Local radiation and phototherapy are the most cost-effective treatments for stage IA mycosis fungoides: A comparative decision analysis model in the United States

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Background: Treatments for early-stage mycosis fungoides (MF) include topical steroids, topical nitrogen mustard, topical bexarotene, narrowband ultraviolet B (NBUVB), psoralen plus ultraviolet A (PUVA), and local radiation. The relative cost-effectiveness of each treatment given the differences in treatment failure, disease progression, and therapy escalation is not established.

Objective: To compare the cost-effectiveness (CE) of treatment options for stage IA MF.

Methods: A state-transition model was constructed with health states of stage IA to stage IV disease, no MF, and death. Treatment-specific remission and relapse rates were obtained from the literature. Lifetime costs were calculated by accounting for medications, office visits, laboratory monitoring, related procedures, work absences, and travel.

Results: The order of CE of the study treatments was determined to be as follows: local radiation, $225,399 for 15.40 life-years (LYs); NBUVB, $344,728 for 15.17 LYs; PUVA, $371,741 for 15.07 LYs; topical corticosteroids, $469,354 for 14.65 LYs; topical nitrogen mustard, $951,662 for 14.29 LYs; and topical bexarotene, 11,892,496 for 13.55 LYs. Sensitivity analyses confirmed the CE rankings.

Limitations: We assumed a constant probability of response, relapse rates, and 3-month treatment intervals.

Conclusions: Local radiation is the most cost-effective treatment for limited local disease, whereas phototherapy (NBUVB or PUVA) is cost-effective for generalized disease. Our findings can serve to inform future studies and recommendations regarding selection of therapy for stage IA MF. (J Am Acad Dermatol 2019;80:485-92.)

Key words: cost-effectiveness; mycosis fungoides; stage IA; treatment.

Mycosis fungoides (MF) is the most common form of primary cutaneous T-cell lymphoma.[1,2] The disease occurs most frequently in middle-aged and older adults and is staged on the basis of skin, blood, lymph node, and visceral involvement. Staging predicts prognosisand

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ranges from having no significant effect on overall survival to carrying a high risk of disease progression and death.[3-6]

Approximately 78% of patients with MF present with stage I (including 39% with stage IA) disease,[4] which is defined as patches or plaques covering less (stage IA) or more (stage IB) than 10% of the patient's body surface area (BSA)[7]; these patients are managed primarily by dermatologists with skin-directed therapy. Patients with stage IA disease have an overall life expectancy comparable to that of a sex-, age-, and race-adjusted population.[3] Common treatments for stage IA disease include topical medications such as topical corticosteroids, nitrogen mustard (NM), and topical bexarotene; phototherapy with narrowband ultraviolet B (NBUVB) or psoralen plus ultraviolet A (PUVA); and local radiation.

CAPSULE SUMMARY

- Little is known about the cost-effectiveness of treatment options for stage IA mycosis fungoides.
- We show that local radiation is the most cost-effective option, followed by narrowband ultraviolet B and psoralen plus ultraviolet A.
- Our findings can help with considerations in treatment selection and inform future comparative studies of therapy for stage IA mycosis fungoides.

Recommendations for choosing among skin-directed therapies are limited; stepwise therapeutic recommendations are not available owing to a lack of comparative studies and the heterogeneity of study design, outcome measures, and patient selection.[8,9] Given the lack of clear guidelines, it is important to consider the differing characteristics of treatment options, such as efficacy, adverse events, indication, and cost, when selecting therapy. We performed a decision analysis from a restricted societal perspective of treatments for stage IA MF by using the available literature on treatment efficacy, cost, risk of advancing disease, and escalation of therapy. In doing so, we introduce CE as another consideration when selecting initial treatment for stage IA MF.

MATERIALS AND METHODS

Model overview

We used TreeAge Pro Healthcare (TreeAge Software, Inc, Williamstown, MA) to construct a model of lifetime cost and survival outcomes of each initial treatment option for stage IA MF. We considered topical bexarotene, topical NM, topical corticosteroids, local radiation, NBUVB, and PUVA as possible treatment options. A state-transition model was chosen to represent the decision process, with iterative cycles of treatment, clearance, progression, and death. We included remission, continued stage IA MF, and progression to stage IB, stage IIA, stage IIB MF stage III, stage IV MF, or death as health states (Fig 1). The decision nodes for each state were (1) survive to receive treatment or die, corresponding to age- and stage-dependent mortality rates, (2) in the case of those who survive to receive treatment, achieve complete remission according to treatment-specific efficacy or have continued disease, and (3) in the case of those with continued disease, maintain stable disease or progress to advanced disease.

All patients began in the stage IA MF health state at the age of 59 years, which was the average age of MF diagnosis.[4] Patients who progressed to subsequent stages of MF (stages IB, IIA, IIB, III, and IV) underwent escalated treatment options, including PUVA (stage IB), NBUVB (stage IB), oral bexarotene (stage IB), methotrexate (stage IB/IIA/IIB), vorinostat (stage IB-IV), romedepsin (stage IIB-IV), pralatrexate (stage IIB-IV), total skin electron beam therapy (stage IB-III), extracorporeal photophoresis (stage III-IV), pentostatin (stage IV), brentuximab (stage IV), alemtuzumab (stage IV), and stem cell transplantation (stage IV). The cost and efficacy of escalated therapy were calculated as an average of the cost and efficacy of the applicable treatment options.

