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REVIEW ARTICLE

Radiologic evaluation of fracture healing

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Abstract
While assessment of fracture healing is a common task for both orthopedic surgeons and radiologists, it remains challenging due to a lack of consensus on imaging and clinical criteria as well as the lack of a true gold standard. Further complicating this evaluation are the wide variations between patients, specific fracture sites, and fracture patterns. Research into the mechanical properties of bone and the process of bone healing has helped to guide the evaluation of fracture union. Development of standardized scoring systems and identification of specific radiologic signs have further clarified the radiologist's role in this process. This article reviews these scoring systems and signs with regard to the biomechanical basis of fracture healing. We present the utility and limitations of current techniques used to assess fracture union as well as newer methods and potential future directions for this field.

Keywords Fracture · Healing · Radiographs · CT · Ultrasound

The process of bone healing

Bone healing is a complex regenerative process, which mimics skeletal development (aside from the initial bleeding and inflammatory phases) [1]. At the site of fracture, a hematoma forms and an inflammatory response is triggered, whereby various growth factors and cytokines result in proliferation and differentiation of mesenchymal progenitor cells into chondrogenic or osteogenic cells [2, 3]. The fracture gap and medullary cavity are soon populated with chondrocytes, which form cartilaginous soft callus [4–6].

At the periphery of a diaphyseal fracture, the deep layer of the periosteum, which is rich in precursor cells, generates osteoblasts and forms woven bone directly through intramembranous ossification [7]. As this hard callus forms from the periphery to the center, cartilage in the fracture gap is converted to woven bone through enchondral ossification [7, 8]. After woven bone fills the gap, cycles of osteoclastic and osteoblastic activity (coupled remodeling), convert woven bone to lamellar bone, and reform the medullary cavity [9, 10].

Biomechanically, fracture union can be defined as the restoration of mechanical properties, such as strength and stiffness [11]. In malunion, the normal physiologic healing process is completed over the expected amount of time. However, the fracture has healed in an abnormal position, often a combination of angulation, rotation, and length. A minority of fractures (5–10%) result in delayed union or nonunion [12]. In delayed union, the fracture healing process occurs over a significantly longer time than expected for the particular fracture pattern (typically 3–6 months).

On the molecular level, nonunion can be subdivided into viable and nonviable subtypes. Viable/vascularized nonunion is characterized by fracture ends that are vascular and capable of biological activity. This includes both hypertrophic nonunion (when callus is present) and, less commonly, oligotrophic nonunion (when callus is absent) [13]. Nonviable/avascular nonunion features fracture ends that have little or no vascularity and is typically referred to as atrophic nonunion, as minimal or no callus formation is present and the fracture line remains visible [14, 15].

There are many risk factors that may disrupt the normal healing process and contribute to delayed union or nonunion [16]. Abnormal blood flow to the fracture site may inhibit the early inflammatory and reparative phases of fracture healing, leading to nonviable nonunion. This may be the result of local

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factors (such as the type and location of injury, presence of serious vascular damage, vascular compression by large hematoma, increased distance from nutrient vessel, and bone loss with fracture gap) as well as systemic factors (such as advanced patient age, comorbid conditions, smoking, alcoholism, and medications) [17]. Viable nonunion results from a disruption of the late/remodeling phase of healing secondary to motion at the fracture site. Hypertrophic nonunion results from insufficient stability, while frank instability leads to oligotrophic nonunion with rounded off-bone ends [13]. Continued motion at the fracture site may lead to the development of interposed synovial tissue and is termed a pseudoarthrosis, which may be characterized on imaging by the presence of fluid or gas at the fracture gap [17]. Infection may complicate any stage of the healing process and may contribute to nonunion in up to 38% of patients [13].

Challenges in clinical practice

Determining when a fracture is healed is a mainstay of orthopedic practice and affects patient management decisions, including weight-bearing status, activity level, and the need for hardware placement and/or revision [14]. The primary goal is to differentiate adequate union from nonunion. Despite its clinical relevance, nonunion has no standardized definition in the orthopedic literature.

The clinical definition of fracture healing typically relies on a multitude of factors, including physical examination findings, radiologic measures, and patient self-assessment. Physical examination criteria most commonly include absence of pain or tenderness at the fracture site on weight-bearing, absence of pain to direct palpation, and the ability to weight-bear [15]. Radiologic evaluation has historically relied upon radiographs and most commonly includes: bridging of the fracture by bone, callus, or trabeculae; bridging of the fracture at three of four cortices; and obliteration of the fracture line and/or cortical continuity [18]. A patient's own assessment of function and pain level has increasingly become an important contributor to management decisions [19].

Research within the last few decades has demonstrated that these three facets of diagnosis (clinical, radiographic, and patient-rated) do not always align. Taking into account the patient's age, profession, and function level further complicates the task of creating a unified definition of fracture union. Moreover, the biomechanical demands at the particular fracture site also play a role. A weight-bearing bone, such as the femur or tibia, necessitates a higher level of bone strength than a non-weight-bearing bone, such as the radius or ulna [20]. In addition, the healing process takes different periods of time in different bone types and different fracture patterns; thus, determining an accepted time-frame for union remains difficult.

Within this environment of uncertainty, it is not surprising to find marked variability in the approach utilized by surgeons to form impressions and determine outcomes. In a survey of 444 orthopedic surgeons, Bhandari et al. demonstrate a lack of consensus regarding both clinical and radiologic criteria used to assess healing as well as significant differences in definitions of delayed union and malunion [21]. A systematic meta-analysis of the orthopedic literature by Corrales et al. highlights the level to which surgeons differ in their practice, wherein a combination of clinical and radiologic measures define healing in 62% of published studies, while radiological criteria alone are utilized in up to 37%. Twelve different clinical criteria are referenced while 11 different radiographic criteria are used in this review [22]. In a randomized controlled study of 51 patients, Dijkman et al. determine that the addition of clinical notes to the adjudication of radiographic fracture healing changes the outcome decision in a substantial number of cases [23].

