Review Article

Lesions of the spinal cord caused by multiple myeloma: A systematic review and meta-analysis regarding the neurosurgical aspects of patient management

ABSTRACT

Background: Multiple Myeloma is a B-cell malignancy which can cause variety of lesions of the spine and spinal cord. The management of patients with spinal cord compression (SCC), and the efficacy and security of minimally invasive therapeutic approaches, are the main topics of discussion.

Methods: To systematically review the scientific literature on neurosurgical aspects of MM spinal cord lesion management, a search was conducted among scientific papers in the databases ScienceDirect, Cochrane Library, and PubMed using keywords and Boolean operators. These comprise MM and lesions of the spine and spinal cord. Each database was searched from the earliest available article to January 2017.

Results: According to the literature, low-dose radiotherapy, antimyeloma medications, and bisphosphonates comprise the mainstay management for symptomatic spinal lesions. The decision to operation is based on presence of myelopathy and degree of spinal cord compression.

Conclusions: As a result of the analysis, the following conclusions may be drawn: (1) surgery is a valuable option for MM patients with symptomatic spinal involvement who experience rapid neurological deterioration with SCC and/or mechanical instability and (2) it is important to ensure that the benefits of surgical treatment outweigh the risks, as patients with MM are susceptible to infections.

Keywords: Lesions of the spine and spinal cord, meta-analysis, multiple myeloma, review

INTRODUCTION

Multiple myeloma (MM) is a B-cell malignancy characterized by the clonal proliferation of neoplastic plasma cells in the bone marrow and is clinically manifested by bone lesions, hypercalcemia, renal dysfunction, and anemia.[1] MM accounts for 1%–2% of all malignancies and is the second most common hematological malignancy immediately after non-Hodgkin's lymphoma. MM is diagnosed at an average age of 69 years[2] and currently has an incidence of 6.6 cases per 100,000 population.[3] There are very few population studies on the incidence of MM in Russia and the Dominican Republic. However, in general, both on a regional and international basis, an increase in the incidence of MM is observed as a result of an increase in the life expectancy of the population.[4]

Daniel Encarnacion, Gennady E Chmutin, Ismail Bozkurt[1,2], Jack Wellington[3], Emmanuel Batista Geraldino[4], Bipin Chaurasia[5]

Department of Neurosurgery of People of Friendship Hospital University, Moscow, Russia, [1]Department of Neurosurgery Medical Park Ankara Hospital, Ankara, Turkey, [2]Deparment of Neurosurgery, School of Medicine, Yuksek Ihtisas University, Ankara, Turkey, [3]Department of Neurosurgery, Branford Teaching Hospital NHS Foundation Trust, Bradford, UK, [4]Deparment of Neurosurgery, Hospital Regional Docente Juan Pablo Pina, San Cristóbal, Dominican Repúblic, [5]Department of Neurosurgery, Neurosurgery Clinic, Birgunj, Nepal

Address for correspondence: Dr. Daniel Encarnacion, Miklukho-Maklaya 6, Department of Neurosurgery, People's Friendship University, Moscow 117198, Russia.
E-mail: danielencarnacion2280@gmail.com

Submitted: 31-Aug-23 **Accepted:** 19-Sep-23
Published: 29-Nov-23

Access this article online	
Website: www.jcvjs.com	Quick Response Code
DOI: 10.4103/jcvjs.jcvjs_111_23	

How to cite this article: Encarnacion D, Chmutin GE, Bozkurt I, Wellington J, Geraldino EB, Chaurasia B. Lesions of the spinal cord caused by multiple myeloma: A systematic review and meta-analysis regarding the neurosurgical aspects of patient management. J Craniovert Jun Spine 2023;14:313-8.

With the advent of proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies, the overall survival of patients with MM has improved significantly. However, despite significant advances in the treatment of patients with MM, most patients eventually experience relapses and complications.[5] Many aspects of the treatment of MM are within the competence of the oncologist and hematologist. However, in some cases, neurosurgical care is required. Thus, spinal injury occurs in about 70% of patients with MM.[6] At the same time, the development of osteolytic foci can lead to pathological fractures, which are present in more than 50% of all patients with MM,[3] which further leads to spinal instability and neurological disorders. Spinal cord compression (SCC) occurs in approximately 10% of all patients with MM.[7,8]

In connection with the foregoing, the purpose of this article was to analyze the management of patients with lesions of the spine and spinal cord in MM. The meta-analysis aimed to determine the efficacy and safety of kyphoplasty and vertebroplasty in the treatment of pathological vertebral fractures in patients with MM.

