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Approval Sheet

Total Skin Electron Therapy for Cutaneous T Cell Lymphoma Using Modern Dual Field Rotational Technique: An Institutional Analysis of Overall Clinical Outcomes and the Effect of Race on Treatment Response

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Total Skin Electron Therapy for Cutaneous T Cell Lymphoma Using Modern Dual Field Rotational Technique: An Institutional Analysis of Overall Clinical Outcomes and the Effect of Race on Treatment Response

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An abstract of

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Abstract

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By Thatcher Heumann

Purpose/Objective(s): To report our experience with rotational total skin electron irradiation (RTSEI) in cutaneous t-cell lymphoma (CTCL), and to examine response by disease stage and race.

Materials/Methods: We reviewed our outcomes of 68 CTCL patients who received RTSEI (≥30 Gy) from 2000- 2013. Primary outcomes were complete clinical response (CCR), recurrence-free survival (RFS), and overall survival (OS). Using log-ranks tests and Cox proportional hazards, OS and RFS were compared across tumor stages at time of RTSEI with further racial subgroup analysis.

Results: Median age at diagnosis and at time of radiation were 52 and 56 years, respectively. Median follow up was 5.1 years, 49% were African American (AA), and 49% were female. At time of treatment, 18, 37, and 13 patients were T-stage 2, 3, and 4, respectively. At 6 weeks post RTSEI, overall CCR was 82% (88%, 83%, 69% for T2, T3, and T4, respectively). Median RFS was 11 months for all patients and 14, 10 and 12 months for stage T2, T3, and T4, respectively. T-stage was not associated with RFS or CCR. Maintenance therapy following RTSEI was associated with improved RFS and OS in both crude and multivariable analysis, controlling for T-stage. Median OS was 76 months and 91 and 59 months for T3 and T4, respectively). With the exception of improved OS with AAs compared to Whites at stage T2, race was not associated with CCR, RFS, or OS.

Conclusions: These results represent the largest RTSEI clinical outcomes study in the modern era using dual field rotational technique. Our observed response rates match or improve upon the standard set by previous outcome studies using conventional TSEI techniques, despite a large percentage of advanced CTCL lesions in our cohort. We found that clinical response following RTSEI did not appear to be affected by T-stage nor race.

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Chapter I: Background/Literature Review

Background on Cutaneous T-Cell Lymphoma:

Cutaneous T-cell lymphoma (CTCL) refers to a group of lymphoproliferative disorders characterized by localization of T lymphocytes to the skin with an overall national incidence of 10.2 cases per million person-years(2). Mycosis fungoides (MF), the most common subtype, comprising 53-73% CTCL diagnoses, has an incidence of 6.4 per 1,000,000 person-years, and most commonly presents at age 55 to 60 years (3-5). It has become increasingly evident that CTCL is quite heterogeneous in terms of presentation, histology, and therapeutic response(6). MF classically presents initially with scaly patches or plaques, which can be pruritic, and evolve into infiltrative plagues with a more generalized distribution. More advanced cutaneous disease presents with skin tumors (dome-shaped solid skin lesions greater than one cm in diameter) and/or with generalized erythroderma (erythema covering at least 80% of body surface area usually accompanied with intense pruritis and scaling) (7). MF is staged with a TNMB classification system: cutaneous disease burden (T), lymph node involvement (N), visceral involvement (M), and blood involvement (B) (8). Adverse prognostic factors include male gender, age greater than 60, advanced cutaneous disease, and extracutaneous spread (8, 9).

Treatment depends on stage (skin-only vs. extracutaneous involvement), and response (or lack thereof) to previous treatments. For skin disease, treatments include corticosteroid ointments, topical chemotherapies, phototherapy/photochemotherapy (psoralen + UVA [PUVA]) or UVB phototherapy), and radiation therapy (either focal or total skin electron irradiation [TSEI]). Multiple agents, including systemic agents, are used throughout the disease course, usually in combination, since the disease will be refractory or recur with initial treatments, even with subsequent therapies. Since MF and CTCL are generally incurable, the numerous therapeutic modalities are prescribed with the aims of decreasing cutaneous disease burden, preventing spread to lymph nodes/viscera, and palliating symptoms(10).

Overview of Total Skin Electron Irradiation:

Total skin electron irradiation (TSEI), as opposed to focal radiation therapy, involves irradiating the entire surface of the skin, and is more penetrating than other cutaneous treatments such as topical chemotherapies and photochemotherapies. Conventional dose TSEI (>30 Gy) has been shown to be effective in treating patients with moderate cutaneous disease - T2 (large or numerous patch or plaque) and T3 (tumorous) disease (10-12) – while the data on effective dosing when treating T4 disease (erythroderma) is limited (13).

Of the various methods used for delivery total skin irradiation, two techniques predominate: large-field/modified Stanford technique and rotational technique. In the case of large electron field technique, the skin surface is irradiated in a discontinuous manner about the patient's longitudinal axis while the patient is standing, with the patient changing position six times, by 60 degrees, during one treatment fraction(14). By contrast, continuous skin irradiation is carried out using rotational technique (RTSEI) which is described as follows: A patient rotates on a platform along a vertical access while single-field or dual irradiating fields shower the patient with electrons as they rotate with dose homogeneity across the patient being compensated by constant rotation during irradiation (14). Because some areas of the body are not fully exposed to ionizing radiation during the total skin treatment, under-dosed areas (i.e. skin folds, axilla, soles of feet, etc.) are boosted with an additional external radiation dose for optimal skin coverage.

Several retrospective reviews of clinical cohorts (sample size range: 41-180) over the past two decades have consistently demonstrated the efficacy of conventional dose (≥30 Gy) TSEI in producing high clinical response rates (10, 15-20). Though the duration of response is still a limitation, previous studies have shown initial complete response rates (90% or higher reduction in skin disease]) to be in the range of greater than 50% for patients with T3 disease and in the range of 90% for those with T1-T2 disease (10, 21, 22). Of note, the majority of institutional cohort studies have been using the large-

field/modified Stanford technique. Clinical outcomes studies using rotational technique are far less numerous and robust. Upon literature review, only one study was found to report the outcomes of the rotational technique (N=44) and it was done using a single-field method (20).

