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Management of skeletal metastases: An orthopaedic surgeon's guide

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Abstract

Skeletal metastasis is a common cause of severe morbidity, reduction in quality of life (QOL) and often early mortality. Its prevalence is rising due to a higher rate of diagnosis, better systemic treatment, longer lives with the disease and higher disease burden rate. As people with cancer live longer and with rising sensitivity of body imaging and surveillance, the incidence of pathological fracture, metastatic epidural cord compression is rising and constitutes a challenge for the orthopedic surgeon to maintain their QOL. Metastatic disease is no longer a death sentence condemning patients to "terminal care." In the era of multidisciplinary care and effective systemic targeted and nontargeted therapy, patient expectations of QOL, even during palliative end of care period is high. We lay emphasis on proving the diagnosis of metastasis by biopsy and histopathology and discuss imaging modalities to help estimate fracture risk and map disease extent. This article discusses at length the evidence and decision-making process of various modalities to treat skeletal metastasis. The modalities range from radiation including image-guided, stereotactic and whole body radiation, systemic targeted or hormonal therapy, spinal decompression with or without stabilization, extended curettage with stabilization, resection in select cases with megaprosthetic or biological reconstruction, percutaneous procedures using radio frequency ablation, cementoplasties and discusses the role of emerging modalities like high frequency ultrasound-guided ablation, cryotherapy and whole body radionuclide therapy. The focus lies on the role of multidisciplinary care, which considers complex decisions on patient centric prognosis, comorbidities, cost, feasibility and expectations in order to maximize outcomes on QOL issues.

Key words: Bone metastases, pathological fracture, skeletal metastases
MeSH terms: Metastases, fracture, pathological, bone cancer

Introduction

Bone is among the most frequent sites of metastatic disease next only to lung and liver. Approximately, 70% of patients who die of breast or prostate cancer have also had bone metastases.[1] Thyroid, lung, and kidney cancers also have a propensity to involve the skeleton. Approximately, 30-65% of patients with metastatic lung cancers will develop bone metastases,[2] as will approximately 47% of patients with advanced thyroid cancer and 30% of patients with advanced renal carcinoma.[3] It is reported that 9-29% of patients with metastases will have a pathological fracture[4] and 90% of fractures require surgery.[5] With advances in treatment, patients with cancer, especially prostate and breast cancer are living longer and thus there is greater responsibility on the orthopedic surgeon to preserve the quality of life (QOL) by preventing and managing skeletal-related events (SRE). SRE include pain, vertebral fractures, cord compression and pathological fractures of long bones. All these have an impact on mobility and functional independence and therefore greatly impact the QOL.

A lot has changed in the last decade in terms of imaging, detection, medical and surgical management. Management of skeletal metastases is no longer a simple task of fixing a fracture, but involves a multidisciplinary coordination between medical oncologists, radiation oncologists and the surgeon. This article updates the orthopedic surgeon on the current concepts in workup and managing skeletal metastases.

Imaging Modalities in Metastatic Disease

The radiographic appearance of metastatic bone tumors have traditionally been described as osteolytic, osteoblastic, or mixed lytic and sclerotic [Figure 1]. Recently, an

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osteoporotic pattern has been described where the lesions appear as "faded" bone without discrete areas of cortical destruction or increased density in theX-ray.[6] It is estimated that there is at least 25-75% loss of mineral before a lesion is visible on X-ray[7,8] implying that the bone is already significantly weak by the time the lesion is radiologically visible. The extent of bony destruction helps assess the risk of fracture. Lytic lesionsdestroying 50% or more of the diaphyseal cortex can result in a 60-90% reduction in bone strength, significantly increasing the risk of fracture.[9]

Some rough guidelines for prophylactic fixation have been proposed based on the amount of cortical destruction on X-rays. Fidler[10] in 1973 suggested prophylactic fixation of the long bone for more than 50% cortical destruction. In 1982, Harrington,[11] after a review of the literature, added the criteria of lesion length more than 2.5 cm, fracture of adjacent lesser trochanter and persistent pain after radiation. It was far too simplistic not factoring several variables and therefore not accurate. In 1989, Mirels[12] proposed a more refined system [Table 1]. Prophylactic fixation was recommended for a score greater than 9 which predicted a 33% risk a score <7 had a low risk of fracture. Though not categorical or absolute, subsequent studies have validated this system as having high sensitivity but low specificity.[12-14]

More accuracy would involve algorithm based evaluation of computerized tomography (CT) images compared withthe opposite side to assess the bony rigidity. This has been used and reported for children with benign tumors.[15] CT-based finite element modeling has also been used to predict fracture risk in long bones.[16] Magnetic resonance imaging (MRI), Dual energy X-ray absorptiometry (DEXA) and quantitative CT have been tried to evaluate fracture risk in vertebral bodies.[17] Once developed, these would provide a far higher accuracy in estimating fracture risk. Currently, however, none of these can still be used practically in the clinic, and Mirels score remains the standard of care. Despite all the enumerated scoring systems to predict fracture risk, pain at rest and activity remains the single most sensitive symptom to predict fracture risk and increasingly more clinicians rely on this to make judgment calls despite equivocal scores.

Computerized tomography and MRI can evaluate suspicious findings on Technetium-99 (99mTc) bone scans and can provide better spatial resolution and three-dimensional anatomic information about the skeleton as well as softtissue involvement [Figure 2]. CT is excellent at assessing the

Table 1: Mirel's score

Score	Site	Pain	Lesion	Size[b]
1	Upper limb	Mild	Blastic	<1/3
2	Lower limb	Moderate	Mixed	1/3-2/3
3	Peritrochanteric	Functional[a]	Lytic	>2/3

[a]This is pain on functional use like weight bearing in lower limb, [b]Size is amount of cortical circumferential segment involved. Mirel's score – >9=High risk of fracture, <7=Low risk of fracture

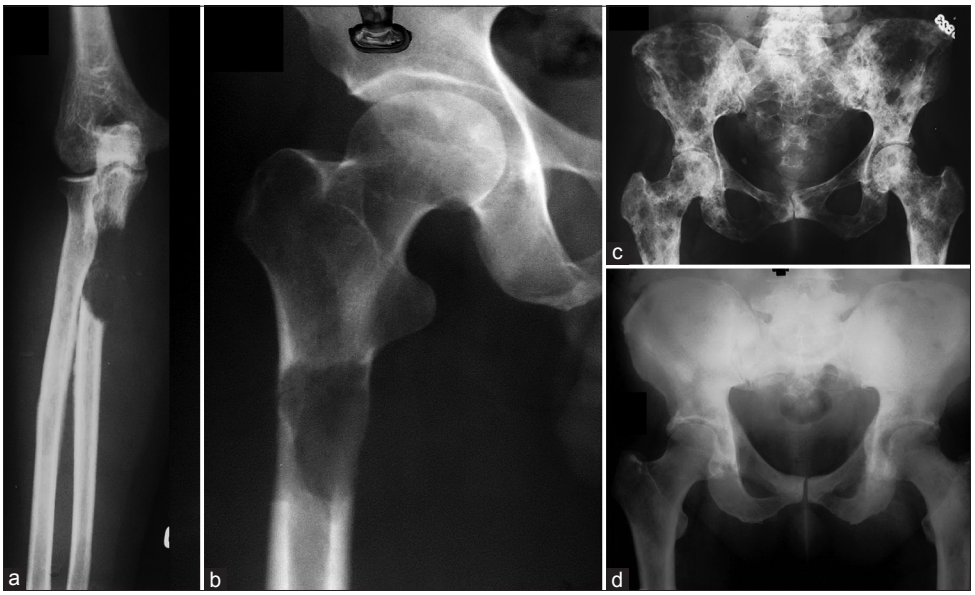

Figure 1: Varied radiological appearance of metastasis-lytic, mixed and blastic. (a) The radiograph of forearm with elbow joint anteroposterior view showing lytic metastasis from lung carcinoma occurring distal to the elbow (Note that metastases below the knee and elbow are rare) (b) The radiograph of hip joint with proximal thigh anteroposterior view showing an impending fracture from a lytic metastasis arising from a colonic primary. Pure lytic lesions are common with renal, lung, thyroid, uterine, adrenal, GI malignancies and melanoma (c) X-ray pelvis with both hip joints anteroposterior view showing extensive lytic and sclerotic metastases to pelvis and both femori from breast cancer. Mixed lesions are known with breast, lung, ovary, cervix, testicular malignancies and lymphoma (d) X-ray pelvis with both hip joints anteroposterior view showing pure sclerotic or blastic metastasis arising from a prostate carcinoma in a 70-year-old male. Pure blastic lesions are common with prostate, bladder cancers, medullary carcinoma thyroid and bronchial carcinoids

