CONSENSUS

Consensus on Surgical Management of Myeloma Bone Disease

The Surgeon's Committee of the Chinese Myeloma Working Group of the International Myeloma Foundation

Myeloma bone disease (MBD), the skeletal lesions caused by multiple myeloma, is also known as skeletal related events and includes bone pain, osteoporosis, pathological fractures, osteolytic bone lesions, spinal instability, spinal cord and nerve root compression and extramedullary plasmacytoma. It is now generally accepted that patients with these complications usually require surgical management and that such treatment is safe and effective. The aims of surgical interventions are to alleviate pain, improve quality of life, treat potential or existing pathological fractures, decompress the spinal cord and nerve roots, and reestablish bone continuity. Thus far, there have not been uniform standards for surgical treatment of MBD. The Surgeon's Committee of the Chinese Myeloma Working Group has therefore achieved a consensus with the aim of providing guidance for clinicians and benefitting patients with MBD. This consensus focuses on the treatment of MBD, including its clinical definition and characteristics, diagnosis and surgical management. This expert consensus document was compiled after discussion and revision by experts from several relevant institutions in China. However, it is only an interim guide that cannot be enforced legally. It will be updated with development of new techniques of treatment.

Key words: Consensus; Myeloma bone disease; Surgery

Introduction

Multiple myeloma (MM) is a lymphoproliferative disease characterized by the clonal proliferation of plasma cells. Approximately 80% of patients with MM have evidence of osteolytic bone lesions, osteoporosis, or fractures at the time of diagnosis; these complications can limit mobility and increase morbidity and mortality. MM is characterized by monoclonal immunoglobulins that can be detected in serum and urine, and bone marrow infiltration. Characteristic clinical symptoms include anemia, infection, renal insufficiency, hypercalcemia and pathologic fractures. Treatment of MM consists of conventional or high dose chemotherapy and subsequent autologous or allogeneic stem cell transplantation, and novel agents such as the immunomodulatory drugs thalidomide and lenalidomide and the proteasome inhibitor bortezomib. These latter drugs combined with conventional chemotherapy have changed the paradigm for treating patients and improved outcome. These new and sometimes more aggressive treatments have resulted in a dramatic increase in progression free survival time and a 10-year survival rate of up to 30%–40%. Recent advances in the treatment of MM have extended patients' life expectancy; thus, increasing importance is now placed on their long-term supportive care and quality of life[1].

It is now generally accepted that bone pain can be alleviated by chemotherapy and/or radiotherapy; however, the effects of chemotherapy and/or radiotherapy are quite limited in MM patients with skeletal related events such as intractable pain, pathological fracture, spinal instability, spinal cord or nerve root compression and huge soft tissue masses. Such patients usually require surgical treatment. Thus, surgical procedures that are safe and effective in relieving pain and improving quality of life of patients with MM are playing an increasingly important role in the management of bone disease in these patients[2].

Chemotherapy remains the main form of therapy for MM, the trend being toward multidisciplinary cooperation. Orthopaedic surgeons should improve the surgical procedures for myeloma bone disease (MBD) and optimize perioperative management and physicians should consult with surgeons on patients with MM complicated by spinal instability, spinal cord compression or pathologic fracture.

At present, there are no uniform standards for surgical treatment of MBD in China. The contributors hope that this

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consensus will help clinicians and benefit patients with MM. This expert consensus document was compiled after discussion and revision by experts from several relevant institutions in China. However, it is only an interim guide that cannot be enforced legally. It will be updated with development of new techniques of treatment.

Definition of MBD

MBD, the skeletal lesions caused by multiple myeloma, is also known as skeletal related events and includes bone pain, osteoporosis, pathological fractures, osteolytic bone lesions, spinal instability, spinal cord and nerve root compression and extramedullary plasmacytomas.