Race and Cutaneous T-Cell Lymphoma:

Previous epidemiologic surveys have reported that the incidence rate among African-Americans (AA) is significantly higher than white MF populations with black-to-white incidence rate ratios of 1.5 to 1.6 (3, 23-26). When compared to white patients, Wilson et al. showed that AA MF patients were significantly younger (mean age at diagnosis of 51.5 [AA] vs. 59.2 [white] years old) and had more advanced cutaneous disease (IR of T-stage 3 or 4: 0.9 [AA] vs. 0.5 [white] per million person-years) (27). Additionally, AAs have also been found to be diagnosed with non-MF CTCL at younger (mean age at diagnosis of 54.5 [AA] vs. 61.2 [white] years old) and more advanced stages (IR 1.2 [AA] vs. 0.6 [white] per million person-years) compared white non-MF CTCL patients (27). With SEER data from 1973-1992, Weinstock and Gardstein reported higher mortality rates among black when compared to whites (relative risk [RR] =2.4)(28). This was further supported in a more recent SEER analysis from 1988-2008 by Nath et al., that demonstrated AAs had poorer survival, compared to white patients, after accounting for demographic factors and tumor stage (23). This etiology behind these observed disparities has yet to been explained, and, though there has been hypotheses of

biological differences, so far genetic and environmental studies have been unrevealing (24, 25).

Race and Radiotherapy:

Based on recent data from the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) program, there were no significant racial differences in radiation utilization found(23). In theory, TSEI therapy should be reliably effective for CTCL regardless of baseline skin pigmentation (as opposed to phototherapy, which has been suggested to be less efficacious in patients with heavily pigmented skin) (21, 23, 29-31). Hinds et al. (n=77, [17 AA, 60 White including Hispanics]) examined whether response to TSEI, and relapse after TSEI differed by race and sex. They found no difference in odds of complete clinical response between AA and White patients at 4-8 week follow up, but did observe an enhanced response rate that was most pronounced in AA women(29). However, this study was limited by small sample size within each subgroup, one follow up date, and no comment on duration of response overall or between subgroups.

Chapter II: Manuscript

Total Skin Electron Therapy for Cutaneous T Cell Lymphoma Using Modern Dual Field Rotational Technique: An Institutional Analysis of Overall Clinical Outcomes and the Effect of Race on Treatment Response

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ABSTRACT

Purpose/Objective(s):

To report our experience with rotational total skin electron irradiation (RTSEI) in cutaneous t-cell lymphoma (CTCL), and to examine response by disease stage and race.

Materials/Methods:

We reviewed our outcomes of 68 CTCL patients who received RTSEI (≥30 Gy) from 2000-2013. Primary outcomes were complete clinical response (CCR), recurrence-free survival (RFS), and overall survival (OS). Using log-ranks tests and Cox proportional hazards, OS and RFS were compared across tumor stages at time of RTSEI with further racial subgroup analysis.

Results:

Median age at diagnosis and at time of radiation were 52 and 56 years, respectively. Median follow up was 5.1 years, 49% were African American (AA), and 49% were female. At time of treatment, 18, 37, and 13 patients were T-stage 2, 3, and 4, respectively. At 6 weeks post RTSEI, overall CCR was 82% (88%, 83%, 69% for T2, T3, and T4, respectively). Median RFS was 11 months for all patients and 14, 10 and 12 months for stage T2, T3,

and T4, respectively. T-stage was not associated with RFS or CCR. Maintenance therapy following RTSEI was associated with improved RFS and OS in both univariate and multivariable regression analysis. Median OS was 76 months and 91 and 59 months for T3 and T4, respectively). With the exception of improved OS with AAs compared to Whites at stage T2, race was not associated with CCR, RFS, or OS.

Conclusions:

These results represent the largest RTSEI clinical outcomes study in the modern era using dual field rotational technique. Our observed response rates match or improve upon the standard set by previous outcome studies using conventional TSEI techniques, despite a large percentage of advanced CTCL lesions in our cohort. We found that clinical response following RTSEI did not appear to be affected by T-stage nor race.

INTRODUCTION

Cutaneous T-cell lymphoma (CTCL) is characterized by localization of T lymphocytes to the skin. The most common subtype is mycosis fungoides (MF), with an overall incidence of 0.55 per 100,000 person-years in the United States and median age of 58 years at diagnosis (3, 4, 6). Although other types of CTCL have variable manifestations, MF typically presents with pruritic patches and plaques and may evolve to cutaneous tumors or erythroderma. The extent and nature of skin involvement (T stage), overall disease stage, and patient age are potential prognostic factors (10). African American (AA) race has been associated with worse survival, after adjusting for other demographic factors and tumor stage (6, 23). The reason for this disparity remains poorly understood(24).

Total skin electron-irradiation (TSEI) is effective for T2 (i.e., generalized patch or plaque) and T3 (tumor) disease(10-12). Retrospective reviews (N=41-180) from recent decades have demonstrated the efficacy of high-dose (≥30 Gy) TSEI in achieving high clinical response rates(10, 15-20). The vast majority of these studies used the large-field/modified Stanford technique in which the skin surface is irradiated in a discontinuous manner with the patient changing position six times, by 60 degrees, during one treatment fraction(14). In contrast, rotational TSEI technique (RTSEI), in which a patient is automatically rotated at a constant speed about the vertical axis while

being irradiated with single or dual-fields, allows for continuous treatment delivery has been previously described(32). Despite its theoretical advantage in dose homogeneity compared to its large field/modified Stanford counterpart, RTSEI technique is less-widely available and its clinical outcomes are largely unknown. As one of largest academic referral centers in the Southeastern US for TSEI, we were able to conduct a rotational-TSEI clinical outcomes study to address this gap in clinical knowledge as well as examine the role of race in achieving clinical response post RTSEI.

METHODS

Patient Population:

Using an institutional review board (IRB)-approved protocol, 110 patients treated with RTSEI were identified from billing records from 2000-2013 at Emory Healthcare-affiliated Hospitals. Patient electronic medical charts and an IRB-approved Dermatology database were used to ascertain information regarding demographics, diagnosis, histology, staging, treatment regimens, RTSEI treatment specifics, clinical response, recurrence and overall survival. Eligibility criteria for the study included: histologically-confirmed CTCL and a completed first course of conventional dose (≥30 Gy) R-TSEI. Of the original 110 patients, 35 were excluded due to primary diagnosis of leukemia cutis

or not undergoing RTSEI. An additional seven were excluded due to RTSEI dose of <30 Gy, leaving 68 eligible patients.