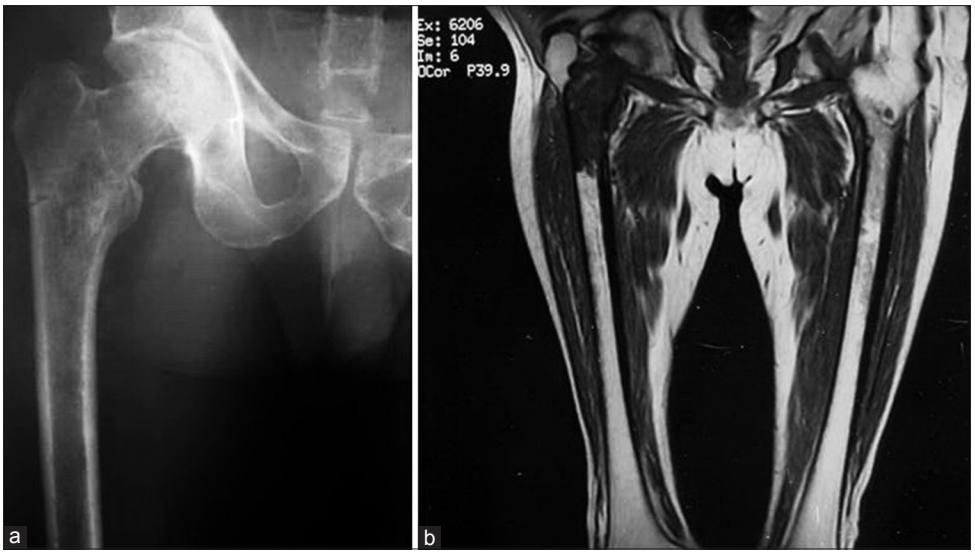

Figure 2: The plain radiograph (a) Underestimates the disease extent identified on magnetic resonance imaging (MRI) images (b) MRI can also identify and delineate soft tissue involvement, joint effusion, skip lesions and other crucial information like relation to neurovascular structures which can critically affect treatment plan

cortical lesions whereas trabecular lesions may be best seen on MRI.[8] MRI is highly sensitive to detect small skeletal metastases not yet detectable on bone scans by revealing abnormal bone marrow; Though MRI is very sensitive, it cannot help differentiate between infection, fracture or inflammation, all of which cause similar marrow signal changes.

Once a lesion is identified as metastatic disease, the clinician needs to know if the lesion is solitary or if there are other sites of disease. 99mTc bone scintigraphy screens the entire skeleton, is very sensitive and has a relative low cost making it the initial imaging modality for detection of bone metastases. It accumulates in areas of increased osteoblastic activity and increased blood flow. Osteoblastic metastases are, therefore, more reliably picked up. Technetium bone scan is false negative for highly aggressive and rapidly growing lytic tumors like myeloma because of minimal reactive bone formation.[18,19] Lytic lesions can appear as "cold" defects but are frequently overlooked.[7] In contrast to plain films, as little as 5-10% change in the ratio of lesion to normal bone is required to detect an abnormality on bone scan. It is estimated that bone scan can detect malignant bone lesions 2-18 months earlier than the radiograph can.[7] This explains why tumors known to have a propensity for skeletal metastases undergo regular screening with bone scan. Bone scan has published sensitivity rates between 62% and 100%, with a specificity of 78-100%.[7] False positives can occur in any area of high bone turnover related to trauma, infection, or arthropathy.[7,20,21] To overcome lack of specificity, correlative imaging with radiographs, CT, or MRI is recommended, especially in the context of equivocal findings (single "hot spot" or few lesions). Lesions like enchondromas, bone islands or healed nonossifying fibromas can appear as hot spots and need differentiation from a metastatic lesion. These are generally obvious on an X-ray. Sometime CT accurately characterizes the lesion. Single-photon emission computed tomography (SPECT) improves the sensitivity and specificity of 99mTc bone scans for detection of small bone metastases,[22,23] by superimposing the hot spot on a CT cut. A focal hot spot with a lytic area is significant for suspected metastases, but MRI still provides better tomographic images. Tuberculosis, particularly in the spine can be a confounding factor in the Asian subcontinent and can coexist with metastatic disease. We recommend a biopsy prior to treatment in any skeletal lesion. The presence of multiple lesions in patients with a known malignancy is more suggestive of metastatic disease, although other nonneoplastic conditions like infection and arthropathy can also have multifocal areas of uptake. Any suspected lesion is further worked up with local X-rays, a focal MRI or CT. MRI is the most accurate when bony destruction is minimal.

Lytic lesions negative on bone scan are better detected by metabolic scans such as fluorodeoxyglucose-positron emission tomography (FDG-PET) because they have a higher than normal glucose metabolism. The poor specificity of the FDG-PET, as well as its lack of anatomic detailing, makes CT and MRI necessary for further characterization. As FDG-PET relies on glucose uptake by the tumor, it can detect early metastases without any bony destruction. It can also help in assessing the response to treatment by showing a corresponding reduction in activity of the tumor. As more knowledge accumulates, its use is increasing for

several malignancies such as lung, breast, and head and neck cancers. Although FDG-PET is superior in detecting osteolytic metastases, it is less sensitive than 99mTc bone scans for detection of osteoblastic metastases.[24,25] It is thus more sensitive than bone scan for myeloma, equivalently sensitive for breast and lung cancers, and less sensitive for prostate cancer. The aggressiveness of the tumor may also influence the sensitivity of detecting bone metastases using FDG-PET.[26] Skeletal PET using F-18 sodium fluoride (NaF-18), a positron-emitting bone-seeking tracer, may improve the utility of PET. The available literature shows that NaF-18 PET is substantially more sensitive and specific than 99mTc bone scan and SPECT[27,28] for detection of metastases, especially for osteolytic lesions, but has a higher cost and involves greater radiation dose.[29] Addition of CT greatly improves the utility of PET by providing better resolution.[28]

Whole body MRI as a tool for systemic surveillance with its zero radiation and excellent anatomic detailing is useful in myeloma for screening the skeleton but unlike PET cannot be used to assess response. PET MRI is a new modality, which also helps decrease radiation and its potential side-effects, while retaining excellent biologic imaging capabilities. Studies are underway to determine its utility and effectiveness in systemic surveillance.

Biopsy and Tumor Markers

A biopsy is a must to prove that the lesion is metastatic. A needle biopsy generally is adequate for most lesions as it provides a diagnosis in over 90% of cases.[30-32] It is important to accurately target the lesion using image guidance (USG/CT/C Arm). A Jamshidi or other trocar cannula based needle is used for entering the bone. For lesions with a soft tissue mass, a tru-cut spring loaded core biopsy needle is adequate and simple to use. Apart from morphology, immunohistochemistry can help give a clue to the possible primary in metastatic disease. Where the primary diagnosis of malignancy has already been made, an FNAC may be used to simply confirm metastatic disease. If the orthopedic surgeon is unfamiliar with the method of doing a needle biopsy or the pathologist is uncomfortable in reporting on the needle biopsy (this often happens in inexperienced centers), it is best to refer the patient to an oncology setup.

Tumor markers are substances that are detected in body fluids (blood/serum/urine) or in tissue (tumor/marrow/bone) that help diagnose, screen, monitor response to therapy and detect a recurrence by minimally or noninvasive methods. Most markers have been proteins that represent a unique genetic signature associated with a particular malignancy. A few commonly used ones are enumerated in the Table 2.

Table 2: Tumor markers

Tumor marker	Disease	Role
Beta 2 microglobulin	Multiple myeloma, chronic lymphocytic leukemia	Prognosis and response evaluation
Beta hCG	Choriocarcinoma and testicular cancer	Evaluation of recurrence and response evaluation
CA 15-3/ CA 27.29	Breast cancer	
CA 19-9	Pancreatic, gall bladder, bile duct cancer	
CA 125	Ovarian cancer	
Calcitonin	Medullary thyroid cancer	
CEA	Colorectal and breast cancer	
Immunoglobulins	Multiple myeloma and waldenstrom macroglobulinemia	
LDH	Germ cell tumors	
PSA	Prostate cancer	
Thyroglobulin	Thyroid cancer	

PSA=Prostate specific antigen, LDH=Lactate dehydrogenase, CEA=Carcinoembryonic antigen, hCG=Human chorionic gonadotropin, CA=Carbohydrate antigen

In spite of full workup like tumor markers, PET-CT and modern immunohistochemistry, the primary may be unknown in about 3-5% of these cases.[33]

Clinical Presentation and Workup

Pathological fracture or impending fracture or painful bony lesion without any known history or treatment for cancer

This is the commonest scenario in which a patient presents to an orthopedic surgeon. Proximal femur and proximal humerus are the most common sites, but any long bone could be affected. Alternatively, the spine may be involved, with or without a vertebral fracture or neurological deficit. The workup is outlined in Figure 3. It is very important not to assume diagnosis of a metastatic lesion just because the patient is elderly as infections and primary sarcomas can have a similar appearance. It is also equally important not to assume that the fracture has resulted from osteoporosis. Either way, one should not be in a hurry to operate as unplanned surgery can lead to inappropriate treatment with permanent, irreversible harm caused to the patient. Assuming metastatic disease and performing intralesional surgery can be a disaster for a primary bone sarcoma [Figure 4]. This is more likely to happen in the proximal femur where chondrosarcomas also present in the elderly and are not always mineralized. Pathological fracture is not an emergency, and a clinician will find it worthwhile to do a complete workup prior to any surgery.

