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Scientific Article

# Effectiveness of low-dose radiation for primary cutaneous anaplastic large cell lymphoma

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**Abstract**

**Purpose:** Primary cutaneous anaplastic large cell lymphoma (pcALCL) is conventionally treated with radiation therapy (RT) doses ≥30 GGy, but effectiveness of lower doses is unclear. We compared responses after a range of RT doses for pcALCL.

**Methods and materials:** From 1999 through 2015, 45 lesions in 21 patients met clinicopathologic pcALCL diagnostic criteria and were treated with RT (<20 Gy, 20-29 Gy, or ≥30 Gy dose). Complete clinical (CR) and partial responses (PR) were compared by dose using Fisher exact test. Progression-free and overall survivals were calculated using the Kaplan-Meier method.

**Results:** Forty-two percent of lesions were treated with <20 Gy, 22% with 20 to 29 Gy, and 35% with ≥30 Gy. Within 12 weeks, 100% responded, with 67% CR and 33% PR; by last follow-up, 87% achieved CR and 13% PR (no difference by RT dose; $P = .84$). Three-year freedom from local relapse was 100%, 86%, and 100% with <20 Gy, 20 to 29 Gy, and ≥30 Gy, respectively ($P = .28$). Many patients ultimately demonstrated other cutaneous or systemic relapse, with 55% 3-year and 29% 10-year progression-free survival. Overall survival at 10 years was 59%, with 2 deaths from complications of disease.

**Conclusions:** Low-dose RT offered excellent local control in the setting of the indolent, chronic course of pcALCL in this patient cohort.



Conflicts of interest: None.

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## Introduction

Primary cutaneous anaplastic large cell lymphoma (pcALCL) is a CD30-positive lymphoproliferative disorder. It is a rare clinical entity that generally follows a chronic course, but it is characterized by large anaplastic cells with comparatively more rapid proliferation than lymphomatoid papulosis, the more indolent in this spectrum of cutaneous disease.[1,2] This natural history to some extent resembles the chronic disease course followed by the more common cutaneous T-cell lymphomas, such as mycosis fungoides.[3] Although lymphomatoid papulosis can spontaneously resolve, historical series suggest that cutaneous ALCL lesions demonstrate excellent local responses to radiation therapy (RT), with response rates as high as 95%.[4-6] Notably, however, because of the rarity of pcALCL, these findings are based on fewer than 100 patients total in the scientific literature. The rarity of pcALCL is a challenge to establishing the optimal evidence-based approach to radiation treatment, particularly with respect to establishing the optimal radiation dose.

In conventional practice, RT doses given to patients with pcALCL customarily exceed 30 Gy.[5,6] Although this treatment approach is consistent with current International Lymphoma Radiation Oncology Group treatment guidelines for radiation,[7] the paradigm diverges from the contemporary evolving approach of low-dose radiation therapy, typically 24 Gy and less, for cutaneous and noncutaneous indolent lymphomas. For these other indolent lymphomas, low-dose radiation treatment courses <30 Gy are increasingly preferred because of comparable tumor control rates but lower risks of toxicity.[8-12] Because of pcALCL's rarity, however, few data exist to establish whether there is similar effectiveness of lower dose RT for pcALCL as is found in RT for other indolent lymphomas, particularly because lesions can present with a fulminant appearance, thick, tumorous, or ulcerated. In a retrospective institutional series, therefore, we sought to compare response rates across a range of RT doses used for treating pcALCL.

## Methods and materials

### Patient cohort

We retrospectively reviewed records of consecutive patients treated between 1999 and 2015 with RT for a pcALCL lesion or lesions. We abstracted covariates, radiation treatment details, and outcomes from the medical record.

### Diagnosis

Patients were required to meet criteria for a clinical diagnosis of pcALCL, including primary involvement of the skin with pathologically confirmed ALCL and no extracutaneous organ disease at diagnosis.[3,13] Patients with multifocal or grouped skin lesions and regional nodal disease at diagnosis were considered acceptable for inclusion in this analysis. All patients had gross disease at the time of RT.