The clinical assessment of fracture union has proven to be challenging and highly subjective. A study by Webb et al. demonstrates that manual assessment of stiffness at fracture sites by orthopedic surgeons is no better than manual assessment by medical students [24]. Another study suggests that, regardless of number of years of training, physicians are inconsistent in their ability to assess the increasing stiffness of a fracture with time [25]. Pain on palpation is an even more unreliable and subjective measure, as individual and cultural differences in perception of pain and in pain tolerance vary so significantly [26].

The role of radiology

Though not sufficient for diagnosis and management decisions alone, radiology plays a key role in helping the orthopedic surgeon to form an impression on the state of fracture healing. Radiographs and CT represent the most commonly used modalities, though other modalities (including ultrasound and nuclear scintigraphy) are undergoing evaluation for their potential utility.

Even if one chooses a specific fracture (e.g., distal radius), there is no consensus within the orthopedic community regarding the appropriate schedule for follow-up imaging. One multi-institutional survey of 40 hand surgeons demonstrated a high degree of variability in the number of radiographic series (ranging from 1 to 6 series per patient) obtained during the course of postoperative follow-up of distal radial fractures. The study demonstrated a mean of 2.6 radiographic series per patient (± 1.0) with imaging obtained at 74% of visits [27].

At our institution, the convention for surveillance imaging of most internally fixed fractures includes radiographs at the following postoperative intervals: 2 weeks, 6 weeks, 3 months, 6 months, and 12 months. For nonoperative fractures with

possible instability, we obtain radiographs at weeks 1, 2, 4, and 6. For stable nonoperative fractures, we obtain radiographs at weeks 2 and 6. Subsequent radiographs are only obtained if there is clinical concern for complication or delayed healing.

Radiography

Due to its low cost, wide availability, and relatively low radiation profile, radiography has classically been the most utilized technique in assessment of fracture healing. The formation and growth of an external callus and the bridging of fracture line by callus are the two processes that are most readily recognized on radiographs in the evaluation of fracture healing [28]. Animal osteotomy experiments have been used to validate the correlation of these findings with the mechanical process of fracture healing, including the correlation of cortical continuity with dynamic torsion performance and cortex-to-callus ratio with stiffness [29, 30].

Several early scoring systems were created in human subjects but these classification systems were complex and difficult to use. One of the first scoring systems, created by Hammer et al. in 1985, utilized fracture line visibility and callus quantity/quality to delineate five stages of union [31, 32]. In 2009, Eastaugh et al. measured callus diameter in two planes on serial radiographs to create a quantifiable unit of callus, called the maximum callus index (defined as the ratio of the maximum callus diameter to bone diameter at the same level of the callus) [28]. While they found a moderate degree of correlation between maximum callus index and biomechanical strength testing, the authors acknowledged that even small differences in radiographic rotation affected measurements and that many fracture patterns would not be amenable to this technique.

In a landmark study by Whelan et al. in 2002, the authors set out to determine the intra- and inter-observer reliability of the various assessment methods available. They found that measuring the number of bridged cortices as well as the absence of fracture line visibility (as judged by orthogonal view radiographs) represented the most reliable methods of assessing fracture healing in their population subset (Fig. 1) [33]. Building on these findings, Whelan et al. developed a new scoring system in 2010 with the goal of standardizing the evaluation of tibial fracture healing. Termed the Radiographic Union Score in Tibial fractures (RUST score), the system assigns a score for each of four cortices based on the presence or absence of callus and fracture line visibility (Table 1) [34].

Animal models using rat tibias served to validate the reliability of this scoring system [35]. Leow et al. found that discordance was frequent in cases in which fracture lines were still visible in the tibial cortex but not the overlying callus. Consequently, it was determined that "fracture line visibility" should evaluate within the callus as opposed to the native cortex—i.e., a callus that fully bridged the cortex was scored a three, even if fracture line was still visible in the tibial cortex itself (Fig. 2). With this definition, the RUST score was found to be a reliable and repeatable outcome measure. In addition, the authors determined that having the immediate postoperative film available for comparison increased the inter-observer reliability of scoring, mainly in helping to avoid erroneously classifying overlapping bone as callus formation. This addition was particularly important in cases of spiral fractures with minor displacement [25].

Building on the success of the RUST score, various authors have adapted Whelan's scoring system for the assessment of fractures in other parts of the skeletal system. The Radiographic Union Score for Hip (RUSH) and the Radiographic Union Score for Radius (RUSS) are two systems that have been tested more recently and have shown promise as reliable scoring tools. The RUSH score includes the standard scoring algorithm of the RUST score, but also adds evaluation of trabecular consolidation and trabecular fracture line disappearance—elements that are particularly important in proximal femoral stability (Fig. 3) [36, 37].

The RUSH score has been applied in evaluating femoral neck and intertrochanteric fractures with improved inter-observer reliability for both types of fractures [36–39]. Chiavaras et al. showed improved agreement between orthopedic surgeons and radiologists in assessing intertrochanteric fracture healing on radiographs using the RUSH score as compared with subjective assessment alone [38]. Frank et al. demonstrated that a 6-month threshold RUSH score of < 18 had 100% specificity and 100% positive predictive value for radiographic nonunion of femoral neck fractures [39]. Inter-observer reliability was noted to be significantly improved when using sequential radiographs instead of a single study from an unknown point in time [37]. The RUSS score has also proven to be a reliable scoring system, though the presence of hardware within the distal radius has contributed to higher rates of discordance among scorers [40].

Beyond scoring systems, authors also focus on identifying individual signs predictive of nonunion. Salih et al. described the "fracture line" sign, in which fracture lucency extends beyond the original cortical boundary but not to the boundary of the callus [41]. This sign was shown to have a high predictive value for hypertrophic nonunion in tibial shaft fractures with positive and negative predictive values of 88.9 and 75.0%, respectively. The authors suggest that this sign indicates the need for longer fracture stabilization and a delay in hardware removal.