It is important to pay attention to small details like revealing an unexpected unpleasant diagnosis to the patient and their family. Diagnosis of metastasis is often not a "death

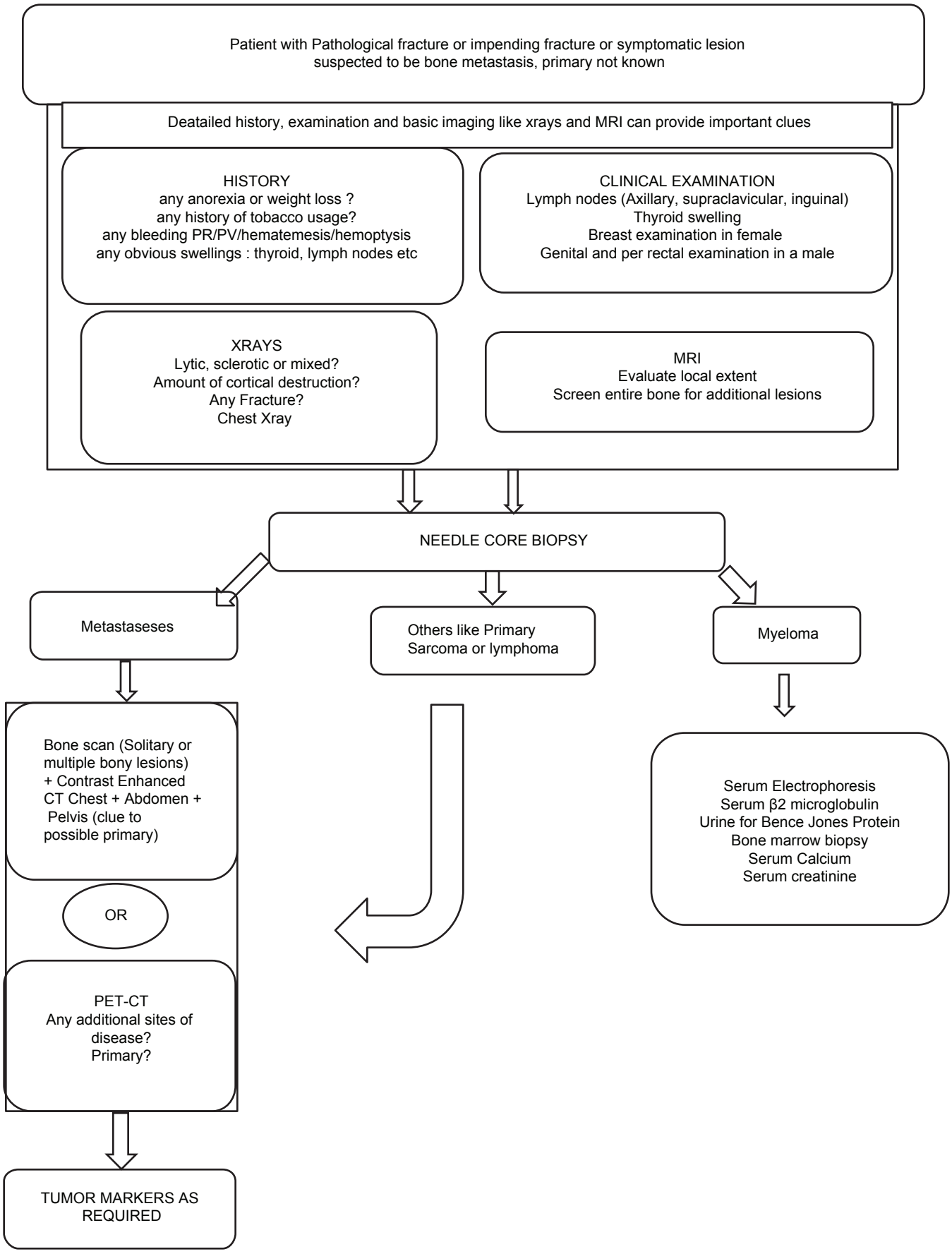

Figure 3: Workup of a patient with a symptomatic bony lesion or impending fracture or pathological fracture from suspected metastases

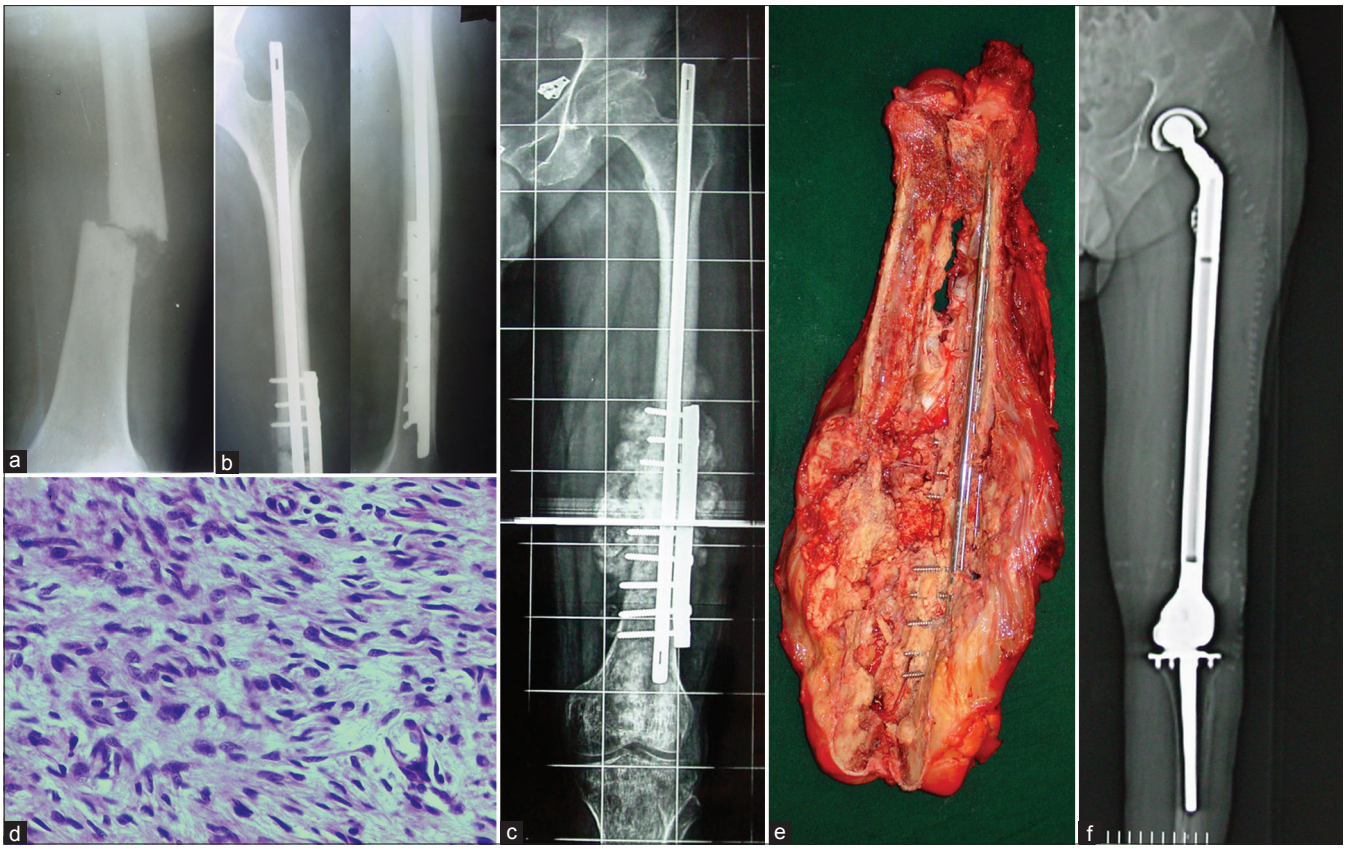

Figure 4: (a) A 50-year-old male with a pathological fracture shaft femur was assumed to have metastasis (b) He underwent immediate fixation with an intramedullary Nail and a derotation plate. No prior biopsy was performed. Figure shows the postoperative X-ray (c) Rapid growth of a bony hard mass at the fracture site a few weeks later prompted a referral. Note the exuberant bone formation (d) Histology proved to be an osteosarcoma (e) Resection involved removing the entire femur. Specimen is bivalved to show the tumor (f) Postoperative X-ray showing the total femur replacement. This would not be necessary were a proper workup done prior to surgery

sentence" and must not prompt resignation and advice for "terminal palliative care." In modern times, patients with metastatic disease can live for several years and early referral to a multidisciplinary oncology team is advised. Once the decision for surgery is made at a multidisciplinary meeting, the surgeon can choose the surgical strategy outlined in the sections below. It is important to estimate a patient's general condition, disease stage and expected survival prior to embarking on any intervention.

