Expert review on soft-tissue plasmacytomas in multiple myeloma: definition, disease assessment and treatment considerations


1Department of Hematology, Hospital Clinic, IDIBAPS, University of Barcelona, Barcelona, Spain, 2Department of Hematology, Ankara University, Ankara, Turkey, 3Istituto di Ematologia “Seràgnoli”, Dipartimento di Medicina Specialistica Diagnostica e Sperimentale, Università degli Studi, Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy, 4Department of Hematology, Amsterdam UMC, VU University, Amsterdam, the Netherlands, 5Dana Farber Cancer Institute, Harvard Medical School, Boston, MA, 6University of Maryland at Baltimore, Baltimore, MD, USA, 7Department of Clinical Hematology, Centre Hospitalier Universitaire de Liège, Liège, Belgium, 8Hematology and Medical Oncology, Department of Clinical Therapeutics, National and Kapodistrian University of Athens, Alexandroupoli Hospital, Athens, Greece, 9Department of Haematology, Mayo Clinic, Rochester, MN, USA, 10Department of Internal Medicine II, University Hospital Würzburg, Würzburg, Germany, 11Interdisciplinary Tumor Center, University of Freiburg, Freiburg, Germany, 12Department of Medicine, Karolinska Institutet, Huddinge, Stockholm, Sweden, 13Myeloma Unit, Città della Salute e della Scienza, University of Torino, Torino, Italy, 14Department of Haemato-And Thérapie, University of Ostrava, Ostrava, Czech Republic, 15Clinica Säo Germaino, São Paulo, Brazil, 16Medical College Department of Hematology, Jagiellonian University, Krakow, Poland, 17University Medical Center Hamburg-Eppendorf, Hamburg, Germany, 18Division of Hematology, Mayo Clinic, Rochester, MN, USA, 19Instituto Português de Oncologia, Lisboa, Portugal, 20Pitières University Hospital, Pitières, France, 21Multiple Myeloma and Amyloidosis Service, Columbia University, New York, NY, USA, 22IBSAL, Cancer Research Center, University Hospital of Salamanca, Salamanca, Spain, 23Amyloidosis Research and Treatment Center, Department of molecular Medicine, University of Pavia, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, 24Department of Clinical Hematology and Cellular Therapy, Hospital Saint-Antoine, Sorbonne University, Paris, 25Hematology Department, University Hospital Hotel-Dieu, Nantes, France, 26Princess Margaret Cancer Center, University of Toronto, Toronto, Canada, 27Berlin, Germany, 28Erasmus MC Cancer Institute, Erasmus University of Rotterdam, Rotterdam, the Netherlands, 29Department of Hematologic Oncology and Blood Disorders, Levine Cancer Institute/Atrium Health, Charlotte, NC, USA, 30Department Hematology and Immunology, Vrije Universiteit Brussel, Brussels, Belgium, 31John Theurer Cancer Center, Hackensack Meridian School of Medicine, Hackensat, NJ, USA, and 32Department of Clinical Molecular Medicine, St. Olav Hospital, NTNU Trondheim, Trondheim, Norway

Summary

In this review, two types of soft-tissue involvement in multiple myeloma are defined: (i) extramedullary (EMD) with haematogenous spread involving only soft tissues and (ii) paraskeletal (PS) with tumour masses arising from skeletal lesions. The incidence of EMD and PS plasmacytomas at diagnosis ranges from 1% to 4.5% and 7% to 34.4% respectively. EMD disease is often associated with high-risk cytogenetics, resistance to therapy and worse prognosis than in PS involvement. In patients with PS involvement a proteasome inhibitor-based regimen may be the best option followed by autologous stem cell transplantation (ASCT) in transplant eligible patients. In patients with EMD disease who are not eligible for ASCT, a proteasome inhibitor-based regimen such as lenalidomide-bortezomib-dexamethasone (RVD) may be the best option, while for those eligible for high-dose therapy a myeloma/lymphoma-like regimen such as bortezomib, thalidomide and dexamethasone (VTD)-RVD/cisplatin, doxorubicin, cyclophosphamide and etoposide (PACE) followed by SCT should be considered. In both EMD and PS disease at relapse many strategies have been tried, but this remains a high-unmet need population.
Keywords: multiple myeloma, plasmacytoma, soft tissue, extramedullary disease, paraskeletal plasmacytomas, prognosis, treatment.

Multiple myeloma (MM) represents ~1% of all cancers and 15% of haematological malignancies. The disease is characterised by a proliferation of plasma cells (PCs) with a strong dependence on the bone marrow (BM) microenvironment. However, in up to one-third of patients with MM the PC proliferation can escape the cellular microenvironment influencing results in soft-tissue plasmacytomas, which can constitute the most prominent disease feature. Surprisingly, only observational data on plasmacytomas in MM are available and no control studies have been reported to date.