Software-based technology is another approach being studied. Lujan et al. developed an objective imaging-based algorithm to quantitatively measure periosteal callus area [42]. The clinician's role is limited to identifying the external cortical fragment volume. The algorithm automatically defines other parameters and calculates a callus volume. The strength of this

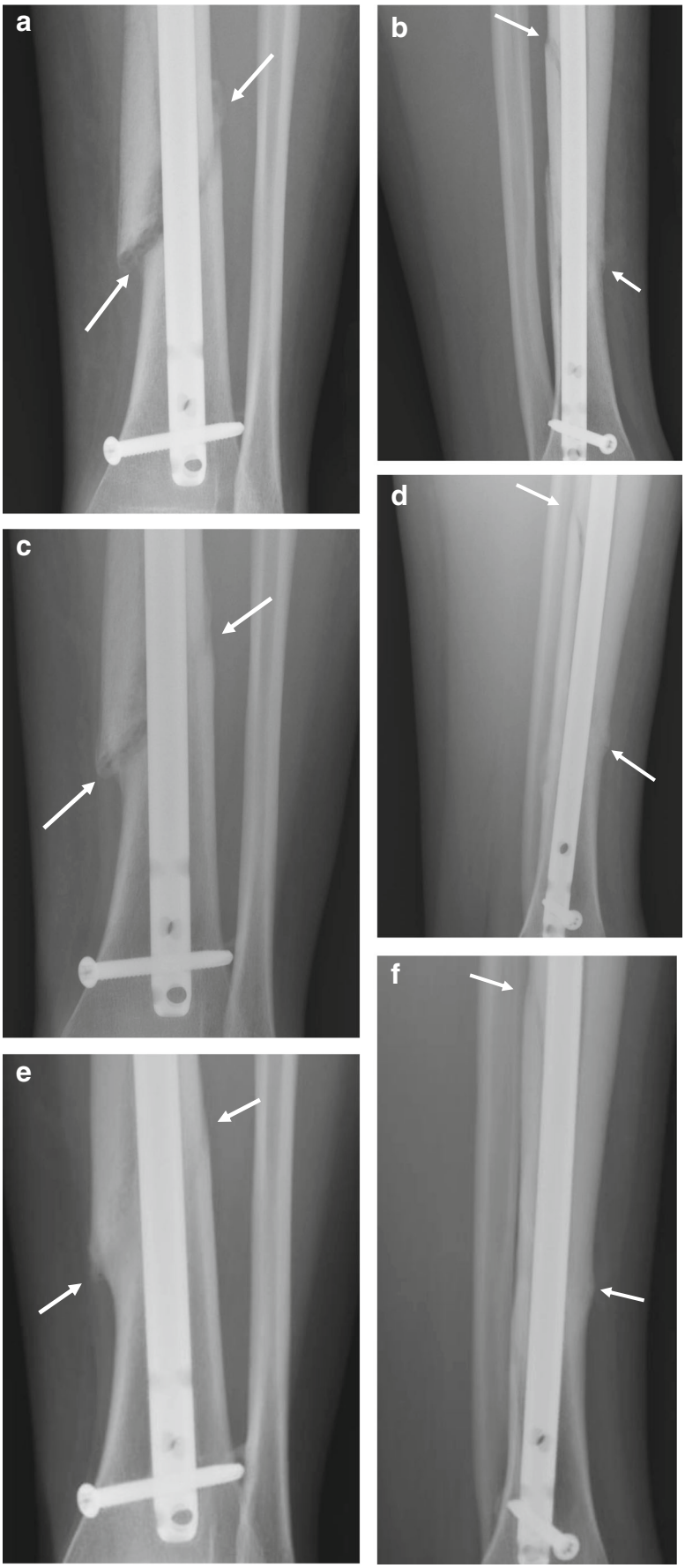

Fig. 1 Serial RUST scores in a 27-year-old female with healing tibial fracture. **a**, **b** AP and lateral radiographs at 1 month post-fixation show callus at the lateral and anterior cortices (1 point each) with visible fracture lucency at all four cortices (1 point each), for a total RUST score of 6. **c**, **d** AP and lateral radiographs at 3 months post-fixation exhibit callus at the medial and posterior cortices (2 points each) with healing at the lateral and anterior cortices (3 points each), for a total RUST score of 10. **e**, **f** AP and lateral radiographs at 12 months post-fixation show complete healing at all four cortices (3 points each), for a total RUST score of 12

Table 1 Simplified scoring charts for calculating the Radiographic Union Score for Tibial (RUST) and Hip (RUSH) fractures

Radiographic Union Score for Tibial Fractures (RUST)
(circle one in each column and add the 4 scores)

	Anterior cortex	Posterior cortex	Medial cortex	Lateral cortex	Total
(+) Fracture line, (−) Callus	1	1	1	1	Minimum 4
(+) Fracture line, (+) Callus	2	2	2	2	–
(−) Fracture line, (+) Bridging callus	3	3	3	3	Maximum 12

Radiographic Union Score for Hip Fractures (RUSH)
(circle one in each of the 5 columns in sections A and B and add the 10 scores)

	Anterior cortex	Posterior cortex	Medial cortex	Lateral cortex	Trabecula	Total
A. Bridging/consolidation						Minimum 10
None	1	1	1	1	1	–
Partial	2	2	2	2	2	Maximum 30
Complete	3	3	3	3	3	
B. Fracture line						
Complete	1	1	1	1	1	
Partial	2	2	2	2	2	
None	3	3	3	3	3	

technique lies mainly in limiting subjective user input, with resultant decreased inter-observer variability when compared to clinician measurements.

Computed tomography

With advancements in the ability to create thinner slices and high-quality multiplanar reconstructions, CT has emerged as a useful modality in the evaluation of fracture healing. Animal studies utilizing invasive manual tests to assess bone strength demonstrated good correlation with CT findings [43, 44]. Grigoryan et al. further validated the utility of CT by demonstrating that CT detected external callus formation earlier than radiographs [45].

