Long term outcomes of mycosis fungoides and Sézary syndrome

Long term outcomes of 1263 patients with Mycosis fungoides and Sézary syndrome from 1982 to 2009

Rakhshandra Talpur, 1 Lotika Singh, 1 Seema Daulat, 1 Ping Liu, 2 Sarah Seyfer, 1 Tanya Trynosky, 1 Wei Wei, 2 Madeleine Duvic 1

1Departments of Dermatology and 2 Biostatistics, University of Texas M. D. Anderson Cancer Center, Houston, Texas

Abbreviated Title: Long term outcomes of mycosis fungoides and Sézary syndrome

Keywords: Mycosis Fungoides, Sézary syndrome, prognosis, lactate dehydrogenase, overall survival.

Grant Support: This research was supported by the NCI MDACC Core Grant CA16672-22, NCI (R21-CA74117), NIAMS K24 CA 86815 and by the CTCL patient education and research fund and the Sherry L Anderson fund for CTCL Research.

Corresponding Author:

Madeleine Duvic, MD
Professor of Medicine and Dermatology
Deputy Chairman, Dept of Dermatology
MD Anderson Cancer Center
1400 Pressler – Unit 1452
Houston, Texas 77027
Email: mduvic@mdanderson.org
Tele: (713) 745-4615
Fax: (713) 745-3597

The work was presented in part at the First World Congress of Cutaneous Lymphomas in Chicago, IL, Sep 22-25, 2010.

Word count: abstract: 250, text: 4841, number of references: 43, Tables: 2, Figures: 3
Long term outcomes of mycosis fungoides and Sézary syndrome

Statement of Translational Relevance

Cutaneous T cell lymphomas, while rare, have great morbidity and may be misdiagnosed or over-treated by clinicians who are unfamiliar with these entities. This is the largest American cohort of CTCL-Mycosis fungoides and Sézary patients studied for prognostic markers, many of whom were on clinical trials. We report survival advantage for patch compared to plaque MF involvement and for number of abnormal circulating cells. CD25+ CD30 expression did not affect the OS, whereas patients with poikiloderma or with lymphomatoid papulosis, a CD30 lymphoproliferative disorder had a significant survival advantage (p=0.02). There is much longer overall survival than reported for the entire cohort and for patients with Sézary Syndrome. This suggests that earlier diagnosis and use of new therapies are having a beneficial effect on patient outcomes. This paper should be of great interest to dermatologists and oncologists treating CTCL.
Long term outcomes of mycosis fungoides and Sézary syndrome

Abstract

Purpose

The purpose of this prospectively collected single center study cohort of MF/SS 1263 patients is to evaluate the significance of stage and risk of disease progression from initial presentation, and to examine other prognostic factors.

Patients and Methods

The prognostic variables effecting overall survival (OS) were examined in a unique prospective cohort of 1263 mycosis fungoides (MF) and Sézary Syndrome (SS) patients seen by one investigator at MD Anderson Cancer Center from 1982-2009. Kaplan and Meier estimates were used to determine median overall survival (OS), progression-free survival (PFS) and disease specific survival (DSS). Cox’s proportional hazards regression model assessed prognostic factors.

Results

Mean age at diagnosis was 55.33 years. Early MF (Stage IA-IIA) represented 71.5% (903 of 1263) and advanced (Stage IIB-IVB), 28.5% (360 of 1263) patients. Progression to a higher stage occurred in 147 patients (11.6 %) of whom 112 (12%) were early and 35 (9.7%) advanced. Death from disease occurred in 102/1263 (8.1%) patients. Median OS was 24.44 years, PFS was 16 years, and median DSS was not reached. OS and PFS were significantly better for early stage patients with patches (T1a/T2a) than with patches/plaques (T1b/T2b). PFS analyzed in 1241 patients found only 337 (27.2%) had disease progression or had died from disease. Risk factors associated with progression or deaths were advanced age, plaque stage, LDH level, and tumor area.
Long term outcomes of mycosis fungoides and Sézary syndrome

Conclusions

Improved outcome of MF/SS, reflected by overall survival and PFS for all stages, may result from earlier diagnosis, new therapies, and aggressive treatment of infections.
**Introduction**

Cutaneous T-cell lymphomas (CTCL) are a heterogeneous group of non-Hodgkin’s lymphomas (NHL) characterized by skin infiltration of neoplastic T-lymphocytes. Mycosis fungoides (MF), and its leukemic variant Sézary syndrome (SS), are characterized by a monoclonal proliferation of CD4+/CD45R0+ peripheral or central memory T-cells respectively, as well as loss of mature T-cell antigens (i.e., CD3,5,7). Incidence rates (IR) for all CTCLs in the US population have been estimated at 7.7/1,000,000 person-years, similar to 6.4/1,000,000 previously reported by a SEER (Surveillance, Epidemiology and End Results) based study using the data from the original 9 registries analyzing 4783 cases of CTCL from 1973-2002. MF is the most common primary cutaneous lymphoma, with incidence rate of 4.1/1,000,000 person-years with a male to female incidence rate of 1.66. With the exception of patients with stage IA, limited patch and/or plaque MF (T1), the overall survival of MF patients is inferior to age-, sex-, and race-matched control populations. Published risk factors for survival in MF and SS include demographics, skin T-stage, presence of extra-cutaneous disease such as lymphadenopathy and peripheral blood involvement, large-cell transformation, as well as increased levels of serum lactate dehydrogenase, β2-microglobulin, eosinophilia, and soluble interleukin 2 receptor.