The most frequent mechanism resulting in soft-tissue plasmacytomas is direct growth from skeletal tumours by disrupting cortical bone. In the present expert review, two different types are defined: (i) EMD or extra-osseous, involving only soft tissues, and (ii) PS consisting of soft-tissue masses arising from bone lesions.

Of interest, a number of patients develop simultaneously or successively both types of plasmacytomas through the disease course. This fact supports that the myeloma clone is the critical factor for soft-tissue myeloma growth in any given patient.

**Incidence**

Data on the incidence of plasmacytomas in MM are only observational. The reported incidence of EMD involvement at diagnosis ranges from 1.7% to 4.5%4,9,13,15,17,18 while the rate of PS plasmacytomas ranges from 7% to 34.4%4-10 (Table I). At relapse, the incidence of EMD disease increases from 3-4% up to 10%,4,9-11,13,15 while the frequency of PS involvement remains similar to that observed at the time of diagnosis, ranging from 6% to 34.2%.5,9,11,12 (Table I). Of interest, when positron emission tomography/computed tomography (PET/CT) imaging is systematically used at the time of diagnosis the reported incidence of EMD disease remains relatively low ranging from 2.4% to 10%.23-25 It is of interest that in two recent studies, 45% and 56% of patients with plasmacytomas at diagnosis had EMD or PS disease at the time of relapse.6,26

It has been suggested that patients undergoing allogeneic transplantation with dose-reduced intensity conditioning (Allo-RIC) have a higher incidence of EMD relapse. Thus, Pérez-Simón et al.27 reported 37% of EMD relapses after Allo-RIC. However, Minnema et al.28 in a series of 54 patients relapsing after Allo-RIC showed a 20-4% incidence of EMD disease (11% in the context of systemic relapse and 9% as localised EMD relapses), defined as the presence of plasmacytomas not originating from skeletal structures. Finally, in a series of 25 patients who relapsed after myeloablative allogeneic transplantation the frequency of EMD relapses was 32%.29 The reasons for the discrepancy between skeletal tumours by disrupting cortical bone. In the present expert review, two different types are defined: (i) EMD or extra-osseous, involving only soft tissues, and (ii) PS consisting of soft-tissue masses arising from bone lesions.

**Table I.** Plasmacytomas in multiple myeloma: incidence at diagnosis and at relapse.

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<th>Paraskeletal (PS), %*</th>
<th>Extramedullary (EMD), %†</th>
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<tr>
<td><strong>At diagnosis</strong></td>
<td>7–34.4</td>
<td>1.75–4.5</td>
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<tr>
<td><strong>At relapse†</strong></td>
<td>6–34.2</td>
<td>3.4–10</td>
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*PS: soft-tissue masses arising from vertebrae, ribs, sternum, skull.
†EMD: skin (single or multiple subcutaneous tumours), liver, pleura, breast, lymph nodes and central nervous system (CNS).
*At relapse >liver, pleura, CNS.
the incidence of plasmacytomas after autologous stem cell transplantation (ASCT)\textsuperscript{30,31} and allogeneic transplantation are unclear. Some facts could account for the higher frequency after the allogeneic procedure: (i) younger patients with poor-risk factors and/or clinically aggressive disease, all associated with a higher probability of EMD involvement, are the most likely subset of patients to undergo an allogeneic transplant; (ii) in the above mentioned series, the frequency of plasmacytomas at diagnosis in patients relapsing with EMD disease after allogeneic transplantation was not reported, but presumably it could be high; and (iii) it has been suggested that the graft-versus-myeloma (GvM) effect is more effective at the BM level than at EMD sites. All the above could contribute to the higher reported incidence of EMD spread after allogeneic transplantation. Interestingly, in a recent study, treatment with lenalidomide before allogeneic transplantation significantly reduced the risk of post-transplant EMD relapse.\textsuperscript{32} Weinstock et al.\textsuperscript{15} reported an incidence of 8.3% of EMD disease in a series of 663 patients who underwent ASCT at the Dana Farber Cancer Institute (DFCI) from 2005 to 2011. Finally, there is no evidence that the relapse pattern is significantly different in patients exposed to novel agents. Although a recent European Society for Blood and Marrow Transplantation (EBMT) Registry study showed an increase between 2005 and 2015 from 6.5% to 23.7%,\textsuperscript{10} the frequency of EMD and PS involvement at our institution has remained constant over the last 45 years.\textsuperscript{33}