Treatment Technique:

RTSEI was administered using a21EX Varian linear accelerator (LINAC) (Varian, Palo Alto, CA) equipped with 6 MeV High-Dose total skin electron (HDTSe) mode at a dose rate of 888 MU/min. RTSEI using dual angles field at gantry angles of 241 degrees and 299 degrees to cover the upper and the lower halves of the patient body. In the 6 MeV HDTSe mode, our LINAC calibration was 2.99 cGy/MU at the maximum depth of at SSD being 100 cm.

All patients were treated using a standard method: 36 Gy delivered at 1.5 Gy per fraction, administered thrice weekly, typically on a Monday-Wednesday-Friday schedule (4.5 Gy/week). Eye shields were used upon treatment initiation; finger/toe nail shields were added after 12Gy. A one-week mid treatment break was allowed after delivery of 18 Gy. Optically stimulated luminescence dose (OSLD) measurements at underdosed areas were taken prior to the mid treatment break. For 84% of patients, these areas received additional boost dosing based on physician preference and clinical assessment of disease response at the end of RTSEI. Thus, the total RTSEI regimen required 9 weeks followed by a 2-3 week boost portion. The patient is placed on a rotating platform at an

extended SSD (315-cm) from the gantry. Both arms are raised overhead and are positioned on the rotator vertical bars. The platform rotates at a constant speed of 4 revolutions per minute to ensure adequate surface dose build up.

Covariates:

The overall study cohort and racial subcohorts were compared across the following covariates: sex, age at diagnosis and start of RTSEI, histology, T-stage at start of RTSEI, maintenance therapy (systemic therapy or topical therapy started within 3-6 months after RTSEI), time from diagnosis to RTSEI, and recurrence.

Outcome Measures:

Key outcome measures were complete clinical response (CCR) rate, recurrence-free survival (RFS), and overall survival (OS). CCR rate was defined as the proportion of follow up patients with at least 90% reduction in cutaneous tumor burden. Patients considered non-complete responders (non CCR) included those with partial response [>50% reduction but less than 90%], stable disease, recurrence, progression, or death) at each of three time points: 1) end of RTSEI treatment, 2) 6 weeks post RTSEI, and 3) 6 months post RTSEI. Patients with no previous record of recurrence, those who did not follow up or had no recorded clinical response at one of the time points were not included in the CCR proportion. Response rates were compared across racial categories and by T-stage

using chi-square or Fisher's exact tests, as appropriate.

For RFS, time to event was calculated as the number of days between start of RTSEI and the date of recurrence. For patients whose cancers did not recur, survival time was censored at the date of last follow-up or date of death. For OS, time to event was calculated as the number of days between diagnosis and the date of death or last known follow up. RFS and OS distributions were estimated using the Kaplan-Meier method. Both RFS and OS were compared across race, T-stage, and previously mentioned covariates, using log-rank tests and Cox proportional hazards models. Multivariate (MV) Cox models were fit, adjusting for T-stage pre-RTSEI which was clinically appropriate. The cutoff for statistical significance for all analyses was set at the two-sided alpha error of 0.05.

RESULTS

Patient Characteristics:

Characteristics of the overall patient cohort are summarized in Table 1. Sixty-eight patients (n=18 [T2], n=37 [T3], n=13 [T4], all T-stages pre-RTSEI) were treated with high dose RTSEI (range= 30-36 Gy [T2=30-36gy; T3=31.5-36 Gy; T4=30-36 Gy]) and included in the analysis. Thirty-three patients (49%) were female, 35 were male (51%), 33 were AA (49%) and 33 were white (49%). Median age at time of diagnosis was 52 years (range 18-

89 years). Median follow up time was 61.4 months. Median time from diagnosis until RTSEI was 20 months (range 0.2 to 118 months). 26 patients (38%) received maintenance therapy following RTSEI. 44 patients (65%) recurred following RTSEI.

Table 2 compares study population trends among the racial subgroups. AA patients were significantly younger at diagnosis (mean 48.1 yrs, p=0.01) and at time of RTSEI (mean 52.4 years, p=0.02) compared to white patients (mean age at diagnosis: 60.5 years; mean age at RTSEI: 59.6 years). AA patients also had a significantly (p=0.01) longer time to RTSEI (median 28.4 months) compared with their white counterparts (median 16.6 months). Whites also had a significantly (p=<.001) higher number of non-MF CTCL subtypes. The distributions of T-stage pre-RTSEI differed significantly between the two racial groups. There were no significant differences between AA and white subcohorts in regards to sex, maintenance therapy, follow up time, or proportion that recurred after RTSEI.

Clinical Response Rates:

Table 3 summarizes the complete clinical response (CCR) rates for the entire cohort and by race. Overall, 93% had a CCR (100%, 92%, and 85% for stages T2, T3 and T4, respectively) immediately post RTSEI. At 6 week follow up, overall CCR rate was 82% (88%, 83%, and 69% for T2, T3 and T4, respectively), and at 6 months it was 44% (42%,

47%, and 38% for T2, T3 and T4, respectively). Caucasians had a CCR of 97%, 81%, 41% at end of RTSEI, 6 week follow up, and 6 month follow up, respectively. African Americans had a CCR rate of 88%, 81%, and 43% at the end of RTSEI, 6 week follow up, and 6 month follow up, respectively. See Table 3 for CCR rates broken down by stage within each racial subgroup. Chi-square and Fisher's exact tests revealed no significant differences in CCR rate between races following end of RTSEI (p=0.4), six-weeks (p=1.0), and six months post-TSEI (p=0.9). Further comparisons between racial groups across respective T-stages also showed no significance difference in CCR. CCR at end of RTSEI was not associated with T-stage at time of RTSEI (p=0.3). The corresponding p-value at six-weeks of follow up was p=0.47 for T-stage at time of RTSEI, and at 6 months of follow-up was p=0.85.

Recurrence Free Survival:

As seen in Table 4, the overall cohort had a median RFS of 11.3 months (14.3, 9.9, 12.1 months for T2, T3, T4, respectively, with no difference across stages (p=0.9). Kaplan-Meier RFS curves stratified by race and by T-stage are shown in Figure 1.

