Role of imaging in low-grade cutaneous B-cell lymphoma presenting in the skin

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Background: Whole-body imaging is the current standard of care for staging all patients presenting with skin lesions of B-cell lymphomas (BCLs), regardless of skin disease extent; however, supporting data are lacking.

Objective: To determine the clinical utility of imaging in the detection of systemic involvement in low-grade cutaneous BCLs in the skin.

Methods: Retrospective cohort analysis of patients presenting with cutaneous lesions of BCLs at Memorial Sloan Kettering Cancer Center and Stanford University during 1997-2016.

Results: At initial staging, of the 522 patients, extracutaneous disease was noted in 3.6% and 8.8% of patients with marginal zone lymphoma (MZL, n = 306) and follicle center lymphoma (FCL, n = 216) histology, respectively. In patients with systemic involvement, imaging alone identified 81.8% (9/11) of MZL cases and 89.4% of follicular lymphoma cases. In primary cutaneous MZL, 1.7% of patients subsequently had extracutaneous involvement (median follow-up 45 months), and in primary cutaneous FCL. 3.0% subsequently had extracutaneous involvement (median follow-up 47 months).

Limitations: This was a retrospective study.

Conclusion: Imaging is effective at identifying patients with systemic involvement in indolent BCLs present in the skin; however, incidence is low. After negative initial staging, primary cutaneous MZL patients may be followed clinically without routine imaging. (J Am Acad Dermatol 2019;81:970-6.)

Key words: imaging; primary cutaneous B-cell lymphoma; prognosis; systemic involvement of cutaneous B-cell lymphoma.

Cutaneous lymphomas are the second most prevalent non-Hodgkin lymphoma.[1] Cutaneous B-cell lymphomas (CBCLs) represent 25% of cutaneous lymphomas, with incidence estimated at 3.1 cases/1 million person-years.[1,2] The World Health Organization (WHO) has categorized primary CBCLs into 4 subtypes: primary cutaneous marginal zone lymphoma (pc-MZL), primary cutaneous follicle center lymphoma (pc-FCL), and primary cutaneous diffuse large B-cell lymphoma (DLBCL) leg type and other.[1,3] pc-MZL and pc-FCL are characterized as low-grade B-cell lymphomas (BCLs) with 95%-99% 5-year survival.

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Primary cutaneous DLBCL leg type portends a more aggressive course.[4]

In addition to primary CBCL, the skin can be a presenting site for low-grade systemic BCLs. In previous studies, CBCL outcomes were defined as those without evidence of systemic disease 6 months after initial presentation,[5] thereby excluding cases that present in the skin as a manifestation of systemic BCLs, as well as those with early progression. Thus, the true incidence of skin as the initial presentation of systemic BCLs is unknown, though suspected to be low. For the cutaneous presentation of indolent BCLs, the current National Comprehensive Cancer Network guidelines recommend a complete work-up, which includes history, physical examination, laboratory studies (complete blood counts with differential, comprehensive metabolic panel, lactate dehydrogenase), and imaging studies (positron emission tomography/contrast-enhanced computed tomography [PET/CT] scan or computed tomography [CT] scan of chest, abdomen, or pelvis) in addition to a discretionary bone marrow (BM) biopsy for staging.[6] In a European registry study, there was a 10% reported incidence of BM involvement in patients with extracutaneous disease with FCL histology and negative imaging studies.[7] On the contrary, pc-MZL appears to be almost uniformly indolent, with only rare cases of subsequent extracutaneous disease.[5]

In this study, we evaluated the utility of imaging studies for detecting extracutaneous involvement in patients with BCLs with initial presentation at staging in the skin and the incidence of systemic dissemination of pc-MZL and pc-FCL after initial negative staging.

CAPSULE SUMMARY

- Whole-body imaging is the current standard of care as part of staging work-up for all patients presenting with skin lesions of B-cell lymphomas; however, the incidence of extracutaneous involvement in indolent cutaneous B-cell lymphomas is unknown.
- Imaging is effective for identifying the small subset of patients with systemic involvement at staging. After negative initial staging, primary cutaneous marginal zone lymphoma patients may be followed clinically without routine imaging.