Long term outcomes of the Stanford cohort of 525 CTCL patients were reported by Kim and Hoppe in 2003; They found a median overall survival of 10 years and survival equal to age matched controls in Stage IA MF. Significant blood involvement (>1000 SS cells/ul) was B1 but is now B2 in the most recent classification system. Thirty-five Stanford patients with B1 or B2 blood involvement had a median survival of...
Long term outcomes of mycosis fungoides and Sézary syndrome

only 3.0 years at a time when combined immunomodulatory treatment was being adopted for first line therapy of SS patients.\textsuperscript{21} In an earlier analysis in patients thus treated,\textsuperscript{21} we found a median overall survival of 7.6 years for erythrodermic CTCL patients with <1000 Sézary cells/ul at baseline, 5.4 years for SS patients with hematology stage H3 or B2 (SS counts >1000 and < 10,000 cells/ul), and only 2.4 years for patients at stage H4 (> 10,000 SS cells/ul).\textsuperscript{16}

Agar et al\textsuperscript{10} published a British cohort of 1,502 patients with long term follow up of 29 years to validate the International Society for Cutaneous Lymphomas (ISCL) European Organization for Research and Treatment of Cancer (EORTC) revision of MF/SS staging system.\textsuperscript{20} In their recent study, early skin stage (T1/T2) was sub-classified into either patches (T1a or T2a) or a combination of patches and plaques (T1b or T2b). Survival with or without lymph node and blood involvement were also examined in advanced patients (Table 1).\textsuperscript{20}

The purpose of this prospectively collected, single center study cohort of MF/SS 1263 patients was to evaluate the significance of stage and risk of disease progression from initial presentation, as well as to examine other prognostic factors. We also compare our findings to the proposed ISCL/EORTC staging criteria and risk factors. OS, DSS, PFS are assessed using univariate and multivariate analysis, similar to Agar et al.\textsuperscript{10}

Patients and Methods

Patient Selection and Staging

A prospective lab protocol and consent, approved by MD Anderson Institutional Review Board, allowed us to create a CTCL patient database including DNA and sera samples. Permission was later granted to conduct a retrospective analysis of 1500 CTCL
Long term outcomes of mycosis fungoides and Sézary syndrome

patients staged and followed at MD Anderson Cancer Center from 1982-2009. Data evaluated included diagnostic skin biopsy with T-cell receptor gene analysis from skin (n= 614) by polymerase chain amplification and immunohistochemistry for CD30 (n=452) and CD25 (n= 513) expression.

Tissue samples and blood at baseline were studied in real time for staging purposes. DNA extracted from paraffin embedded tissue blocks was subjected to polymerase chain amplification using primers and conditions as previously described by Vega et al.\textsuperscript{22} As a control for the DNA sample, beta hemoglobin was amplified for comparison. Initially, manual Sézary cell counts were determined by a hematopathologist and later abandoned based on our published study correlating SS cell numbers with CD4+CD26- absolute counts determined by flow cytometry. Multi-color flow cytometry was used to quantitate numbers of CD3+CD4+, CD3+CD8+, CD3+CD7- and CD4+CD26- for each patient.\textsuperscript{23} Immunochemistry analysis of V beta usage was conducted on aberrant T-cell clones by flow cytometry.\textsuperscript{22}

T-cell receptor beta and gamma gene rearrangements in peripheral blood were assessed by multiplex PCR using a two tube multicolor system, capillary electrophoresis and BIOMED-2 primers.\textsuperscript{22} We considered significant blood involvement or B2 as >1000 cells/ul or > 35\% CD4+CD26- cells with a clonal population noted on the scattergram. The B0/B1/B2 classification system which was first used by us in the early 1990s was later also adopted by the ISCL/EORTC classification described by Olsen et al.\textsuperscript{20} The classification of blood involvement is B0 < 500 Sézary cells/ul; B1 >500 and < 1000 cells/ul; and B2 >1000 cells/ul or > 35\% of lymphocytes as CD4+CD26- or CD4+CD7-cells. Patients classified as SS were required to have $\geq$ 80\% erythroderma as well as B2
Long term outcomes of mycosis fungoides and Sézary syndrome

(>1000 atypical circulating cells), and evidence of a peripheral T-cell clone. One hundred and eighty-six patients were confirmed to have SS based on immunohistochemical detection by flow cytometry of peripheral blood samples and molecular assessment of the T-cell receptor at presentation. All SS patients were treated upfront with immunomodulatory therapy including photopheresis plus biological response modifiers.21

Patients with >1.5 cm palpable peripheral lymphadenopathy underwent fine needle aspiration or excisional lymph node biopsy for immunohistochemistry and molecular TCR analysis as described above. We used the updated ISCL/EORTC classification20 for lymph nodes: N1 (dermatopathic lymphadenopathy), N2 (dermatopathic lymphadenopathy with early involvement by MF), N3 (partial effacement of LN architecture, many atypical cerebriform mononuclear cells), and N4 (complete effacement).

All patients had an automated total white blood cell counts, serum lactic dehydrogenase LDH levels (n= 1148), and B2 microglobulin levels (n=834) at baseline. When indicated by stage > IIA, patients underwent additional staging evaluation, including bone-marrow biopsy and imaging studies (CT scans or PET/CT). Suspected involvement of any visceral sites was confirmed with biopsy whenever possible.

Clinical features evaluated at diagnosis included T stage as body surface area involved with patches alone, patches & plaques and plaques alone, presence of histologically confirmed folliculotropic MF, poikiloderma, hypopigmentation, papules of lymphomatoid papulosis, and tumors with or without large cell transformation (LCT) in skin and lymph nodes. LCT was defined as >25% of atypical lymphocytes with nuclei >
Long term outcomes of mycosis fungoides and Sézary syndrome

four times normal size.\textsuperscript{17} The T staging system remained constant throughout the study time although determination of extent of skin lesions by body surface area was later adopted with weighting factors as the mSWAT assessment tool. Tumors were evaluated for risk as solitary versus multiple, localized or regional and for presence or absence of histologic large cell transformation.

Patients diagnosed elsewhere and referred to MDACC were included in the study if baseline diagnostic biopsy for MF or SS counts were available, or if the patient was untreated prior to presentation. The dates for last follow up and cause of death was confirmed from the clinical records and patients’ families and physicians were queried with regard to the cause of death whenever possible. The MD Anderson tumor registry was helpful in routinely determining survival and disease status in 100 patients who did not return regularly to the clinic.

