A Clinical Analysis of Two Indolent Lymphoma Entities: Mantle Cell Lymphoma and Marginal Zone Lymphoma (Including the Mucosa-Associated Lymphoid Tissue and Monocytoid B-Cell Subcategories): A Southwest Oncology Group Study

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The objectives of this study were (1) to determine the clinical presentation and natural history associated with two newly recognized pathologic entities termed mantle cell lymphoma (MCL) and marginal zone lymphoma (MZL), including the mucosa-associated lymphoid tissue (MALT) and monocytoid B-cell subcategories, and (2) to determine whether these entities differ clinically from the other relatively indolent non-Hodgkin's lymphomas with which they have been previously classified. We reviewed the conventional pathology and clinical course of 376 patients who had no prior therapy; had stage III/IV disease; were classified as Working Formulation categories A, B, C, D, or E; and received cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) on Southwest Oncology Group (SWOG) studies no. 7204, 7426, or 7713. All slides were reviewed by the three pathologists who reached a consensus diagnosis. Age, sex, performance status, bone marrow and/or gastrointestinal involvement, failure-free survival, and overall survival were compared among all the categories. We found that (1) MCL and MZL each represent approximately 10% of stage III or IV patients previously classified as Working Formulation categories A through E and treated with CHOP on SWOG clinical trials; (2) the failure-free survival and overall survival of patients with MZL is the same as that of patients with Working Formulation categories A through E, but the failure-free survival and overall survival of the monocytoid B-cell patients were higher than that of the MALT lymphoma patients ($P = .009$ and .007, respectively); and (3) the failure-free survival and overall survival of patients with MCL is significantly worse than that of patients with Working Formulation categories A through E ($P = .0002$ and .0001, respectively). In conclusion, patients with advanced stage MALT lymphomas may have a more aggressive course than previously recognized. Patients with MCL do not have an indolent lymphoma and are candidates for innovative therapy.

MORE THAN 10 YEARS have elapsed since the publication of the National Cancer Institute's Working Formulation (WF) that provided a common language for translating between the Rappaport, Lukes-Collins, Kiel, and World Health Organization lymphoma classification schemes.[1] In the intervening years, several new pathologic entities have been recognized using morphologic, immunologic, and genetic methods. These new entities are not easily categorized in the existing classification schemes. Furthermore, the clinical behavior of these new entities has been generally described only at single institutions in small series of patients who have been treated with a variety of therapeutic approaches.

Among these new entities are cases of lymphoma that have been classified as lymphocytic lymphoma of intermediate differentiation, intermediate lymphocytic lymphoma, centrocytic lymphoma, or mantle zone lymphoma.[2-5] The term "mantle cell lymphoma" (MCL) has been recently proposed to replace these terms[6] and will be used throughout this report. Lymphomas of mantle cell type have a characteristic morphologic appearance with both distinctive microanatomic and cytologic features.[3-6] Specifically, MCL is comprised of small lymphoid cells with slightly irregular nuclear outlines and without admixed large transformed cells. Initially, MCL grows around residual normal germinal centers, giving an expanded mantle zone pattern. This zonal or "nodular" pattern progresses to a diffuse effacing pattern. The MCL phenotype is also characterized by expression of Pan B antigens ($CD20^+$, $CD22^+$), monotypic Ig (IgM^+ D^+) and coexpression of the Pan T antigen CD5.[7-9] MCL also has a characteristic chromosomal translocation t(11;14) involving the Ig heavy chain locus and the *bcl*-1 oncogene that results in the overexpression of a gene known as *PRAD1*, which encodes for *cyclin D1*.[10-14]

A second group of patients have been described as having low-grade B-cell lymphoma of mucosa-associated lymphoid tissue (MALT)[15-17] or monocytoid B-cell (MCBC) lymphoma.[18-21] The term "marginal zone B-cell lymphoma" (MZL) has been proposed to encompass both of these subcategories and will be used here.[22] The MZL designation derives from a common microanatomic feature; both lymphomas involve the marginal B-cell compartment of lymphoid tissue outside the follicular mantle zone.[15,16] Both variants also manifest secondary involvement of benign germinal centers described as follicular colonization.[23] The two entities also show considerable overlap with regard to cellular composition.[15-18,21] By definition, MCBC lymphoma is composed chiefly of clear cells with reniform or oval nuclei. MALT lymphoma often includes MCBCs as either a predominant or minority component. The two entities also have a virtually identical immunophenotype.[22] Their common immunophenotype is positive for surface Ig, not of IgD type, positive for B-cell markers CD19, CD20, and CD22 and negative for CD5 and CD23. There is no genetic rearrangement for either *bcl*-1 or *bcl*-2 loci.[22]

