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Surgical management of bone metastases from urological malignancies: an analysis of 70 cases

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Objective: The purpose of this study was to evaluate symptomatic bone metastases from urological malignancies and the efficacy of surgical treatment of bone metastases in achieving local tumor control.

Methods: This was a retrospective observational study of patients diagnosed with bone metastases from urological malignancies who died from their diseases between 2002 and 2013. Data on clinicopathology, number and sites of bone metastasis, time to first and subsequent metastasis, survival after metastasis, nature of metastasis (blastic, mixed, lytic), type of surgical reconstruction, systemic affections, and visceral organ metastasis for 70 bone metastases from deceased urological malignancies patients (55 male, 15 female) with evidence of bone metastasis were statistically analyzed.

Results: Forty-three patients (61.42%) had renal cell carcinoma (RCC), 15 patients (21.43%) had prostate cancer, and 12 patients (17.15%) had bladder carcinoma as primary diagnosis. Osteolytic lesions were most prevalent (n=61; 87%). The most common surgical modality for extremities was wide resection with prosthetic replacement (42 patients), followed by wide resection or wide resection with bone cement application with internal fixation (21 patients); 65 patients were treated with limb salvage procedures, and 2 patients were treated with amputation. Overall median survival was 13 months for RCC, 16 months for prostate carcinoma, and 11 months for bladder carcinoma patients.

Conclusion: Detection of bone metastases in patients with urological malignancies influences the treatment strategy. Diagnosis of bone metastases may be delayed in urologic malignities; thus, these patients receive long-term clinical follow-up.

Keywords: Bladder carcinoma; bone metastasis; prostate carcinoma; renal cell carcinoma; surgical treatment.

Level of Evidence: Level III Retrospective Observational

Following the lungs and liver, bone is the most common site of cancer metastases and results in the greatest morbidity. Bone metastases can be debilitating for patients, resulting in severe pain, pathologic fractures, spinal cord compression, and hypercalcemia. Moreover, the presence of bone metastases is a strong predictor of patient survival. Prevention of complications caused by bone metastases through early detection can reduce patient morbidity and cost of treatment.

Urological malignancies such as renal, prostate, and bladder cancers have a high incidence of bone metastatic spread, with rates as high as 70% in prostate cancer.[1] Renal cell carcinoma (RCC) is characterized by a lack of early warning signs, which results in a high proportion

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of cases initially diagnosed with locally advanced disease or metastasis. RCC metastasizes via the lymphatic or venous routes, and the lung parenchyma, bone, liver, and brain are the most common sites of metastases.[2,3] Nearly one-third of patients present with metastatic disease, and another 20% experience recurrence and develop metastatic RCC after nephrectomy.[2,4] With regard to prostate cancer, although advances in treatment have extended life expectancy, 65–75% of patients with advanced disease will develop bone metastases, resulting in accelerated bone resorption and a loss of skeletal integrity.[5] Bladder cancer is the second most prevalent malignant disease in elderly men, due to the propensity of the urothelium for metachronous malignant tumors.[6]

As part of the assessment and surveillance of malignancies, clinical assessment, bone markers, radiological imaging, and tissue biopsies are vital tools in the diagnosis of bone spread. The purpose of this study was to summarize the modalities used for diagnosis and surgical treatment of bone metastases and contextualize them with urological malignancies. Additionally, current treatment strategies and outcomes of surgical interventions are discussed.

Patients and methods

This was a retrospective observational study of patients diagnosed with bone metastases from urological malignancies who died from their diseases between 2002 and 2013. Patients' medical records were reviewed and assessed for the following variables: age, sex, histological subtype, number and sites of bone metastasis, Memorial Sloan Kettering Cancer Center (MSKCC) risk score,[7] time to detection of bone metastasis, times to first and subsequent metastasis, survival after metastasis, nature of metastasis (blastic, mixed, lytic), biopsy, type of surgical reconstruction, systemic affections, and visceral organ metastasis. MSKCC data contributes to the outcome, with the criteria as elevated lactate dehydrogenase (LDH) (>1.5 times the upper limit of normal), elevated corrected calcium (>10 mg/dl), poor performance status (Karnofsky Performance Status Scale <80%), anemia (below lower limit of normal), and absence of prior nephrectomy. If any of these factors were present at initial diagnosis, they were considered to have negative prognostic significance. Patients with no risk factors were considered to have good risk, patients with 1 to 2 risk factors were considered to have intermediate risk, and patients with 3 or more risk factors were considered to have poor risk.[7] The type of surgical intervention was decided according to Mirels' Staging System and protocols established by Capanna et al.[8–10]

Descriptive statistics were used for patient demographics and incidence. All survival intervals were determined using the Kaplan-Meier method. Differences in median time to first skeletal-related event were evaluated using the log-rank test. SPSS software version 14.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. A value of $p<0.05$ was con-sidered statistically significant.

