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Clinical and radiological evaluation of fracture union in pathologic fractures after closed intramedullary nailing and adjuvant radiotherapy: A retrospective study

Клиничка и радиолошка евалуација спојених патолошких прелома након затвореног интрамедуларног закивања и помоћне радиотерапије: ретроспективна студија

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SUMMARY

Objective/Aim Pathologic fractures are devastating complications in metastatic bone disease. Treatment of these condition varies, including systemic therapies and surgical interventions. Lack of evidence still exists for standardized care.

The aim of this study is to analyze radiological healing response and clinical outcomes after intramedullary nailing and adjuvant radiotherapy in complete pathologic fractures of femur or humerus

Methods A total of 19 patients who presented with pathological fracture were retrospectively reviewed. Data regarding demographic characteristics, clinical outcomes and radiologic images were obtained from hospital records. All patients in this cohort were treated with closed, unreamed intramedullary nailing (IMN) and adjuvant radiation treatment.

Results Pain relief and full range of motion was obtained in all patients. The mean postoperative Musculoskeletal Tumor Society (MSTS) scores at last follow-up were 69% (range 50–85). All patients demonstrated complete radiographic healing between 2 and 6 months. Only one patient required reoperation for refracture at the tip of the nail which was revised with a longer nail.

Conclusion Our study demonstrated that pathologic fractures managed with closed unreamed IMN and adjuvant multifractional 20 Gy dose radiotherapy yielded good clinical outcomes with complete radiologic response regardless of patient's life expectancy, adjuvant treatments and overall condition. Closed unreamed IMN was also associated with decreased surgical time in these high-risk patients.

Level of Evidence: Case series, Level IV

Keywords: pathologic fracture; intramedullary nailing; adjuvant radiotherapy; bone healing

САЖЕТАК

Увод/Циљ Патолошки преломи су тешке компликације у метастатској болести костију. Лечење ових стања варира, укључујући системске терапије и хируршке интервенције. Мањак доказа и даље постоји за стандардизовану негу.

Циљ ове студије је да се анализира одговор на радиолошко лечење и клиничке исходе након интрамедуларног закивања, и помоћне радиотерапије у комплетним патолошким преломима бутне или надлактичне кости

Методе Ретроспективно је прегледано 19 пацијена-та који су имали патолошки прелом. Подаци о де-мографским карактеристикама, клиничким исходи-ма и радиолошким сликама добијени су из бол-ничких картона. Сви пацијенти у овој студији лечени су затвореним, неримованим интрамеду-ларним закивањем (НИЗ) и помоћним третманом зрачења.

Резултати Ублажавање бола и пуни опсег покрета постигнути су код свих пацијената. Средњи постоперативни резултати Друштва за мишићно-скелетне туморе на последњем праћењу били су 69% (распон 50–85%). Сви пацијенти су показали потпуно радиографско зарастање након 2–6 месеци. Само једном пацијенту је била потребна реопе-рација ради прелома на врху клина који је замењен дужим клином.

Закључак Наша студија је показала да су патоло-шки преломи управљани затвореним неинфициран-им НИЗ и адјувантном мултифракционом радио-терапијом од 20 *Gy* дали добре клиничке резултате са потпуним радиолошким одговором без обзира на очекивани животни век пацијента, адјувантне третмане и укупно стање. Затворени неримовани НИЗ такође је повезан са смањеним временом операције код ових високо ризичних пацијената.

Ниво доказа: серија случајева, ниво IV

Кључне речи: патолошки прелом; интрамедуларно закивање; помоћна радиотерапија; зарастање костију

INTRODUCTION

Prolonged survival in patients with carcinoma has increased the overall frequency of metastatic disease. Bone is the third common site after lung and liver. Metastatic bone disease commonly involves the spine, followed by femur and humerus. [1]

