Chapter 7

The Role of Radiology and Radiotherapy for Multiple Myeloma

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http://dx.doi.org/10.5772/intechopen.75397

Abstract

Skeletal-related events occur in 80% of patients with multiple myeloma (MM). Osteoporosis, osteoclastic destructions, pathological fractures of the bone, spinal cord and compression can impair patients' quality of life and reduce survival. Many imaging techniques can be used for the detection of MM bone lesions. Many clinical studies suggest modern imaging techniques for their greater sensitivity. Radiotherapy is a treatment of choice for solitary plasmacytoma of the bone and extramedullary plasmacytomas. However, radiation treatment of MM can be used as a palliative approach for uncontrolled pain, impending pathological fractures and in the cases of spinal cord compression. Radiotherapy induces analgesic effect in 75–100% of patients and promotes a recalcification in 40–60%. In patients with spinal cord compression, radiation therapy is given along with dexamethasone, and up to half of patients may experience improvement. It is well known that pain perception, response to analgesics and pain relief effect of radiotherapy are quite different for multiple myeloma patients. Clinical, laboratory and genetic factors may influence the pain perception and analgesic effect of radiotherapy. Side effects of radiation are generally mild, are limited to the radiotherapy site and can be predicted.

Keywords: multiple myeloma, bone disease, analgesic effect, palliative radiotherapy, radiation dose

1. Introduction

Skeletal-related events are one of the signs of multiple myeloma (MM) [1, 2]. Osteoclastic destructions increase the risk of pathologic fractures and spinal cord compression syndrome, which reduces patients' quality of life, increases treatment costs and worsens patient

survival [3]. Radiotherapy is a treatment approach used in patients with solitary plasmacytomas. However, the role of radiation treatment of MM is palliative: to induce an analgesic effect in osteolytic lesions, to promote recalcification in the sites of impending pathological fractures and symptom control in spinal cord compression [4].

Despite the enormous development in MM treatment approaches and response to systemic therapy, patients are often in need of pain control due to slow repair of bone lesions. Chemotherapy treatment alone is insufficient for patients suffering from pain caused by osteolytic bone destruction or in case of an impending fracture at the destruction site. Seventy percent of patients receive radiation at least once during their MM therapy [5]. Where radiotherapy is applied, pain can be reduced by 75–100% from the starting level [5–12]. Recalcification of bone destructions caused by MM is observed in 40–60% of the cases after radiation treatment [5, 7, 12, 13]. Good results in the treatment of bone damages due to MM can be achieved when applying other supportive therapy measures, such as bisphosphonates, vertebroplasty and surgery methods, alongside radiation therapy.

It has been known for a long time that pain perception is not the same for all patients. The response to analgesics, pain relief and the effect of radiotherapy are very individual. The above can be determined by a different secretion of anti-inflammatory cytokines (IL-6, IL-10, TNFα, IL-1), which participate in the pathogenesis of the pain caused by a chronic disease and their concentration in blood serum. Circulating cytokines and inflammatory proteins are related to pain, cognitive functions, depression, fatigue and sleep disturbances [14–16]. The secretion of anti-inflammatory cytokines is regulated genetically. Cytokine genes are very polymorphous. Polymorphisms in regulatory regions, including promoters and non-transmittable areas, in a majority of the cases can change the gene expression in vitro [15]. Thus, the above has an impact on the secretion of cytokines and their concentration in blood serum, which determines the pain perception threshold and a different response of patients to analgesics and radiotherapy.

2. The role of imaging

Around 70–80% of patients have osteolytic lesions at diagnosis of MM, and up to 90% develop lytic lesions during the course of the disease [17]. The International Myeloma Working Group updated criteria for the diagnosis of symptomatic MM and revealed the value of modern imaging such as computed tomography (CT), whole-body low-dose computed tomography (LDCT), positron emission tomography/computed tomography (PET/CT) and magnetic resonance imaging (MRI) [18]. Modern imaging techniques had a greater sensitivity than conventional radiographic skeletal survey for the detection of MM bone lesions with as many as 80% or more lesions detected by the newer imaging techniques [18]. A summary of different imaging techniques is detailed in **Table 1**.

2.1. Conventional radiographic skeletal survey

Whole-body X-rays imagine (including plain radiographs of the whole skeleton) have been widely used for the detection of bone lesions at diagnosis and during the course of the disease. Osteolytic bone lesions are more common in the scull, vertebrae, ribs and pelvis. Although the