### Covariates and radiation treatment

The following variables were abstracted from the medical record: sociodemographic characteristics, lesion location, stage at the time of treatment (classified as relapsed vs initial presentation; for patients receiving RT at initial presentation, the lesion was classified based on TNM stage)[14] and lesion size (in centimeters, if measured), ALK positivity, treatment history (including surgery, chemotherapy, and targeted therapy). Radiation treatment details were also abstracted, including dose and fractionation for each lesion and course treated and the total number of radiation courses per patient (to account for new treatment to a different lesion or retreatment to a previously treated lesion). In statistical analysis, radiation dose was categorized as <20 Gy, 20 to 29 Gy, and ≥30 Gy.

### Outcomes

Local clinical response (CR) was assessed by physical examination by the treating radiation oncologist and/or dermatologist. Initial response was recorded within 12 weeks of radiation treatment. Subsequent response and local failures were captured by a comprehensive review of the medical record until death or last date of follow-up, using the record of clinical examinations and medical photographs to indicate any relapse of the treated lesion. A complete CR was defined as 100% clearance of the treated lesion, including clearance of nodularity, ulcer, plaque, scaling, or pigmentation changes. A partial response (PR) was defined as 50% to 99% clearance of the lesion, including reduction in the size. Patients with either CR or PR were considered to have any response.[5] Additionally, relapse from new cutaneous lesions or subsequent progression with nodal or systemic disease was recorded. Death and the date and cause of death (from disease vs other cause) were also abstracted. All charts were abstracted until patient death or last visit (through February 2016).

### Statistical analysis

Where relevant, analyses used *patients* or *lesions* as the unit of analysis. Univariate associations between patient characteristics and radiation dose group were tested using the Fisher exact (for categorical variables) and Wilcoxon rank sum or Kruskal Wallis tests (for continuous variables). The associations between lesion response (at 12 weeks and at least follow-up) and radiation dose group were tested using

the Fisher exact test. Freedom from local progression, progression-free survival (accounting both for cutaneous and systemic disease relapses), and overall survival were analyzed using the Kaplan-Meier method. Times to events were calculated from the last date of RT. An exploratory multivariate parsimonious exact logistic regression model was conducted, with covariate selected a priori based on clinical significance (the primary independent variable of interest being RT dose) and statistical significance ($P < .05$) in univariate analyses. Categorical variables were compared using dummy variable levels compared against the referent category. This model was considered exploratory and hypothesis-generating only, given the small sample size. All analyses were conducted with SAS statistical software (Cary, NC) and assumed a 2-tailed alpha = 0.05. This retrospective study was approved by our institutional review board and granted exemption.

## Results

### Patient, lesion, and treatment characteristics

A total of 45 lesions were found in 21 patients. Median patient follow-up was 21 months (range, 2-149). Reflecting practice trends, the median follow-up was shorter in patients treated with lower RT doses, but this difference was not found to be statistically significantly different (with median 11-month follow-up for <20 Gy [range, 3-43], 35 months for 20-29 Gy [range, 8-78], and 55 months for ≥30 Gy [range, 2-149]; $P = .38$).

The median age of patients was 53 years (interquartile range [IQR], 45-66). Seventy-one percent of patients were men, 62% were white, and 95% of patients with available ALK status had ALK negative tumors (with 2 patients lacking ALK status on pathology). At the time of radiation, 81% were treated in the setting of a new diagnosis; of these, 28% were T1a, 17% T1b, 33% T2a, 11% T3a, and 6% T3b. Of the 45 lesions, 29% were in the head/neck, 47% extremities, and 24% in the torso. Median size was 4 cm (IQR, 2-7).