Statistical Analysis

We used the methods of Kaplan and Meier\textsuperscript{24} to estimate the median overall survival (OS), disease specific survival (DSS), and progression free survival (PFS). For the analysis of OS, death was counted as an event. For the analysis of DSS, MF-related death was considered as an event. For the analysis of PFS, first disease progression or MF-related death were considered as events. Cox’s proportional hazards regression model\textsuperscript{25} was used to test the statistical significance of potential prognostic factors for OS, DSS, and PFS. The Cox modeling was done in a univariate fashion. From this model we estimated the hazard ratio for each potential prognostic factor with a 95% confidence interval.
Long term outcomes of mycosis fungoides and Sézary syndrome

All potential prognostic factors with a p-value < 0.10 from the univariate analysis were then included in a saturated model, and backward elimination was used to remove factors from the model based on the likelihood ratio test in the multiple regression analysis. All analyses were performed using SAS 9.2 by SAS Institute, Cary, NC, USA.

Results

Patient characteristics

Clinical characteristics, stage, median survival, OS/DSS and PFS are summarized in Tables 1 & 2. Mean age at diagnosis was 55.33 years (range 8-91 years). The majority of patients (73.4%) were Caucasian; the remainder were of African American (12.9%) or Hispanic descent (10.9%). Unexpectedly, the male to female ratio was almost equal at 1.1:1. Early stage (IA-IIA) MF patients (n=903) represented 71.5% of all patients with 447 (49.5%) females and 456 (50.5%) males. Of note, in advanced stage patients (IIB-IVB) (n=360) representing 28.5% of all patients, 145 (40.2%) were females and 215 (59.7%) were males.

We also had the opportunity to address survival in several non-classical MF subsets which have been analyzed for survival in the literature(Table 2). Folliculotropic MF has been associated with reduced survival or progression compared with classic MF. Hypopigmented or juvenile MF more common in skin types III or IV and poikilodermatous have been suggested to have a more indolent clinical course. Clinical and histologic variants of MF included 45 folliculotropic MF (3.6%), 64 poikilodermatous MF (5.1%), 54 hypopigmented MF (4.3%), 45 MF with lymphomatoid papulosis (3.6%), and 109 MF with large-cell transformation in skin or nodes (8.7%).
Long term outcomes of mycosis fungoides and Sézary syndrome

The majority of MF patients were diagnosed with skin stage T1 (<10% involvement) (41.2%) and T2 (>10% and <80% skin involvement) (32%). Using the EROTC staging proposal to classify early patients by T stage at diagnosis, 382 of 520 T1 patients had patches (T1a), and 138 had patches and plaques (T1b). Among 403 T2 patients, 198 had patches (T2a), and 205 had patches and plaques (T2b). Eleven percent of all patients presented with skin tumors (T3). There were 184 patients (15.4%) with Sézary syndrome: erythroderma (T4) and B2 blood involvement. Seventy patients (5.6%) with criteria for SS had bone marrow involvement at baseline. At initial presentation and staging, only three patients had extracutaneous disease in central nervous system, lung, or liver, excluding bone marrow involvement.

Blood involvement by flow cytometry was assessed at baseline in all advanced patients and in the majority of early stage patients. Among these 1263 patients, 205 (16.2%) had some degree of blood involvement: 192 patients (15.2%) had B2 and 13 (1.0%) had B1. Ninety-four percent or 490 of 522 of stage IA (T1) patients had flow cytometry of blood performed at baseline: 10 were B1 and 3 were B2. Thus, only 2.4% of early stage IA patients had measurable SS cells by flow cytometry at baseline.

Serum lactate dehydrogenase levels (LDH) in 1158 patients at baseline, were normal in 890 or 77% of patients and were elevated (> 618 IU/L) in 268 patients, including 92 early stage patients and 176 advanced stage patients.

Standard Treatment Approach

Our treatment approach adopted in the mid-1980s was to identify and treat infections, to avoid use of immunosuppressive therapies for as long as possible, and to treat patients as conservatively as possible, while trying for complete, durable remissions.
Long term outcomes of mycosis fungoides and Sézary syndrome

In total, 578 of the patients in this analysis were treated on clinical trials including 39.6% (358 of 903) with early stage MF and 61% or 220 of 360 with advanced disease. The treatment algorithms used were similar to recent NCCI guidelines. Early stage patients first received only skin directed therapies. Biological response modifiers or experimental agents were added if patients became refractory or progressed beyond IA.

As previously reported in 1996 and updated in 2003, beginning in 1987 all new MF/SS patients (n=95) with stage ≥ IB (T2) received multimodality therapy on protocol: acutane and interferon x 4 months followed by total skin electron beam radiation and maintenance with interferon x 1 year and topical nitrogen mustard maintenance for 2 years or if not in complete response, indefinitely until progression. Patients with advanced disease (>IIa) including nodal disease also received multi-agent chemotherapy with cytoxan, methotrexate, etoposide, and dexamethasone x 6 cycles prior to their beam. The overall complete response rate for this study was 60% with a median overall survival of 145 and 36 months for early versus late stage patients, respectively.

Patients who relapsed were treated by stage with either skin directed therapy or experimental agents on clinical trials.

After the completion of the combined modality therapy, new SS patients were treated initially on multi-modality therapy with ECP and biological therapy as reported previously and on clinical trials if they progressed. In the 1990s, denileukin diftitox was studied in trials for early patients with < 3 prior therapies (n=15) and for advanced stage with >3 prior therapies (n=6) as described. After approval, it was used predominantly for late stage patients with tumors as first line therapy. Beginning in 1996, both early (n=10) and late (n=30) patients who had failed at least one prior systemic...
Long term outcomes of mycosis fungoides and Sézary syndrome

therapy were treated on oral bexarotene at 300 mg/m2.\textsuperscript{34,35} After approval, bexarotene was used in combination with skin directed therapies for refractory early patients and was also used as front-line systemic therapy. Among the 1263 MF patients in this analysis, 320 were treated with oral bexarotene including 166 or 18.3\% of 903 early stage patients and 42.7\% or 154 of 360 of advanced stage patients.