Results

A total of 326 patients were analyzed, 70 of whom received surgical treatment for bone and soft tissue metastases. Twenty-seven patients (38.57%) had bone metastasis at the time of diagnosis, and 43 (61.42%) developed bone metastasis after diagnosis. Surgical intervention was performed on 70 lesions in 55 (75%) men and 15 (25%) women (median age: 63 years; range: 35–83 years). Forty-three patients (61.42%) were given a primary diagnosis of RCC, 15 patients (21.43%) of prostate cancer, and 12 patients (17.15%) of bladder carcinoma. The primary metastasis site was the femur in 37 patients (52.85%), humerus in 18 patients (25.71%), tibia in 4 patients (5.7%), and sacrum in 3 patients (4.28%). Iliac wing, acetabulum, and isolated soft tissue metastasis were the primary metastasis sites in 2 patients each (2.85%, respectively). Talus and radius involvement was noted in 1 patient each (1.42%, respectively). Among 60 patients (85.71%) with long bone involvement, 40 patients (57.14%) had proximal metaphyseal involvement, 14 patients (20%) had diaphyseal involvement, and 6 patients (8.57%) had distal metaphyseal involvement (Table 1).

Most patients (n=57; 81.43%) had multiple bone metastases. The spinal column was the most common site of bone metastasis. Spinal column and pelvic metastasis was recorded in 17 patients (24.29%), isolated spinal metastasis was recorded in 13 patients (18.57%), and isolated pelvic metastasis was recorded in 13 patients (18.57%). Metastasis at long bones, rib and sacrum were observed in 14 patients (20.00%). Osteolytic lesions were more prevalent (n=61; 87%) than mixed or osteoblastic lesions (Table 1). Visceral metastasis was present in 33 patients (19 pulmonary, 6 surrenal gland, 5 surrenal gland with pulmonary, and 3 liver metastasis).

Among patients without bone metastasis at primary diagnosis of RCC (n=24), the median time to diagnosis of bone metastasis was 26 months (range: 4–186 months), 14 months (range: 4–34 months) in prostate cancer patients (n=8), and 18 months (range: 5–216 months) in bladder cancer patients (n=11). In the overall population, the median time to diagnosis of bone metastasis was 7 months (range: 0–186 months) in RCC

Table 1. Baseline patient demographics.

Characteristic	Patients (n=70)	
	n	%
Median age (years)	63	35–83
Sex		
Male	55	75.57
Female	15	21.42
Tumor type		
Renal cancer	43	61.42
Prostate cancer	15	21.43
Bladder cancer	12	17.15
Number of bone metastases		
1	13	18.57
>2	57	81.43
Metastasis location of lesion		
Spinal column + pelvis	17	24.29
Pelvis	13	18.57
Spinal column	13	18.57
Long bones	9	12.9
Rib	3	4.3
Sacrum	2	2.8
Lesion type:		
Osteolytic	61	87.14
Osteoblastic	5	7.14
Mixed	2	2.85
Unknown	2	2.85
Bone placement		
Proximal metaphyseal	40	57.14
Diaphysis	14	20
Distal metaphyseal	6	8.57
Unknown	10	14.29
Reconstruction		
ERPF	28	40.0
Resection + Cementing + IF	19	27.14
ERPH	9	12.85
ERPT	1	1.43
ERDF	2	2.85
ERE	2	2.85
Wide resection (soft tissue)	2	2.85
Amputation	2	2.85

ERPF: Endoprosthetic replacement proximal femur; ERPH: Endoprosthetic replacement proximal humerus; ERPT: Endoprosthetic replacement proximal tibia; ERDF: Endoprosthetic replacement distal femur; ERE: Endoprosthetic replacement elbow.

patients, 4 months (range: 0–34 months) in prostate cancer, and 17 months (range: 0–216 months) in bladder cancer patients (Figure 1).

