



# Multiple Myeloma (Part 1) – Update on Epidemiology, Diagnostic Criteria, Systemic Treatment and Prognosis

## *Mieloma múltiplo (Parte 1) – Atualização sobre epidemiologia, critérios diagnósticos, tratamento sistêmico e prognóstico*

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### Abstract

#### Keywords

- ▶ epidemiology
- ▶ monoclonal gammopathy of undetermined significance
- ▶ multiple myeloma
- ▶ smoldering multiple myeloma
- ▶ plasmacytoma
- ▶ prognosis

Multiple myeloma (MM) is a hematological malignancy characterized by unregulated and clonal proliferation of plasma cells in the bone marrow; these cells produce and secrete an anomalous monoclonal immunoglobulin, or a fragment of this, called M protein. The clinical manifestations of MM result from the proliferation of these plasmocytes, the excessive production of monoclonal immunoglobulin and the suppression of normal humoral immunity, leading to hypercalcemia, bone destruction, renal failure, suppression of hematopoiesis and humoral immunity, increasing the risk for the development of infections. The increase in life expectancy of the world population led to a concomitant increase in the prevalence of MM, a pathology that usually affects the elderly population. The aim of this review is to update the reader on epidemiology, diagnostic criteria, differential diagnosis with other monoclonal gammopathies, systemic treatment and prognosis of MM.

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## Resumo

### Palavras-chave

- ▶ epidemiologia
- ▶ gamopatia monoclonal de significância indeterminada
- ▶ mieloma múltiplo
- ▶ mieloma múltiplo latente
- ▶ plasmocitoma
- ▶ prognóstico

O mieloma múltiplo (MM) constitui neoplasia maligna de origem hematológica caracterizada pela proliferação desregulada e clonal de plasmócitos na medula óssea; estas células produzem e secretam imunoglobulina monoclonal anômala, ou um fragmento desta, denominado proteína M. As manifestações clínicas do MM decorrem da proliferação destes plasmócitos, da produção excessiva de imunoglobulina monoclonal e da supressão da imunidade humoral normal, levando à hipercalcemia, destruição óssea, insuficiência renal, supressão da hematopoiese e da imunidade humoral, aumentando o risco para o desenvolvimento de infecções. O aumento na expectativa de vida da população mundial levou a concomitante incremento na prevalência do MM, patologia que habitualmente acomete a população idosa. O objetivo desta revisão é atualizar o leitor sobre a epidemiologia, critérios diagnósticos, diagnóstico diferencial com outras gamopatias monoclonais, tratamento sistêmico e prognóstico do MM.

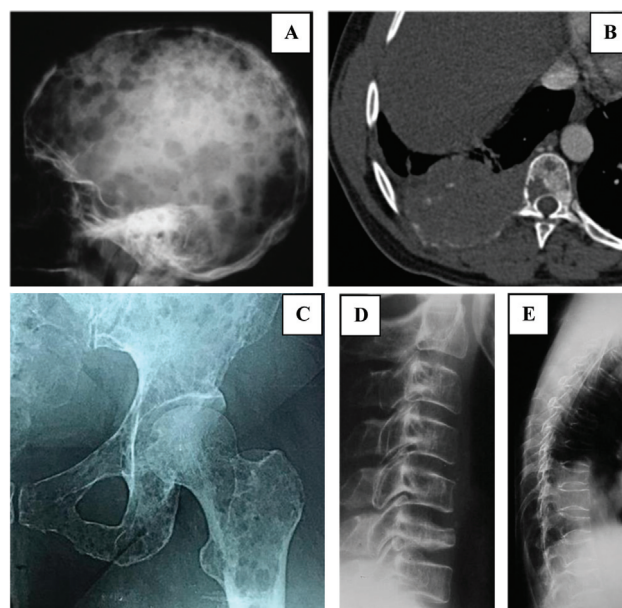
## Introduction

Normal plasma cells originate in the bone marrow and are an important part of the immune system, especially because they produce antibodies that help fight infections and other diseases.<sup>1-3</sup>