Lesions were treated across a range of radiation doses on a single treatment course, from 4 to 43.2 Gy delivered at 1.8 to 3 Gy per fraction (6 lesions treated at 2.4-3 Gy per fraction); with a median RT dose of 24 Gy (IQR, 12-32). Specifically, 42% of lesions were treated with <20 Gy, 22% with 20 to 29 Gy, and 35% with ≥30 Gy. The most common dose fractionation schemes used were 12 Gy in 6 fractions (5 lesions) and 30 Gy in 10 fractions (3 lesions). Eighty percent of lesions were treated with electrons and 20% with photons. There were no statistically significant differences in the use of RT doses by patient or lesion characteristics, except lesion size. Lesions >3 cm vs ≤3 cm were more likely to be treated with ≥20 Gy ($P = .03$) (Table 1).

**Table 1** Patient, lesion, and treatment characteristics

| Characteristic | N | % |
|---|---|---|
| Patients as unit of analysis | | |
| Sex | | |
| Female | 6 | 29 |
| Male | 15 | 71 |
| Ethnicity | | |
| White | 13 | 62 |
| Black | 3 | 14 |
| Hispanic | 3 | 14 |
| Asian | 2 | 10 |
| Age | | |
| Median | 58 | |
| Interquartile range | 45-66 | |
| T stage at the time of treatment | | |
| T1a | 5 | 24 |
| T1b | 3 | 14 |
| T2a | 6 | 29 |
| T3a | 2 | 10 |
| T3b | 1 | 4 |
| Recurrent | 4 | 19 |
| CD 30+ | | |
| Yes | 21 | 100 |
| ALK+ | | |
| No | 18 | 86 |
| Yes | 1 | 5 |
| Unknown | 2 | 10 |
| Lesions as unit of analysis | | |
| Lesion location | | |
| Head and neck | 13 | 23 |
| Extremity | 21 | 47 |
| Torso | 11 | 24 |
| Lesion size (cm) | | |
| ≤3 | 17 | 38 |
| >3 | 25 | 56 |
| Unknown | 3 | 7 |

### Response rates after RT

Within 12 weeks, any clinical response was demonstrated in 100% of lesions (excluding n = 3 lesions with unknown response within that period because of the absence of a recorded description or photograph of the RT-treated lesion by 12 weeks). Specifically, 70% demonstrated CR and 30% PR. There was no significant difference in 12-week response by RT dose groups (76% CR for <20 Gy; 60% CR for 20-29 Gy; and 69% CR for ≥30 Gy; $P = .83$). By last follow-up, 7 of 12 lesions with early PR ultimately attained CR (including 2 lesions treated with 4 Gy in 2 fractions), up to 6 months after treatment. This translated to a total of 87% of lesions ultimately achieving CR and 13% PR, including 100% CR by last follow-up in the 12 lesions treated with ≤12 Gy. Of note, these 7 lesions occurred in 4 patients, all of whom required intervening systemic therapies. For patients treated in the relapsed/persistent disease setting, 12-week CR rate was 67%

**Table 2** Multivariate exact logistic regression testing association between radiation treatment dose and complete clinical response vs partial response

| Variable | OR | 95% | CI | *P* value |
|---|---|---|---|---|
| Radiation treatment dose | | | | |
| <20 | 1.03 | 0.11 | 8.32 | 1.00 |
| 20-29 | 0.75 | 0.11 | 4.73 | 1.00 |
| ≥30 Gy (referent) | - | - | - | - |
| Lesion size | | | | |
| ≤3 cm (referent) | - | - | - | - |
| >3 cm | 1.39 | 0.25 | 8.46 | .95 |
| Unknown | 0.86 | 0.01 | 14.98 | 1.00 |

CI, confidence interval; OR, odds ratio.

compared with 81% of those newly presenting, but this difference was not statistically significantly different ($P = .33$).

Four of the lesions that initially and persistently demonstrated PR were in the same patient, who was seen in 2 separate treatment courses separated by 3 months, the first for 1 lesion and the second for 3 separate lesions. The lesions in this patient were treated to 25.2 to 30 Gy. One of the fields during the second course of treatment overlapped with the initial field, and this was the only patient who underwent in-field retreatment.