Pathologic fractures are one of the disabling complications in metastatic bone disease and comprise 10% of all metastatic bone lesions. These fractures cause severe pain, morbidity and even mortality. [2] Conservative treatment usually is not enough to reduce pain and provide functional improvement. [3] With the improvement in treatment modalities for cancer, implant technologies and surgical fixation, there is overall decrease in complications and the ability to satisfy the treatment goals for these subsets of patients with complex needs. Pathologic fractures should be managed appropriately such that the patient can receive relevant oncological treatment as soon as possible after surgery. Treating orthopedic surgeon must be aware of the compromised healing characteristics of the pathologic bone, increased infection rate and other associated perioperative complications such as thromboembolism and thereby direct treatment accordingly. The primary goal is to obtain immediate functional recovery without causing a delay in application of appropriate adjuvant treatments. This in turn requires an optimal surgical procedure that minimizes postoperative surgical and systemic complications such as pulmonary embolism, implant failure and disease progression. After primary diagnosis of pathologic fracture has been clearly established, timing of surgery and receiving chemo- (CT) or radiotherapy (RT) often need to be addressed in a multidisciplinary approach. Preoperative planning should include patient's expected survival by considering possible complications of available surgical options ranging from stabilization with an intramedullary nailing (IMN) and plate osteosynthesis to resection and endoprosthetic reconstruction (EPR).

Among these, intramedullary fixation has emerged as a preferred surgical technique in the treatment of metastatic bone disease, although it has been reported that healing may not be accomplished. [4, 5] Previous studies demonstrated improved clinical outcomes for surgical fixation and adjuvant radiotherapy; however convincing data regarding radiological fracture healing is limited to small case series. [3, 6]

The aim of this study is to analyze radiological and clinical improvements after unreamed intramedullary nailing and adjuvant radiotherapy in terms of bone healing and clinical outcomes.

METHODS

Between 2016 to 2019, 19 patients with pathological fractures due to solid organ metastases or multiple myeloma were treated with locked intramedullary nailing at our tertiary teaching hospital. This study was approved by the institutional review board. Retrospective chart review was carried out to collect demographic data (age, gender), type of primary lesion, previous history of pathologic fracture and radiotherapy, metastatic status, location of the lesion within the bone, nail dimensions, length of hospital stay, postoperative complications, postoperative survival and functional and radiological outcomes. Inclusion criteria included patients with multiple metastases with pathologic humerus and femur fractures that underwent intramedullary nailing. Exclusion criteria were endoprosthetic reconstruction, inadequate follow-up, incomplete data due to death within 2 months after operation.

Before development of an impending or a complete pathologic fracture, all cases except two patients had a routine follow up by a medical oncology division and appropriate systemic therapy was administered according to treatment protocol of primary disease. Positron Emission Tomography-Computerized Tomography (PET-CT) was used to identify

any other skeletal and visceral metastases in our patients. Pathologic fracture with pain was primary indication for surgery, in accordance with Mirrels' criteria. Patients who were deemed stable with reasonable life expectancy (> 3 months) based on PATHFx estimation, eligible for surgery were operated. Our cases included multimetastatic patients and they were all evaluated by our multidisciplinary tumor board before surgery. Biopsy was preferred for investigating the impending or completely fractured bone lesions as the last step in our diagnostic algorithm. We had first obtained routine laboratory tests and performed radiological investigations. If the patient had an unknown origin of primary lesion (2 patients in our study cohort), percutaneous needle biopsy under general anesthesia was performed. One week after, if the pathology was confirmed as metastatic bone lesion we proceed with intramedullary nailing. In patients with a known primary malignancy, tissue specimen was obtained for frozen pathological evaluation. If the result was confirmed as metastatic carcinoma, then we performed intramedullary nailing as previously planned. No preoperative embolization was performed for relatively vascular lesions like renal cell carcinoma, angiosarcoma and myeloma. Nailing was performed for all metadiaphyseal fractures of the humerus and femur. Fractures involving femoral head and distal end of humerus were excluded.

Follow-up duration was defined from completion of XRT to last clinical/radiologic evaluation. Every patient was followed up for a minimum of two months (range: 2–16 months). The median age at the time of the surgery was 65.5 years (range 53–86 years). None of the patients had any history of prior XRT before surgery. All patients received postoperative bisphosphonate treatment after radiotherapy.