MATERIALS AND METHODS

To systematically review the scientific literature on neurosurgical aspects of the management of patients with lesions of the spine and spinal cord in MM, a search was conducted among scientific papers in the ScienceDirect, Cochrane Library, and PubMed databases using keywords encompassing MM and lesions of the spine and spinal cord. Each database was searched from the earliest available article to January 2017.

The search process for scientific papers for meta-analysis was conducted on the basis of two main resources: PubMed and Cochrane Central Register of Controlled Trials [Figure 1].

The following keywords were used to build a search strategy: spine, pathological fractures, neurological deficit, SCC, surgery, complications, MM, and myeloma. In addition, the authors expanded the analysis for the literature by manually searching the literature lists of relevant articles. The included studies had to meet the following criteria:

- Patients with lesions of the spine and spinal cord in MM
- Patients over the age of 18 years
- Performed surgical treatment
- Complications have been reported
- One or more outcomes were reported.

RESULTS

A review of the scientific literature revealed, according to a study in a prospective population of 361 patients who were treated for spinal MM lesions between January 2014 and 2017, over a period of around 60 months, where it was shown that the condition of the spine in the MM does not influence survival. Therefore, we have to take into account the prognostic factors present before surgery, which are the International Staging System (ISS) score, *immunoglobulin G*, and the systemic treatment of the disease. MM is a highly heterogeneous disease with an overall survival of more than 10 years.

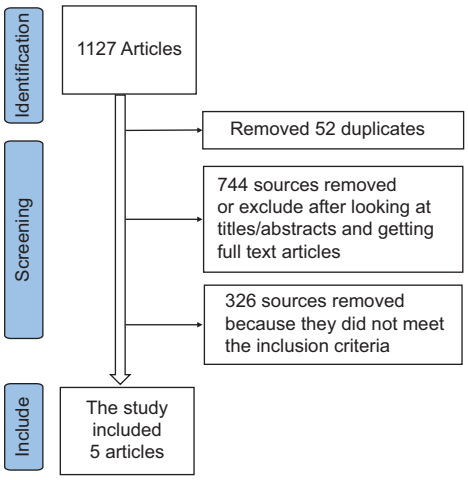

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol outlining the systematic review and meta-analysis flowchart of this article

According to another relevant study, an international Phase 3, double-blind, double-dummy, randomized, active-controlled study of patients from 259 centers and 29 countries was conducted on patients aged 18 years or older with MM. One thousand seven hundred and eighteen patients between 2012 and 2016 were assigned a total of 859 for each treatment group. According to the study, the drug of choice was denosumab, which was not inferior to zoledronic acid in the elapsed time of the choice. One thousand seven hundred and two patients in another group were administered the lowest dose of the investigated drug and included in the assured analysis. Eight hundred and fifty were administered denosumab and 852 zoledronic acid. The most common adverse effects with denosumab and zoledronic acid were neutropenia, anemia, thrombocytopenia and pneumonia.

The spinal lesions, if symptomatic, are treated primarily with a combination of low-dose radiotherapy, antimyeloma drugs, and bisphosphonates.[9] The decision to operate is made on the basis of the neurological status of myelopathy and degree of SCC, tumor chemo-radiosensitivity, mechanical instability, and the degree of systemic and concomitant diseases. In general, due to the lack of scientific data, the indications for surgical intervention in patients with MM with symptomatic