PATIENTS AND METHODS

We retrospectively reviewed patients evaluated at Memorial Sloan Kettering Cancer Center (MSKCC) and the Cutaneous Lymphoma Clinic at Stanford University who had diagnoses of BCL in the skin during 1997-2016. Patients were identified by searching in the institutional database of MSKCC and the cutaneous lymphoma and pathology databases of Stanford University. In this study, CBCL patients were initially stratified by their cutaneous presentation of marginal zone or follicle center histology. Cohorts with MZL or FCL histology included both primary and secondary cutaneous presentations. Then, patients were further subcategorized as pc-MZL or pc-FCL and systemic MZL or follicular lymphoma (FL), with secondary skin involvement upon staging. We included patients with the following inclusion criteria: they had MZL or FCL histology confirmed by pathologists at MSKCC or Stanford on the basis of histopathologic and immunophenotypic data, their skin was the initial recognized site of involvement, and imaging studies (neck, chest, abdomen, and pelvic CT or whole-body PET/CT scans) were completed as part of their initial work-up. Molecular data was incorporated when available. Patients seeking treatment at MSKCC or Stanford with initial diagnoses and disease management performed outside these institutions were included in the study only if their diagnosis was biopsy proven and they were adequately staged per the aforementioned criteria.

Demographic data included age, sex, ethnicity, personal and family history of lymphoma, and incidence of secondary malignancies. Clinical findings included TNM stage, anatomic sites, lymphadenopathy, and B symptoms (fever, night sweats, weight loss). Additional staging work-up included complete blood count with differential, complete metabolic panel, lactate dehydrogenase, imaging studies (neck [if clinically indicated], chest, abdomen, and pelvic CT scan with contrast or whole-body PET/CT scan), bone marrow (BM) biopsy, and histopathology of any additional biopsy tissues. Patients were stratified into skin categories T1, T2, or T3[8] according to the number and size of skin lesions and their anatomic distribution. The treating clinician interpreted images (CT or PET/CT) as suggestive for extracutaneous disease.

Histopathology

All patients were regrouped according to the WHO and European Organisation for Research and Treatment of Cancer classification.[1,3] Dermatopathologists at the respective institutions who specialized in cutaneous lymphomas

Abbreviations used:

BCL:	B-cell lymphoma
BM:	bone marrow
CBCL:	cutaneous B-cell lymphoma
CT:	computed tomography
DLBCL:	diffuse large B-cell lymphoma
FCL:	follicle center lymphoma
FL:	follicular lymphoma
MSKCC:	Memorial Sloan Kettering Cancer Center
MZL:	marginal zone lymphoma
pc-FCL:	primary cutaneous follicle center lymphoma
pc-MZL:	primary cutaneous marginal zone lymphoma
PET/CT:	positron emission tomography/contrast-enhanced computed tomography
WHO:	World Health Organization

confirmed diagnoses with the aid of histopathologic, immunohistochemical, and cytogenetic data. Any cases without a biopsy confirmation were excluded. Immunohistochemical work-up performed at the time of diagnosis and subsequently for skin biopsies included CD3, CD5, CD10, CD20, CD79a, bcl-2, bcl-6, multiple myeloma oncogene 1 (MUM-1), and κ and λ light chain predominance.[1,3] Additional diagnostic studies included identifying immunoglobulin heavy and light chain monoclonality by PCR whenever available.