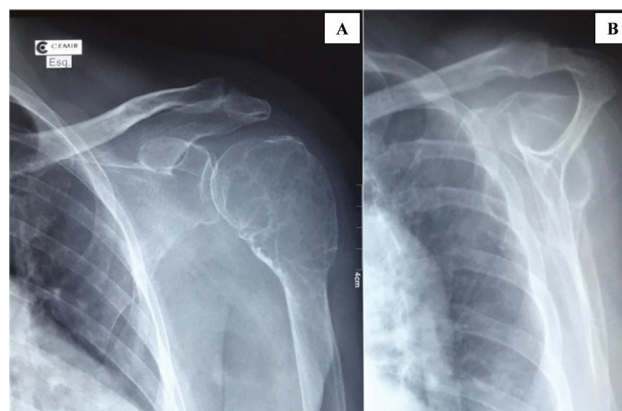
Multiple myeloma (MM), also called Kähler's disease, myelomatosis, and plasmacytic myeloma,<sup>1</sup> is a malignant neoplasm of hematological origin characterized by dysregulated and clonal proliferation of plasma cells in the bone marrow.<sup>1,2,4-8</sup> These cells produce and secrete anomalous monoclonal immunoglobulin, or a fragment thereof, called M protein,<sup>1,3,6-10</sup> comprising a heavy [(IgG  $\gamma$ , IgA  $\alpha$ , IgM  $\mu$ , IgD  $\delta$ , or IgE  $\epsilon$ ] and a light (*kappa*- $\kappa$  and *lambda*- $\lambda$ ) chain classes.<sup>9</sup>

MM was first described in the literature by William Macintyre (1850), who recognized proteinuria in samples obtained from a patient who had excruciating pain in the chest and thoracolumbar region for about a year.<sup>9,11</sup> These samples were previously sent (1848) to Henry Bence Jones, a renowned chemical pathologist, who analyzed them in detail, confirming the discovery.<sup>9,11</sup> The disease, however, was not recognized until 1889, when Otto Kähler published the eight-year follow-up (1879-1887) of a 46-year-old patient who presented typical findings of this pathology (bone pain, albuminuria, anemia, severe kyphosis, recurrent bronchial infections and loss of height) – Kähler recognized that the protein identified in the patient's urine had the same characteristics described by Bence Jones.<sup>11</sup>

MM clinical manifestations result from neoplastic plasma cells proliferation, excessive production of monoclonal immunoglobulin and normal humoral immunity suppression.<sup>1,9,10</sup> The pathophysiological consequences of the disease's progression include: hypercalcemia,<sup>5,12</sup> bone destruction (► **Figs. 1** and **2**),<sup>1,4,5,9,10,12</sup> renal failure,<sup>4,12</sup> suppression of hematopoiesis<sup>4,10,12</sup> and humoral immunity,<sup>9</sup> increasing the risk for the development of infections.<sup>4,9,10,12</sup> Approximately 1% to 2% of patients have extramedullary disease at diagnosis, while 8% develop this condition in the course of the disease.<sup>12</sup>



**Fig. 1** (A–E) Main anatomical locations of MM. (A) skull; (B) costal arches; (C) femur; and (D, E) spine.



**Fig. 2** (A, B) Female patient, 68 years old, afro-descendant, with MM, presenting bone lesion in the proximal segment of the left humerus.

The increase in life expectancy of the world population led to a concomitant increase in the prevalence of multiple myeloma, a pathology that usually affects the elderly population.

The objective of this review is to update the reader on the epidemiology, diagnostic criteria, differential diagnosis with other monoclonal gammopathies, systemic treatment and prognosis of MM.

## Epidemiology

MM corresponds to 1% of all malignant neoplasms.<sup>3,4,9,12</sup> Its incidence increases with age and reaches its maximum during the seventh decade of life.<sup>9</sup> It is the second malignant neoplasm of hematological origin in order of frequency (inferior only to lymphomas),<sup>4,10</sup> corresponding to approximately 10% of the total number of cases,<sup>2,10,12</sup> and it is also the most common primary malignant bone tumor (47%).<sup>13</sup> In the United States, based on data obtained between the years of 2017 and 2019, it has been estimated that approximately 0.8% of men and women will be diagnosed with MM at some point in their lives.<sup>14</sup>

MM is most often diagnosed among people aged 65 to 74 years;<sup>14</sup> very few cases occur in individuals under the age of 40.<sup>3</sup> In the United States, according to data obtained between 2015 and 2019, the median age of patients at diagnosis was 69 years. It is slightly more common in men than in women and twice as frequent in Afro-descendants, when compared to Caucasians,<sup>3,4,9-12</sup> being less frequent in Asian populations<sup>10</sup> - studies conducted in Brazil, however, point to a higher prevalence in females and in white individuals.<sup>4,15</sup>