Clinical assessment was made using Musculoskeletal Tumor Society rating scale (MSTS) score. Radiologic assessment was made based on plain radiographs according to

radiological response criteria as described by Harada: complete response, partial response, no change, and progressive disease. [7]

Surgical technique:

Intramedullary nailing of femur: Patient was placed on a traction table in a supine position. Fracture reduction was achieved under fluoroscopic guidance. A 2–3-centimeter incision was made proximal to the greater trochanter and the fascia was split so as to palpate the tip of the greater trochanter. Entry point is determined on the medial face of the greater trochanter. After guidewire was inserted, intramedullary nail (*Trigen InterTan; Smith and Nephew, Memphis, TN*) was inserted with appropriate length and size by using template X-rays. No intramedullary reaming was performed, and no cement was used. Proximal and distal locking was performed. Patients were allowed to weight bear as tolerated immediately after the surgery. Postoperative external beam radiation (20 Gy in five fractions) to the affected long bone was administered at 14 days post-procedure after stitches were removed.

Intramedullary nailing of the humerus: Patient was placed in beach-chair position. Fracture was reduced under scopy control. Anterolateral approach was made to expose the site of nail entry. Entry point of the nail was at the center of humeral head just posterior to bicipital groove. Unreamed technique was performed according to manufacturer's instructions. Nail was inserted with appropriate length and diameter by using template X-rays. Proximal locking was made using two or three screws. Distal locking was performed using endopin technique (*InSafeLock [TST, Istanbul, Turkey]).* Patients were immobilized in a sling. Gentle pendulum exercises were begun as tolerated. External beam radiation (20 Gy in five fractions) to the affected long bone was administered at 14 days post-procedure after stitches were removed.

RESULTS

Details regarding pathologic fractures in humerus and femur are shown in Table 1 and 2, respectively. Lung (n = 5) and breast carcinoma (n = 6) were the most common primary lesions, followed by renal cell (n = 2), prostate (n = 2), multiple myeloma, malign epitelioma, angiosarcoma and nasopharyngeal carcinoma (one patient for each type). All patients had multiple bone metastasis or lesions. There was no concomitant pathological fracture in another extremity, except one patient with bilateral pathologic humeral fractures (case 9). Patients also had an expected survival of at least 3 months according to PATHFx model. [8]

The median hospital stay was three days (range 1–7 days). No complication was observed related to RT (i.e.: wound dehiscence, pathologic fracture, infection). No re-irradiation was performed.

Pain relief was obtained in all lesions. All patients regained preoperative mobility at their last control. All lesions achieved complete radiological response with a median of four months (range: 2–16 months) after radiotherapy (Figure 1 and 2). One patient with left pathologic femur fracture underwent prophylactic fixation for right impending femur fracture (Figure 3). The only complication requiring reoperation was a refracture distal to short proximal femoral nail due to tumor recurrence. This was also revised with a long intramedullary implant with bony union thereafter (Figure 4). All patients were alive at the time of last follow-up.

DISCUSSION

There are only few studies evaluating outcomes and bone healing after fixation of pathological fractures and adjuvant radiotherapy for treatment of metastatic bone lesions. (3)(6)(9) Previous studies generally put emphasis on surgical decision making based on survival, clinical outcomes and perioperative complications. [10]

The data on bone healing potential after surgical fixation of complete pathologic fractures dates back to early 1980's. Apart from this, clinical effects of radiotherapy in pathologic fractures are also inconclusive. [1] It is generally assumed that postoperative radiotherapy will increase the likelihood of delayed union and nonunion; however adjuvant multifraction RT has been recommended to accelerate bone healing, control disease progression and avoid implant failure in the literature. [10,11]

Harada suggested that healing of the metastatic lesions can be accomplished with only radiotherapy in impending fracture cases and non-progressive metastatic bone disease. [7]

In complete pathologic fractures, bone healing can be improved with internal fixation and adjuvant radiotherapy. Gainor et al. demonstrated that internal fixation of pathologic fractures resulted in improved union in cases who survived six months or longer. He also added that union rate in patients receiving adjuvant radiotherapy was found to be higher in internal fixation group compared to cast immobilization. Additionally, internal fixation was recommended as necessary for patients whom received greater than 30 Gy dose due to its inhibitory effect on callus formation. [6]