Patients who experienced complete remission and who entered the no-MF stage had a baseline risk of death corresponding to that in the 2014 US mortality tables.[10] Those in the no-MF stage could continue to be clear of MF or relapse and re-enter the stage IA health state based on relapse rates in the literature.[4] Patients who advanced to stages IB to IV from stage IA were assumed to remain in that advanced stage or die at age- and stage-dependent mortality rates. Death was the final absorbing health state (Fig 1).

Health benefits

Rates and time to complete remission and relapse were abstracted from randomized controlled trials when available and/or weighted analyses of retrospective cohort studies (Table I[11-39]). We searched the PubMed database for all studies evaluating the efficacy of the included treatment modalities for MF up to December 19, 2016. The search was

Abbreviations used:

BSA:	body surface area
CE:	cost-effectiveness
FDA:	Food and Drug Administration
LY:	life-year
MF:	mycosis fungoides
NBUVB:	narrowband ultraviolet B
NM:	nitrogen mustard
PSA:	probabilistic sensitivity analysis
PUVA:	psoralen ultraviolet A

performed by using the key words *mycosis fungoides*, *cutaneous T-cell lymphoma*, *efficacy*, and nomenclature variations of each of the treatment modalities. The text and references of the returned studies were searched for other relevant sources. With the exception of studies in which information was available only for stage I disease,[14,15,18,19,25,30,32-34,38] stage IA MF–specific rates and times to complete response and relapse were extracted for the 6 treatment options. When more than 1 complete response rate or relapse rate for each therapy was available from the literature, we used Comprehensive Meta Analysis software (version 3, Biostat, Engelwood, NJ) to combine the information for an overall complete response and relapse rate (Supplemental Table I[17-32]; available at http://www.jaad.org).

There are several large cohort studies that provide overall and disease-specific survival estimations for patients with MF.[3-6] We based our cycle probabilities of overall survival and progression on the largest and most recent of these.[4] The probability of clearance for a particular treatment was assumed to be constant, regardless of the number of cycles elapsed. Some treatments, namely, PUVA and local radiation, have an upper limit on treatments, and in this model the efficacy of that treatment was set to 0 after 16 three-month cycles (384 treatments) with PUVA and 6 total treatments (1 per cycle) with local radiation.[40,41] For all therapeutic modalities, the number of treatments received by patients in the simulation varied in a distribution. For radiation and PUVA, the majority of patients received far fewer treatments than the limit.

No information of health-related quality of life was available for the varying health states; thus, overall life expectancy was used as the measure of health benefit. The risk of death at each health state was calculated combining baseline age-adjusted rates from the US mortality life tables and MF stage-dependent mortality rates from the literature. A discount of 3% was placed on future life-years (LYs) gained.[42]

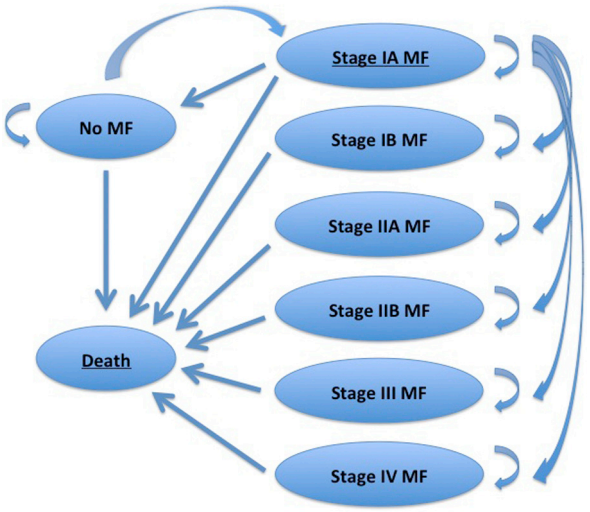

Fig 1. State-transition diagram. Patients entered the model with stage IA mycosis fungoides (MF); death was the absorbing state.

Costs

The costs of each treatment for stage IA MF (topical bexarotene, topical NM, topical corticosteroids, local radiation, NBUVB, and PUVA) were calculated from a restricted societal perspective to include the cost of medications, office visits/hospitalizations, laboratory monitoring, related procedures for a treatment duration of 3 months, work missed, and transportation/parking costs (Table II[43,44]). All costs were calculated in US dollars. The regimen (based on clinical practice) of each treatment is detailed in Supplemental Table II (available at http://www.jaad.org). Approximate regimens and costs of advanced therapy for advanced-stage MF were estimated in a similar fashion. We assumed a prototypical patient of 70 kg with a BSA of 1.75 m^2 and an affected area of up to 10% of BSA, which is the upper limit of stage IA MF.[45] Each month was assumed to contain 30 days and each cycle was assumed to last for 3 months (12 weeks). The fingertip unit was used; it was assumed to equal 0.46 g of ointment, with 0.6 FTU (the equivalent of 0.8% of BSA) required to cover the palm and fingers.[7,46]

Costs for medications were calculated by using the wholesale acquisition cost.[43] The cost of corticosteroid was calculated by using that of the least expensive class I topical corticosteroids. Costs for office visits, treatment sessions, and laboratory monitoring were obtained from the 2016 Medicare National Median Physician Reimbursement Schedule and 2017 Clinical Diagnostic Laboratory Fee Schedule midpoint fees.[44,47] Searches were made by using Current Procedural Terminology codes.[44] The cost of dermatology visits was conservatively

Table I. Per-cycle probabilities for complete remission and relapse for each treatment option for patients with stage IA mycosis fungoides