In the United States, the annual incidence of MM was 7.1 per 100,000 men and women between the years 2015 and 2019<sup>14</sup> - every year, more than 32,000 new cases are diagnosed,<sup>12</sup> with an estimated 34,470 cases in 2022. In 2019, there were 159,787 MM carriers in that country.<sup>14</sup> Between the years 2015 and 2019 the percentage of deaths from MM was higher among people aged 75 to 84 years (median of 75 years); the annual mortality rate was 3.2 per 100,000 men and women - almost 13,000 patients die annually due to this disease,<sup>12</sup> with an estimate for 12,640 deaths in 2022, That's 2.1 percent of all cancer-related deaths estimated for this year in that nation.<sup>14</sup>

## Diagnostic Criteria

If MM is suspected, the presence of M protein should be investigated by laboratory tests such as protein electrophoresis, immunofixation, and serum *free light chains* (FLC).<sup>5</sup> Approximately 2% of patients have non-secretive disease and, therefore, evidence of M protein may be undetectable on these tests.<sup>12</sup>

Bone marrow studies performed at the time of initial diagnosis should include *fluorescent hybridization in situ* (FISH) to detect possible trisomies t(11;14), t(4;14), t(14;16), t(6;14), t(14;20), and del(17p). Conventional karyotyping can be used to detect hypodiploidy and deletion,<sup>13</sup> but if FISH studies are performed, their additional value in initial risk

stratification is limited. The *genetic expression profile* (GEP), if available, may provide additional prognostic value.<sup>12</sup>

Diagnosis requires  $\geq 10\%$  clonal plasma cells in the bone marrow or a biopsy showing plasmocytoma associated with evidence of one or more *MM-defining events* (*multiple myeloma defining events*, MDE): CRAB (hypercalcemia, renal dysfunction, anemia, and/or lytic bone lesions), features related to plasma cell disorder, as well as three specific biomarkers: clonal plasmocytosis in the bone marrow  $\geq 60\%$ , proportion of involved/uninvolved CLF  $\geq 100$  (provided that the CLC involved is  $\geq 100$  mg/L), or  $>1$  focal lesion detected on magnetic resonance imaging (MRI).<sup>12</sup>

The criteria reviewed (2015) by the International Myeloma Working Group (IMWG) for the diagnosis of MM and related disorders (monoclonal gammopathies) are shown in **Table 1**.

## Other monoclonal gammopathies

Almost all patients with MM evolve from an asymptomatic premalignant stage called *monoclonal gammopathy of undetermined significance* (MGUS) (**Table 1**),<sup>4,6,12</sup> which is the most common monoclonal gammopathy,<sup>16</sup> present in more than 3% of the population over 50 years of age,<sup>10,12,16</sup> and in more than 5% from the age of 70 years.<sup>10,16</sup> It is about twice as prevalent in afro-descendants as in caucasians.<sup>12</sup> Approximately 25% of patients with MGUS develop MM, amyloidosis, macroglobulinemia or other lymphoproliferative diseases,<sup>10,16</sup> with an actuarial rate of 16% up to 10 years, 33% up to 20 years and 45% up to 25 years.<sup>16</sup> The predominant M protein is IgG  $\gamma$  (55.5%), followed by IgM  $\mu$  (20%), IgA  $\alpha$  (10%), biclonal (8%), light chain (6%) and IgD  $\delta$  ( $<0.5\%$ )<sup>11,16</sup> - the concentration of M protein, the type of immunoglobulin, medullary plasma cell infiltration greater than 5% and the presence of monoclonal light chain in the urine can be used in risk stratification in MGUS.<sup>10,16</sup> MGUS progresses to MM or related malignancy at a rate of 1% per year.<sup>10,12,16</sup> As this pathology is asymptomatic, it is believed that  $>50\%$  of the individuals diagnosed were already carriers of this condition more than 10 years before its diagnosis.<sup>12</sup> Its variants of presentation, according to the diagnostic criteria (**Table 1**), are: non-IgM MGUS, IgM MGUS and MGUS light chain.