Townsend compared clinical results of 29 patients who underwent surgery alone with 35 patients who received postoperative adjuvant radiotherapy. The median dose of RT was 30 Gy. On multivariate analysis, postoperative RT has been found to be an independent positive factor for functional improvement with decreased secondary surgery rates; however he did not evaluate union. [12]

Redmond administered adjuvant radiotherapy on 11 cases with 14 humerus pathologic fractures whom underwent static intramedullary nailing. He obtained good to excellent results with osseous healing in seven of eleven fractures whom survived at least three months. No major complication except one case who underwent screw removal due to irritation was noted. [3] Atesok reported on 22 pathologic humeral fractures managed with intramedullary

nailing 20 of whom received adjuvan RT. [9] Union was observed in 88% (15/17) of all the patients who survived at least for 3 months after the procedure. Ofluoglu treated 23 patients with pathological humerus fractures who underwent intramedullary nailing and low dose adjuvant RT. [13] At 4 weeks after surgery, 20 patients were alive and 12 cases had complete union. Van Geffen reported that they experienced similar pain scores with remarkable less complication in radiotherapy group relative to non-irradiated cases after intramedullary nailing although there are few RT cases. (21% irradiated vs 14% not irradiated) [14] Moura et reported on 82 patients with pathologic humerus fractures treated with intramedullary nailing and adjuvant radiotherapy. [15] He stated that closed unreamed static locked nailing was a fast, safe, and effective surgery with low morbidity. He also emphasized that closed intramedullary nailing decreased the risk of impaired healing after adjuvant radiotherapy.

Moon et al performed intramedullary nailing in 40 patients with sarcoma metastasis. 11 patients received either preoperative or postoperative radiotherapy 11 patients received either preoperative or postoperative radiotherapy. Fracture union was not achieved in majority of cases; however he concluded that multimetastatic patients with primary bone and soft tissue sarcomas and poor survival had palliative benefit. [16]

Our findings are in concordance with these studies. Clinical improvement and radiological healing was achieved in the short term, regardless of over-all disease specific survival from primary disease. All these studies indicate that benefits of multifraction RT outweigh the risks reported in literature. According to radiological outcomes of the current study, it is possible that this regimen will boost bone healing after surgical fixation of pathologic fractures. Compared to preoperative RT, postoperative RT is more advantageous in terms of lower risk of wound complications and availability of pathologic evaluation for individualized adjuvant treatment. To minimize these potential risks, our study group received low dose postoperative RT (20Gy) after intramedullary stabilization with a complete

radiologic response. Compared to endoprosthetic reconstruction and plate fixation, these patients may benefit from closed unreamed intramedullary nailing with less postoperative wound problems in a manner that will allow patients for immediate commencement of radiotherapy and medical oncology treatment.

Another important issue is that proximal and distal locking should be performed to ensure enhanced stability. The only revision was due to a short proximal femoral nail in our study cohort. This representative case demonstrated that stabilizing the entire length of the long bone obviates the need of re-surgery due to disease progression. Protecting the entire bone has been also associated with increased survival in a recent study. [17] Like femoral lesions, all humeral lesions have been satisfactorily managed with intramedullary nailing. The same technical rules were applied for these lesions. Proximal and distal static locking was performed. Although cementation of the fractured fragments provide initial stability, in long term implant failure risks increase as the fracture does not heal due to cement. [18] Intramedullary reaming in pathologic fracture is another important point. This issue is controversial and we did not prefer reaming due to possible tumoral contamination and vascular tumoral spread. In line with our opinion, a recent study by Younis supported the use of unreamed intramedullary nailing in pathologic humerus fractures with the advantages of less blood loss, systemic complications and decreased hospital stay. [19]