The bone metastasis free time of RCC patients was correlated with MSKCC risk score; the median time between primer diagnosis and bone metastasis in the good risk group was 70 months (range: 0–186 months), 22 months (range: 0–64 months) in the intermediate risk group, and 0 months (range: 0–24 months) in the poor risk group ($p<0.05$).

According to the literature,[7] surgical treatment, especially en bloc resection, is highly recommended for the treatment of solitary bone metastasis for RCC. En bloc resection was selected for solitary bone metastasis, resulting in surgical treatment outcomes that were statistically better than those of multiple metastases ($p<0.05$). In patients with single metastasis, mean survival was 18 months, and in patients with multiple metastasis mean survival was 9 months. RCC patients with solitary bone metastases had better survival rates in comparison with multiple bone and other end organ metastases, concordant with the literature.

Overall median survival was 13 months for RCC patients, 16 months for prostate carcinoma patients, and 11 months for bladder carcinoma patients.

Kaplan-Meier survival analysis is a nonparametric method of summarizing survival event probabilities in a tabular and graphical form. Survival times of 3 major urinary system malignancies are described in Figure 2.

Biopsy was performed for all patients in order to exclude a primary bone or soft tissue malignancy. Incisional biopsy (n=44; 62.86%), trucut biopsy (22; 31.43%) was performed inmost of the patients while in a minor group (4; 5.71%), the diagnosis was confirmed via frozen sections during the surgery. Anatomical sites of metastasis were summarized in Table 1.

According to Mirels' scoring system, 5 patients scored ≤7 points, 21 scored 8 points, and 42 scored ≥9 points. Prophylactic fixation and tumor resection with endoprosthetic replacement in patients with scores of ≥9 points were performed; radiotherapy or chemother-

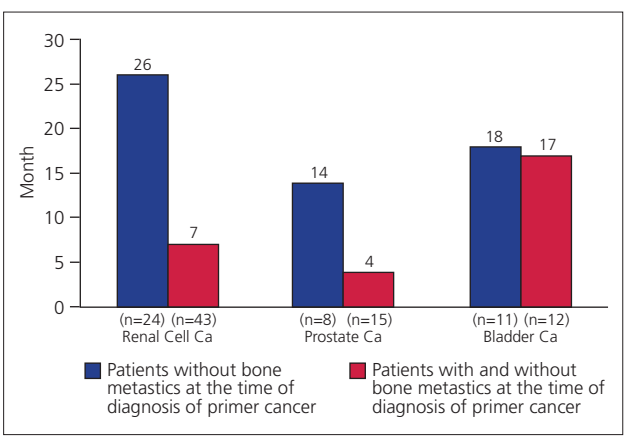

Fig. 1. Median time interval of bone metastasis after the diagnosis of primer cancer (Ca: cancer). [Color figure can be viewed in the online issue, which is available at www.aott.org.tr]

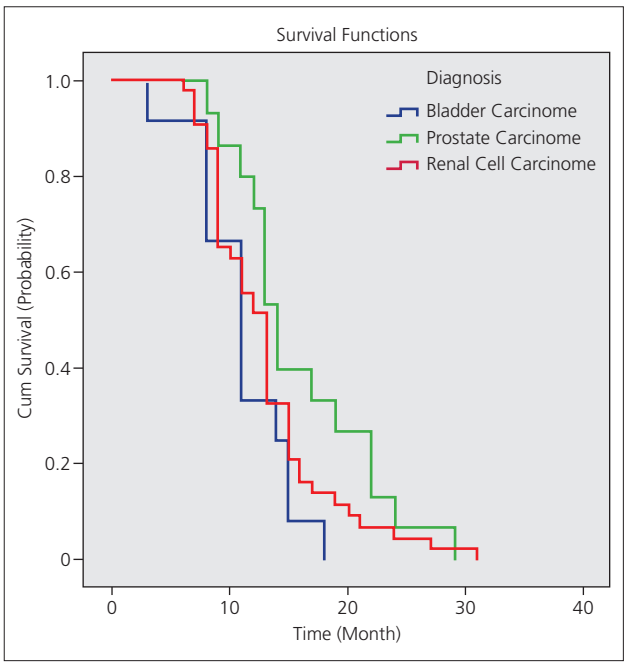

Fig. 2. Kaplan-Meier survival analysis of 3 chief urological malignancies. [Color figure can be viewed in the online issue, which is available at www.aott.org.tr]

apy was administered to patients with scores ≤7 points, and mode of treatment was determined patient specific in patients with scores of 8. This scoring system was not applied to the 2 patients with isolated soft tissue metastasis; these patients underwent wide resection. Ten patients were Class 1, 4 patients were Class 2, 51 patients were Class 3, and 3 patients were Class 4 with Cappana's Staging System.