The use of novel agents has been claimed as a risk factor for the development of EMD disease. However, evidence of such an association is lacking. In fact, only the presence of plasmacytomas at diagnosis was associated with the development of soft-tissue involvement at recurrence after ASCT.\textsuperscript{5,26} This supports the notion that the characteristics inherent to the myeloma clone rather than the treatment itself are primarily responsible for EMD spread in MM. Supportive of this, in a recent publication, the DFCI group reported no increase of EMD or PS disease in patients with newly diagnosed myeloma treated with bortezomib/lenalidomide combinations.\textsuperscript{12} In the same study, a sensitivity analysis at 5 years of follow-up also showed no significant difference in the rates of EMD progression associated with lenalidomide- or bortezomib-based regimens.\textsuperscript{12} However, the data are limited and better control of medullary disease with novel drugs can result in prolongation of survival, which in itself can lead to a higher risk of clonal evolution resulting in plasmacytomas at the time of progression.\textsuperscript{34–36}

**Types of plasmacytoma growth and location**

Table I summarises the most common locations of soft-tissue plasmacytomas in MM. Local growth resulting in PS involvement is the most common finding and, as already mentioned, consists of soft-tissue masses arising from focal skeletal lesions. The more common locations are vertebrae, ribs, sternum, skull and pelvis. The haematogenous spread consists of: (i) single or multiple highly vascularised large subcutaneous nodules with a red-purple appearance; (ii) multiple small nodules located at any organ, particularly in skin, liver, breast or kidney; (iii) pleura; (iv) lymph nodes; (v) paramedullary, next to the spine with no demonstrable breakout from bone; and (vi) central nervous system (CNS). In many instances the lactate dehydrogenase (LDH) serum levels are increased in patients with EMD myeloma involvement, so a significant increase in serum LDH is suspicious of EMD disease and constitute the indication for imaging techniques, particularly PET/CT. Skin is the most frequent location at diagnosis, while there is an increased rate of liver, pleura and CNS involvement at relapse.\textsuperscript{4,9,13,15} In a retrospective multicentre series of 53 patients with cutaneous involvement there was a predominance of immunoglobulin A (IgA) and light chain myeloma. Of note, there was no correlation between CD56 negativity and skin infiltration. The median survival from skin involvement was only 8.5 months. In addition, patients with IgA myeloma and with plasmablastic morphological had a shorter survival.\textsuperscript{36}

The frequency of leptomeningeal involvement is estimated at about 1–2%.\textsuperscript{37–42} The dominant clinical picture consists of symptoms from increased intracranial pressure, cranial nerve palsies, paraparesis and/or confusion. Magnetic resonance imaging (MRI) may show leptomeningeal enhancement or meningeal-based lesions resembling intraparenchymatous masses. The cerebrosplinal fluid (CSF) typically reveals PCs with plasmablastic morphology and additional EMD involvement is frequently observed. Usually, CNS involvement is seen in advanced phases of the disease along with the involvement of other EMD sites. However, in some instances, leptomeningeal involvement can be the first manifestation of relapse in patients in complete remission (CR). In these cases with a relatively short time between diagnosis and clinical CNS involvement, it is likely that viable myeloma cells were seeded at the CNS sanctuary early in the disease resulting in local relapse, usually followed by systemic myeloma progression. In a multicentre retrospective study with 172 patients with CNS involvement (22% at diagnosis and 78% later in the course of the disease) the median survival from CNS disease was 7 months. At least one previous line of therapy and poor-risk cytogenetic abnormalities by fluorescence in situ hybridisation (FISH) were associated with a significantly shorter survival.\textsuperscript{42} In a single-institution study including 37 patients with CNS involvement (nine at diagnosis, 28 at relapse) the median overall survival (OS) was 4.6 months, with nine patients surviving for >1 year. All these patients with longer survival underwent CNS radiation therapy and most of them intrathecal chemotherapy and novel agent-based systemic therapy. Patients with CNS involvement at the time of diagnosis had significantly longer OS compared to those at relapse (9.9 vs. 4.1 months).\textsuperscript{43}

Plasmacytomas can occasionally be seeded by surgical invasive procedures performed over the course of the disease.
Thus, they can arise from laparotomy scars or catheter insertions and can even precede systemic relapses. It is possible that the inflammatory process associated with the tissue injury can facilitate the migration of myeloma cells into the skin to create a reservoir of viable cells eventually able to proliferate. In contrast with this hypothesis, the appearance of an EMD soft-tissue plasmacytoma along the scar from surgery performed 10 years before the diagnosis of MM in a young patient with MM (Fig 1 - PET/CT) has been reported. Extensive EMD involvement resulting from bone surgery or fractures has been reported. In this regard, it is of interest that in the severe combined immunodeficiency (SCID)-human myeloma model, cells from patients with plasmacytomas directly injected to the fetal graft bone proliferate into contiguous soft tissues beyond the bone graft, which is consistent with the clinical behaviour of myeloma cells in patients.

