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Multiple myeloma - Section 13

# Minimal residual disease (MRD) in multiple myeloma: prognostic and therapeutic implications (including imaging)

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**Take home messages**

- MRD is a powerful predictor of survival outcomes in myeloma regardless of type of therapy, line of therapy, clinical stage and biological risk.
- MRD may be assessed by flow cytometry, based on aberrant plasma cell phenotypes or next generation sequencing approaches, based upon unique immunoglobulin gene sequences and assays with a minimum sensitivity of 10-5 are recommended.
- MRD is best considered as a continuous prognostic variable as sequential improvements in outcome are demonstrable with each log depletion of disease.

## Introduction

Multiple myeloma, for the majority of patients, remains an incurable disorder with a relapsing and remitting course. This remains the case despite high rates of complete response (CR) seen with modern multi-drug combinations arguing for the presence of persisting disease in the majority of patients. Minimal residual disease (MRD) refers to the presence of persisting neoplastic plasma cells in the bone marrow of patients achieving high quality M protein responses. The significance of MRD, at least in the post ASCT setting, was first established in 2002[1,2] and a large body of data has now emerged which has further clarified its applicability. This has shown that MRD is an independent predictor of survival outcomes regardless of type of therapy, line of therapy, clinical stage and biological risk. The International Myeloma Working Group (IMWG) criteria propose a level of 10-5 define to MRD-negativity.[3]

## Current state of the art

### Methodology and sensitivity

MRD in myeloma is currently assessed by two main methodologies. Multiparameter flow cytometry (MFC) is a well-established method which utilizes the phenotypic aberrancies seen in myeloma plasma cells compared to normal. Assessment of light chain restriction in this setting has limited sensitivity as a result of the regeneration of normal polytypic plasma cells.[4] There is a broad consensus with respect to the principles of MRD analysis by MFC[5,6] and it is applicable to >95% of patients and can provide results in real time. The EuroFlow method is a 2-tube 8-colour method and is in widespread use but other assays have been reported with similar levels of sensitivity and performance.[7,8]

MRD in myeloma as in other B-cell disorders, may also be assessed by virtue of the unique immunoglobulin gene sequences seen in each patient. Traditional approaches have required that patient or allele-specific sequences be used as primers in real-time quantitative PCR assays (ASO RQ-PCR). This has been evaluated in myeloma but has limited applicability as a consequence of lack of clonality detection, unsuccessful sequencing and suboptimal ASO performance.[9] These limitations have however been overcome with the advent of so-called next-generation sequencing (NGS) technologies. This has been evaluated in myeloma and appears applicable to >95% of patients with a sensitivity of 10-6 which is achievable with as few as 2 million cells.[10,*11]

### Areas of clinical application

The prognostic significance of MRD was first established, by Spanish and UK groups in 2002[1,2] and a large body of confirmatory data has since emerged, and this has been evaluated in a recent meta-analysis by Munshi et al In this analysis of 1273 patients from 14 published studies MRD-negativity was associated with a significant prolongation of PFS (HR 0.41; 95% CI 0.36–0.48; $p < 0.0001$). Impact on OS was assessed in 1100 patients included from 10 studies with clear survival benefit noted (HR 0.57; 95% CI 0.46–0.71; $p < 0.0001$). Broadly comparable results were also noted when the analysis was limited to those patients with documented conventional CR (HRs of 0.44 and 0.47 for PFS and OS respectively).[*12]

In an analysis of 609 patients from 3 Spanish clinical trials Lahuerta and colleagues have further clarified the clinical utility of MRD. They demonstrated the superiority of MRD-negativity over conventional CR as MRD-positive CR patients had an

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outcome similar to MRD-positive patients failing to achieve CR. Furthermore, they were able to confirm the prognostic impact of MRD and superiority over CR among transplant-eligible and transplant-ineligible patients, and in sub-groups stratified according to disease stage (ISS) and cytogenetic risk profile. It interesting to note that the greatest impact of MRD-negativity was seen in transplant-ineligible patients and those with high-risk cytogenetics.[*13] It is also noteworthy that MRD-negativity has also now been demonstrated in the relapse setting with highly-efficacious daratumumab-containing regimens and that this has similar predictive value at least in terms of PFS.[14,15]

Sequential MRD monitoring has been used in a number of studies and can provide useful insights into complex multicomponent therapies. These studies have demonstrated that a significant proportion of patients can show a further depletion of disease with maintenance therapies and that this has an impact on outcome. Furthermore, it is clear that the re-emergence of disease typically heralds clinical relapse.[16–18]

MRD has traditionally been considered to be a simple dichotomous variable with values determined by the sensitivity of the assay used. MRD assays do also allow for reproducible disease quantification and this can provide additional prognostic information. In an analysis from the UK Myeloma IX trial it was possible to demonstrate, with a relatively insensitive MFC method (10-4), an approximate 1-year OS benefit with each log depletion of disease. This pattern has been also recently been demonstrated with highly sensitive NGS with further improvements noted at 10-5 and 10-6.[11,*19]

MRD strategies, in particular those based on MFC have added value in that they can be employed in the routine diagnostic setting allowing for diagnosis and risk assessment in monoclonal gammopathy of undetermined significance, amyloidosis and plasmacytoma of bone.[20–22]

### Imaging

Patchy distribution of bone marrow disease and extramedullary disease represent a limitation for traditional bone marrow based MRD assessment. Functional imaging with positron emission tomography (PET) and diffusion-weighted magnetic resonance imaging (DW-MRI) may overcome this and allow further clarification of residual disease status in some patients. In a recent study, Rasche et al evaluated CR patients with MFC, PET and DW-MRI. Residual focal lesions (FL) were noted in 24% of patients and this was associated with an inferior PFS regardless of biological risk and ISS. DW-MRI detected residual disease in a greater proportion of patients than PET, but some FL were only demonstrable with the latter. It noteworthy that FL were demonstrable in patients who were MRD-negative by MFC at 10-5 and that the best outcomes were seen patients who were MRD-negative and without residual FL.[*23]

## Future perspectives

MRD is now firmly established as an independent prognostic factor in myeloma and is widely applicable regardless of type and line of therapy, disease stage and biological risk. It should be routinely evaluated in all clinical trials and used to prospectively evaluate clinical interventions in academic studies. It also has the capacity to allow for accelerated drug approvals and European Medicines Agency have recently published guidance in this regard (https://ema.europa.eu/en/documents/scientific-guideline/draft-guideline-use-minimal-residual-disease-clinical-endpoint-multiple-myeloma-studies_en.pdf). Sequential monitoring is likely to be required for patient monitoring and ongoing efforts are needed to develop non-invasive methods of assessment.

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**Study showing the potential value of functional imaging and MRD assessment in determining outcome in MM.**