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Although these numerous overlapping morphologic and immunophenotypic features suggest closely related lymphomas, they also have microanatomic and distributional differences reflecting the fact that the extranodal MALT lymphoma is mucosa-based and the MCBC lymphoma is node-based.[22] In particular, the MALT lymphoma has one specific, defining microanatomic feature, called a lymphoepithelial lesion that consists of distinctive lacunae of lymphoma cells within the mucosa.[15-17] This clustered trophism for the epithelium of affected extranodal parenchymal is the characteristic MALT lymphoma feature. In contrast, the MCBC lymphoma, which lacks the lymphoepithelioid lesion, has as its defining microanatomic property a lymph node growth pattern of confluent sinuses filled with small lymphoid cells with abundant clear cytoplasm.

These new entities have now been included in the recent ''Proposal for an International Consensus on the Classification of Lymphoid Neoplasms.''[22] To determine the clinical presentation and natural history associated with newly recognized pathologic entities termed MCL and MZL and to determine whether these entities differ clinically from the other indolent lymphomas with which they have been previously classified, we reviewed the pathology and clinical course of 376 previously untreated patients with advanced stage disease and WF categories A, B, C, D, or E, who received cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) on Southwest Oncology Group (SWOG) studies no. 7204, 7426, or 7713.

PATIENTS AND METHODS

All patients were entered on three sequential randomized clinical trials (SWOG no. 7204, 7426, and 7713) between 1972 and 1983, had stage III or IV non-Hodgkin's lymphoma, and received full-dose CHOP chemotherapy or CHOP plus immunotherapy. Patient selection and eligibility criteria have been previously described.[24]

Pathologic Review

Each of the new entities in question has a distinctive microanatomic and cytologic definition allowing accurate histologic diagnosis. It is recognized that immunophenotyping, molecular probes, and cytogenetics may be needed to resolve occasional classification issues in these cases. However, for multi-institutional group study purposes, initial morphologic definition for protocol assignment is critical. To this end a morphologic review of historic SWOG low and intermediate grade lymphomas (WF A through E) was initiated.

Two of the authors (P.M.B., T.M.G.) are signatories of the recent ''Proposal for an International Consensus on the Classification of Lymphoid Neoplasms,''[22] and the third (B.N.N.) is a widely published authority on the subject of MCBC lymphoma[20] as well as on low grade lymphomas in general. Thus, the newly formulated criteria were already familiar to these pathologists and could be applied readily to the microscopic and microanatomic diagnosis of these entities. Consensus morphologic diagnosis was achieved by joint review and agreement on all cases at a multiheaded microscope.

The specific morphologic criteria are shown in Figs 1 to 3 and are described below.

MCL

MCL is morphologically homogeneous, being comprised of small, slightly irregular lymphocytes with small nucleoli and scant cytoplasm (Fig 1). These ''centrocytes'' of the Kiel scheme are less irregular than the cleaved cells of follicular lymphoma (FL; category B through D) or the diffuse small cleaved cell lymphoma (category E) of the WF. MCL is further distinguished from diffuse small cleaved cell lymphoma by its near-absence of large transformed cells. It is distinguished from FL by the more scattered follicular dendritic cells relative to the tightly formed, dense follicular dendritic cells or dendritic reticulum cells in FL.[22] Finally, MCL can be