Tumour characteristics at EMD sites

Plasma cells from EMD disease typically show immature or plasmablastic morphology. In contrast, myeloma cells from PS masses are less undifferentiated and usually show a plasmacytoma morphology. Katodritou et al. reported that six of seven patients with EMD relapse displayed anaplastic morphology with CD56 negativity at EMD sites. Two patients lost CD56 expression at the EMD location compared with BMPCs. Of interest, it has been reported that CD56 is rarely expressed in plasma cell leukemia (PCL) and that CD56 is downregulated in myeloma cells from CNS involvement. In contrast, another study showed no significant differences in CD56 expression between medullary and EMD myeloma and between intramedullary myeloma and solitary plasmacytoma of bone. More studies are required to establish the role of CD56 in EMD myeloma dissemination. The information on genetic abnormalities in EMD myeloma is limited. It has been suggested that 17p deletion is involved in EMD myeloma progression. Thus 17p deletion was reported in eight of nine patients with MM and CNS involvement. López Anglada et al. reported a patient with MM and EMD involvement harbouring t(4;14) in the BM and t(4;14) plus 17p deletion in EMD plasmacytomas. In this regard, one study on paired biopsies from medullary and EMD sites from 12 patients with EMD involvement showed p53 nuclear expression in 75% (nine of 12) of patients at EMD sites versus only 8% (one of 12) in the BM samples. However, a limitation of this study is that it was based on immunohistochemistry and not on molecular genetics. Besse et al. in another paired sample study, showed that PCs at EMD sites harbour more genetic aberrations than in the BM. In contrast, Katodritou et al. reported that four of nine patients with EMD relapse had t(4;14) or t(14;16) in BMPCs at diagnosis with no additional cytogenetic changes at EMD sites. In two reports from Billecke et al. EMD and soft-tissue plasmacytomas arising from skeletal lesions showed a similar incidence of deletion 17p ranging from 21% to 32%. Of note, in these studies the frequency of deletion 17p was higher than the usually reported from BMPCs or from osteolytic lesions. In one of the above series, three patients had deletion 17p at EMD sites and not in the BM, suggesting a role of deletion 17p in EMD myeloma progression. For a meaningful interpretation of these results the study of the
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clonal signature to confirm or deny that the same clone is present in all involved sites would be required. A higher incidence of (4;14) in haematogenous spread versus PS plasmacytomas (37% vs. 18%) has been reported.58 Deng et al59 reported that patients with EMD disease had a higher prevalence of p53 deletion at FISH analysis (34-5% vs. 11-9%) and significantly greater LDH levels compared with those without EMD disease. Rasche et al60 reported that 10 of 19 (52%) patients who relapsed with prominent haematogenous EMD involvement had high-risk cytogenetics at the time of relapse. In a large Spanish transplantation trial, the proportion of patients with high-risk cytogenetics was similar in patients with and without PS involvement (24% vs. 21%).61 Therefore, the genetic abnormalities harboured by BMPCs are not associated ‘per se’ with soft-tissue involvement. However, the Arkansas group performed molecular gene expression profiling (GEP) studies on BMPCs and found that haematogenous EMD disease was associated with high-risk features, particularly MAFB gene overexpression and markers of highly proliferative disease.13 The cumulative incidence of EMD disease was significantly increased in patients with GEP-defined high-risk disease at baseline and with baseline cytogenetic abnormalities. They concluded that the haematogenous EMD spread was more prevalent in genomically defined high-risk myeloma.13 This could help to identify EMD-unique genes that might be targeted by new drugs or different treatment approaches. Finally, MYC overexpression and a higher proliferation rate leading to a more aggressive behaviour have been reported in PCs from EMD sites.54,59,60