Treatment option	Baseline probabilities for complete remission,* (time)	Standard deviation, distribution used for sensitivity analysis	Baseline probabilities for relapse,* (time)	Standard deviation, distribution used for sensitivity analysis	References
Topical corticosteroids	63% (9 mo)	0.03, beta	40% (9 mo)	0.03, beta	11
Topical nitrogen mustard	36% (9 mo)	0.029, beta	34% (12 mo)	0.038, beta	12, 13
Topical bexarotene	24% (4.7 mo)	0.048, beta	50% (3.25 mo)	0.111, beta	14, 15
PUVA	65% (7.2 mo)	0.034, beta	55% (32.5 mo)	0.057, beta	16-20
NBUVB	78% (12.3 mo)	0.039, beta	41% (22 mo)	0.036, beta	17-32
Local radiation	94% (9.3 mo)	0.015, beta	11% (9.25 mo)	0.048, beta	33-39

NBUVB, Narrowband ultraviolet B; *PUVA*, psoralen plus ultraviolet A.
*Compiled from the literature; multiple studies were compiled with meta-analysis techniques.

Table II. Cost for 3-month cycle by treatment option

Treatment option	Baseline cost	Standard deviation, distribution used for sensitivity analysis	References
Topical corticosteroids	$1214	$250, gamma	43, 44
Topical nitrogen mustard	$17,469	$1500, gamma	43, 44
Topical bexarotene	$384,059	$5000, gamma	43, 44
PUVA	$10,582	$200, gamma	43, 44
NBUVB	$5604	$500, gamma	43, 44
Local radiation	$3484	$200, gamma	43, 44

NBUVB, Narrowband ultraviolet B; *PUVA*, psoralen plus ultraviolet A.

calculated by using level III Expanded Problem Focused return visits. The costs of work missed on account of care and transport were based on the US Department of Labor July 2017 national average hourly wage.[48] All unit costs are presented in Supplemental Tables II and III (available at http://www.jaad.org), and a sample cost calculation is presented in Supplemental Table IV (available at http://www.jaad.org). Future costs were discounted at an annual rate of 3%.[42]

Calculation of CE

The model was created with 3-month cycles, corresponding to the shortest treatment and follow-up length, and run for 160 cycles (approximately 40 years). The model was run with Monte Carlo first-order microsimulation with a sampling of 100,000 individuals. Incremental CE ratios were calculated by using the difference in total simulated cost divided by the difference in total number of LYs. Treatments that demonstrated higher cost and lower health effectiveness or showed higher incremental CE ratios than other treatments were considered "dominated."

One-way and 2-way sensitivity analyses were performed individually, then together, on values within the range of the 95% confidence interval for complete remission rate and relapse rate for local radiation and phototherapy. Probabilistic sensitivity analysis was done with distributions of the probability of complete remission, relapse, and cost for each of the 6 treatment options (Tables I and II). A probabilistic sensitivity analysis acceptability curve was also performed, evaluating the dominance of each treatment strategy at a willingness-to-pay threshold from $0 to $400,000.

All data utilized in this study were obtained from publically available sources. Review by the Beth Israel Deaconess Medical Center Institutional Review Board was waived.

RESULTS

Local radiation was the most cost-effective and the undominated strategy ($225,399 for 15.40 LYs), followed by NBUVB ($344,728 for 15.17 LYs), PUVA ($371,741 for 15.07 LYs), topical corticosteroids ($469,354 for 14.65 LYs), topical NM ($951,662 for 14.29 LYs), and topical bexarotene ($11,892,496 for 13.55 LYs) (Table III and Fig 2).

Effectiveness of treatment ranged from 13.55 to 15.40 LYs. Local radiation was the option with the highest effectiveness (15.40 LYs), whereas topical bexarotene was the least effective option (13.55 LYs). Topical bexarotene was the most expensive

Table III. Aggregate health benefits and cost by treatment option with distribution range for stage IA mycosis fungoides

Treatment option	Cost (95% confidence interval)	Effectiveness in years (95% confidence interval)
Local radiation	$225,399 ($1742-$2,030,372)	15.40 (2.53-23.03)
NBUVB	$344,728 ($8365-$2,742,049)	15.17 (2.29-23.19)
PUVA	$371,741 ($5291-$2,652,559)	15.07 (2.29-22.95)
Topical corticosteroids	$469,354 ($4167-$3,055,679)	14.65 (2.06-22.95)
Topical nitrogen mustard	$951,662 ($60,374-$3,484,453)	14.29 (2.06-22.87)
Topical bexarotene	$11,892,496 ($1,543,984-$25,006,532)	13.55 (1.82-22.54)

NBUVB, Narrowband ultraviolet B; *PUVA*, psoralen plus ultraviolet A.

