

Comprehensive evaluation of disease characteristics and outcomes of patients with extramedullary multiple myeloma in the modern era

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Abstract

Multiple myeloma (MM) derives from the clonal proliferation of plasma cells, primarily residing in the bone marrow. However, MM cells can disseminate systemically, leading to osseous or soft tissue extramedullary disease (EMM) or plasma cell leukemia (PCL). The presence of EMM or PCL has historically been linked to poor prognosis and aggressive features. In this study, we analyzed 201 patients with EMM treated at our institution between January 1, 2010, and November 30, 2023. Among these patients, 25 had primary PCL, 19 had secondary PCL, 89 were diagnosed with EMM at the time of MM diagnosis, 29 developed EMM after therapy, and 39 had solitary plasmacytoma (SP), with 20 progressing into MM. Patients with EMM at the time of MM diagnosis or SP progressing to MM exhibited a median overall survival (OS) comparable to those with MM alone (7.5 years or not reached). However, the presence of EMM was associated with worse prognosis in specific groups: primary PCL (median OS: 26 months), secondary PCL (median OS: 1.6 months), and secondary EMM (median OS: 16 months). Additional prognostic features included high Revised International Staging System, chromosomal abnormalities (1q+, 17p deletion, and 13q deletion), and elevated lactate dehydrogenase values at presentation. While the site of EMM did not correlate with inferior outcomes, osseous SP increased the risk of progression to overt MM. In conclusion, the presence of EMM confers variable prognosis, emphasizing the need for more effective therapeutic strategies, particularly for patients with PCL or those developing EMM later during treatment.

Introduction

Plasma cell dyscrasias are clonal proliferations of plasma cells (PC), resulting in a spectrum of clinical conditions, ranging from the asymptomatic presence of a monoclonal protein in the blood or urine to symptomatic disease with organ damage.¹ Usually, multiple myeloma (MM) cells remain in the bone marrow (BM), relying on the support from the BM niche to survive. However, MM cells can become independent from the BM niche and disseminate systemically. These more aggressive forms of plasma cell dyscrasias include osseous and soft tissue extramedullary disease (EMM)²⁻⁴ and plasma cell leukemia (PCL).^{5,6} Moreover, a solitary plasmacytoma (SP) mass, which is a localized infiltration of PC in the bones or other sites,^{7,8} can also progress to overt MM.⁹ Historically, the presence of EMM or PCL has been considered a poor prognostic factor, often associated with

aggressive genetic features, and an overall survival (OS) of only a few months.^{3,4,10,11} In recent years, the approval of more effective therapies and the widespread use of sensitive diagnostic strategies have slightly improved outcomes. However, the development of EMM, especially after prior therapies for MM, remains an unmet need^{4,10,12} and data regarding the most effective treatments are quite limited. In this study, we investigated the patient and disease characteristics, trends in therapies and outcomes, and prognostic factors of 201 patients with PCL or EMM treated at our institution (Figure 1).

Methods

Patient population

Medical records of all adult patients diagnosed with EMM (primary or secondary PCL, osseous or soft tissue plas-

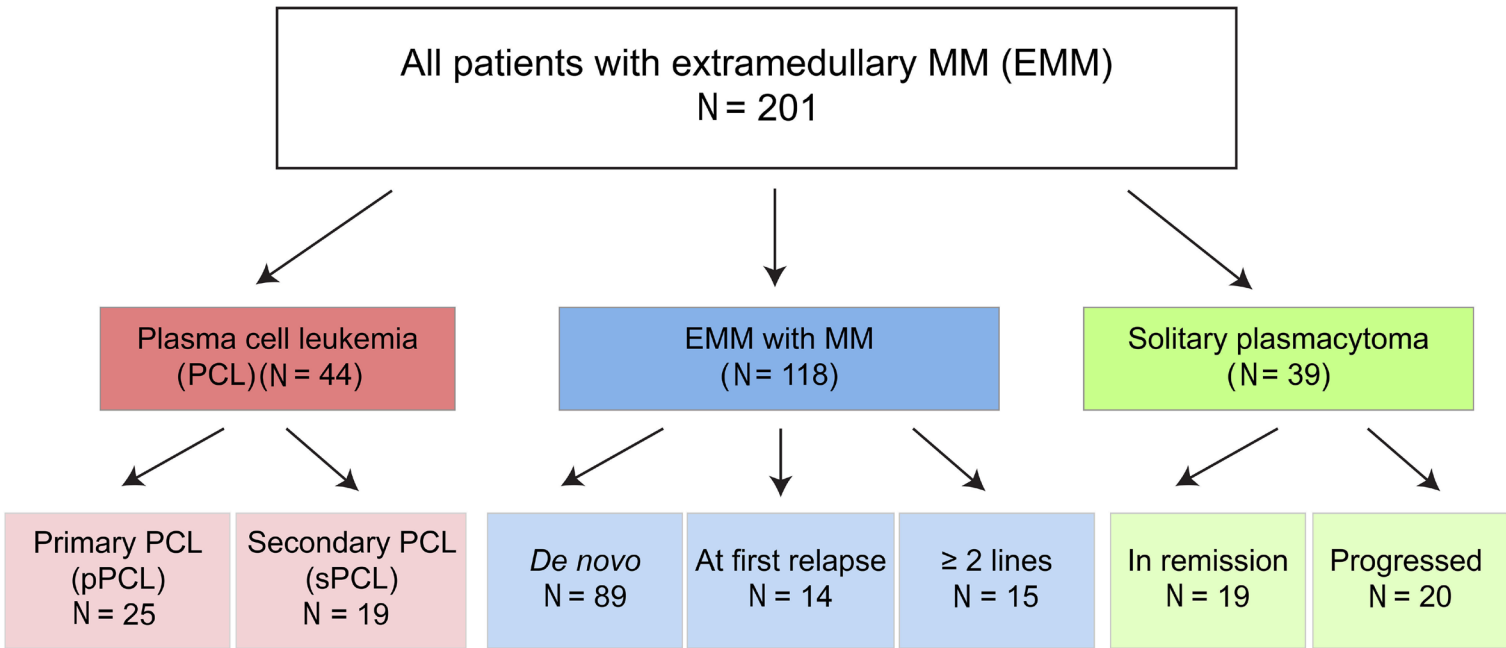


Figure 1. Consort diagram describing all the patients with extramedullary myeloma identified and included in this study. MM: multiple myeloma.

macytoma either with concomitant systemic involvement or as solitary presentation) were reviewed to include all patients seen at our center between January 1, 2010, and November 30, 2023. This study was approved by the Ohio State University Institutional Review Board (OSU 2010C0126 and OSU-23386). International staging system (ISS) and response criteria were based on the consensus criteria of the International Myeloma Working Group. High-risk cytogenetics were defined by the detection of t(4;14), t(14;16), t(14;20), or 17p deletion by fluorescence *in situ* hybridization (FISH). PCL, EMM, and SP were defined based on consensus guidelines,^{3,7,10,13} as described in the *Online Supplementary Appendix*.