Statistical analysis

Overall survival and disease specific survival were calculated for the pc-MZL, pc-MZL with subsequent extracutaneous disease, systemic MZL, pc-FCL, pc-FCL with subsequent extracutaneous disease, and FL groups. Survival curves were estimated by using the Kaplan–Meier method, and the upper and lower 95% confidence bands were calculated by using the Greenwood formula. Differences between curves were analyzed by using the log-rank test. Fisher's exact test was performed for univariate analyses of the FCL cohort to evaluate factors predictive of systemic disease. Overall survival curves were estimated for patients with BM biopsies by using the Kaplan–Meier method and compared by using the log rank test to determine differences in prognoses. All statistical tests were 2-sided. *P* values <.05 were considered statistically significant. Statistical analyses were conducted in R3.3.2.[9]

RESULTS

Study population

A total of 522 CBCL patients met all of the inclusion criteria. In the MZL histology cohort, 183 patients were evaluated at MSKCC, 124 at Stanford, and 1 at both centers. In the FCL histology cohort, 105 patients were evaluated at MSKCC and 111 at Stanford. The median follow-up was 27 (range 0-222) months for the MZL histology cohort and 33 (range 0-263) months for the FCL histology cohort. A total of 401 patients were followed for >6 months; median follow-up was 45 (range 6-222) months for the MZL cohort and 47 (range 6-263) months for the FCL cohort. The clinical characteristics of the entire cohort at diagnosis are listed in Table I. Study algorithms showing further classification for MZL and FCL histology cohorts are outlined in Fig 1, *A* and *B*.

Table I. Clinical characteristics of 522 cutaneous B-cell lymphoma patients

Characteristic	MZL histology, n = 306	FCL histology, n = 216
Age at diagnosis, y, median (range)	48 (12-88)	56 (17-92)
Sex, % (n)		
Male	60.5 (185)	66.7 (144)
Female	39.5 (121)	33.3 (72)
ISCL-EORTC T classification,[3] % (n)		
T1	41.5 (127)	54.6 (118)
T2	29.7 (91)	34.7 (75)
T3	28.7 (88)	10.6 (23)
Location of skin lesions, % (n)		
Head and neck	23.9 (73)	62.5 (135)
Trunk	46.4 (142)	34.7 (75)
Upper limbs	49.3 (151)	12.9 (28)
Lower limbs	12.8 (39)	3.7 (8)
Median follow-up, months, median (range)	27 (0-222)	33 (0-263)
Cases with long follow-up, >6 months, n (%)	235 (76.8)	165 (76.4)
Long follow-up, months, median (range)	45 (6-222)	47 (6-263)

EORTC, European Organisation for Research and Treatment of Cancer; *FCL*, Follicle center lymphoma; *ISCL*, International Society for Cutaneous Lymphoma; *MZL*, marginal-zone lymphoma.

Incidence of extracutaneous disease in CBCL at initial staging

Extracutaneous disease was confirmed in 3.6% (11/306) patients with MZL histology and 8.8% (19/216) patients with FCL histology; imaging studies identified 81.8% (9/11) of patients with systemic MZL and 89.4% (17/19) of patients with FL. Four patients with extracutaneous disease (2 systemic MZL and 2 FL) with negative imaging were identified by BM biopsy or peripheral blood flow cytometry.

In total, 10.8% (33/306) of MZL histology cases and 17.9% (39/216) of FCL histology cases had imaging suggestive of systemic disease, and of these,