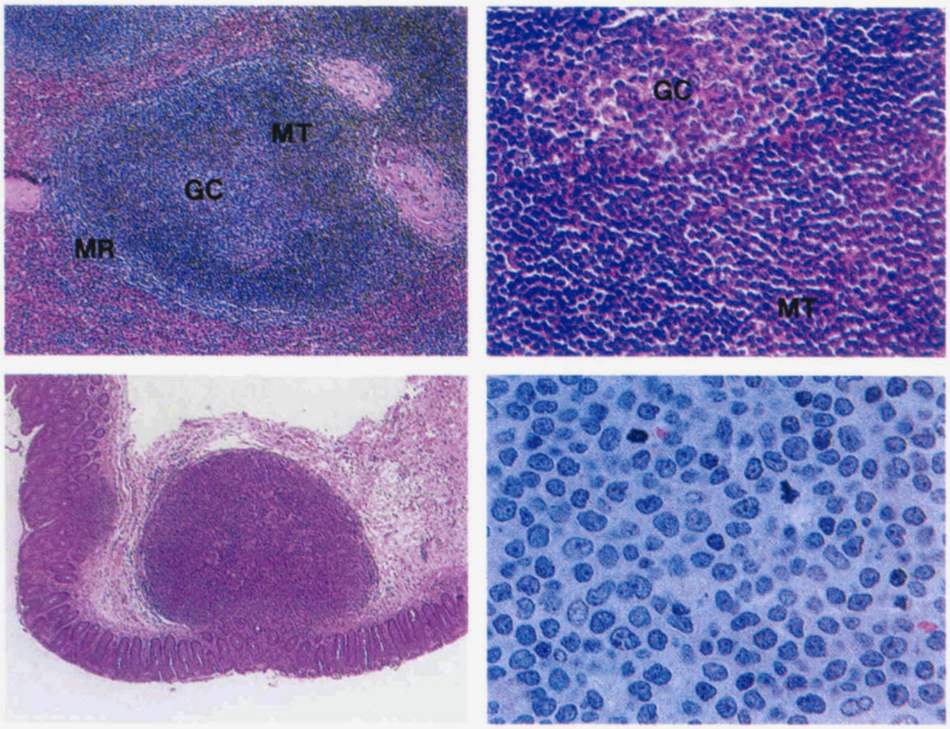

Fig 1. MCL is shown. The upper panels show splenic involvement with MCL. Note expansion of the mantle zone (MT) between the germinal center (GC) and outer marginal zone (MR). The lower left panel shows MCL-related intestinal polyposis. The lower right panel shows MCL infiltrate characterized by homogenous proliferation of small lymphoid cells with slightly irregular nuclear outlines and elevated mitotic rate.

