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Low-dose Hypofractionated Total Skin Electron Beam Therapy for Adult Cutaneous T-cell Lymphoma

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Abstract:	OBJECTIVES: Historically, the standard of care for total skin electron beam therapy (TSEBT) delivered 30-36 Gray (Gy) over 5-10 weeks. Given the high-risk of relapse, a majority of patients require additional treatments. Therefore, attempts to utilize a shortened course of TSEBT have been investigated. METHODS: We conducted a single-institution retrospective review to evaluate disease response, control, and toxicity using a low-dose, hypofractionated course of TSEBT (HTSEBT) in patients with mycosis fungoides. RESULTS: 40 patients received 57 courses of HTSEBT. Median dose (Gy)/fractionation was 12 / 3, spanning a median time of 2.4 weeks. Overall response rate of patients assessed (n=54) was 100%. Thirty-one courses (57.4%) resulted in a complete response and 23 courses (42.6%) resulted in a partial response. Cumulative incidence of progressive skin disease at 3 months was 37.2%, at 6 months, 56.9%, and at 1 year, 81.5%. Of the 40 patients treated with a first course of HTSEBT, 31 received subsequent courses of RT. Cumulative incidence of subsequent treatment was 28.0% at 3 months, 46.8% at 6 months, and 70.0% at one year. Patients who underwent repeat courses of HTSEBT continued to have similar treatment responses to repeat courses without increased toxicities. Toxicities from all courses were acceptable with the exception of one patient who experienced grade 4 skin toxicity (moist desquamation requiring hospitalization).

	CONCLUSIONS: Low-dose, HTSEBT provides good palliation in patients with CTCL with a satisfactory response and toxicity profile. HTSEBT allows therapy to be completed in far fewer treatments. Low-dose HTSEBT is an appropriate treatment option for patients unable to come for daily treatment. HTSEBT provides a way to decrease exposure to other patients and staff during public health emergencies such as the COVID-19 pandemic.

Low-dose Hypofractionated Total Skin Electron Beam Therapy for Adult Cutaneous T-cell Lymphoma

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ABSTRACT

OBJECTIVES:

Historically, the standard of care for total skin electron beam therapy (TSEBT) delivered 30-36 Gray (Gy) over 5-10 weeks. Given the high-risk of relapse, a majority of patients require additional treatments. Therefore, attempts to utilize a shortened course of TSEBT have been investigated.

METHODS:

We conducted a single-institution retrospective review to evaluate disease response, control, and toxicity using a low-dose, hypofractionated course of TSEBT (HTSEBT) in patients with mycosis fungoides.

RESULTS:

40 patients received 57 courses of HTSEBT. Median dose (Gy)/fractionation was 12 / 3, spanning a median time of 2.4 weeks. Overall response rate of patients assessed (n=54) was 100%. Thirty-one courses (57.4%) resulted in a complete response and 23 courses (42.6%) resulted in a partial response. Cumulative incidence of progressive skin disease at 3 months was 37.2%, at 6 months, 56.9%, and at 1 year, 81.5%. Of the 40 patients treated with a first course of HTSEBT, 31 received subsequent courses of RT. Cumulative incidence of subsequent treatment was 28.0% at 3 months, 46.8% at 6 months, and 70.0% at one year. Patients who underwent repeat courses of HTSEBT continued to have similar treatment responses to repeat courses without increased toxicities. Toxicities from all courses were acceptable with the exception of

one patient who experienced grade 4 skin toxicity (moist desquamation requiring hospitalization).

CONCLUSIONS:

Low-dose, HTSEBT provides good palliation in patients with CTCL with a satisfactory response and toxicity profile. HTSEBT allows therapy to be completed in far fewer treatments. Low-dose HTSEBT is an appropriate treatment option for patients unable to come for daily treatment. HTSEBT provides a way to decrease exposure to other patients and staff during public health emergencies such as the COVID-19 pandemic.

INTRODUCTION:

Total skin electron beam therapy (TSEBT) is a highly effective palliative treatment for patients with mycosis fungoides and other forms of cutaneous T cell lymphoma. Dose guidelines published by The National Comprehensive Cancer Network (NCCN) recommend a total dose of 12 to 36 Gray (Gy) in TSEBT patients, while the International Lymphoma Radiation Oncology Group have recommended total doses ranging from 8-36 Gy [1, 2]. Despite a lack of guidelines regarding fraction size, most reports have described a daily dose of 1 Gy administered 4 to 5 times per week [3].

Following TSEBT, most patients will experience progressive disease within 6 to 12 months. Low-dose TSEBT, using 12 Gy in 8-12 fractions, has the potential to decrease the burden of treatment for patients. Favorable results, including response rates of 87-88% have been reported by Stanford [4] and the UK Cutaneous Lymphoma Group [5].

Hypofractionated regimens are more convenient for patients [6, 7]. We have combined the concept of low dose palliative TSEBT with hypofractionation, resulting in a regimen that can generally be completed with 4 or fewer treatments. Previous results have been published from a database of patients with cutaneous lymphoma who were treated with radiation therapy using a variety of techniques, including focal radiation therapy, regional radiation therapy and TSEBT between January 2000 through September 2017 [8]. This study was undertaken to provide a detailed assessment of outcomes in the subset of patients treated with hypofractionated total skin electron beam therapy (HTSEBT), further defined below. The database in this subset of patients was updated to include all patients treated with HTSEBT from 2000 to 2020.

METHODS & MATERIALS:

This study was performed with institutional review board approval utilizing the aforementioned institutional database. Patients included in this study had a diagnosis of CTCL and were treated with HTSEBT, defined as ≥ 2.5 Gy per fraction typically given once every one to two weeks, delivered at the xxx in xxx, xxx from January 2000 to January 2020. This report includes a description of an illustrative case, including photographs. Written permission was obtained from the patient to disclose this case-specific information.

Patients were included for analysis if age 18 or older, Eastern Cooperative Oncology Group performance status 0 to 3, had biopsy-confirmed stage IB to III CTCL. Patient characteristics, treatment details, toxicities, and oncologic outcomes were recorded and updated for each patient. Additionally, given the rarity of centers delivering TSEBT, the two-way travel distance by road between our center and each patient's home was collected (https://www.google.com/map).

The primary objectives of this study were to examine the effectiveness and toxicity of HTSEBT. Endpoints included clinical response of cutaneous lesions, date of progressive skin disease and date of subsequent radiotherapy treatments. Toxicities were recorded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Electrons with an extended source to surface distance were utilized to deliver total skin electron therapy [9]. For 55 of 57 courses, the Stanford technique was utilized [10]. The Stanford technique has the patient assume six standing poses at 60-degree increments: anterior, posterior, right anterior oblique, right posterior oblique, left anterior oblique, and left posterior oblique At each angle, two fields, are treated, one for the upper body and a second for the lower body,

resulting in a total of 12 fields. A thin polycarbonate scattering panel was used at approximately 212 cm from the isocenter. A 6-MeV energy linear accelerator in High Dose Total Skin Electron treatment mode was used to deliver dual electron fields at each of the six positions with central rays ± 20 degrees from the horizontal. In all treatments where the patient could stand, 12 fields were treated daily. Two courses were delivered using a lying-on-the floor position due to poor performance status and inability to remain standing throughout the length of treatment [9, 11]. Most patients had significant debility and were unable to tolerate eye shields because of an unacceptable risk of falling. Accordingly, eye shields were not routinely used.