Statistical analysis

We performed three separate analyses to compare disease characteristics associated with outcomes in: (i) patients with primary PCL (pPCL) or secondary PCL (sPCL); (ii) patients with osseous EMM or soft tissue EMM (excluding PCL) at diagnosis (*de novo*), at first relapse, or after ≥2 lines of therapy (secondary EMM); (iii) patients with SP who did or did not progress to overt MM (Figure 1). Descriptive statistics were used to summarize the patient and disease characteristics in each cohort, with median and range for continuous variables, and frequency and percentage for categorical variables. A Cox regression model was used to identify prognostic factors for progression-free survival (PFS) and OS.

Results

Baseline characteristics of patients with plasma cell leukemias

In our institutional registry, we identified 25 patients with

pPCL and 19 patients with sPCL, diagnosed between January 2010 and November 2022 (Table 1). Median age at diagnosis was 56 years (range, 35-80) for pPCL and 67 years (range, 40-83) for sPCL. No differences were observed in sex, race, or MM type between the two groups. FISH analysis was performed at time of pPCL or initial MM diagnosis in 42 patients, revealing higher rates of t(11;14), 17p deletion, and 1q+ compared to published data in patients with MM alone¹ (t(11;14): pPCL=26.1%, sPCL=36.9%; 17p deletion: pPCL=30.4%, sPCL=15.8%; 1q+: pPCL=34.8%, sPCL=63.2%). Five of 19 patients had repeated BM biopsies at time of transformation to sPCL. New chromosomal abnormalities were identified in all patients including *MYC* rearrangements (3/5), 17p deletions (4/5), and 1q+ (1/5), suggesting clonal evolution. While the percentage of circulating PC (pPCL=26.4%, range, 10-81%; sPCL=38%, range, 11-87%), the levels of β-2 microglobulin (B2M), and the ISS stages at time of pPCL diagnosis or transformation to sPCL were comparable between groups, median lactate dehydrogenase (LDH) values were higher in patients with sPCL (pPCL: 278 U/L, range, 108-2,718; sPCL: 530 U/L, range, 145-3,232; *P*=0.008), indicating rapid disease kinetics at transformation. pPCL cells often downregulate adhesion markers such as CD56 and CD27 to evade the BM niche, while upregulating CD20, CD19, CD45, and CD44.^{14,15} Additionally, surface expression of specific antigens is influenced by prior therapies, as demonstrated by CD38 downregulation following treatment with anti-CD38 monoclonal antibodies.^{16,17} In our cohort, seven of 13 patients with sPCL and available flow cytometry data at time of transformation have received anti-CD38 monoclonal antibodies between 0-12 months prior, potentially affecting CD38 expression. To better understand immunophenotypic differences between pPCL and sPCL, we first analyzed peripheral blood (PB) samples. Median CD56 clone size was higher in sPCL compared to

Table 1. Demographics and clinical characteristics of patients with primary plasma cell leukemia or secondary plasma cell leukemia.

Cohort characteristics	All, N=44	pPCL, N=25	sPCL, N=19	P
Age, years, median (range)	65 (35-83)	56 (35-80)	67 (40-83)	0.21
Sex, N (%)				1.00
Male	25 (56.8)	14 (56.0)	11 (57.8)	
Female	19 (43.2)	11 (44.0)	8 (42.2)	
Race, N (%)				0.11
Non-Hispanic White	36 (81.8)	18 (72.0)	18 (94.7)	
Non-Hispanic Black	8 (18.2)	7 (28.0)	1 (5.3)	
MM type, N (%)				0.58
IgA	10 (22.7)	6 (24.0)	4 (21.0)	
IgG	22 (50.0)	16 (52.0)	9 (47.4)	
LCD	10 (22.7)	6 (24.0)	4 (21.0)	
Other	2 (4.6)	0	2 (10.6)	
Cytogenetic risk group, N (%)	N=42	At PCL diagnosis, N=23	At MM diagnosis, N=19	0.45
Standard	25 (59.5)	12 (52.2)	13 (68.4)	
High	17 (40.5)	11 (47.8)	6 (31.6)	
1q+, N (%)				0.13
No	22 (52.4)	15 (65.2)	7 (36.8)	
Yes	20 (47.6)	8 (34.8)	12 (63.2)	
13q deletion, N (%)				0.45
No	17 (40.5)	11 (47.8)	6 (31.6)	
Yes	25 (59.5)	12 (52.2)	13 (68.4)	
17p deletion, N (%)				0.30
No	32 (76.2)	16 (69.6)	16 (84.2)	
Yes	10 (23.8)	7 (30.4)	3 (15.8)	
Translocation (11;14), N (%)				0.68
No	29 (69.1)	17 (73.9)	12 (63.1)	
Yes	13 (30.9)	6 (26.1)	7 (36.9)	
Translocation (4;14), N (%)				1.00
No	36 (85.7)	20 (86.9)	16 (84.2)	
Yes	6 (14.3)	3 (13.1)	3 (15.8)	
MYC rearrangement, N (%)				1.00
No	34 (81.0)	19 (82.6)	15 (78.9)	
Yes	8 (19.0)	4 (17.4)	4 (21.1)	
LDH, U/L, median (range), N=40	278 (108-3,232)	278 (108-2,718)	530 (145-3,232)	0.008
B2M, mg/L, median (range), N=31	6.2 (1.7-25.7)	6.15 (1.7-25.7)	6.4 (2-24)	0.91
ISS stage at pPCL or sPCL diagnosis	N=34	N=21	N=13	0.79
1-2	16 (47.0)	9 (42.9)	7 (53.8)	
3	18 (53.0)	12 (57.1)	6 (46.2)	

pPCL: primary plasma cell leukemia; sPCL: secondary plasma cell leukemia; MM: multiple myeloma; LCD: light chain disease; MYC: myelocytomatosis; LDH: lactate dehydrogenase; B2M: β -2 microglobulin; ISS: international staging system.

pPCL (pPCL=24.7%, sPCL=46.3%; Figure 2A), while median CD38 and CD28 clone sizes were lower (CD38: pPCL=98.0%, sPCL=74.0%; CD28: pPCL=27.0%, sPCL=9.3%; *Online Supplementary Figure S1A*; *Online Supplementary Table S1*). No significant differences were observed in other surface markers, including CD117, often downregulated in PCL, or CD20, which is more frequently expressed in PCL than in MM (*Online Supplementary Figure S1A*). Comparing the BM phenotype at initial pPCL or MM diagnosis, both groups exhibited similar profiles, except for greater CD28 clone size in patients with pPCL, a marker of BM long-living normal PC¹⁸ (pPCL=10.5%, sPCL=1.3%; *Online Supplementary Figure S1B*). Next, we assessed differences between PB and BM

phenotypes in patients with pPCL or sPCL. While median values remained consistent between PB and BM phenotypes in pPCL (*Online Supplementary Figure S1C*), CD38, CD56, and CD28 clone sizes varied greatly between PB and BM in each individual patient (*Online Supplementary Figure S1D*), reflecting variabilities between sites. In patients with sPCL, additional differences were also noted in CD56 and CD28 clone sizes (CD56: PB=46.3%, BM=2%; CD28: PB=1.3%, CD28 BM=9.3%; $P=0.08$; *Online Supplementary Figure S1E*).