Advanced patients with tumors received radiation, single agent monotherapy, or were enrolled on small phase II clinical trials. These included gemcitabine (n=25),\textsuperscript{36} sapacitabine (n=11), bexarotene plus interferon (n=7), forodesine (n=47), interleukin 12 (n=8), CpG (n=12), liposomal doxorubicin (n=17), humax CD4 monoclonal antibody (n=14), histone deacetylase inhibitors vorinostat (n=39)\textsuperscript{37,38} and romidepsin (n=3), panobinostat (n=12), or pralatrexate (n=15).\textsuperscript{39} From 2001 to 2009, 19 advanced patients (5\% of 360) received total body electron beam followed by allogeneic stem cell transplantation.\textsuperscript{40}

Overall and Disease Free Survival and Deaths

Median OS for all MF/SS patients was 24.44 years for the entire study period. The median OS for females was 32.04 years and was 20.70 years for males (Table 1). The median OS for patients whose age was < 42 years was 35.8 years but for age > 66, OS was only 7.6 years. The Kaplan-Meir plots of overall survival by NCI I-IV staging and by T-stages are shown in Figure 1A and B.

Median disease specific survival (DSS) was not reached (Table 2). A total of 273 of 1255 (21.8\%) patients died, with 102 (37.4\%) deaths attributed to MF/SS. Other related causes of death included sepsis (n=5), pneumonia, renal failure, cardiopulmonary
Long term outcomes of mycosis fungoides and Sézary syndrome

events, and secondary malignancies. Among 184 patients with Sézary Syndrome, 106 (57.6%) died with a median overall survival of 4.98 years. Among non-SS patients, 162 patients of 1065 (15.2%) died and the median survival was 29.28 years.

OS and DSS by skin T stage

Although the median OS and DSS for T1 patients were not reached (Table 2, Figure 2A), stage IA MF patients with only patches and no plaques (T1a) did significantly better than patients with both (T1b) (Table 2). Likewise, although the OS and DSS were not reached for T2a patients (>10% patches only), OS was 16.9 years and DSS was 26.26 years for T2b patients with >10% patch/plaque disease (Figure 2A). Median overall survival for patients with tumors T3 was 5.96 years, similar to OS of 5.0 years for stage T4, erythrodermic patients (Figure 1B). The overall survival rate by T stage at 5, 10 and 20 years respectively, was 95%, 89% and 82% for T1; 87%, 78%, and 61% for T2: 57%, 46% and 36% for T3; and 52%, 29%, and 12% for T4.

OS and DSS by Node (N) classification

One hundred thirty-eight patients (10.9%) had nodal disease (N1-N4) at diagnosis. Median OS for N0 was 26.26 years, and DSS was not reached for N0. Median OS for patients staged as N1-2 was 10.2 years and as N3-4 was 4.47 years, compared to N0 (no nodal disease) OS of 26.26 years for N0 (Table 1). Worse outcomes were observed for N4 patients whose median OS was 2.85 years (Table 2). The DSS for N1-3 was 16.91 years and DSS for N4 (effacement) was 9.01 years.

OS and DSS by Peripheral Blood (B) classification

One hundred thirty-eight patients (10.9%) had nodal disease (N1-N4) at diagnosis. Median OS for N0 was 26.26 years, and DSS was not reached for N0. Median OS for patients staged as N1-2 was 10.2 years and as N3-4 was 4.47 years, compared to N0 (no nodal disease) OS of 26.26 years for N0 (Table 1). Worse outcomes were observed for N4 patients whose median OS was 2.85 years (Table 2). The DSS for N1-3 was 16.91 years and DSS for N4 (effacement) was 9.01 years.
Long term outcomes of mycosis fungoides and Sézary syndrome

Peripheral blood involvement by flow was present to some degree in 205 patients. Only 13 patients were classified as B1 while 192 had B2 involvement, and classified as SS (Stage IVA1) (Figure 3). As expected, a significant difference in OS and DSS of patients was noted between those classified as B0 and B2 ($P < .0001$) (Figure 3). The sample size for B1 patients was too small for comparison. The OS for B2 was 4.64 years compared to OS for patients with B0 of 29.28 years (Figure 3). Of note, the DSS for B2 was 18.14 years while for B0 was not reached.

OS and DSS by Clinical Stage (IA- IVB)

The majority of MF patients (894 or 71.8%) presented at an early stage I-IIA MF with 360 (28.9%) presenting at advanced stages (≥IIB -IVB) (Tables 1 and 2) and Figure 1A and Figure 2B. The predictive value of age was greater in stages I-III and less valuable in stage IV patients. Not unexpectedly, patients who were staged as IIB - IV at diagnosis were more likely to have disease progression or die from MF than patients with early stage at diagnosis.

Progression Free Survival (PFS)

Analysis of PFS was defined as the first disease progression or MF-related death. The median PFS was 16.0 years for all patients. Figure 2B shows PFS by disease stage. The PFS for T1 was not reached, for T2 was 24 years, for T3 was 5.86 years and for T4 was 5.00 years. By univariate analysis, earlier stage and younger age at diagnosis, and Caucasian race were significantly associated with a favorable PFS. Disease progression was noted in 348 patients (27.6%) and there was an increased risk of disease progression with advancing age. The risk of progression of disease was significant for B2 compared
Long term outcomes of mycosis fungoides and Sézary syndrome
to B0-1 (P < .0001) because more patients with B2 disease died. Older patients (> 55 yrs)
and African Americans were more likely to have disease progression or die from MF than
younger patients or Caucasian patients, respectively.41

Prognostic Factors

Advanced age at diagnosis was an important negative predictive factor in both univariate
and multivariate analysis (P< .01). Advanced age (>66 years) at diagnosis was an
important negative predictive factor in both univariate (p<0.0001) and multivariate
analysis (p<0.0001). Levels of lactate dehydrogenase (LDH), elevated white blood cell
count (WBC), and beta 2 microglobulin by univariate analysis were also significant
(p<0.0001) (Table 2). Large-cell transformation was associated with reduced OS/DSS
and decreased progression free survival (p <.0001) (Table 2). Expression of CD25 or
CD30 in the skin biopsy had no significant effect on the survival (OS, DSS, and PFS).
Generalized tumors compared to regional tumor(s) was associated with a significantly
worse overall survival outcome than a solitary tumor (P <.0001) (Table 2).