Primary is known: The skeletal lesion is picked up on workup or during periodic followup

This presentation is now becoming more frequent as routine surveillance screening with a technetium bone scan or PET-CT often picks up an asymptomatic bony lesion or on followup. Alternatively a bony lesion is detected because of symptoms in a patient known to have a primary cancer. Asymptomatic lesions tend to be smaller, and an opinion is sought by the treating oncologist as to the best line of treatment. A surgeon must not assume that a lesion is metastases even if the primary is known [Figure 5] as infection, benign lesions or primary bone sarcomas (second malignancy) can confound the diagnosis. A needle biopsy can establish the diagnosis. A discussion with the multidisciplinary team which includes at least a medical oncologist and radiation oncologist and preferably also

Figure 5: This 54-year-old lady was treated for breast cancer 4 years prior to having this pathological fracture through the proximal femur. It was assumed to be metastasis. A radiologically obvious chondrosarcoma was missed. The treatment and prognosis were radically different, reinforcing the need for histopathological confirmation with a biopsy

an interventional radiologist is required to make the final treatment decision.

Treatment of Skeletal Metastases

The treatment of skeletal metastases is aimed first at maintaining or improving QOL and then at disease control and possible cure. Asymptomatic Metastases detected on workup may require systemic therapy and radiation, primarily aimed at disease control and preventing SRE that include pain, cord compression and fracture. For symptomatic lesions, the treatment is aimed at pain elimination and maintaining ambulation and neurological function. For every lesion, a decision is made by a multidisciplinary team regarding need for analgesia, radiation, systemic medical treatment (chemotherapy, hormonal therapy, targeted therapy or agents to improve bone strength) and need for intervention either minimally invasive (radiofrequency ablation [RFA], cementoplasty, vertebroplasty etc.) or open orthopedic surgery (decompression of spinal cord or vertebral or long bone stabilization). Decision making is best-customized to the individual patient but still based done on evidence-based protocols. With the improvement in systemic treatment, radiation as well as percutaneous interventions, the need for open surgery is much reduced. Logically, the least invasive methods are used upfront reserving the surgical option for the nonresponsive cases in pathological fracture or paraplegia from spinal cord compression.

Bone strengthening (systemic treatment) treatment for prevention of skeletal-related events

The advent of bisphosphonates revolutionized prevention of SRE in both lytic and blastic metastases. By their action on bone turnover they exerted numerous beneficial effects like decreased lysis and associated hypercalcemia, reduced microfractures and insufficiency fractures and associated pain and vertebral fracture induced cord compressions resulting in reduced hospitalizations and improved QOL parameters. These drugs have been useful in pure lytic, blastic and mixed lesions. Zoledronate and pamidronate are time tested pyrophosphate analogues that the work by inhibiting farnesyl pyrophosphataseand causing osteoclast lysis and apoptosis.[34] There is also some evidence suggesting direct antineoplastic activity. Bisphosphonates have been shown to reduce bone-related skeletal events and are widely used for bone metastases in breast cancer, multiple myeloma, lung cancer, and prostate cancer (which also has a level of osteolytic activity).[35,36] The primary side-effects associated with bisphosphonate treatment include anemia, gastrointestinal symptoms (e.g. nausea, vomiting, diarrhea, or constipation), fatigue, fever, weakness, arthralgia, myalgia and less commonly, hypocalcaemia. It is essential to measure serum creatinine before zoledronic acid administration and adjust dosage for renal insufficiency. Since bisphosphonates are known to decrease Vitamin D levels, it is recommended to supplement Vitamin D and calcium before and throughout the duration of bisphosphonate treatment. Osteonecrosis of the jaw (ONJ) is rare, but serious complication of bisphosphonate use most commonly associated with the amino bisphosphonates. A dental evaluation and preemptive dental treatment is recommended to reduce ONJ.[37-39]

Denosumab, a fully human monoclonal antibody to RANKL, is a more potent inhibitor of osteoclastogenesis andbone resorption than bisphosphonates. It has been approved for the treatment of postmenopausal osteoporosis as well as bone metastases from solid tumors and multiple myeloma. It has convenient subcutaneous dosing and is virtually free of immediate adverse events. The incidence of hypocalcemia is a little higher[40] making Vitamin D and calcium supplementation mandatory. The incidence of ONJ is similar but acute reaction like bodyache and flu-like syndrome is much less common than with bisphosphonates.[40] Denosumab was reported superior to zoledronic acid in preventing SRE in a recently concluded randomized trial.[40] It was also easier to administer, it had virtually no short term side-effects and did not need dose adjustments for renal toxicity. The main drawback currently is its high cost. The dosing schedule in all trials has been 120 mg subcutaneously as a monthly dose.

Radiation Therapy

External radiation has a strong role in palliation of pain and local tumor control. Various forms of radiation include external-beam radiation therapy (EBRT) given as multiple fractions or as a single fraction in high dose, stereotactic body radiotherapy and cyber knife radiosurgery. Sophisticated methods of two-dimensionaland three-dimensional conformal radiation therapy (RT), image-guided intensity modulated RT and tomotherapy, have improved precise delivery of radiation and minimized side effects.

The decision for dosage and fraction is determined by location, symptoms, tumor volume and indication for treatment viz. palliation of pain versus medium term tumor control. In most cases for palliative pain relief, equal pain relief is noted by conventional 30 Gy given in 10 fractions versus single dose of 8-10 Gy.[41] Although rate of re-radiation is higher in a single fraction group,[42] it is attractive for its convenience and rapid relief. Evidence shows no difference for response in spinal versus non spinal site and histology of the disease.[41-43] The decision is thus made on life expectancy and patient expectations viz. a patient who has a life expectancy of less than 3 months shall most likely benefit by a single fraction high dose strategy.

The role of hemi-body or whole body radiation is going down with increasing availability of radionuclide therapy that is especially useful in multiple sclerotic bone metastases. Radioiodine is a part of standard treatment for metastases from thyroid cancer. The isotopes for palliative painrelief in use include strontium 89, samarium153 and phosphorous 32. Samarium is the most commonly used isotope in the North American continent. These radionuclides attach to hydroxyapatite and are effective in areas of increased bone turnover. Side effects include debilitating marrow depression which may worsen with repetitive and heavily pre-treated patients. In most cases, adequate repetitive treatment is possible with a tolerable myelosupression. Access and availability in India is yet an unresolved issue. There are no randomized trials evaluating the efficacy of combining bisphosphonates or denosumab with RT. A recent Cochrane review showed equal efficacy of various radionuclides in symptom relief and marrow suppression.[44]

A radiation oncologist's opinion on radio responsiveness of the disease to be treated is a must. E.g., radio resistant painful skeletal metastases from renal cell cancer are unlikely to respond and perhaps are best treated with a surgical modality.

Minimally Invasive Modalities

Upto 30% of patients do not have adequate relief after EBRT. In the modern world, percutaneous modalities like RFA, cryoablation and high intensity focused ultrasound and microwave can relieve the pain and improve bone strength without risk of morbidity from open surgery. RFA is the most common modality used, and multiple studies have shown successful pain relief, decrease in opioid use, and improvement in QOL with minimum complications.[45-47] Most studies have combined cementoplasty (cement injection) after RF ablation particularly for periacetabular lesions. Upto 80% patients have improvement on pain and mobility scores and are able to ambulate independently with low interventional morbidity and complications.[48,49] Cryoablation, with its ability to visualize the ice ball beyond which there is no thermal injury has an advantage over RFA where burn margins are not visible on CT. The postoperative inflammation and pain reported by RF ablated patients seems to be less in cryoablated patients. Although not compared head to head with RF ablation, cryoablation seems to be an attractive modality.[50,51]

High intensity focused ultrasound (HIFU) uses focused ultrasound energy to generate heat. Magnetic resonance guidance is used with HIFU to allow accurate visualization. Published data shows promising results with almost complete pain relief in a high percentage of individuals.[52-56] Lesions less than a cm from the skin surface are unsuitable due to the risk of skin burn. Microwave is another form of thermoablative method under investigation with the advantage of higher ablation volume and faster ablation time.[57-60]

Decision making factors and perioperative considerations

Once a lesion has been completely characterized by full workup including a biopsy, a plan of management is made. Very few conditions like a fracture or impending fracture or neurological deficit warrant early or emergent surgery. Even in emergency, an MRI followed by a biopsy and frozen section can provide a diagnosis in a very short time. If metastasis is strongly suspected as when the primary is known and imaging documents multiple lesions, a frozen section at time of surgery can be used before proceeding to intralesional palliative surgery. This approach is contraindicated in solitary lesions where resection may be considered for metastatic disease and where there is a higher likelihood of the lesion being infection, primary sarcoma or another nonmetastatic lesion. A surgeon must assess whether surgery will provide a QOL. Fixing a painful fracture even in a nonambulatory patient with a limited lifespan is justified if pain relief was not obtained through pharmacological methods or other nonsurgical methods. The most common indications for surgery would be a pathological fracture or an impending fracture. Failure of nonsurgical treatment and pain is also an indication for surgery.