Treatment and outcomes of patients with plasma cell leukemias

As initial therapy for pPCL, 13 of 25 (52%) patients re-

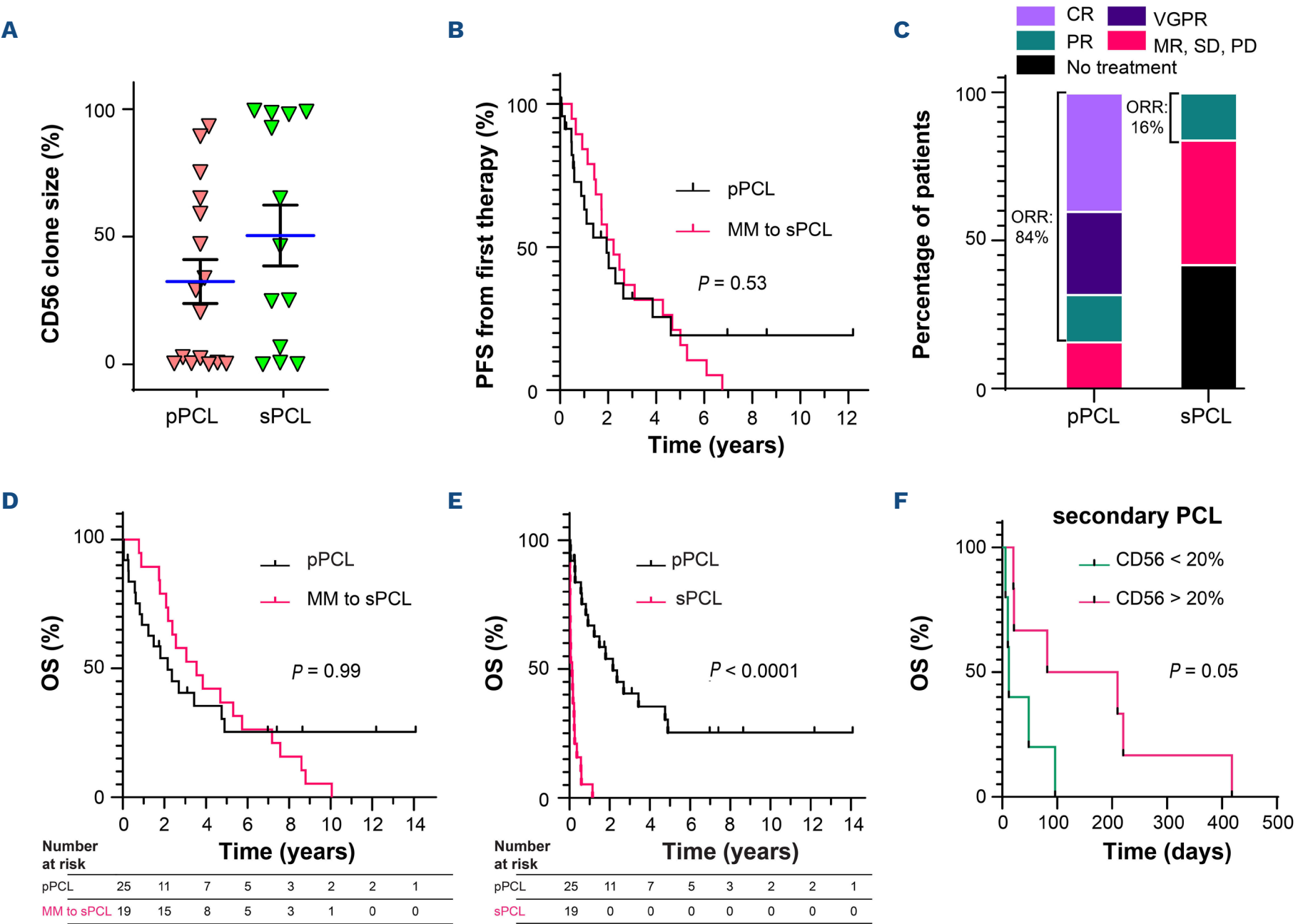


Figure 2. Characteristics and outcomes of patients with plasma cell leukemia. (A) CD56 clone sizes in the peripheral blood of patients with primary plasma cell leukemia (pPCL) or secondary PCL (sPCL). (B) Kaplan-Meier estimates of progression-free survival (PFS) from the day of first therapy among patients with pPCL (N=25) or patients with multiple myeloma (MM) who later developed sPCL (MM to sPCL, N=19). Time is calculated from first day of therapy for pPCL or for MM (MM to sPCL) to death or last follow-up. $P=0.53$. (C) Response rates to first-line therapy in patients with pPCL or sPCL. CR: complete responses; VGPR: very good partial responses; PR: partial responses; MR: minimal responses; SD: stable disease; PD: progressive disease. Overall response rate (ORR) includes CR, VGPR, and PR. $P<0.0001$. (D) Kaplan-Meier estimates of overall survival (OS) among patients with primary PCL (pPCL, N=25) or secondary PCL (sPCL, N=19) from date of diagnosis (either pPCL or initial MM) to death or last follow-up. $P=0.99$. (E) Kaplan-Meier estimates of OS among patients with pPCL (N=25) or sPCL (N=19) from date of diagnosis or transformation to death or last follow-up. $P<0.0001$. (F) Kaplan-Meier estimates of OS among patients with sPCL based on CD56 clone size (<20%, N=5; >20%, N=6) from date of transformation to death or last follow-up. $P=0.05$.

