Predicting risk of progression in relapsed multiple myeloma using traditional risk models, focal lesion assessment with PET-CT and minimal residual disease status

Novel therapeutic strategies have dramatically increased the depth of response and survival rates in multiple myeloma (MM), but the disease remains incurable in most patients because of eventual relapse.[1] The timing and disease course of relapsed MM can be highly variable, and most often the presentation of the first relapse can give more information on disease biology and overall prognosis than parameters identified at diagnosis.[2] The dynamic change of clinical parameters during the disease course has recently shown to significantly impact survival in MM patients,[3] underscoring that prognostic models, such as fluorescence *in situ* hybridization (FISH), International Staging System (ISS), revised-ISS (RISS) and gene expression profiling (GEP) in addition to focal lesion (FL) assessment can be useful prognostic tools at initial diagnosis,[4,5] even though they have not been fully validated in the relapse setting. Furthermore, in contrast to newly diagnosed myeloma, it is unknown whether the depth of response after salvage therapy also affects long term outcome in relapsed disease.[6] This is particularly true for the achievement of minimal residual disease (MRD) negativity, a powerful prognostic tool in newly diagnosed MM,[7] even though its importance in relapsed disease has started to be elucidated only recently.[8]

In order to explore whether reassessment of initial prognostic markers at relapse increases accuracy in predicting outcome after relapse and to determine whether MRD achievement after the first relapse improves outcome, we investigated 120 patients who relapsed after MM diagnosis and initial treatment on our total therapy (TT) 2-6 protocols between 2000-2016. All patients achieved a complete response (CR) and subsequently relapsed, with the first relapse occurring after January 2014, the time point at which MRD assessment by eight-color flow cytometry was established systematically at the University of Arkansas for Medical Sciences.[9] The majority of patients received an immunomodulatory imide drug (IMiD)-based triplet as second line, either in combination with a proteasome inhibitor (64%) or a CD38 targeting monoclonal antibody (27%). The median time to first relapse after initial diagnosis and treatment was 5 years (range, 0.9-18 years) with a median follow up after first relapse of 1.57 years (range, 0.18-6.0 years). Patients' characteristics are presented in Table 1.

GEP70 classified 17% as high-risk (HR) patients at diagnosis. The proportion increased significantly to 35% at relapse (P<0.05). While the diagnostic GEP70 classification retained significant prognostic value at relapse with HR patients having significantly worse PFS (median: 0.93 years *vs.* 1.86 years; P=0.03), and OS (median: 2.12 years *vs.* 5.01 years; P<0.01) (*Online Supplementary Figure S1A and B*), reassessment of GEP70 at relapse improved prognostic accuracy with a median PFS of 0.76 years for HR *versus* 2.15 years for low-risk (LR) patients, P<0.01, and a median OS of 1.87 years for HR, while LR patients had not reached their median OS, P<0.01, Figure 1A and B. Similarly, we saw that reassessment of FISH and RISS at relapse improved accuracy in outcome prediction over initial assessment at diagnosis. HR FISH alterations were characterized by translocations t(4;14) and t(14;16) and deletion 17p. In particular the proportion of patients with del17p increased significantly from 12.5% (n=11/88) at diagnosis to 28% (n=17/59) at relapse. Despite the relatively small number of patients with FISH at relapse, reassessment of FISH improved the predictive accuracy for PFS (median: 1.16 years *vs.* 1.75 years; P=0.1) and OS (median: 2.86 years *vs.* 4.38 years; P<0.05) (Figure 1C and D) compared to assessment at diagnosis (*Online Supplementary Figure S1C and D*). Furthermore, reassessment of RISS at relapse, was a more accurate tool in predicting PFS (median PFS RISS I: 1.8 years *vs.* median PFS RISS II/III: 1.15 years; P<0.05) and OS (median OS RISS I: not reached *vs.* median OS RISS II/III: 2.9 years, P<0.01) (Figure 1E and F), compared to RISS evaluation at diagnosis (*Online Supplementary Figure S1E and F*). Of note is that very few patients presented with RISS III at relapse, which is likely due to early detection of relapsing disease in most patients, and hence still a relatively small tumor burden with low β-2-microglobulin values and normal albumin and lactate dehydrogenase (LDH). In contrast to GEP70, FISH and RISS, we only saw a modest prognostic impact of ISS evaluation at diagnosis or even

Table 1. Patient characteristics at diagnosis and relapse.