As shown in Table 5, poorer RFS was associated with lack of maintenance therapy following RTSEI in univariate (HR=2.2; 95% CI: 1.1-4.1, p=0.02) and multivariate [not shown in table] (HR=2.6; 95% CI: 1.2-5.4, p=0.01) analyses when controlling for T-

stage. Race (p=0.3), sex (p=0.9), T-stage (p=0.9), histology (MF versus non-MF, p=0.4), age at diagnosis (60 or more years old versus < 60, p=0.5), time from diagnosis to start of TSEI (20 or more months vs. < 20, p=0.9) were not significantly associated with RFS in univariate or multivariate analyses.

Overall survival (OS):

As shown in Table 6, median OS estimates were 75.8 months for the overall cohort, 90.7 months for T3 stage and 59.3 months for T4 stage. Median OS could not be calculated for T2 stage because more than 50% of patients with this stage survived to the end of follow up. When comparing racial groups, median OS was 74.5 months for whites and 127.5 months for AA patients (p=0.04). When stratified by T-stage, AA had significantly higher OS than whites at T2 stage (p=0.03). Kaplan-Meier OS curves stratified by T-stage and race, respectively, are displayed in Figure 2.

As shown in Table 7, poorer OS was associated with age of diagnosis 60 years or older compared to those who were diagnosed with CTCL at age less than 60 (HR=2.4; 95% CI: 1.1-5.0, p=0.03). This significant trend continued on multivariate analysis (not shown in table) controlling for T-stage and maintenance therapy (HR=2.4; 95% CI: 1.1-5.3). Improved OS was also associated with maintenance therapy following RTSEI in univariate (HR=2.7; 95% CI: 1.1-6.4, p=0.02) and multivariate analysis (not shown in

table) when controlling for T-stage and age at diagnosis (HR=3.6; 95% CI 1.4-9.0). Race (p=0.4), sex (p=0.2), T-stage (p=0.4), histology (MF versus non-MF, p=0.8), time from diagnosis to start of TSEI (20 or more months vs. < 20, p=0.1) were not significantly associated with OS in univariate or multivariate analyses.

DISCUSSION

We examined the clinical response of CTCL patients treated to a conventional (>30gy) dose using dual beam rotational TSEI (RTSEI) technique at our institution. In theory, RTSEI provides greater dose homogeneity compared with other stationary or dynamic TSEI techniques. Our data show that conventional dose dual field RTSEI is an effective, well-tolerated modality, regardless of disease stage and race. These results represent the largest RTSEI clinical outcomes study in the modern era using dual field rotational technique.

Clinical Response Performance:

A summary of previous TSEI clinical outcome studies (Table 8) shows our observed CCR rates match or improve upon those achieved elsewhere. Our overall CCR rates at 6 weeks post-TSEI of 83% surpasses the 63% reported in the largest TSEI study (n=180) conducted by Navi et al. using the Stanford technique(10). After a 4- to 6-week follow

up, the Stanford study reported CCR estimates of 75% for T2 and 47% for T3 cutaneous disease; lower than the corresponding stage-specific CCR rates of 88% and 83% at 6 week of follow up in our study(10). In contrast to the Navi study, we also analyzed the data for T4 disease and observed a CCR rate of 69% at 6-weeks post-TSEI. As shown in Table 5, this surpasses other published studies reporting CCR at similar follow up for T4 lesions(15, 20, 29). Our results are also more favorable than those reported by Freedman and colleagues in the only other RTSEI (single beam) outcome study (N=44) that had an overall CCR rate of 73% (91% [T2], 71% [T3], 58% [T4]) at an unknown follow up time(20). In addition to showing strong CCR rates overall, the current study indicates that effectiveness of conventional-dose RTSEI is similar across all presenting T-stages regardless of follow up duration. Other studies have reported a loss of efficacy with TSEI treatment with higher T-stages and have questioned the efficacy for TSEI in treating T4 disease (10, 19, 20). The more favorable T3 and T4 clinical response in our study may be due to increased depth of penetration and greater uniformity of the dose distribution with RTSEI.

Recurrence Free Survival Performance:

While our median RFS values were comparable to those in previous TSEI cohorts(10, 15, 20), Figure 1 shows that a large proportion of patients CTCL still recurred within a year. Similar to CCR rates, RFS in our study did not differ across T-stages. This appears to be in disagreement with findings in previous studies. In the Navi et al. study, T2 patients had

fewer and more delayed recurrences than those with T3 disease(10). Part of the difference, or lack thereof in RFS, is likely due to small numbers. Though not significant, on simple observation, T4s appeared to have better RFS than T3s (12.1 vs. 9.9 months), suggesting that it may be difficult to distinguish an advanced/heavily pretreated T3 from a T4, in some cases. Also, T4s may have been more aggressively managed compared to T3s. Future studies with larger numbers could test this hypothesis.

Another important finding of our study is the clear benefit of maintenance therapy. This observation is in accordance with some (33, 34) but not all (10, 35, 36) previous reports. In a previous study, the lack of improvement due to maintenance therapy was attributed to the relatively small number of pretreatments and short duration of adjuvant Nitrogen Mustard (NH2)(10). Though, we did not record the total number of different treatments prior to the first course of RTSEI, no particular class of pretreatment (dermatologic, antineoplastic, phototherapy, or topical agents, respectively) in our study was associated with RFS.

Overall Survival (OS) Performance:

In total, our cohort had a 5-year OS of 61.2%, comparable to previous studies by Navi (5-year OS 63%)(10) and Wagner (5-year OS 58%)(18). Our study included a higher number of T4 stage patients (n=13). Ysebaert et al reported 5-year OS of 90%(19); however, this

study included only patients with T1-2 stage disease. When stratified by T stage, T3 had a median OS of 7.6 years, and T4 had a median OS of 4.9 years. These values are similar to or favorable when compared to previous OS median values for T3 disease(10, 15, 20) and T4 disease(15, 20) when taking into account varying definitions of beginning time points for OS (date of diagnosis vs. start of TSEI). In our study, we also found no significant difference in OS between T stages, which differs from previous studies that found a significant decrease in OS between T stages (10, 15, 19, 20).