ceived chemotherapy with bortezomib, either as VD-PACE (bortezomib, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide, 7/25 patients) or CyBorD (cyclophosphamide, bortezomib, dexamethasone, 6/25 patients). The remaining 12 patients (48%) received bortezomib, lenalidomide, and dexamethasone (VRD) or carfilzomib, lenalidomide, and dexamethasone (KRD). Induction therapy was followed by autologous stem cell transplant (ASCT) in 11 of 25 (44%) patients, with one patient undergoing two consecutive transplants. Seventeen of 25 (68%) patients with pPCL achieved a very good partial response (VGPR) or better after induction therapy, four of 25 (16%) achieved a partial response (PR), and the remaining patients had minimal responses (MR). No significant differences in overall response rates (ORR) were observed comparing chemotherapy-based regimens (VD-PACE or CyBorD) to proteasome inhibitor-based combinations (VRD or KRD) ($P=0.09$; *Online Supplementary Figure S2A*). Patients treated with VD-PACE had a lower ORR (57%) compared to those receiving other regimens (94%), but this difference did not reach statistical significance ($P=0.053$; *Online Supplementary Figure S2B*). Maintenance therapy was started in 12 patients, with either lenalidomide, bortezomib, or a combination of two drugs. Median PFS from day of first therapy was 1.01 years (95% confidence interval [CI]: 0.56–3). At the time of relapse, a variety of treatment regimens were employed, often incorporating chemotherapy, and three patients underwent allogeneic stem cell transplantation. Patients who later developed sPCL received frontline therapy for MM with either CyBorD or VRD, followed by ASCT in 11 of 19 (57.8%) patients. Fourteen of 19 (73.9%) patients achieved a VGPR or better. PFS from first therapy for MM was 2.22 years (95% CI: 1.71–5), which is similar to that of patients with high-risk myeloma^{19,20} or pPCL ($P=0.53$; Figure 2B). The median time to transform to sPCL was 3.5 years (range, 0.74–9.8). At the time of transformation patients with sPCL were already heavily pre-treated (median prior lines: 5, range, 1–12). Eight of 19 (42.1%) of them did not receive treatment and succumbed to progressive disease. The remaining 11 patients received a chemotherapy-based regimen (4/11, 36%), a carfilzomib-based regimen (5/11, 45%), or an anti-CD38 antibody-based regimen (2/11, 19%). No patients achieved a VGPR or better and only three of 11 (27.3%) patients achieved a PR. While the ORR from first therapy was 84% (95% CI: 64–95%) in patients with pPCL, it was only 16% (95% CI: 3–40%) in patients treated for sPCL ($P<0.0001$; Figure 2C). Median duration of response among the patients who received treatment for sPCL was only 1.6 months, likely due to the high refractoriness of their disease (*Online Supplementary Figure S2C*). The OS of patients with pPCL and sPCL remained inferior compared to those with MM. For patients with pPCL, the median OS from the date of pPCL diagnosis was 2.17 years (95% CI: 1.23–not reached [NR]). For patients with MM who transformed to sPCL, the OS was 3.55 years from the

initial MM diagnosis (range, 2.38–7.58; $P=0.99$; Figure 2D). However, when measured from the time of transformation, the median OS drastically decreased to 1.6 months (0.3 years, range, 0.04–0.37; $P<0.0001$; Figure 2E).

Independent factors associated with OS among the patients with pPCL included the presence of 17p deletion (univariable analysis hazard ratio [UVA HR] =4.06, 95% CI: 1.26–13.1; $P=0.02$; multivariable analysis [MVA HR] =3.82, 95% CI: 1.22–11.98; $P=0.022$; *Online Supplementary Table S2*; *Online Supplementary Figure S2D*) and the percentage of circulating PC (HR=1.02, 95% CI: 0.99–1.04; $P=0.09$).

In patients with sPCL (*Online Supplementary Table S3*), elevated LDH levels were associated with inferior OS in both UVA and MVA models (UVA HR=1.11, 95% CI: 1.02–1.21; $P=0.01$; MVA HR=1.17, 95% CI: 0.99–1.38; $P=0.059$). Instead, CD56 clone size was associated with a better OS (HR=0.98, 95% CI: 0.97–1.0; $P=0.065$), potentially indicating a less niche-independent phenotype (Figure 2F).

Baseline characteristics of patients with extramedullary multiple myeloma

Excluding patients with PCL, we identified 118 patients with EMM in our registry (*Online Supplementary Figure S3A*). Osseous plasmacytomas were present in 84 of 118 (71.2%) patients (47 paraspinal and 37 cases originating from other contiguous bones), while the remaining 34 patients had soft tissue plasmacytomas, with skin, muscle or lymph nodal involvement (9 patients), osteo-dural involvement (8 patients), central nervous system (CNS) involvement indicated by orbital involvement or positive cerebrospinal fluid for PC (4 patients), or visceral involvement (3 patients with lung, testis, or larynx).

Among the entire cohort, 88 of 118 (74.6%) patients received local radiation therapy at the site of plasmacytoma followed by systemic therapy, while 30 (25.4%) patients received systemic therapy alone. As induction systemic therapy, 37 (31.3%) patients received VRD, 58 (49.2%) patients received bortezomib-dexamethasone (VD) or lenalidomide-dexamethasone (RD), five (4.2%) patients received daratumumab-VRD, and 18 (15.3%) patients received other regimens including carfilzomib or cyclophosphamide. ASCT was used for consolidation in 88 of 118 (74.6%) patients. Maintenance therapy was started in 90 of 118 (76.3%) patients. Among these, 72/90 (80%) patients received a single drug (lenalidomide or bortezomib), while 18 of 90 (20%) patients were treated with two agents (18/90, 20%). The ORR from initial therapy was 95%, while the PFS from MM diagnosis in the entire cohort was 2.49 years. Factors associated with inferior PFS in the UVA included age (HR=1.03, 95% CI: 1–1.05), 13q deletion (HR=1.54, 95% CI: 1.01–2.34), 17p deletion (HR=2.49, 95% CI: 1.26–4.9), high R-ISS stage (stage 2: HR=2.23, 95% CI: 1.37–3.63; stage 3: HR=3.66, 95% CI: 1.61–8.31), site of EMM (HR=1.52, 95% CI: 0.99–2.33), and timing of EMM (at first relapse: HR=2.23, 95% CI: 1.23–4.04; after ≥ 2 lines of therapy: HR=2.14, 95%

CI: 1.21-3.79); while the use of ASCT improved PFS as expected (HR=0.48, 95% CI: 0.31-0.76). Age (HR=1.04, 95% CI: 1.01-1.07), 17p deletion (HR=1.69, 95% CI: 0.78-3.66), and high R-ISS (stage 2: HR=2.02, 95% CI: 1.22-3.35; stage 3: HR=3.84, 95% CI: 1.54-9.54) remained significant in the MVA. Site of EMM did not affect ORR (osseous: 95%, 95% CI: 88-99%; soft tissue: 94%, 95% CI: 80-99%; $P=1.0$) or complete response (CR) rates (osseous: 32%, 95% CI: 22-43%; soft tissue: 41%, 95% CI: 25-59%; $P=0.35$; Figure 3A). However, patients with osseous EMM had a shorter PFS (median: 2.47 years, 95% CI: 2.15-4.07), with an estimated 5-year PFS of 30% (95% CI: 22-42%), compared to patients with soft tissue EMM who had a median PFS of 2.89 years (95% CI: 1.76-4.37), with an estimated 5-year PFS of 23% (95% CI: 12-43%; *Online Supplementary Table S4*; Figure 3B). The median OS in the entire cohort was 6.39 years (95%