Initial follow-up and assessment of response was largely completed by radiation oncology teams with experience in the treatment and assessment of cutaneous lymphoma. At follow-up visits, response assessment was recorded in the medical record. Pre-treatment and post-treatment photography of either the entire body or large areas of the body (for example, the entire trunk) was extensively used at follow-up to aid in assessing and documenting response. Patients were not routinely seen by a hematologist or dermatologist at the time of initial follow-up and response assessment. Full details regarding personnel involved in response assessment is described in the Results. Follow-up subsequent to assessment of response was generally performed at the time of patient-reported progression of disease, which initiated prompt scheduling of the patient for a visit with the patient's physician.

Response to treatment was assessed according to International Society for Cutaneous Lymphoma (ISCL) criteria [12] with the exception of a subdivision of patients with partial response, as described below. Complete response was defined as 100% clearance of skin lesions. Initial analysis of the data subdivided partial response (PR) into $PR_{\geq 50\text{-}95}$, which were cases with ≥ 50%-95% clearance of skin lesions and near complete response, $NCR_{>95\text{-}99,}$ defined as > 95%-

99% clearance. In a post-hoc analysis, we sought to provide preliminary evidence regarding the validity of this subdivision of partial response by determining if time to progressive skin disease in patients with $NCR_{>95-99}$ was more prolonged than in patients with $PR_{\geq 50-95}$.

Progressive skin disease was defined as ≥25% increase in skin disease from baseline or any disease recurrence in those with a complete response. Date of skin progression was recorded as the date assessed by the physician. Subsequent radiotherapy treatments were collected as repeat total skin therapy, repeat focal treatment, or both. Date of subsequent radiotherapy treatment, defined as time from completion of total skin radiotherapy to subsequent start of radiotherapy treatment was collected for applicable patients. Toxicities were retrospectively assessed according to CTCAE version 4.03 using medical photographs and information in the medical record, obtained through clinic follow-up appointments, telephone communication, or outside hospital records.

All outcomes were assessed starting on the date that the radiation therapy was completed. The cumulative incidence of skin progression and subsequent radiotherapy delivery was estimated treating death as a competing risk. A univariate cox model was calculated to discern a difference in skin progression based on course number for patients that underwent repeat courses of HTSEBT. In a post hoc analysis, the cumulative incidence of skin progression and subsequent radiotherapy was estimated (using death as a competing risk factor) by grouping patients into cohorts based on response to first course of HTSEBT. In the first analysis, patients were grouped into CR, $PR_{\geq 50-95}$, and $NCR_{>95-99}$ and in the second analysis, patients were grouped into CR and PR alone, eliminating the $NCR_{>95-99}$ cohort. Univariate cox models were calculated to discern a difference in time to progressive skin disease or subsequent radiotherapeutic interventions

amongst these various groupings. Data was analyzed using SAS Version 9.4. A two-sided P value of ≤ 0.05 was considered significant in all analyses.

RESULTS:

Forty-seven patients were identified as having one or more courses of HTSEBT. Seven patients were excluded from the analysis: 5 patients with atypical histology and 2 patients declined use of their medical record for research purposes. Therefore, 40 patients who received 57 courses of hypofractionated TSEBT were included; including 14 patients who received a second course of HTSEBT and 3 who received a third course of HTSEBT. With the exception of a single patient, no patients were treated with antineoplastic pharmaceutical agents or other therapies for cutaneous lymphoma during their HTSEBT course or prior to assessment of response. One patient was inadvertently left on oral bexarotene during RT, despite having experienced progression on this agent. Bexarotene was promptly discontinued after the first fraction.

Of the 40 patients evaluated (Table 1), median age at diagnosis was 67 years old (range, 33 – 93). Patients were predominantly male (70%). Eighty-one percent of patients had ECOG performance status 0 or 1 prior to course of radiotherapy. Most patients had stage IB or IIB disease prior to initiation of RT. The median round-trip distance between patients' homes and our treatment center was 284 miles (range, 4 – 1,150).

Median dose and fractionation was 12 Gy in 3 fractions, spanning a median time of 2.4 weeks. The most common regimen was 12 Gy in 3 fractions (17 courses of treatment, 29.8%). The second most common regimen was 8 Gy in 2 fractions (14 courses of treatment, 24.6%). Additional dose and fractionation schemes are shown in Table 2.

Three patient courses had no reported follow-up, but still contributed to the database with regard to presenting features, toxicity and distance traveled from home. Of the remaining 54 courses, patients were assessed for response at a median follow up of 29 days (range 7 – 216 days; inter-quartile range 19 – 65.5 days). Forty-nine of 54 responses (91%) were assessed at the time of follow-up by a radiation oncology team with experience in the treatment and assessment of cutaneous lymphoma. Of the 49 responses assessed in office, all cases were evaluated by the initial treating provider with the exception of one case that was transitioned between two radiation oncology providers at the time of retirement of the initial treating radiation oncologist. Two cases were assessed in follow-up by the patient's hematologist. The other three responses were recorded after a thorough conversation with the patient on the phone regarding disease burden. All patients with complete responses were evaluated in office by the treating radiation oncologist.

The overall response rate for patients was 100%. Thirty-one courses (57.4%) resulted in a complete response and 23 courses (42.6%) resulted in a partial response (Table 3).

An exploratory analysis did not provide evidence for the validity of subdivision of patients with PR. Specifically, patients with $NCR_{>95-99}$ did not have a more prolonged time to skin progression than those with $PR_{\geq 50-95}$ (Figure 1). Accordingly, we eliminated the subdivision of near complete response from our summary of response rates (Table 3). Additional post-hoc analyses did demonstrate that patients who experienced a CR had a more prolonged time to skin progression than patients who experienced a PR (Figure 2).

The median time to skin progression was 89 days. As previously stated, we utilized the principle that a > 25% increase in disease constituted progression in patients who previously had

a partial response. It was not possible to calculate the percentage increase in disease in the context of a retrospective study. However, it was our uniform experience that progression was sufficiently dramatic as to clearly be above the 25% threshold. Cumulative incidence of progressive skin disease at 3 months was 37.2%, at 6 months, 56.9%, and at 1 year, 81.5% (Table 4, Figure 3).

Thirty-nine courses of subsequent radiotherapy were delivered. This comprised of 17 repeat HTSEBT courses and 23 repeat focal skin treatments. Cumulative incidence of subsequent treatment (either HTSEBT or focal skin treatment) was 28.0% at 3 months, 46.8% at 6 months, and 70.0% at one year. (Table 4, Figure 4a). Cumulative incidence of repeat HTSEBT was 9.6% at 3 months, 14.4% at 6 months and 30.8% at 1 year (Table 4, Figure 4b). The cumulative incidence of repeat HTSEBT or focal treatment was longer for patients with a complete response to their prior treatment as compared to a partial response, 32.5% (95% CI 18.9 – 56.0) at 6 months versus 64.8% (95% CI 47.2 – 89.0), respectively (hazard ratio 3.28, $p < 0.01$).

Patients who underwent repeat courses of HTSEBT did not experience more rapid skin progression than seen following a first course of radiation therapy (Figure 5). With the first courses of treatment as reference, the hazard ratio for skin progression for a second course of treatment was 0.52 (95% CI, 0.12 – 2.19) and 0.87 (95% CI, 0.38 – 2.00) for a third course of treatment.