Among the relatively small numbers of patients with rarer MF variants
(folliculotrophic, poikiloderma, hypopigmented, and MF associated with lymphomatoid
Papulosis), only poikiloderma and MF with lymphomatoid papulosis had significantly
better outcomes of OS/DSS and a reduced risk of disease progression compared to all MF
patients (Table 2).

Discussion

This is the largest to date, single institution, US study to report survival and risk
factors for progression from MF and SS. Our cohort consists of 1263 MF/SS patients
Long term outcomes of mycosis fungoides and Sézary syndrome

with a mean age of 55.53 years prospectively followed and treated by a single clinician for 27 years. Kim et al previously reported inferior survival in Stage IB (>10% patch or plaques) compared to IA patients (< 10% patches or plaques) in a cohort of 525 patients. Because of her observation, new T1a/b and T2a/b sub-stages were incorporated into the ISCL/EORTC new staging revisions to be examined in future CTCL cohorts. We are the first US center to validate the ISCL/EORTC revised T1 and T2 staging for patch versus patch/plaque sub-sets (T1a/b and T2a/b). Our study also confirms the difference in T1 and T2 subsets reported recently by Agar et al. in a large British cohort of 1502 patients with median age of 54 years, followed for 29 years in the same time period (1980-2009). Both studies found that inferior survival was associated with the presence of plaques (T1b/T2b) in Stage IA and IB patients. Our study also further validates prognostic markers including advanced age, LDH and B2-microglobulin levels, white count and presence of large cell transformation in univariate analysis.

An unexpected finding in our cohort was the near equal ratio of females 1.1:1 to males because a male-female predominance ratio of 1.72 was reported from the SEER database analysis. The overall male to female incidence in our cohort was almost equal among the early stage patients (48.9% female, 51% male). Others reported the incidence among males exceeds females, but did examine stage. In our study, males represented a higher proportion of advanced stages (59.7% males and 40.3%, females). But in early stage (IA-IIA) MF patients (n=903), representing 71.5% of the cohort, 447 (49.5%) were females and 456 (50.5%) were males. The overall proportion of early stage patients (71.5%) was identical to 71% reported by Agar et al and was also similar to 66.8% early patients in the Stanford cohort. In our study, the percentage of males
Long term outcomes of mycosis fungoides and Sézary syndrome

(59.7%; 215) out-numbered females (40.2%; 145) in the 360 patients with advanced stages at diagnosis but the ratio was no different in early disease.

Another difference is that overall survival among female patients was 32.04 years compared to only 20.7 years in male MF patients, but the p value was not significant. A sub-group of young African American females in our cohort may have inferior survival and increased risk of progression.\textsuperscript{41} In the recent British study, median overall survival was also superior in females (24.1 years) compared to males (13.4 years) (p=<.001).\textsuperscript{10} In the 525 patient 1993 Stanford cohort, an OS of 13.5 years was reported for females versus 10 years for males.\textsuperscript{9} Thus, inferior overall survival in males versus females has now been reported in three studies including our own. The reason for the higher incidence of males with MF and their increased representation at higher stages is unknown.

Overall survival for the early T1 patients was not reached in our cohort as reported in the 2003 Stanford cohort of Kim et al.\textsuperscript{9} Overall survival for T1 was 35.5 years in the British study with 29 years of follow-up similar to 24.44 years with 27 year follow-up in our study.\textsuperscript{10} Favorable OS is likely influenced by the high percentage (71%) of early stage MF patients within all the cohorts. In Agar et al, median survival and OS/DSS decreased as skin stage (T1-4) progressed, and disease progression increased with advancing age.\textsuperscript{10} Kim et al also reported that the risk of disease progression worsened with advanced T classification finding greater risk in patients with T2 compared with T1 (P<.001) and in T3 or T4 compared to T2 (P<.001).\textsuperscript{9} TNM stage beyond IA was associated with inferior survival whereas IA patients’ survival was no different than age matched controls.\textsuperscript{4,9}
Long term outcomes of mycosis fungoides and Sézary syndrome

Among our T2 patients, improved OS and DFS were noted for T2a (>10% body with patches only) compared to T2b (>10% plaques with patches) (OS - p<.0001; DSS p=.0.003). In the retrospective cohort analysis of T2 patients at Stanford over 35.5 years, disease progression occurred in 20% of T2 patients with patches and plaques and was significantly worse than sex-matched controls. These studies suggest that patients with plaques need aggressive topical and systemic therapy compared to patients with patches who may be managed by skin directed therapy alone.

The influence of blood involvement on survival and PFS is a moving target as more sensitive flow cytometry studies and markers are replacing manual cell counts at most CTCL centers. The presence of a T-cell clone in peripheral blood was found to be an independent prognostic marker for MF patients. The revised EORTC/ISCL staging system proposed grading blood involvement as B0 (<5% or absence of blood), B1 (aleukemic >500 and <1000 cells/ul) or B2 (leukemic >1000 cells/ul), replacing the former B0 or B1 criteria. Erythroderma (T4) with B2 blood involvement defining SS has been associated with poor outcome and overall survival. Kim et al reported an OS of only 2.5 years while Agar’s study reported a 3.1 year OS in SS patients.

Our study has shown superior survival for patients with blood involvement in this American cohort. We prospectively collected flow cytometry data on almost all patients at baseline regardless of stage. Only twelve of 490 IA patients (2.4%) had abnormal baseline flow cytometry: ten had B1 and three had B2 blood involvement. None of the B1 patients had nodal involvement, and there was no significant difference in the survival between B0 and B1 in early stage patients. The British group previously reported that H4
Long term outcomes of mycosis fungoides and Sézary syndrome

or >10,000 SS cells/ul was associated with poor overall survival of 2.5 years. 

