Floccinaucinihilipilification: is there a continuing role for the radiographic skeletal survey?

Daniel I. Rosenthal¹

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When I was a resident, a new imaging device was getting a lot of attention. It was known as the “CAT scanner.”

I went to the program director and asked if we would be getting one. “No” he said, “it’s a passing fad.”

In the long run, of course, everything passes, but the CAT (or CT) scanner has been with us for almost 50 years and seems likely to go on for a while longer.

The radiographic skeletal survey is older still. Radiography has been used to search for skeletal lesions since the discovery of the X-ray (1895). For the detection of most malignant skeletal conditions, radiographic screening yielded to the isotope bone scan once it became practical (1970s) because it was recognized that radiographs were not very sensitive to early bone involvement. However, the radiographic skeletal survey remained in use for multiple myeloma because it was determined that a significant portion of myeloma lesions did not take up isotope.

This did not indicate that the radiographic survey was more sensitive for myeloma than it was for other forms of skeletal malignancy, but only that the bone scan was less sensitive.

We learned the same lesson about the insensitivity of radiography when CT, then MRI, and most recently PET and

PET/CT came along: each modality was shown to be more sensitive than radiography for the detection of all types of skeletal malignancy, especially in the axial skeleton.

Despite the fact that the superior sensitivity of cross-sectional imaging for detection of bone lesions has been apparent for decades, it has not been possible to dislodge radiography from its place in the evaluation of multiple myeloma (MM).

As recently as the last 10 years, authoritative publications argued that the skeletal survey remained the standard method for the imaging evaluation of multiple myeloma [1].

These recommendations were made even though accumulating evidence indicates that each of the three cross-sectional techniques (CT, MRI, and PET/CT) is superior to radiography for lesion detection, both for skeletal lesions in general and even for the special case of myeloma [2].

It is clear that radiography is inferior to whole-body CT for detection of myeloma lesions, and the difference is not trivial. CT scan has been shown to detect many more lesions than skeletal survey, upstaging the disease in more than half of patients [3–5].

Radiographic survey is also inferior to whole-body MRI. The difference is also not subtle. Most (more than half!) patients with apparently solitary plasmacytoma at skeletal surveys are upstaged with MRI [6].

Detection of lesions on MRI that are not visible on radiography can be clinically significant. In two independent datasets of patients with smoldering multiple myeloma, the first of which included 149 patients assessed by whole-body MRI, and the second of 67 patients assessed with only spinal MRI, an optimal cutoff of two or more focal lesions without underlying osteolytic lesions has been found to be of prognostic significance for progression to symptomatic disease with a 2-year rate of progression of 70–80%. At the time of this publication, comparable data for PET were not available. NOTE: although the demonstration of lesions on MRI has prognostic significance in the absence of bone lesions, this fact alone does not prove the superiority of MRI. It must also

Key points

1. The radiographic skeletal survey is less sensitive than newer modalities (CT, MRI, PET) in detecting skeletal lesions of multiple myeloma.
2. The skeletal survey is less sensitive than those modalities in demonstrating the effects of treatment.
3. Interpretation of the newer modalities requires more specialized expertise and takes more time than the interpretations of radiographs.
4. Availability of the new modalities may be limited partly by payment policies.
5. Convergence by medical experts upon a single preferred method could help to ensure payment and encourage development of interpretation and reporting tools.

✉ Daniel I. Rosenthal
DIRosenthal@mgm.harvard.edu

¹ Massachusetts General Hospital, Harvard University,
Boston, MA 02114, USA

be shown that initiation of treatment based upon MRI findings will give better results. This has not been proven, although I would not bet against it.

Radiographic survey is also inferior to whole-body PET/CT in detection of lesions [7].

However, despite the fact that each of the cross-sectional imaging methods is superior to radiography, a recent survey of physicians in the UK found that the skeletal survey remained the most frequent first-line imaging test. Only 9.8% of responders offered first-line whole-body MRI [8]. There are various reasons that these numbers may not be directly transferable to other locations; however, they illustrate the point that practice patterns may not reflect what is known to be medically optimal.