The most common acute radiation-induced side effects were grade 1 or 2 and included pruritus (n=9, 16%), diffuse erythema (n=12, 21%), skin pain or discomfort (n=8, 14%), lower extremity swelling (n=5, 9%), swelling localized around the original lesions (n= 1, 2%), finger swelling (n=1, 2%), upper lip swelling (n=1, 2%), and desquamation or blister formation (n=9,

16%). Four patients reported acute fatigue (7%) and 2 patients experienced eye irritation and dryness (5%). Treatment-related alopecia was reported in 41% (n=22) of cases, while nail ridging was present in 17% of cases (n=9). No acute grade 3 toxicity was observed. One patient experienced acute grade 4 diffuse moist desquamation requiring hospitalization. Two patients reported late hyperpigmentation.

DISCUSSION:

Multiple previous studies have analyzed response rates of TSEBT delivered with a total dose of 30 to 36 Gray delivered over 5 to 10 weeks. These studies typically describe an excellent overall response rate of greater than 90%, with complete response rates ranging between 60% to 95% [10, 13]. While these noted a median time until disease progression varying from 6 to 12 months [10, 13], patients on average spend approximately 2-3 months undergoing treatment. Results from a pooled analysis of phase II clinical trials published by Hoppe et al. in 2015 [4] analyzed 33 patients treated with low-dose total skin electron beam radiotherapy, 12 Gy delivered as 1 Gy per fraction over 3 weeks. In this series, the response rate was 88% and the complete response rate was 27% [4].

Hypofractionated low dose total skin electron beam therapy resulted in a 100% response rate in evaluable patients in the present study, with 57.4% experiencing a complete response and 42.6% experiencing a partial response. The durability of response was very heterogeneous, with 62.8% free of skin progression at 3 months and 43.1% free of skin progression at 6 months.

Our results do not provide evidence that a subdivision of partial response into patients with >95% clearance of disease and those with 50-95% clearance of disease is clinically useful

(Figure 1). Validation of any subdivision of partial response is needed before use in routine clinical practice or use as a measure of patient benefit. Validation studies would preferably use prospectively acquired data and could include evaluation of symptoms at the time of response assessment and determination of the prognostic significance of different levels of response.

A decreased likelihood of response has been reported following re-treatment with TSEBT [10]. In contrast, the response rate was 100% among evaluable patients following a second or third course of HTSEBT in the present study. Patients treated with a second or third course of HTSEBT did not experience a more rapid rate of skin progression than was observed following a first course of HTSEBT (Figure 5).

Treatment was generally well tolerated and our regimen compares favorably with other published toxicity data [14, 15]. An exception occurred in one patient, who experienced grade 4 toxicity. The patient presented with severely painful erythroderma and was not a candidate for other treatment options. Because of the potential for severe cutaneous toxicity, erythroderma has been described as a relative contraindication to TSEBT [16, 17]. Prior to proceeding with palliative TSEBT, the patient was provided with thorough informed consent, including the option of supportive measures only. The patient expressed a preference to proceed with HTSEBT and received a total dose of 8 Gy delivered in 2 fractions over 2 weeks. Two days after the second fraction, the patient developed grade 4 skin toxicity, requiring hospitalization. After recovery from toxicity, the patient had a complete response to treatment and was pain free (21 days after radiotherapy delivery). The patient was again in severe pain following recurrence 3 months later and a second course of palliative treatment was discussed, again with thorough informed consent. Based on the palliation obtained from the first course, the patient requested re-treatment. A second course of 4.5 Gy delivered in a single fraction HTSEBT had a similar outcome with

regard to toxicity. No follow-up in disease response is available after the patient's second course of HTSEBT.

This retrospective study has several limitations. The patients represent a heterogeneous population, in particular with respect to stage, and the stage could not be determined in 7% of the cases. Scheduling of follow-up was not standardized. Direct comparison to other studies is difficult as the Modified Severity Weighted Assessment Tool (mSWAT) was not recorded, similar to other retrospective studies [18,19] and one prospective study [20]. Reliable information regarding other non-radiotherapeutic treatments subsequent to last assessment of response was not available and is not reported. Another limitation of this study is that some toxicities were almost certainly under-reported, particularly alopecia and nail ridging.

Our overall response rate was 100%, similar to that of other comparable studies [6, 7, 20-22] studies utilizing hypofractionated or low-dose TSEBT. The rate of 57.4% for complete response is lower that other complete response rates reported in hypofractionated series, including a complete response rate of 83% reported by Le Bourgeois and colleagues using 30 Gy in 12 fractions over 40 days [6], and a complete response rate of 90% reported by Nisce and colleagues [7] in patients treated with 4 Gy weekly for 4 to 6 fractions. Notably, these series include hypofractionation, but to a higher total dose. In comparable low-dose series [20-22], not utilizing hypofractionation, our response rate appears similar or improved. Kamstrup et al. [20] reported a 57% complete response rate after delivering 10 Gy in 10 fractions over 2.5 weeks, while Georgakopoulos et al. [22] and Rivers et al. [21] reported a 25% complete response rate after delivery of 12 Gy in 6 fractions over 3 weeks or $\leq$12 Gy in standard fractionation over an uncertain time interval. Our results provide the first response of combined low dose and hypofractionated TSEBT.

Total skin electron beam therapy is a highly specialized form of radiation therapy that is only available in a limited number of centers. As such, it places a significant burden on many patients who need this treatment. The median roundtrip distance between our treatment center and patients' homes was 284 miles. We instituted HTSEBT in response to patients who were unable to come for daily treatment due to one or more of the following factors: limitations in patient resources, inability or unwillingness to travel over long distances and remain at our center for several weeks, inability to tolerate daily treatment or unwillingness to consent to daily treatment.

These findings are also relevant to health system emergencies, such as the COVID-19 pandemic. Multiple centers have recommended hypofractionation, whenever possible, during this health system emergency [23-26]. Decreasing the number of radiation fractions from 12, as in the Stanford report [4], to 3 or 4, may be particularly desirable during an infectious disease outbreak, both for the protection of patients with cutaneous T cell lymphoma and the protection of other patients and healthcare workers. HSTSEBT may also be a consideration when healthcare resources are limited.

The case of one of our patients is particularly illustrative with regard to the utility of HTSEBT. She had a 12-year history of mycosis fungoides, and prior systemic treatment and focal radiation therapy elsewhere. At the time of her presentation, she had extensive, severely painful ulcerative disease (Figure 6A). She was on intravenous antibiotics because of infection related to loss of skin integrity. Standing for TSEBT was extraordinarily painful and the patient expressed both an inability and unwillingness to come for daily treatment. She was treated with HTSEBT, 12 Gy in 3 fractions over 18 days. By the time she completed treatment, her pain had dramatically improved and she had much less difficulty tolerating her last session of HTSEBT.

She experienced a dramatic response as documented at follow-up (Figure 6B). She experienced multiple areas of limited recurrence over the ensuing 7 months, treated on each occasion with palliative single-fraction radiation therapy, always resulting in complete in-field response, and then experienced spontaneous resolution of all remaining lesions, including lesions deep to the skin, as documented by PET scan 15 months after initiation of TSEBT. She remains free of disease and is working full time as of last follow-up, 3 years after starting palliative TSEBT. This favorable outcome would not have been possible without the use of HTSEBT

CONCLUSION

Low dose hypofractionated total skin electron beam therapy provides good palliation in patients with cutaneous T-cell lymphoma with a satisfactory response rate and an acceptable toxicity profile. HTSEBT provides an opportunity for treatment with a high response rate for patients who otherwise might not otherwise be candidates for TSEBT. It is an option that should be considered during health system emergencies, when prolonged courses of radiation therapy need to be avoided due to limitations in resources or for protection of patients and their healthcare providers.