In some patients, a more advanced, intermediate, asymptomatic premalignant stage, known as *smoldering multiple myeloma* (SMM), may occur (**Table 1**),<sup>6,12</sup> SMM progresses to MM at a rate of approximately 10% per year for the first five years after diagnosis, 3% per year for the following five years, and, thereafter, 1.5% per year. This progression ratio is influenced by the underlying cytogenetic profile: patients with t(4;14), del(17p) and gain(1q) translocation have a higher risk of progression from MGUS or SMM to MM.<sup>12</sup>

Solitary plasmocytoma (SP) (**Table 1**) is an uncommon type of plasmacytic dyscrasia,<sup>17,18</sup> representing approximately 2-5% of all monoclonal gammopathies.<sup>17,18</sup> It is characterized by localized proliferation of neoplastic plasma cells,<sup>16-18</sup> with no evidence of other skeletal lesions on imaging, absence of MM-related signs and symptoms, and morphologically normal bone marrow biopsy (solitary

**Table 1** International Myeloma Working Group (IMWG) criteria for the MM diagnosis and other monoclonal gammopathies

Disorder	Definition of the Disease
Monoclonal gammopathy of undetermined significance (Non-IgM MGUS)	All 3 criteria must be met: <ul style="list-style-type: none"> <li>• Serum monoclonal protein (Non-IgM) &lt;3 g/dl;</li> <li>• Clonal plasma cells in the bone marrow &lt;10%;<sup>a</sup></li> <li>• Absence of target organ damage, such as hypercalcemia, renal failure, anemia, or bone lesions (CRAB) that can be attributed to proliferative plasma cell disorder.</li> </ul>
Latent Multiple Myeloma (SMM)	Both criteria must be met: <ul style="list-style-type: none"> <li>• Serum monoclonal protein (IgG or IgA) ≥3 g/dl, or monoclonal urinary protein &gt;500 mg in 24 hours and/or 10%-60% of clonal plasma cells in the bone marrow;</li> <li>• Absence of events defining myeloma or amyloidosis.</li> </ul>
Multiple Myeloma (MM)	Both criteria must be met: <ul style="list-style-type: none"> <li>• Clonal plasma cells in the bone marrow &lt;10% or bone or extramedullary plasmocytoma confirmed by biopsy;</li> <li>• Any one or more of the events that define myeloma: <ul style="list-style-type: none"> <li>• Evidence of target organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically: <ul style="list-style-type: none"> <li>➤ Hypercalcemia: serum calcium &gt;0.25 mmol/l (&gt;1 mg/dl) higher than the upper limit of normal or &gt;2.75 mmol/l (&gt;11 mg/dl);</li> <li>➤ Renal failure: <i>creatinine clearance</i> &lt;40 ml per minute or serum creatinine &gt;177 mmol/l (&gt;2 mg/dl);</li> <li>➤ Anemia: hemoglobin value &gt;2 g/dl below the lower limit of normal, or a hemoglobin value &lt;10 g/dl;</li> <li>➤ Bone lesions: one or more osteolytic lesions on skeletal radiographs, computed tomography (CT), or positron emission tomography-CT (PET-CT).</li> </ul> </li> <li>• Percentage of clonal plasma cells in the bone marrow ≥60%;</li> <li>• Free serum light chain ratio (FLC) involved/uninvolved ≥100 (the level of free light chain involved should be ≥100 mg/l);</li> <li>• &gt;1 focal lesion on magnetic resonance imaging (MRI) studies (at least 5 mm in size).</li> </ul> </li> </ul>
Monoclonal gammopathy of undetermined significance IgM (IgM MGUS)	All 3 criteria must be met: <ul style="list-style-type: none"> <li>• IgM monoclonal serum protein &lt;3 g/dl;</li> <li>• Lymphoplasmocytic infiltration of the bone marrow &lt;10%</li> <li>• No evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly that can be attributed to the underlying lymphoproliferative disorder.</li> </ul>
Light Chain MGUS	All criteria must be met: <ul style="list-style-type: none"> <li>• Abnormal FLC proportion (&lt;0.26 or &gt;1.65);</li> <li>• Increased level of appropriate light chain involved (increased <i>kappa</i> FLC in patients with a ratio &gt;1.65 and increased <i>lambda</i> FLC in patients with a ratio &lt;0.26);</li> <li>• There is no expression of heavy chain immunoglobulin in immunofixation;</li> <li>• Absence of damage to target organs that can be attributed to the proliferative disorder of plasma cells;</li> <li>• Clonal plasma cells in the bone marrow &lt;10%;</li> <li>• Monoclonal urinary protein &lt;500 mg/24 hours.</li> </ul>
Solitary Plasmocytoma	All 4 criteria must be met: <ul style="list-style-type: none"> <li>• Biopsy showing solitary lesion in bone or soft tissues, with evidence of clonal plasma cells;</li> <li>• Normal bone marrow, no evidence of clonal plasma cells;</li> <li>• Normal investigation of the skeleton, MRI (or CT) of the spine and pelvis (except for the primary solitary lesion);</li> <li>• Absence of target organ damage such as hypercalcemia, renal failure, anemia, or bone lesions (CRAB) that can be attributed to lymphoplasmocyte proliferative disorder.</li> </ul>
Solitary Plasmocytoma with Minimal Medullary Involvement <sup>b</sup>	All 4 criteria must be met: <ul style="list-style-type: none"> <li>• Biopsy showing solitary lesion in bone or soft tissues, with evidence of clonal plasma cells;</li> <li>• Clonal plasma cells in the bone marrow &lt;10%;</li> <li>• Normal investigation of the skeleton, MRI (or CT) of the spine and pelvis (except for the primary solitary lesion);</li> <li>• Absence of target organ damage such as hypercalcemia, renal failure, anemia, or bone lesions (CRAB) that can be attributed to lymphoplasmocyte proliferative disorder.</li> </ul>