After full staging, a decision is made whether the intention of treatment is curative or palliative. For instance, a patient with operable renal cell cancer and a solitary bone metastasis in femur is selected for R0 resection at both the sites of disease, whereas, same disease with multiple skeletal and spinal metastases is selected for intralesional treatment with palliative intent. The expected lifespan also is an important decision making factor. A longer lifespan favors resection rather than the curettage, for example in hormone-sensitive breast cancer with multiple skeletal metastases and impending fracture of the femoral neck. Longer survival increases the risk of local recurrence with an intralesional surgery and therefore resection may be preferred. It is better to overestimate the survival than underestimate as resurgery in metastatic disease may not be possible or may be risky with advancing disease and deteriorating general condition. The site of disease also matters as disease close to the joint is best resected whencompared to diaphyseal disease. Tumors non-responsive to radiation like renal cell cancer are more likely to require surgery. An unfit patient with poor general condition, coagulopathy or hypercalcemia will also not be a candidate for surgery. Conditions like parkinsonism

that make a patient unreliable for following instructions of limited weight bearing make the surgical option more likely. Finally, the experience and expertise of the surgeon as well as available infrastructure facilities will decide the option of treatment. For example, nonavailability of tumor embolization may go against doing the intralesional surgery in the proximal femur for a large thyroid metastasis.

Once surgery is considered, other factors must be considered that will affect the patient outcome. The patient should have a general condition which allows them to withstand the stress of an operation. Many cancer patients are elderly and have limited physiological reserve due to age or the treatment particularly chemotherapy. It is estimated that 60% of patients may have medical comorbidities.[61] It is important to have a physician and anesthetist evaluate this prior to surgery. Highest mortality related to surgery and anesthesia occurs from cardiac-related events. Patients with renal failure are at particular risk for nonfatal perioperative complications (60%), particularly hyperkalemia, pneumonia, and hypotension.[62] The serum albumin is a quick method to screen the patient's nutritional status. A serum albumin less than 2 g/dL is an indicator of severe nutritional impairment and a risk for wound healing problems.[63] Cancer patients often suffer from an array of electrolyte disturbances related to calcium, magnesium, potassium, sodium and phosphorus which may require correction prior to surgery. The importance and risks with these are commonly underestimated. The risk of hypercalcemia in particular is high and has been estimated to be 5-20%.[64]

Ewer and Ali[65] offer a risk categorization that is geared specifically to oncology patients, which is based on the physical examination, laboratory data, cardiac function, arterial blood gases, and ventilation mechanics. Nonsurgical methods are recommendedfor patients in the high-risk category.

Blood transfusions are frequently needed perioperatively. Oncology patients are often immunocompromised and susceptible to blood-borne pathogens, in particular, cytomegalovirus. Irradiated blood products reduce the risk of this transmissible viral agent. Leukocyte depletion filters reduce the febrile reaction. Intraoperative autologous blood transfusion can reduce the need for banked blood particularly in planned elective surgery. Platelet transfusions and Fresh frozen plasma may be required to correct coagulation disorder. Preoperative tumor embolization upto 24–36 h prior to surgery particularly for very vascular lesions like metastases from kidney and thyroid cancer can reduce the bleeding and need for transfusion.

Deep venous thrombosis is also a perioperative risk both from the malignancy and from immobility in these patients. Adequate prophylaxis or sometimes placement of filters in the inferior vena cava may be required.

Cardiopulmonary dysfunction and hypotension arising from marrow embolism during or following intramedullary instrumentation either for nailing or joint replacement is an underestimated and potentially fatal but avoidable complication.[66] This results from release of showers of vasoactive, inflammatory and thrombogenic substances from the intramedullary canal.[67] The risk of systemic hypotension after manipulation and pressurization of the femoral canal is highly variable and has been reported from 5% to 50%.[68] Choong reported a 20% incidence of hypotension and mortality of 10% or more has been reported after hypotensive episodes.[67,69] Strategies suggested reducing this incidence include pulse lavage to remove tissue and vasoactive products from the intramedullary canal.[70-72] Flexible, small diameter drive shafts to allow the intramedullary contents to escape up the femoral canal,[73] and proximal and distal venting of the canal to reduce build-up of pressure.[74] Additional steps like maintaining normovolemia increased inspired oxygen and decreased volatile agent concentration,[68] and maintaining aortic perfusion pressure with vasopressors like norepinephrine is recommended.[75,76] It is best to perform this surgery electively in the normal daylight working hours when best anesthesia and surgical expertise is available.[67]

If nonsurgical option is chosen, it avoids dangers of open surgery but involves protected weight bearing with crutches or walker and possible use of external orthosis along with radiation. Fracture risk is still present and can happen without warning. Weight bearing can be resumed once lesion has healed radiologically.

Surgery for spinal metastases

Vertebrae are common sites for skeletal involvement, thoracic followed by lumbar and less commonly cervical and sacral segments. Autopsy studies have shown that as many as 70% of patients with cancer have spinal metastases.[77] Spinal metastases with spinal cord compression occur in 5-14% of cancer patients.[77,78] Most metastatic disease is extradural, but rarely intradural or even intramedullary deposits can occur. Surgical techniques today allow more extensive disease to be tackled with lesser morbidity and sometimes even disease control. The main indications for surgery being restoration of neurological function and spinal stability and rarely disease control.

The MRI is able to assess the extent of epidural disease and cord compression. MRI also reveals if the compression is from the soft epidural tumor or from a bony retropulsed fragment.

Round cell tumors like Ewings sarcoma and lymphoma as well as prostate metastases are extremely sensitive to systemic treatment (former to steroids and chemotherapy drugs and latter to androgen deprivation by castration) and can be given a chance at recovery without open surgery [Figure 6]. Tumors located in the junctional regions such as the occipitocervical, cervicothoracic, thoracolumbar, and lumbosacral junctions and in the mobile segments of the spine (C3 through C6 and L2 through L4) are more likely to be associated with instability. Movement-related pain which is absent on recumbency, more than 50% vertebral height collapse, bilateral facet and pedicle involvement or any subluxation or translation points to instability. Severe instability also requires surgery as systemic treatment is unlikely to provide the required stability.[79]

Historically, surgery without fixation was equivalent to EBRT.[80] Patchell *et al*.[81] showed that surgery with EBRT was clearly superior to EBRT alone in maintaining ambulation. 62% of the patients who were nonambulatory at the time of recruitment regained the ability to walk. Literature reveals ambulatory rates ranging from 74% to 100% after surgery, with 57-82% of nonambulatory patients regaining ambulation.[82] Cochrane database review[83] of 2008 reported that surgery prior to radiotherapy gave better recovery of function in selected cases. The authors suggest that radiotherapy alone may suffice for ambulant patients with stable spines but there is evidence of benefit from decompressive surgery in ambulant patients with poor prognostic factors for radiotherapy and in nonambulant patients with a single area of compression, paraplegia <48 h, nonradiosensitive tumours and a predicted survival of more than 3 months. Improvement in pain has been observed in more than 90% of patients who underwent instrumented stabilization.[84] In contrast, Rades *et al*. in a matched pair analysis found no benefit of surgery with RT compared to RT alone, particularly in elderly patients.[85,86] we would recommend a customized approach taking into account several patient and disease-related factors as discussed above.

Figure 6: MRI T2W sagittal image showing (a) metastasis with cord compression (prostate) (b) Response to orchidectomy can often be dramatic as shown in the image on the right and may obviate the need for immediate surgery

The amount of surgery ranges from simple decompression to an *enbloc* resection and fixation. Several rating scales have been proposed[87,88] especially to aid selection of patients for more extensive resection. Patients with solitary metastases with favorable histology like breast cancer are more often selected for the *enbloc* resections in view of longer life and therefore need to maintain QOL. Solitary Metastases from lung or Renal cancer which are often radioresistant are also candidates for resection rather than simple decompression and fixation.[89] The approach and the fixation are dictated by the lesion and in this modern era of superspecialization, we recommend that the spine specialists be involved in the surgical care of these patients. As a basic rule, one must do the minimum required to achieve the goal of pain-free ambulation for as long as possible. The anterior or posterior approach depends on the exact site, experience of the surgeon and the procedure to be carried out. The posterior approach is most favored due to the ease, familiarity and ability to decompress as well as stabilize well. Preoperative embolization helps reduce bleeding and transfusion-related morbidity particularly in hypervascular tumors like thyroid and renal cell carcinoma (RCC) metastases. Preoperative embolization also allows better vision and therefore better decompression.