Assessment of soft-tissue involvement in multiple myeloma

Assessment of plasmacytomas

In some patients plasmacytomas can be assessed by physical examination (e.g. a palpable mass). However, in most instances radiographic imaging techniques are needed.62,63 MRI is useful in the assessment of both the nature (EMD versus PS) and the extent of soft-tissue disease, particularly when evaluating the spine.64 Thus, MRI is mandatory in patients with suspicion of spinal cord or nerve root compression in order to accurately assess the level and extent of the lesions and the degree of epidural space involvement.64 MRI is also mandatory when CNS involvement is suspected, as well as CSF studies looking for a monoclonal (M)-protein and PCs. The typical findings are leptomeningeal enhancement and/or meningeal-based lesions resembling intraparenchymatous masses.64 Fluorodeoxyglucose (FDG)-PET/CT is the most useful whole body technique in patients in whom soft-tissue involvement is suspected.65–67 In a recent systematic review, its sensitivity and specificity were 96% and 78% respectively.68 Thus, PET/CT is the whole body imaging technique of choice to detect EMD or PS involvement in MM. The main limitation of PET/CT has been the non-standardisation of visual criteria and the possible lack of interobserver reproducibility.69,70 Hopefully, the recent work on standardisation of 18F-FDG PET/CT according to the Deauville criteria, based on the joint analysis of two prospective randomised Phase III trials, will be helpful.71 Along with the metabolic uptake [standardised uptake value (SUV)] it is important to carefully look at: (i) the findings of the companion CT (co-localisation), (ii) the nature of soft-tissue components (i.e. EMD versus soft-tissue masses arising from bones, (iii) high-risk areas of cord compression or skull-base invasion and (iv) potential false positive findings, particularly healing bone fractures, stress fractures or bone infarcts of the femoral head, as well as degenerative/arthritis processes resembling soft-tissue involvement with high metabolic uptake. In conclusion, a PET/CT should be done in patients in whom soft-tissue myeloma involvement is suspected based on clinical symptoms or considered at high-risk (i.e. patients with high LDH), as well as at the time of biochemical relapse in patients with a previous history of plasmacytomas, given the high frequency of soft-tissue involvement at relapse in this population.

Assessment of response to therapy

The uniform response criteria by the International Myeloma Working Group (IMWG) requires the disappearance of soft-tissue masses for a CR and a decrease ≥50% for partial remission (PR).72 However, there is no specification on the required decrease of plasmacytomas to declare very good PR (VGPR). As the serum and urine paraprotein requirements for VGPR are very stringent (i.e. serum M-protein decrease ≥90% and urine light chain protein excretion <100 mg/24 h), we recommend that for VGPR assignment evidence of active plasmacytoma must have disappeared on physical examination and/or imaging techniques.73 Conversely, there is no recommendation by the IMWG on the required frequency of plasmacytomas assessment. We believe that clinical assessment (i.e. measurement of a palpable soft-tissue mass) should be performed at the beginning of each treatment cycle, while the assessment of plasmacytomas identified by imaging techniques, ideally by PET/CT (considering size and metabolic uptake) and/or MRI, should be done at 3 months after the initiation and subsequently at the physician’s discretion if there is still persistent active disease. If after 3 months of therapy there is still active disease, the continuation of the same therapy, the administration of radiation therapy or a switch to an alternative treatment should be considered depending on the degree of paraprotein and plasmacytoma response. In case that the plasmacytoma decrease is <50%, local radiation and/or switch of systemic therapy should be considered, while with a decrease of ≥50% in the plasmacytoma size (PR or better) the continuation of the same therapy is recommended. If the plasmacytoma has disappeared and if there is no evidence of active disease at a potential residual site (i.e. CR)72 it would be reasonable to perform
yearly imaging as part of follow-up and at any time if plasmacytoma recurrence is suspected or if progressive disease occurs as defined by an increase in the M-protein or clinical deterioration. Progression is defined as the recurrence of a known plasmacytoma that had disappeared with therapy, the appearance of any new area of soft-tissue involvement or the increase in ≥25% of existing lesions.25 Concerning the follow-up of plasmacytoma, it is important to consider that some lesions can be differently perceived with different imaging techniques or variously interpreted by different radiologists. Ideally, the same reader with the use of the same imaging technique should report the baseline and follow-up assessments for a particular patient in order to minimise both the inter-technique and the inter-reader variability.73