<sup>a</sup>Bone marrow biopsy may be delayed in patients with low-risk MGUS (IgG, M protein <15 g/l, with normal free light chain ratio) in whom there are no MM-related clinical features.

<sup>b</sup>Solitary plasmocytoma with 10% or more clonal plasma cells is considered as MM.

Fonte: Traduzido a partir de Rajkumar SV. Multiple myeloma: 2020 update on diagnosis, risk-stratification, and management. *Am J Hematol.* 2020;95(5):548-567.



plasmacytoma variant) or with very low plasmacytic clonal infiltration (<10%, solitary plasmacytoma variant with minimal medullary involvement) (►Table 1).<sup>17,18</sup> SP can be subdivided into two entities: bone SP and soft tissue SP (extramedullary).<sup>16-18</sup> The incidence of bone SP is approximately 40% higher than that of extramedullary SP.<sup>17,18</sup> Bone SP occurs more frequently in the axial skeleton,<sup>16,19</sup> being twice as frequent in the spine than in other sites, besides constituting the most common malignant primary tumor in this location (30% of all cases),<sup>19</sup> while extramedullary SP is more frequently observed in the head and neck.<sup>16-19</sup> The variants have a very different clinical course and prognosis, particularly regarding the progression to MM, being worse in bone SP.<sup>17</sup> The median age at SP diagnosis (55-60 years) is significantly lower than that observed in patients with MM; and the distribution by gender shows male predominance, ranging from 1.2 to 2:1.<sup>17,19</sup> SP has a higher incidence in afro-descendants, being about 30% more frequent than in Caucasians, and has a lower incidence in the Asian population.<sup>18</sup>

Confirmation of the presence of the monoclonal protein is essential to differentiate monoclonal gammopathies from polyclonal gammopathies since the former are neoplastic or potentially neoplastic entities while the latter result from inflammatory or infectious processes.<sup>19</sup>

## Systemic Treatment

It is important to understand that MM is treatable, but not curable. Treatment plans vary and are tailor-made for each individual – basic parameters such as the patient's age, pattern of disease progression, prognosis, and patient preference should be applied in this planning.