Surgery for metastases of appendicular skeleton

The surgical procedure chosen will have to be customized to the region involved, skill and experience of the surgeon, infrastructure available, costs that patient can bear and expected survival.

Solitary lesions require special mention as they are biologically different and associated with better survival. In selected cases, resection of solitary lesions may improve disease-free survival and even cure.[90-94] If the primary is unknown after the extensive workup, a solitary metastatic lesion should be resected rather than treated with intralesional surgery if morbidity is acceptable.[95]

The usual surgical options vary from internal fixation with a nail or plate with or without cement and endoprosthetic arthroplasty. The exact choice depends on the location, amount of bone loss and responsiveness of lesion to systemic therapy. Non responsive lesions are best resected to minimize the risk and morbidity of a local recurrence [Figure 7]. It may be wise to resect those lesions where patient is expected

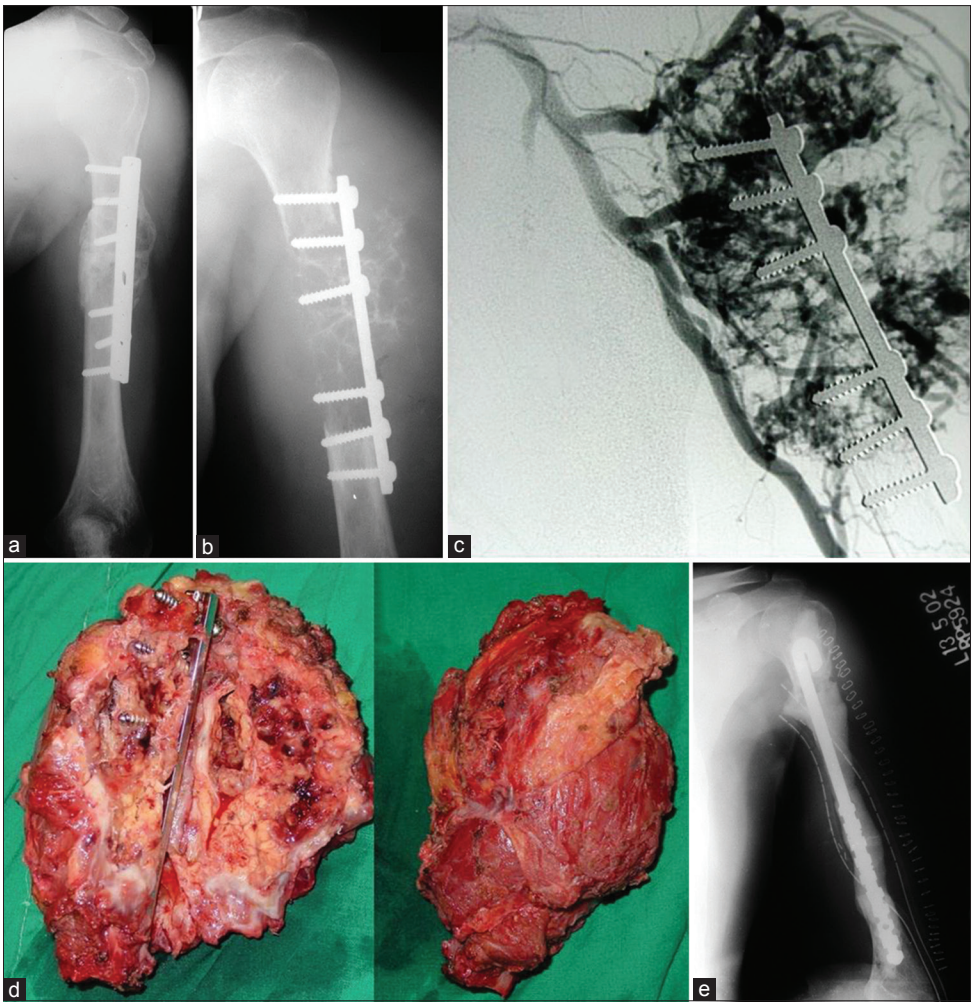

Figure 7: X-ray of the arms with shoulder joint anteroposterior view (a and b) showing local recurrence after previous cementing + fixation in renal cell carcinoma metastasis (c) Angiogram showing the hypervascularity. Preoperative embolisation is a must especially if intralesional surgery is contemplated (d) Resection specimen (e) Postoperative X-ray showing a nail-cement spacer. This is a cost effective construct in the upperlimb and sometimes in the lowerlimb

to have long survival [Figure 8]. Periarticular lesions are often resected and reconstructed with arthroplasty. Diaphyseal lesions can also be resected and reconstructed with a diaphyseal prosthesis [Figure 9] but they are mostly treated with intralesional surgery with or without cement depending on the bone loss. Nails or rods being inside the medullary canal are considered load sharing compared to plates which are external to the bone and considered load bearing. As a general rule, nails are preferred in the lower limbs and plates in the upper limb. Wherever possible, the maximum length of the bone is stabilized inorder to minimize a future fracture at another location. Even when a closed nailing is done for an impending fracture, the lesion should be debulked maximum possible, especially in lesions less responsive to radiation as this reduces the risk and morbidity of local recurrence.[96] Bone cement or polymethyl methacrylate (PMMA) is excellent in filling up areas of bone loss and providing compressive strength to the construct. Bone grafting is, usually, avoided in metastatic lesions as radiation used postoperatively would prevent incorporation. Doses below 3000 rad have been shown not to prevent callus formation.[97] Besides, the goal is to provide immediate mobility for which strength provided by PMMA is ideal. For the same reasons, cemented arthroplasty is preferred over uncemented arthroplasty. With extensive bone loss, resection is preferred. The rate of pathological fracture healing has been reported as 67% for myeloma, 44% for RCC, 37% for breast carcinoma and 0% for lung carcinom.[97] The surgeon is advised to assume that the fracture will not heal, and patient will survive, so that a durable construct is provided. Better to overestimate survival than underestimate. One must keep in mind the fact that a patient operated for metastatic disease may never be fit to undergo another surgery for a complication like implant failure or for local recurrence.

Pelvic and periacetabular defects

Surgery is only required for those lesions that compromise the load transfer from the lower limb to spine. These are

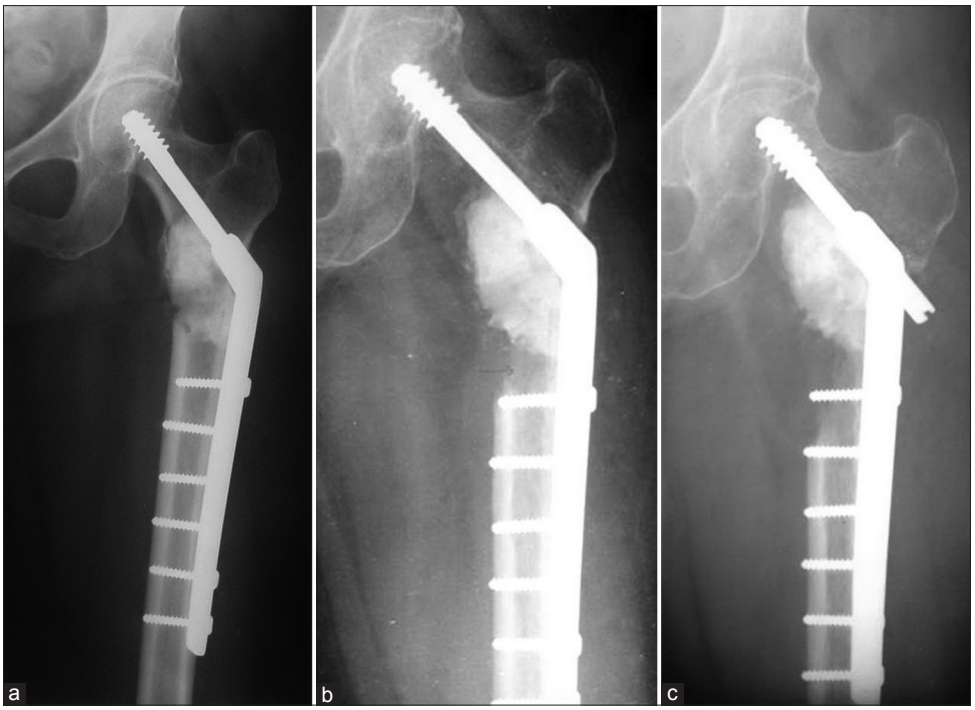

Figure 8: (a) Postoperative X-ray after intralesional curetting and cementing of a metastatic lesion from breast cancer (b) Local recurrence is seen within a year despite postoperative radiotherapy (c) Progressive disease which required resection. In patients with long expected survival, primary resection may obviate need for more surgery in future