**Prognosis**

Using a time-dependant statistical analysis, Varettoni et al.6 showed that the presence of soft-tissue involvement at any time during the course of the disease was associated with significantly shorter progression-free survival (PFS) and OS. Wu et al.5 reported that the presence of plasmacytomas was associated with poorer prognosis in patients treated with conventional chemotherapy. However, in the above two studies, patients who received ASCT had similar outcome, irrespective of the presence or absence of plasmacytomas, suggesting that high-dose melphalan may overcome the negative impact of soft-tissue involvement in this setting. A report from South Korea showed similar results.74 In a recent EBMT Registry study, patients with PS involvement who received up-front ASCT had similar PFS and OS as those with no plasmacytomas.10 In contrast, patients with EMD had significantly shorter PFS rates at 3 years after ASCT than those with PS involvement or those without plasmacytomas and also significantly worse OS rates.10 In this study, tandem ASCT did not improve the outcome of patients with plasmacytomas, neither with PS nor with EMD disease. In contrast, in a Programa Español para el tratamiento de las Hemopatías Malignas (PETHEMA) transplantation trial there were no significant differences in PFS between patients with or without PS involvement; however, the OS was significantly shorter in those with plasmacytomas.61 Finally, in a meta-analysis of eight recent Italian trials using new drugs the detrimental effect of EMD disease at diagnosis was limited.75 Of note, in all the four above mentioned studies, the vast majority of patients had PS involvement and very few had EMD disease. Importantly, in the era or novel agents, Usmani et al.15 reported that EMD spread was associated with a significantly poorer PFS and OS, regardless of whether patients were treated according to ‘Total Therapy’ protocols involving intensive chemotherapy. In other studies in which PET/CT was systematically performed at the time of up-front therapy initiation, the presence of EMD disease was associated with a significantly shorter PFS and OS, despite the incidence being only between 6% and 10%.22–25 Pour et al.11 reported in the relapsed setting that patients with soft-tissue involvement had poorer prognosis than those relapsing with no plasmacytoma. Importantly, the survival of those with EMD disease was significantly shorter when compared with that of patients with PS masses. Similar results have been reported by others.76,77 In our own series, the median survival of 29 patients with EMD disease at diagnosis was significantly shorter than that of 191 patients with PS plasmacytomas (1.8 vs. 3.5 years).33 A multicentre study of 127 patients with EMD disease also showed dismal outcome.78 The prognosis is particularly poor in patients with CNS involvement who have a median survival of <3 months,38,39 and even when novel agents are used outcomes to date have been dismal.41,79,80 Survival may be improved by the combination of radiation therapy (cranial or craniospinal) along with systemic plus intrathecal therapy, but this constitutes an area of exquisite unmet medical need.17,37

**Treatment approach**

**General considerations**

As outlined above, the outcome of patients with EMD involvement is worse than those with PS disease. This could be a consequence of intrinsically more aggressive disease and/or different drug sensitivity. Unfortunately, most of the published series include both types of plasmacytomas under the term ‘extramedullary disease’ and definitive conclusions cannot be drawn. However, some considerations can be made. First, alkylating agents are effective as front-line therapy, particularly high-dose melphalan, for PS involvement. In this regard, Varettoni et al.6 reported that 72% of patients with soft-tissue involvement at the time of diagnosis achieved at least a PR. Similarly, Wu et al.5 found that in patients who received initial conventional therapy the PR rate was 52% and 50%, irrespective of the presence or absence of plasmacytomas. The response rate was also similar at 90% versus 91% in patients who received high-dose therapy intensification. On the other hand, the results of an EBMT Registry study showed that patients with PS plasmacytomas who underwent ASCT had similar survival outcomes as those without soft-tissue myeloma involvement.10 Second, the data concerning the efficacy of newer agents are limited. Bortezomib seems to be of benefit in patients with PS disease with less evidence for EMD involvement.51–53 Carfilzomib showed limited efficacy in relapsed patients with MM and plasmacytomas, particularly in those with EMD disease.54,55 The efficacy of ixazomib is unknown. In contrast, marizomib, which is able to cross the blood–brain barrier, has shown efficacy in CNS involvement,56 an observation initially recognised by the results of a Phase I study in >60 patients with relapsed/refractory MM (RRMM).87 The efficacy of immunomodulatory drugs (IMiDs) in this context is also limited. In a single-institution series, none of the 11 patients with
plasmacytomas (seven patients with PS involvement and four with EMD disease) responded to single-agent thalidomide. The failure of soft-tissue involvement to respond to single-agent thalidomide has also been reported by others. There are no published data on the efficacy of lenalidomide on plasmacytomas in the relapse setting. Concerning pomalidomide plus low-dose dexamethasone, the Mayo Clinic group reported that four of 13 patients (31%) with EMD disease responded with two CRs and two PRs. In contrast, the Catalan Myeloma Group only observed two responses (one CR and one PR) amongst 21 patients with RRMM treated with pomalidomide and dexamethasone. Third, a dissociation between PR and soft-tissue response has been observed. Also, progression of plasmacytomas despite good BM and serological response in patients receiving thalidomide has been reported. These phenomena have also been observed with bortezomib and carfilzomib.