The persistence of the radiographic survey has mostly been attributed to greater availability and convenience, lower radiation exposure and cost, and greater ease of use [9]. In view of these considerations, despite its poor sensitivity, the skeletal survey might have some advantages over the other modalities.

Availability

It is undoubtedly true that radiography is more available than the other methods. It can often be obtained on a walk-in basis. MRI requires an appointment that might last for an 1 h or more, and availability of these appointments varies greatly from place to place. The importance of this difference in availability is a matter of degree. If obtaining an appointment results in a wait of a week or two, then foregoing the better study in favor of the more available one would seem to be an example of unreasonable impatience. However, a delay of 6 months could have clinical consequences and would be another matter entirely.

In the developed world, the cross-sectional modalities have proliferated rapidly (to the chagrin of those who focus upon cost-control) [10]. For example, in the USA, CT scans are performed at the rate of approximately 80 million per year, and MRI at the rate of approximately 40 million. Compare these numbers to the annual incidence of multiple myeloma (32,000) [11]. If every myeloma patient had an MRI survey, it would require only 0.08% of the MRI capacity. It is very unlikely that scanners would be unavailable to accommodate myeloma patients in a timely fashion, although practical availability may be constrained to some degree by geographical inequities, and even more by reimbursement policies. The latter would hopefully be subject to change if the medical community would come to consensus concerning the proper approach to follow patients with myeloma and monoclonal gammopathy of undetermined significance (MGUS).

Patient convenience

Cross-sectional techniques are generally more comfortable for the patient than radiography because they are done in the supine position, and do not require the numerous changes of position that are necessary for radiography. Proper positioning for radiographs can be difficult and even painful for patients with significant bone disease. Although many people do not realize it, with modern CT equipment, the total examination time for a whole-body CT scan is actually shorter than it is for a radiographic skeletal survey [4]. In our institution, a radiographic survey requires approximately 45 min, while a whole-body CT scan can be performed in 15–20 min. MRI and PET/CT remain time-consuming examinations.

Radiation exposure

Radiation considerations may be important when one considers the high prevalence of MGUS in the population (3–4% of the population > age 50) [12], and the fact that periodic re-imaging will likely be required for these individuals.

It is true that CT scans deliver more radiation than skeletal survey with plain films. This was particularly true until relatively recently when low-dose CT techniques became widespread. Nevertheless, the radiation dose of even modern low-dose CT protocols is ~2–4 times higher than that of a digital skeletal survey [13]. While this is a significant difference, the absolute radiation exposure is not high (approximately 1 μ Sv for the skeletal survey and up to 3 μ Sv for “low-dose” CT). These numbers should be compared to the dose of 31 μ Sv delivered by a conventional CT scan of the abdomen and pelvis prior to the era of low-dose CT [14].

Work is underway to lower the radiation exposure even more. For example, the application of 0.6 mm of additional Sn filtration to the scanner has the potential to lower doses into the 1 mS range; significantly less than is required for a radiographic survey. Unfortunately, such low levels of exposure are not achievable with PET/CT which continues to deliver radiation doses in the range of 11–20 μ Sv [15].

MRI, of course, uses no ionizing radiation at all.

Therefore, based upon radiation considerations alone, there is no reason to prefer a skeletal survey to either a low-dose CT or whole-body MRI.

Ease of interpretation

Reading a whole-body examination such as a low-dose whole-body computed tomography (WBCT) or whole-body magnetic resonance imaging (WBMRI) can be a lengthy and demanding process. Tools that can help make the process

faster, more reproducible, and easier to communicate are desperately needed. There is no doubt that such tools are within reach. For example, subtraction maps can be created to focus attention on parts of the skeleton that have changed from a baseline examination. Although it was shown that this can be done rapidly and efficiently, tools for this purpose are not yet robust or widely disseminated [16]. Tools to facilitate the speed of interpretation and reporting are important to improve the practicality of clinical applications [17].

There is also a need to organize and standardize the reporting of whole-body MRI for multiple myeloma and a need for comparability of both the technique and the report [18].

If a single imaging method were selected to be performed on all potential myeloma patients, the increased level of experience might lead to greater ease of interpretation and stimulate the development of software tools and standardized reporting approaches.