CI: 5.58-8.77). Factors associated with inferior OS in the UVA and MVA (*Online Supplementary Table S5*) were similar to those associated with PFS, including age (UVA HR=1.04, 95% CI: 1.01-1.08; MVA HR=1.06, 95% CI: 1.02-1.09), high R-ISS (stage 2: UVA HR=2.51, 95% CI: 1.37-4.59, MVA HR=2.59, 95% CI: 1.37-4.89; stage 3: UVA HR=8.87, 95% CI: 3.56-22.1, MVA HR=12.17, 95% CI: 4.33-34.17), 1q+ (UVA HR=1.6, 95% CI: 0.98-2.69), 13q deletion (UVA HR=1.66, 95% CI: 1.03-2.69), and timing of EMM (at first relapse: UVA HR=2.37, 95% CI: 1.25-4.49; MVA HR=2.55, 95% CI: 1.22-5.30; after ≥ 2 lines of therapy: UVA HR=1.69, 95% CI: 0.91-3.13, MVA HR=1.29, 95% CI: 0.65-2.59). In our cohort, the site of EMM did not significantly affect survival, with a median OS of 7.18 years for patients with osseous EMM (95% CI: 5.64-12.44) versus 5.96 years for patients with soft tissue EMM (95% CI: 4.93-8.47; *Online Supplementary Figure S3B*). Finally,

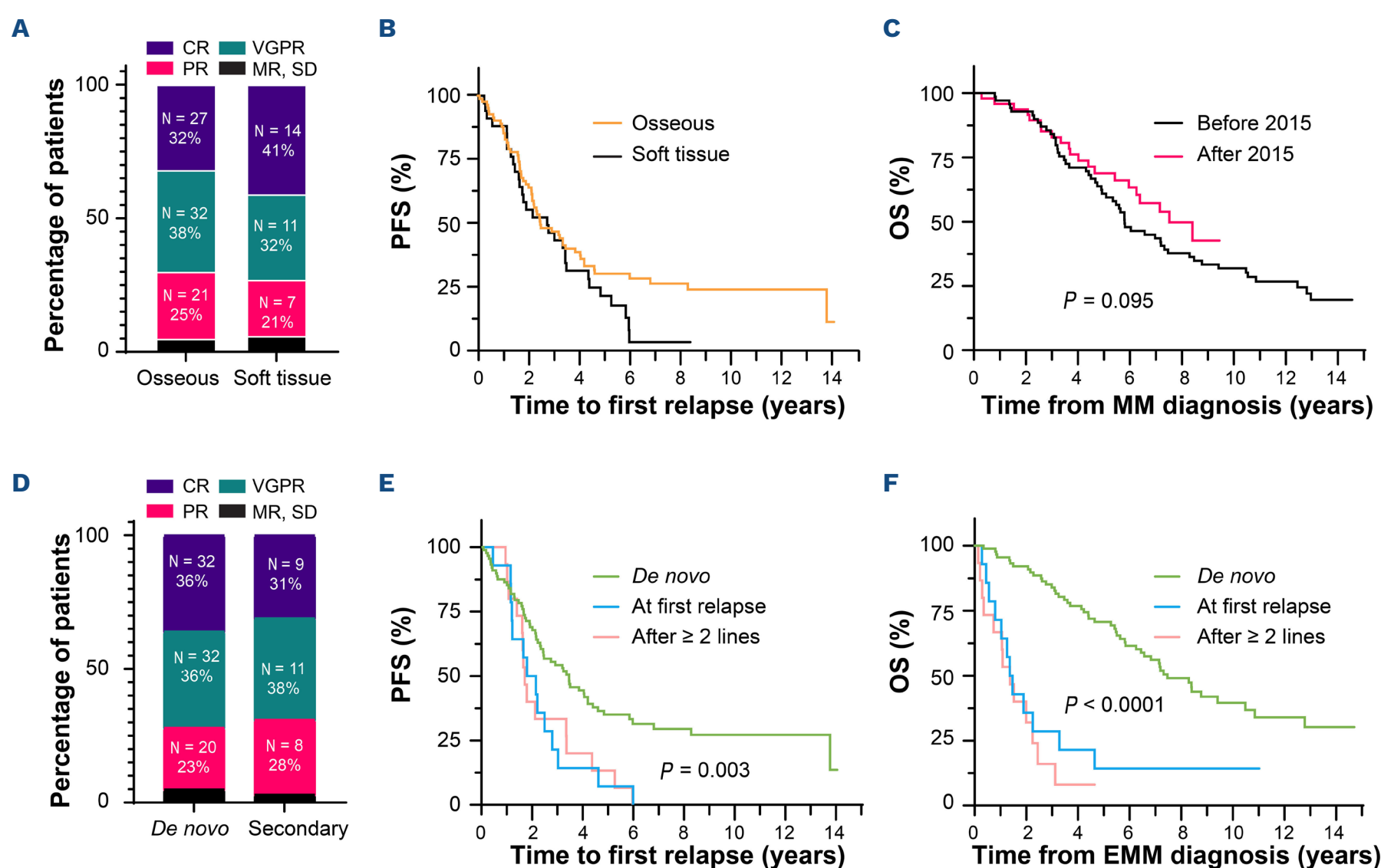


Figure 3. Characteristics and outcomes of patients with extramedullary myeloma. (A) Response rates to first line therapy in patients with osseous extramedullary multiple myeloma (EMM) (N=84) or soft tissue EMM (N=34). CR: complete response; VGPR: very good partial response; PR: partial response; MR: minimal response; SD: stable disease. P =not significant (NS). (B) Kaplan-Meier estimates of progression-free survival (PFS) among patients with osseous EMM (N=84) or soft tissue EMM (N=34) from date of original MM diagnosis to disease progression or last follow-up. (C) Kaplan-Meier estimates of overall survival (OS) among patients with EMM diagnosed before (N=70) or after (N=48) January 2015 from date of original MM diagnosis to death or last follow-up. $P=0.095$. (D) Response rates to first-line therapy in patients with *de novo* EMM (N=89) or secondary EMM (N=29). P =NS. (E) Kaplan-Meier estimates of PFS among patients with *de novo* EMM (N=89), EMM at first relapse (N=14), or EMM after ≥ 2 lines of therapy (N=13) from date of original MM diagnosis to disease progression or last follow-up. $P=0.003$. (F) Kaplan-Meier estimates of OS among patients with *de novo* EMM (N=89), EMM at first relapse (N=14), or EMM after ≥ 2 lines of therapy (N=13) from date of EMM diagnosis to death or last follow-up. $P<0.0001$.

we evaluated OS based on the year of diagnosis to determine whether novel therapies improved the outcomes. The median OS in patients diagnosed before January 2015 (N=70) was 5.79 years (95% CI: 4.93–7.47), while median OS in patients diagnosed after January 2015 (N=48) was not reached (NR) (95% CI: 6.26–NR; $P=0.095$; Figure 3C), indicating an improvement over time.