For femoral neck and head lesions, endoprosthetic reconstruction should be preferred. Nevertheless, given their high implant costs, fixation with long intramedullary nailing may be a more cost-effective option for pathologic fractures in metaphyseal and diaphyseal long bone lesions by avoiding additional surgeries due to complications specific to arthroplasty. (i.e.dislocation, intraop bleeding, infection) [20]

Osteosynthesis with plate fixation is less preferred for pathological fracture fixation as quality of bone stock proximal and distal to fracture is abnormal and reliable fixation may be

harder to achieve. Hoellwarth et al analyzed 105 interventions due to pathologic humerus fractures which were managed by photodynamic therapy, intramedullary nailing, and plate fixation. [21] Although reoperation rates were similar at each time point, intramedullary nailing had lowest rate of broken implants compared to plate fixation. This study supports our preference of intramedullary nailing against plate fixation.

Furthermore, the intramedullary nail stabilizes the full metaphyseo-diaphyseal length of the bone and is a load sharing device compared to a plate which is a load bearing device. Lastly, one important point is that solitary or oligo bone lesions due to solid organ metastases deserve a different approach. Wide resection as is the norm for a primary malignant bone tumors may prolong survival and be curative in selected cases. Prior to stabilization of pathological fracture, surgeon should be sure about the histologic subtype of the malignant cells. Diagnostic work-up for these lesions should follow the established orthopedic oncology principles.

Limitations of this study include small sample size and retrospective study design. Although femur and humerus are most commonly affected long bones, tibia is another common site for pathologic fractures where intramedullary nailing is advocated. There is no control group for comparison and further studies comparing IMN to plate fixation with adjuvant radiotherapy or RT alone in patients who are not eligible for surgery will be very helpful.

CONCLUSION

In multimetastatic cases, closed unreamed IMN of humeral and femoral diaphyseal pathologic fractures with adjuvant low dose RT offered good osseous healing with minimal complications and improved quality of life as reflected in there MSTS scores.

Conflict of interest: None declared.

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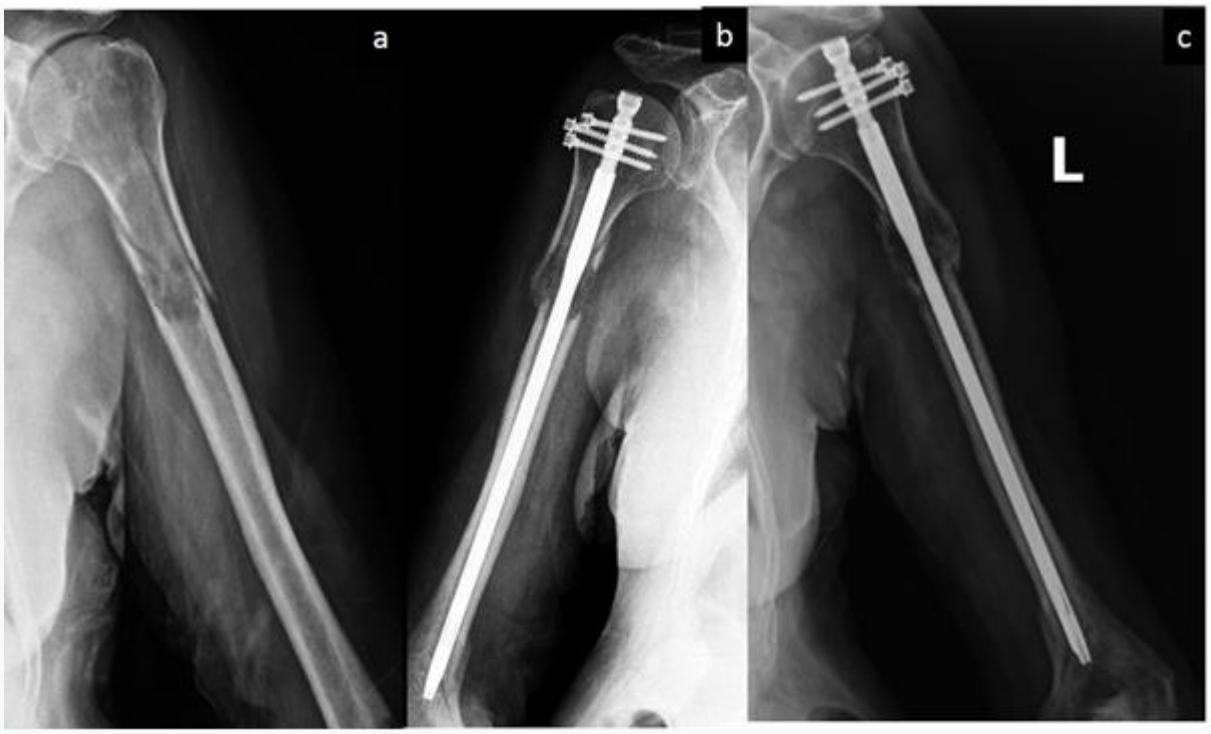