Though the association between lesion size and CR within 12 weeks was not statistically significant, the absolute rates of initial CR were higher in lesions <3 cm (71% CR in ≤3 cm vs 61% CR in >3 cm; $P = .43$) as well as CR by last follow-up (94% CR in ≤3 cm vs 83% CR in >3 cm; $P = .37$). In an exploratory multivariable exact logistic model, there were no differences by RT dose in the adjusted odds of CR vs PR by 12 weeks, even after adjusting for the size of the lesion ($P = 1.00$). Size of lesion remained nonsignificant as a predictor variable (Table 2).

## In-field (local) relapses after RT

Ultimately, 3-year actuarial freedom from a local relapse in the radiation field was 100% for <20 Gy; 83% for 20 to 29 Gy; and 100% for ≥30 Gy; $P = .28$ (Fig 1). One lesion that demonstrated initial excellent CR relapsed within the RT field 11 months after treatment to 25.2 Gy in only 1 patient.

## Disease outcomes

Patients generally experienced a chronic and indolent course. Actuarial overall survival at 10 years remained at 59%; however, 2 deaths appeared to occur with complications of disease (infection/sepsis after chemotherapy in 1 patient and graft versus host disease and liver failure in a second patient who eventually required stem cell transplant). These deaths were in patients who presented with larger lesions (7 and 9 cm). For all patients, the majority ultimately demonstrated other cutaneous or nodal/systemic relapse, with 55% 3-year and 20% 10-year progression-free survival (Figs 2 and 3).

## Discussion

In our study of patients with pcALCL lesions, there were excellent CR and partial local response rates to radiation treatment, with similarly excellent responses even after using low to intermediate doses of radiation. Moreover, in a direct comparison, these response rates rivaled the response to radiation treatment to 30 Gy and higher. Our data represent a novel addition to the scientific literature given the sample size of our study cohort (in the context of a rare disease), the number of patients treated with <20 Gy dose