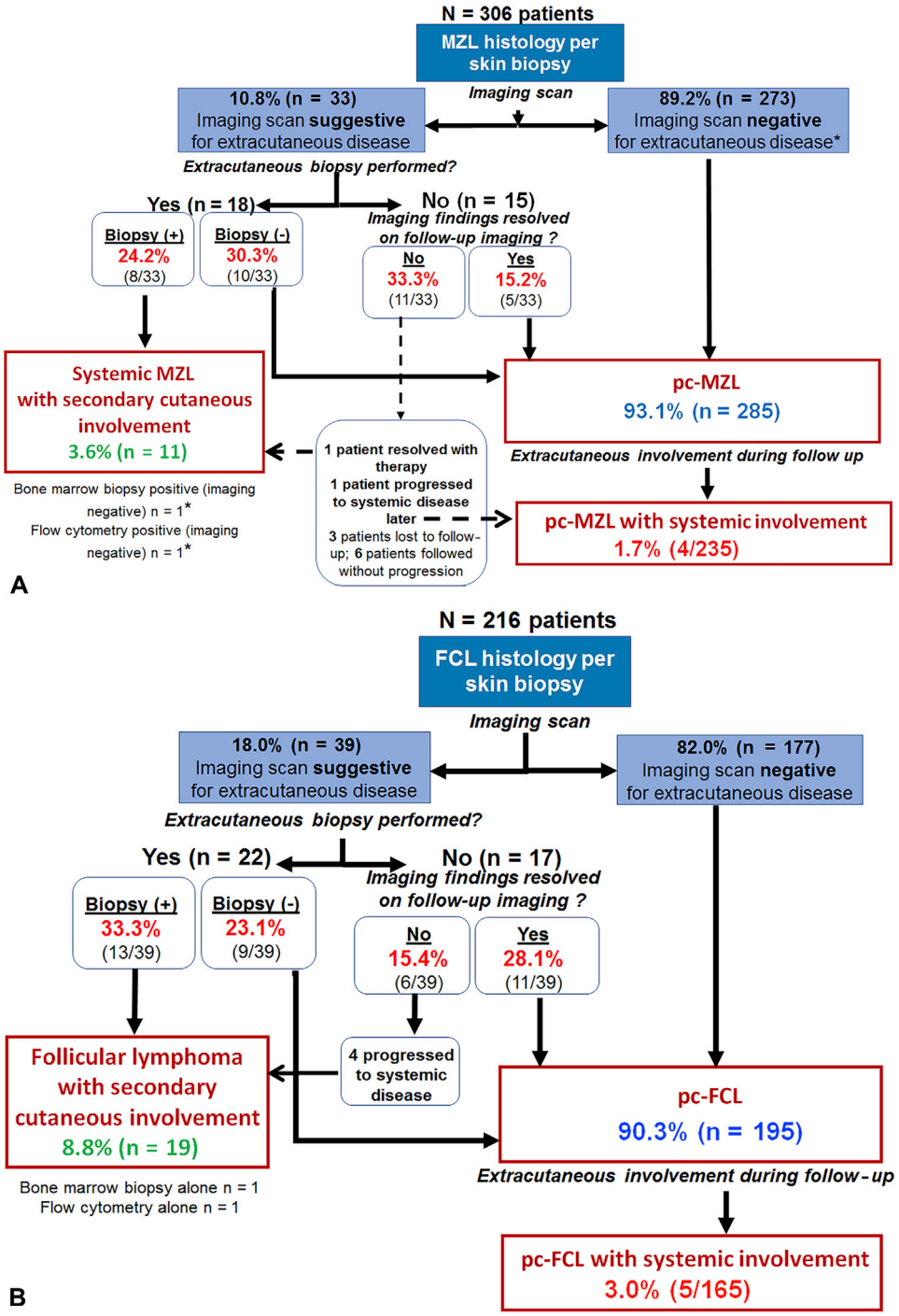

Fig 1. A, Classification of patients with MZL histology. **B**, Classification of patients with FCL histology. *FCL*, Follicle center lymphoma; *MZL*, marginal zone; *pc-FCL*, primary cutaneous follicle center lymphoma; *pc-MZL*, primary cutaneous marginal zone lymphoma.

45.5% (15/33) of the MZL histology cases and 51.3% (20/39) of the FCL histology cases were false-positives, defined as biopsy negative for lymphoma or resolution on subsequent imaging without intervening therapy (Fig 1, *A* and *B*).

Of the patients with positive imaging who were followed without further histologic confirmation, 1 of 11 MZL histology patients and 4 of 6 FCL histology patients progressed with systemic involvement and 1 of 11 MZL histology patients responded to systemic

therapy; none died of disease. Three patients with MZL histology and 2 patients with FCL histology were lost to follow-up. One patient with MZL was initially negative on lymph node biopsy but had disease 16 years later (classified as pc-MZL with systemic involvement). The remaining 6 patients with MZL histology remained stable over a median follow-up of 81 (range 27-146) months; however, because of the lack of confirmation of systemic disease, these patients were included in the pc-MZL group for survival analyses.