	At diagnosis	At relapse
Age in yrs, (range)	59 (32-75)	64 (37-81)
GEP high risk	20/115 (17.4%)	27/77 (35%)**
ISS stage		
1	47/120 (39%)	95/112 (84.8%)**
2	39/120 (33%)	12/112 (10.7%)**
3	34/120 (28%)	4/112 (3.8%)**
FISH		
Translocation t4;14	11/84 (13%)	11/59 (18.6%)
Translocation t14;16	3/84 (3.75%)	3/59 (5%)
Deletion 17p	10/84 (12%)	17/59 (28.8%)**
R-ISS stage		
1	16/84 (19%)	22/57 (38.6) *
2	54/84 (64.3%)	32/57 (56%)
3	14/84 (16.7%)	3/57 (5%)*
Focal lesions by PET		
0	39/114 (34%)	62/112 (55%)*
1-3	26/114 (23%)	36/112 (32%)*
>3	49/114 (43%)	14/112 (12.5%)**
Treatment at relapse		
IMiD+PI		77/120 (64%)
CD38 ab + IMiD		32/120 (27%)
CD38 ab + PI		4/120 (4%)
other#		6/120 (5%)
Salvage ASCT at relapse+		30/120 (25%)
Best response	First line therapy	2nd line therapy
sCR/CR	120/120 (100%)	60/119 (50.4%)
VGPR		22/119 (18.5%)
PR		17/119 (14.3%)
SD		16/119 (13.4%)
PD		4/119 (3.4%)

*P<0.05, **P<0.001 comparing presentation at relapse to diagnosis, McNemar's test; #: regimen including intravenous chemotherapy such as cytoxan, adriamycin, etoposide, cisplatin (PACE, Metronomic, PACMED); +: salvage autologous stem cell transplant (ASCT) was performed in selected patients after brief reinduction with novel agents or intrvenous chemotherapy. GEP: gene expression profiling; ISS: International Staging System; FISH: fluorescence *in situ* hybridization; RISS: revised-ISS; PET: positron emission tomography; IMiD: immunomodulatory imide drug; PI: protease inhibitor; CR: complete remission; VGPR: very good partial remission, PR: partial response; SD: stable disease; PD: progressive disease.