Treatment and outcomes of patients with *de novo* or secondary extramedullary multiple myeloma

The timing of EMM diagnosis predicted OS in both the UVA and MVA. Eighty-nine of 118 (74.5%) patients had EMM at the time of MM diagnosis (*de novo* EMM), 14 of 118 (11.8%) developed EMM at first relapse, and 15 of 118 (13.7%) developed EMM after ≥ 2 lines of therapy (secondary EMM; Table 2). As induction therapy, patients with *de novo* EMM (N=89) or secondary EMM (N=29) received similar regimens, including VRD (*de novo*: 30/89, 33.7%; secondary EMM: 7/29, 24.1%) or VD/RD (*de novo*: 41/89, 46%; secondary EMM: 17/29, 58.6%) followed by ASCT in 61/89 (68.5%) and 27/29 (93.1%) patients, respectively. Maintenance therapy was started in 65 of 89 (73%) and 25/29 (86%) patients. The ORR was similar between patients with *de novo* or secondary EMM (94% and 97%, respectively; $P=1.0$). Following induction therapy, CR was achieved in 32/89 (36%) patients with *de novo* EMM and in nine of 29 (31%) patients with secondary EMM ($P=0.662$; Figure 3D).

Patients with EMM at diagnosis had a longer response to induction treatment (median: 3.36 years, 95% CI: 2.34–4.31) compared to patients who developed EMM at first relapse (median: 1.98 years, 95% CI: 1.22–4.62) or after ≥ 2 lines of therapy (median: 1.71 years, 95% CI: 1.61–4.37; $P=0.0025$; Figure 3E). The estimated 5-year PFS was 34% (95% CI: 25–46%), 7% (95% CI: 1–47%), and 13% (95% CI: 4–48%) in patients with *de novo* EMM, EMM at first relapse, or EMM after ≥ 2 lines of therapy, respectively (Online Supplementary Table S6). This finding indicates that patients who experience rapid relapse with EMM acquired a more aggressive disease phenotype, resulting in poor outcomes. The median OS from MM diagnosis in patients with *de novo* EMM was 7.52 years (95% CI: 6.26–12.8), 4.62 years in patients with EMM at first relapse (95% CI: 2.95–NR), and 5.82 years in patients with EMM after ≥ 2 lines of therapy (95% CI: 3.66–NR) (Online Supplementary Figure S3C; Online Supplementary Table S7).

At relapse, patients with secondary EMM had received a median of two prior lines (range, 1–10) and were treated with current standard therapies, including anti-CD38 antibodies (daratumumab or isatuximab), carfilzomib, pomalidomide, anti-BCMA (B-cell maturation antigen) therapies, or chemotherapy (VD-PACE, ASCT, or allogeneic stem cell transplant). Despite these therapies, the median OS from EMM diagnosis remained shorter in patients with EMM at first relapse (1.25 years, 95% CI: 0.62–NR) or after ≥ 2 lines of therapy (1.37 years, 95% CI: 0.73–NR), compared to

patients with *de novo* EMM (7.47 years, 95% CI: 6.26–NR; Figure 3F), following a similar trend as sPCL.

Baseline characteristics and risk of progression in patients with solitary plasmacytomas

SP was the initial presentation of 39 patients in our database (Table 3). Twenty-eight of 39 (71.8%) patients had osseous localization, while the remaining 11 patients had cutaneous, oral, nasopharyngeal cavities, or muscular involvement (soft tissue SP). The median age at diagnosis was 57 years. All patients had normal hemoglobin, creatinine, and calcium levels. A serum monoclonal protein was detected in 22 of 39 (59.4%) patients, and the free light chain (FLC) ratio was abnormal in 17 of 39 (48.6%) patients. The percentage of BM plasma cells was $<10\%$ in all the patients. Clonality, identified by κ or λ restriction, was observed in 17 of 39 (43.6%) patients. Of these 17 patients, nine aberrantly expressed CD56. The median LDH level was 158 U/L (range, 109–528), with five of 29 (17.2%) patients having LDH over our laboratory upper limit of 190 U/L. Skeletal surveys were performed on all patients; positron emission tomography (PET) scans were obtained in 27 of 39 (69.3%) patients, while the remaining patients, except for three, underwent computed tomography (CT) imaging of the chest, abdomen, and pelvis, as well as magnetic resonance imaging (MRI) of the spine. No additional osseous or soft tissue lesions were detected in any of the patients.

All patients with SP received localized therapies: 38 of 39 (97.4%) patients received local radiation therapy either alone (34/39, 87.2%) or in combination with resection; one patient had surgical resection only. Twenty patients (51.3%) progressed to overt MM requiring additional treatment, while 19 patients remained in remission after a median follow-up of 8.9 years (95% CI: 7.87–11.6).

We then assessed the risk factors and clinical outcomes of patients who progressed to active MM. Among these 20 patients, the median time to progression was 1.4 years (95% CI: 0.25–12). The 1, 5, and 10-year risks of progression were 21% (95% CI: 9.6–35%), 46% (95% CI: 28–62%), and 71% (95% CI: 40–88%), respectively. In the competing risk analysis, the presence of osseous SP (Figure 4A) and elevated LDH levels (Figure 4B) were associated with an increased risk of progression in both the UVA and MVA models (Online Supplementary Table S8), while the percentage of BM PC was not, in disagreement with a recent publication.⁷ Median OS from MM diagnosis was very favorable for these patients, with the median OS being NR (95% CI: 9.8 years–NR; Figure 4C).

Discussion

EMM is an uncommon complication of MM, that manifests in different forms. In patients with newly diagnosed MM, the incidence of pPLC or *de novo* EMM ranges from 0.5%

to 5%.^{2,21} However, in cases of relapsed or refractory MM, the occurrence of EMM increases significantly, affecting up to 30% of patients (secondary EMM). Traditionally, the prognosis for patients with EMM has been unfavorable,^{2,13} attributed not only to the aggressive disease biology but also

to the prior exposure to conventional anti-MM therapies. Indeed, the efficacy of novel therapeutic agents has been suboptimal, with inferior ORR, alongside shorter PFS compared to patients without EMM.^{22,23} Our study investigated the characteristics, therapies, and outcomes of patients

Table 2. Demographics and clinical characteristics of patients with extramedullary myeloma.