Figure 1 (case 2) a) Anteroposterior view of the pathologic humerus fracture due to lung carcinoma (79-year-old male); b) Postoperative view; c) four-month follow-up; Note callus formation at the fracture site, indicating complete response to adjuvant radiotherapy

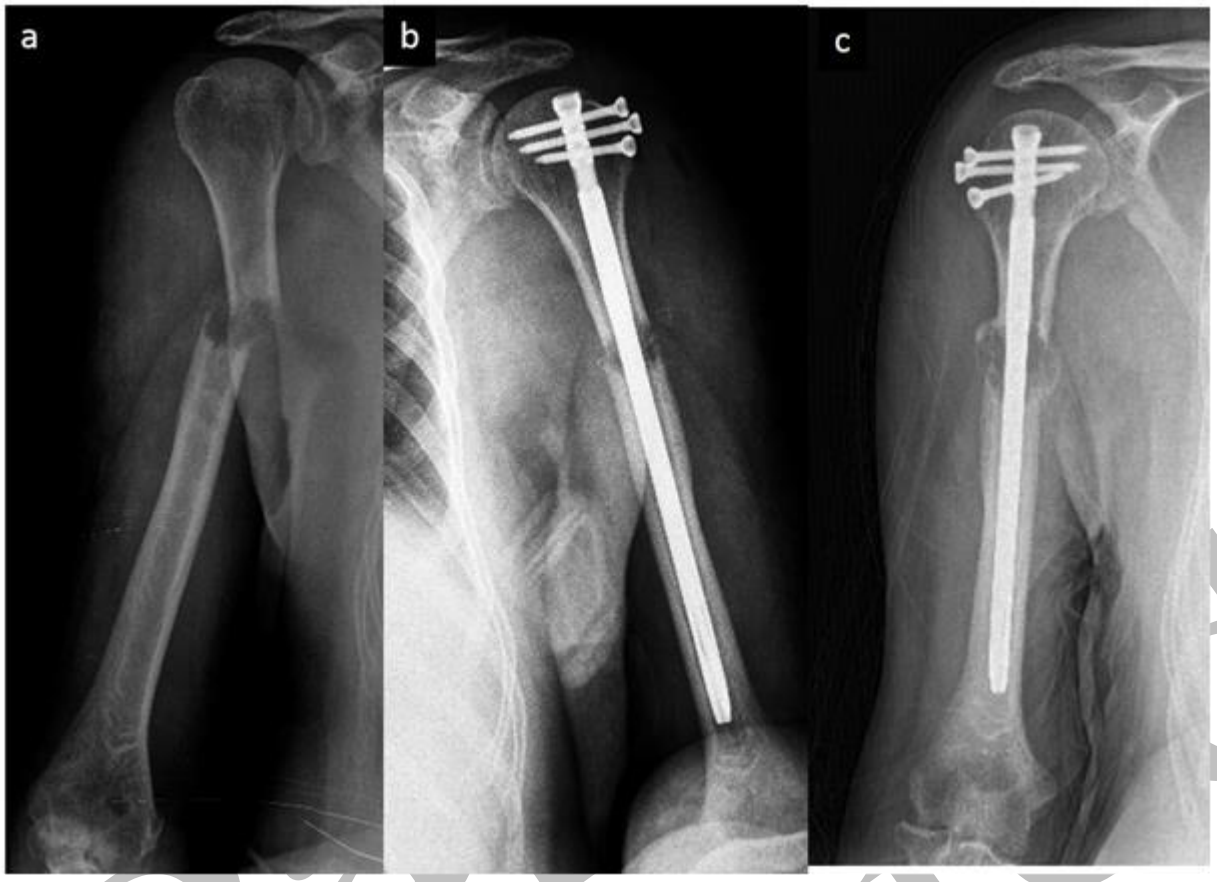

Figure 2 (case 8) a) Anteroposterior view of the pathologic humerus fracture due to renal cell carcinoma (72-year-old male); b) Postoperative view; c) three-month follow-up; Note callus formation at the fracture site, indicating complete response to adjuvant radiotherapy

Figure 3 (case 17) a) Anteroposterior view of the bilateral femoral metastatic lesions with left impending and right complete fracture (62-year-old female, breast carcinoma); b) Magnetic resonance imaging view of the bilateral femoral metastatic lesions; c) Postoperative view of the bilateral femur; d) three-month follow-up; Callus formation at fracture site, indicating complete response to adjuvant radiotherapy (white arrow)

Figure 4 (case 18) a) Anteroposterior view of the femoral metastatic lesion with a pathologic fracture of the proximal third of femur which is fixed with intramedullary nail (71-year-old male, lung carcinoma); b) Postoperative radiograph; c) At three-month follow-up, patient presented with fixation failure due to short intramedullary implant; anteroposterior radiograph demonstrated stress riser effect of the short nail; d) Postoperative view of long revision intramedullary nailing; e) Radiotherapy was given due to progression; f) 15-month follow-up; Pain relief and satisfactory clinical improvement was obtained; Screw-out was observed but this complication did not interfere with patient's clinical outcome