The most common surgical modality for extremities, was wide resection with prosthetic replacement (42 patients), followed by wide resection or wide resection with bone cement application with internal fixation (21 patients). 65 patients were treated with limb salvage procedures and 2 patients were treated with amputation (Table 1).

The most common site of bone metastasis involvement in 42 patients who underwent wide resection and cemented endoprosthetic replacement with the tumor resection prosthesis femur (n=30; 28 proximal femur, 2 distal femur), humerus (n=11; 9 proximal humerus, 2 distal humerus), and proximal tibia (1 patient). Functional evaluations were made with the Musculoskeletal Tumor Society (MSTS) scoring system.[11] Mean follow-up time was 9 months.

All patients were able to walk without crutches in the postoperative period. Mean MSTS score was 54.9% (range: 35–80%) ($p<0.001$). MSTS scores were higher in the proximal femur prosthesis group.

Discussion

We evaluated surgical treatment of metastatic urological malignancies of the bone, which may be justified to relieve pain and prevent morbidity associated with pathological fracture. Our series represents a highly selective group of patients, as all patients had bone metastatic urological malignacy that had been undergone surgical intervention. Early detection of skeletal metastasis is important for to allow the execution of treatment strategies such as surgical fixation, radiotherapy, or bisphosphonate therapy to improve patient quality of life.[12]

Hypercalcemia is usually due to calcium release as a result of malignant bone destruction. Measuring serum calcium is not routinely conducted as part of urological malignancy assessment, with the exception of RCC.[13,14]

Persistent pain from a metastatic lesion despite medical treatment has also been found to be a significant predictor of increased pathological fracture risk.

The most commonly used imaging modalities are radiographs, radioisotope bone scans, computed tomography (CT), and magnetic resonance imaging (MRI) scans. Lytic bone metastases must be sized >1 cm and have destroyed 30–50% of bone density in order to be seen on radiographs.

CT scans are best at representing bone quality, bone destruction, calcified tumor matrix, and cortical erosions.

Positron emission tomography (PET) and CT scanning are increasingly available, which we selected over isotope scans to determine the extent of tumor spread. Bone metastases detection sensitivity ranges from 62–100%, and specificity ranges from 96–100%.[15] Bone scintigraphy is considered the most reliable method for early detection and monitoring of bone metastases in cancer patients.[16]

MRI scans are highly sensitive and specific and are superior at demonstrating marrow replacement and skip lesions, quantifying edema, and assessing neurovascular involvement.[17]

Generally at the first diagnosis of bone metastasis histological confirmation is adviced via needle biopsy. If the results of needle biopsy is inconclusive and especially the lesion is solitary, open biopsy should be performed.

Cheville et al. found the median time between diagnosis and tumor metastasis was 1.4 years (range: 0-14 years) among 68 patient with bone metastatic prostat cancer.[18] In this study median the metastasis free interval was 4 months (range 0-34 months).

In RCC, distant metastases are found in 30–60% of patients during course of disease, however; fewer than

20% of patients with RCC have overt metastasis at initial presentation.[19,20] In a study by Kollender et al., the median interval from primary diagnosis of RCC to detection of metastatic disease was 7.5 months (range: 0–30 months).[21] In a study by Santini et al., among patients without bone metastasis at primary diagnosis of RCC (n=269), median time to diagnosis of bone metastasis was 25 months (range: 1–288 months). Median time to the appearance of bone metastasis in the overall population was 8 months (range: 0–288 months).[22] In the present study, for patients without bone metastasis at primary diagnosis of RCC, median time to diagnosis of bone metastasis was 26 months, while it was 7 months in the overall population (Figure 1).

In their study Shinagare et al.reported 94 patients with metastatic transtional cell carcinoma of bladder, the mean metastasis free interval was 12 months (range: 0-192 months).[23] In the present study, metastasis free interval was 17 months (range: 0–216 months) in bladder cancer patients.