BIBLIOGRAPHY

1. National Comprehensive Cancer Network. *Primary Cutaneous Lymphoma (Version 1.2020)*. March 23, 2020]; Available from: https://www.nccn.org/professionals/physician_gls/pdf/primary_cutaneous.pdf.
2. Specht, L., et al., *Modern radiation therapy for primary cutaneous lymphomas: field and dose guidelines from the International Lymphoma Radiation Oncology Group.* Int J Radiat Oncol Biol Phys, 2015. **92**(1): p. 32-9.
3. Moraes, F.Y.d., et al., *Literature review of clinical results of total skin electron irradiation (TSEBT) of mycosis fungoides in adults.* Reports of practical oncology and radiotherapy : journal of Greatpoland Cancer Center in Poznan and Polish Society of Radiation Oncology, 2013. **19**(2): p. 92-98.
4. Hoppe, R.T., et al., *Low-dose total skin electron beam therapy as an effective modality to reduce disease burden in patients with mycosis fungoides: results of a pooled analysis from 3 phase-II clinical trials.* J Am Acad Dermatol, 2015. **72**(2): p. 286-92.
5. Morris, S., et al., *The Results of Low-Dose Total Skin Electron Beam Radiation Therapy (TSEB) in Patients With Mycosis Fungoides From the UK Cutaneous Lymphoma Group.* Int J Radiat Oncol Biol Phys, 2017. **99**(3): p. 627-633.
6. Le Bourgeois, J.P., et al., *The indications for total cutaneous electron beam radiation therapy of mycosis fungoides.* Int J Radiat Oncol Biol Phys, 1987. **13**(2): p. 189-93.
7. Nisce, L.Z., et al., *Total skin electron beam therapy for cutaneous lymphomas and leukemias.* Int J Radiat Oncol Biol Phys, 1982. **8**(9): p. 1587-92.
8. King, B.J., et al., *Skin-directed radiation therapy for cutaneous lymphoma: The Mayo Clinic experience.* J Am Acad Dermatol, 2020. **82**(3): p. 634-641.
9. Deufel, C.L. and J.A. Antolak, *Total skin electron therapy in the lying-on-the-floor position using a customized flattening filter to eliminate field junctions.* J Appl Clin Med Phys, 2013. **14**(5): p. 115-26.
10. Navi, D., et al., *The Stanford University experience with conventional-dose, total skin electron-beam therapy in the treatment of generalized patch or plaque (T2) and tumor (T3) mycosis fungoides.* Arch Dermatol, 2011. **147**(5): p. 561-7.
11. Evans, J.D., et al., *Clinical application of lying-on-the-floor total skin electron irradiation for frail patients with cutaneous lymphoma: An emphasis on the importance of in vivo dosimetry.* Adv Radiat Oncol, 2016. **1**(2): p. 101-105.
12. Olsen, E.A., et al., *Clinical end points and response criteria in mycosis fungoides and Sezary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer.* J Clin Oncol, 2011. **29**(18): p. 2598-607.
13. Morris, S.L., et al., *Results of a 5-week schedule of modern total skin electron beam radiation therapy.* Int J Radiat Oncol Biol Phys, 2013. **86**(5): p. 936-41.
14. Micaily, B., E.C. Vonderheid, and L.W. Brady, *Combined moderate dose electron beam radiotherapy and topical chemotherapy for cutaneous T-Cell lymphoma.* Int J Radiat Oncol Biol Phys, 1983. **9**(4): p. 475-9.
15. Kroeger, K., et al., *Low-dose total skin electron beam therapy for cutaneous lymphoma : Minimal risk of acute toxicities.* Strahlenther Onkol, 2017. **193**(12): p. 1024-1030.
16. Hoppe, R.T., G.S. Wood, and E.A. Abel, *Mycosis fungoides and the Sezary syndrome: pathology, staging, and treatment.* Curr Probl Cancer, 1990. **14**(6): p. 293-371.

17. Hoppe, R.T., *Total skin electron beam therapy in the management of mycosis fungoides.* Front Radiat Ther Oncol, 1991. **25**: p. 80-9; discussion 132-3.
18. Harrison, C., et al., *Revisiting low-dose total skin electron beam therapy in mycosis fungoides.* Int J Radiat Oncol Biol Phys, 2011. **81**(4): p. e651-7.
19. Elsayad, K., et al., *Total Skin Electron Beam for Primary Cutaneous T-cell Lymphoma.* Int J Radiat Oncol Biol Phys, 2015. **93**(5): p. 1077-86.
20. Kamstrup, M.R., et al., *Low-dose (10-Gy) total skin electron beam therapy for cutaneous T-cell lymphoma: an open clinical study and pooled data analysis.* Int J Radiat Oncol Biol Phys, 2015. **92**(1): p. 138-43.
21. Rivers, C.I. and A.K. Singh, *Total Skin Electron Beam Therapy for Mycosis Fungoides Revisited With Adjuvant Systemic Therapy.* Clinical Lymphoma Myeloma and Leukemia, 2019. **19**(2): p. 83-88.
22. Georgakopoulos, I., et al., *Clinical application of Total Skin Electron Beam (TSEB) therapy for the management of T cell cutaneous lymphomas. The evolving role of low dose (12 Gy) treatment schedule.* Clinical and Translational Radiation Oncology, 2019. **15**: p. 26-30.
23. Achard, V., P. Tsoutsou, and T. Zilli, *Radiotherapy in the time of the Coronavirus pandemic: when less is better.* Int J Radiat Oncol Biol Phys, 2020.
24. Zaorsky, N.G., et al., *Prostate Cancer Radiotherapy Recommendations in Response to COVID-19.* Advances in Radiation Oncology, 2020.
25. Filippi, A.R., et al., *COVID-19 OUTBREAK IN NORTHERN ITALY: FIRST PRACTICAL INDICATIONS FOR RADIOTHERAPY DEPARTMENTS.* International Journal of Radiation Oncology • Biology • Physics.
26. Wang, H. and L. Zhang, *Risk of COVID-19 for patients with cancer.* Lancet Oncol, 2020. **21**(4): p. e181.

Figure Legends

Figure 1: Cumulative Incidence of Progressive Skin Disease based upon response to initial course of HTSEBT (CR vs. NCR$_{>95\text{-}99}$ vs. PR$_{\geq 50\text{-}95}$).

Figure 2: Cumulative Incidence of Progressive Skin Disease based upon response to initial course of HTSEBT (CR vs. PR).

Figure 3: Cumulative Incidence of Progressive Skin Disease following completion of all courses of HTSEBT.

Figure 4: Cumulative Incidence of Repeat Treatment, including focal or repeat HTSEBT (4a) or repeat HTSEBT alone (4b), following completion of HTSEBT.