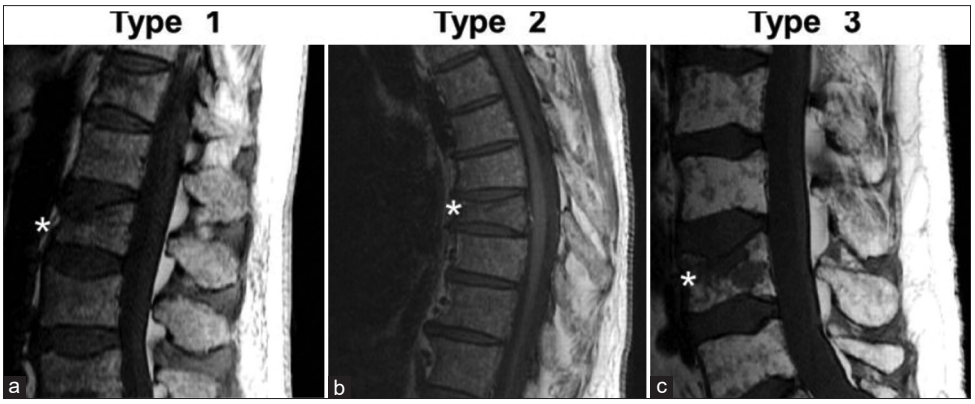

Figure 2: Sagittal magnetic resonance imaging T1 according to the types of fractures. The stars show the postoperative fractures. (a) Osteoporotic fracture Type 1 fracture, osteoporotic type. Note the high intensity of the T1 signal, preserved according to the fractured vertebral body. There is no focal intervertebral lesion and there is no evidence at the pedicle level of epidural or paraspinal involvement. (b) Traumatic fracture Type 2 fracture, uncertain of underlying injuries. There was no focal, epidural, or paraspinal lesion in the treated vertebral body. (c) Myelomatous fracture Type 3 fracture, clear evidence of a myelomatous lesion within the vertebral body

spinal lesions remain controversial, while the standards of surgical treatment have yet to be established.[10]

According to the studies, a rapid neurological deterioration with or without SCC (61%) is the main indication for urgent surgical decompression. The second most common indication for surgery is mechanical instability (35%), in which patients suffer from moderate to severe pain and have a Spinal Instability Neoplastic Score of 9–13.[3]

DISCUSSION

According to the authors, it should be noted that acute SCC requires emergency medical care within 24 h after diagnosis.[11-13] The goals of treatment are to prevent further neurological damage, preserve motor function, and relieve pain. All patients are given a loading dose of corticosteroids as first-line therapy. Radiation therapy may be the primary treatment if SCC is caused by a plasmacytoma, with surgery only needed if the spine is unstable or the compression is caused by bone fragments from a vertebral body fracture. Chemotherapy and targeted therapy can be used in patients with minimal neurological dysfunction. Surgery can be thought of as an immediate alternative to pain relief as radiotherapy may take several days to many weeks to have a positive effect.[14] The study shows that decompressive surgery combined with radiotherapy is also preferred over radiotherapy alone for the management of SCC patients.[13] Patients with SCC and no loss of neurological function may not require surgery and can be managed with chemoradiotherapy and corticosteroids.[15] Another study showed that partial resection of plasmacytoma followed by chemotherapy appears to be an effective treatment for SCC associated with MM due to fewer complications. The percentage of postoperative neurological recovery varies

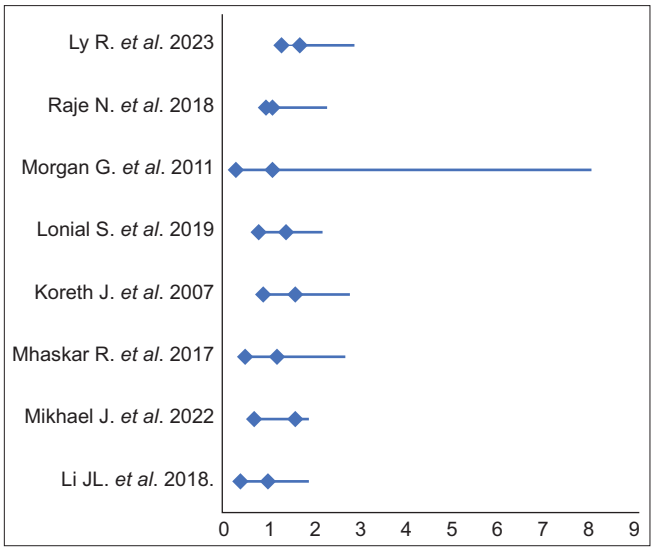

Figure 3: OR lesions of the spinal cord caused by multiple myeloma studies

widely in the literature, with some reporting dramatic improvement.[16-23] Others report moderate recovery, and the data vary due to different patient populations.[17] Before surgery, complications in spinal tumor surgery are relatively high, from 5% to 76% (mean: 26.9%), where surgical site infection is one of the most common.[19] The incidence of surgical site infection after spinal tumor removal surgery ranges from 3.51% to 20% (median: 10.22%).[18]

