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ACR Appropriateness Criteria® on Metastatic Bone Disease

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Appropriate imaging modalities for screening, staging, and surveillance of patients with suspected and documented metastatic disease to bone include ^{99m}Tc bone scanning, MRI, CT, radiography, and 2-[^{18}F]fluoro-2-deoxyglucose–PET. Clinical scenarios reviewed include asymptomatic stage 1 breast carcinoma, symptomatic stage 2 breast carcinoma, abnormal bone scan results with breast carcinoma, pathologic fracture with known metastatic breast carcinoma, asymptomatic well-differentiated and poorly differentiated prostate carcinoma, vertebral fracture with history of malignancy, non-small-cell lung carcinoma staging, symptomatic multiple myeloma, osteosarcoma staging and surveillance, and suspected bone metastasis in a pregnant patient. No single imaging modality is consistently best for the assessment of metastatic bone disease across all tumor types and clinical situations. In some cases, no imaging is indicated. The recommendations contained herein are the result of evidence-based consensus by the ACR Appropriateness Criteria® Expert Panel on Musculoskeletal Radiology.

Key Words: Appropriateness Criteria®, metastatic disease, bone, imaging, screening, surveillance, staging

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SUMMARY OF LITERATURE REVIEW

There are several imaging and interventional techniques for the initial detection and follow-up of metastatic bone disease: radiography, radionuclide bone scanning, CT, MRI, fine-needle aspiration, and core-needle biopsy. Newer techniques include 2-[^{18}F]fluoro-2-deoxyglucose (FDG)–PET, FDG-PET/CT, and whole-body MRI [1-4].

Except for a few limitations, radionuclide bone scanning remains the primary imaging examination used to detect osseous metastasis. It has been repeatedly shown to be more sensitive than radiography [5]. Bone scans are sensitive in detecting osseous abnormalities, but they are

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Variant 1. Stage 1 carcinoma of the breast; initial presentation: asymptomatic

Radiologic Procedure	Rating	Comments	RRL
X-ray radiographic survey whole body	1		Medium
Percutaneous biopsy area of interest	1		NS
MRI area of interest with or without contrast	1		None
^{99m}Tc bone scan whole body	1		Medium
Myelography and postmyelography CT spine	1		High
FDG-PET whole body	1		High

Note: Rating scale: 1 = least appropriate, 9 = most appropriate. FDG = 2-[^{18}F]fluoro-2-deoxyglucose; NS = not specified; RRL = relative radiation level.

nonspecific. After an abnormality has been detected, it should be x-rayed to make sure it does not represent a benign process such as osteoarthritis, inflammatory arthritis, or fracture [6]. One of the major advantages of radionuclide bone scanning is that it allows for a total-body survey. This is important because approximately 13% of metastatic lesions occur in the appendicular skeleton in regions that are usually not included on a skeletal survey [7]. Krishnamurthy et al [7] pointed out that most metastatic skeletal lesions could be asymptomatic and that serum alkaline phosphatase level is a poor indicator of early metastases. Highly aggressive metastases may show "cold" or photopenic areas on a bone scan. Multiple myeloma can frequently show photopenic lesions or negative bone scan results [8,9]. Bone scans are also insensitive in detecting skeletal lesions due to Langerhans cell histiocytosis (histiocytosis X), and radiographic surveys are recommended for patients with this disease [10,11]. Diffuse bony metastasis may present with a pattern of intense uniform radionuclide uptake (superscan), which can be misinterpreted as negative findings.

Solitary sites of increased radionuclide uptake in patients with known malignancy are a common occurrence, and they could pose a diagnostic problem because of the nonspecific nature of these abnormalities on bone scintigraphy. On the other hand, Boxer et al [12] reported that approximately 21% of patients with breast cancer relapsed with solitary bone lesions, most commonly in the spine. The spine was the most common site for both solitary and multiple metastases. Tumeh et al [13] reported that solitary rib metastases in cancer patients are uncommon and that 90% of "hot" rib lesions on bone scanning are due to benign causes. A solitary sternal "hot" lesion in a patient with breast carcinoma has an 80% probability of being due to metastatic disease [14]. When a patient with a known primary tumor develops a solitary lesion on a bone scan, further diagnostic evaluation should be undertaken, starting with radiography and, if that is not diagnostic, proceeding to CT, MRI, or even biopsy [15,16]. Some authors advocate single-photon emission CT (SPECT) imaging as an ef-

Variant 2. Stage 2 carcinoma of the breast; initial presentation, with back and hip pain

Radiologic Procedure	Rating	Comments	RRL
^{99m}Tc bone scan whole body	9	To be done first to evaluate for presence of lesions suspicious for metastatic disease.	Medium
X-ray spine and hip	9	Radiographs obtained after bone scan if needed for further lesion characterization.	Medium
FDG-PET whole body	5	If results of bone scan are negative and the results of the PET examination will influence the use of systemic treatment.	High
^{99m}Tc bone scan with SPECT hip and spine	1		Medium
Myelography and postmyelography CT spine	1		High
CT hip and spine with or without contrast	1		Medium
X-ray radiographic survey whole body	1		Medium
MRI hip and spine with or without contrast	1		None

Note: Rating scale: 1 = least appropriate, 9 = most appropriate. FDG = 2-[^{18}F]fluoro-2-deoxyglucose; RRL = relative radiation level.