Clinical Characteristics and Manifestations of MBD

Most patients with MM are elderly, their median age being 69 years in western countries and 59 years in China. The ratio of males to females with MM is 1.54:1 in China[3]. Bone lesions often involve flat bones, including the skull, spine, pelvis, ribs and sternum. The most commonly involved skeletal structure is the spine; other common sites include long bones (proximal portions of the humerus and femur). Spinal involvement is associated with severe pain, disability, pulmonary dysfunction and poor clinical outcomes[4].

Bone pain is the most frequent symptom experienced by patients with MBD; the incidence of pain being up to 73.2%. Pain most often occurs in the lower back and chest[4]. During the course of their disease, pathological fractures occur in more than 50% of patients with MM, absence of pain thus being relatively unusual. Sudden onset or exacerbation of bone pain indicates pathological fracture or progression of MBD. Neurologic damage occurs in about 8%–10% of patients with spinal MM, sometimes causing paraplegia and bowel and bladder dysfunction. Some patients also develop extramedullary plasmocytomas and pathological fractures in long bones[5].

Diagnosis of MBD

The following three factors are essential for the diagnosis of MBD: clinical diagnosis of MM, symptoms and signs of bone disease and supportive findings on imaging.

Diagnosis of MM

It is not difficult to make a diagnosis of MBD in a patient with a history of MM or in whom MM has already been diagnosed by a hematologist. After other diseases have been excluded, a diagnosis of MM should be considered in any patient attending an orthopaedic clinic because of bone pain, bone destruction, pathological fracture, soft tissue masses or nerve compression (Fig. 1). When a solitary bone or extramedullary plasmacytoma is diagnosed, laboratory investigations to exclude MM should be arranged, the definitive diagnosis being made by pathological examination of tissue obtained by aspiration or open biopsy[6] (Fig. 2).

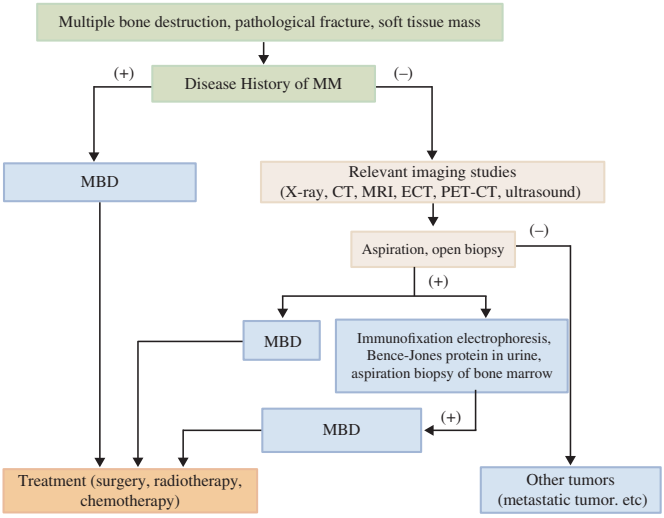

Fig. 1 Diagnostic flow diagram for patients suspected of having MM presenting to the orthopaedic outpatient clinic.

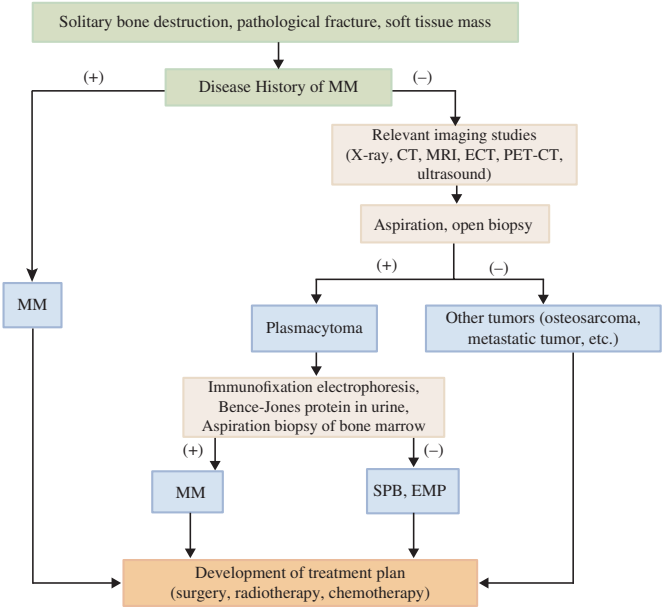

Fig. 2 Diagnostic flow diagram for patients suspected of having solitary bone plasmacytomas (SBP) or extramedullary plasmacytomas (EMP).