Despite evidence of its utility, CT is not routinely used for evaluation of fracture union due to its higher cost and higher radiation profile. However, it has become a useful adjunct modality in cases with equivocal findings on radiographs. A 2006 study by Krestan et al. demonstrated that radiography is an unreliable diagnostic technique when used alone. Defining fracture union as complete, partial, or incomplete based on the presence of bridging

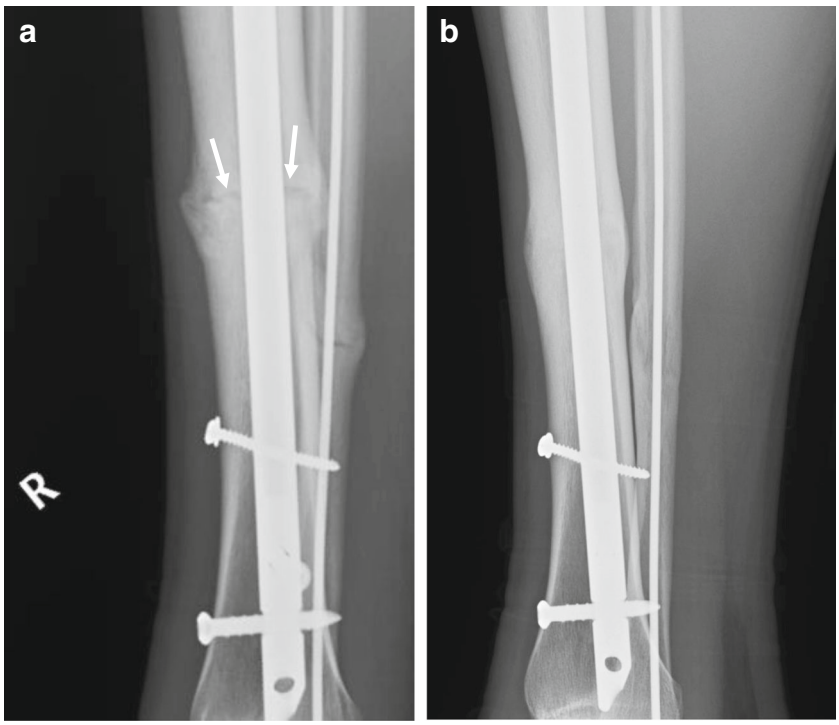

Fig. 2 Fracture line visibility in native cortex (but not the overlying callus) in a 27-year-old male with healing tibial fracture. **a** Lateral radiograph at 6 months post-fixation shows bridging callus with persistent fracture lucency only within the native cortex (*arrows*). **b** Lateral radiograph at 12 months post-fixation demonstrates complete fracture healing

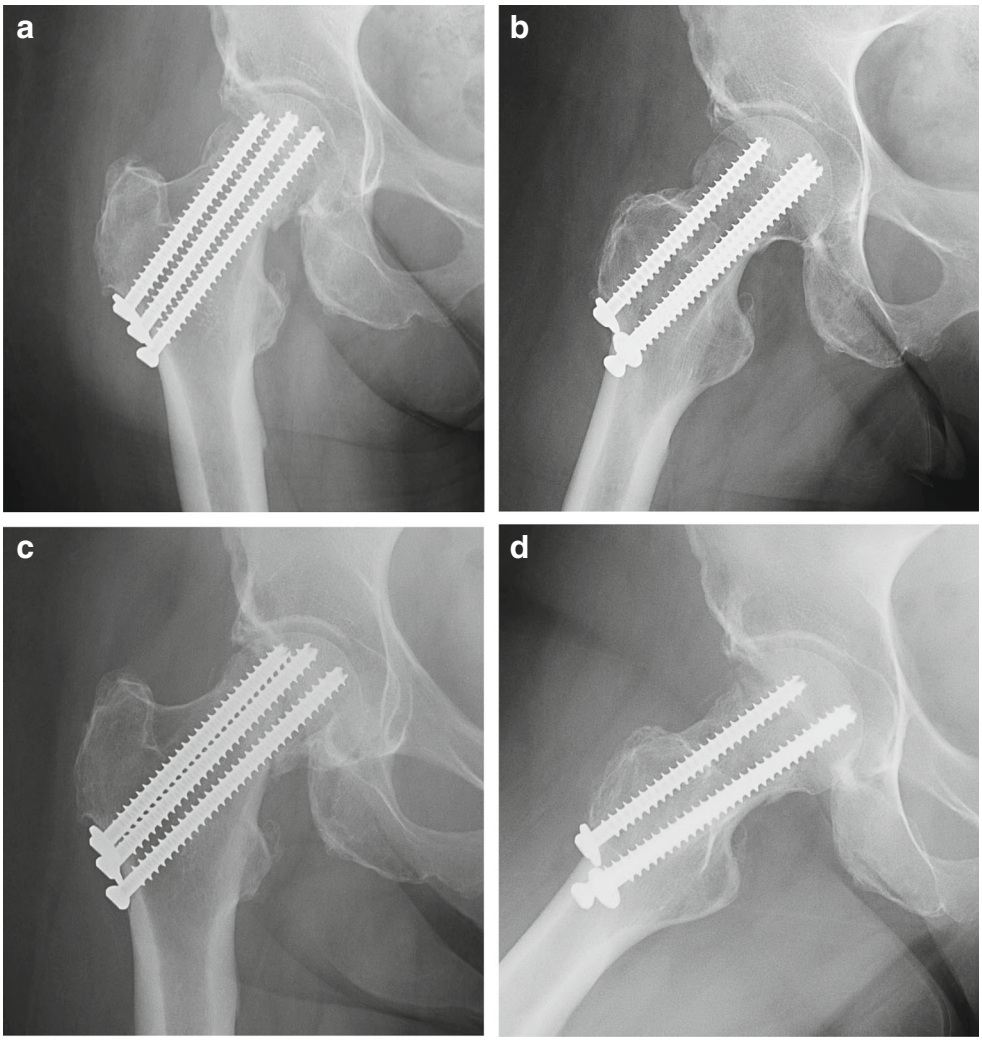

Fig. 3 Serial RUSH scores in a 71-year-old female with subcapital femoral neck fracture. **a**, **b** AP and frog-leg lateral radiographs at 1 month post-fixation show partial bridging at the anterior/medial/lateral cortices (3 + 3 + 3 points), partial fracture line disappearance at the posterior cortex (4 points), and partial trabecular consolidation with partial line disappearance (4 points), for a total RUSH score of 17. **c**, **d** AP and frog-leg lateral radiographs at 6 months post-fixation exhibit interval complete bridging at the posterior cortex with persistent partial fracture line (5 points), partial fracture line disappearance at the lateral cortex (3 points), and unchanged appearance of the anterior cortex, medial cortex, and trabecula (3 + 3 + 4 points), for a total RUSH score of 19. The patient required conversion to arthroplasty at 12 months for persistent pain related to nonunion