Our previous retrospective analysis of 124 erythrodermic (T4) patients reported by Vidulich et al, reported that OS was 5.1 years in erythrodermic patients regardless of degree of blood involvement, 7.6 years for B0-B1 (H0-2), 5.4 years for H3 (B2 >1000 -<10,000), and only 2.4 years for H4 blood involvement (>10,000 SS cells/ul). 

Five and ten year survival estimates were 51% and 29% for all erythrodermic CTCL patients. In the current analysis, OS for patients with B2 was 4.64 years compared to OS of 29.28 years with no blood involvement (Figure 3). DSS for B2 was 18.14 years and for B0 was not reached. Our recent analysis suggests that B2 involvement confers a significant difference in the OS and DSS between B0 and B2 (p <.001) but that “H4” or “B3” (>10,000 SS cells/ul) has the worst prognosis and could be used to stage blood.

The Stanford report included 35 SS patients whose OS was 3 years for B1 (now B2 > 1000 SS cells/ul). Many of the SS patients also had nodal involvement which may have influenced survival in their patients. The major cause of death in erythrodermic and SS patients is line sepsis which is often from staphylococcus aureus. Staphylococcus was prospectively cultured from up 60% of SS patients from our center and was aggressively treated and prevented with antibiotics and skin care.

We and others identified LDH and B-2 macroglobulin as independent prognostic markers. Elevated serum LDH was an independent predictor of poor survival and increased progression risk in univariate and multivariate analysis. Elevated B-2 microglobulin levels were also associated with a reduction in median survival. Our patients with B-2 microglobulin > 1.8 mg/L had reduction in median survival and progression of disease, but this may reflect an age effect since older age was associated
Long term outcomes of mycosis fungoides and Sézary syndrome

with poor prognosis as well as rising B2 microglobulin levels. A Sézary cell count of \( \geq 10,000 \mu L \) was another significant prognostic factor for survival and progression risk in univariate analysis as we have previously suggested.

In Agar’s study, folliculotropic MF, in 189 patients, showed increased risk of disease progression (RDP) in univariate analysis. In the multivariate model, folliculotropism became an independent significant factor for survival and progression outcomes. Our study did not show an increased risk of progression or examine treatment differences. Our study had a smaller sample size with folliculotropic MF representing only 3.6% of all our patients compared to 12.6% in the British cohort.

Large cell transformation (LCT) has been associated with progression and poor outcome, especially when it occurs within two years of diagnosis. In a small study of 115 MF or SS patients reported from MD Anderson, the incidence of LCT was 26% with a cumulative probability of 39% over 12 years. In our larger cohort of 1263 patients, only 8.7% patients had biopsy proven large cell transformation in skin. This is comparable to the incidence of 5% previously reported by Agar and Whittaker et al. Large cell transformation was associated with increased risk of disease progression, and decreased median OS and DSS in both univariate and multivariate analysis (\( p=.0001 \)) (Table 2). Of interest, T-cell biomarkers including CD25 (the alpha chain of the T-cell receptor) and CD30 (a TNF-like receptor), often associated with LCT, were not significant for any of the three survival outcomes (OS, DSS and PFS).

Like Agar’s study, our purpose was to validate the ISCL/EORTC revised staging for MF/SS, and to confirm outcome in early versus late stages. Outcome analysis of the two US and British cohorts may allow validation of a Cutaneous...
Long term outcomes of mycosis fungoides and Sézary syndrome

Lymphoma International Prognostic Index, CLIPi. Confirmation of prognostic variables should allow identification of patients to select for more aggressive therapy based on risk category. Improved outcome reflected in overall survival, PFS, and DFS at all stages in our cohort, may result from earlier diagnosis, access to new therapies, and early treatment of co-existing infections.

Authors’ disclosure of potential conflict of interest

The author(s) have no competing financial interests.

Author Contribution

Conception and design: Rakhshandra Talpur, Madeleine Duvic, Ping Liu

Development of methodology and acquisition of data: Rakhshandra Talpur, Lotika Singh, Seema Daulat, Sarah Seyfer, Tanya Trynosky, Madeleine Duvic

Data analysis and interpretation: Rakhshandra Talpur, Lotika Singh, Seema Daulat, Ping Liu, Wei Wei, Madeleine Duvic

Manuscript writing, review: All authors

Grant Support

This research was supported by the NCI MDACC Core Grant CA16672-22, NCI (R21-CA74117), NIAMS K24 CA 86815, the Sherry L Anderson fund for CTCL Research and by the CTCL patient education and research fund.
Long term outcomes of mycosis fungoides and Sézary syndrome

References


Long term outcomes of mycosis fungoides and Sézary syndrome


Long term outcomes of mycosis fungoides and Sézary syndrome


Long term outcomes of mycosis fungoides and Sézary syndrome


Long term outcomes of mycosis fungoides and Sézary syndrome


**Long term outcomes of mycosis fungoides and Sézary syndrome**


40. Duvic M, Donato M, Dabaja B et al. Total skin electron beam and non-myeloablative
Long term outcomes of mycosis fungoides and Sézary syndrome


Long term outcomes of mycosis fungoides and Sézary syndrome

Table Legends

**Table 1.** Comparison of OS for reported factors in large MF cohort studies

**Table 2.** Univariate analysis of ISCL/EORTC T-stage classification and effect of histological and biochemical factors on overall survival, disease specific survival, progression free survival.
Long term outcomes of mycosis fungoides and Sézary syndrome

Figure Legends

Figure 1. Survival Outcomes by Kaplan-Meier

[A] Survival outcome by clinical TNM stage (IA, IB, IIA, IIB, III/IVA, IVB)

[B] Survival outcome according to T1-4 classification ISCL/EORTC

Figure 2.

[A] Survival outcomes including OS, DFS and PFS (A) comparing patch (T1a+ T2a) with patch plaque (T1b + T2b),

[B] Survival time by IA-IIA vs. IIB-IVB TNM Stages.