Supportive Findings on Imaging

X-Ray films and CT

Imaging plays an important role in the diagnosis of MBD. The typical manifestation on X-ray films of patients with MBD is osteolytic destruction with a "moth-eaten" appearance; however, it is difficult to identify early pathological changes by conventional X-ray examination because of the complex structure of the axial skeleton and overlapping soft tissue[7]. Lesions in the pelvis can be difficult to detect because of bowel gas. CT examination is more sensitive than plain X-ray films,

increasing the rate of detection by 4%–33%. Whole body low-dose CT is currently the standard imaging examination method in Europe because it has high sensitivity and image quality and can be used to guide needle biopsy.

MRI

Magnetic resonance imaging, which does not involve irradiation, can safely be performed repeatedly. Bone marrow infiltration and the type of infiltration can be identified by MRI, which can also be used to guide bone marrow biopsy. MRI is the most valuable imaging method for making a diagnosis of a spinal lesion of MM. Lesions in the spine and compression of the spinal cord and nerve roots can be detected earlier by MRI than by CT.

Emission computed tomography and PET-CT

Although emission computed tomography can be used to examine bone formation, it is unsuitable for detecting MBD, which is mainly characterized by more osteolytic destruction than bone formation. It is sensitive to early bone lesions in the ribs, vertebral bodies and sternum. In recent years, positron emission tomography (PET)-CT has provided a better means of assessing prognosis and minimal residual disease in patients with MM, because it can detect lesions that MRI cannot. PET-CT is better than MRI for detecting MM lesions, assessing their extent and the proliferative activity of tumor cells, detecting extramedullary lesions and evaluating therapeutic efficacy. PET-CT can differentiate between active and stable pathological changes, but does not detect lesions that are smaller than 0.5 cm. Although the sensitivity of whole body PET-CT is high, its specificity is poor. It is therefore necessary to obtain a bone marrow aspirate and examine it pathologically to make a definitive final diagnosis[8,9] (Table 1).

Surgical Treatment of MBD

Purposes of Surgical Treatment

Because the purpose of surgical treatment is not radical cure of MM, doctors should mainly focus on alleviating pain and improving quality of life. The aims of surgical treatment are to treat potential or existing pathological fractures, decompress the spinal cord and nerve roots, relieve pain, improve mobility, and reestablish bone continuity and the spinal stability[10–14]. However, thus far, no randomized clinical trials have confirmed that surgical treatment can prolong overall survival.

Indications and Contraindications of Surgical Treatment

Indications

Indications for surgical treatment of MM include: (i) spinal instability; (ii) potential or existing pathological fracture caused by MM[15]; (iii) progressive impairment of neurological function due to spinal cord or nerve root compression caused by MM[16,17]; (iv) intractable pain clearly attributable to a site of MBD; (v) solitary plasmacytoma of bone[18]; (vi) soft tissue plasmacytoma in limbs or spine; (vii) pathological or potential fracture of a long bone; and (viii) needle or open biopsy providing pathological evidence for further treatment.

Contraindications to surgical treatment of MM

Contraindications to surgical treatment of MM include the following: (i) poor physical condition; (ii) untreatable dysfunction of heart, lungs and kidney; (iii) severe coagulation disturbance that is difficult to correct; and (iv) uncontrollable serious infection.