and bone gaps, the authors determined that radiographs either underestimated or overestimated fusion in 37% of cases (Fig. 4) [46]. Multiple studies have validated selective CT evaluation in difficult cases with indeterminate radiographic findings [47–49].

The role of CT continues to grow with the push towards less subjective means of assessment. CT images are more amenable to quantitative and volumetric measurements than radiographs, and CT can thus be used to evaluate macrostructural and microstructural properties of healing bone [50]. Animal models have demonstrated bone strength to correlate with callus volume and fracture bone mineral density [51, 52]. Utilizing Hounsfield units and volumetric data to measure the bone mineral formation in the fracture gap itself has already been shown to reliably demonstrate interval healing over sequential scans [53].

One drawback of CT is that metal implants introduce artifacts and degrade image and reconstruction quality. Beam attenuation from metallic prostheses contributes to beam hardening artifact, photon starvation, increased noise, and radiation scatter [54]. Methods for decreasing metallic artifact on conventional CT scans (such as increasing tube voltage or current) aim to combat beam hardening artifact and photon starvation, but result in decreased soft tissue contrast and higher radiation dose. Dual-energy CT scanners and subsequent post-processing (Fig. 4) allow for the benefits of a higher energy beam (e.g., decreased beam hardening) while preserving the benefits of lower energy monochromatic scans (e.g., adequate soft tissue definition, conventional radiation dose). Even with optimal dose-reduction techniques, it is neither practical nor prudent to obtain CT as routine fracture follow-up for every patient. At our institution, we typically obtain CT for patients with poor radiographic union and clinically concerning pain at 3 months post-fracture. Other considerations for follow-up CT include fractures with a risk of avascular necrosis that are difficult to evaluate radiographically (e.g., scaphoid) and to evaluate fracture healing prior to hardware removal.

Ultrasound

Ultrasound is quickly gaining popularity in musculoskeletal imaging as it is a non-invasive, relatively low-cost modality