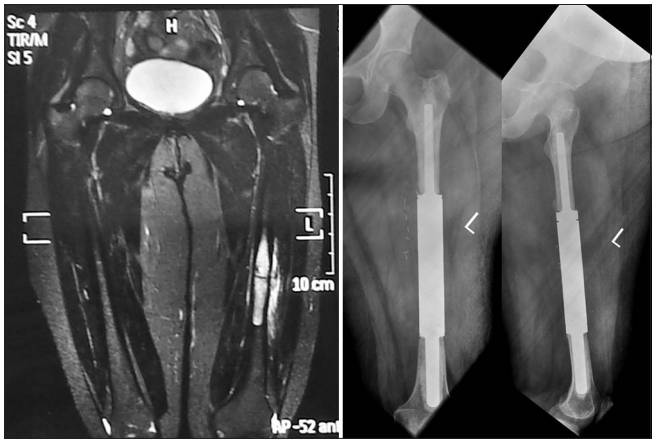

Figure 9: A solitary diaphyseal metastasis from uterine leiomyosarcoma treated with resection and diaphyseal prosthesis. It allowed immediate weight bearing ambulation and preservation of native hip and knee

lesions that affect the superior and medial acetabular walls, as well as the medial column of the pelvis and the posterior ilium in the region of the sacroiliac joint. Posterior Ilium lesions not involving the acetabulum can be treated by intralesional debulking and cement augmentation. Acetabular lesions that are contained (with an intact medial wall) can be reconstructed by a cemented arthroplasty. Uncemented cups run the risk of loosening and migration from failure to osteointegrate from radiation used postoperatively or from osteolysis due to disease progression. Protrusio acetabular cups compensate for deficiencies ofthe medial wall, while cement and pin

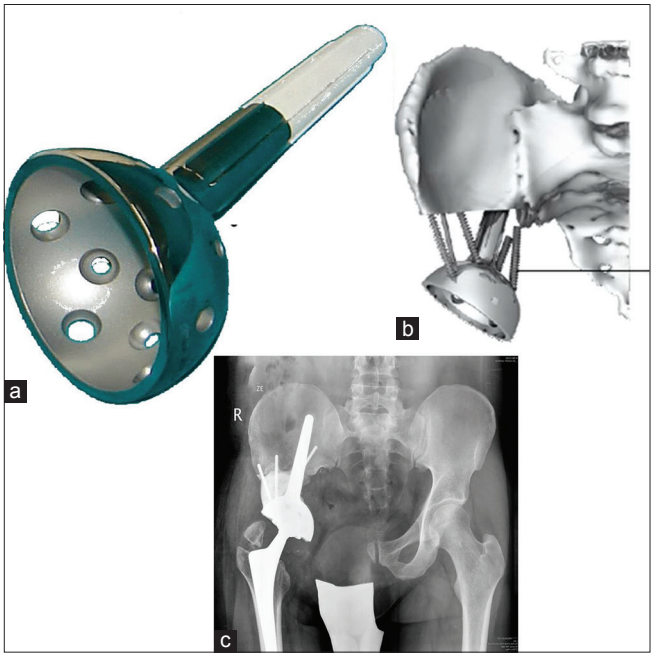

Figure 10: (a) Inverted ice cream cone prosthesis from Stanmore implants worldwide (Stanmore,UK) is useful in reconstructing large periacetabular defects and allows immediate weight bearing (b) The stem is hydroxyapatite coated and anchors in the strong posterior ilium while cement screw struts fashioned allow additional mechanical integrity. It can often be combined with a constrained liner to prevent dislocations (c) Postoperative x-ray showing the implant in place

fixation[5,97-101] (modified Harrington method) can be used effectively to reconstruct large defects in the acetabular

column and dome.[102] Massive bone loss may require resection or reconstruction with an acetabular prosthesis. Stemmed acetabular implants now available (an inverted ice cream cone prosthesis or pedestal cup) allow anchorage of the acetabular shell into the posterior ilium with the stem [Figure 10]. Immediate weight bearing is possible with these implants. Alternatively, a customs acetabular or pelvic prosthesis may be used. As these resections and reconstructions are massive and involve significant blood loss and risk of complications, it is important to have determined preoperatively that the benefits outweigh the risks. Pain relief and immediate weight bearing are the obvious advantages of this reconstruction.[102]

Proximal femur

Lesions of the femoral neck and head are best treated with hip arthroplasty as internal fixation has high failure rate.[100] Hemiarthroplasty is adequate when acetabulum is not involved,[103,104] else an acetabular surfacing is done as well. A routine acetabular replacement would increase the risk of dislocation and is, therefore, reserved for lesions that involve the acetabulum as well. For extensive lesions, proximal femur megaprosthesis is used. A constrained liner can be used in cases judged to be at high risk for dislocation. Cemented stem is preferred as uncemented stems may loosen and fail over a period of time due to nonintegration after radiation or tumor-induced osteolysis. The benefit of a long stem has been that it prevents fracture from another lesion that may appear in the future as entire length of bone can be spanned. However, long stemmed implants increase the chance of embolism from longer canal instrumentation increase.[105,106] The best indication for a longer stem is when a diaphyseal disease is present in addition to the disease in the neck or head. With modern surveillance, should a distal disease appear, it can be tackled on its merit subsequently.

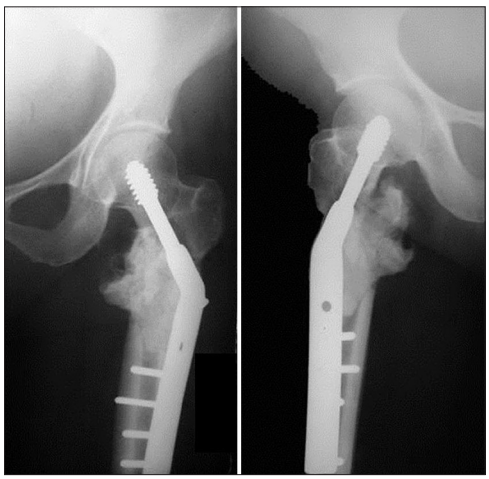

Figure 11: X-ray of hip joint anteroposterior view showing challenge of cementing in intertrochanteric lesions. Calcar has to be built up to allow least chances of failure in a high stress zone

The management of intertrochanteric lesions is more controversial, and opinion is divided between fixation and prosthetic replacement. Most orthopedic surgeons are familiar with the DHS and also the now available gamma nail. If fixation is used it is imperative to confirm that the head and neck offer good purchase as the construct depends on this. The challenge lies in reconstructing the void in the calcar area with cement [Figure 11]. The great advantage is lesser surgery and hip joint preservation. If replacement arthroplasty is chosen, a calcar replacement type or megaprosthesis is chosen.[107] The diseased bone is completely or almost completely excised reducing the risk of local recurrence. Additionally, there is no reliance on that diseased bone for weight bearing. We have generally preferred this option owing to its reliability in restoring ambulation though there is a higher risk of infection, trochanteric fracture or hip dislocation as compared to internal fixation.

The subtrochanteric zone is a high-stress zone with loads reaching 6 times body weight.[108] This poses a great challenge to most internal fixation devices, particularly the nail-plate devices. The implants of choice are, therefore, the intramedullary nail or prosthetic replacement. The nail is preferred for smaller lesions where adequate fixation is possible, and replacement preferred for more bone loss,

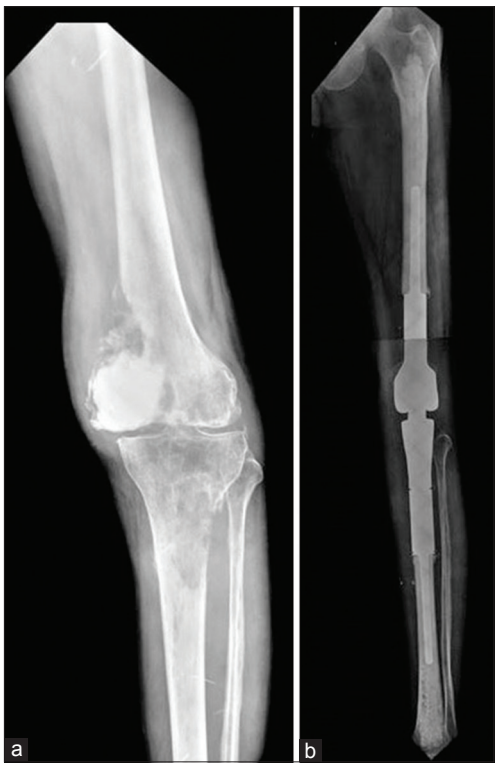

Figure 12: (a) Extensive involvement of distal femur and tibia in a case of renal cell carcinoma resistant to therapy. Intralesional surgery with cement had been done earlier (b) Composite resection of distal femur with proximal tibia over a fixed hinge prosthesis allowing immediate weight bearing

and also if secure purchase in the head and neck is in doubt.