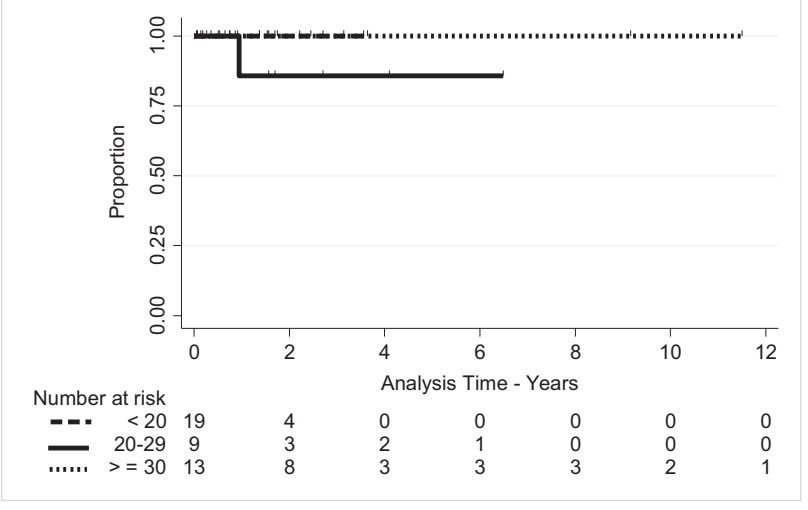


**Figure 1** Local relapse-free survival by dose group.

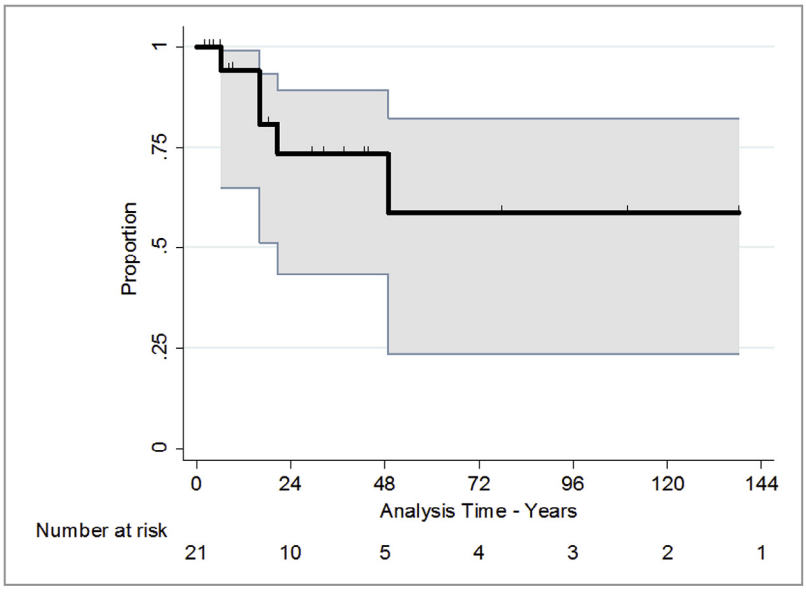


**Figure 2** Actuarial overall survival.

radiation, and our study design, which enabled a direct comparison between radiation dose groups, a comparison that was not feasible in prior studies.

Our results underscore the feasibility and potential effectiveness of using lower doses of radiation for pcALCL to achieve a high rate of CR. This local response rate can also be interpreted in the context of the overall disease outcomes. In particular, chronic relapses, and not infrequently extracutaneous progression over many years, remain the norm for patients, despite a relatively lower risk of death from disease.[15] Regardless of the intensity of radiation dose, local relapse within the radiation field was not significantly changed; similarly, regardless of the intensity of radiation dose, the overall natural history of disease in the patient also remained unchanged. Accordingly, regarding the optimal role of local radiation treatment, minimizing intensity, cost, toxicity, and length of therapy is appealing for this relatively indolent but invariably chronic disease requiring multiple treatment courses over time. This treatment paradigm shifts from the conventional paradigm of higher dose radiation, which to date has remained the standard for pcALCL. Nonetheless, such a shift in the paradigm of treatment would mimic recent shifts in approaches to radiation treatment of other indolent lymphomas.[9,11]

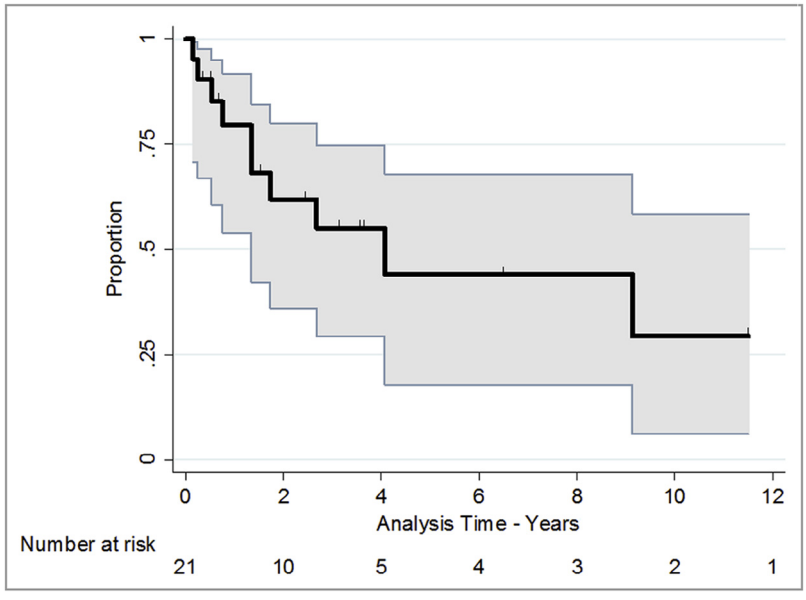


**Figure 3** Actuarial progression free-survival.

Moreover, such a treatment approach could additionally benefit a small but distinct proportion of patients who may initially demonstrate PR but ultimately achieve CR after more time—for example, up to as long as 6 months in this study (although in our small sample, such patients did undergo additional systemic therapy during that period; therefore, the optimal period of additional observation with any further treatment after initial PR remains to be defined).