Both younger age and maintenance therapy were independently associated with longer OS when controlling for the other, respectively, and for T-stage. The age association (60 years or older vs. less than 60 years old) is consistent with previous prognostic indicator studies (9) and, is somewhat intuitive in that we would expect those diagnosed at younger ages to have a longer overall survival compared to those diagnosed later in life. This is due to what OS is measuring, the multiple lines treatments available for CTCL, and, that CTCL, in general, is not associated with as high of mortality as more common, aggressive cancers (i.e. lung, colon, etc.). The more interesting finding was that maintenance therapy, which was associated with significantly improved RFS, also was shown to improve OS even when accounting for age and T-stage. Of note, although there was a trend towards significance for longer OS associated with patients who had 20 or more months between diagnosis and RTSEI treatment, this association was likely due to more aggressive/advanced disease requiring RTSEI earlier. When, T-stage was

accounted for in the multivariate analysis, this trend towards significance was no longer observed.

RTSEI Outcomes by Race:

Consistent with epidemiologic data(27), the AA CTCL patients in our study were significantly younger than their white counterparts. Notably, nearly one-third (30%) of the AA patients had T4 disease at the time of RTSEI compared to only 9% among whites. This difference may be explained by racial disparities in disease aggressiveness,(23) inequalities in access to care (treatment delay), or both.

We found no racial differences in RFS within each T-stage category. The 6-week CCR rates in both white (80.7%) and AA (81.3%) patients were higher than the rates reported in the only other TSEI study that looked at response and relapse by race with similar follow-up(29). The CCR estimates following standard Stanford TSEI technique in that study were 38% for whites, and 59% for AA patients, but the racial difference was not significant(29). Hinds et al.(29) suggested a possible interaction between gender and race for outcomes, but we found no significant interaction between race and sex on multivariate analysis, controlling for T-stage, for RFS (p=0.428) and OS (p=0.658).

Although multiple SEER database studies have showed poor overall survival of AA(28, 37) even when controlling for demographic factors and tumor stage(23), there was no significant difference between white and AA in our study. In fact when stratified by T-stage Pre-RTSEI, AAs had significantly improved OS compared to whites at stage T2 ($p=0.03$), suggesting that earlier use of RTSEI may actually be more effective in AA than their non-AA counterpart. However, a firm conclusion should be approached cautiously given the small sample size when stratified by stage. Larger studies are needed to confirm this effect.

Limitations:

This retrospective cohort, though one of the largest among TSEI clinical experiences (and the largest using the rotational method), is still limited by the small sample size. For this reason, a more definitive interpretation of some of the analyses (particularly those that used stratification) is difficult due to unstable and imprecise estimates. Although we found a significant positive effect of maintenance therapy on RFS, the analyses included all maintenance treatment modalities. The limited sample size precluded a more detailed examination of the data by specific type of maintenance therapy. Since biopsies were rarely performed on the suspected areas of recurrence, we sometimes relied on the clinical judgment of a radiation oncologist or dermatologist to ascertain RFS. Censoring in CCR ratios was also a potentially limiting factor. When patient did not follow up or did not have a recorded clinical response at one of the time

points with no previous record of recurrence, they were not included in the CCR calculations. Without complete follow up, the direction of bias, if any, remains unclear. Finally, given the chance for changes in technology and management of CTCL over time, we confirmed that there were no changes in technique of RTSEI during our study period.

Strengths:

Overall, our clinical outcomes for CCR, RFS, and OS compare favorably with past conventional dose TSEI clinical experience studies, even when accounting for the relatively large percentage of advanced stage patients in our cohort. Not only was this the first modern outcomes study examining dual-field RTSEI technique, our study includes a relatively large number of CTCL patients, a relatively large percentage of AA patients, and more advance stage patients than included in several prior reports. This study was also unique in terms of documenting clinical response across multiple time points. Because this was a single institution experience, every patient underwent radiation treatment using the same technique with minimal variability in regiments and dosage schedules. This uniformity proved valuable for comparisons made between racial groups and different disease stages.

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Tables and Figures

Table 1: Characteristics and Descriptive Statistics for RTSEI Study Cohort (N=68)

Variable	Statistic	Level/Units	Cohort (N=68)
Race	N (%)	White	33 (48.5)
		African American (AA)	33 (48.5)
		Other	2 (3)
Sex	N (%)	Female	33 (48.5)
		Male	35 (51.5)
Age at Diagnosis	Median	Years	51.7
	Mean		53.1
Age at Start of RTSEI	Median	Years	55.5
	Mean		55.5
Time from Diagnosis to RTSEI	Median	Months	20.2
	Mean		28.9
Pre-RTSEI Tumor (T) Stage	N (%)	T2	18 (26.5)
		T3	37 (54.4)
		T4	13 (19.1)
Histology	N (%)	MF	53 (77.9)
		Non-MF Subtype	15 (22.1)
Maintenance Therapy Post-RTSEI	N (%)	No	42 (61.8)
		Yes	26 (38.2)
Recurrence following RTSEI	N (%)	No/Unknown	24 (35.3)
		Yes	44 (64.7)

RTSEI=Rotational Total Skin Electron Irradiation; T2 = Patches/Plaques >10% body surface; T3 = 1+ tumor > 1 cm in diameter, T4 = Erythema >80% of body surface); MF=Mycosis Fungoides; Maintenance Therapy = systemic therapy or topical therapy started within 3-6 months after RTSEI

Table 2: Descriptive Statistics of Racial Subgroups and Comparisons

Variable	Statistic	Level/Units	White (n=33)	AA (n=33)	p-value
Sex	N (%)	Female	14 (42.4)	18 (54.6)	0.3
		Male	19 (57.6)	15 (45.4)	
Age at Diagnosis	Median	Years	60.5	44.8	**0.01**
	Mean		57.8	48.1	
Age at Start of RTSEI	Median	Years	62.3	50	**0.02**
	Mean		59.6	52.37	
Time from Diagnosis to RTSEI	Median	Months	16.6	28.4	**0.01**
	Mean		21.2	37.9	
Pre-RTSEI Tumor (T) Stage	N (%)	T2	7 (21.2)	11 (33.3)	**0.02**
		T3	23 (69.7)	12 (36.4)	
		T4	3 (9.1)	10 (30.3)	
Histology	N (%)	MF	20 (60.6)	32 (97)	**<.001**
		Non-MF Subtype	13 (39.4)	1 (3)	
Maintenance Therapy Post-RTSEI	N (%)	No	21 (63.6)	20 (60.6)	0.8
		Yes	12 (36.4)	13 (39.4)	
Recurrence following RTSEI	N (%)	No/Unknown	12 (36.4)	11 (33.3)	0.8
		Yes	21 (63.6)	22 (66.7)	

Abbreviations as in Table 1; AA= African Americans

Table 3: Complete Clinical Response (CCR) Rates by T Stage and stratified by Race at follow up time points: (A) End of Treatment; (B) Six-Weeks Post Treatment; (C) Six-Months Post Treatment.

