Cutaneous T-Cell Lymphoma: Trends in Radiation Doses and Patterns of Care 2004-2015

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Abstract. *Background and Aim:* Radiotherapy is an effective treatment for cutaneous T-cell lymphoma (CTCL). Since 2009, studies have advocated for low-dose radiotherapy (<30 Gy) given it results in similar response rates and less toxicity compared to higher doses (≥30 Gy). We aimed to see if low-dose radiotherapy has been adopted on a national scale in the USA. *Materials and Methods:* A total of 11,292 adult patients with CTCL were identified in the National Cancer Database. Logistic regression models were created to evaluate predictors for use of low-dose radiotherapy. *Results:* A minority of patients received low-dose radiotherapy (22.4%). The annual percentage of patients receiving low-dose radiotherapy increased from 17.2% in 2009 to 38.4% in 2015. High-volume facilities were associated with use of low-dose radiotherapy (5th quintile vs. bottom two quintiles, odds ratio(OR)=1.76, 95% confidence interval(CI)=1.22-2.54, p=0.003). *Conclusion:* Although the radiotherapy dose administered is decreasing, most patients with CTCL are still receiving doses that may be higher than needed to palliate their disease effectively.

Cutaneous T-cell lymphoma (CTCL) is a rare neoplasm characterized by a clonal expansion of neoplastic T-cells that are localized to the skin (25, 30). Treatment for CTCL varies depending on disease stage and clinical responsiveness. For early-stage disease, treatments typically include topical agents (corticosteroids, nitrogen mustard, retinoids, or imiquimod) (3, 9, 15, 31), psoralen plus ultraviolet A photochemotherapy

phototherapy (23), ultraviolet B phototherapy (7), and localized radiation therapy (RT) for symptomatic lesions (22, 27, 28). For more advanced or refractory disease, additional treatment options include systemic therapies (retinoids, methotrexate, histone deacetylase inhibitors, antibodies to cluster of differentiation (CD) 30, antibodies to CD52 or interferon) (4, 5, 12, 16, 32) and total skin electron beam therapy (TSEBT) (2, 6, 8, 10, 14, 27, 28).

TSEBT is one of the most effective modalities for obtaining partial or complete responses for skin lesions in CTCL (2). Treatment is delivered with the patient in several positions at an extended distance from the source by using external-beam electron RT targeted to deliver superficial doses to the skin. Historically, TSEBT was administered to total doses of ≥30 Gy in 1.5- to 2-Gy fractions (2, 13, 19, 21, 24), a regimen that was highly effective but was also associated with significant morbidity. Since 2011, several studies have been published advocating that low-dose TSEBT (<30 Gy) be used for CTCL, given the similarities in overall response rates, the lesser toxicity, and the shorter treatment times compared with higher doses (≥30 Gy) RT (2, 6, 8, 10, 14, 17). Use of low-dose TSEBT also makes re-irradiating recurrent skin disease more feasible because it minimizes the cumulative skin dose. This is particularly important because most patients treated with RT experience recurrence (2). The current National Comprehensive Cancer Network guidelines recommend a dose range of 12-36 Gy, but also emphasize the advantages of using lower doses, including fewer complications and the ability to re-treat progressive disease (11). The use of low-dose localized RT in the treatment of CTCL has also been studied, starting in 2009, with regimens of 2×4 Gy fractions (20) and 1×7-8 Gy (29) leading to complete response rates of 92% and 94%, respectively.

Given the recent interest in using low-dose RT for CTCL [2009 for localized RT (20) and 2011 for TSEBT (8)], we sought to evaluate RT usage as part of the patterns of care for CTCL on a national scale. To do so, the National Cancer Data Base (NCDB) was retrospectively evaluated to identify

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Key Words: Radiotherapy, cutaneous T-cell lymphoma, patterns of care.

Figure 1. Process for selecting patients from the National Cancer Data Base for this analysis. NHL, Non-Hodgkin lymphoma; CTCL, cutaneous T-cell lymphoma; MF, mycosis fungoides; RT, radiation therapy; EBRT, external-beam radiation therapy.

trends in RT usage and dose for CTCL. Demographic factors associated with the relative decrease in use of RT were also examined. Finally, factors associated with the administration of lower-dose as opposed to higher dose RT were analyzed.