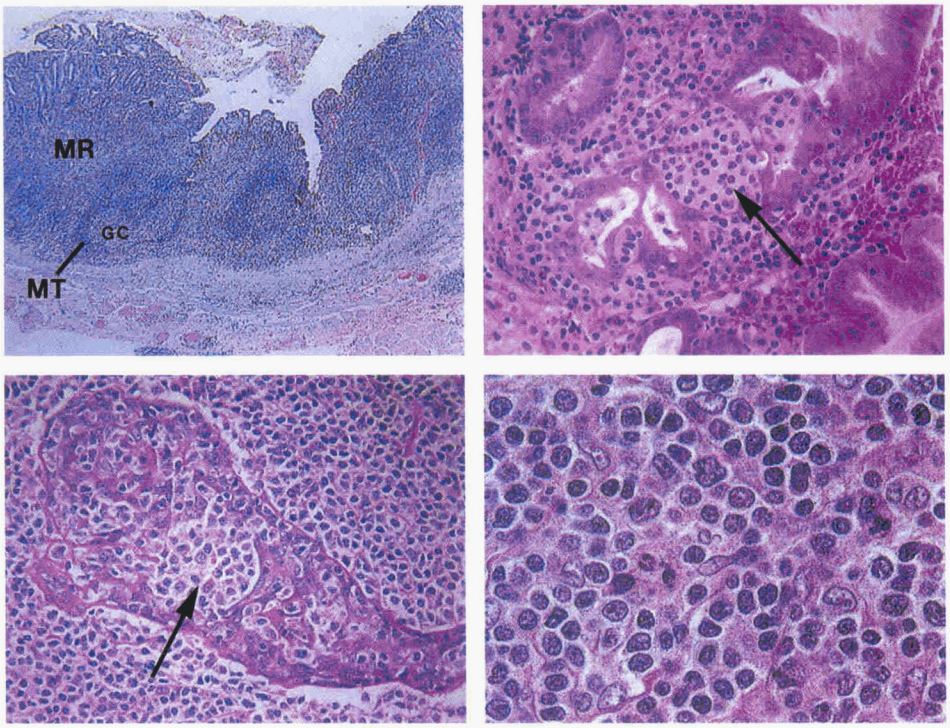

Fig 2. MALT lymphoma is shown. The upper left panel shows gastric MALT lymphoma with intact germinal centers (GC) and mantle zones (MT) with adjacent marginal zone (MR) expansion. In the upper right and lower left panels are MALT-associated lymphoepithelial lesions (+) comprised of lacunae of lymphoid cells (centrocyte-like) with the epithelium. The lower right panels shows MALT lymphoma infiltrate characterized by predominance of centrocyte-like cells.

further distinguished from category A (small lymphocytic leukemia [SLL]) by the absence of proliferation centers together with the greater irregularity of nuclear outlines in MCL.[3-6,22]

The histologic growth pattern included both nodular and diffuse types. The nodular pattern included cases growing in the mantle zone around residual germinal centers as well as those replacing germinal centers. Most commonly, the nodular pattern observed consisted of follicles infiltrated and expanded by centrocytic cells. Occasionally, naked germinal centers were found. This zonal or nodular pattern of expanded mantle zones often eventuated in a diffuse pattern of nodal effacement.

Besides the nodular and diffuse variants, a third variant was identified, the lymphoblastoid or blastoid MCL. This blastoid variant was characterized by small blastic lymphoid cells with finely dispersed

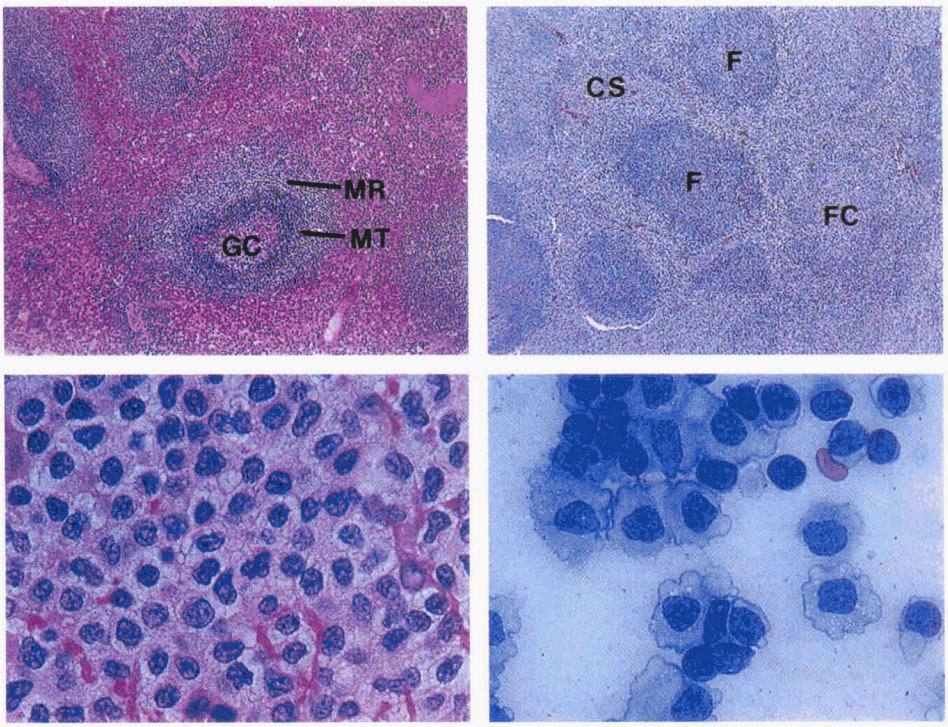

Fig 3. MCBC lymphoma is shown. The upper left panel shows splenic involvement by MCBC lymphoma with expanded marginal zone (MR), outside the mantle zone (MT) and germinal center (GC). This lesion gives a target-like effect microanatomically. The upper right panel shows MCBC lymphoma filling the outer marginal zones surrounding the follicles (F) of this lymph node produce a pattern of pale, confluent sinuses (CS). One follicle shows internal follicular colonization (FC). The lower left panel shows MCBC lymphoma infiltrate characterized by a predominance of small lymphoid cells with slightly lobated nuclei and abundant pale cytoplasm. In the lower right panel, touch preparation (Wright Giemsa stain) shows monocytoid lymphoma cells with characteristic pale abundant cytoplasm.