Figure 5: Cumulative Incidence of Progressive Skin Disease, following completion of HTSEBT, based on HTSEBT course number. (1=1st course, 2=2nd course, 3=3rd course)

Figure 6: A) Extensive ulcerative lesions prior to hypo-fractionated total skin electron beam therapy. B) Complete response of lesions on the trunk 45 days following completion of HTSEBT, 12 Gy in 3 fractions, given over 18 days.

Figure 1

Click here to access/download;Figure;Fig1.tif

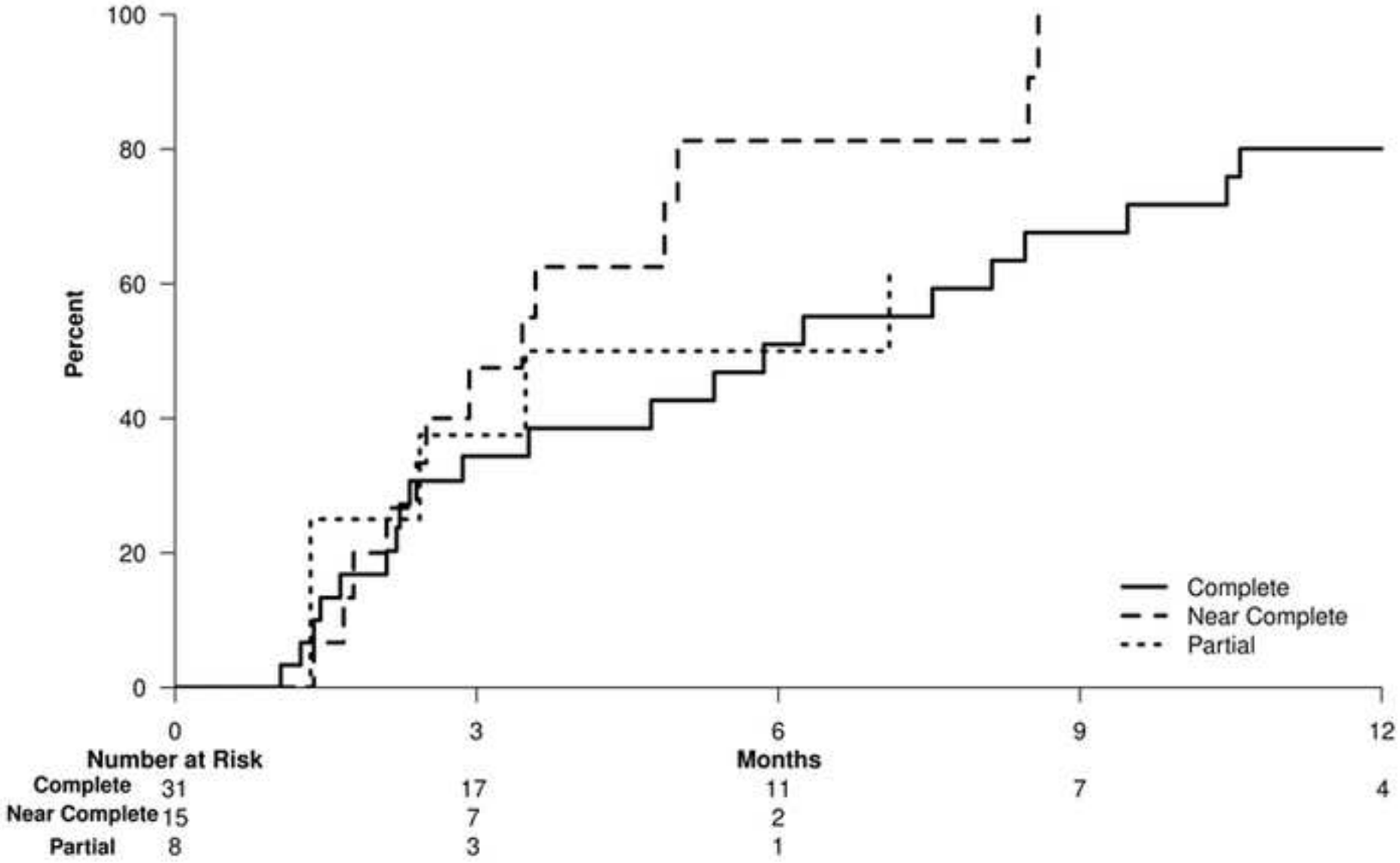


Figure 2

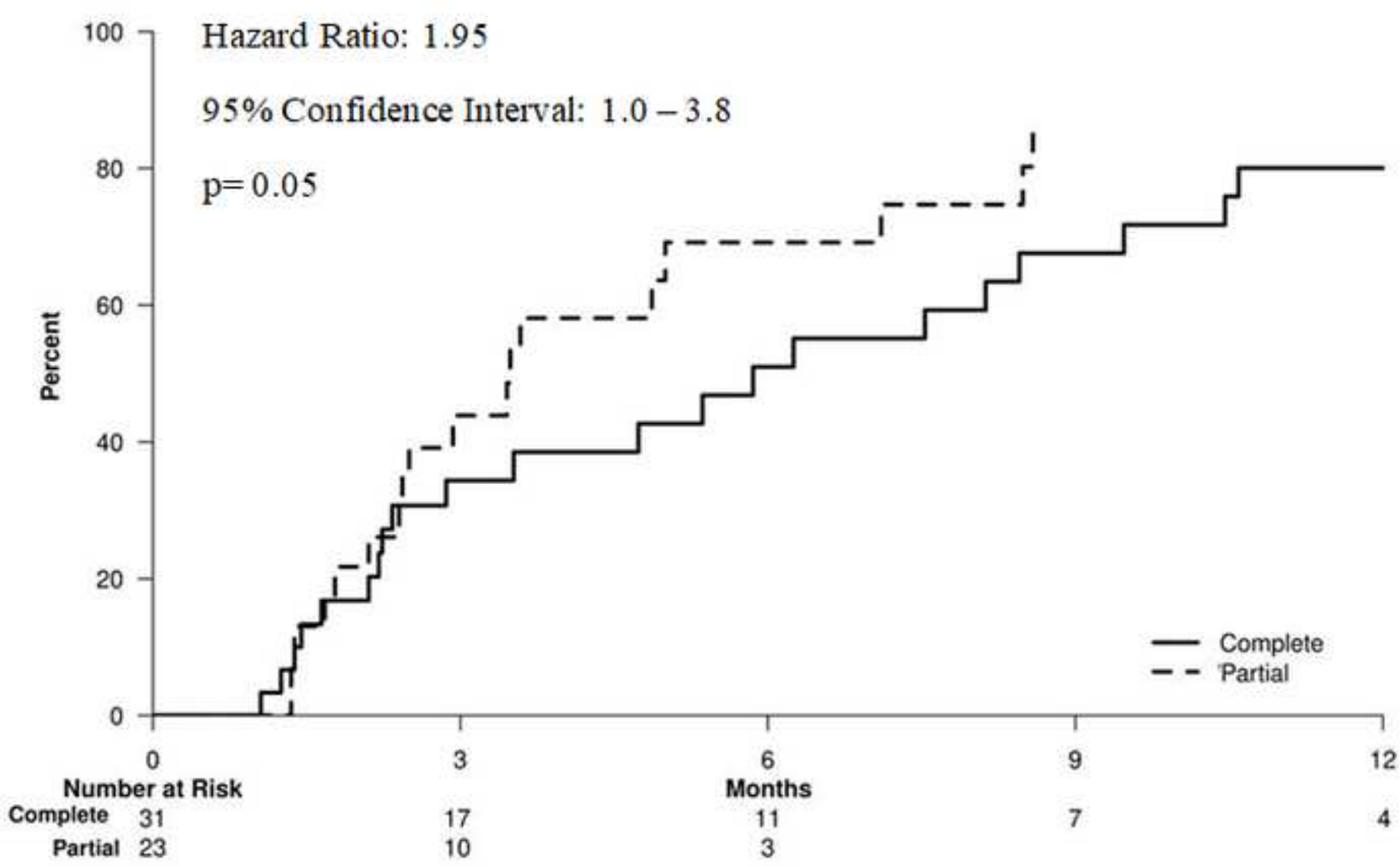


Figure 3

Click here to access/download;Figure;Fig3.tif

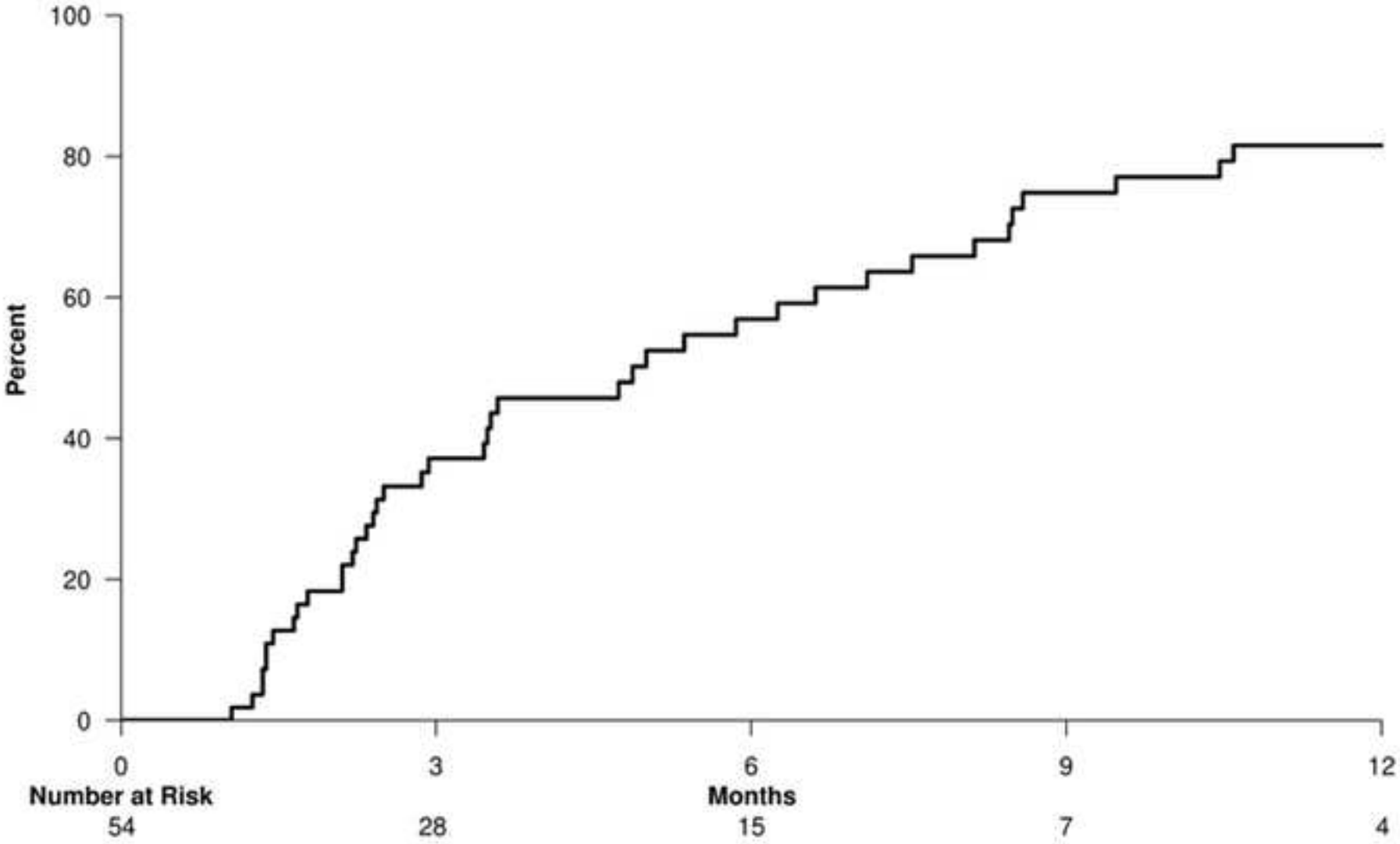
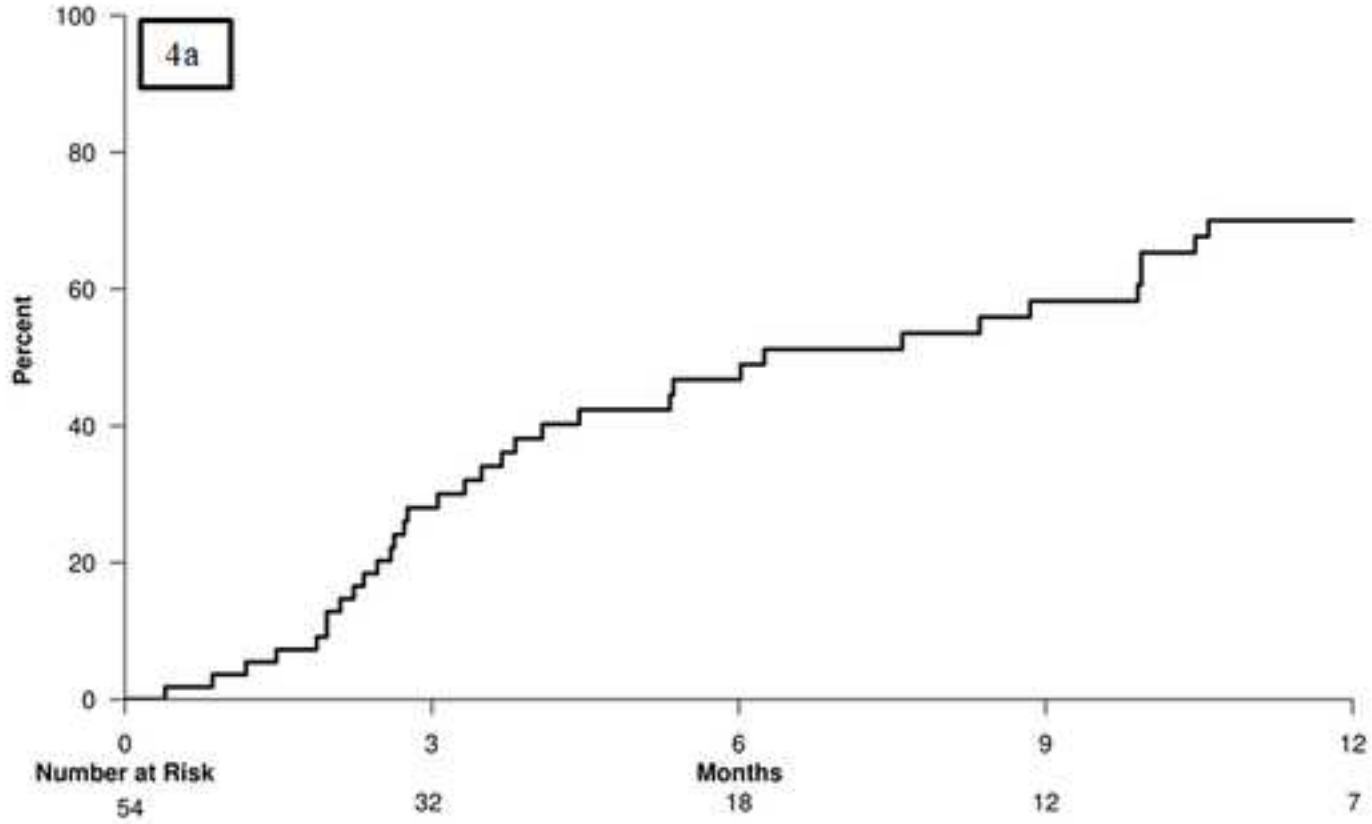