Options for management of skeletal metastases include radiotherapy, surgery, chemotherapy, hormonal therapy, and immunotherapy.[24]

The goals of surgery for impending or pathologic fracture in the setting of metastatic disease are to provide pain relief and a functionally stable and durable construct. Patients with longer expected survival require more aggressive treatment with wide resection megaprosthetic reconstruction and postoperative radiation therapy. In contrast, patients with shorter expected survival may benefit from a less aggressive treatment with rigid internal fixation and adjuvant radiation therapy.[25] In patients with pathological fractures, wide resection is justified for solitary metastasis, favorable tumor histotype, good general condition, and long recurrence-free interval from treatment of primary cancer. Because of their osteoblastic nature, pathological fractures are rarely seen and have a high potential for union after fixation. Renal bone lesions are most often osteolytic and aggressive; soft tissue expansion is common, and there is very little potential for spontaneous union.

Due to the high vascularity of renal metastases, preoperative selective embolization is recommended to reduce bleeding during the operation. Solitary diaphyseal lesions, particularly from a renal primary, may be resected and treated with an intercalary reconstruction.

Highly stressed anatomical sites are particularly at risk of pathological fracture. These include the neck of the femur, the supracondylar area, and the proximal third and midshaft of the humerus.

The proximal femur is the most common site for pathological fracture and demands surgery in all patients except for those with a life expectancy <6 weeks. Internal fixation of metastatic femoral neck fracture is unwise, given the unacceptably high risk of further subsequent pathologic fracture. Therefore, we prefer to use a cephalomedullary nail, locked proximally and distally for maximum stability, which is biomechanically superior. In more proximal lesions, we prefer conventional arthroplasty or tumor endoprosthesis (Figures 3d–f). In cases where the acetabulum is not involved, we advocate a cemented total hip replacement rather than a bipolar prosthesis. Periacetabular lesions are usually painful under weight-bearing conditions and are at risk of mechanical failure with consequent progressive protrusio acetabuli. Acetabular insufficiency due to metastatic disease is a common problem in patients who undergo total prosthetic replacement.[26] For these reasons, resection of the proximal femur and reconstruction with a cemented modular megaprosthesis is our preferred method of treatment.

Distal diaphyseal femoral lesions have been treated successfully by retrograde nailing, with good pain relief and function achieved in over 80% of cases.[27] Curettage with internal fixation is also an option in the distal femur, particularly using locking plates or unreamed interlocking nails (Figures 3g, h). When more than half of the epiphysis or metaphysis of the distal femur is replaced by tumor, endoprosthetic replacement with a rotating hinge prosthesis is our preferred treatment method.

Endoprosthetic replacement of the proximal tibia is not as successful as in the distal femur because of problems with soft tissue cover. Foot and ankle metastases distal to the knee are far less common than those occurring more proximally. Options for treatment include local curettage with cementation or in some cases below-knee amputation. A metastatic lesion involving less than half of the epiphyseal or metaphyseal area may be treated successfully by open curettage and plate fixation, filling the defect with polymethylmethacrylate. When the lesion involves more than one half of the epiphyseal or metaphyseal area, an intra-articular resection is indicated. Reconstruction of the distal femur and/or proximal tibia may be performed using modular cemented megaprostheses.

The proximal humerus is at risk for pathological fractures because of the extreme bending and rotational forces from the muscle insertions. The recommended treatment for metastases in the proximal humerus is shoulder arthroplasty. While intramedullary nailing–either antegrade, using a standard long humeral nail, or

retrograde–can treat the majority of metastatic lesions in the diaphysis of the humerus, the distal humerus is more complex. Endoprosthetic replacements are available but infrequently utilized (Figures 3a–c). Plating augmented with polymethylmethacrylate bone cement is adequate.[28]

The indications for amputation must be individualized; in general, improper or infected biopsy sites, pathological fractures with large hematomas, neurovascular or joint tumor involvement, and excision of a great muscle unit that diminishes adequate function of the limb are included as such. In the present study, there were 2 cases of amputation.

Patients with urological skeletal metastases must be managed appropriately to improve life expectancy and quality of life. Prognosis is important in determining the appropriate surgical treatment, with simple measures reserved for those with the poorest prognosis and resection and reconstruction reserved for those expected to survive >1 year. Metastases of the prostate are generally early, multiple, and osteoblastic in nature, so they rarely require surgical intervention. Because of the osteoblastic metastasis of the prostate, the pathologic fractures may heal with osteosynthesis, though this is almost impossible in RCC metastases due to their osteolytic nature.

Conflics of Interest: No conflicts declared.