TABLE 1 Advantages and disadvantages of different imaging examinations for diagnosis of MBD[7,8]

Imaging examination	Advantages	Disadvantages
Whole body radiographs	Low cost; readily available; detect lesions in skull and limbs	Low sensitivity and positivity; detects lesions only after appearance of bone destruction; patient discomfort because of repeated positioning and examination; lengthy process to collect image
Whole body low-dose CT	High sensitivity and positivity; performance of aspiration biopsy and operation directed by 3-D imaging; informs radiotherapy planning; demonstrates the scale of extramedullary lesions, detects bone marrow invasion and osteolytic bone destruction; enables evaluation of tumor load; rapid data collection; lower cost than MRI or PET; little patient discomfort	Expensive; may miss lesions in skull and ribs; difficult to determine the number of lesions; high radiation exposure
PET-CT	Reflects the activity of lesions; enables evaluation of the activity of lesions pre- and post-operatively; images of extramedullary lesions can be obtained; facilitates evaluation of prognosis pre- and postoperatively; new radionuclides used to identify different diseases	Expensive; limited diagnostic value; difficult to identify active infection and inflammation; low resolution of lesions smaller than 0.5 mm; insensitive to MM with low activity of fluorodeoxyglucose
MRI	No radiation exposure; enables evaluation of location and scale of lesions infiltrating bone marrow and local lesions; displays spinal cord compression and lesions in soft tissue; the number of lesions can indicate prognosis; displays extramedullary lesions; 3-D reconstruction image can assist biopsy, surgery and radiotherapy directed by CT	Expensive; lengthy process to collect data; unsuitable for patients with claustrophobia or with metal in their bodies; contrast agent is contraindicated in patients with severe renal impairment; infiltration of bone marrow may be misdiagnosed as osteolytic lesions; limitations of electric field and motion artifacts

Preoperative Staging and Prognosis

Methods for staging and estimating prognosis in patients with MBD who are eligible for surgical treatment have not yet been established. Because the main aim of surgery is to improve the quality of life of patients with MM, it is very important to establish a scoring system for prognosis that can estimate survival time. It is also necessary to assess the symptoms, such as pain and evidence of neurological damage, of patients with MBD.

Multiple myeloma should be classified and staged both pre- and post-operatively according to the D/S, ISS and R-ISS staging systems[19]. Neurological function should be graded according to Frankel grade, together with evaluation of bladder, bowel and sexual function[10,20,21]. Pain should be evaluated by a visual analogue score system, and quality of life by the Karnofsky scoring system[22]. All these evaluation systems are useful for evaluating therapeutic benefits pre- and post-operatively. Some other medical evaluation systems should also be utilized in patients with MM[23,24].

Anesthesia

General anesthesia is the approach of choice because intraspinal and other methods of inducing anesthesia are invasive and may lead to bleeding and infection. Patients with MBD are usually in poor physical condition; general anesthesia enables better control of blood pressure, oxygen saturation and respiratory rate.

Preoperative Preparation

Patients with MBD are generally in poorer condition (e.g., poor appetite, emaciation and thin skin) than those with other orthopaedic diseases and consequently require special attention. Patients with MM are generally elderly and many have complications such as diabetes and hypertension, necessitating evaluation of their general condition and administration of the corresponding treatment. Because most patients with MM have received chemotherapy or radiotherapy preoperatively, their immune function is frequently impaired. Complications such as hypercalcemia, anemia, coagulation abnormalities and hypoproteinemia may also affect surgery; in particular, care should be taken to rectify anemia. Operative procedures should not be performed until hemoglobin concentrations and platelet counts of more than 10 g/L and 80×10^9/L, respectively, have been achieved[2,13]. In addition to routinely-required surgical instruments, gelatin sponges and hemostatic gauze should also be prepared, as should other materials such as allogenic and artificial bone and bone cement, preoperatively.

Surgical Management

Spine Surgery in Patients with MM

In clinical practice, open and minimally invasive surgery can be performed separately or in combination.