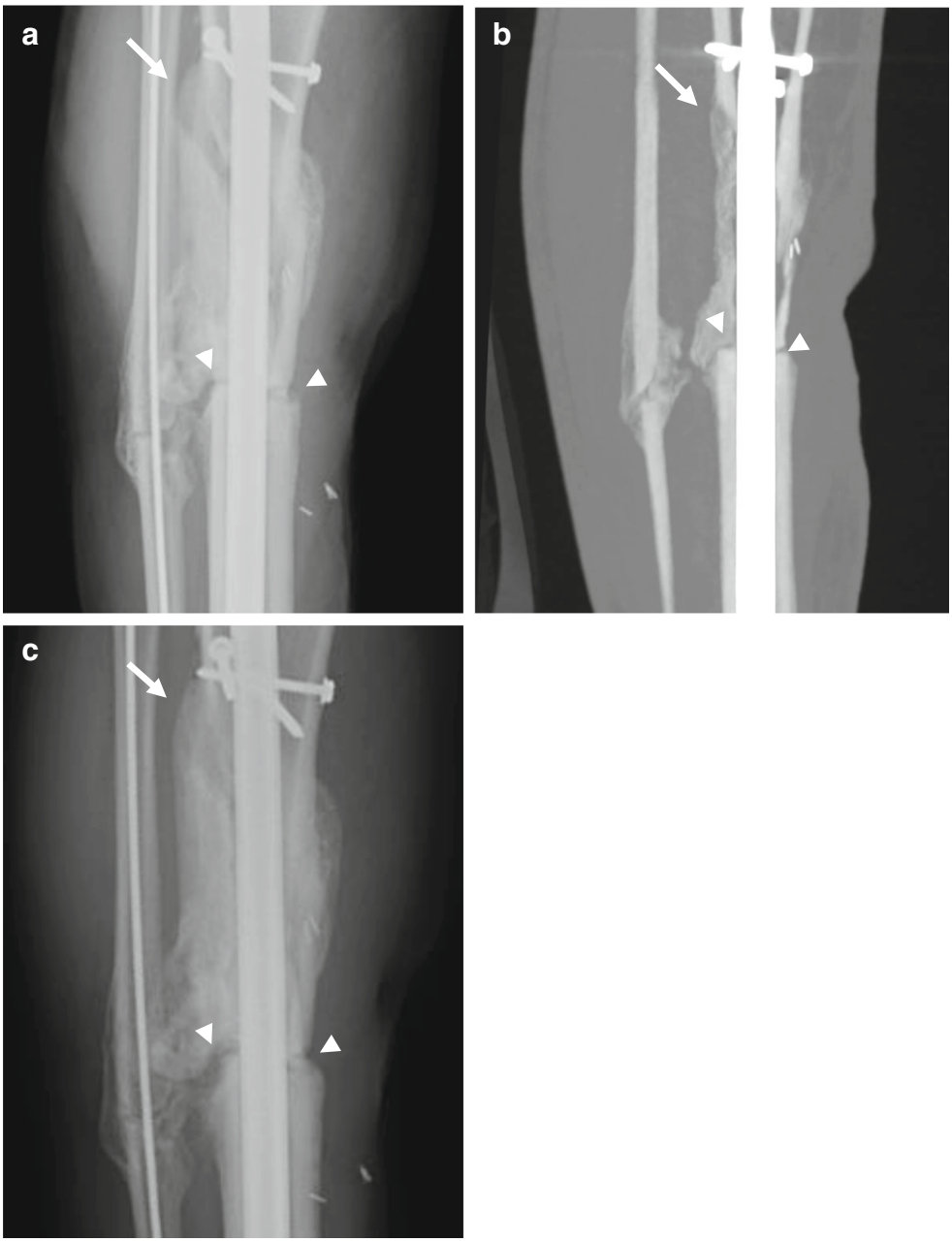

Fig. 4 Dual-energy CT improves detection of bridging callus in a 31-year-old male with Gustilo grade IIIB open tibial fracture that required rotational muscle flap reconstruction. **a** AP radiograph at 6 months post-fracture demonstrates suspected nonunion at the proximal (*arrow*) and distal (*arrowheads*) margins of a spiral tibial fracture. **b** Curved coronal 8-mm MIP reconstruction from same-day dual-energy CT (composite 110 keV, 260 mA) reveals bridging callus at the proximal fracture margin (*arrow*) while the distal fracture margin exhibits persistent fracture lucency and sclerotic margins (*arrowheads*). **c** AP radiograph at 12 months post-fracture exhibits complete healing of the proximal fracture margin (*arrow*) with nonunion at the distal fracture margin (*arrowheads*)

with no associated ionizing radiation. In assessing fracture sites, only the outer cortical surface and overlying soft tissues are adequately visualized, and fractures of deeper bones are poorly evaluated. Despite these limitations, there are advantages to ultrasound. Whereas evidence of healing on radiographs and CT is dependent on the deposition of mineralization within callus (which typically does not occur until 6–8 weeks post fracture), sonographic signs of healing can be identified as early as 1–2 weeks post fracture [55].

Early work by Moed et al. on canine tibia demonstrated that callus at fracture gaps demonstrates hyperechogenic signal on sonographic imaging [56]. Based on these findings, Moed et al. conducted a pilot study that demonstrated that sequential ultrasounds could accurately predict cases of nonunion in tibial shaft fractures treated with interlocking nails [57]. The authors assessed the echogenicity of the soft tissue at the fracture gap relative to the echogenicity of the tibialis anterior muscle, as well as the continuity of the periosteum. Fracture healing was defined as hyperechoic tissue filling the fracture gap and obscuring visualization of an intramedullary nail. Notably, ultrasound reliably predicted healing before it was radiographically apparent. A larger-scale study reaffirmed these findings [58]. The presence of hardware in these cases was noted to be useful as it provided an easily identified sonographic landmark in the evaluation of adjacent tissues.

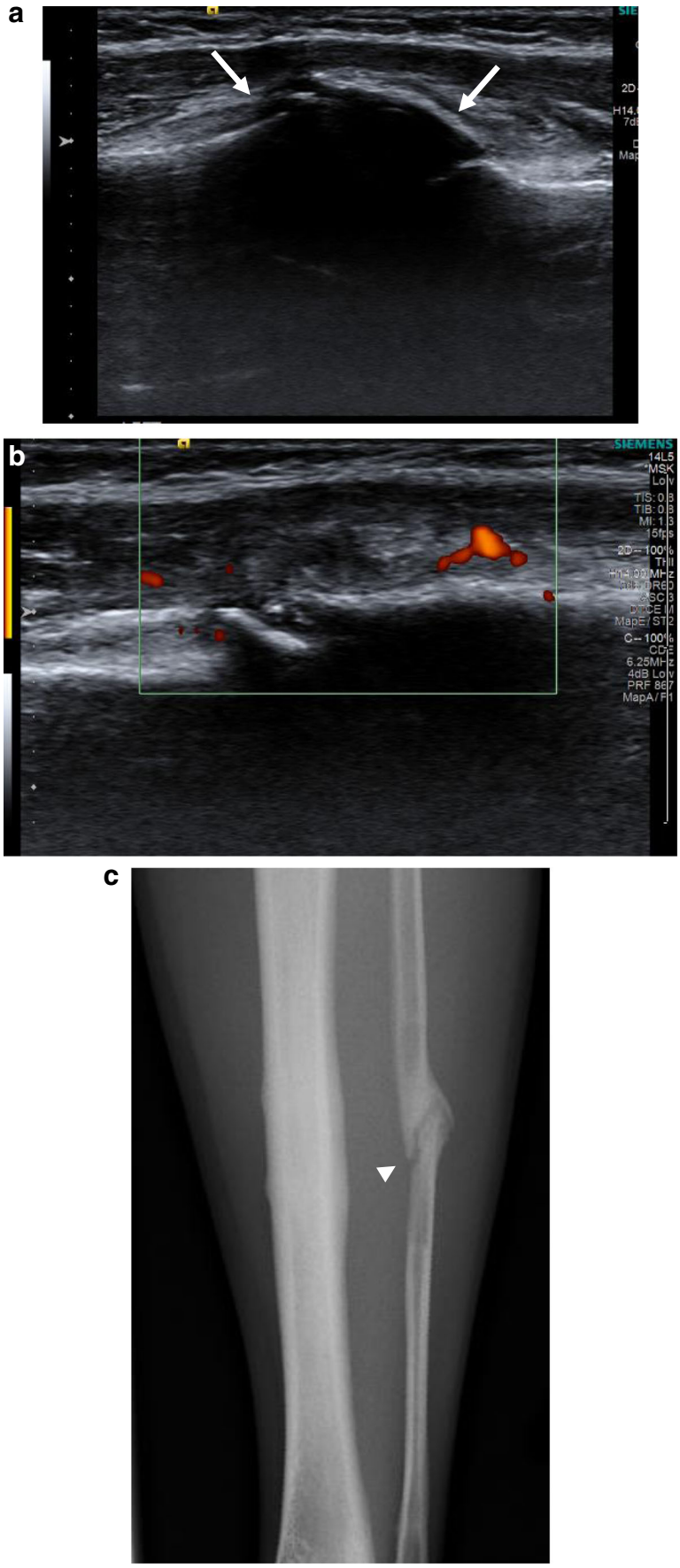

Fig. 5 Ultrasound of healing fibular fracture in a 30-year-old female. **a** Grayscale sonographic image shows a mound of bridging callus (*arrow*) at the lateral/superficial cortex of a fibular fracture with associated shadowing. **b** Color Doppler image demonstrates hyperemia of the adjacent soft tissues. **c** Frontal radiograph from the same date reveals persistent fracture lucency at the medial/deep cortex (*arrowhead*), which could not be visualized sonographically