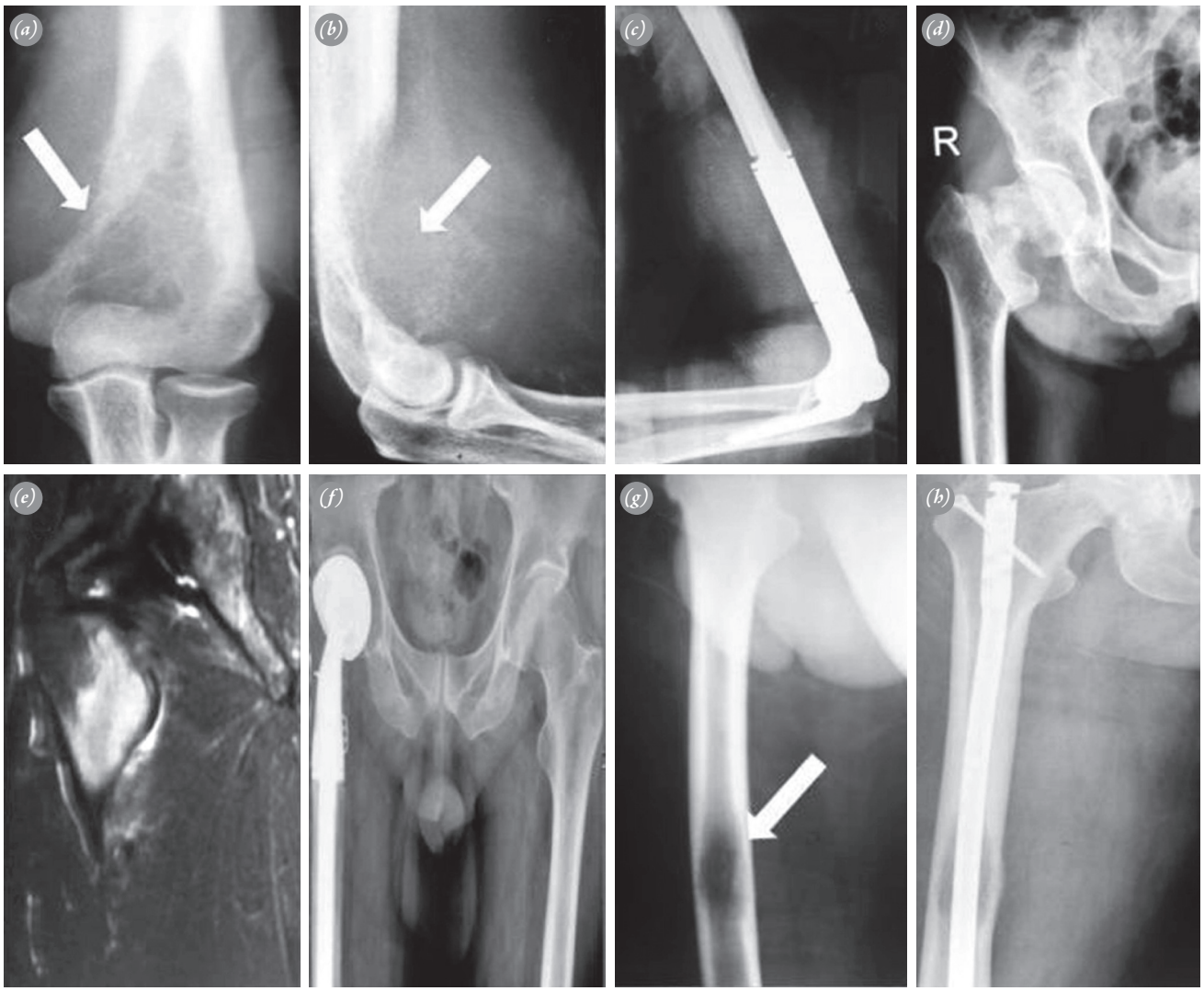

Fig. 3. **(a)** AP and **(b)** lateral radiograph of a single metastasis of renal carcinoma to the distal humerus; **(c)** Postoperative X-ray showing the endoprosthetic replacement of the distal humerus; **(d)** Osteoblastic metastasis of the right proximal femur, showing a pathological fracture on AP radio-graph; **(e)** MRI image; **(f)** Postoperative X-ray of endoprosthetic replacement of the proximal femur; **(g)** Lytic skeletal metastases of bladder cancer of the right femoral diaphysis on AP X-ray; **(h)** Patient treated with an unreamed interlocking nail.

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