Cohort characteristics	All, N=118	De novo, N=89	At first relapse, N=14	After >2 lines, N=15
Sex, N (%)				
Male	83 (70.3)	65 (73.0)	9 (64.3)	9 (60.0)
Female	35 (29.7)	24 (27.0)	5 (35.7)	6 (40.0)
Race, N (%)				
Non-Hispanic White	98 (83.5)	72 (80.9)	13 (92.8)	13 (86.7)
Non-Hispanic Black	15 (12.7)	12 (13.5)	1 (7.2)	2 (13.3)
Other	5 (3.8)	5 (5.6)	0	0
MM type, N (%)				
IgG	59 (50)	45 (50.6)	6 (42.8)	8 (53.4)
IgA	27 (22.9)	21 (23.6)	3 (21.4)	3 (20.0)
LCD	25 (21.2)	18 (20.2)	5 (35.8)	2 (13.3)
Other	7 (5.9)	5 (5.6)	0 (0.0)	2 (13.3)
Cytogenetic risk group, N (%)	N=113	N=86	N=13	N=14
Standard	93 (82.3)	72 (83.7)	9 (69.2)	12 (85.7)
High	20 (17.7)	14 (16.3)	4 (30.8)	2 (14.3)
1q +, N (%)				
No	71 (62.8)	54 (62.8)	7 (53.8)	10 (71.4)
Yes	42 (37.2)	32 (37.2)	6 (46.2)	4 (28.6)
13q deletion, N (%)				
No	68 (60.2)	52 (60.5)	6 (46.2)	10 (71.4)
Yes	45 (39.8)	34 (39.5)	7 (53.8)	4 (28.6)
17p deletion, N (%)				
No	103 (91.2)	80 (93.0)	10 (76.9)	13 (92.8)
Yes	10 (8.8)	6 (7.0)	3 (23.1)	1 (7.2)
Translocation (11;14), N (%)				
No	98 (86.7)	74 (86.0)	12 (92.3)	12 (85.7)
Yes	15 (13.3)	12 (14.0)	1 (7.7)	2 (14.3)
Translocation (4;14), N (%)				
No	105 (92.9)	80 (93.0)	12 (92.3)	13 (92.8)
Yes	8 (7.1)	6 (7.0)	1 (7.7)	1 (7.2)
R-ISS stage at diagnosis, N (%)	N=104	N=78	N=13	N=13
1	36 (34.6)	30 (38.5)	3 (23.0)	3 (23.0)
2	60 (57.7)	44 (56.4)	7 (54.0)	9 (69.2)
3	8 (7.7)	4 (5.1)	3 (23.0)	1 (7.8)
EMM site, N (%)				
Osseous	84 (72.2)	67 (75.3)	9 (64.3)	8 (53.3)
Soft tissue	34 (28.8)	22 (24.7)	5 (35.7)	7 (46.7)

LCD: light chain disease; LDH: lactate dehydrogenase; B2M: β -2 microglobulin; R-ISS: revised international staging system; MM: multiple myeloma; EMM: extramedullary MM.

Table 3. Demographics and clinical characteristics of patients with solitary plasmacytoma.

Cohort characteristics	All, N=39	SP, N=19	SP to MM, N=20	P
Age, years at diagnosis, median (range)	57 (38-77)	55 (38-77)	58.5 (46-74)	0.58
Sex, N (%)				0.32
Male	26 (66.7)	11 (57.9)	15 (75.0)	
Female	13 (33.3)	8 (42.1)	5 (25.0)	
Race, N (%)				0.135
Non-Hispanic White	35 (89.8)	17 (89.5)	18 (90.0)	
Non-Hispanic Black	2 (5.1)	2 (10.5)	0 (0.0)	
Other	2 (5.1)	0.0	2 (10.0)	
Family history of MM, N (%)				0.661
No	34 (87.2)	16 (84.2)	18 (90.0)	
Yes	5 (12.8)	3 (15.8)	2 (10.0)	
Site of plasmacytoma, N (%)				0.14
Bone	28 (71.8)	10 (52.6)	18 (90.0)	
Soft tissue	11 (28.2)	9 (47.4)	2 (10.0)	
Monoclonal protein, N (%)	N=37	N=19	N=18	0.184
No	15 (40.6)	10 (52.6)	5 (27.8)	
Yes	22 (59.4)	9 (47.4)	13 (72.2)	
Abnormal KLC ratio, N (%)	N=35	N=19	N=16	0.738
No	18 (51.4)	9 (47.4)	9 (56.3)	
Yes	17 (48.6)	10 (52.6)	7 (43.7)	
Bone marrow clonality, N (%)				0.523
No	22 (56.4)	12 (63.2)	10 (50.0)	
Yes	17 (43.6)	7 (36.8)	10 (50.0)	
Aberrant BM PC phenotype, N (%)	N=17	N=6	N=11	
No	8	3 (50)	5 (45.5)	
Yes	9	3 (50)	6 (54.5)	
Hemoglobin, g/dL, median (range)	13.7 (10.1-16.5)	13.8 (11.7-16.5)	13.3 (10.1-16.1)	0.198
Creatinine, mg/dL, median (range)	0.85 (0.39-1.43)	0.75 (0.39-1.18)	0.87 (0.59-1.43)	0.87
Calcium, mg/dL, median (range)	9.3 (7.9-10.5)	9.3 (8.6-10.5)	9.2 (7.9-10.1)	0.86
Albumin, g/dL, median (range)	4.1 (2.4-4.7)	4.2 (2.4-4.7)	3.9 (3.4-4.6)	0.88
LDH, U/L, median (range)	155 (109-528)	154 (115-194)	160 (109-528)	0.156
B2M, mg/L, median (range)	1.9 (1-3)	1.9 (1-3)	1.9 (1.2-2.69)	0.67
Treatment, N (%)				0.579
XRT only	34 (87.1)	16 (84.2)	18 (90.0)	
XRT + resection	4 (10.2)	2 (10.5)	2 (10.0)	
Resection only	1 (2.7)	1 (5.3)	0 (0.0)	
Radiation dose (Gy), median (range)	34 (87.1)	16 (84.2)	18 (90.0)	0.81

SP: solitary plasmacytoma; MM: multiple myeloma; KLC: κ light chain; LDH: lactate dehydrogenase; B2M: β -2 microglobulin; XRT: radiation therapy.

with systemic dissemination of their MM over the past 15 years, including 118 patients with extramedullary MM, 44 patients with PCL, and 39 patients with SP.

We initially focused our analysis on patients presenting with extramedullary disease, either as pPCL or *de novo* EMM. Historically, pPCL has been the most aggressive and lethal form of EMM. Despite these patients often being candidates for intensive treatments such as allogeneic stem cell transplantation, their median OS has only modestly improved from 7 months to 20–24 months in recent years, and remains inferior to that of patients with MM alone.^{12,13} Our cohort confirms this trend, with a median OS of 26 months, including three patients who achieved long-term remission after allogeneic stem cell transplant. In contrast, patients with *de novo* osseous or soft tissue EMM exhibited considerably better outcomes, with a median OS of 7.5 years. Similarly, patients with SP who later progressed to active MM also had favorable outcomes.