It should be noted that patients who undergo emergency surgery develop more infectious complications than patients who undergo elective surgery for tumor removal. The recurrence in patients with MM surgery ranges from 6% to 11%.[3] It should be noted that balloon kyphoplasty and vertebroplasty are widely used and give positive results in the treatment of painful vertebral compression fractures associated with MM. However, the role of minimally invasive

surgery (MIS) in the treatment of myeloma lesions of the spine remains unclear and the need for it is controversial. The dynamics of pain syndrome and complications post-MIS20-24 are presented in Table 1.

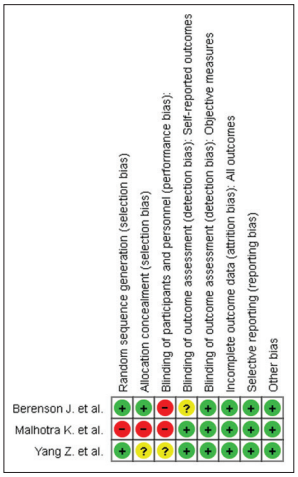

Figure 4: Bias risk summary

Thus, vertebroplasty and kyphoplasty are safe and effective procedures in the treatment of pathological fractures of the vertebral bodies in patients with MM. The effectiveness of pain relief was evaluated. In total, we identified 3 studies[21,24,25] that met our selection criteria [Figures 2-4 and Table 2].[26-34]

In general, these studies were free of detection, attribution, and reporting errors.

However, performance bias and selection bias were observed Figure 5.

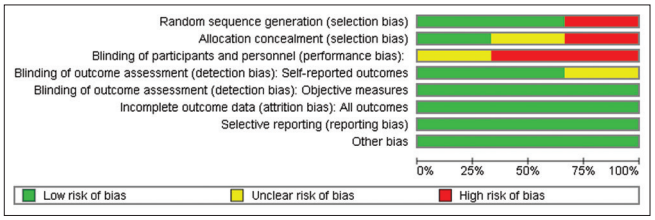

Figure 5: The total risk of bias

Table 1: Dynamics of pain syndrome postminimally invasive surgery

Authors	Number of patients	Complications	*P*
Garland *et al*.	26	-	<0.003
Chen *et al*.	24	Of 24 patients, 4 had a cement leak	<0.05
Berenson *et al*.	70	Back pain (4 out of 70) and symptomatic vertebral fractures (2 out of 70). One patient in the kyphoplasty group had non-Q-wave intraoperative myocardial infarction	<0.0001
Tancioni *et al*.	11	In 3 cases out of 11, there was a cement leak	<0.05
McDonald *et al*.	67	-	<0.0001

Table 2: Comparative studies of patients with spinal cord multiple myeloma

Authors/years	Types of study	CI 95% total	*P*
Ly *et al*., 2023	Prospective	HR: 0.748, 95% CI: 0.318–1.759/HR: 2.753, 95% CI: 1.230–6.130	0.4
Raje *et al*., 2018	RCT phase 3 study	HR: 0.98, 95% CI: 0.85–1.14	0.14
Morgan *et al*., 2011	RCT	OR: 1.1, HR: 0.74, 95% CI: 0.62–0.87	0.04
Lonial *et al*., 2020	RCT phase 3 study	HR: 0.28, 95% CI: 0.12–0.62	0.02
Koreth *et al*., 2007	RCT	OR: 3.01, 95% CI: 1.64–5.50/HDT: 0.92 (95% CI: 0.74–1.13)	0.01
Mhaskar *et al*., 2017	RCT	HR: 0.90, 95% CI: 0.76–1.07/RR: 1.23, 95% CI: 0.95–1.59	0.04
Mikhael *et al*., 2023	RCT	A ratio of <0.26 indicates a lambda clone and a ratio of >1.65 suggests a kappa clone 48	0.03
Li *et al*., 2018	RCT	HR: 0.59, 95% CI: 0.54–0.64, OS: HR: 0.93, 95% CI: 0.87–1.00	0.001