Incidence of systemic involvement in pc-MZL and pc-FCL

After initial staging, 306 patients were given pc-MZL diagnoses; of these, 233 patients were followed >6 months for a median follow-up of 45 months. During this long-term follow-up, extracutaneous disease developed in 1.7% (4/227) of patients with negative initial staging. One patient had central nervous system involvement (confirmed by immunoglobulin heavy chain clonality) 42 months after the initial diagnosis (with 4 negative imaging scans). One patient had disease involving the skull base and dura 184 months after the initial diagnosis (with 3 negative imaging scans). One patient had disease involving the nasopharynx 50 months after initial diagnosis (1 negative imaging scan), and another had lymph node involvement in the neck 117 months after initial diagnosis (1 negative imaging scan). All these cases were initially identified by clinical symptoms and subsequently confirmed by directed imaging and histologic evaluation. All patients were treated; their disease resolved, and all were alive during the study period. Of note, 1 patient with MZL and skin disease only at staging showed transformation to a higher-grade DLBCL after conclusion of the study period.

In the pc-FCL cohort, 165 patients were followed >6 months for a median follow-up of 47 months. During this follow-up, 3.0% (5/165) of patients with initial negative staging later had systemic disease. DLBCL developed in the lymph nodes and parotid gland of 2 patients, and FL developed in the lymph nodes of 2 patients; 1 patient had FL involvement of the colon. All patients except 1 (4/5) were bcl-2 positive at diagnosis, despite negative initial staging. The median time to systemic disease presentation was 6 (range 3-13) years. Four patients with systemic involvement were identified by imaging and 1 by physical examination.

Disease-specific survival and overall survival

The 10-year overall survival for the pc-MZL group was 92.8%, significantly better than the systemic MZL with cutaneous presentation group at 83.3% ($P < .001$). Likewise, the 10-year overall survival for the pc-FCL and FL with cutaneous presentation groups was 93.3% and 67.4%, respectively ($P < .001$). The 10-year disease-specific survival for the pc-MZL and pc-FCL groups were 100% for both and 83.3% and 81.6% for the systemic MZL and FL groups, respectively. The overall survival and disease-specific survival curves are shown for pc-MZL, systemic MZL, pc-FCL, and FL in Fig 2.

Of the 14 MZL patients with systemic involvement (at presentation and in follow-up), 2 died secondary to MZL, 1 with transformation to a higher-grade lymphoma. Of the 24 pc-FCL and FL patients with systemic involvement (at presentation and in follow-up), 3 died of disease and 1 died from complications of graft versus host disease after stem-cell transplantation.

Transformation to high-grade lymphoma

Of the 19 FL patients, 2 had systemic disease histologically consistent with DLBCL (bone, heart, testis) at presentation; both patients were alive at the conclusion of follow-up and in remission after treatment. Of the remaining 17 patients with FL, 6 experienced transformation to DLBCL during follow-up, of which 2 subsequently died of disease (both had systemic FL at presentation). Disease included lymph node, parotid gland, lung, and ocular (vitreal) involvement; 1 patient progressed with central nervous system disease in the setting of high-dose immunosuppression for autoimmune retinitis.

Yield of BM biopsy

BM biopsy was performed in 38.2% (117/306) of MZL histology cases, yielding 5 (4.2%) positive patients, of which 2 subsequently died of disease. In the FCL histology cohort, 44% (95/216) of patients had BM biopsies; 8 (8.4%) patients were positive, and 3 died. In the entire cohort (n = 522, of which 212 had a BM biopsy), 2 patients (0.9%) with extracutaneous disease were detected on BM biopsy, despite having negative imaging. In FL patients, overall survival stratified by BM involvement did not show a significant difference between the BM biopsy positive versus negative groups, although the sample size was small (n = 15).