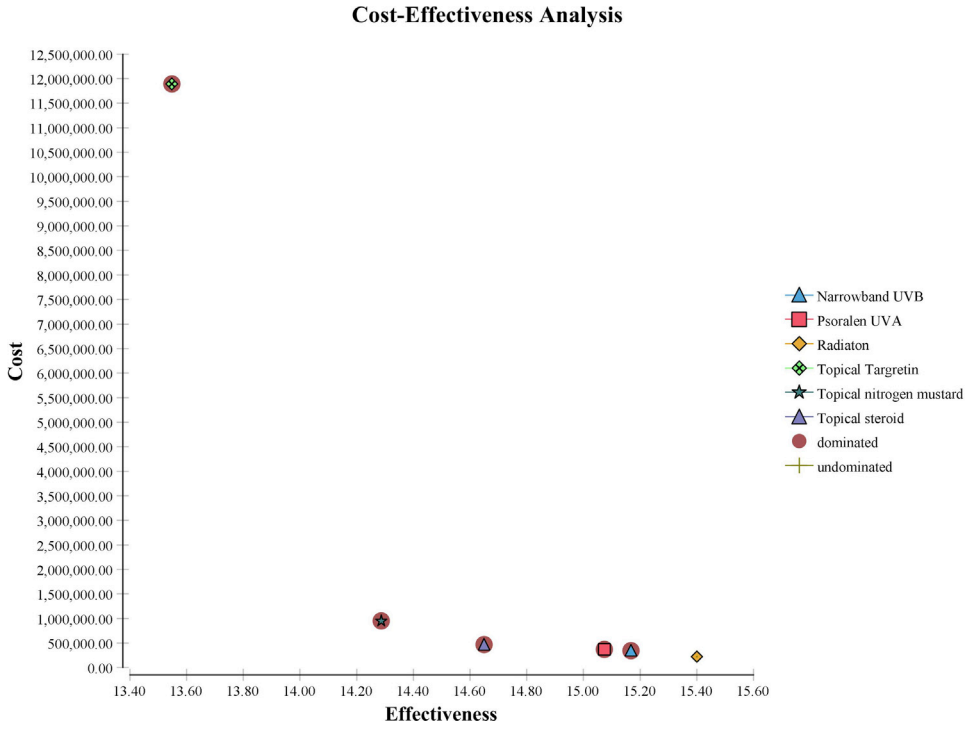

Fig 2. Lifetime cost-effectiveness of stage IA mycosis fungoides treatment options: radiation, narrowband ultraviolet light therapy, psoralen plus ultraviolet A (UVA) light therapy, topical corticosteroids, topical nitrogen mustard, and topical bexarotene. *UVB*, Ultraviolet B.

treatment option ($11,892,496), whereas local radiation was the least expensive ($225,399).

Both 1-way and 2-way sensitivity analyses altering effectiveness and relapse rates of local radiation separately and then together over intervals within their 95% confidence range validated dominance of the local radiation strategy. Probabilistic sensitivity analysis (PSA) demonstrated a significant overlap between the effectiveness and costs of NBUVB and PUVA. PSA analysis using distributions of the probability of remission, relapse, and costs for the 6 treatment options confirmed the order of CE. The PSA acceptability curve also confirmed the dominance of local radiation across all willingness-to-pay thresholds from $0 to $400,000 (Fig 3).

DISCUSSION

We have demonstrated that local radiation is the most cost-effective treatment option for stage IA MF from a restricted societal perspective among active treatment options, taking into consideration the risk for progression of disease and therapy. NBUVB and PUVA follow, respectively, and topical bexarotene was the least cost-effective treatment option.

Our study demonstrates that whereas effectiveness varied among treatment options (13.55-15.40 LYs), the main driver of CE among the treatment options was cost ($225,399-$11,892,496). Given the large variation in cost with smaller differences in efficacy, CE deserves careful consideration

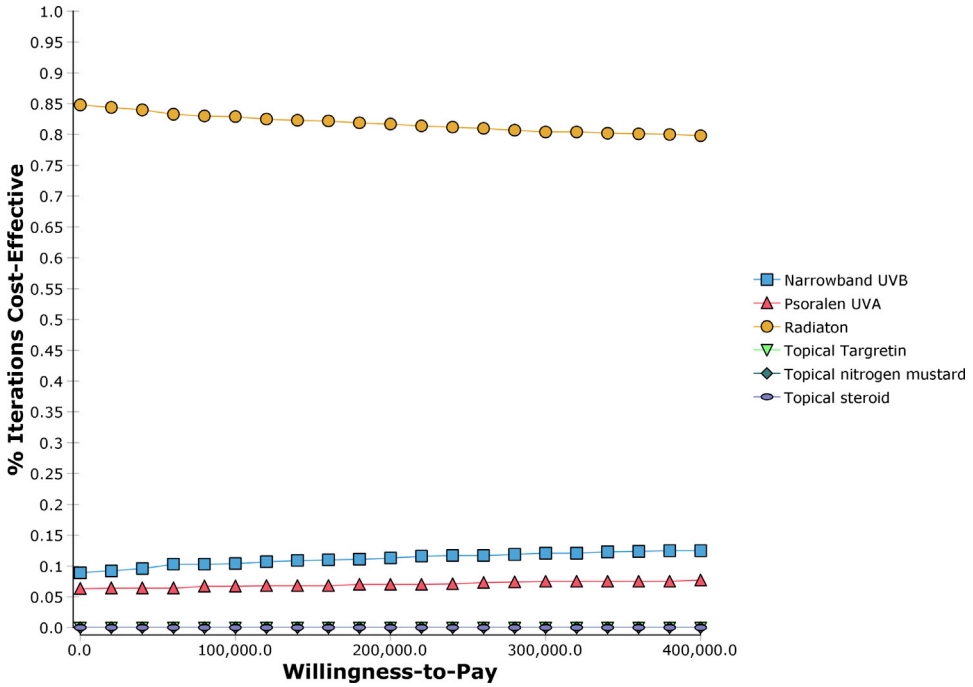

Fig 3. Probabilistic sensitivity analysis acceptability curve showing dominance of radiation strategy at each willingness-to-pay threshold. *UVA*, Ultraviolet A; *UVB*, ultraviolet B.

when selecting treatment options for early-stage MF.