chromatin and a high mitotic rate as defined by Jaffe and coworkers.[25]

MZL

MALT lymphoma. All cases diagnosed as MALT lymphoma involved extranodal sites and all specifically had the distinctive microanatomic features of a lymphoepithelial lesions with several centrocyte-like lymphocytes clustered within epithelial lacunae (Fig 2).[15-17,23] In addition, most showed submucosal lymphoma spread around reactive lymphoid follicles to produce a marginal zone pattern, and some showed follicular colonization by centrocyte-like cells.

Cytologically, the lymphoid cells ranged from small round (WF category A) to small cleaved (WF category E) to slightly cleaved (centrocyte-like) cells. Typically, there were degrees of admixed monocytoid cells with slightly lobated (reniform) nuclei with abundant clear cytoplasm. Plasmacytoid differentiation was common. The various cell components were sometimes stratified in the mucosa, giving a multiphasic appearance.[15-17,23]

MCBC lymphoma. These lymphomas occurred in a lymph node distribution, the principle criterion for distinction from MALT lymphoma.[18-21] The distinctive microanatomic features included an interfollicular marginal zone nodal growth pattern with confluent sinuses (Fig 3). In some cases, germinal centers were filled with MCBCs, representing a pattern of follicular colonization (Fig 3).[18-20] The MCBCs are small lymphoid cells with slightly lobated (reniform) nuclei, inapparent nucleoli, and abundant clear cytoplasm. Plasma cells and histiocytes were sometimes admixed. These nodal MCBC lymphomas were distinguished from reactive monocytoid infiltrates primarily by advanced architectural effacement of nodal elements. Other criteria favoring malignancy were cellular pleomorphism, nuclear irregularity, and higher mitotic rate.[20] There was a high association of composite lymphoma in MCBC lymphomas, in particular with low grade FL components, suggesting that this lymphoma may evolve with varying morphologic expression.[20,21]

Statistical Methods

Survival time was defined as the time from patient registration to the time of death from any cause. Patients last known to be alive were censored at the date of last contact. Failure-free survival time was measured from registration to progression, relapse, or death from any cause. Survival distributions were estimated using the method reported by Kaplan and Meier.[26] Differences in survival between patient groups were analyzed using log-rank tests.[27] All reported significance tests are two-sided and are not corrected for multiple comparisons. Data analysis is based on follow-up information in the SWOG Statistical Center of June 1, 1994; therefore, the median follow-up is 16.5 years.

Table 1. Pathologic Categories

Original Diagnosis	Total	MCL	MZL
WF A (SL)/DLWD	70	6	5
WF B (FSC)/NLPD	171	9	15
WF C (FM)/NM	40	0	5
WF D (FL)/NH	29	0	5
WF E (DSC)/DLPD	66	21	13
Total reviewed	376	36 (10)	43 (11)

Percentages are shown in parentheses.

Abbreviations: SL, small lymphocytic; DLWD, diffuse lymphoma, well differentiated; FSC, follicular small cleaved; NLPD, nodular lymphoma, poorly differentiated; FM, follicular mixed; NM, nodular mixed; FL, follicular, large; NH, nodular histiocytic; DSC, diffuse small cleaved; DLPD, diffuse lymphoma, poorly differentiated.

RESULTS

Pathologic Categorization

The slides from 376 patients with stage III or IV disease who had been previously classified as having WF categories A through E by the SWOG Lymphoma Pathology Committee were reanalyzed by three pathologists (B.N., P.B., and T.G.). The results are shown in Table 1 using both the original Rappaport and WF terminology. A diagnosis of MCL was made in 36 patients (10%). The majority of these patients had been previously categorized as WF category E (diffuse small cleaved cell); the remaining patients were identified in WF A and B categories. No patients were identified in WF C or D. A diagnosis of MZL was made in 43 patients (11%). These patients were identified in each of the WF categories A through E. As a result of this comprehensive pathology review, 49 additional cases were excluded from WF A through E as well as the MCL and MZL categories. Thus, 248 cases remained in WF A through E.