A)

Follow-Up Period	**End of RTSEI**				
	Entire Cohort		**By Race**		
T-Stage Pre-RTSEI	N (%)	p-value	White N (%)	AA N (%)	p-value
ALL	63 (93)	-	32 (97)	29	0.4
T2	18 (100)	0.3	7 (100)	11	
T3	34 (92)		22 (96)	10	0.3
T4	11 (85)		3 (100)	8 (80)	

B)

Follow-Up Period	**Six-Weeks Post-RTSEI**				
	Entire Cohort		**By Race**		
T-Stage Pre-RTSEI	N (%)	p-value	White N (%)	AA N (%)	p-value
ALL	53 (82)	-	25 (81)	26 (81)	1
T2	15 (88)	0.5	5 (83)	10 (90)	1
T3	29 (83)		18 (82)	9 (82)	1
T4	9 (69)		2 (67)	7 (70)	1

C)

Follow-Up Period	**Six-Months Post-RTSEI**				
	Entire Cohort		**By Race**		
T-Stage Pre-RTSEI	N (%)	p-value	White N (%)	AA N (%)	p-value
ALL	27 (44)	-	12 (41)	13 (43)	0.9
T2	5 (42)	0.8	1 (33)	4 (44)	1
T3	17 (47)		10 (43)	5 (45)	1
T4	5 (38)		1 (33)	4 (40)	1

CCR percentage = the proportion of follow up patients with at least 90% reduction in cutaneous tumor burden. Patients considered non-complete responders (non CCR) included those with partial response [>50% reduction but less than 90%], stable disease, recurrence, progression, or death) at each of the three above follow up time points. Patients with no previous record of recurrence, those who did not follow up or had no recorded clinical response at one of the time points were not included in the CCR proportion. These were compared across racial categories and by T-stage using chi-square or Fisher's exact tests, as appropriate.

Table 4: Summary of Recurrence-Free Survival (RFS) by T-Stage Pre-RTSEI and stratified by Race

T-Stage Pre-RTSEI	Median RFS (months)				
	Entire Cohort		By Race		
		p-value	White	AA	p-value
All Stages	11.3	-	11.4	11.0	0.3
T2	14.3	0.9	19.1	6.0	0.1
T3	9.9		9.2	9.7	0.7
T4	12.1		4.8	13.2	0.9

AA = African American; RFS: Time to event= number of days between start of RTSEI and documented recurrence. *For patients whose cancers did not recur, survival time was censored at the date of last follow-up or date of death. P-values calculated using log-rank tests. Significance assessed at 0.05.

Table 5: Predictors of Recurrence Free Survival – Cox Proportional Hazards Model (Univariate Analysis)

Variable	Level/Units	Hazard Ratio (HR)	95% Confidence Interval	p-value
Race	White	0.7	0.4-1.3	0.3
	AA	-		
Sex	Female	1.0	0.6-1.9	0.9
	Male	-		
Pre-RTSEI Tumor (T) Stage	T2	1.1	0.4-2.5	0.9
	T3	0.9	0.4-1.9	
	T4	-		
Histology	Non-MF	0.7	0.3-1.6	0.4
	MF	-		
Diagnosis to RTSEI Time[^]	20 or more	1.0	0.5-1.8	0.9
	>20	-		
Age at Diagnosis (years)[@]	60 or more	0.8	0.4-1.5	0.5
	>60	-		
Maintenance Therapy Post-RTSEI[*]	No Treatment	2.2	1.1-4.1	**0.02**
	Treatment	-		

[^]20 months was chosen since it was median time to RTSEI for the cohort. [@]60 years of age was chosen based on age prognostic cutoff in CLIPi score (Benton et al., 2013) *On

Multivariate analysis, controlling for T-stage, patients who did not receive maintenance therapy post-RTSEI had significantly poorer RFS (HR=2.6; 95% CI: 1.2-5.4).

Table 6: Summary of Overall Survival (OS) by T-Stage Pre-RTSEI and stratified by Race

T-Stage Pre-RTSEI	Median OS (months)				
	Entire Cohort		By Race		
		p-value	White	AA	p-value
All Stages	75.8	-	74.5	127.5	0.4
T2	N/A	0.4	57.8	N/A	**0.03**
T3	90.7		103.3	75.8	0.6
T4	59.3		56.8	59.3	0.4

AA=African American; For OS: Time to event equals the number of days between diagnosis and the date of death or last known follow up. P-values calculated using log-rank tests. Significance assessed at 0.05. N/A - Kaplan-Meier OS median value not reached for Entire Cohort or AA at T2 stage.

Table 7: Predictors of Overall Survival - Cox Proportional Hazards Model (Univariate Analysis)

Variable	Level	Hazard Ratio (HR)	95% Confidence Interval	p-value
Race	White	1.4	0.7-2.9	0.4
	African American	-		
Sex	Female	0.6	0.3-1.3	0.2
	Male	-		
Pre-RTSEI Tumor (T) Stage	T2	0.5	0.2-1.4	0.4
	T3	0.7	0.3-1.6	
	T4	-		
Histology	Non-MF Subtype	1.1	0.5-2.6	0.8
	MF	-		
Diagnosis to RTSEI Time[^]	20 or more	0.5	0.2-1.0	0.06
	>20	-		
Age at Diagnosis (years)[@]*	60 or more	2.4	1.1-5.0	**0.03**
	>60	-		
Maintenance Therapy Post-RTSEI*	No Treatment	2.7	1.1-6.5	**0.02**
	Treatment	-		

[^]20 months was chosen since it was median time to RTSEI for the cohort. [@]60 years of age was chosen based on age prognostic cutoff in CLIPi score (Benton et al., 2013) *On multivariate analysis, accounting for T-stage and age at diagnosis/maintenance therapy, respectively, patients who did not receive maintenance therapy post-RTSEI continued to

