of disease. Eight patients received antracycline-based chemotherapy before the radiotherapy course. These patients were treated with six/eight cycles of chemotherapy. One case was treated with interferon-alpha therapy for 3 years, followed by irradiation after appearance of relapses. As front-line therapy, 11 patients were treated exclusively with surgery, 12 patients with radiation therapy and 15 patients with chemotherapy and radiotherapy. Thirty-six out of 38 (94.7%) patients presented a complete response. During radiotherapy, one patient presented progression of the disease (leg-type) and one patient presented a progression to loco-regional lymph nodes.

A relapse was observed in 16 patients (41.6%), after a mean relapse-free survival of 16 months (range of 2-72 months) with an EFS of 53% at 5 years (Figure 2). All relapses included only the cutaneous site. The relapses were recorded near or at the site of surgical scar in all 11 patients who did not undergo chemo-and/or radiotherapy. Moreover in all the other cases, the relapse occurred in another skin site (but in the same loco-regional district). In 9 patients, single episode of relapse was recorded, moreover 7 patients experienced more than 2 consecutive episodes during follow-up. The consecutive episodes of relapse were all treated with radiotherapy alone. All patients (11 out of 11), who had undergone surgery as exclusive therapy experienced a

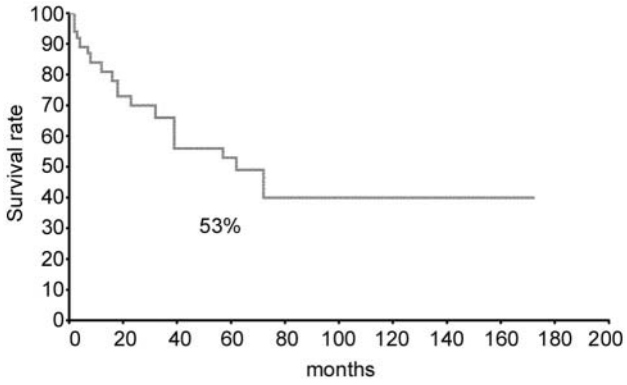

Figure 2. *Event-free survival of the 38 patients with primary cutaneous lymphomas.*

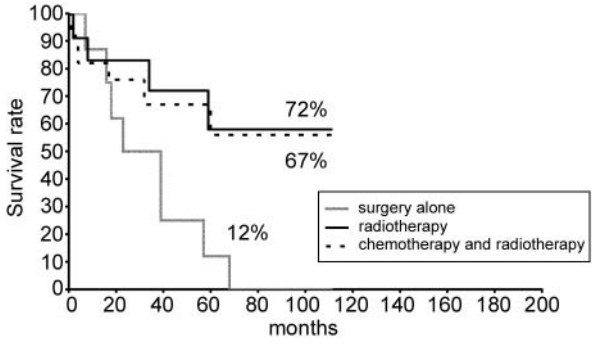

Figure 3. *Event-free survival of the 38 patients with primary cutaneous lymphomas according to therapy.*

relapse. In the group of 27 patients treated with radiotherapy or chemo-radiotherapy we observed five relapses, with a relapse rate of 100% and 18.5%, respectively. The median time of relapse of both groups was similar (31 months *vs.* 24 months, respectively). Moreover, no difference regarding the relapse rate (40% *vs.* 31%) and the median time of relapse (18 months *vs.* 24 months) between radiotherapy *versus* chemo-radiotherapy group, respectively, was found. The 5-year EFS for surgery, radiotherapy and chemo-radiotherapy was 12%, 72% and 67%, respectively, with a statistically significant difference ($p<0.01$), confirmed by Cox logistic regression analysis ($p<0.020$) (Figure 3).

At relapse, the 11 patients of the surgery-alone group underwent radiotherapy (9/11) and chemo-radiotherapy (2/11), respectively; the 3 patients previously treated with radiotherapy and the 2 patients previously treated with combined approach also underwent radiotherapy. In univariate analysis with event-free survival as an end-point, the risk factors, such as age, histology and skin site were not statistically significant. The radiotherapy course was well tolerated, without grade 3-4 (WHO) cutaneous toxicity, even after chemotherapy (9). No grade 3-4 (WHO) chemotherapy-related toxicity was recorded .

Discussion

In recent years it has been established that primary cutaneous lymphomas are a neoplastic skin disease with a favourable prognosis after a specific treatment with radiotherapy or poly-chemotherapy, especially for some subtypes. The extent of skin involvement, histological subtype and presence of extracutaneous disease are the most important indications predictive of survival in patients with cutaneous lymphomas, as reported in most published papers. The EORTC/WHO classification currently represents the most precise classification scheme, considering the peculiar character of cutaneous lymphoma, but the standard therapeutic approach of this disease is still matter of debate. Considering the low incidence of this subset of lymphoma, its epidemiology, it is difficult to plan very large multi-institutional randomized studies. Interestingly, recent effort was made to produce a prognostic index in B-cell cutaneous lymphomas by Smith *et al.*, using the association between histology and skin site to identify several risk groups with different OS rates (5). In another study, Zinzani *et al.* identified the clinicopathological features (DLBCL, leg-type) as the worse prognostic factor regarding OS, while a single cutaneous lesion was the only independent prognostic factor for disease-free survival in B-cell cutaneous lymphomas (6).