Relevant minimally invasive spinal surgical procedures include percutaneous kyphoplasty and vertebroplasty (PKP/PVP), which are mainly performed to manage MM-related vertebral bone destruction, with or without concomitant pathological compression fractures but without spinal cord compression syndrome[25,26]. PKP/PVP can immediately relieve pain and stabilize fractured vertebral bodies and can be performed separately or in combination with open surgery. Obtaining a biopsy for pathological examination during kyphoplasty can result in further definition or correction of the diagnosis[27,28]. There is reportedly no significant difference between unilateral and bilateral approaches in relieving pain, restoring vertebral height, the quantity of bone cement required and complications such as leakage of bone cement[29]. A unilateral approach is therefore adequate. Some researchers have concluded that it is unnecessary to perform radiofrequency ablation during PKP/PVP[30].

Open spinal surgical procedures are chosen according to the number, location and size of bone lesions. Surgical approaches include direct anterior, posterior and combined anterior-posterior approaches. The purposes of surgery include removal of as much tumor as possible, decompression, spinal reconstruction and internal fixation[31–33]. Suitable internal fixation systems include titanium plates, pedicle screw spinal systems and lateral mass screw fixation systems, whereas suitable reconstructive implants include artificial vertebral bodies, titanium mesh, bone cement and allograft bone. The fixators and implants are chosen according to the patient's condition and the requirements of the particular procedure. Fixators made of titanium are recommended because they do not impair follow-up assessment by MRI. In addition to facilitating shaping, bone cement can kill tumor cells; it is therefore the first choice for implanting in bone defects after removing tumor masses. Open surgery can reduce the internal pressure of bone and the dough stage of bone cement can reduce the risk of pulmonary embolism. Autologous bone grafts are not recommended because they are more likely to be absorbed in patients with MBD[2].

A combination of open spinal and minimally invasive surgery is typically used to treat patients with multiple MM spinal lesions, because this has the advantages of both types of surgery, decreasing bleeding volume and other complications. The main goal of such procedures is to reestablish spine stability, reduce bone tumor mass and decompress the spinal cord; wide or radical resection is unnecessary for MBD of the spine. The patient's general condition and prognosis must be considered preoperatively and reconstruction methods chosen according to the patient's specific needs. Spine surgery is highly risky and demanding; thus, it is very important that surgeons performing it are experienced in spinal tumor surgery.

Surgery for Pathological Fractures of the Long Bones

The benefits of surgical treatment for pathological fractures of long limb bones include pain relief, restoration of bone continuity and limb function and improved quality of life. Appropriate surgical procedures include resection or curettage of bone lesions, filling of defects with bone cement and

TABLE 2 Fracture location and recommended surgery[35–37]

Fracture type	Recommended surgery	Evidence grade
Impending fracture of the femoral neck	Cemented hemiarthroplasty	B
Completed fracture of the femoral neck	Cemented hemiarthroplasty	B
Impending fracture of the inter-trochanteric region	Intramedullary nail or plate and screws	B
Completed fracture of the inter-trochanteric region	Intramedullary nail or plate and screws	C
Completed fracture of the inter-trochanteric region with good proximal bone	Intramedullary nail or plate and screws	C
Complete fracture of the inter-trochanteric region with poor proximal bone	Cemented upper femoral prosthesis	C
Impending fracture of the sub-trochanteric region	Intramedullary nail or plate and screws	C
Completed fracture of the sub-trochanteric region	Intramedullary nail or plate and screws	C
Completed fracture of the sub-trochanteric region with good proximal bone	Intramedullary nail or plate and screws	C
Completed fracture of the sub-trochanteric region with poor proximal bone	Intramedullary nail or plate and screws	C

internal fixation as indicated with screws, titanium plates, intramedullary nails or interlocking intramedullary nails and so on[34].