The 36 patients with MCL could be further subclassified into nodular, diffuse, or blastic variants. The results of that subdivision were are follows: nodular, 14 (39%); diffuse, 10 (28%); and blastic, 12 (33%). The 43 patients with MZL could be further subclassified into MALT, MCBC, and not classifiable variants. The results of that subdivision were as follows: MALT, 19 (44%); MCBC, 21 (49%); and not classifiable, 3 (7%). Thirteen of 21 (62%) patients with MCBC lymphoma had concomitant presence of follicular lymphoma (''composite lymphoma''), whereas 7 of 19 (37%) patients with MALT had composite lymphoma.

Clinical Presentation

The clinical characteristics of the patients with MCL and MZL were compared to the remaining 248 patients in WF categories A through E. The results are shown in Table 2. Median age of the three groups ranged from 51 to 55 years. There was a male predominance in patients with MCL (81%) compared with those with MZL (51%) or WF A through E (54%; $P = .009$). Over 90% of the patients in each group were ambulatory (SWOG performance status [PS] 2). The percentage of patients with bone marrow involvement ranged from 46% to 53%. The percentage of patients with gastrointestinal (GI) involvement was increased in both the mantle cell group (19%) and the marginal zone group (23%) compared with that of the remaining WF A through E patients (4%; $P < .001$).

As noted previously, the subclassification of the MCLs resulted in three groups of between 10 and 14 patients. Therefore, it is difficult to convincingly separate the clinical

Table 2. Patient Characteristics

	WF A-E (n = 248)	MCL (n = 36)	MZL (n = 43)
Median age in years (range)	55 (18-81)	55 (18-76)	51 (23-76)
% Male (95% CI)	54 (48-61)	81 (64-92)	51 (35-67)
% PS > 2	8	3	5
% Bone marrow	46	53	49
% GI disease (95% CI)	4 (2-7)	19 (8-36)	23 (12-39)

Abbreviations: CI, confidence interval; PS,

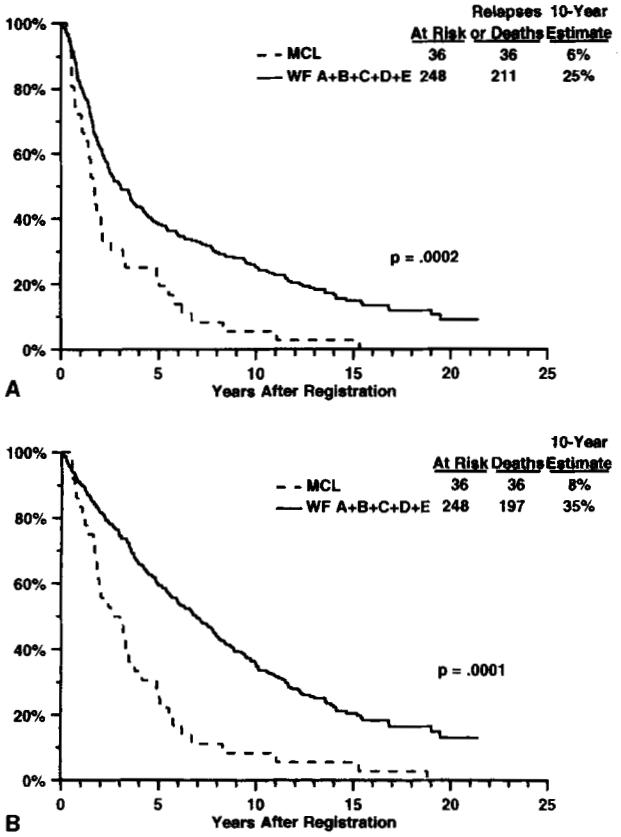

Fig 4. MCL. (A) The failure-free survival curve for 36 patients with MCL compared with 248 patients with WF A through E is shown. (B) The overall survival of 36 patients with MCL compared with 248 patients with WF A through E is shown.

characteristics of these subgroups. The blastic subgroup was younger; the diffuse group had fewer males; and the nodular group had the highest percentage with GI involvement. In addition to the fact that the MALT lymphomas were mucosa-based and all extranodal, whereas the MCBC lymphomas were node-based, the subclassification of the MZLs into MALT lymphomas and MCBC lymphomas failed to show any significant differences in clinical presentation except that the MALT lymphoma group did have more patients with GI involvement than the MCBC group (8 of 19 [42%] *v* 2 of 21 [10%]; $P = .03$). The extranodal sites of involvement for the MALT lymphomas included the following: 8, GI; 4, skin; 2, parotid; 2, lung; 2, breast; and 1, nasopharynx. Nodal involvement was found in 15 of 19 (79%) of MALT lymphomas.