Materials and Methods

The NCDB is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society, which consists of de-identified information regarding patient demographics, tumor characteristics, first-course treatment for the corresponding diagnosis, and survival for approximately 70% of the US population (1). All pertinent cases are reported regularly from CoC-accredited centers and compiled into a unified dataset, which is then validated. The data used in the study were derived from a de-identified NCDB file (2004-2015). The American College of Surgeons and the CoC have not verified and are not responsible for the analytic or statistical methodology employed, nor the conclusions drawn from these data by the investigators. As all patient information in the NCDB database is de-identified, this study was exempt from Institutional Review Board evaluation.

A total of 12,628 adult patients with CTCL in the NCDB diagnosed from 2004 through 2015 were identified using the histology codes from the international Classification of Disease for Oncology, Third Edition (ICD-O-3). The codes used in this study

included primary CTCL (#9700), *mycosis fungoides* (#9709), or CD30+ T-cell lymphoma (#9718) with the primary site being skin. Patients receiving unconventional forms of RT such as radiosurgery, isotopes, or implants (n=119) were excluded. Patients receiving RT to areas other than skin (n=994) and those with mis-recorded RT doses (n=143) were also excluded. The final cohort consisted of 11,292 patients, including 2,108 who received RT as initial therapy and 9,184 who did not (Figure 1).

Chi-square tests were used to assess differences in the proportions of patients who received RT for CTCL between different years. Univariate and multivariable logistic regression models were used to evaluate the likelihood of receipt (*versus* no receipt) of RT, and to evaluate the likelihood of receipt of RT doses <30 Gy *versus* ≥30 Gy. Covariates included age, sex, race, comorbidity (Charlson–Deyo comorbidity score), sociodemographic factors, facility type, year of diagnosis, disease stage, and therapy received. For the low-dose *versus* high-dose RT analysis, a facility volume variable was also added as we theorized that facilities with high treatment volumes would be more likely to offer low-dose RT. The facility volume was defined as the average number of patients treated annually at each of the facilities in the NCDB that treated at least one patients with CTCL with RT at diagnosis from 2004 through 2015. Facilities were then grouped together by quintiles of average number of patients treated per year. Analyses were performed with STATA (version 13; STATA Corp., College Station, TX, USA). and *p*-values of 0.05 or less were considered to indicate statistically significant differences.

Table I. Patient characteristics.

Characteristic	RT not given, n (%)	RT given, n (%)	p-Value
Total	9,184	2,108	
Age, years			
18-39	1,212 (3.2)	169 (8.0)	<0.001
40-59	3,162 (34.4)	691 (32.8)	
≥60	4,810 (52.4)	1,248 (59.2)	
Gender			
Male	5,126 (55.8)	1,306 (62.0)	<0.001
Female	4,058 (44.2)	802 (38.0)	
Race			
White	6,951 (75.7)	1,816 (86.2)	<0.001
Black	1,634 (18.0)	203 (9.4)	
Asian	252 (2.5)	37 (1.6)	
Unknown	347 (3.8)	52 (2.8)	
Comorbidity score			
0	8,178 (89.8)	1,871 (89.3)	0.485
≥1	931 (10.2)	225 (10.7)	
Median Income			
<\$48,000	3,407 (37.1)	679 (32.2)	<0.001
≥\$48,000	5,680 (62.0)	1,406 (66.7)	
Unknown	97 (1.1)	34 (1.1)	
Insurance			
Uninsured	302 (3.3)	44 (2.1)	<0.001
Government	3,964 (43.2)	1,005 (47.7)	
Private	4,555 (49.5)	1,013 (48.0)	
Unknown	363 (4.0)	46 (2.2)	
Facility type			
Non-academic	2,041 (22.2)	975 (46.3)	<0.001
Academic or research center	5,931 (64.6)	964 (45.7)	
Unknown	1,212 (13.2)	169 (8.0)	
Facility volume*			
Bottom two quintiles ^a	777 (8.5)	482 (22.9)	<0.001
3rd quintile ^b	268 (2.9)	212 (10.1)	
4th quintile ^c	986 (10.7)	451 (21.4)	
5th quintile ^d	7,153 (77.9)	963 (45.7)	
Disease stage			
I	6,022 (65.6)	1,389 (65.9)	<0.001
II	644 (7.0)	282 (13.4)	
III	490 (5.3)	61 (2.9)	
IV	766 (8.3)	125 (5.9)	
Unknown	1,262 (13.7)	251 (11.9)	
Chemotherapy			
No	5,563 (60.6)	1,526 (72.4)	<0.001
Yes	2,657 (29.0)	367 (17.4)	
Unknown	964 (10.5)	215 (10.2)	
RT dose, Gy			
0	9,184 (100)	0 (0)	<0.001
<20		177 (8.4)	
20-<30		292 (13.9)	
≥30		1,639 (77.8)	

RT, Radiation therapy. *Patients per year: ^a<1, ^b1-1.25, ^c1.25-2, ^d>2.