Yield of clinical parameters

Additional clinical data of the 11 systemic MZL and 19 FL patients confirmed to have systemic disease are summarized in Table I. In FL, 89.4% of patients demonstrated involvement of the skin of the

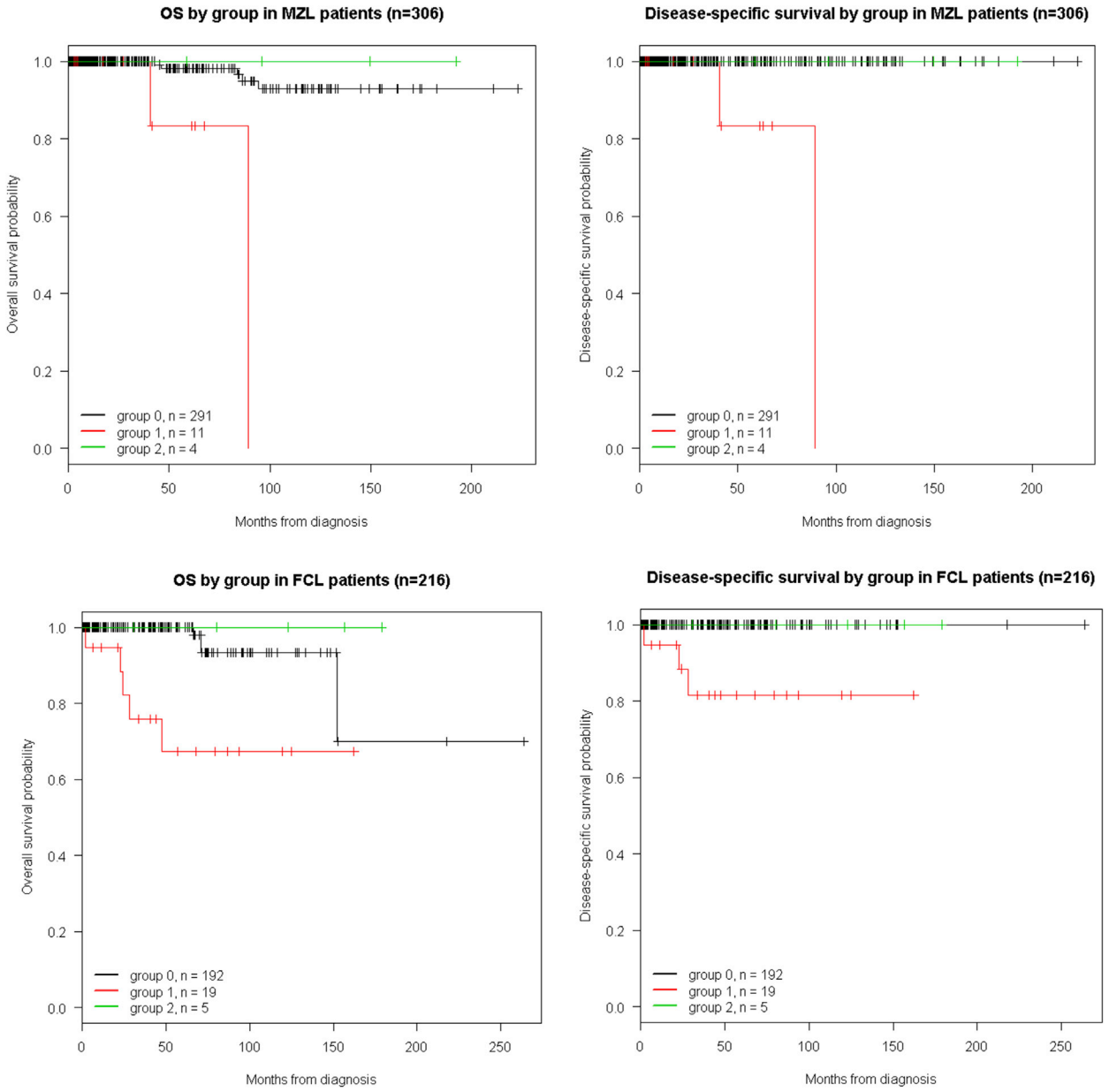

Fig 2. Overall survival and disease-specific survival for patients with MZL histology (n = 306) or FCL histology (n = 216). Group 0 includes patients with primary cutaneous MZL or FCL, group 1 includes patients with systemic MZL or follicular lymphoma presenting initially in the skin, and group 2 includes patients with primary cutaneous MZL or FCL with subsequent secondary involvement. *FCL*, Follicle center lymphoma; *MZL*, marginal zone; *OS*, overall survival.