http://dx.doi.org/10.5772/intechopen.75397

Imaging technique	Advantages	Limitations
Whole-body skeletal survey	Low cost	Low sensitivity
	Available in many centres	Only advance bone disease could be detected
	Validated technique	Reduced for the differential diagnosis between malignant and benign fractures
		Difficulty to assess certain areas
		Lack of detection of lytic lesions response to the treatment
		Dependent on the observer
		Imaging process is long and not well tolerable for patients
Whole-body low-dose computed tomography	A higher diagnostic sensitivity for the detection of osteolytic bone lesions	More expensive then whole-body skeletal survey
	Higher-quality images for planning biopsies and therapeutic interventions	Approach is available in some centres
	A low radiation dose compared with standard CT	Reduced for the differential diagnosis between malignant and benign fractures
	Superiority in estimating fracture risk and bone instability	Unclear prognostic significance
	Shorter duration of the examination	
Magnetic resonance imaging	A high sensitivity for the early detection of marrow infiltration by myeloma cells	High cost
	More sensitive in detecting multiple bone lesions and exclude asymptomatic myeloma	Imaging process is long and not well tolerable for patients
	The ability to detect spinal cord or nerve compression and the presence of soft-tissue masses	Unsuitable for patients with metal objects, contrast contraindicated
	Higher-quality images for planning biopsies and therapeutic interventions	
	Valuable for differential diagnosis between malignant and benign fractures	
	Prognostic significance	
	No radiation exposure	
Positron emission tomography/ computed tomography	A higher accuracy approach for the early detection of lesions and exclude asymptomatic myeloma	High cost
	Useful to evaluate disease activity before and after treatment	Lack of availability in many centres
	Detects osseous and extramedullary disease	Limited by false-positive results of inflammation
	A better definition of complete response and minimal residual disease	Lack of standardisation
	Prognostic significance	

Table 1. A summary of different imaging techniques for multiple myeloma patients.

whole-body X-ray was the standard of care for many years, it has several limitations: for a lytic lesion to become apparent, more than 30% loss of trabecular bone must occur; it is difficult to assess certain areas, such as the pelvis and the spine; there are limitations: the detection of lytic lesion response to anti-myeloma therapy because of a delayed evidence of healing; specificity is reduced for the differential diagnosis of myeloma-related fracture and benign fracture (very important, particularly in cases of new vertebral compression fractures in the absence of other criteria of relapse); it is dependent on the observer, and studies are long and often not tolerable for patients in severe pain [19].

2.2. Whole-body low-dose computed tomography

Whole-body LDCT allows the detection of osteolytic bone lesions in the whole skeleton with a greater sensitivity and a low radiation dose compared with standard CT. Advantages of whole-body LDCT over conventional skeletal survey include a higher diagnostic sensitivity for the detection of osteolytic lesions, especially in areas where the whole-body X-ray detection rate is low (i.e. pelvis and spine); superiority in estimating fracture risk and bone instability; shorter duration of the examination, which is an important issue for patients in pain; the production of higher-quality images for planning biopsies and therapeutic interventions; and the demonstration of unsuspected manifestations of myeloma or other diseases [19]. Major deficiencies of whole-body LDCT are the lack of specificity for the differential diagnosis between malignant and osteoporotic fractures and also the fact that this diagnostic approach is available in some centres only. In several studies, whole-body LDCT was found to be superior to whole-body X-ray for the detection of osteolytic lesions [19]. In one retrospective study, the total number of bone lesions detected by whole-body LDCT was 968 and the number of bone lesions detected by whole-body X-ray was only 248 ($p < .001$), which means that 61% of patients with normal whole-body skeleton X-ray images had more than one osteolytic bone lesion on the whole-body LDCT scan, and such patients should receive antimyeloma therapy [20]. This was confirmed by another prospective study, where whole-body LDCT revealed osteolytic bone lesions in 23% of patients with negative conventional radiographic skeletal X-ray scans, especially in the axial skeleton ($p < .001$) [21]. The same study proved that whole-body LDCT is superior in detecting lesions in patients with osteopaenia and osteoporosis [21].

2.3. Magnetic resonance imaging

MRI has been established as a valuable technique for imaging multiple myeloma because of its superior soft-tissue contrast resolution. MRI has a high sensitivity for the early detection of marrow infiltration by myeloma cells. Five MRI patterns of marrow involvement have been recognised in multiple myeloma: a focal pattern that consists of localised areas of myeloma cell infiltration of 5 mm or greater in diameter, a diffuse pattern characterised by an almost complete replacement of normal marrow by myeloma cells, a combined diffuse and focal pattern, a normal bone marrow pattern and a variegated or "salt and pepper" pattern with innumerable small bone marrow focal lesions [19].

Several studies showed that MRI is generally more sensitive in detecting multiple lesions compared to conventional radiographic skeletal survey. The systematic review of studies

compared modern and conventional imaging techniques in the detection of bone lesions and confirmed the superiority of MRI over conventional skeletal X-ray, mainly in the axial skeleton [22].

Because of its high sensitivity in revealing bone marrow involvement, MRI is now used for the discrimination between smouldering and symptomatic multiple myeloma. Several studies have shown that approximately 40–50% of patients with normal whole-body X-ray scan had abnormal findings on MRI examinations [19].