Cost

Of course, CT, MRI, and PET/CT scanners cost more to purchase and operate than conventional radiography. However, the question is: cost to whom? The cost of providing the service is sensitive to equipment cost, real estate costs, staffing, and maintenance. It needs to be amortized over the life of the equipment and defrayed by the intensity of use. The cost to the patient is determined by whether or not cross-sectional examinations are a covered service for following the progression of plasma cell disorders. This is a function of the way in which health care financing is done and varies greatly from one location to another, making it difficult to compare this feature among the modalities. In the USA, and probably elsewhere, whole-body imaging is sometimes used as a screening tool (think “executive physicals”) something that is covered by few third payers. It is important to indicate that following MGUS or myeloma is NOT a screening examination.

For all of these complex reasons, it is impossible to compare costs, much less perform a cost/benefit analysis.

If the arguments in favor of radiography are weak, which of the alternatives should be chosen?

To some extent, we are victims of an embarrassment of riches. Three competing methodologies — WBMRI, WBCT, and PET-CT — are all recognized as superior to radiography in detection of lesions. Debate continues over which cross-sectional imaging modality is better in for particular contexts [19]. This is unfortunate, because the lack of consensus has the effect of fragmenting the potential market, and this undoubtedly retards developments that could make the entire process more efficient and beneficial.

Multiple myeloma is similar to metastatic disease in that the target of the disease is the cellular marrow. Lysis of bone is a

consequence of the marrow deposits, but is not necessarily an early finding. MRI and PET-CT can detect the abnormal marrow even when there is no bone destruction, and thus have a theoretical advantage over CT and radiography. However, myeloma differs from most metastatic malignancies in that the marrow may be abnormal (having elevated numbers of plasma cells) for a very long “pre-malignant” period (MGUS and smoldering myeloma), but the recognition of bone destruction has been a defining event that marks the transition to frank myeloma.

MRI, CT, PET/CT, and radiography demonstrate fundamentally different things. Radiography is not very good at contrast resolution and mostly detects areas where bone has been destroyed. CT detects bone destruction as well, but with greater sensitivity and better anatomical detail. CT also has the ability to recognize marrow replacement due to replacement of marrow fat by tumor, something that might occur with or without bone destruction. However, with CT, the findings of marrow replacement without bone destruction can be subtle and difficult to recognize. MRI detects marrow replacement best of all, based upon changes in the proportions of fat and water in the marrow. MRI may reveal a continuous spectrum of marrow cellularity from normal to densely hypercellular marrow. However, it can be difficult to distinguish hypercellular but otherwise normal red marrow from marrow infiltrated by myeloma, especially in patients who may have been treated with GCSF. PET scans are sensitive to increased glucose metabolism, something that might occur either with or without lytic bone lesions [12]. Extra medullary myeloma can be detected with PET or MRI; CT is much less successful for this purpose. Extramedullary myeloma is not rare. Studies have reported frequencies ranging from 7 to 20% at presentation and 6–20% during disease progression [20].

Part of the difficulty of deciding upon an appropriate imaging technique is related to the definition. Myeloma has historically been distinguished from its precursor forms (MGUS and smoldering myeloma) by the occurrence of “end-organ damage” represented by the somewhat ominous acronym “CRAB criteria” (hypercalcemia, renal impairment, anemia, and bone lesions). Diagnosis of MGUS and smoldering myeloma can only be made in the absence of CRAB criteria. The situation is analogous to the old definition of osteoporosis, which was not considered to be present until fracture had occurred. This definition of osteoporosis was abandoned as experience was gained with improved methods of measuring bone density.