Table 1. Details about the pathologic humeral fractures

Case	Age (years)	Gender	Follow-up (months)	Primary lesion	Localization	Dimension of intramedullary nail*	Duration of operation (min.)	Length of hospital stay (days)	Complication	MSTS score (%)
1	56	male	3	Myeloma	Proximal	240×8	35	3	None	70
2	79	male	4	Lung	Proximal/ diaphyseal	280×7	30	4	None	70
3	53	female	5	Malignant epithelial carcinoma	Diaphysis	200×7	20	5	None	85
4	57	male	16	Nasopharyngeal carcinoma	Proximal	220×7	25	2	None	85
5	56	female	6	Angiosarcoma	Diaphysis	220×8	25	3	None	80
6	86	male	4	Lung	Diaphysis	280×9	35	6	None	70
7	86	female	5	Breast	Diaphysis	220×9	45	7	None	70
8	72	male	3	Renal cell	Diaphysis	240×8	30	3	None	75
9	71	female	3	Breast	Diaphysis	240×7	20	5	None	75

* The dimension of implant is given as Length (cm) x Diameter (mm)

Table 2. Details about the pathologic femoral fractures

Case	Age (years)	Gender	Follow-up (months)	Primary lesion	Localization	Dimension of intramedullary nail*	Duration of operation (min.)	Length of hospital stay (days)	Complication	MSTS score (%)
10	62	male	8	Lung	subtrochanteric	400×10	65	3	None	65
11	69	male	13	Prostate	subtrochanteric	250×11	75	4	None	70
12	77	female	14	Breast	diaphysis	360×11	80	5	None	60
13	58	female	2	Breast	diaphysis	340×10	55	2	None	50
14	59	female	3	Breast	diaphysis	60×9	45	3	None	60
15	80	male	2	Lung	intertrochanteric	250×12	75	6	None	70
16	84	male	3	Prostate	intertrochanteric	220×10	40	7	None	55
17	62	female	3	Breast	subtrochanteric	360×10 (right: impending left: pathologic)	85	6	None	60
18	71	male	15	Lung	intertrochanteric	220×10	45	7	Exchange nail	70
19	62	male	16	Renal cell	Subtrochanteric / diaphysis	360×10	75	5	None	75

* The dimension of implant is given as Length (cm) x Diameter (mm)