head and neck region, and 57.9% had T1 disease at presentation. Univariate analyses (Fisher's exact test) for all patients with systemic involvement (at presentation and during follow-up) were significant for the following parameters at presentation: bcl-2 positivity ($P < .001$), elevated lactate dehydrogenase ($P = .009$), deep subcutaneous involvement on histology ($P = .006$), and clinical involvement of lower extremities ($P = .03$).

Low incidence of systemic disease in the MZL histology cohort limited similar analyses. Clinical and laboratory parameters studied in systemic MZL revealed that 63.6% of patients had disease on the trunk, 54.5% had deep subcutaneous histology, and 45.5% had T3 disease and 36.4% T1 disease at presentation. In 11 patients with systemic MZL, 10 (90.9%) patients had either T3 stage, deep subcutaneous involvement, or both.

DISCUSSION

We confirmed the overall excellent prognosis of low-grade BCLs presenting in the skin, where the great majority prove to be primary cutaneous lymphomas. Given the low probability of identifying systemic disease at presentation in patients with MZL histology in the skin, the use of imaging at staging might be individualized. To better screen for systemic involvement at presentation, we studied other clinical and laboratory parameters; however, the yield of laboratory testing was limited, as shown in other previous studies.[10] Of the patients with systemic MZL, most (90.9%) had either multifocal or extensive skin involvement (T3 disease) and large, deep lesions despite limited skin disease. On the basis of these findings, we suggest that these presentations should lead to a thorough staging evaluation. BM biopsy is often not required as routine staging in MZL histology,[8] and we confirmed the low incidence of BM involvement in our study. The development of extracutaneous disease during follow-up in patients with pc-MZL was detected in those with clinical signs and symptoms, typically years after their initial diagnosis, and patients were treated and their disease resolved. Hence, pc-MZL patients may be followed clinically with imaging reserved for times when signs or symptoms dictate.

In patients with FCL histology, the incidence of systemic involvement at presentation was low (8.8%) but higher than that for MZL histology. Bcl-2 positivity at presentation, elevated lactate dehydrogenase, deep subcutaneous involvement, or lower extremities as site of presentation should prompt systemic evaluation. Of note, 58% of patients with FL had limited (T1) skin disease. Systemic involvement in pc-FCL might occur years after initial presentation and was most frequent in those with bcl-2 positivity at presentation. However, the overall risk is low, and the use of clinical surveillance and symptom-guided imaging is preferred. Additional data is needed to guide the frequency of routine imaging in this population.

Previous data suggests that BM biopsy might be an important component of staging to rule out FL in patients with FCL histology.[7] However, in our series, imaging studies detected all but 1 FL case, which was positive by BM biopsy alone. Despite the low levels of BM screening, the overall excellent prognosis of pc-MZL and pc-FCL groups with very low levels of subsequent systemic involvement and excellent disease-specific and overall survivals is reassuring.

Limitations of our study include its retrospective nature. Moreover, the low numbers of patients with systemic involvement with MZL histology precluded further analysis of this cohort. The prognostic value of some clinical parameters was inconsistent, although our cohort might have been underpowered to detect subtle differences in prognosis with differences in clinical parameters.

In summary, we demonstrate that imaging modalities are effective at detecting extracutaneous involvement present in the small subset of patients with low-grade CBCLs presenting in the skin. Incidence of extracutaneous disease is higher in patients with FCL histology than those with MZL histology, which should be considered while counseling patients at initial and follow-up visits. Given the rarity of low-grade cutaneous lymphomas, a larger data set is needed to confirm our findings and determine additional clinical and histopathologic prognostic indicators. A multicenter collaboration platform, such as the Cutaneous Lymphoma International Collaboration or US Cutaneous Lymphoma Consortium, is well-equipped to provide more insightful and effective prognostic data in CBCLs.

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