The myeloma literature appears to be trending toward recognition that abnormal plasma cell accumulations might be accepted as defining myeloma in addition to the presence of bone destruction, at least for the purpose of deciding when to begin treatment. The International Myeloma Working Group guidelines of 2014 recommend that patients with more than 1 “unequivocal focal lesions” be started on therapy; “unequivocal” was defined as >5 mm [21]. This change has led to some

confusion about the distinction between a “focal deposit” and a “lytic lesion.” For example, in one recent paper, a finding of two or more 5-mm or larger focal lesions seen at MRI (or a single 5-mm or larger osteolytic lesion) is considered to be a myeloma biomarker. Radiologists will be familiar with the concept that a “focal deposit” on MRI is NOT the same thing as a “lytic lesion” since it may be seen either with or without bone destruction. Similarly, increased uptake can be observed on PET imaging in areas without lytic lesions [12]. As long as destruction of mineralized bone is part of the definition of multiple myeloma, the two CT techniques have a slight advantage as they are best suited to recognize bone destruction. However, the concept of “end-organ” damage as part of the definition of myeloma seems to be nearing the end of its useful life.

It begs the question of what to do with diffuse marrow infiltration, something that is best seen with MRI but not currently regarded as a myeloma-defining event [22].

Defining the precise transition to myeloma would be nothing more than a dry academic exercise if it did not have implications for when treatment should be initiated. There is no intrinsic reason that these should be linked. Medicine offers many examples in which “premorbid” conditions are treated (consider osteoporosis, mild hypertension elevated cholesterol levels, etc.)

However, use of the more sensitive cross-sectional studies MRI, PET, and/or PET/CT will result in many patients being upstaged when compared to radiography, and will probably cause more patients to begin treatment. Is this good or bad? If there is any valid role left for the radiographic survey, it would depend upon the argument that there is no benefit to such early treatment.

In a study of patients with either MM or SM, 25.5% had a negative skeletal survey and a positive WBCT for osteolytic lesions ($P < 0.0001$). This included 12 patients who would have been classified as with smoldering myeloma on skeletal survey but were upstaged to MM on CT. The presence of lytic bone lesions as detected with WBCT was shown to be of borderline prognostic significance in predicting transition to symptomatic myeloma ($P = 0.051$), with a median time to progression of 38 versus 82 months for those without bone destruction. However, no improvement in overall survival was found by early detection [13].

Conversely, it has been shown that the use of whole-body MRI does result in the largest rise in quality-adjusted life years compared with CT or FDG PET/CT [6]. However, earlier detection will have this effect even if the early initiation of therapy is ineffective. This is because by changing the definition, patients will appear to be living longer with their disease. The same arguments have been made for lung cancer and breast cancer screening.

Finally, we need to consider the role (if any) of the radiographic skeletal survey in following the effects of treatment which might be different from those used to determine when to initiate treatment.

At the present time, the literature suggests that PET is a better predictor of lesion viability than MRI [4] and is therefore more sensitive than MRI to early changes due to treatment [23].

PET uptake may disappear from regions in which the MRI remains abnormal. This is clearly an effect of treatment. What is not known at this time is whether the treatment is necessarily effective (i.e., curative or resulting in no lesion progression) [12]. Both methods, PET and MRI, are more sensitive than radiographs.

Both PET and MRI are also subject to “false positives” due to bone marrow hyperplasia (which can occur during recovery after chemotherapy or following the application of growth factors), but this effect is more prominent with PET/CT than MRI [4].

Conclusion

Is there any remaining use for the radiographic skeletal survey? It is clear that all of the other modalities discussed in this article have greater sensitivity and specificity for diagnosis, as well as greater predictive value in recognizing the effect of therapy.

...And yet, there might still be a role for whole-body XR imaging in one very special (and improbable) circumstance. If it were to turn out that treatment can wait until lesions appear on skeletal survey without any adverse effects on outcome, then possibly the skeletal survey may still have a role to play. I do not know of any data bearing directly on this question, but I doubt it.

Therefore, X-ray survey is neither recommended for initial diagnosis of MGUS, smoldering myeloma, or MM, nor is it recommended for evaluating the response to treatment or follow-up for recurrence.

The conventional X-ray skeletal survey is obsolete [24], and doctors need to accept the idea that their actions, or lack of actions, have resulted in continued use of this superannuated technology. Convergence on one of the modern approaches would lessen the ambiguity of which to choose, encourage clinicians to obtain the “proper” study and not the most convenient one, encourage the development of tools for interpretation and reporting, and also encourage development of realistic payment guidelines.

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