Data are lacking on the T-cell cutaneous lymphomas other than Mycosis Fungoide and Sezary Syndrome, showing only CD30 positivity as prognostic factor (11).

In our study, 16 relapses were recorded from 2 months to 6 years after the end of radiation therapy. No relevant prognostic impact on event-free survival was seen for the prognostic factors considered, such as age or skin site, probably due to the small number of our series. Grange *et al.* presented a European multicenter study of 145 cases with PCLBCL (4). They found that round-cell morphology, location on the leg and multiple skin lesions at diagnosis were very important prognostic factors, while characteristics, such as age and gender had no important effect on prognosis. Patients with skin lesions on the head or trunk rarely developed extracutaneous disease and had an excellent prognosis with overall and disease-specific 5-year survival rates of 85% and 94%, respectively. In contrast, patients with PCLBCL-leg developed extracutaneous disease more often and had a significantly poorer prognosis with overall and disease-specific 5-year survival rates of 42% and 52%, respectively. In our experience, the only patient with leg-type PCL showed progression during treatment and died of lymphoma. As reported by some authors, the

histology (B-cell *vs.* T-cell) was related to the overall and disease-free survival; in our cases a different event-free survival was observed between the two groups, without statistical significance ($p<0.08$), but the T-cell patient group was too small for critical comment.

On the other hand, in our series the diagnosis of primary T-cell cutaneous lymphoma was made on the basis of clinical and histological criteria. The CD30 immunophenotype was detected in 5 out of 9 patients and it was not possible in our series to differentiate between CD30 anaplastic primary T-cell lymphoma and lymphomatoid papulosis. These 9 patients with primary T-cell cutaneous lymphoma had a 5-year EFS of 53%, but no lymphoma-related death was recorded.

The indolent course of some sub-types of primary T-cell cutaneous lymphoma was confirmed by several authors for whom the "wait-and-watch" approach or local therapy seemed justified, excluding patients with extracutaneous disease (12-13).

As single or combined modality, radiotherapy actually seems to offer the best clinical local control of most of subtypes of PCL. In clinically localized disease, radiotherapy has a good local control, even if early or late relapses are described, without decrease of survival (6). Eich's study showed that RT is the treatment of choice for localized B-cell cutaneous lymphoma with radiation fields that should have a margin of at least 2-3 cm of healthy skin and should receive a total dose of at least 40 Gy (14). In the Italian Study Group for Cutaneous Lymphomas, 467 patients with PCBCL were treated as first-line treatment with radiotherapy (52.5%) or chemotherapy (24.8%) with a complete response rate of 91% and a relapse rate of 46.7%: the 5- and 10-year OS rates were 94% and 85%, respectively, without differences regarding the treatment. (6). In a retrospective study in 34 patients with primary CBCL, Smith *et al.* described the indolent course of this disease which may be treated with local radiotherapy alone, with a five-year OS of 100% for all hystological subtypes other than Leg/DLB, (5-yr OS 33%) (15). The studies of Rijlaarsdam *et al.* of 55 patients with primary cutaneous follicle center B-cell lymphomas treated with radiotherapy and chemotherapy showed a disease-free survival at 2 years of 85% for 40 patients treated with radiotherapy and 87% for 15 treated with antracycline-based polychemotherapy (16). These authors therefore recommended radiotherapy alone in patients with localized disease and polichemotherapy for widespread cutaneous disease.

Whether cases of multifocal disease have a less favorable prognosis and should be treated with aggressive multiagent chemotherapy is a matter for debate. In patients with multifocal CBCL irradiation of all visible sites may be equally effective as has been demonstrated by Bekkenk and Willemze in a study group including 29 patients (17). In our study the multiple localization was not a poor prognostic factor, regardless the therapeutic approach.

At present there are no universal consensus guidelines for treatment of primary cutaneous lymphomas. In our study, we demonstrated a 5-year event-free survival of 12% in the group of patients with "wait-and-watch" approach after surgery, and 72% and 67% in radiotherapy and chemotherapy-radiotherapy treated patients, respectively, but no significant difference was recorded between the two latter. In our series of patients, 15 out of 38 (40%) underwent a combined approach, because we treated these patients like other types of stage I extranodal lymphoma.

To our mind, the exclusive surgery or "wait-and-watch" approach as a first line therapy were not a reasonable strategy; however in carefully selected cases, on the basis of histological features (*i.e.,* lymphomatoid papulosis, pT-cell CD30+ localized, marginal B-cell cutaneous lymphoma) this approach can be made without a decrease in survival rate. In our experience, radiotherapy alone or chemo-radiotherapy produced a comparable relapse rate but, importantly, a comparable overall survival rate. Thereafter, if patients suffered consecutive relapses during follow-up, they were rescued with conventional second-line therapy, in particular with radiotherapy alone (15).

In the coming years, the choice between different strategies will be based on clinical-biological behaviour of cutaneous neoplastic lymphoid cells. Accurate diagnosis, staging procedures and identification of prognostic factors, are paramount in providing a rational basis for therapeutic intervention. In this new era of the management of primary cutaneous lymphomas, radiotherapy, in an exclusive or combined setting, still represents a safe and effective therapeutic option, especially in some B-cell histological sub-types.

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