As the undominated strategy in our model, local radiation is one of the most effective treatments for early-stage MF and is recommended for unilesional disease and disease with limited BSA involvement.[49] In our study, the rates and time to relapse and remission were calculated on the basis of studies in the literature in which radiotherapy was indicated and used in patients with both unilesional and multilesional disease.[33-39] Local radiation has the benefit of being able to penetrate deep lesions with minimal side effect profiles. Reports in the literature of skin breakdown, scarring, and secondary cutaneous malignancies with limited exposure are rare.[49,50] However, use of local radiation may be tempered by accessibility, convenience, and patient preferences for other treatment options.

NBUVB and PUVA, which are important treatment options for generalized cutaneous MF, were ranked second and third, respectively, in terms of CE in our study. NBUVB had a slightly higher efficacy at a slightly lower cost, but the 2 options demonstrated comparable CE ratios. PSA demonstrated significant overlap between the 2 treatment options. As such, from a CE perspective, it is difficult to choose between the 2 options without drawing upon other clinical parameters. Currently, PUVA is recommended over NBUVB for thicker or folliculotropic lesions, although PUVA carries a risk of secondary skin carcinogenicity and limited exposure is recommended.[41,51] Other considerations such as the relative contraindication of PUVA but not NBUVB in pregnant patients and those with severe liver disease can aid in treatment decision making.[51] A limitation of phototherapy is accessibility; home NBUVB units are available to patients; however, because of varying regimens and limited literature, this option was not explored in our study.

Although topical NM (mechlorethamine hydrochloride) in gel formulation was only approved in 2013 by the US Food and Drug Administration (FDA) for stage IA/IB MF previously treated with skin-directed therapy, it is one of the earliest treatments for the disease.[52] As with PUVA, long-term remissions with use of NM have been reported in a subset of patients.[12] In our study, topical NM was ranked second to last in CE. Compared with topical corticosteroids, topical NM was far more expensive ($951,662 for NM vs $469,354 for corticosteroids) for an inferior efficacy (14.29 LYs for NM vs 14.65 LYs for corticosteroids), supporting indications for topical NM only after trial of another topical therapy.

Bexarotene (Targretin [Ligand Pharmaceuticals, La Jolla, California]) is a synthetic retinoid that has been approved by the FDA for refractory stage IA and IB MF or for patients who have otherwise not tolerated other therapies.[14] It is expensive (wholesale acquisition cost, $486/g), and the response rates are low.[53] Here we demonstrated that topical

bexarotene has the least favorable CE ratio, which supports its use only in refractory disease or when other treatments are not tolerated.

We made some simplifying assumptions for the purposes of the study, which should be taken into account. We assumed a constant probability of treatment responses and relapse rates. Only active treatment options were examined. Although the European Organization of Research and Treatment of Cancer notes that close observation for stage IA MF is also an option, information on complete response and relapse is limited for those who do not receive any treatment.[8,9] Our study is limited to FDA-approved topical treatment options for MF, but off-label uses of agents such as tazarotene merit future studies.[54,55] In addition, although combination therapies can be used in clinical practice, only monotherapies were examined in this study owing to limitations in the literature. Our model did not consider instances in which relapsed patients go directly from no MF to a more advanced stage and vice versa. All treatment courses were assumed to have a duration of 3 months (12 weeks). Cost analysis was based on an aggregate payer and societal perspective and does not reflect individual costs such as insurance copays. Other variables such as side effect profiles including secondary skin malignancies, patient preference, accessibility, and other clinical considerations were beyond the scope of this study.

Despite limitations to the scope of our model and data available in the literature, our study is, to our knowledge, the first decision analysis modeling CE as an additional factor for consideration in the treatment of stage IA MF. We incorporated all available information on societal costs, complete response rates, and relapse rates for each treatment. In our study, local radiation was the most cost-effective option, followed by phototherapy, and these options should be given first consideration for localized and generalized disease, respectively. The findings are compatible with what is observed in the clinical setting and may serve as a basis to help inform future studies and recommendations regarding selection of therapy for stage IA MF.