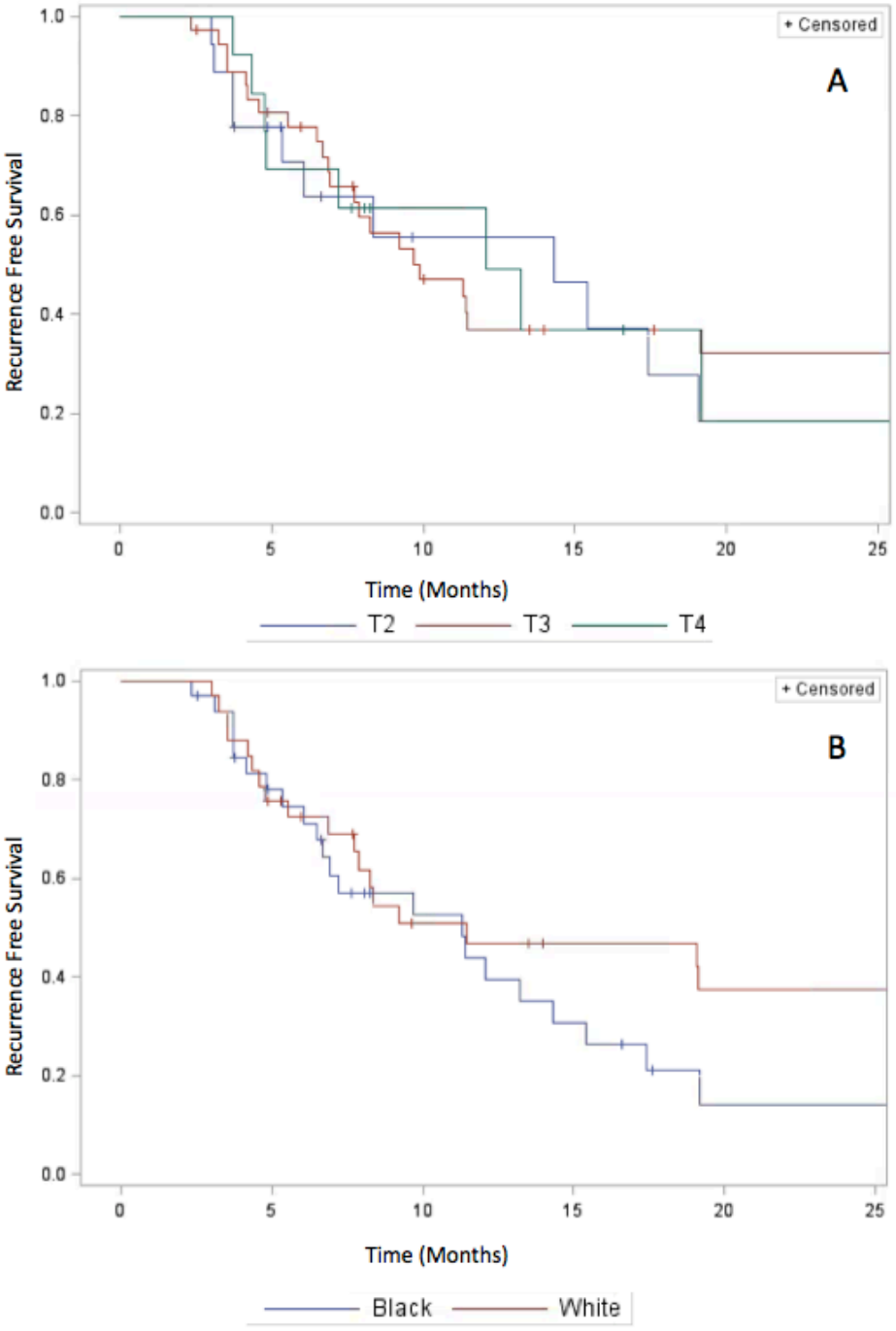
have significantly poorer observed OS (HR=3.6; 95% CI 1.4-9.0) as well as patients who were 60 years or older at time of diagnosis (HR=2.4; 95% CI: 1.1-5.3).

Table 8: Summary of Mycosis Fungoides/ CTCL TSEI Comparative Outcomes of Institutional Clinical Experiences

						Complete Clinical Response Rates (%)				Median RFS (months)				Median OS (months)			
Author	Year	Institution	N	Technique	Follow Up	Pre-TSEI Tumor (T) Stage											
						ALL	T2	T3	T4	ALL	T2	T3	T4	ALL	T2	T3	T4
Heumann	**2015**	**Emory, Georgia**	**68**	**Dual Beam Rotational**	**6 weeks**	**82**	**88**	**83**	**69**	**11.3**	**14.3**	**9.9**	**12.1**	**76**	**N/A**	**91**	**59**
Morris	2013	St John, UK	41	Modified Stanford	1-3 months	51	59	47	33	12	18	9	9	35	56	25	46
Hinds	2013	Johns Hopkins, Maryland	77	Modified Stanford	4-6weeks	43	45	42	12	-	-	-	-	-	-	-	-
Wagner	2013	Utah, Utah	41	Modified Stanford	1 month	56	-	-	-	-	-	-	-	-	-	-	-
Navi	2011	Stanford, California	180	Modified Stanford	4-6weeks	63	75	47	-	-	29	9	-	-	130.8	56.4	-
Parida	2009	New Delhi, India	4	Modified Stanford	-	-	-	-	-	-	-	-	-	-	-	-	-
Funk	2008	Heidelberg, Germany	18	Modified Stanford	-	50	-	-	-	-	-	-	-	12	-	-	-
Parida	2005	New Delhi India,	7	Modified Stanford	6 weeks	86	-	-	-	-	-	-	-	-	-	-	-
Ysebaert	2004	Dijon, France,	57	Mobile Couch	3 months	86	85	-	-	12	-	-	-	-	-	-	-
Freeman	1992	McGill, Canada	44	Single Beam Rotational	-	73	91	71	68	5	19	4	-	43	63	16	23