Results

Patient characteristics are detailed in Table I. The cohorts were unbalanced with respect to all variables except for

Table II. Annual utilization of radiation therapy for the treatment of cutaneous T-Cell lymphoma.

Year of diagnosis	Patients not given RT, n	Percentage of patients treated annually	Patients given RT (<20/20-<30/≥30 Gy), n	Percentage of patients treated annually
2004	549	78.2	153 (12/22/119)	21.8
2005	634	76.3	197 (9/21/167)	23.7
2006	631	77.7	181 (9/19/153)	22.3
2007	668	82.3	144 (8/17/119)	17.7
2008	695	79.3	181 (9/15/157)	20.7
2009	870	81.5	198 (12/22/164)	18.5
2010	774	78.8	208 (12/26/170)	21.2
2011	758	80.3	186 (10/39/137)	19.7
2012	854	84.9	152 (12/18/122)	15.1
2013	895	85.1	157 (19/27/111)	14.9
2014	943	85.4	161 (27/31/103)	14.6
2015	913	82.8	190 (38/35/117)	17.2

comorbidity score as follows. The RT cohort had higher proportions of older patients, male patients, and wealthier patients relative to the no-RT cohort. The no-RT cohort had higher proportions of patients seen at an academic center and patients treated at facilities with the highest-volume quintile. Most patients given RT (77.8%) received doses of ≥30 Gy; 13.9% received doses of 20-30 Gy, and only 8.4% received doses <20 Gy. Table II and Figure 2 indicate RT doses administered by year.

The percentage of patients receiving RT as initial therapy decreased each year, from 21.8% in 2004 to 17.2% in 2015. From 2011 through 2015, the percentage of patients treated with RT who received <20 Gy increased from 5.4% to 20.0%, and the percentage of patients treated with RT who received ≥30 Gy decreased from 73.7% to 61.6%. Multivariable linear regression to evaluate variables associated with use of RT indicated that comorbidity score and type of insurance were not associated with receipt (*versus* no receipt) of RT (Table III). Unknown facility type was excluded from the multivariable logistic regression model due to co-linearity. In terms of trends over time, when year of diagnosis was analyzed as a continuous variable, the year of diagnosis was associated with lower use of RT [odds ratio (OR)=0.95, 95% confidence interval (CI)=0.94-0.96, $p<0.001$]. Other variables significantly associated with lower use of RT on multivariate analysis included being Black (*versus* White: OR=0.56, 95% CI=0.47-0.66, $p<0.001$), Asian (*versus* white: OR=0.65, 95% CI=0.45-0.93, $p=0.018$), female (*versus* male: OR=0.81, 95% CI=0.73-0.90, $p<0.001$), treated at an academic or research center (*versus* nonacademic center: OR=0.34, 95% CI=0.31-0.38, $p<0.001$), and receiving chemotherapy (*versus* no chemotherapy: OR=0.47, 95% CI=0.41-0.54, $p<0.001$).

Figure 2. Yearly percentage of patients with cutaneous T-cell lymphoma receiving radiotherapy (RT) as initial therapy as a function of year of diagnosis and according to radiation dose. The solid vertical line indicates the date of the first report advocating for low-dose local RT (28) and the dashed vertical line indicates the date of the first report advocating low-dose total skin electron beam therapy (19).

Findings from multivariable logistic regression evaluating predictors of receipt of low-dose *versus* high-dose RT are shown in Table IV. The facility volume variable included in this analysis was derived as follows. In all, 643 NCDDB-coding facilities treated at least one patient with CTCL with RT from 2004 through 2015. Based on the average number of patients treated with RT annually, the highest (5th) quintile of facility volume was determined to be more than two patients annually. In terms of year of diagnosis, patients with CTCL were more likely to receive low-dose RT in more recent years (OR=1.12, 95% CI=1.08-1.16, $p<0.001$) (Table IV). Treatment at a high-volume facility was also associated with receipt of low-dose RT (5th quintile *vs.* bottom two quintiles, odds ratio(OR)=1.76, 95% confidence interval(CI)=1.22-2.54, $p=0.003$). Academic facilities seemed to offer low-dose RT more often than did nonacademic centers (OR=1.26, 95% CI=0.93-1.72), but this apparent difference was not statistically significant ($p=0.140$).