Figure 4

Click here to access/download;Figure;Fig4.tif



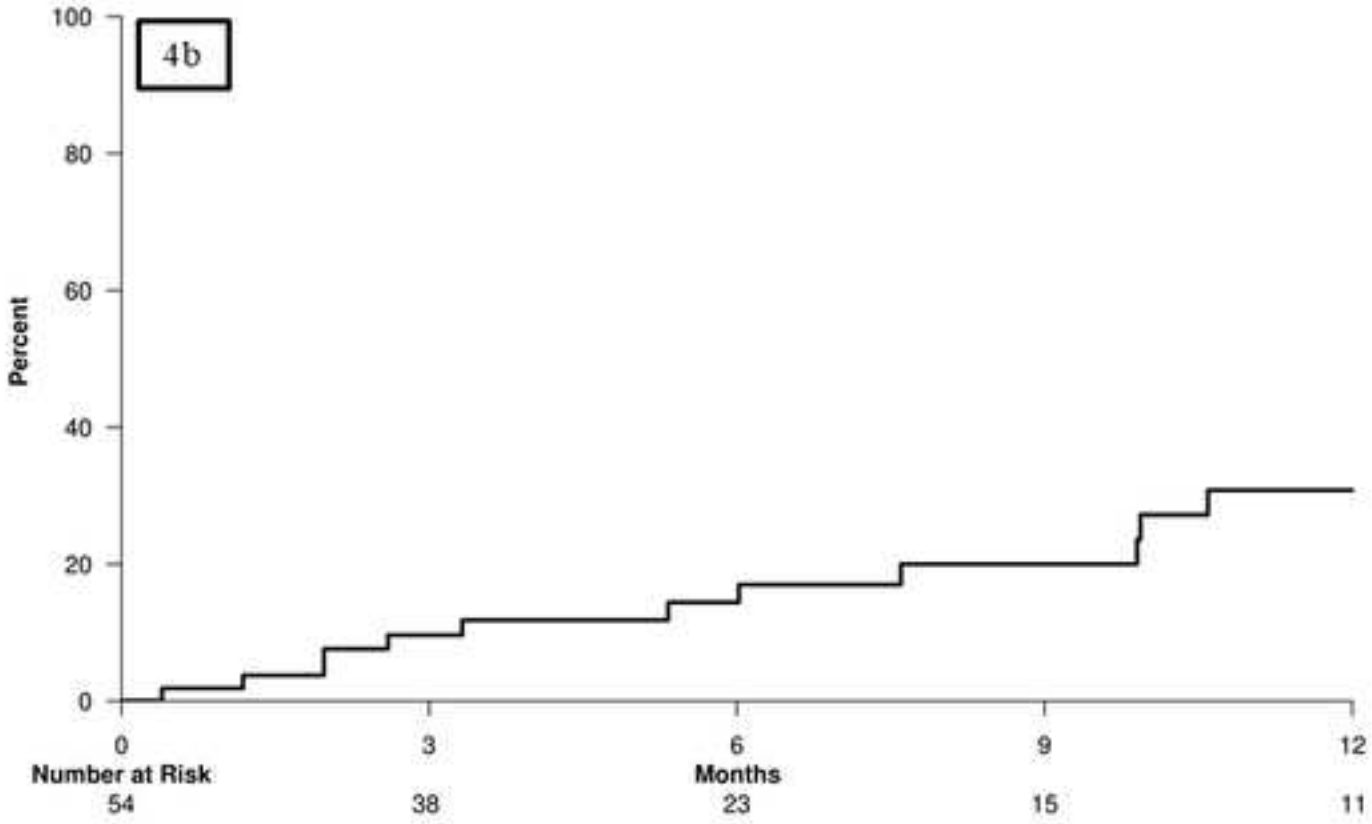


Figure 5

Click here to access/download;Figure;Fig5.tif

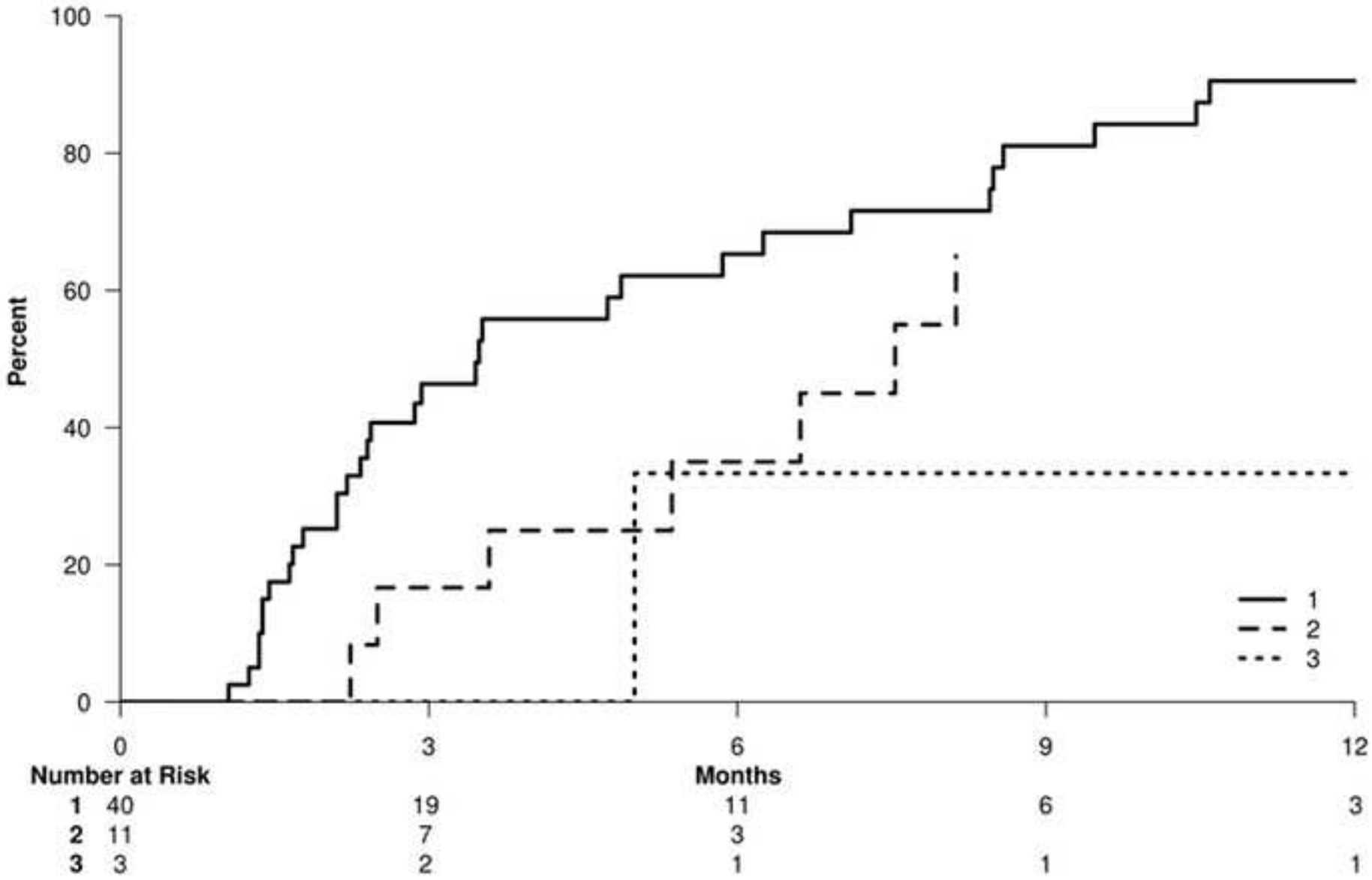
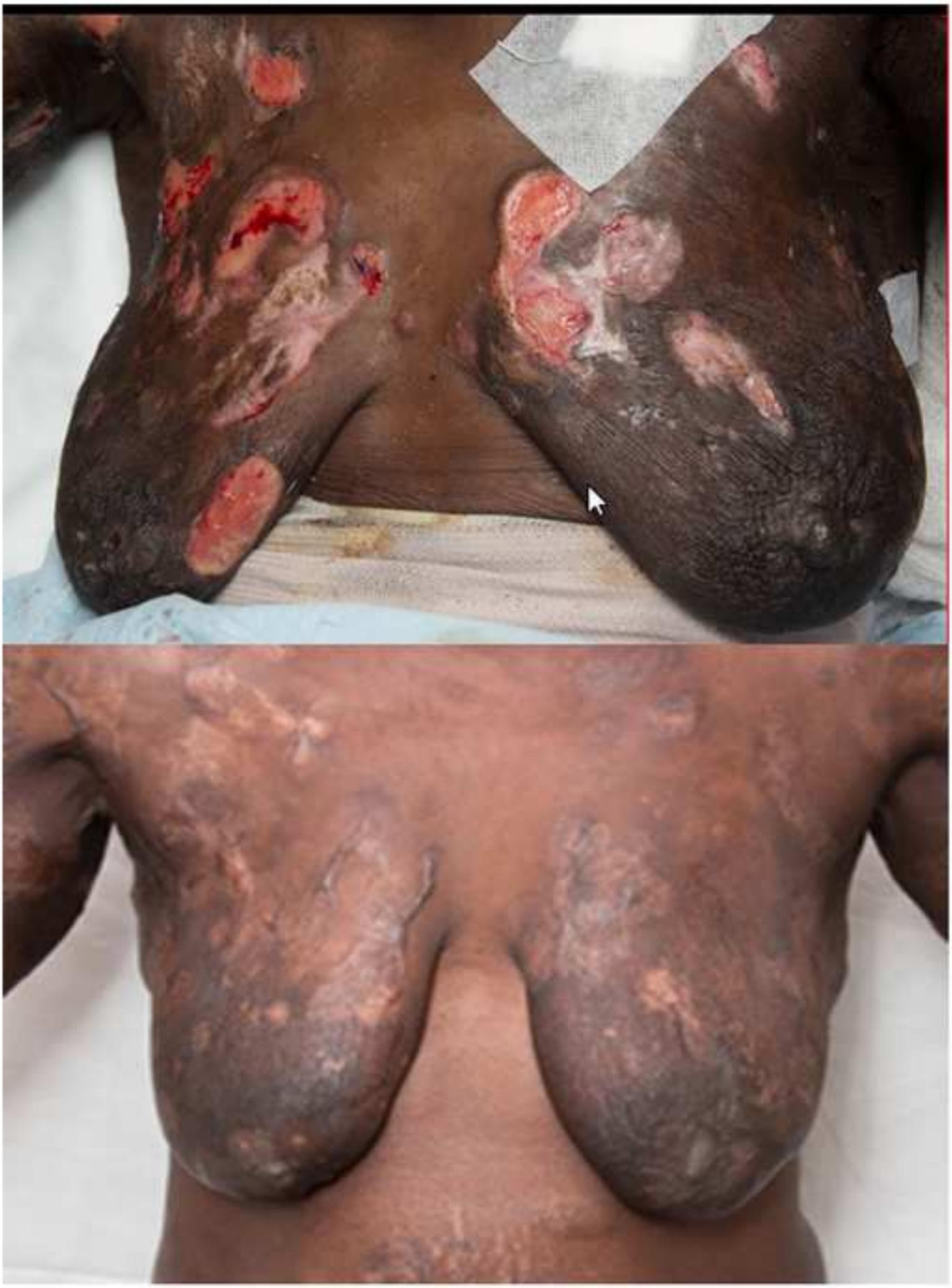


Figure 6

Click here to access/download;Figure;Fig6.tif



Patients	N=40
Age	
Median	67.0
Range	(33.0 – 93.0)
Gender	
F	12 (30.0%)
M	28 (70.0%)
HTSEBT Course	
Single	26 (65.0%)
Multiple	14 (35.0%)
Courses	N=57
ECOG at Treatment	
0	13 (22.8%)
1	33 (57.9%)
2	6 (10.5%)
3	5 (8.8%)
Stage	
Unknown	4 (7.0%)
IA	1 (1.8%)
IB	4 (7.0%)
IIB	6 (10.5%)
III	2 (3.5%)
IVA	38 (66.7%)
IVB	2 (3.5%)
T-Stage	
T1b	1 (1.8%)
T2	36 (63.2%)
T3	15 (26.3%)
T4	5 (8.7%)

Table 1. Patient demographics and characteristics of each patient prior to course of hypofractionated total skin electron beam therapy (HTSEBT).

Total Dose (Gy)	Number of Fractions				
	1	2	3	4	5
	Number of cases (total n=57)				
2.5	1				
3.5	1				
4	4	1			
4.5	4				
8		14		1	
9			2		
12			17	1	
12.5			1		
14				1	
15			1		1
16				4	
20					2
26.4				1	

Table 2. Dose and fractionation regimens

Response	# of Courses (N=57)	% of Assessed (N=54)
Complete	31	57.4
Partial	23	42.6
Not evaluable	3	-

Table 3. Response rate following HTSEBT.

Outcome	3 months	6 months	1 year
Cumulative Incidence of Progressive Skin Disease, %	37.2 (26.2 – 52.7)	56.9 (44.6 – 72.6)	81.5 (71.3 – 93.2)
Cumulative Incidence of Subsequent Treatment (focal or HTSEBT), %	28.0 (18.2 – 43.1)	46.8 (34.8 – 62.8)	70.0 (58.1 – 84.5)
Cumulative Incidence of Subsequent HTSEBT, %	9.62 (4.18– 22.2)	14.4 (7.2– 28.8)	30.8 (18.8– 50.5)

Table 4. Progressive skin disease and subsequent treatment outcomes (with 95% confidence intervals)