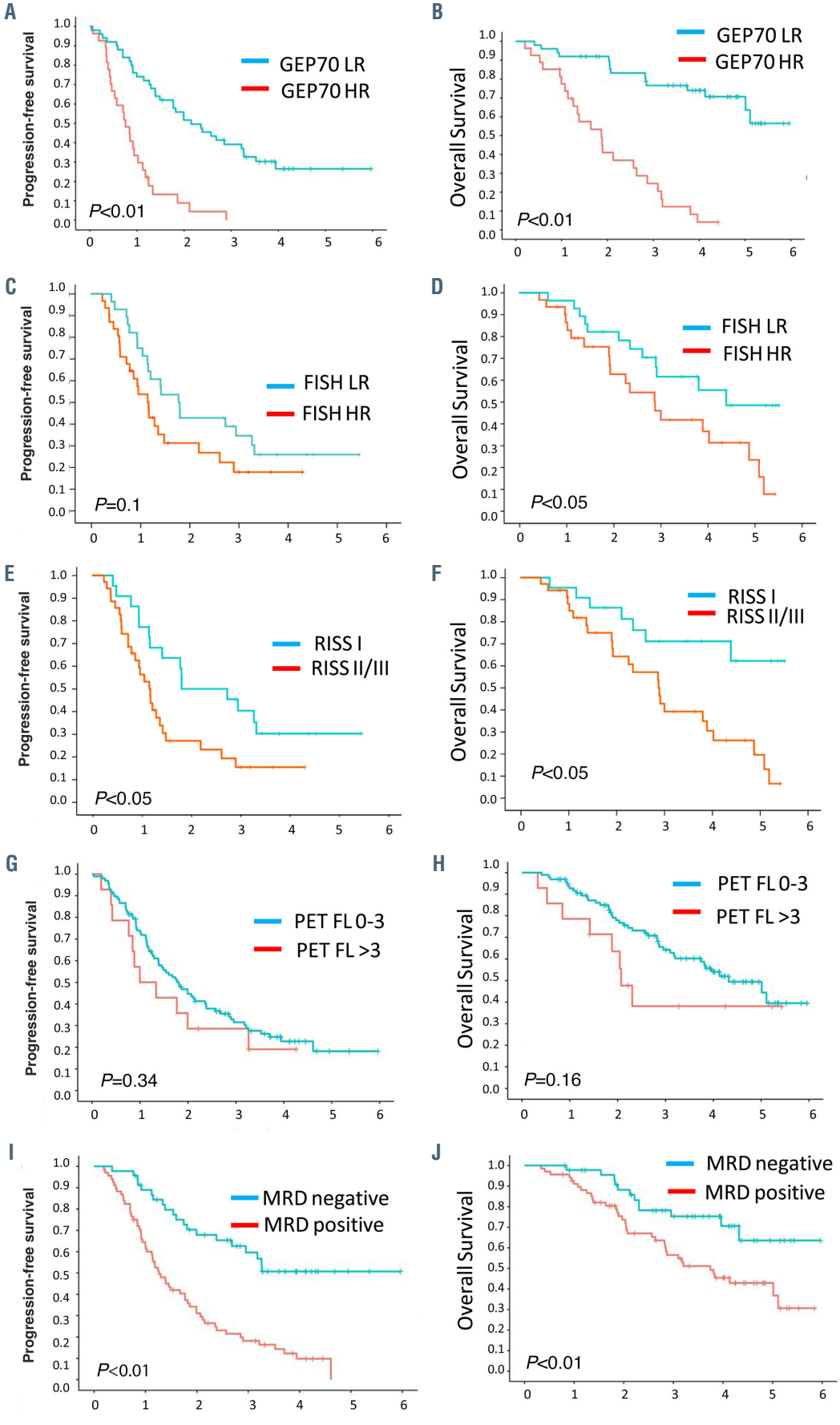

Figure 1. Legend on following page.

Figure 1. Reassessment of traditional risk factors in first multiple myeloma relapse shows improved prognostic accuracy compared to their evaluation at diagnosis (shown in the *Online Supplementary Appendix*). GEP70 high-risk (HR) patients at relapse had significant worse progression-free survival (PFS) (A), and OS (B) compared to low-risk (LR) patients, *P*<0.01. HR fluorescence *in situ* hybridization (FISH) included translocation t14;16, t4;14 and del 17p and showed worse PFS (*P*=0.1) (C) and OS (*P*<0.05) (D), compared to patients with LR FISH. Assessment of revised International Staging System (RISS) at relapse showed significant worse PFS, E, and OS, F, for patients with RISS 2+3 compared to patients with RISS stage I. The presence of >3 focal lesions by positron emission tomography and computed tomography (PET CT) at relapse was associated with worse PFS (H) and OS (I) in first relapse. The results were not significant, likely due to the relative small patient number. Achievement of minimal residual disease (MRD) negativity after first relapse was a powerful marker for significantly improved PFS (J) and OS (K).

at first relapse with a mild non-significant trend to improved clinical outcome in earlier stages after relapsed disease (*Online Supplementary Figure S2A and D*).