Figure 3. Survival outcomes OS, DFS and PFS for blood stages B0, B1 and B2.
### Table 1

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Long term outcome of 525 pts, Kim YH 2003</th>
<th>Validation of ISCL/EORTC 1502 pts, Agar NS 2010</th>
<th>MDACC study of 1263 MF/SS pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycosis Fungoides (n=)</td>
<td>490</td>
<td>1398</td>
<td>1062</td>
</tr>
<tr>
<td>Sézary Syndrome (n=)</td>
<td>35</td>
<td>104</td>
<td>186</td>
</tr>
<tr>
<td>Male (n=)</td>
<td>330</td>
<td>933</td>
<td>663</td>
</tr>
<tr>
<td>Median OS</td>
<td>10 years</td>
<td>13.4 years</td>
<td>20.7 years</td>
</tr>
<tr>
<td>Female (n=)</td>
<td>195</td>
<td>569</td>
<td>585</td>
</tr>
<tr>
<td>Median OS</td>
<td>13.5 years</td>
<td>24.1 years</td>
<td>32.0 years</td>
</tr>
<tr>
<td><strong>T classification</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 (n=)</td>
<td>159</td>
<td>443</td>
<td>521</td>
</tr>
<tr>
<td>Median OS</td>
<td>Not reached</td>
<td>35.5 years</td>
<td>Not reached</td>
</tr>
<tr>
<td>T2 (n=)</td>
<td>192</td>
<td>628</td>
<td>395</td>
</tr>
<tr>
<td>Median OS</td>
<td>12.1 years</td>
<td>21.5 years</td>
<td>26.26 years</td>
</tr>
<tr>
<td>T3 (n=)</td>
<td>96</td>
<td>182</td>
<td>136</td>
</tr>
<tr>
<td>Median OS</td>
<td>3.3 years</td>
<td>4.1 years</td>
<td>5.96 years</td>
</tr>
<tr>
<td>T4 (n=)</td>
<td>78</td>
<td>234</td>
<td>188</td>
</tr>
<tr>
<td>Median OS</td>
<td>4 years</td>
<td>3.9 years</td>
<td>5.00 years</td>
</tr>
<tr>
<td>Folliculotropic MF (n=)</td>
<td>189</td>
<td></td>
<td>44</td>
</tr>
<tr>
<td>Median OS</td>
<td>12.2 years</td>
<td></td>
<td>Not reached</td>
</tr>
<tr>
<td>Poikiloderma</td>
<td>168</td>
<td></td>
<td>63</td>
</tr>
<tr>
<td>Median OS</td>
<td>20.1 years</td>
<td></td>
<td>Not reached</td>
</tr>
<tr>
<td>Hypopigmented MF (n=)</td>
<td>51</td>
<td></td>
<td>54</td>
</tr>
<tr>
<td>Median OS</td>
<td>Not reached</td>
<td></td>
<td>Not reached</td>
</tr>
<tr>
<td>Lyp and MF (n=)</td>
<td>74</td>
<td></td>
<td>45</td>
</tr>
<tr>
<td>Median OS</td>
<td>Not reached</td>
<td></td>
<td>32.04 years</td>
</tr>
<tr>
<td>B0 (n=)</td>
<td>490</td>
<td>1327</td>
<td>1042</td>
</tr>
<tr>
<td>Median OS</td>
<td>12.3 years</td>
<td>24.5 years</td>
<td>29.28 years</td>
</tr>
<tr>
<td>B1 (n=)</td>
<td>35</td>
<td>71</td>
<td>13</td>
</tr>
<tr>
<td>Median OS</td>
<td>3 years</td>
<td>3.2 years</td>
<td>Not reached</td>
</tr>
<tr>
<td>B2 (n=)</td>
<td>0</td>
<td>104</td>
<td>186</td>
</tr>
<tr>
<td>Median OS</td>
<td>3.1 years</td>
<td>4.64 years</td>
<td></td>
</tr>
<tr>
<td>N0 (n=)</td>
<td>345</td>
<td>1220</td>
<td>1112</td>
</tr>
<tr>
<td>Median OS</td>
<td>17.4 years</td>
<td>22.8 years</td>
<td>26.26 years</td>
</tr>
<tr>
<td>N1 (n=)</td>
<td>147</td>
<td>87</td>
<td>55</td>
</tr>
<tr>
<td>Median OS</td>
<td>6.5 years</td>
<td>5.2 years</td>
<td>16.91 years</td>
</tr>
<tr>
<td>N2 (n=)</td>
<td>8</td>
<td></td>
<td>28</td>
</tr>
<tr>
<td>Median OS</td>
<td>1.1 years</td>
<td></td>
<td>5.43 years</td>
</tr>
<tr>
<td>N3 (n=)</td>
<td>33</td>
<td>40</td>
<td>18</td>
</tr>
<tr>
<td>Median OS</td>
<td>1.7 years</td>
<td>2 years</td>
<td>6.13 years</td>
</tr>
<tr>
<td>N4 (n=)</td>
<td></td>
<td></td>
<td>33</td>
</tr>
<tr>
<td>Median OS</td>
<td></td>
<td></td>
<td>2.85 years</td>
</tr>
<tr>
<td>Extracutaneous (n=)</td>
<td>77</td>
<td>13</td>
<td>70</td>
</tr>
<tr>
<td>Median OS</td>
<td>1.1 years</td>
<td>1.4 years</td>
<td>4.42 years</td>
</tr>
</tbody>
</table>