Patients who progressed to sPCL or secondary EMM had already received multiple lines of therapies for MM. At the time of transformation, they were often ineligible for further therapies due to rapid disease progression, persistent cytopenias, or limited treatment options. As a result, outcomes in this group were particularly poor, with a median OS of <2 months for sPCL and 16 months for secondary EMM, underscoring the urgent need for more effective therapies in this population.

Substantial heterogeneity among extramedullary lesions could exist as well as biological differences within the EMM cells and between EMM cells and MM cells residing in the BM.^{24,25} Cells of PCL or EMM origin exhibited higher rates of chromosomal abnormalities such as 17p deletion, 1q+, and t(11;14) compared to MM cells.^{1,24} Moreover, patients with sPCL acquired additional chromosomal abnormalities at transformation. In EMM, t(11;14) prevalence aligned with MM, while 1q+ increased slightly, and 17p deletion remains unchanged. Notably, 17p deletion predicted shorter OS in

pPCL, 1q+ correlated with poorer prognosis in EMM, while t(11;14) had no impact on outcomes.

Immunophenotyping or immunohistochemistry analyses could offer additional insights into the biological differences of EMM.¹⁴ Typically, the expression of adhesion molecules, such as CD56 and CD117, is reduced, facilitating the dissemination from the BM niche to other tissues.¹⁵ Notably, the absence of CD56 is common in primary PCL,^{14,26} while data regarding the expression of CD56 in sPCL, soft tissue, or osseous plasmacytomas are limited.^{27,28} Our findings confirmed a reduced expression of CD56 in pPCL, while CD56 expression was preserved in 11 of 13 (85%) patients with sPCL, 14 of 22 (64%) patients with osseous plasmacytomas, and 12 of 15 (80%) patients with soft tissue plasmacytomas. Moreover, we noted site-dependent variations in CD56 clone size between the PB and BM samples of each patient. Finally, we established a correlation between CD56 negativity and poorer outcomes in patients with sPCL. This contrasts with the behavior of MM cells,²⁹ underscoring again the differences in behaviors between MM cells and EMM cells.

Limitations of this study include its retrospective and single-center nature, spanning 15 years. The absence of standardized treatment guidelines resulted in various approaches influenced by physician preferences, referrals from community hospitals, and the year of diagnosis. Additionally, diagnostic workups were incomplete for some patients, particularly in secondary EMM or PCL, where repeat BM biopsies were often omitted, limiting FISH and flow cytometry assessments. Similarly, patients with SP frequently lacked monoclonal urinary light chain data, and their FISH studies were inconclusive due to low dividing cell fractions. Access to these data could have significantly enhanced the robustness of our models.^{3,9,30} Additionally, most genomic and immunophenotypic data originated from BM biopsies at diagnosis, limiting our ability to capture

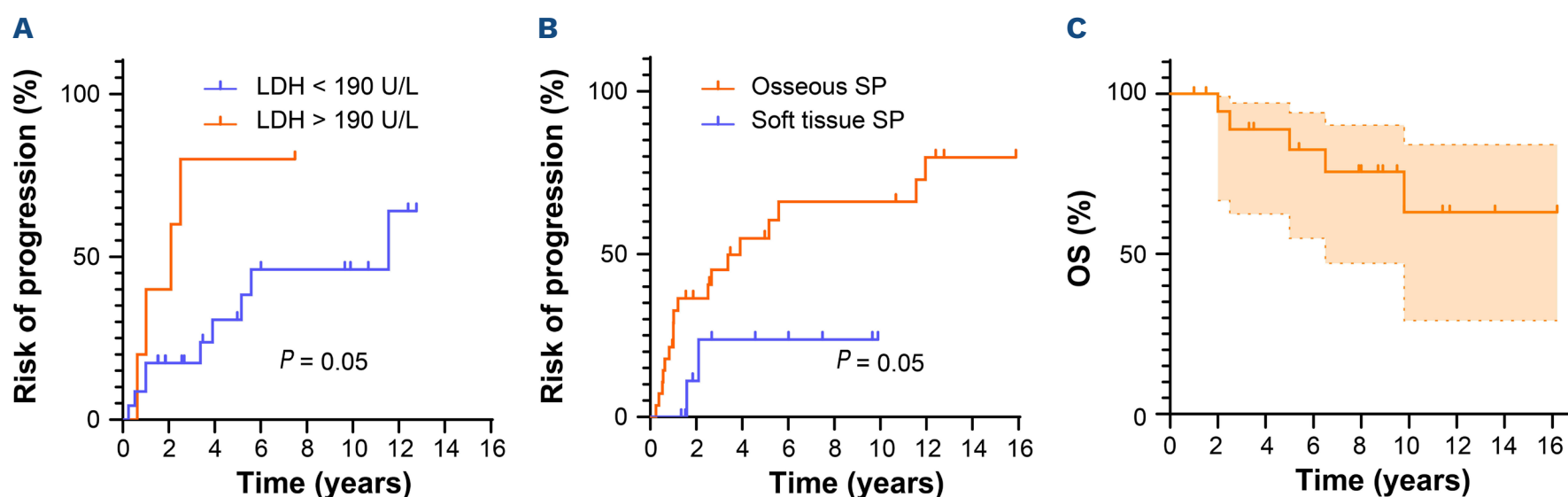


Figure 4. Characteristics and risk of progression of patients with solitary plasmacytoma. (A) Kaplan-Meier estimates of progression with high lactate dehydrogenase (LDH) levels (>190 U/L, N=5) or normal LDH levels (<190 U/L, N=23). $P=0.05$. (B) Kaplan-Meier estimates of progression with osseous solitary plasmacytoma (SP) (N=11) or soft tissue SP (N=28). $P=0.05$. (C) Overall survival (OS) in 20 patients diagnosed with SP who progressed to multiple myeloma.

the heterogeneity within extramedullary lesions or across different anatomical sites.

In conclusion, EMM still presents significant clinical challenges, particularly due to its poor outcomes in patients with PCL or those who develop EMM later during treatment. Addressing these challenges requires the development of more effective therapeutic strategies and the inclusion of these patients in clinical trials. Additionally, advancing our understanding of the specific genetic characteristics of EMM is essential to drive the development of precision medicine approaches and ultimately improve patient outcomes.

Disclosures

No conflicts of interest to disclose.

Contributions

MB wrote the IRB protocol, performed chart review, collected and analyzed patient data, and drafted the manuscript. SB performed statistical analysis and wrote the statistical method section. DS drafted the manuscript. NB, AK, SR,

EU, DB, and AR consented patients on the MM registry and provided comments to the project. FC wrote the IRB protocol, designed the study, supervised data collection and accuracy, created the figures, analyzed the data, and wrote the manuscript.

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Data-sharing statement

Data will be available upon request or are publicly available.

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