Tumor lesions should be resected and a prosthetic femoral head inserted for pathological fracture of the femoral neck[35]. In patients with femoral trochanteric and bone destruction, pathological fracture should be prevented by appropriate bed rest and timing of surgery. Pathological fractures of lower limb long bone should initially be fixed temporarily with a plaster cast or traction, followed by surgical fixation as soon as possible. The same principles apply to upper extremity pathological fractures; however, the upper limbs are non-weight-bearing. Internal fixation procedures are the treatment of choice because, unlike external fixation, they enable resection of tumor and reestablishment of bone continuity. Chemotherapy and radiation are not effective modalities for treating pathological fractures in the long bones of limbs[36,37].

The choice of fixation system and surgical procedure depends on the patient's general condition and life expectancy, previous response to chemotherapy, fracture site (e.g., femoral neck, sub-trochanteric, inter-trochanteric), number, size and location of lesions and the extent of bone invasion[34] (Table 2). The relationships between lesion location, potential fracture risk and recommended measures are shown in Table 3.

Preoperative evaluation consists of plain X-ray films and CT and MRI scanning. With limb bone lesions, entire length anteroposterior and lateral X-ray films should be taken to evaluate the location and number of lesions. If there are lesions in the distal and proximal parts of the same long bone, longer titanium plates or intramedullary nails should be chosen. CT is useful for evaluating the extent of bone lesions to determine whether to use an intramedullary nail or perform proximal femoral replacement; intramedullary nailing should be performed only when bone quality is good. MRI is useful for evaluating tumor size and extent and helping to predict surgical blood loss.

Pelvic Surgery

Myeloma lesions in the pelvis are usually large when diagnosed, lesions of the iliac crest characteristically extending into the pelvis or pelvic fossa. A wide or marginal excision of such lesions can usually be performed without compromising any vital structure in the lower extremity. If the lesions have not destroyed the integrity of the pelvic ring, appropriate procedures include resection or shaving of the lesion and filling of defects with bone cement, whereas if the lesion has destroyed pelvic ring integrity, thus creating pelvic instability, it is necessary to reconstruct the pelvis. Generally, titanium plates and screws are the first choice. It is better to use bone cement rather than allografts to fill the defects; autogenic bone is contraindicated. Myeloma in the sacrum can cause intractable pain and bowel and bladder dysfunction, which should be actively treated surgically. The surgical approach, performance of partial or total sacrectomy and reconstruction should be selected according to the site(s) of the lesions.

Surgical Treatment of Huge Soft Tissue Masses in Patients with Extramedullary Plasmacytomas (EMPs)

Radiation and chemotherapy are relatively ineffective for EMPs with huge soft tissue masses, such masses

TABLE 3 Relationships between lesion location, potential fracture risk and recommended measures[36]

Lesion location	Fracture risk	Recommended measure
Lower medial bone cortex of femoral neck	High	Prevent by fixation
Center of the femoral neck	Low	Bed rest or walk with brace
Upper lateral bone cortex of femoral neck	Low	Bed rest or walk with brace
Bone cortex anterior to femoral neck	Low	Bed rest or walk with brace
Lesser trochanter of inter-trochanteric region	High	Prevent by fixation
Anteromedial inter-trochanteric region	High	Prevent by fixation
Inter-trochanteric and sub-trochanteric regions	High	Prevent by fixation
Femoral shaft	High	Prevent by fixation
Femoral condyle	High	Prevent by fixation
Tibial plateau	High	Prevent by fixation
Clavicle	High	Prevent by fixation
Humerus	High	Brace or preventive fixation

characteristically enlarging during these treatments. When these masses develop or continue to grow, surgical removal is indicated; it can greatly reduce the tumor burden, decompresses nerve and vascular entrapment and relieve pain. The main surgical procedure is wide excision based on the principles for operating on bone and soft tissue sarcomas. Because MBD differs from primary bone and soft tissue sarcomas in that it is a systemic disease, it is difficult to completely remove all lesions. If wide excision cannot be performed, marginal or intralesional excision is indicated. As much of the lesion as possible should be removed; however, major vessels, nerves and organs involved by the lesion must be separated out and protected during the procedure.