MRI has the ability to detect spinal cord or nerve compression and the presence of soft-tissue masses and is recommended in patients with extraosseous lesions. MRI is the approach to define the degree of involvement and to evaluate for cord compression for surgical intervention or radiation therapy. Unfortunately, almost any skeletal tumour has the same signal-intensity profile as multiple myeloma. MRI is not disease-specific, and additional tests should be used to establish the diagnosis of multiple myeloma. MRI is also recommended for patients with a solitary bone plasmacytoma. MRI may demonstrate unsuspected bone lesions, and for such patients, systemic treatment must be given instead of radiation therapy, which is the treatment of choice for solitary bone plasmacytoma.

MRI also can provide important information for prognosis. Patients with diffuse MRI pattern experienced a poorer overall survival (OS) compared with patients with focal or normal patterns [19]. One study of 611 multiple myeloma patients showed that the presence of more than seven focal lesions was an independent predictor of poorer prognosis and that resolution of all focal lesions was an indicator of superior survival [23].

The major advantage of MRI over the whole-body LDCT or conventional CT is the discrimination between myelomatous and normal marrow. This is extremely helpful to differentiate myeloma from osteoporotic fractures in more than 90% of cases [19].

2.4. Positron emission tomography/computed tomography

PET/CT is a new imaging technique, which can be applied in the diagnosis, stage and prognosis of tumour and to evaluate the efficacy of the treatment. PET/CT provides information about the sites and number of lesions, hypermetabolic activity of the involved area (depending on F-18 fluorodeoxyglucose (FDG) uptake). Furthermore, PET/CT detects osseous and extramedullary disease in patients at diagnosis and relapse. PET/CT is a higher accuracy approach than traditional imaging techniques in the diagnosis of multiple myeloma. However, there is no uniform conclusion about the diagnostic accuracy of PET/CT for multiple myeloma because of the controversy on the variety of results.

The large meta-analysis has shown that PET/CT is more sensitive compared with conventional skeletal X-ray for the detection of bone lesions in multiple myeloma [22]. The higher detection rate of PET/CT over conventional skeletal X-ray scan for the presence of osteolytic lesions is especially important for patients with smouldering multiple myeloma. In the studies related to smouldering multiple myeloma, 16–39% of patients with normal whole-body X-ray had positive PET/CT results [19]. The probability of progression to symptomatic multiple myeloma within 2 years was 58–75% for patients with a positive PET/CT [19].

PET/CT may be used for the diagnosis of solitary bone plasmacytoma and extramedullary disease. It is not clear whether PET/CT or MRI is more preferable. PET/CT also has a value for patients with nonsecretory or oligosecretory MM for the detection of active lesions.

PET/CT has been tested for a better definition of complete response (CR) to MM therapy and as an independent factor for survival prognosis at diagnosis and after treatment. Approximately 30% of patients at CR had a positive PET/CT. In addition, PET/CT negativity was an independent predicted factor for prolonged PFS and OS in patients with a CR, patients with a positive PET/CT in CR and median PFS was 50 months compared to 90 months for patients with a negative PET/CT [24].

However, PET/CT remains a high-cost method, and there is lack of availability in many centres and may be limited by false-positive results caused by inflammation from other underlying diseases.

3. Radiotherapy for solitary plasmacytomas

The solitary plasmacytoma is a localised accumulation of monoclonal plasma cells without systemic plasma cell disease manifestation. Regarding location, it can be classified into solitary plasmacytoma of bone (SBP) and extramedullary plasmacytoma (EMP) [25]. SBP generally occurs in the vertebra and skull; however, EMP is most frequently observed in head and neck [25]. Plasmacytomas are radiosensitive neoplasms, and radiotherapy has a potentially curative effect for both SBP and EMP [4].

3.1. Radiotherapy for solitary plasmacytoma of bone

Radiotherapy with a curative intent is the treatment of choice, resulting in local control in more than 80% of patients with SBP [25, 26]. In some cases, as bone instability, rapid progression of neurological symptoms and surgical intervention are required, the results of surgery alone are not optimal and carry high rates of local relapse [27]. Currently, the standard of treatment for SBP is radiotherapy. Optimal-dosing guidelines have not been established due to the absence of prospective randomised studies. The United Kingdom Myeloma Forum recommend radiotherapy at least 40 Gy in 20 fractions [28]. For bulky disease (>5 cm), a higher-dose 50 Gy in 25 fractions was recommended [28]. Approximately 30% of patients who received higher doses than 50 Gy remained without evidence of any local disease failures [25]. In clinical practice, a radiation dose of 45–50 Gy in 20–25 fractions is recommended for the treatment of SBP.

The optimal target volume for radiotherapy planning in SBP is to encompass the tumour volume plus a margin of at least 1.5–2 cm on the tumour detectable by MRI [25, 26]. In case of vertebral involvement, fields typically include one to two uninvolved vertebrae above and below the affected level [25]. Prophylactic regional lymph node irradiation is not necessary in SBP.