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REFERENCES

1. Bradford PT, Devesa SS, Anderson WF, Toro JR. Cutaneous lymphoma incidence patterns in the United States: a population-based study of 3884 cases. *Blood*. 2009;113(21):5064-5073.
2. Criscione VD, Weinstock MA. Incidence of cutaneous T-cell lymphoma in the United States, 1973-2002. *Arch Dermatol*. 2007;143(7):854-859.
3. Kim YH, Liu HL, Mraz-Gernhard S, Varghese A, Hoppe RT. Long-term outcome of 525 patients with mycosis fungoides and Sézary syndrome: clinical prognostic factors and risk for disease progression. *Arch Dermatol*. 2003;139(7):857-866.
4. Quaglino P, Pimpinelli N, Berti E, et al. Time course, clinical pathways, and long-term hazards risk trends of disease progression in patients with classic mycosis fungoides. *Cancer*. 2012;118(23):5830-5839.
5. Agar NS, Wedgeworth E, Crichton S, et al. Survival outcomes and prognostic factors in mycosis fungoides/Sézary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. *J Clin Oncol*. 2010;28(31):4730-4739.
6. van Doorn R, Van Haselen CW, van Voorst Vader PC, et al. Mycosis fungoides: disease evolution and prognosis of 309 Dutch patients. *Arch Dermatol*. 2000;136(4):504-510.
7. Olsen E, Vonderheid E, Pimpinelli N, et al. Revisions to the staging and classification of mycosis fungoides and Sézary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). *Blood*. 2007;110(6):1713-1722.
8. Weberschock T, Strametz R, Lorenz M. Interventions for mycosis fungoides. *Cochrane Database Syst Rev*. 2011;9.
9. Wu PA, Huang V, Bigby ME. Interventions for mycosis fungoides: critical commentary on a Cochrane Systematic Review. *Br J Dermatol*. 2014;170(5):1015-1020.
10. Social Security Administration. Actuarial life table. Available at: https://www.ssa.gov/oact/STATS/table4c6.html#ss. Accessed February 15, 2017.
11. Zackheim HS, Kashani-Sabet M, Amin S. Topical corticosteroids for mycosis fungoides: experience in 79 patients. *Arch Dermatol*. 1998;134(8):949-954.
12. Kim YH, Martinez G, Varghese A, Hoppe RT. Topical nitrogen mustard in the management of mycosis fungoides: update of the Stanford experience. *Arch Dermatol*. 2003;139(2):165-173.
13. Lessin SR, Duvic M, Guitart J, et al. Topical chemotherapy in cutaneous T-cell lymphoma: positive results of a randomized, controlled, multicenter trial testing the efficacy and safety of a novel mechlorethamine, 0.02%, gel in mycosis fungoides. *JAMA Dermatol*. 2013;149(1):25-32.
14. Heald P, Mehlmauer M, Martin AG, Crowley CA, Yocum RC, Reich SD, Worldwide Bexarotene Study Group. Topical bexarotene therapy for patients with refractory or persistent early-stage cutaneous T-cell lymphoma: results of the phase III clinical trial. *J Am Acad Dermatol*. 2003;49(5):801-815.
15. Breneman D, Duvic M, Kuzel T, Yocum R, Truglia J, Stevens VJ. Phase 1 and 2 trial of bexarotene gel for skin-directed treatment of patients with cutaneous T-cell lymphoma. *Arch Dermatol*. 2002;138(3):325-332.
16. Querfeld C, Rosen ST, Kuzel TM, et al. Long-term follow-up of patients with early-stage cutaneous T-cell lymphoma who achieved complete remission with psoralen plus UV-A monotherapy. *Arch Dermatol*. 2005;141(3):305-311.
17. Ponte P, Serrão V, Apetato M. Efficacy of narrowband UVB vs. PUVA in patients with early-stage mycosis fungoides. *J Eur Acad Dermatol Venereol*. 2010;24(6):716-721.
18. Diederen PV, van Weelden H, Sanders CJ, Toonstra J, van Vloten WA. Narrowband UVB and psoralen-UVA in the treatment of early-stage mycosis fungoides: a retrospective study. *J Am Acad Dermatol*. 2003;48(2):215-219.