Autologous stem cell transplantation (TACT) is the first treatment option in MM. From the perspective of treatment and prognosis, MM patients are stratified into three groups: (1) those newly diagnosed and eligible for TACT, (2) those newly diagnosed and not eligible for TACT, and (3) those with relapsed and/or refractory MM.<sup>9</sup>

For patients eligible for TACT, the first step in treatment is the introduction of a triple cocktail including chemotherapy, proteasome inhibitor, and corticosteroids (e.g., bortezomib, lenalidomide, and dexamethasone).<sup>9</sup> Patients are treated with three to four cycles of induction therapy prior to stem cell collection.<sup>12</sup> The stem cells are then collected through central venous access, and then high-dose chemotherapy is initiated.<sup>9</sup> Patients can immediately undergo TACT or resume induction therapy, delaying TACT until the first relapse. There are many options for initial therapy – these regimens can also be used at the time of relapse. In general, dexamethasone at low doses (40 mg once weekly) is preferred in all treatment regimens as it minimizes toxicity.<sup>12</sup>

In patients with newly diagnosed MM and ineligible for TACT due to age or other comorbidities, the treatment plan is to control the side effects of MM and its progression as much as possible.<sup>9</sup> Normally, treatment is performed using a regimen based on the use of a chemotherapeutic agent, such as lenalidomide, which reduces the production of monoclonal proteins, especially in relapses, and bortezomib<sup>9</sup> or daratu-

mumab,<sup>12</sup> as additive therapy to dexamethasone – this combined action results in greater lethality for anomalous plasma cells.<sup>7</sup> Although melphalan-based regimens have been extensively tested in these patients, they are not recommended due to concerns regarding stem cell damage, secondary myelodysplastic syndrome, and leukemia.<sup>12</sup>

Almost all MM patients go through relapses. The duration of remission in these relapses decreases with each regimen. The median progression of disease-free survival and overall survival in patients with relapsed MM, refractory to lenalidomide and bortezomib, were low before the introduction of daratumumab. The choice of treatment regimen in a relapse is complicated and affected by several factors, including relapse time, response to previous therapy, aggressiveness of relapse, and performance status. Patients eligible for TACT should be considered for the procedure if they have never done so, or if they have had excellent duration of remission (36 months or more) with treatment maintenance. In terms of drug therapy, a triple regimen, containing at least two new drugs to which the patient is not refractory, should be considered. Patients previously treated with lenalidomide often relapse when using a regimen containing the same drug – in patients refractory to lenalidomide treatment, one option is to consider pomalidomide-based regimens.<sup>12</sup>

Recently, the Food and Drug Administration (FDA) approved the first chimeric antigen receptor (CAR) T-cell (T-cell) immunotherapy for MM. This is the idecabtagene vicleucel (Abecma) indicated for patients with refractory or relapsed MM after at least four different types of treatment. Abecma targets the B-cell maturation antigen (BCMA) present on the surface of neoplastic cells. Immune system T cells are collected, genetically modified, multiplied and reinfused into the patient, where they bind to BCMA, leading to the death of tumor cells by apoptosis. The main advantage for the patient is the single infusion, which requires a maximum of two weeks of hospitalization; in addition, modified T cells may persist in the patient's body for a long time, recognizing and attacking neoplastic cells if and when there are relapses.

## Prognosis

Overall survival in MM, affected by characteristics of the carrier of the pathology, tumor burden, presence of cytogenetic abnormalities and response to therapy, has improved significantly in the last 15 years. The initial impact came from the introduction of thalidomide, bortezomib and lenalidomide. In the last decade, carfilzomib, pomalidomide, panobinostat, ixazomib, elotuzumab, daratumumab, isatuximab and selinexor have been approved for the treatment of relapses, promising to further improve outcomes.<sup>12</sup>

The age of patients with MM is an important factor in the prognostic classification. Patients over 65 years old have a very low survival rate when compared to younger patients.<sup>10</sup> Similar findings are observed in patients with SP aged over 60 years.<sup>18</sup>

Tumor burden in MM has traditionally been assessed using the Durie-Salmon Staging (DSS) and the International Staging System (ISS).<sup>12</sup>

The biological behavior of the disease is related to the molecular subtype of MM and the presence or absence of secondary cytogenetic abnormalities, such as del(17p), gain(1q), or del(1p). In addition to cytogenetic risk factors, two other markers associated with the aggressiveness of the disease are elevated lactic dehydrogenase, and the presence of circulating plasma cells detected in peripheral blood smears (plasmacytic leukemia). Each of the biomarkers used in the diagnosis of MM (clonal plasmocytosis in the bone marrow  $\geq 60\%$ , proportion of CLF involved/uninvolved  $\geq 100$ , or  $> 1$  focal lesion detected on MRI) is associated with a risk of approximately 80% for progression of symptomatic damage in target organs - attention to these criteria allows early diagnosis and initiation of therapy before these damages occur.<sup>12</sup>