Discussion

Our key findings from this analysis are as follows: The use of RT as the initial treatment of CTCL is decreasing, as is the dose of RT used in the treatment of CTCL; high-volume facilities are more likely to offer low-dose RT to patients with CTCL; and even though a higher proportion of patients received doses <30 Gy in recent years, most patients still receive doses ≥ 30 Gy.

Before 2011, all the published studies of TSEBT for CTCL reported outcomes after doses of an average of 30 Gy

or more (2). Although disease severity varied in the patients in these studies, overall response rates generally exceeded 95%, and complete response rates ranged from 47% for T3 disease to 97% for T1 disease (19, 24). The 2011 study by Harrison *et al.* was the first modern study to show that treating *mycosis fungoides* with TSEBT doses from 10 to <30 Gy could lead to overall response rates of 95% or more. They further found that overall and complete response rates were similar between patients receiving 20 to <30 Gy and 10 to 20 Gy (97% to 98% overall response, 34% to 35% complete response). However, these rates were generally lower than those in previous reports of high-dose TSEBT. For example, Harrison's group reported a response rate of 35% for patients with T3 disease given 10-20 Gy (8) as compared with 47% for patients with T3 disease given 30-40 Gy in a study by Navi *et al.* (19). Nevertheless, because high-dose TSEBT is seldom curative, Harrison and colleagues noted that treatment with <30 Gy TSEBT is advantageous given the adequate overall response rate (>95%), abbreviated treatment times, and feasibility of re-treatment with no significant differences in overall or progression-free survival (8). Lower doses are also associated with fewer grade 3 toxic effects than are higher doses, as well as less permanent alopecia, less fingernail loss, and no anhidrosis (10).

The first report of low-dose localized RT for CTCL was by Neelis *et al.* in 2009 (20). They analyzed 65 lesions treated with a regimen of 2 $\times$ 4 Gy fractions and showed a complete response rate of 92%. In their median follow-up time of 9.6

Table III. Results of multivariable linear regression evaluating radiotherapy for cutaneous T-cell lymphoma.

Variable	Odds ratio	95% Confidence interval	p-Value
Age, years			
18-39	1.00		
40-59	3.18	2.61-3.88	<0.001
≥60	3.25	2.66-3.98	<0.001
Gender			
Male	1.00		
Female	0.81	0.73-0.90	<0.001
Race			
White	1.00		
Black	0.56	0.47-0.66	<0.001
Asian	0.65	0.45-0.93	0.018
Unknown	0.67	0.49-0.91	0.011
Comorbidity score			
0	1.00		
≥1	0.91	0.78-1.08	0.285
Income			
<\$48,000	1.00		
≥\$48,000	1.20	1.08-1.34	0.001
Unknown	1.02	0.62-1.66	0.946
Insurance			
Uninsured	1.00		
Government	1.21	0.87-1.70	0.264
Private	1.23	0.87-1.74	0.243
Unknown	0.64	0.40-1.01	0.054
Facility type			
Non-academic center	1.00		
Academic or research center	0.34	0.31-0.38	<0.001
Year of diagnosis			
Continuous	0.95	0.94-0.96	<0.001
Disease stage			
I	1.00		
II	2.41	2.04-2.84	<0.001
III	0.67	0.51-0.89	0.006
IV	0.83	0.67-1.03	0.094
Unknown	0.78	0.67-0.91	0.002
Chemotherapy			
No	1.00		
Yes	0.47	0.41-0.52	<0.001
Unknown	0.80	0.68-0.95	0.009

Table IV. Results of multivariable linear regression evaluating receipt of low-dose radiotherapy (<30 Gy) versus high-dose radiotherapy for cutaneous T-cell lymphoma.