3.2. Radiotherapy for extramedullary plasmacytoma

Like SBP, EMPs are highly radiosensitive; almost all patients (80–100%) achieve local control, and approximately 50–65% of patients remain free of disease longer than 10 years [26]. Due

to a lesser number of patients and the absence of randomised prospective studies, the optimal dose of radiotherapy is not established. Current evidence-based recommendations by the United Kingdom Myeloma forum are similar to those for SBP [28]. The recommendations include radiotherapy dose of 40 Gy in 20 fractions for tumours of <5 cm and up to 50 Gy in 25 fractions for tumours of ≥5 cm with at least a 2-cm margin encompassing the primary tumour [28]. If cervical nodes are involved (or in Waldeyer's ring tumours), these should be included in the radiotherapy field [28].

Surgery may be an acceptable treatment method combined with radiotherapy. A combination of a higher dose of radiation and surgery predicted for better PFS [25]. Surgical procedures of the head and neck are not recommended, but surgery may be considered for other sites of the disease [26].

4. Indications for radiotherapy in multiple myeloma

Radiotherapy can produce a curative effect for both solitary plasmacytoma of bone and extramedullary plasmacytomas; however, its role in the treatment of MM patients is only palliative. The most common indications for radiotherapy in MM are pain relief in the sites of bone destructions, the prevention of pathological fractures or to decrease the pain in the fracture site, to evoke the recalcification, the management of spinal cord compression syndrome and the treatment of extramedullary disease.

4.1. Palliation for pain

Pain is the most common symptom experienced by MM patients. Up to 67% of patients report pain at diagnosis, and it may be present for several months before the diagnosis [29]. Local radiotherapy is effective for pain relief. It produces an analgesic effect by inhibiting chemical pain mediators and causing tumour shrinkage. There is a debate on the effect of radiation dose on pain relief.

Results of randomised clinical studies revealed the same effect of pain relief when applying two different radiotherapy regimens (8 Gy/1 fr and 3 Gy × 10 fr) for the treatment of patients with solid tumour metastases, though the application of a single fraction of 8 Gy treatment produces more recurrent treatment episodes [30–33]. The earlier data, however, cannot be directly applied in the treatment of patients with MM, since their future prospects are better (the average survival reaches 30–40 months), whereas the average survival among the patients with solid tumour metastases in bones is about 9 months [5]. In the meta-analyses by Sze et al. [34] and Wu et al. [35], no significant difference in the overall and complete response in pain reduction between single- (SF) and multiple-fraction (MF) palliative radiotherapy was observed. Chow et al. in the systematic review analysed 16 randomised trials comparing SF versus MF for bone metastases: no significant difference was found regarding response rates [30]. An increased risk for pathological fractures and spinal cord compressions was observed in the SF regimen, which was statistically insignificant, while retreatment in the SF regimen was 2.5-fold higher [30]. The role of different palliative radiotherapy regimens for MM is not well established due to lack of clinical trials. Medical literature provides only a small number

of studies dealing with various radiotherapy regimens for the treatment of patients with multiple myeloma as well as impact of the radiotherapy regimen on pain relief at the sites of bone destructions [5–12]. However, final recommendations concerning the choice of the radiation therapy regime have not been presented yet.

Some clinical studies did not find a significant difference between the radiation dose and pain relief after radiotherapy [5, 8, 10, 12]; however, Adamietz et al. [6] and Minova et al. [11] reported that for adequate pain relief, higher doses would be obtained. Pain relief occurred in 80–92% [6, 11]. Adamietz et al. affirmed that local long-term palliation effect can only be achieved by a high radiation dose [6], whereas Leigh et al. analysed 101 patients and observed pain reduction in 97% of patients (complete in 26%) with a median dose 3–60 Gy. Only 6% of patients were retreated for the relapse which occurred after a median interval of 16 months [10]. This study showed the durable symptom relief after a mean total dose of 10 Gy [10].

Clinical, laboratory and genetic factors may influence pain perception and analgesic effects of radiotherapy. Retrospective studies published by Adamietz et al. [6] and Mose et al. [12] indicated that the incidence of pain relief was higher in patients treated with concurrent chemotherapy which had a significant impact on a positive response to radiotherapy, but other studies did not show this relationship [5, 10]. Mose et al. reported that not only concurrent chemotherapy but also the Karnofsky performance above 70% had a significant impact on a positive analgesic response to radiation treatment, whereas the total radiation dose, gender, age, irradiated site and bisphosphonates had no effect on pain relief [12]. In other study performed by Stolting et al., significant parameters for pain relief in the multivariate analysis were completeness of therapy, patients younger than 60 years and a single dose of 2 Gy; other parameters like Karnofsky index, concurrent chemotherapy and total dose were insignificant [5].

Medical literature provides several studies which have revealed that the polymorphism of inflammatory cytokine genes influences pain perception and analgesics dose. Furthermore, the altered levels of fatigue, depression and response to analgesics in pancreatic, lung or breast cancer have been described [15, 36–43]. These types of studies, however, have not been conducted for patients with multiple myeloma, though during the formation of bone destructions, anti-inflammatory cytokines are emitted by plasma cells and bone marrow stroma cells. No study has been performed worldwide, which would deal with the impact of polymorphism of genes encoding for cytokines in response to radiotherapy.