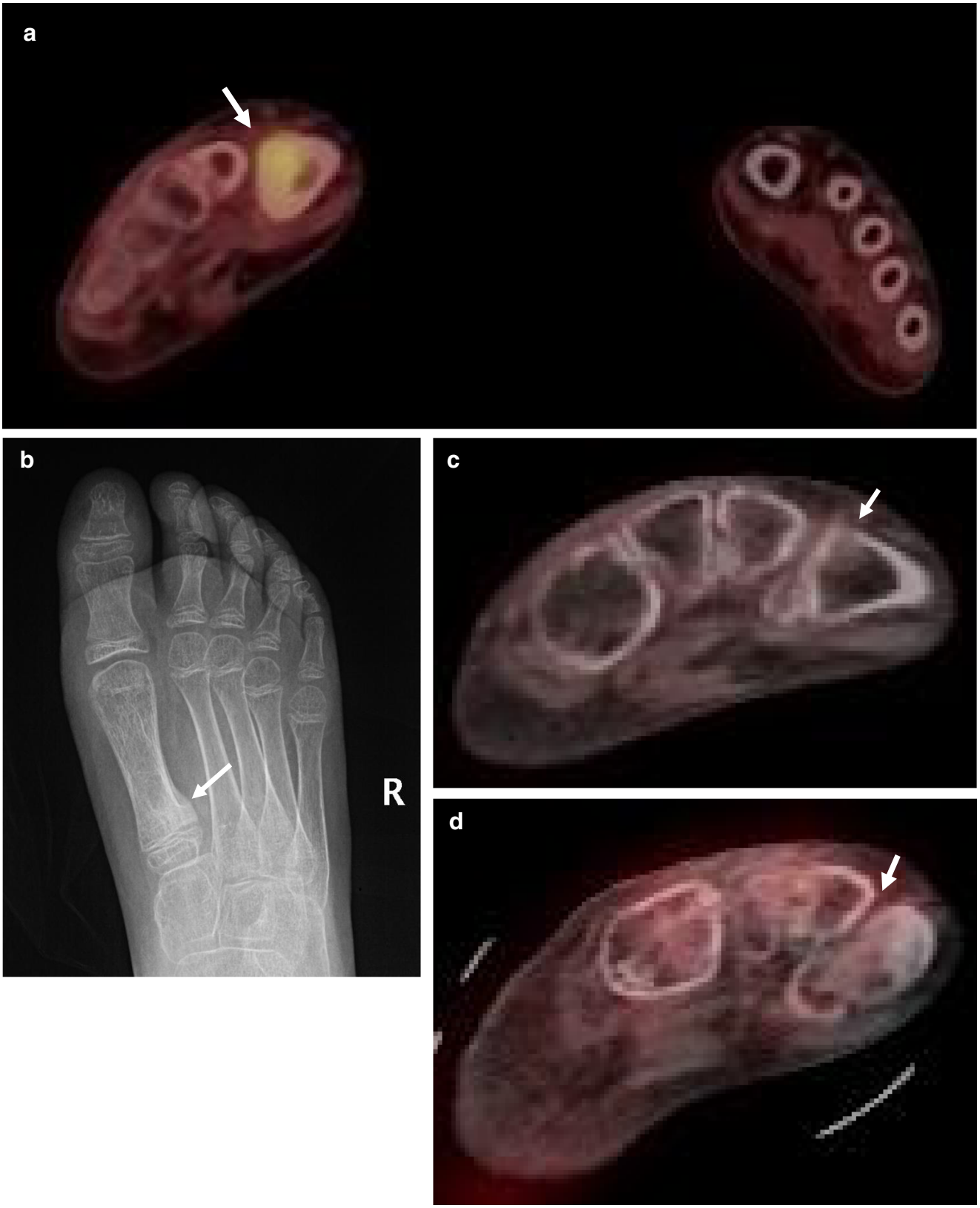

Fig. 7 Incidental metatarsal fracture in an 11-year-old male on serial PET/CT scans obtained for femoral osteosarcoma surveillance. **a** Fused axial PET/CT image shows hypermetabolic activity (*arrow*) at the right first metatarsal base. **b** Follow-up AP radiograph one month later shows corresponding healing fracture of the right first metatarsal base (*arrow*). **c**, **d** Of note, this hypermetabolic activity was not present at the right first metatarsal base (*arrows*) on PET/CTs obtained 3 months before (**c**) and 3 months after (**d**) the scan **a**

Wawrzyk et al. demonstrated a correlation between ultrasound and radiographic imaging of callus formation in pediatric long bone fractures, suggesting the possibility of its use as an alternative to radiographs in children [58]. However, a major limitation of sonographic evaluation (as compared with radiography and CT) lies in its inability to evaluate the deeper cortical surfaces due to shadowing from the more superficial cortex (Fig. 5).

The utility of ultrasound continues to grow, with both newer techniques and newer strategies being studied. By attaching a position sensing device to the ultrasound probe, 3D reconstructed images can be generated, which can help in interpretation of complex fracture pattern healing [55]. In addition, Doppler imaging has the potential to identify the angiogenesis associated with secondary bone healing. Animal studies have demonstrated that 2D power Doppler imaging can identify the neovascularization of fracture healing in long bones in the early reparative phase [59, 60].