Surgical Treatment of Solitary Plasmacytomas of Bone

A few solitary plasmacytomas of bone may progress to MM; however, if it is diagnosed and treated early, the prognosis can be excellent. Solitary plasmacytomas of bone that are limited and easy to remove should be treated with wide excision. Radiation therapy is better performed postoperatively. Solitary plasmacytomas of bone are likely to be cured with appropriate surgical resection and radiotherapy[38,39].

Surgical Treatment of Extramedullary Plasmacytomas of Limbs and Spine

In general, extramedullary plasmacytoma in sites other than the limbs and spine can be adequately treated with radiotherapy; however, the extramedullary plasmacytomas in the limbs or spine should be treated by either an intralesional procedure or marginal or wide excision. The first choice is wide excision and the second marginal excision. Simple radiotherapy or post-radiotherapy surgery is indicated if the tumor is removed by an intralesional procedure. The therapeutic schedule should be planned by a team of orthopaedists, hematologists and radiation physicians[40].

Treatment of Nerve Compression in Patients with MM

MM is usually complicated by peripheral neuropathy; attention should be paid to the differential diagnosis. Surgical procedures can be indicated in patients with nerve compression caused by amyloidosis in MM, the focused being on relieving and releasing the nerves. Tumor resection and skull reconstruction should be performed on patients with skull lesions that are compressing brain tissue.

Biopsy

Biopsy, an important step in the diagnosis of MM, must be preceded by careful clinical evaluation and assessment of imaging findings. Needle or open biopsies can be performed. The choice of type of biopsy depends on how superficially the lesion is located, how much trauma would be involved, whether the lesion is operable, the proximity of the lesion to important nerves and vessels and the possible influence on subsequent treatment. Orthopaedists and hematologists should review all image data and discuss the procedure before biopsy. Needle tract seeding is a complication of bone biopsy of malignant tumors; however, it is still unclear whether or not such seeding commonly occurs in MBD[41]. Myelomatous infiltration of soft tissues following internal fixation of a pathological fracture has been reported[42].

Rehabilitation

Without postoperative rehabilitative training of limbs, joints and lower back muscles, patients may develop muscle atrophy, joint adhesion and joint stiffness. After surgery, patients should therefore perform functional exercises and try to walk as soon as possible under their doctors' instructions with the aim of restoring daily living and improving the quality of life.

Postoperative rehabilitation should be carried out step by step. In the early stage (the first week) after surgery, passive exercises are performed with the assistance of patients' relatives, nurses or physical therapists. In the second postoperative week, patients with MM lesions in the spine should perform lumbodorsal muscle exercises (15–30 min every time, three times per day) and straight-leg-raising (both lower limbs alternately, 30 times per day). Flexion and extension exercising of joints should be performed postoperatively provided the lesions are not located adjacent to joints. Patients with lesions in the extremities should perform exercises to enhance muscle strength before they begin ambulation with the help of a walking aid in the third week.

These exercises should be performed harmoniously and gradually; excessive exercise is inadvisable. Psychological rehabilitation training should also be considered and clinicians should reassure and encourage the patients before and after surgery.

Postoperative Follow-up

Follow-up evaluations include pain score (VAS), neurological function (Frankel grade), bladder and bowel function, sexual function, and quality of life (Karnofsky scoring system). Skeletal X-ray films, CT or MRI images should be obtained 1–2 weeks postoperatively. Patients with MM are usually followed up 6 weeks, 3 months, 6 months and 12 months after surgery. Overall survival data can be obtained by telephone or in the out-patient clinic in cooperation with the hematologists.

Patients receiving follow-up chemotherapy should have full blood counts, M-protein concentrations in serum and urine and serum creatinine concentrations checked together with bone marrow aspiration every 3–4 months. Skeletal X-ray films or MRI should be performed to detect new bone lesions.

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