Some findings in laboratory tests routinely performed in patients with MM allow us to indicate more active disease: high levels of  $\beta 2$  microglobulin, low levels of serum albumin, serum creatinine above normal, lactic dehydrogenase above normal, C-reactive protein above normal, hemoglobin below normal and platelet count below normal. Other special tests

such as plasma cell labeling index (PCLI) indicating high percentage of plasma cells, iFISH (interphase fluorescence in situ hybridization) demonstrating chromosome 13 absence and/or other cytogenetic abnormalities and evaluation of microvascular bone marrow density (microvascular density, MVD), demonstrating growth of new blood vessels in the bone marrow, also suggest more active disease.

Survival can range from a few months to more than a decade.<sup>10</sup> In the United States, the five-year relative survival rate was 57.9% between 2012 and 2018.<sup>14</sup> According to the American Cancer Society,<sup>2</sup> following the staging system reviewed for MM (2015) by the International Myeloma Working Group (IMWG)<sup>20,21</sup> (► **Table 2**), stage I survival was not determined; in stage II it was 83 months; and in stage III, it was 43 months.

## Final Considerations

Multiple myeloma (MM) is a plasma cell neoplasm characterized by abnormal clonal proliferation of plasma cells in the bone marrow, with production of monoclonal

**Table 2** R-ISS for MM is an algorithm for risk stratification that has improved prognostic power when compared to the three widely used prognostic indicators that it incorporates: (1) ISS, determined by serum  $\beta 2$ -microglobulin and albumin levels; (2) the presence of any one or more of the three specific chromosomal abnormalities [del(17p), and/or t(4;14) translocation, and/or t(14;16) translocation] detected by iFISH; and (3) LDH level. In patients with newly diagnosed MM, R-ISS allows the identification of three distinct myeloma entities, with significantly different survival outcomes

Determination of the patient's ISS stage	
ISS Stage	Criteria
I	Serum $\beta 2$ -microglobulin $< 3.5$ mg/l Serum albumin $\geq 3.5$ g/dl
II	Not ISS I or ISS III Serum $\beta 2$ -microglobulin $\geq 3.5$ mg/l, but $< 5.5$ mg/l or Serum albumin $< 3.5$ g/dl
III	Serum $\beta 2$ -microglobulin $\geq 5.5$ mg/l
Determination of risk according to chromosomal abnormalities detected by iFISH.	
Risk	Criteria
Standard Risk	Chromosomal abnormalities without high risk
High Risk	Presence of del(17p), and/or t(4;14) translocation, and/or t(14,16) translocation
Determination of the risk according to the level of lactic dehydrogenase (LDH)	
Risk	Criteria
Standard Risk	Normal serum LDH, $<$ the upper limit of normal as defined by the laboratory
High Risk	High serum LDH, $>$ the upper limit of normal as defined by the laboratory
Identification of the patient's R-ISS stage, according to the criteria determined above	
R-ISS Stage	Criteria
I	ISS stage I and standard risk for chromosomal abnormalities by iFISH and normal DHL
II	Not R-ISS I or R-ISS III
III	ISS stage III and/or high risk for chromosomal abnormalities by iFISH or high DHL

Abbreviation: LDH, lactic dehydrogenase; iFISH, interphase fluorescence in situ hybridization; ISS, International Staging System; MM, multiple myeloma; R-ISS, Revised International Staging System.

Source: Translated and adapted from Managing Myeloma [Internet]. Medicom Worldwide, Inc. Links; c2020. Revised International Staging System for Multiple Myeloma [cited 2020 Mar 12]. Available from: <https://www.managingmyeloma.com/tools/revised-international-staging-system-for-multiple-myeloma?task=download.file&format=raw&dclid=1042>.

immunoglobulins, associated with organic dysfunctions. It represents 1% of all malignant neoplasms, and usually affects the elderly population, around the age of 70. Overall survival in MM is affected by characteristics of the carrier of the pathology (especially age, worse >65 years), tumor burden, presence of cytogenetic abnormalities and response to therapy, which has improved significantly in the last 15 years. An adequate understanding of the diagnostic criteria and the appropriate treatment for each patient with MM is very important to obtain the maximum possible control over the side effects of the disease and its progression.

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#### Conflict of Interest

The authors declare no conflicts of interest.

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