19. El-Mofty M, El-Darouty M, Salonas M, et al. Narrow band UVB (311 nm), psoralen UVB (311 nm) and PUVA therapy in the treatment of early-stage mycosis fungoides: a right—left comparative study. *Photodermatol Photoimmunol Photomed*. 2005;21(6):281-286.
20. Ahmad K, Rogers S, McNicholas PD, Collins P. Narrowband UVB and PUVA in the treatment of mycosis fungoides: a retrospective study. *Acta Derm Venereol*. 2007;87(5):413-417.
21. Resnik KS, Vonderheid EC. Home UV phototherapy of early mycosis fungoides: long-term follow-up observations in thirty-one patients. *J Am Acad Dermatol*. 1993;29(1):73-77.
22. Gathers RC, Scherschun L, Malick F, Fivenson DP, Lim HW. Narrowband UVB phototherapy for early-stage mycosis fungoides. *J Am Acad Dermatol*. 2002;47(2):191-197.
23. Dereure O, Picot E, Comte C, Bessis D, Guillot B. Treatment of early stages of mycosis fungoides with narrowband ultraviolet B. *Dermatology*. 2009;218(1):1-6.
24. Gökdemir G, Barutcuoğlu B, Sakız D, Köşlü A. Narrowband UVB phototherapy for early-stage mycosis fungoides: evaluation of clinical and histopathological changes. *J Eur Acad Dermatol Venereol*. 2006;20(7):804-809.
25. Hofer A, Cerroni L, Kerl H, Wolf P. Narrowband (311-nm) UV-B therapy for small plaque parapsoriasis and early-stage mycosis fungoides. *Arch Dermatol*. 1999;135(11):1377-1380.
26. Clark C, Dawe RS, Evans AT, Lowe G, Ferguson J. Narrowband TL-01 phototherapy for patch-stage mycosis fungoides. *Arch Dermatol*. 2000;136(6):748-752.
27. Pavlotsky F, Barzilai A, Kasem R, Shpiro D, Trau H. UVB in the management of early stage mycosis fungoides. *J Eur Acad Dermatol Venereol*. 2006;20(5):565-572.
28. Boztepe G, Sahin S, Ayhan M, Erkin G, Kolemen F. Narrowband ultraviolet B phototherapy to clear and maintain clearance in patients with mycosis fungoides. *J Am Acad Dermatol*. 2005;53(2):242-246.
29. Ghodsi SZ, Hallaji Z, Balighi K, Safar F, Chams-Davatchi C. Narrow-band UVB in the treatment of early stage mycosis fungoides: report of 16 patients. *Clin Exp Dermatol*. 2005;30(4):376-378.
30. Kural Y, Onsun N, Aygin S, Demirkesen C, Büyükbabani N. Efficacy of narrowband UVB phototherapy in early stage of mycosis fungoides. *J Eur Acad Dermatol Venereol*. 2006;20(1):103-104.
31. Ramsay DL, Lish KM, Yalowitz CB, Soter NA. Ultraviolet-B phototherapy for early-stage cutaneous T-cell lymphoma. *Arch Dermatol*. 1992;128(7):931-933.
32. Brazzelli V, Antoninetti M, Palazzini S, Prestinari F, Borroni G. Narrow-band ultraviolet therapy in early-stage mycosis fungoides: study on 20 patients. *Photodermatol Photoimmunol Photomed*. 2007;23(6):229-233.
33. Thomas TO, Agrawal P, Guitart J, et al. Outcome of patients treated with a single-fraction dose of palliative radiation for cutaneous T-cell lymphoma. *Int J Radiat Oncol Biol Phys*. 2013;85(3):747-753.
34. Cotter GW, Baglan RT, Wasserman TH, Mill W. Palliative radiation treatment of cutaneous mycosis fungoides—a dose response. *Int J Radiat Oncol Biol Phys*. 1983;9(10):1477-1480.
35. Micaily B, Miyamoto C, Kantor G, et al. Radiotherapy for unilesional mycosis fungoides. *Int J Radiat Oncol Biol Phys*. 1998;42(2):361-364.
36. Wilson LD, Kacinski BM, Jones GW. Local superficial radiotherapy in the management of minimal stage IA cutaneous T-cell lymphoma (mycosis fungoides). *Int J Radiat Oncol Biol Phys*. 1998;40(1):109-115.
37. Heald PW, Glusac EJ. Unilesional cutaneous T-cell lymphoma: clinical features, therapy, and follow-up of 10 patients with a treatment-responsive mycosis fungoides variant. *J Am Acad Dermatol*. 2000;42(2):283-285.
38. Neelis KJ, Schimmel EC, Vermeer MH, Senff NJ, Willemze R, Noordijk EM. Low-dose palliative radiotherapy for cutaneous B-and T-cell lymphomas. *Int J Radiat Oncol Biol Phys*. 2009;74(1):154-158.
39. Piccinno R, Caccialanza M, Percivalle S. Minimal stage IA mycosis fungoides. Results of radiotherapy in 15 patients. *J Dermatolog Treat*. 2009;20(3):165-168.
40. Specht L, Dabaja B, Illidge T, Wilson LD, Hoppe RT, Group IL. 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):32-39.
41. Stern RS. The risk of squamous cell and basal cell cancer associated with psoralen and ultraviolet A therapy: a 30-year prospective study. *J Am Acad Dermatol*. 2012;66(4):553-562.
42. Hunink MGM, Glasziou PP, Siegel JE, et al. *Decision Making in Health and Medicine with CD-ROM: Integrating Evidence and Values*. Cambridge, UK: Cambridge University Press; 2001.
43. Truven Health Analytics Micromedex Solutions. RED BOOK online search. Available at: http://www.micromedexsolutions.com/. Accessed February 15, 2017.
44. American Medical Association. *CPT* code/Relative Value search. Available at: https://apps.ama-assn.org/CptSearch/user/search/cptSearch.do. Accessed February 15, 2017.
45. Sacco JJ, Botten J, Macbeth F, Bagust A, Clark P. The average body surface area of adult cancer patients in the UK: a multicentre retrospective study. *PLoS One*. 2010;5(1):e8933.
46. Long CC, Finlay AY. The finger-tip unit—a new practical measure. *Clin Exp Dermatol*. 1991;16(6):444-447.
47. US Centers for Medicare and Medicaid Services. Clinical laboratory and physician fee schedule. Available at: http://www.cms.hhs.gov/home/medicare.asp. Accessed February 15, 2017.
48. US Department of Labor. Employment, hours, and earnings from the Current Employment Statistics survey (national). Available at: https://data.bls.gov/timeseries/CES0500000003?data_tool=XGtable. Accessed August 28, 2017.
49. Tandberg DJ, Craciunescu O, Kelsey CR. Radiation therapy for cutaneous T-cell lymphomas. *Dermatol Clin*. 2015;33(4):703-713.
50. Volden G, Larsen TE. Squamous cell carcinoma appearing in x-ray-treated mycosis fungoides. *Acta Derm Venereol*. 1977;57(4):341-343.
51. Olsen EA, Hodak E, Anderson T, et al. Guidelines for phototherapy of mycosis fungoides and Sézary syndrome: a consensus statement of the United States Cutaneous Lymphoma Consortium. *J Am Acad Dermatol*. 2016;74(1):27-58.
52. Jawed SI, Myskowski PL, Horwitz S, Moskowitz A, Querfeld C. Primary cutaneous T-cell lymphoma (mycosis fungoides and Sézary syndrome): part II. Prognosis, management, and future directions. *J Am Acad Dermatol*. 2014;70(2):223.e1-223.e17.
53. Fernandez-Guarino M. Emerging treatment options for early mycosis fungoides. *Clin Cosmet Investig Dermatol*. 2013;6:61.
54. Besner Morin C, Roberge D, Turchin I, Petrogiannis-Haliotis T, Popradi G, Pehr K. Tazarotene 0.1% cream as monotherapy for early-stage cutaneous T-cell lymphoma. *J Cutan Med Surg*. 2016;20(3):244-248.
55. Apisarnthanarax N, Talpur R, Ward S, Ni X, Kim HW, Duvic M. Tazarotene 0.1% gel for refractory mycosis fungoides lesions: an open-label pilot study. *J Am Acad Dermatol*. 2004;50(4):600-607.