Hundred and one patients were involved in a randomised prospective clinical study performed at the Lithuanian University of Health Sciences [44]. Two different radiation treatment regimens of bone destructions due to multiple myeloma were compared. MF radiotherapy regime (3 Gy × 10 fr) was applied to 58 patients and SF (8 Gy × 1 fr) regime was applied to 43 patients. Pain relief was obtained in 84.5% of patients in MF regimen group (complete response 69.4%) and 74.4% of patients in SF regimen group (complete response 68.8%). No significant differences were observed in analgesic response between the groups. No significant differences were observed in the period of time before reaching the analgesic effect of radiotherapy: in both groups, analgesic effect was achieved in the first 4 weeks.

Univariate statistical analysis revealed that the age under 65 years (p = 0.016), stage II of the disease (according to Durie-Salmon classification) (p = 0.03) and recalcification in the irradiated site (p = 0.011) were significant parameters for analgesic response after radiotherapy, whereas other parameters (gender, Karnofsky index, paraprotein type, haemoglobin level, surgery, pain score at the admission, total radiation dose, bisphosphonates and concurrent chemotherapy) were not significant.

All parameters mentioned earlier were included in binary logistic regression model for the analysis of their influence to pain relief. Using a stepwise variable removal method (backward conditional), it was found that the following attributes have a significant impact on analgesic response after radiation treatment for pain relief: female gender, age under 65, IgG MM type and the presence of recalcification in the irradiated site. Other factors analysed, including the total radiation dose, were not significant for pain relief after radiation treatment. Results of analgesic response from clinical trials of palliative radiotherapy in the treatment of MM patients are shown in **Table 2**.

The study performed by Rudzianskiene et al. involved analysis of 12 gene polymorphisms of six cytokines (IL-6, IL-10, TNFα, IL-1α, IL-1β and IL-1RA) participating in the pathogenesis of the pain syndrome in bone destruction sites. The aim was to evaluate the influence of interleukins on the perception of pain and response to radiotherapy in MM patients [44].

Univariate statistical analysis was used to assess associations between severe pain status (8–10 points on VAS) before radiation treatment and genotype groups of each cytokine gene studied. None of the genotypes analysed was found to be significant for the perception of severe pain before treatment; yet, a marginal relation was observed that patients with GG genotype of IL1RN c.1812G > A polymorphism more often indicated severe pain before radiotherapy, compared to patients with GA and AA genotypes (relative risk (RR) 0.43; 95% confidence interval (CI) 0.18–1.06; p = 0.068) [44].

Multivariate logistic analysis included all the earlier clinical, demographic and symptom factors, as well as genotype groups of each cytokine gene analysed. Based on multivariate logistic regression, the following factors were determined to have a significant impact on severe pain before radiation treatment: Karnofsky index ≥60% and IL1RN c.1812G > A polymorphism GG genotype. Other factors analysed were not significant for the perception of severe pain before radiation treatment [44].

A comparison of a decrease in pain perception points before radiotherapy and during the monitored period, that is, after 4, 12 and 24 weeks, among patients with different genotypes was carried out. The analysis revealed that patients with IL-1α-encoding gene IL1A c.889C > T CC genotype had a significantly better response to radiation therapy and indicated milder pain after 12 and 24 weeks, compared to patients with TT and CT genotypes. Furthermore, patients with IL-1β-encoding gene IL1B c. 3953C > T CC genotype indicated significantly more often milder pain scores after radiotherapy in 12 and 24 weeks, compared to patients with TT and CT genotypes. Patients with IL-1RA-encoding gene IL1RN c.11100 T > C CC genotype had a faster response to radiation therapy, that is, a significant decrease in pain points was observed after 4 weeks, compared to patients with TT and CT genotypes [44].

Clinical study	Number of patients	Number of irradiated sites	Total dose (Gy)	Overall response (%)	Complete response (%)	Comments
Adamietz et al. [6]	70	70	2–30	39.6–80*	n/a	Local long-term palliation effect can only be achieved by high radiation dose and concurrent chemotherapy.
Leigh et al. [10]	101	306	3–60	91	n/a	There was no significance difference between analgesic response and higher radiation dose, and there was no influence of concurrent chemotherapy.
Mose et al. [12]	42	71	18–45	85	34.3	There was no significance difference between analgesic response and higher radiation dose, response is better with concurrent chemotherapy.
Yaneva et al. [9]	87	87	17–20	89.6	26.9	The total dose relationship with an analgesic response has not been evaluated. Radiotherapy has no influence on overall survival.
Stolting et al. [5]	138	272	2–60	85.3	22.2	There was no significance difference between analgesic response and higher radiation dose, and there was no influence of concurrent chemotherapy.
Minowa et al. [11]	29	53	4–60	92	n/a	Longer analgesic response was after higher radiation dose treatment.
Balducci et al. [7]	52	52	16–50	91	51.2	The total dose and concurrent chemotherapy relationship with an analgesic response has not been evaluated.
Rudzianskiene et al. [44]	101	101	8 Gy vs. 30 Gy	74.4 vs. 84.5	68.8 vs. 69.4	There was no significant difference between analgesic response and higher radiation dose, and there was no influence of concurrent chemotherapy.