Failure-Free Survival and Survival

The failure-free survival for the 36 patients with MCL was significantly shorter than that of the 248 remaining patients with WF A through E, as shown in Fig 4A. The 10-year failure-free survival estimate was only 6% compared with 25% for WF A through E ($P = .0002$). The overall 10-year estimated survival, as shown in Fig 4, was also significantly reduced for the MCL patients (8%) as compared with that of the patients with WF A through E (35%; $P = .0001$). In fact, the failure-free survival and overall survival estimates for the patients with MCL were lower than those for WF A, WF B, WF C, WF D, or WF E when examined as separate groups (data not shown).

The subclassification of the MCLs into blastic, diffuse, and nodular did result in statistically different failure-free survival and overall survival curves ($P = .05$ for both), as shown in Figs 5A and B, although the biologic significance of these differences is not clear because the 10-year failure-free survival estimates were 0%, 10%, and 7%, respectively.

In contrast, the failure-free survival for the 43 patients with MZL was similar to that of the 248 remaining patients with WF A through E, as shown in Fig 6A. The 10-year failure-free survival estimate was 36% compared with the 25% for WF A through E ($P = .26$). The overall 10-year estimated survival, as shown in Fig 6B, was also not significantly reduced for the MZL patients (39%) as compared with that of the patients with WF A through E ($P = .83$). Furthermore, if one prefers to compare the failure-free survival and overall survival for the 43 MZL patients with that of the 210 patients in the classically defined low grade lymphomas (WF A, B, and C), the results are also similar ($P = .22$ and .89, respectively).

The subclassification of the MZLs into the MALT

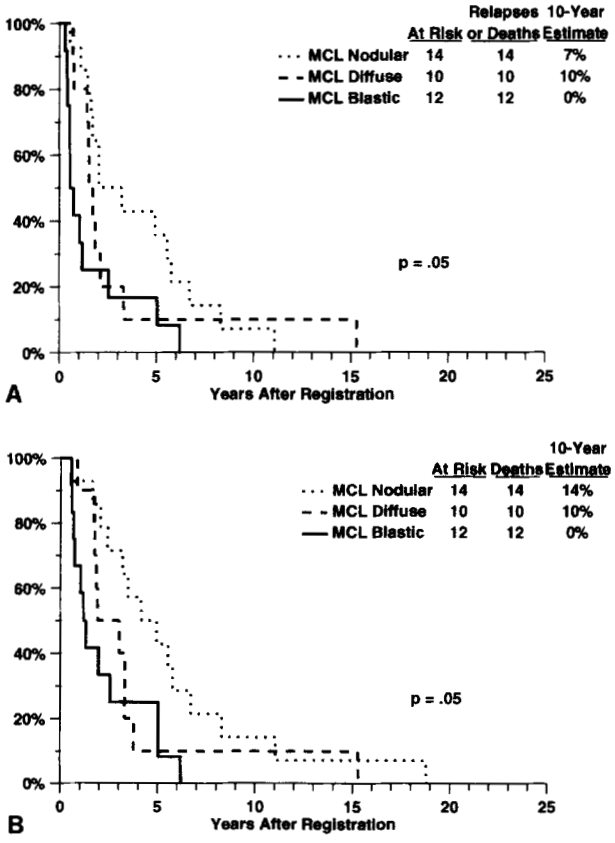

Fig 5. MCL subcategories. (A) The failure-free survival curve for 14 patients with nodular variant, 10 patients with diffuse variant, and 12 patients with blastic variant is shown. (B) The overall survival for 14 patients with nodular variant, 10 patients with diffuse variant, and 12 patients with blastic variant is shown.

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