RCT - Randomized controlled trial; HR - Hazard ratio; CI - Confidence interval; OR - Odds ratio; RR - Risk ratio; HDT - High dose therapy; OS - Overall survival

Table 3: Meta analysis results:Vertebroplasty/kyphoplasty/conservative treatment

Vertebroplasty			Kyphoplasty		Conservative treatment
Study or subgroup	Events	Total	Events	Weight M-H	Odds ratio 95%, CI
Berenson J *et al*.	26	68	14	60 29.3%	2.03 [0.94, 4.41]
Malhotra K *et al*.	47	84	48	94 50.2%	1.22 [0.67, 2.20]
Yang Z *et al*.	25	38	18	38 20.5%	2.14 [0.85, 5.39]
Total (95% CI)					
Total events:		190		192 100.0%	1.59[1.05, 2.41]

Heterogeneity: tau2=0.0; Chi^2=1.57, df=2 (*P*=0.46); I^2 =0%. Test for overall effect *Z*=2.17 (*P*=0.03). Test for subgroup differences: Not applicable

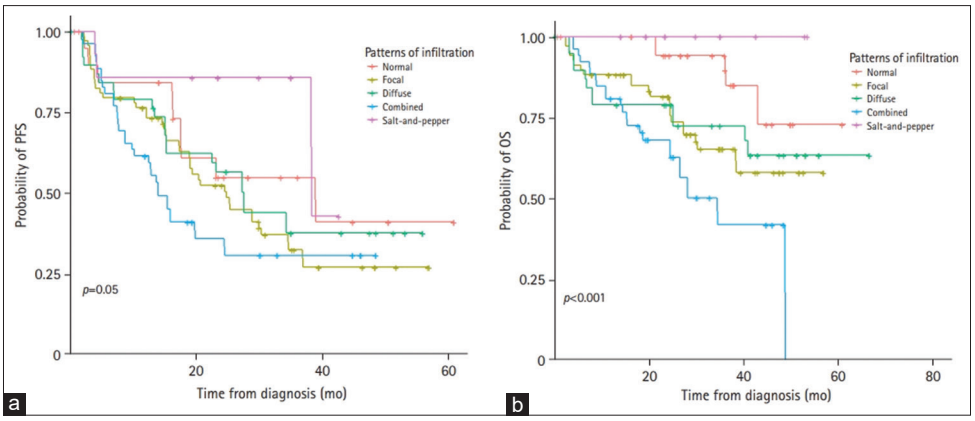

Figure 6: Kaplan–Meier survival curve showing magnetic resonance imaging patterns of the spine. Patients show various prognoses, (a) Progression-free survival and, (b) Overall survival

Figure 6 shows overall survival and prognosis of patients treated for multiple myeloma.

Total subgroup differences are not applicable.[22]

As we can observe, in general, there is a bias in favor of vertebroplasty and kyphoplasty relative to conservative treatment ($P = 0.03$) Table 3. However, only two of these studies were randomized controlled. Concurrently, in general, there is a lack of high-quality studies evaluating the role of MIS in the treatment of myeloma lesions of the spine.

CONCLUSIONS

As a result of the analysis, the following conclusions may be drawn:

1. Surgery is a valuable option for MM patients with symptomatic spinal involvement who experience rapid neurological deterioration with SCC and/or mechanical instability
2. It is important to ensure that the benefits of surgical treatment outweigh the risks, as patients with MM are susceptible to infections
3. Vertebroplasty and kyphoplasty are safe and effective procedures in the treatment of pathological fractures of the vertebral bodies in patients with MM
4. Low-dose radiation therapy with antimyeloma drugs and bisphosphonates is recommended
5. The drug of choice denosumab is recommended over zoledronic acid
6. Decompressive craniotomy plus radiotherapy is recommended in the presence of plasmacytoma rather than radiotherapy alone.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Yang Q, Li X, Zhang F, Yang Q, Zhou W, Liu J. Efficacy and safety of CAR-T therapy for relapse or refractory multiple myeloma: A systematic review and meta-analysis. Int J Med Sci 2021;18:1786-97.
2. Palumbo A, Anderson K. Multiple myeloma. N Engl J Med 2011;364:1046-60.
3. Milavec H, Ravikumar N, Syn NL, Yentia Soekojo C, Chng WJ, Kumar N. Surgical management of multiple myeloma with symptomatic involvement of the spine. Int J Spine Surg 2020;14:785-94.
4. Samura BB. Prognostic role of circulating N-terminal fragment of pro-brain natriuretic peptide in patients after treatment of multiple myeloma. Emergency medicine 2017;(6 (85)):57-61.
5. Kraj M, Pogłód R, Maj S, Pawlikowski J, Sokołowska U, Szczepanik J. Comparative evaluation of safety and efficacy of pamidronate and zoledronic acid in multiple myeloma patients (single center experience). Acta Pol Pharm 2002;59:478-82.
6. Sharma A, Sackett M, Bueddefeld D, Lambert P, Wadhwa V, Kotb R, *et al*. Spinal Involvement in Myeloma: Incidence, Survival and Impact of Radiotherapy. Cureus Journal of Medical Science 2017.
7. Wallington M, Mendis S, Premawardhana U, Sanders P, Shahsavar-Haghighi K. Local control and survival in spinal cord compression from lymphoma and myeloma. Radiother Oncol 1997;42:43-7.
8. Macdonald AG, Lynch D, Garbett I, Nazeer N. Malignant spinal cord compression. J R Coll Physicians Edinb 2019;49:151-6.
9. Newman WC, Laufer I, Bilsky MH. Neurologic, oncologic, mechanical, and systemic and other decision frameworks for spinal disease. Neurosurg Clin N Am 2020;31:151-66.
10. Quidet M, Zairi F, Boyle E, Facon T, Vieillard MH, Machuron F, *et al*. Evaluation of the relevance of surgery in patients with multiple myeloma harboring symptomatic spinal involvement: A retrospective case series. World Neurosurg 2018;114:e356-65.
11. Kyriakou C, Molloy S, Vrionis F, Alberico R, Bastian L, Zonder JA, *et al*. The role of cement augmentation with percutaneous vertebroplasty and balloon kyphoplasty for the treatment of vertebral compression fractures in multiple myeloma: A consensus statement from the International Myeloma Working Group (IMWG). Blood Cancer J 2019;9:27.
12. Almetrek MA, Mahjari AA, Aldharman SS, Amer KA, Balobaid MF, Madkhali A, *et al*. Surgical intervention for spinal lesions due to multiple myeloma: A case report. Cureus 2023;15:e33505.
13. Chen B, Cai L, Zhou F. Management of acute spinal cord compression in multiple myeloma. Crit Rev Oncol Hematol 2021;160:103205.