Imaging with positron emission tomography and computed tomography (PET CT) was performed at diagnosis (n=120) and at relapse (n=111). Of the 120 patients in our study cohort, 69% (n=75) had at least one 18 F-fluorodeoxyglucose (FDG) avid lesion at diagnosis. Sequential PET CT studies during first line treatment confirmed resolution of PET avid lesions during initial treatment. At first relapse, 44.5% (n=50/112) had at least one lesion. Of these, 68% (n=34/50) had also presented with a FL at diagnosis and 46% (n=23/50) had at least one FL at the same site as at initial diagnosis. The presence of >3 FL by PET at diagnosis, a previously identified adverse risk factor[10] only had a small and non-significant adverse prognostic impact on outcome after first relapse with a median PFS of 1.4 years compared to 1.8 years for patients with 0-3 FL and a median OS of 3.9 years compared to 4.8 years (*Online Supplementary Figure S3A and B*). Reassessment of focal lesions by PET CT at relapse improved the prognostic value of this test, albeit not significantly (median PFS for 0-3 FL: 1.8 years *vs.* 1.0 year for >3 FL and median OS: 4.4 years for 0-3 FL *vs.* 2.1 years for >3 FL) (Figure 1H and I). In a further step we evaluated the prognostic significance of MRD achievement after the first relapse. In total, 116 patients had sequential MRD assessment by flow cytometry, as previously described,[9] after initiation of a second line therapy of which 47 (40.5%) achieved MRD negativity. Nearly all of the MRD-negative patients also achieved a CR (n=45/47), while the remaining two patients had achieved a VGPR. Achievement of a deep response with MRD negativity during second line treatment was a strong predictor of outcome with a median PFS to second relapse of 1.3 years for patients who did not achieve MRD negativity compared to not reached for patients who achieved MRD negativity (*P*<0.01) (Figure 1J). Median OS was equally significantly better and not reached for patients who achieved MRD negativity compared to 3.7 years for patients who remained MRD-positive (Figure 1K). The time to achievement of MRD negativity varied greatly, reaching from 0.6 to 3 years with a median of 1.02 years. Intriguingly, a slower response to treatment and later achievement of MRD negativity (>1.02 years, n=24), was associated with significant better PFS (median PFS not reached *vs.* 1.6 years) and OS (median OS not reached *vs.* 2.8 years) compared to patients who achieved rapid MRD negativity(<1.02 years, n=23) (*Online Supplementary Figure S3C and D*). In a final step, we evaluated the association between aforementioned independent risk factors and the hazards of experiencing death as well as progression using a multivariable Cox proportional hazards model (*Online Supplementary Table S1A and B*). FISH and RISS were excluded from the analysis due to the overall small patient number that was assessed at relapse. Age at progression and time from initial MM diagnosis to first progression were included, as they previously had shown to be of prognostic significance in relapsed MM disease.[11,12] High risk by GEP70 and the presence of >3 FL were significantly and independently associated with worse PFS and OS as was older age at first progression. Similarly, achievement of MRD negativity after first relapse was a significant and independent prognostic marker for improved outcome. Though prolonged time to first relapse (TT1P) was suggestive of improved PFS and OS, the results were not quite significant in this cohort, suggesting that TT1P as a prognostic marker is determined by other more significant variables. Our study provides a strong rationale to incorporate reassessment of GEP, FISH and RISS at first relapse to improve clinical prognostication. We further underscore the importance of FL assessment at relapse, a practice that is currently inconsistently performed. The importance of identifying focal lesions can be vital to clinical management, as we show that patients with an increased number of FL tend to have worse outcome and furthermore previous reports indicate that bone marrow content and peripheral myeloma markers do not always correlate with the presence of focal lesions.[13] Lastly, we show that MRD negativity after first relapse is associated with significantly better PFS and OS, which is in line with a previous report.[8] Currently available therapies are increasingly effective, making the achievement of deep responses in relapsed disease a realistic goal.[14] While the present study is limited by a relatively small patient size and differences in treatment at relapse, the investigated prognostic factors have been shown to be valid independent of the treatment modality.[15] Furthermore, key characteristics of our study are that all patients were uniformly treated during upfront therapy and had been exposed to a protease inhibitor, an IMiD and stem cell transplantation, which are all currently part of standard first line treatment in newly diagnosed MM. Taken together our study provides important insight into prognostic features at first relapse that could help clinicians to reclassify patients and also suggests to treat patients – if performance status permits - to a deep clinical response.

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