*Without concurrent chemotherapy.

Table 2. A summary of published data on palliative radiotherapy analgesic response in the treatment of patients with MM.

4.2. To evoke the recalcification

Multiple myeloma is a disease inducing osteolytic process which leads to an increased risk of pathologic fracture or spinal cord compression and severe pain with a negative impact on

the quality of life. According to the study, recalcification is achieved after some months and occurs in 40–50% of the irradiated bone destructions in patients with multiple myeloma [5, 7, 12, 13]. Palliative radiotherapy can be applied to avoid the impending or actual pathological fracture. However, the high-risk lesions should be first stabilised by orthopaedic measures and combined with post-operative radiation treatment for the improvement of pain and local control. Several retrospective studies, a majority of which included small patients' cohorts, have demonstrated that there is no relation between the total radiation dose and recalcification in the sites of bone destructions.

Mose et al. found that the stabilisation of the irradiated bone could be achieved in 46.4% of cases, and concurrent chemotherapy reinforces this effect [12]. Also, Stolting et al. reported a recalcification rate of 44.7% and the importance of concurrent chemotherapy for recalcification [5]. The study performed by Rudzianskiene et al. showed an overall response of recalcification with single-fraction radiotherapy of 35.9%, and in multi-fraction radiotherapy group, the response rate was 32.1% [44]. Binary logistic regression did not show a significant impact of concurrent chemotherapy on recalcification [44].

Koswig and Budach [45] found that an MF regimen (3 Gy × 10) significantly increases the bone density in the area of metastases from solid tumours compared with single fraction (8 Gy) in contrast to pain relief effect; also, Stolting et al. reported that recalcification was detected at total doses of >40 Gy for MM patients [5]. Balducci et al. found recalcification in 50% cases with a median total dose of 38 Gy and reported the importance of the early using of radiotherapy to avoid pathological fractures [7]. However, the studies published by Mose et al. [12] and Rudzianskiene et al. [44] did not show any influence of the total radiation dose on recalcification.

Mose et al. reported that not only concurrent chemotherapy but also the Karnofsky index above 70% and bisphosphonates had a significant impact on a positive recalcification effect to radiation treatment [12]. Also, in a clinical study performed by Rudzianskiene et al., the Karnofsky index more than 60% has a positive impact on recalcification in the irradiated site [44]. This study also founded that a haemoglobin level of less than 80 g/l, clinical stage II according to Durie-Salmon and a decrease in pain in the irradiated site are significant parameters for the recalcification [44].

The clinical study performed by Mose et al. showed that higher recalcification rates depend on the usage of bisphosphonates [12], but other study did not demonstrate such a relation [5]. In the clinical study reported by Rudzianskiene et al., the use of bisphosphonates was also an insignificant parameter but this may be due to the small sample of patients (only 18%) taking bisphosphonates [44].

Results of recalcification response from clinical trials of palliative radiotherapy in the treatment of MM patients are shown in **Table 3**.

4.3. The treatment of spinal cord compression

Epidural spinal cord compression that can cause pain and neurological impairment occurs in 5–20% of all patients with multiple myeloma at various disease stages and leads to disability [46, 47]. Pain is the first and more common presenting symptom followed by motor

Clinical study	Number of patients	Number of irradiated sites	Total dose (Gy)	Overall response (%)	Comments
Stolting et al. [5]	138	272	2–60	44.7	There was no significance difference between recalcification response and higher radiation dose, usage of bisphosphonates, concurrent chemotherapy increase response of recalcification.
Balducci et al. [7]	52	52	16–50	50	The influence of total radiation dose, concurrent chemotherapy and bisphosphonates was not evaluated.
Mose et al. [12]	42	71	18–45	46.4	There was no significance difference between recalcification response and total radiation dose, concurrent chemotherapy and bisphosphonates increase response of recalcification.
Rudzianskiene et al. [44]	101	101	8 Gy vs. 30 Gy	35.9 vs. 32.1	There was no significant difference between recalcification response and higher radiation dose, usage of bisphosphonates and there was no influence of concurrent chemotherapy.

Table 3. A summary of published data on palliative radiotherapy recalcification response in the treatment of patients with MM.

deficiency, sensory symptoms and bowel and bladder dysfunction [48]. Immediate diagnosis and treatment are very important in the preservation of neurological function in patients with spinal cord compression. Pain control, relief of spinal cord compression and improvement of neurologic function are the main goals of treatment. High-dose steroids must soon be initiated upon spinal cord compression diagnosed to obtain an antineoplastic and an antioedema effect [49]. In patients with neurologic symptoms directly due to cord compression, radiation therapy is given along with dexamethasone, and up to half of patients may have improvement of motor function [50]. In the largest retrospective studies, radiotherapy alone improves motor function in 75% of patients with spinal cord compression due to MM. A 1-year local control was 100% and a 1-year survival was 94% [51].