14. De Felice F, Piccioli A, Musio D, Tombolini V. The role of radiation therapy in bone metastases management. Oncotarget 2017;8:25691-9.
15. Qian J, Jing J, Tian D, Yang H. Partial tumor resection combined with chemotherapy for multiple myeloma spinal cord compression. Ann Surg Oncol 2014;21:3661-7.
16. Shen J, Du X, Zhao L, Luo H, Xu Z. Comparative analysis of the surgical treatment results for multiple myeloma bone disease of the spine and the long bone/soft tissue. Oncol Lett 2018;15:10017-25.
17. Amelot A, Cristini J, Salaud C, Moles A, Hamel O, Moreau P, *et al*. Overall survival in spine myeloma metastases: Difficulties in predicting with prognostic scores. Spine (Phila Pa 1976) 2017;42:400-6.
18. Luksanapruksa P, Buchowski JM, Zebala LP, Kepler CK, Singhatanadgige W, Bumpass DB. Perioperative complications of spinal metastases surgery. Clin Spine Surg 2017;30:4-13.
19. Sebaaly A, Shedid D, Boubez G, Zairi F, Kanhonou M, Yuh SJ, *et al*. Surgical site infection in spinal metastasis: Incidence and risk factors. Spine J 2018;18:1382-7.
20. Garland P, Gishen P, Rahemtulla A. Percutaneous vertebroplasty to treat painful myelomatous vertebral deposits-long-term efficacy outcomes. Ann Hematol 2011;90:95-100.
21. Chen LH, Hsieh MK, Niu CC, Fu TS, Lai PL, Chen WJ. Percutaneous vertebroplasty for pathological vertebral compression fractures secondary to multiple myeloma. Arch Orthop Trauma Surg 2012;132:759-64.
22. Berenson J, Pflugmacher R, Jarzem P, Zonder J, Schechtman K, Tillman JB, *et al*. Balloon kyphoplasty versus non-surgical fracture management for treatment of painful vertebral body compression fractures in patients with cancer: A multicentre, randomised controlled trial. Lancet Oncol 2011;12:225-35.
23. Tancioni F, Lorenzetti M, Navarria P, Nozza A, Castagna L, Gaetani P, *et al*. Vertebroplasty for pain relief and spinal stabilization in multiple myeloma. Neurol Sci 2010;31:151-7.
24. McDonald RJ, Trout AT, Gray LA, Dispenzieri A, Thielen KR, Kallmes DF. Vertebroplasty in multiple myeloma: Outcomes in a large patient series. AJNR Am J Neuroradiol 2008;29:642-8.
25. Malhotra K, Butler JS, Yu HM, Selvadurai S, D'Sa S, Rabin N, *et al*. Spinal disease in myeloma: Cohort analysis at a specialist spinal surgery centre indicates benefit of early surgical augmentation or bracing. BMC Cancer 2016;16:444.
26. Ly R, Terrier LM, Cognacq G, Benboubker L, Destrieux C, Velut S, *et al*. Spinal lesions in multiple myeloma: Primary bone tumors with distinct prognostic factors. Surg Oncol 2023;48:101927.
27. Raje N, Terpos E, Willenbacher W, Shimizu K, García-Sanz R, Durie B, *et al*. Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma: An international, double-blind, double-dummy, randomised, controlled, phase 3 study. Lancet Oncol 2018;19:370-81.
28. Morgan GJ, Child JA, Gregory WM, Szubert AJ, Cocks K, Bell SE, *et al*. Effects of zoledronic acid versus clodronic acid on skeletal morbidity in patients with newly diagnosed multiple myeloma (MRC Myeloma IX): Secondary outcomes from a randomised controlled trial. Lancet Oncol 2011;12:743-52.
29. Lonial S, Jacobus S, Fonseca R, Weiss M, Kumar S, Orlowski RZ, *et al*. Randomized trial of lenalidomide versus observation in smoldering multiple myeloma. J Clin Oncol 2020;38:1126-37.
30. Lee JM, Cho HJ, Moon JH, Sohn SK, Park B, Baek DW. Clinical impact of spine magnetic resonance imaging as a valuable prognostic tool for patients with multiple myeloma: A retrospective study. J Yeungnam Med Sci 2022;39:300-8.
31. Koreth J, Cutler CS, Djulbegovic B, Behl R, Schlossman RL, Munshi NC, *et al*. High-dose therapy with single autologous transplantation versus chemotherapy for newly diagnosed multiple myeloma: A systematic review and meta-analysis of randomized controlled trials. Biol Blood Marrow Transplant 2007;13:183-96.
32. Mhaskar R, Kumar A, Miladinovic B, Djulbegovic B. Bisphosphonates in multiple myeloma: An updated network meta-analysis. Cochrane Database Syst Rev 2017;12:CD003188.
33. Mikhael J, Bhutani M, Cole CE. Multiple myeloma for the primary care provider: A practical review to promote earlier diagnosis among diverse populations. Am J Med 2023;136:33-41.
34. Li JL, Fan GY, Liu YJ, Zeng ZH, Huang JJ, Yang ZM, *et al*. Long-term efficacy of maintenance therapy for multiple myeloma: A quantitative synthesis of 22 randomized controlled trials. Front Pharmacol 2018;9:430.