Variable	Odds ratio	95% Confidence interval	p-Value
Age, years			
18-39	1.00		
40-59	0.68	0.43-1.08	0.100
≥60	0.69	0.43-1.10	0.115
Gender			
Female	1.00		
Male	1.00	0.80-1.26	0.972
White	1.00		
Race			
Black	0.90	0.63-1.30	0.590
Asian	0.59	0.23-1.48	0.259
Unknown	0.73	0.36-1.50	0.396
Comorbidity score			
0	1.00		
≥1	1.14	0.81-1.61	0.450
Income			
<\$48,000	1.00		
≥\$48,000	0.95	0.75-1.20	0.654
Unknown	0.84	0.27-2.57	0.754
Insurance			
Uninsured	1.00		
Government	1.20	0.55-2.62	0.647
Private	1.29	0.58-2.88	0.529
Unknown	2.80	1.02-7.68	0.045
Facility type			
Non-academic center	1.00		
Academic or research center	1.26	0.93-1.72	0.140
Year of diagnosis			
Continuous	1.12	1.08-1.16	<0.001
Disease stage			
I	1.00		
II	1.91	1.41-2.59	<0.001
III	2.39	1.35-4.21	0.003
IV	2.63	1.73-4.01	<0.001
Unknown	1.73	1.24-2.42	0.001
Chemotherapy			
No	1.00		
Yes	1.42	1.07-1.87	0.014
Unknown	0.79	0.54-1.16	0.224
Facility volume*			
Bottom two quintiles ^a	1.00		
3rd quintile ^b	1.08	0.68-1.70	0.750
4th quintile ^c	1.21	0.85-1.73	0.299
5th quintile ^d	1.76	1.22-2.54	0.003

RT, Radiation therapy. *Patients per year: ^a<1, ^b1-1.25, ^c1.25-2, ^d>2.

months, only three lesions with complete response required retreatment. Another study conducted more recently evaluating lower dose localized RT in CTCL yielded similar results with doses of 7-8 Gy in a single fraction (29). These studies have led to the most recent International Lymphoma Radiation Oncology Group guidelines for skin lymphoma to recommend considering doses of 8 Gy in 1-2 fractions for localized RT for patients with CTCL without large tumors or large-cell transformation. The guidelines in general encourage the use of localized RT doses of 20-24 Gy given that local recurrence is rarely above this dose range. In fact, the only subset of

CTCL for which doses of ≥30 Gy was recommended was subcutaneous panniculitis-like T-cell lymphoma (≥40 Gy), a rare entity that likely represented only a small percentage of the patients in our study (26).

Our own analysis of the NCDB data showed increasing use of low-dose RT regimens for patients with CTCL. We

also identified several factors associated with the adoption of low-dose RT, including high facility volume and more recent treatment. However, most patients receiving RT for CTCL are treated with doses ≥ 30 Gy. Collectively, these findings suggest that low-dose RT for CTCL is being adopted slowly, and its adoption is driven in part by institutional experience. Considering the recent literature on low-dose TSEBT and local RT, our findings also suggest that many patients may be receiving doses higher than necessary to achieve an effective response with minimal toxicity.

We also found that the proportions of patients with CTCL treated with RT as part of initial therapy are trending downward with more recent diagnosis. Reasons why are unclear, but it is possible that as practitioners gain understanding of the indolent nature of this disease, they tend to defer the use of RT. We found several factors associated with underuse of RT that may reflect healthcare disparities, specifically that Black and Asian patients were much less likely to receive RT than were White and male patients. This finding stands in contrast to a previous study of the Surveillance, Epidemiology, and End Results database showing no racial differences in the administration of RT for patients with *mycosis fungoides* (18). However, our finding that younger patients and women were also less likely to receive RT was in line with their results. Surprisingly, we also found that patients treated at an academic or research center were less likely to receive upfront RT. This may reflect the availability of other treatments and clinical trials at such centers, as practitioners may hold off RT until other treatment options have failed.

This study did have several inherent limitations. As alluded to earlier, the NCDB records only the initial treatment of patients with CTCL. Because CTCL is an indolent disease with a long natural history, patients who were not treated initially with RT may have gone on to receive RT later. As is the case in any retrospective review, we may not have been able to control for unknown variables that may have been unbalanced between the study groups. In addition, exactly which adjuvant therapies were given to the patients in this study is unknown, as variables used to code chemotherapy or other forms of treatment are broad and can encompass any number of other therapeutic agents. Notably, the NCDB does not code specifically for TSEBT or localized RT, so the combined trends for both treatment modalities are reported here.

In conclusion, although RT doses for patients with CTCL have been trending downwards since past reports of adequate response rates and lower toxicity with RT doses of <30 Gy, most patients with CTCL are still receiving RT doses of 30 Gy or more. This pattern seems to be driven, in part, by institutional experience, as higher-volume facilities are more likely to offer low-dose RT for CTCL. Overall, RT has been used less often for the upfront treatment of CTCL in more recent years, and factors associated with the underutilization

of RT include Black or Asian race, female gender, and treatment at an academic or research center.

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