## Prior studies

Our results help to address a clinically relevant knowledge gap in the literature: the paucity of data on the impact of RT dose on response rates in pcALCL. The largest contemporary study to date of RT in patients with pcALCL evaluated 63 lesions in 56 patients, with 95% CR and 5% PR after a median dose of 35 Gy and median tumor size of 2.25 cm.[5] In other studies representing 22 patients total, no patients were treated with radiation doses <34 Gy, and complete clinical response rates were noted to be 100% in both studies.[4,6] Although CR rates in our study were comparatively lower (even in patients treated with doses ≥30 Gy), our inclusion criteria were broader and extended beyond the initial/primary course of treatment for patients. As a result, patients may have had prior courses of therapy, including systemic chemotherapy and brentuximab, and prior evidence of local relapse to other treatment modalities. Accordingly, our results add to the current literature to demonstrate acceptable rates of local response to RT even in this more heterogeneous spectrum of presentations, including patients with some poorer prognostic factors, such as history of relapsed disease and larger lesion sizes.

Utilization of low-dose RT to treat the more commonly seen mycosis fungoides represents an evolving paradigm in this disease. Historical data in patients treated with RT for mycosis fungoides demonstrated a dose response with local and total skin RT, historically rendering RT doses >30 Gy as the conventional standard. More recently, however, there has been increased recognition that cutaneous control after lower doses of RT may be lower, but still comparable. For example, a prior study demonstrated that total skin electron beam therapy for patients with mycosis fungoides still demonstrated 88% overall response with 12 Gy. Most notably, skin toxicities with this lower dose were quite mild.[9] As a result, a contemporary shift has emerged in the conceptualization of the risk-benefit ratio of low-dose RT in mycosis fungoides patients. Increasing support by expert opinion suggests that small incremental benefits in local control after RT doses >30 Gy may not be outweighed by the toxicity and intensity of long RT regiments. For mycosis fungoides, the International Lymphoma Radiation Oncology Group consensus field and dose guidelines now recommend RT doses ranging from 6 Gy to >30 Gy as acceptable.[7]

Our study results also signal the ongoing need for further evaluation of 2 additional clinical scenarios in future studies of RT for pcALCL. The first is for pcALCL patients who undergo RT and have only PR within 12 weeks. In our cohort, more than one-half of patients with initial PR ultimately achieved CR after a longer follow-up; therefore, these results suggest that, given the overall indolent course of the disease, extended posttreatment observation may be a reasonable treatment option for patients who do not achieve a brisk CR. Future studies may seek to determine the optimal watchful waiting period before considering an additional salvage therapy, including retreatment with RT. The second scenario is for pcALCL patients with large lesions. Size more than 3 to 5 cm appeared to render a poorer prognosis, both for local and long-term disease outcome (including death from disease). Relapsed lesions also tended to be larger. In our retrospective series, patients with larger tumors were more likely to be treated with doses >20 Gy; nonetheless, our exploratory multivariate model did not identify any differences in RT response after adjusting for lesion size and RT dose. As a result, the optimally effective low dose RT for this higher risk group requires continued investigation.

Our study has several limitations to consider. This was a retrospective single-institution study, with the potential for residual confounding from tumor characteristics that may have affected selection of treatment dose (eg, higher doses for larger lesions); in particular, given the limited sample size and more limited length of follow-up for patients treated with <20 Gy, a definitive conclusion of noninferiority requires validation in additional studies. Second, pcALCL remains a clinical diagnosis, and thus secondary cutaneous disease from systemic ALCL could not be ruled out, although all patients received a standard workup to attempt exclusion of systemic ALCL. Nonetheless, the effectiveness of lower doses of RT was consistently seen in the entire cohort; therefore, if such misclassification bias had a confounding association with local response, this misclassification would theoretically still bias results toward the null.

## Conclusion

Lower radiation doses for pcALCL can offer excellent local control, with high rates of CRs in this disease. Given the indolent but invariably chronic disease course requiring multiple treatment courses over time, minimizing intensity, cost, and toxicity of therapy remains an appealing treatment option for this indolent, but invariably chronic disease.

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