**Long term outcomes of mycosis fungoides and Sézary syndrome**

**TABLE 2**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Overall Survival</th>
<th>Disease Specific Survival</th>
<th>Progession Free Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>P</td>
</tr>
<tr>
<td><strong>T classification</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1a vs T4</td>
<td>0.05</td>
<td>0.03 to 0.09</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>T1b vs T4</td>
<td>0.17</td>
<td>0.11 to 0.28</td>
<td>0.21</td>
</tr>
<tr>
<td>T2a vs T4</td>
<td>0.08</td>
<td>0.04 to 0.16</td>
<td>0.06</td>
</tr>
<tr>
<td>T2b vs T4</td>
<td>0.33</td>
<td>0.23 to 0.47</td>
<td>0.31</td>
</tr>
<tr>
<td>T3 vs T4</td>
<td>0.68</td>
<td>0.49 to 0.94</td>
<td>1.09</td>
</tr>
<tr>
<td><strong>N classification</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0 vs N4</td>
<td>0.27</td>
<td>0.17 to 0.45</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>N1 vs N4</td>
<td>0.37</td>
<td>0.19 to 0.75</td>
<td>0.32</td>
</tr>
<tr>
<td>N2 vs N4</td>
<td>0.98</td>
<td>0.51 to 1.90</td>
<td>1.11</td>
</tr>
<tr>
<td>N3 vs N4</td>
<td>0.92</td>
<td>0.40 to 2.13</td>
<td>1.09</td>
</tr>
<tr>
<td><strong>B classification</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B0 vs B2</td>
<td>0.19</td>
<td>0.15 to 0.25</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>B1 vs B2</td>
<td>0.11</td>
<td>0.01 to 0.80</td>
<td>0.31</td>
</tr>
<tr>
<td><strong>M classification</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0 vs M1</td>
<td>0.27</td>
<td>0.19 to 0.38</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>Sezary Syndrome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No vs Yes</td>
<td>0.2</td>
<td>0.15 to 0.25</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>Folliculotropic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No vs Yes</td>
<td>1.19</td>
<td>0.56 to 2.53</td>
<td>1.6</td>
</tr>
<tr>
<td><strong>Poikiloderma</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No vs Yes</td>
<td>2.83</td>
<td>1.26 to 6.37</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Hypopigmented</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No vs Yes</td>
<td>1.56</td>
<td>0.73 to 3.32</td>
<td>0.24</td>
</tr>
<tr>
<td><strong>MF with Lyp</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No vs Yes</td>
<td>5.58</td>
<td>1.38 to 22.42</td>
<td>0.02</td>
</tr>
</tbody>
</table>
## Long term outcomes of mycosis fungoides and Sézary syndrome

<table>
<thead>
<tr>
<th></th>
<th>LCT skin and node</th>
<th>Tumor Distribution</th>
<th>LDH</th>
<th>WBC</th>
<th>Sex</th>
<th>B2-microglobulin</th>
<th>CD25 Expression</th>
<th>CD30 Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No vs Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LCT skin and node</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No vs Yes</td>
<td>0.13</td>
<td>0.08 to 0.20</td>
<td>&lt;.0001</td>
<td>0.06</td>
<td>0.03 to 0.13</td>
<td>&lt;.0001</td>
<td>0.33</td>
<td>.24 to .45</td>
</tr>
<tr>
<td>Tumor Distribution</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localized vs solitary</td>
<td>0.81</td>
<td>0.36 to 1.78</td>
<td>&lt;.0001</td>
<td>0.77</td>
<td>0.23 to 2.52</td>
<td>&lt;.0001</td>
<td>1.06</td>
<td>0.52 to 2.15</td>
</tr>
<tr>
<td>Regional vs solitary</td>
<td>0.87</td>
<td>0.25 to 2.94</td>
<td></td>
<td>1.89</td>
<td>0.51 to 7.02</td>
<td></td>
<td>0.73</td>
<td>0.21 to 2.44</td>
</tr>
<tr>
<td>Generalized vs solitary</td>
<td>1.34</td>
<td>0.74 to 2.41</td>
<td></td>
<td>1.52</td>
<td>0.65 to 3.56</td>
<td></td>
<td>1.17</td>
<td>0.66 to 2.08</td>
</tr>
<tr>
<td>LDH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal vs High</td>
<td>0.25</td>
<td>0.19 to 0.32</td>
<td>&lt;.0001</td>
<td>0.22</td>
<td>0.15 to 0.34</td>
<td>&lt;.0001</td>
<td>0.3</td>
<td>0.24 to 0.37</td>
</tr>
<tr>
<td>WBC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal vs High</td>
<td>0.35</td>
<td>0.25 to 0.48</td>
<td>&lt;.0001</td>
<td>0.27</td>
<td>0.16 to 0.44</td>
<td>&lt;.0001</td>
<td>0.42</td>
<td>0.31 to 0.56</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female vs Male</td>
<td>0.84</td>
<td>0.65 to 1.07</td>
<td>0.16</td>
<td>0.91</td>
<td>0.16 to 1.36</td>
<td>0.67</td>
<td>0.87</td>
<td>0.70 to 1.08</td>
</tr>
<tr>
<td>B2-microglobulin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1.8 vs &gt; 1.8</td>
<td>0.153</td>
<td>0.08 to 0.26</td>
<td>&lt;.0001</td>
<td>0.1</td>
<td>0.03 to 0.28</td>
<td>&lt;.0001</td>
<td>0.22</td>
<td>0.14 to 0.34</td>
</tr>
<tr>
<td>CD25 Expression</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 20% vs &gt; 20%</td>
<td>0.81</td>
<td>0.58 to 1.15</td>
<td>0.25</td>
<td>0.73</td>
<td>0.44 to 1.19</td>
<td>0.21</td>
<td>0.76</td>
<td>0.56 to 1.03</td>
</tr>
<tr>
<td>CD30 Expression</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No vs Yes</td>
<td>0.92</td>
<td>0.57 to 1.49</td>
<td>0.76</td>
<td>0.98</td>
<td>0.48 to 2.00</td>
<td>0.97</td>
<td>1.03</td>
<td>0.67 to 1.59</td>
</tr>
</tbody>
</table>

HR= hazard ratio, CI= confidence interval, p= p-value
Figure 3
Long term outcomes of 1263 patients with Mycosis fungoides and Sézary syndrome from 1982 to 2009

Rakhshandra Talpur, Lotika Singh, Seema Daulat, et al.

Clin Cancer Res  Published OnlineFirst July 31, 2012.

Updated version  Access the most recent version of this article at: doi:10.1158/1078-0432.CCR-12-0604

Author Manuscript  Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions  To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.