Fourth, concerning more novel drugs, there are very limited data on the efficacy of daratumumab, with one study showing an overall response rate (ORR) of 17% in CD38 monoclonal antibody (MoAb)-naive patients. A recent single institution report showed very modest efficacy of single-agent daratumumab in advanced patients with relapsed myeloma, including EMD disease. Isatuximab associated with pomalidomide and dexamethasone (Isa-Pd) resulted in 50% ORR (seven of 14) compared with only 10% (one of 10) with pomalidomide and dexamethasone (Pd) in patients with RRMM and soft-tissue plasmacytomas. Also, the PFS was also longer with Isa-Pd compared with Pd (4.57 vs. 1.56 months). Of interest, melphalan has resulted in a significant response rate in both EMD and PS disease, with an overall response (PR or better) of 23% (13/55 patients) and similar duration of response between patients with or without plasmacytomas. Selinexor and dexamethasone showed a response rate of 31% (five of 16). However, in this study only 16 out of 27 patients with plasmacytomas were available for response evaluation. Venetoclax could be considered for relapsed patients with soft-tissue involvement and with ≥11 CRd or ≥14 PRd, but there are no reported data.

It must be noted that the small sample size and the absence of controlled trials are important shortcomings in the assessment of the efficacy of anti-myeloma therapy on soft-tissue involvement in MM and consequently it is difficult to recommend specific treatment approaches.

**Up-front therapy for patients with PS plasmacytomas**

Considering that cytotoxic agents and in particular alkylating drugs, as well as bortezomib, are the most active agents in patients with PS plasmacytomas, the treatment of choice for patients not immediately proceeding to ASCT may be the combination of bortezomib with melphalan, prednisone and daratumumab (Dara-VMP) or lenalidomide bortezomib and dexamethasone (RVD). Assuming that high-dose melphalan can overcome the poor prognosis of PS involvement and that a proteasome inhibitor-based regimen, particularly bortezomib, thalidomide and dexamethasone (VTD) or RVD likely with a MoAb, such as daratumumab, constitutes the best preparative induction regimen; the best option for patients eligible for ASCT should be an induction proteasome inhibitor-based regimen followed by high-dose melphalan/autologous stem cell support (Table II). It seems that tandem ASCT is of no additional benefit. Local radiation therapy should be urgently administered in cases of spinal cord compression and also considered in patients with severe compressive pain, in those with bulky plasmacytomas, as well as in patients with persistent local disease after systemic therapy. Unfortunately, there is a lack of prospective clinical trials on patients with MM presenting with plasmacytomas. Recently, the Gruppo Italiano Malattie EMatologiche dell’Adulto (GIMEMA) group published the outcome of 267 patients with soft-tissue involvement (243 PS) included in eight prospective trials, using bortezomib, lenalidomide or carfilzomib compared with 2065 patients without plasmacytomas. The median PFS was similar in both groups (25.3 vs. 25.2 months), while the median OS was significantly shorter in patients with soft-tissue involvement (63.5 vs. 79.9 months). The authors conclude that in patients treated with new drugs the detrimental effect of PS involvement at diagnosis is limited and that both proteasome inhibitors and lenalidomide are effective in this situation.

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<th>Paraskeletal (PS)</th>
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<td>Elderly</td>
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<tr>
<td>MPV/daratumumab</td>
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<td>Bortezomib-based regimen (VTD, PAD, RVD) ± daratumumab + ASCT*</td>
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<td></td>
<td>VTD or RVD-PACE → allogenic-transplantation</td>
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<td>VTD or RVD-PACE → tandem ASCT-allo-RIC</td>
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*ASCT may overcome the poor prognosis of PS plasmacytoma.*
Up-front therapy for EMD disease

Patients with overt haematogenous myeloma spread should be considered as having an ultra-high-risk disease with an extremely poor outcome, as current treatment approaches are unsatisfactory. However, until more effective options are available, the VMP or RVD regimens seem to be the treatment of choice for patients who are not eligible for ASCT.100,102 Considering that daratumumab improves the efficacy of VMP and also RVD, the addition of a CD38-targeting MoAb would be most reasonable. For transplant-eligible patients, a combined intensive anti-myeloma/anti-lymphoma regimen such as VTD or VRD/cisplatin, doxorubicin, cyclophosphamide and etoposide (PACE)103 followed by a tandem ASCT or ASCT followed by Allo-RIC seems theoretically an alternative option104 (Table II). Although these patients usually respond to induction therapy, early relapse is very common.105 For this reason, a suggested approach could be an intensive short induction (such as two or three cycles of VTD or VRD-PACE) immediately followed by the high-dose approach if appropriate. In case of tandem transplantation, the interval between the first and second procedure should also be as short as possible in order to avoid disease progression while waiting for the allogeneic procedure, but this may be challenging. In patients with high-risk cytogenetics tandem ASCT seems to be of benefit.106 However, the EBMT Registry has recently reported no benefit of tandem ASCT over single ASCT in patients with EMD disease,10 further emphasising the need for new approaches. In this regard, the European Myeloma Network (EMN) is conducting a Phase II trial of daratumumab combined with bortezomib, cyclophosphamide and dexamethasone in patients with MM and EMD disease at diagnosis and first relapse (EMN19 study, NCT 04166565).