Supplemental Table I. Example of meta-analysis technique calculations for time and rates of relapse and complete remission for NBUVB

Reference	Size of cohort of patients with stage IA MF, n	Complete remission rate, %	Time to remission, mo	Relapse rate, %	Time to relapse, mo
Resnik and Vonderheid, 1993[21]	31	74		77	51
Ponte et al, 2010[17]	6	83	11.5	83.3	18.9
Diederen et al, 2003[18,*]	21	81	14		24.5
El-Mofty et al, 2005[19,*]	10	80			
Ahmad et al, 2007[20]	10	60			
Gathers et al, 2002[22]	12	67	12	31	13
Dereure et al, 2009[23]	17	88	2.3	39	20.1
Gökdemir et al, 2006[24]	6	100	3	4	7
Hofer et al, 1999[25,*]	6	83		100	6
Clark et al, 2000[26]	8	75	2.1	50	20
Pavlotsky et al, 2006[27]	32	84		35	
Boztepe et al, 2005[28]	14	78		27	26
Ghodsi et al., 2005[29]	16	75		50	4.5
Kural et al., 2006[30,*]	23	83		30	8
Ramsay et al, 1992[31]	32	71	5	20	22
Brazzelli et al., 2007[32,*]	20	90			8
Random effects event rate		0.78 (0.72-0.83)		0.41 (0.28-0.56)	

Blank cells indicate that no information was available.
MF, Mycosis fungoides; *NBUVB*, narrowband ultraviolet B.
*Stage IA—specific data were not available; stage I disease data were used.

Supplemental Table II. Regimens of first-line treatment options

Treatment option	Medications	Visits
Topical bexarotene	Bexarotene: daily for the first wk, BID for the next wk, TID for the next 4 wk and 4 d, QID for the next 4 wk, then 2 wk with no therapy	Dermatology visit and follow-up at 3 mo
Topical nitrogen mustard	Mechlorethamine hydrochloride, 0.016% gel once daily for 3 mo	Dermatology visit and follow-up at 3 mo
Topical corticosteroids	Betamethasone dipropionate 0.05% ointment BID for a mo, then 2 wk of therapy followed by 2 wk of no therapy for 2 mo	Dermatology visit and follow-up at 3 mo
Local radiation	Local radiation: 12 Gy in 3 fractions	Dermatology visit and follow-up Radiation oncology visit initial and follow-up Radiation oncology treatment planning Radiation treatment delivery Continuing medical physics consultation Radiation treatment management
NBUVB	NBUVB: 3 times/wk for 3 mo	Dermatology visit and follow-up every 4 wk
PUVA	UVA Phototherapy: twice weekly for 3 mo Methoxalen, 30 mg each session	Dermatology visit and follow-up every 4 wk Biannual eye examinations, yearly fundus photograph

The following assumptions have been applied throughout: each regimen duration is 3 months or 90 days; the affected area is equal to 10% of the body surface area; the palm and fingers are equal to 0.8% BSA; of the body surface area; 1 fingertip unit is equal to 0.46 g; 0.6 fingertip units is required to cover the palm and fingers (or 0.8% of body surface area).

BID, Twice a day; *NBUVB*, narrowband ultraviolet B; *PUVA*, psoralen plus ultraviolet A; *QID*, four times a day; *TID*, three times a day; *UVA*, ultraviolet A.

Supplemental Table III. Unit costs for medication, visits, treatment sessions, and laboratory monitoring for first-line treatment options

Indicator	Cost
Medications	Wholesale acquisition cost
Topical bexarotene 1% gel, 60 g	$29,159.06
Betamethasone dipropionate 0.05%, 50 g	$133.63
Mechlorethamine hydrochloride 0.016% gel, 60 g	$3355.00
Oxsoralen-Ultra, 10-mg capsules, 50 capsules	$4245.87
Items/CPT codes	Medicare reimbursement cost
Dermatology visit level III/99213	$53.52
Radiation oncology consult/99243	$100.45
Radiation oncology follow-up/99212	$26.27
Radiation treatment delivery/77408/G6008	$201.58
Radiation oncology treatment planning, intermediate/77262	$119.29
Continuing medical physics consultation/77336	$91.91
Radiation treatment management/77431	$107.92
UVB therapy/96910	$83.5
PUVA therapy/96912	$106.82
Eye examination/92012	$94.35
Fundus photograph/92250	$89.75
Cost of missed work	Cost
2 h lost per session (of PUVA, NBUVB, or local radiation)	$26.36/h
Estimated transportation and parking costs for sessions of PUVA, NBUVB, or local radiation	$15

CPT, Current Procedural Terminology; *NBUVB*, narrowband ultraviolet B; *PUVA*, psoralen plus ultraviolet A; *UVB*, ultraviolet B.

Supplemental Table IV. Example of cost calculation for NBUVB

Regimen	Unit costs	Calculations	Subtotal
NBUVB: 3 times per wk for 3 mo	UVB therapy/96910: $83.5	$83.5/session × 3 sessions/wk × 12wks	$3006
Dermatology visit and follow-up every 4 wk	Dermatology visit level III/99213: $53.52	$53.52/visit × 3 visits	$160.56
Work missed: 2 h lost per session	$26.36/h	$26.36/h × 2 h/session × 36 sessions	$1897.92
Transportation and parking cost per session	$15/session	$15/session × 36 sessions	$540
Total cost			$5604.48

NBUVB, Narrowband ultraviolet B; *PUVA*, psoralen plus ultraviolet A; *UVB*, ultraviolet B.