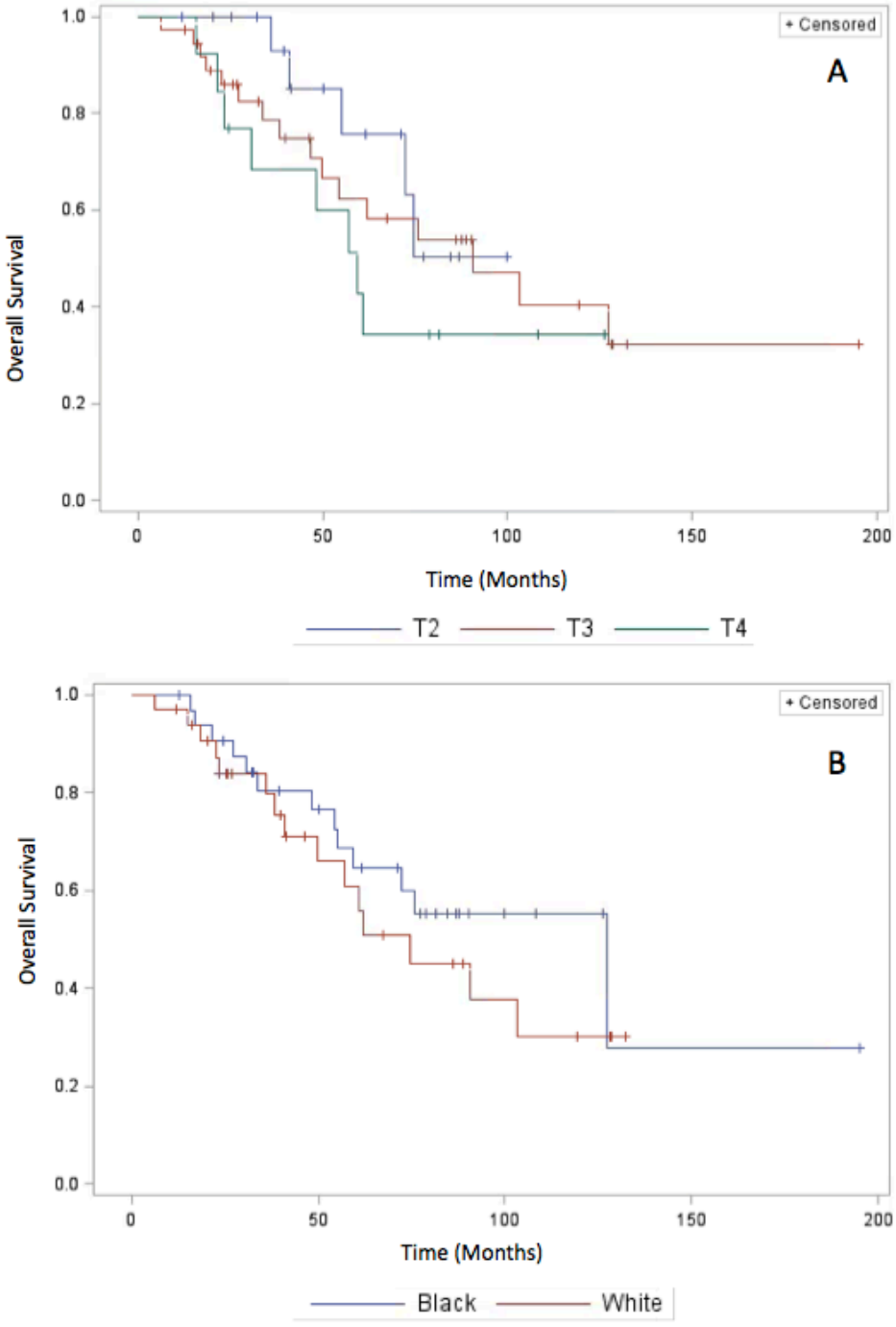
ALL= Total Cohort (All T-stages together); N/A- Kaplan-Meier OS median value not reached for T2 stage patients.

Figure 1: Recurrence-Free Survival (RFS) Kaplan Meir (KM) Curves



(A) RFS KM Curve, entire cohort, stratified by T-stage pre-RTSEI; (B) RFS KM Curve, entire cohort, stratified by Race

Figure 2: Overall Survival (OS) Kaplan Meir (KM) Curves



(A) OS KM Curve, entire cohort, stratified by T-stage pre-RTSEI; (B) OS KM Curve, entire cohort, stratified by Race

Chapter III: Summary, Public Health Implications, & Future Directions

Summary:

This study reports the first single institutional outcomes following conventional-dose, dual beam rotational total skin electron irradiation (RTSEI). Complete clinical response rates, recurrence-free, and overall survival outcomes were compared across pre-treatment tumor stage categories, and by race. The reported results show that conventional dose dual field RTSEI is an effective, well-tolerated modality, regardless of disease stage and race. Our study represents one of the largest, most diverse RTSEI cohorts in terms of overall number of patients and proportion of African Americans.

Public Health Implications:

Because mycosis fungoides and other CTCLs are rare in the general population, the research on the disease is relatively limited. This may be a small population, but the incidence of this type of cancer continues to increase especially among African Americans(6). Though MF and CTCL are mostly known as indolent cancers, they can be associated with high morbidity and susceptibility to deadly super-imposed infections in the more advanced cutaneous stages. Mortality rates increase when the cancer spreads to the lymph nodes and extra-cutaneous organs. While certain prognostic indicators have been identified (9), the etiology and biological mechanisms behind these predisposing factors for CTCL and disparities remain unclear(6). Because of this, a large

focus of the research, such as the current study, is on the treatment phase for the population affected with this disease rather than prevention.

This particular study reports findings that show an effective tool and technique for treating moderate to advanced stages of MF and CTCL. This is important from a public health standpoint because the population affected with this disease usually develop treatment resistance to multiple lines of therapy. Thus, if/when a patient fails on initial dermatologic therapies, phototherapies, and even systemic chemotherapies, there is still an effective therapy, TSEI, available to these patients, regardless of how advanced their disease is at the time. The rotational technique may further optimize the clinical efficacy of this therapy. More studies will be needed, but combining this type of radiation therapy with current or new systemic therapies (i.e. immunotherapies) may offer a potential cure for this small but significant population.

Future Directions:

Even with our encouraging results, recurrence post-RTSEI remains frequent and maintenance therapy and/or better consolidation therapy following first-course RTSEI should be considered. Future studies should focus on the benefit of these specific therapies combined with RTSEI and the overall clinical outcomes, while also evaluating patterns of recurrence, quality of life, toxicity metrics, and the role of a second course of

RTSEI in the maintenance setting or in the retreatment setting. This will be best done through collaborative studies with multi-institutional participation to ensure larger patient samples and more highly powered studies. At the same time, disease etiologic mechanisms and risk factors must be further clarified to better identify populations at risk for the development of CTCL to allow for earlier and more targeted therapy of the disease.