Treatment at relapse

The prognosis of patients relapsing with soft-tissue involvement either EMD or PS is extremely poor.4,9,11,18,59 Given the fact that currently many patients have already received bortezomib-based front-line regimens frequently with IMiDs, the most effective treatment at relapse consists of lymphoma-like regimens such as PACE, dexamethasone, cyclophosphamide, etoposide, and cisplatin (DCEP) or dexamethasone, carmustine, etoposide, doxorubicin, melphalan (Dexa-BEAM)105–107 (Table III). The response rate is ~50%, but the duration of response is short, lasting for a median of only 4 months.108,109 In patients who are eligible for SCT an appropriate approach would be the administration of two or three chemotherapy cycles followed by a high-dose procedure, provided that the patient is in response at the time of transplant, as there appears to be no meaningful role for ASCT in patients with resistant disease and the utility of allo-SCT may also be very limited. In patients relapsing after a durable response to bortezomib, proteasome inhibition-based therapy could also be an option. Alternatively, in patients initially treated with IMiD-based therapy, rescue with proteasome inhibitor-based regimens maybe effective. The initial results with melflufen are encouraging and melflufen-based regimens could be of help.97 For patients with CNS involvement craniospinal radiation, triple intrathecal chemotherapy (glucocorticoids, methotrexate and cytarabine) and systemic IMiD-based therapy is recommended.43 With the limitations of most standard approaches in the control of EMD disease, newer immunotherapeutic strategies such as toxin immunocugl conjugate MoAbs, bi-specific antibodies against CD3 and B-cell maturation antigen (BCMA) recruiting endogenous T cells and autologous chimeric antigen receptor (CAR) T cells, mainly directed against BCMA present on the malignant PC surface are promising.110 Belantamab mafodotin, a MoAb against BCMA conjugated with monomethyl auristin F (MMAF), have shown only limited efficacy.111 Some rapid and deep responses have been reported after CAR-T cell treatment with disappearance of extensive EMD disease including cord compression, extraspinal plasmacytoma and pleural involvement in one patient or the disappearance of a large abdominal mass on CT after CAR-T cell infusion in another patient.112 In two recent publications where EMD disease was prevalent (27% and 28% respectively),114,115 good quality responses have been reported. Thus, in one of the studies, eight of the nine patients with EMD disease responded to CAR-T, including four CRs and two VGPRs.115 However, there are some shortcomings: (i) short follow-up in the majority of trials, (ii) scarce information in the clinical trials on the response and PFS of patients with EMD disease in studies evaluating CAR-T cell or bi-specific antibodies, and (iii) the specific response in PS or haematogenous spread plasmacytoma is not fully described.

Table III. Treatment at relapse.

<table>
<thead>
<tr>
<th>Lymphoma-like regimen*</th>
<th>PACE</th>
<th>DT-PACE</th>
<th>DCEP</th>
<th>Dexa-BEAM</th>
<th>HDT/SCT</th>
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<tbody>
<tr>
<td>Novel agent combinations (e.g. carfilzomib-based combinations – such as KPD, KCyD, others - PVD, selinexor-based combinations, isatuximab-based combinations)</td>
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<td>Immunotherapy: CAR-T cell therapy, bi-specific antibodies (BiTEs)</td>
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<td>CAR, chimeric antigen receptor; DCEP, dexamethasone, cyclophosphamide, etoposide and cisplatin; Dexa-BEAM, dexamethasone, carmustine, cytarabine, etoposide and melphalan; HDT, high-dose therapy; KCyD, carfilzomib, cyclophosphamide and dexamethasone; KPD, carfilzomib, pomalidomide and dexamethasone; (DT-)PACE, (dexamethasone, thalidomide-) cisplatin, doxorubicin, cyclophosphamide and etoposide; PVD, pomalidomide, bortezomib and dexamethasone; SCT, stem cell transplantation.</td>
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<td>*Short response duration.</td>
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Author Contributions
Laura Rosiñol and Joan Bladé wrote the first drafts, which circulated three times among all the authors who made comments. All the authors approved the final version of the manuscript.

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