Nuclear medicine

Tc99m-MDP bone scan is a functional imaging technique in which radiotracer uptake corresponds to blood flow and new bone

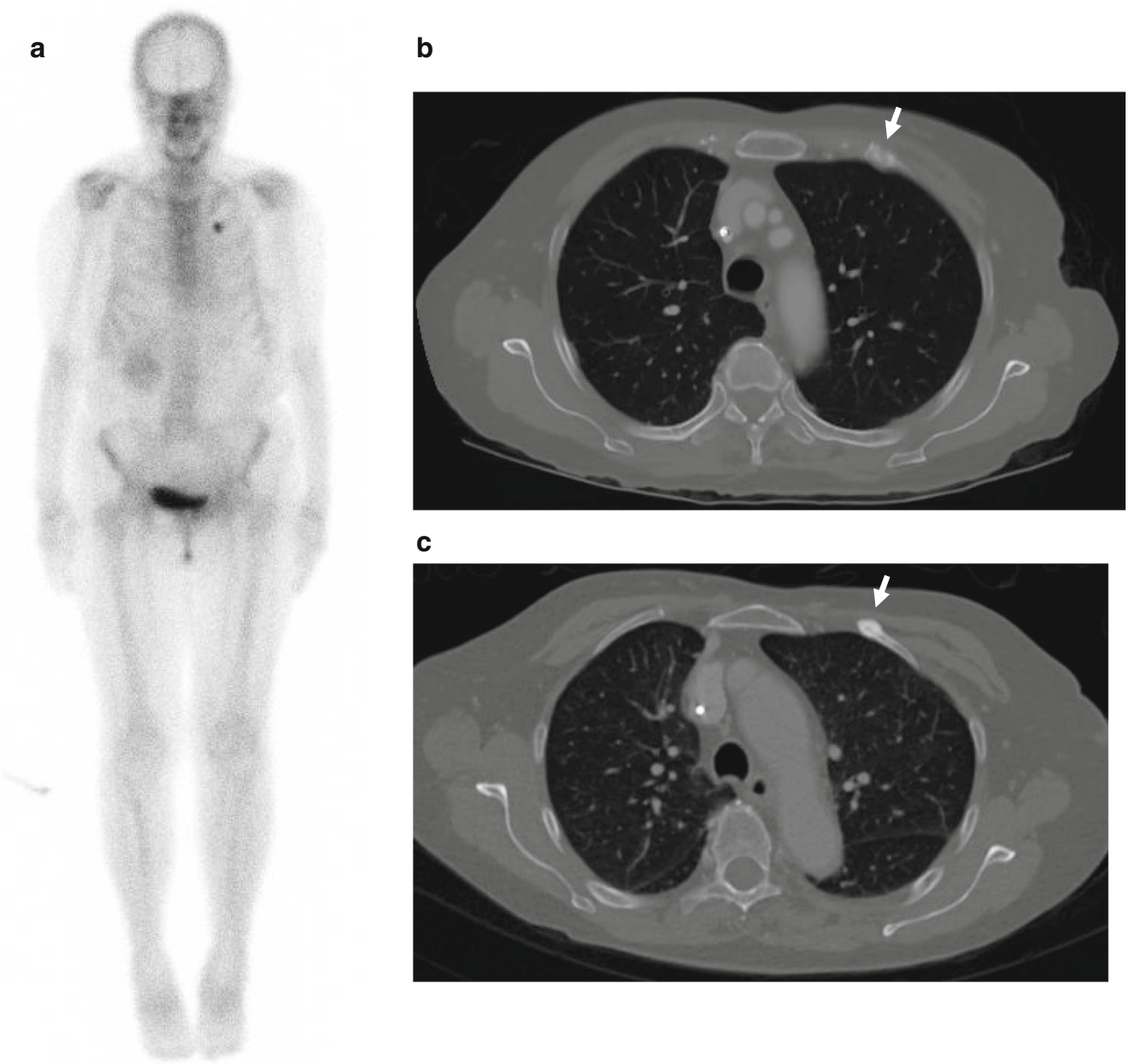

Fig. 6 Tc99-MDP bone scan reveals healing rib fracture in an 85-year-old female with metastatic bladder cancer. **a** Whole-body AP image from bone scan shows increased Tc99-MDP uptake at the anterior left second rib. **b** Concurrent axial CT image shows subacute fracture of the left second rib with mild adjacent callus (*arrow*). **c** Axial CT image at 3-month follow-up reveals interval healing of the left second rib fracture (*arrow*)

formation. Normal fracture healing follows a predictable pattern on bone scintigraphy consisting of diffuse uptake at the fracture site during the acute phase, linear uptake during the subacute phase (Fig. 6), and diminishing uptake as healing progresses [17].

While radiographically apparent callus formation indicates biologic activity and viability, the absence of callus formation may be seen with both viable oligotrophic nonunion and nonviable atrophic nonunion. In cases where callus is absent, the pattern of uptake on bone scan may be helpful in differentiating viable from nonviable nonunion, as a photon deficient area is suggestive of nonviability, and the lack of a photon deficient area suggests viability [61].

Uptake of 18F-FDG on PET/CT has been shown to correlate with osteoblastic activity and bone formation [62, 63]. Using serial scans over the course of a few weeks in an in vivo rat model, Hsu et al. demonstrated increasing uptake in fractures that went on to heal, compared to decreasing uptake in fractures that went on to nonunion, suggesting that 18F-FDG may have a role in early prediction of nonunion [64, 65]. However, PET/CT has not been used in routine fracture follow-up primarily due to its high radiation profile compared with other imaging modalities. In current clinical practice, it is still used primarily for oncologic surveillance with fracture healing as an incidental secondary finding (Fig. 7).

Conclusions

Assessment of fracture union is an important part of orthopedic practice and relies on a multitude of factors, many of which are subjective. Research on the mechanical properties of bone and the process of bone healing has helped guide current practice to focus on callus formation as a key indicator and predictor of fracture union. Radiographs, CT, and ultrasound are all viable options to evaluate fracture union, each with unique advantages and limitations for this goal. Development of uniform scoring systems and identification of individual signs has helped standardize the radiologist's approach to these cases. Continuing work on obtaining computerized measurements and optimizing imaging techniques will help bring increased objectivity to this complex topic.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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