Radiation treatment can be used as fractionated external beam radiotherapy (EBRT) or stereotactic body RT (SBRT). Both methods are effective for palliative treatment and local tumour control. SBRT is a non-invasive treatment option for spinal disease in the absence of a high-grade spinal cord compression. SBRT allows the treatment of small- or moderate-sized tumours, even in close proximity to the spinal cord, in either a single or a limited number of dose fractions [48]. SBRT with a single 24 Gy fraction gives excellent tumour control [48].

Since myeloma is a very radiosensitive tumour, EBRT is an appropriate approach for patients who are not considered surgical treatment and it is also indicated after decompression intervention. There was no randomised trial that compared radiotherapy alone to radiotherapy plus upfront neurosurgery. Thus, radiotherapy alone is considered the standard treatment of

SCC from myeloma [52]. Several fractionation regimens: single-fraction, short-course multi-fraction and longer-course multi-fraction regimens are used for the treatment of spinal cord compression. Radiotherapy either 30 Gy in 10 fractions or lower radiation doses must be provided as an optimal approach causing the long-lasting local control [50]. Several clinical studies have examined the impact of multi-fraction regimens versus single-fraction regimens on pain relief and functional outcomes, local tumour control and overall survival [12, 52–55]. Rades et al. compared short-course 8 Gy in one fraction or 20 Gy in five fraction regimens with long-course 30–40 Gy in 10–20 fraction regimens [53]. There were no significant differences in functional or overall survival between the groups. However, a better local control (77 vs. 61%) and a 12-month progression-free survival (72 vs. 55%) were significantly better in long-course radiotherapy regimen group [53]. A phase III randomised multicentre Italian trial demonstrated a similar effect in functional outcomes and overall survival between two fractions of 8 Gy (16 Gy total dose) or a single dose of 8 Gy radiotherapy in patients with spinal cord compression and a short life expectancy [54].

Multiple myeloma patients with spinal cord compression have a comparably good survival, living for years after treatment in the era of novel drugs [55]. Only very few clinical studies can be found in the study, investigating radiotherapy of spinal cord compression in MM patients [12, 52, 55], and the appropriate radiotherapy regimen for the treatment of spinal cord compression in MM patients has not been defined yet. Rades et al. reported that the improvement of motor function was more frequent after long-course radiotherapy than after short-course at 6 months (67 vs. 43%) and at 12 months (76 vs. 40%) [55]. However, Mose et al. demonstrated that 65% of patients with spinal cord compression after radiotherapy experienced neurological improvement, and Karnofsky index, gender, age, site of myelocompression and the total radiation dose did not influence this effect [12].

One retrospective study was performed to find a predictive tool that allows the estimation of overall survival (OS) of elderly myeloma patients (aged ≥65 years) presenting with myeloma-induced spinal cord compression [52]. Rades et al. found that myeloma type (HR 3.31; 95% CI 1.75–6.49; $p < 0.001$), ECOG-PS (HR 5.33; 95% CI 2.67–11.11; $p < 0.001$), ambulatory status (HR 2.71; 95% CI 1.65–4.57; $p < 0.001$) and age (HR 1.95; 95% CI 1.03–3.78; $p = 0.040$) were significantly associated with survival, but fractionation regimen was not a predictive tool for OS [52].

The choice of radiotherapy regimen in the treatment of spinal cord compression should be based on the expectancy of patient's life. Longer-course programs, which result in a better local control than single-fraction and short-course programs, are the preferred treatment for patients with a more favourable survival prognosis. By contrast, patients with a poor prognosis are better candidates for multi-fraction short-course or single-fraction radiotherapy [52].

5. Surgery and radiation treatment

Surgical management of MM-related bone lesions sometimes is carried out due to disease sensitivity of radiation treatment and chemotherapy. The most common indications for surgical procedures are unstable fractures and spinal cord compression when bone fragments

protrude from a vertebral fracture [49]. Vertebroplasty and kyphoplasty are carried out by fibroscopic percutaneous injection of polymethylmethacrylate into the fractured vertebrae in order to relieve pain. These procedures should be considered for symptomatic vertebral compression fractures, and this is a procedure of choice to improve the quality of life [3]. Vertebroplasty combined with post-operative radiotherapy is an effective approach in the pain palliation, maintaining the stability of vertebral column and improving the quality of life of patients. Some randomised clinical studies demonstrated that surgery and post-operative radiotherapy are more effective in the treatment of vertebral fractures than radiotherapy alone [56, 57]. Treating these patients with radiotherapy before surgery procedure allows for tumour shrinkage and can enable these patients to become candidates for vertebroplasty [58]. The study performed by Hirsch et al. reported that the timing of radiotherapy, before or after vertebroplasty, did not significantly impact outcomes of these procedures [58].