Femoral diaphysis

Lesions of the femoral diaphysis are best treated with an intramedullary nail that not only spans the entire femur but also includes fixation into the femoral neck and head. It is important to ensure that there is no disease in head and neck and that the bone is strong enough for the purchase of interlocking screw failing which failure rates are higher. Calcar replacing or megaprosthetic arthroplasty are preferred in these situations.[107] Titanium nails would be preferred to stainless steel as they can be thinner and stronger allowing lesser instrumentation of the canal and lesser risk of failure. For solitary lesions, resection is done, and reconstruction options available include a diaphyseal replacement prosthesis, a nail-cement spacer or reconstruction with bone (allograft or autograft depending on the length of the defect).

For distal femoral defects, curettage and cementing with or without fixation can be used for smaller defects. Larger defects can be treated with resection and megaprosthetic replacement.

Lesions in Tibia are much less common than in femur and are managed much like in femur. Curettage or resection of proximal tibial lesions depends on the size of the lesion. Sometimes a resection of both distal femur and proximal tibia is required to restore ambulation [Figure 12]. Tibial shaft lesions are treated with the same principles as femoral shaft lesions [Figure 13]. Shows a distal femoral fracture with a tibial lesion in a patient with myeloma treated with a distal femur megaprosthesis and a custom long stem tibial component to bypass the tibial lesion which was curetted and cemented.

Figure 13: (a) Preoperative X-rays of a 70 year old with recalcitrant but indolent myeloma affecting the distal femur and tibial shaft (b) Reconstruction was done in a single step with a distal femur megaprosthesis with a custom tibial tray with a long stem. The patient, a practicing lawyer was back to work in 4 weeks after surgery

Metastases in the Upper Extremity

In contrast to the lower extremity, the upper extremity being non weight bearing has much less need for endoprosthetic reconstructions. Plate or rod fixation with cement is generally adequate for most lesions with prosthesis being reserved for proximal humerus fractures with massive bone loss. Whether a standard Neers type prosthesis is used or a megaprosthesis is used depends on remaining bone stock. Resections generally require a megaprosthetic type of replacement [Figure 14]. This type of replacement is associated with poor shoulder function, as a normal

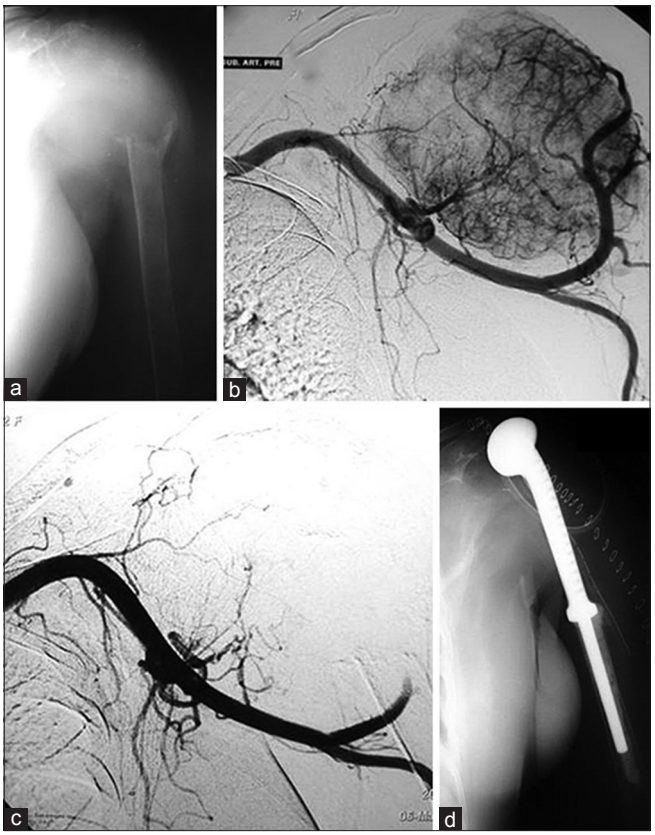

Figure 14: (a) Proximal humeral metastasis from thyroid cancer in a 55-year-old lady (b) Hypervascularity seen on the angiogram (c) preoperative embolization has obliterated hypervascularity (d) Resection was done as thyroid malignancies are associated with relatively long survivals even with extensive bony metastases. Resection greatly minimizes the risk of local recurrence. The embolization makes the surgery easier

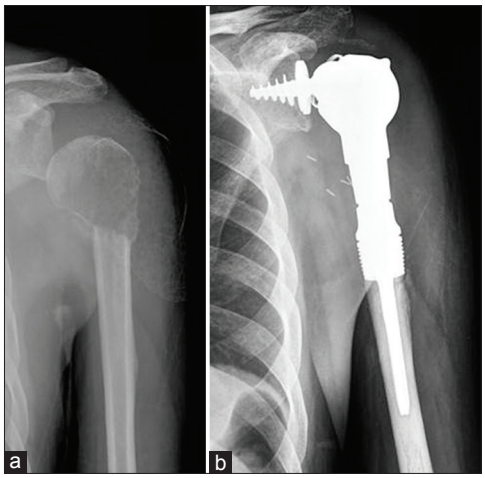

Figure 15: (a) The radiograph depicts a 56-year-old male who presented with a pathological fracture while serving during a game of tennis. Biopsy revealed a metastatic cancer. Positron emission tomography-computerised tomography (PET-CT) showed this to be solitary metastases from renal cell carcinoma (b) Resection and reconstruction with a reverse shoulder type of implant (Stanmore Implants Worldwide, UK) preserving the deltoid muscle and axillary nerve allows better abduction and flexion

attachment sites for the rotator cuff musculature are lost. A reverse type of shoulder prosthesis can be used where glenoid is preserved and where the deltoid muscle and axillary nerve are spared [Figure 15]. A reverse shoulder can provide stability as well as reasonable active flexion and abduction. Both nails and plates can be used depending on the situation as well as surgeon preference. As in the femur, we prefer to fix long to avoid future disease related fractures in the same bone. For scapular lesions, a partial or total scapulectomy is performed generally when resection is chosen. Distal humerus and forearm bone are rarely involved, and resection is required only for large lesions or solitary metastases. Custom implants can sometimes provide good solutions in the forearm [Figure 16].

Conclusions

With the increasing survivals of patients with metastatic disease, a proper workup prior to surgery including a biopsy and early involvement of a multidisciplinary oncology team is recommended. Percutaneous modalities can relieve pain and provide rigidity to bone without the morbidity of open surgery. Surgery should be well planned and properly executed. We emphasize that pathological fractures are not an emergency and proper workup is mandatory before any intervention. The patient's longevity should be over estimated than underestimated, and one must assume that fracture will not heal and plan a construct accordingly. Perioperative steps and intraoperative care can reduce bleeding and embolic events. Resections are done in selected cases particularly for solitary metastases. Wherever possible, an opinion

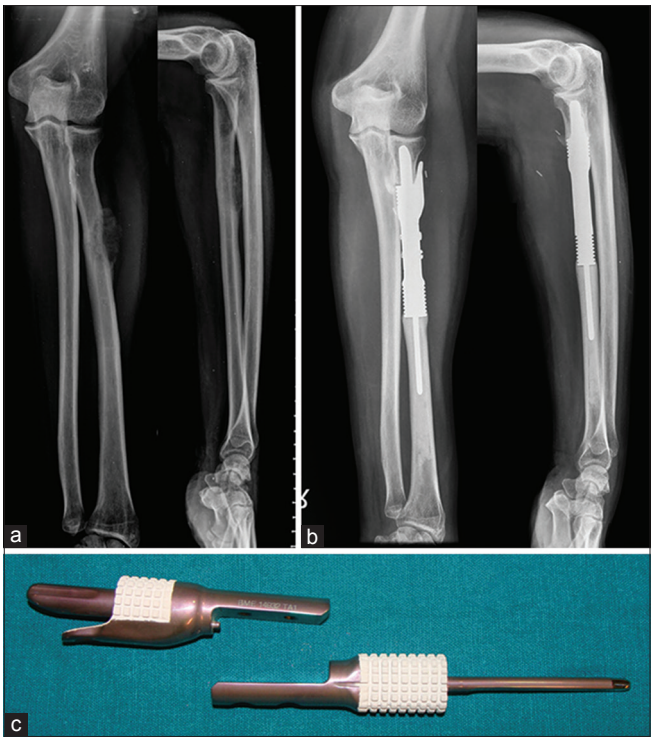

Figure 16: (a) Proximal radius lesion which on biopsy was a metastatic carcinoma. Positron emission tomography-computerised tomography revealed a lung primary with this lesion being a solitary metastasis (b) After chemotherapy, both lesions underwent resection. The radius was reconstructed with a custom intercalary prosthesis (c) Custom prosthesis, proximal and distal segments

from an orthopedic oncologist be sought to ensure that best possible care is being provided. Even if cure is not possible, proper management of metastatic disease can provide QOL for a reasonable amount of time.

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