6. Side effects

Radiotherapy is generally well tolerated. The external beam localised fields' radiotherapy offers advantage of few acute and late toxicities. The potential side effects of radiotherapy are related to the fraction dose, total radiation dose, volume of the target, toxicities from other treatment approaches and the radiosensitivity of healthy surrounding tissues. The radiotherapy planning process uses established tolerance doses to avoid irreversible damage of critical organs, such as the lung, kidney, liver and spinal cord. Organ tolerances are based on the conventional radiotherapy (1.8–2 Gy per fraction daily, five times a week). When unconventional

Acute side effects	
	Clinical manifestation
Systemic side effects	Fatigue, anorexia, nausea/vomiting
Skin	Erythema, itching, dry desquamation, blister formation, hair loss in the treatment area
Mouth, oesophagus	Sore throat, dry mouth, trouble swallowing, taste loss
Small/large intestine	Loose stools/diarrhoea, cramps, bleeding, incontinence, rectal irritation
Haematologic	Neutropaenia, anaemia, thrombocytopaenia
Bladder	Bladder spasms, cystitis, urinary frequency, incontinence, haematuria
Late side effects	
Skin	Telangiectasia, atrophy, ulceration, pigmentation changes
Mouth, oesophagus	Xerostomia, sialitis, difficulty in swallowing, ulceration, trismus, osteoradionecrosis, fistula
Small/large intestine	Diarrhoea, cramping/colic, bowel movement, obstruction, bleeding, fistula, necrosis
Bladder	Haematuria, epithelial atrophy, reduction in bladder capacity

Table 4. A summary of most common side effects of radiation treatment.

fractionation regimens are introduced, the total radiation dose must be adjusted to avoid high risk of side effects, as lower total doses limit acute toxicity. In general, palliative radiotherapy doses are delivered with a larger dose per fraction. These hypofractionated regimens may provide the benefit of earlier response but with a greater risk of late side effects [59]. Late side effects occur from months to years after radiation treatment, and patients with a short life expectancy may not live long enough to experience such risks.

Side effects of radiation are generally mild, limited to the radiotherapy site and can be predicted. Most acute side effects arising within 90 days are self-limited, lasting days to weeks and resolve within few weeks with supportive care. Acute toxicities as fatigue, nausea/vomiting, mucositis, oesophagitis and bowel irritation are often easily managed and reversible. The more critical side effects are late side effects, emergent from cellular and vascular atrophy, and lead to the reduction of normal tissue function and organ dysfunction, which may develop months to years later, but they are very rare.

In 1982, the Radiation Therapy Oncology Group (RTOG) developed the Radiation Morbidity Scoring Criteria to classify radiotherapy effects. RTOG score has been widely employed and is accepted and acknowledged by medical communities [60].

Skin reactions are usually nominal during radiation treatment for bone metastases and are treated similar to burns. Patients treated with large volumes including pelvis, epigastrium or thoracolumbar spine region may experience nausea and/or vomiting. Prophylactic antiemetics can be administered 30–60 min prior to radiotherapy and continued on as needed. Hematologic side effects are mild and transient, but bone marrow suppression may occur if the patients are receiving treatment to large targets, when the total radiation dose is moderate or high, and a significant proportion of marrow is included, especially in heavily pretreated patients. Mucositis and oesophagitis causing difficult and painful swallowing occur after treatment to the head and neck or thorax. It should be treated with dietary modifications, oral rinses, antifungals, analgesics and cytoprotective agents. Radiation enteritis manifested by cramping; frequent, loose stools and occasionally bleeding may occur if large amounts of small intestine are included. Treating the pelvis may also result in short-lived diarrhoea [61]. A summary of clinical manifestations of the most common side effects of radiation treatment is shown in **Table 4**.

No significant differences were observed between SF and MF radiotherapy for bone metastases of solid tumours in the systematic review performed by Chow et al. [30]. Only two studies reported more acute toxicities (characterised as grades 2–4) in the group of MF regimens than in SF [30].

Based on the analysis of medical literature, the side effects of radiotherapy in multiple myeloma patients were generally mild. Balducci et al. [7] identified 44% of patients (n = 23) with side effects (grades 1–2): haematological toxicity in 48%, gastroenteric toxicity in 26%, pharyngeal toxicity in 9% and cutaneous toxicity in 17% patients. Mose et al. [12] reported about 54% side effects mostly of grades 1–2; grade 3 in 4% (haematological side effects, mucositis, creatinine level). These data correspond with Matuschek et al. [62] as this study reported 37% side effects with 50% grade 1 and 47.2% grade 2 and one patient grade 3 dysphagia.

7. Conclusions

Radiotherapy continues to be an effective palliative treatment approach in the management of bone disease in MM patients inducing an analgesic effect in osteolytic lesions, promoting recalcification in the sites of impending pathological fractures and controlling the symptoms in spinal cord compression without significant toxicity. No difference in the efficacy for pain relief and recalcification has been observed using different radiotherapy regimens. However, the choice of radiotherapy regimen in the treatment of spinal cord compression should be based on the expectancy of patient's survival. Multi-fraction regimens, which result in a better local control, are the preferred treatment for patients with a more favourable survival prognosis.

Conflict of interest

M. Rudzianskiene, V. Rudzianskas, R. Dambrauskiene and R. Gerbutavicius declare that they have no competing interests.

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