Variant 3. Breast carcinoma; follow-up bone scan reveals single "hot" lesion in spine

Radiologic Procedure	Rating	Comments	RRL
X-ray spine "hot" area(s)	9		Low
MRI spine without contrast	9	If results of radiography are negative.	None
FDG-PET whole body	5	If results of the PET examination will influence the use of systemic treatment.	High
MRI spine with contrast	1		None
Myelography and postmyelography CT spine	1		High
Percutaneous biopsy spine	1		NS
X-ray radiographic survey whole body	1		Medium
CT spine with or without contrast	1		Medium

Note: Rating scale: 1 = least appropriate, 9 = most appropriate. FDG = 2-[^{18}F]fluoro-2-deoxyglucose; NS = not specified; RRL = relative radiation level.

fective method for differentiating malignant from benign lesions in the spine [17].

Breast Cancer

In stage 1 breast carcinoma, in which the results of bone scintigraphy are usually negative, most authorities believe that routine baseline and follow-up bone scans are probably unwarranted because of the very low true-positive yield [18,19]. The panel does not recommend any imaging studies of the skeleton in asymptomatic patients with stage 1 carcinoma of the breast when they present initially (see Variant 1). Bone scanning, FDG-PET [20,21], and PET/CT [22,23] have been shown to be useful in the preoperative staging and postoperative follow-up of stages 2, 3, and 4 breast carcinoma.

If a patient with stage 2 breast carcinoma presents with back and hip pain, the panel recommends radiography of the back and hip and radionuclide bone scanning (see Variant 2). Other studies may be needed depending on the results of radiography and bone scanning. In patients with known breast carcinoma who are discovered to have a single "hot" area in the spine on bone scanning, the panel recommends radiography of the "hot" area. If radiographic results are negative, the panel recommends MRI (see Variant 3). For lesion localization and needle guidance, a CT scan is recommended if a needle biopsy is warranted. The panel recommends adding SPECT imaging if the results of planar radionuclide bone scanning are equivocal. In patients discovered to have multiple "hot" lesions in the spine, the panel recommends radiography of these "hot" lesions; MRI is also recommended if radiographic results are negative (see Variant 4). A CT scan becomes necessary if a needle biopsy is to be performed.

For a "hot" lesion of the sternum in a patient with known breast carcinoma, the panel recommends radiography, followed by MRI, to help in the diagnosis (see Variant 5). MRI should be performed with the patient prone to minimize respiratory artifacts, and the use of an opposed-phase (also referred to as in and out of phase)

Variant 4. Breast carcinoma; 3 "hot" areas in spine revealed by bone scan; no back pain

Radiologic Procedure	Rating	Comments	RRL
X-ray spine "hot" area(s)	9		Low
MRI spine without contrast	9	If results of radiography are negative.	None
FDG-PET whole body	5	If results of the PET examination will influence the use of systemic treatment.	High
SPECT spine	5	SPECT added to bone scan in equivocal lesions.	Medium
MRI spine with contrast	1		None
Percutaneous biopsy spine	1		NS
Myelography and postmyelography CT spine	1		High
CT spine "hot" area with or without contrast	1		Low
X-ray radiographic survey whole body	1		Medium

Note: Rating scale: 1 = least appropriate, 9 = most appropriate. FDG = 2-[^{18}F]fluoro-2-deoxyglucose; NS = not specified; RRL = relative radiation level.

Variant 5. History of treated breast carcinoma; now has single "hot" lesion revealed by bone scan in sternum

Radiologic Procedure	Rating	Comments	RRL
CT sternum without contrast	9		Medium
MRI sternum without contrast	8	If patient can tolerate prone imaging. Use of opposed-phase sequence helpful to assess for marrow obliterating process.	None
X-ray sternum	5	Difficult area to image with radiography.	Low
FDG-PET whole body	5	If results of the PET examination will influence the use of systemic treatment.	High
SPECT sternum	5		Medium
X-ray radiographic survey whole body	1		Medium

Note: Rating scale: 1 = least appropriate, 9 = most appropriate. FDG = 2-[^{18}F]fluoro-2-deoxyglucose; RRL = relative radiation level.

sequence is suggested to best assess for marrow replacement by tumor. Computed tomography is useful for localization if fine-needle aspiration or core biopsy is required.

Long Bone Fracture

In a patient with known metastatic carcinoma presenting with a pathologic fracture of a long bone on radiography, the panel recommends a radionuclide bone scan to look for other metastatic sites in the skeleton (see Variant 6).

Prostate Cancer

Studies have shown that for staging and follow-up of patients with prostate carcinoma, radionuclide bone scans are not necessary unless the prostate specific antigen (PSA) level is ≥20 ng/mL or the primary tumor is poorly differentiated [24-27]. For routine staging purposes (no bone pain), the panel agrees with these studies (see Variant 7). However, the panel recommends a radionuclide bone scan for patients with prostate-specific antigen levels not >20 ng/mL or poorly differentiated primary tumors (see Variant 8).

Non–small-cell Lung Cancer

In patients with non-small-cell carcinoma of the lung, bone is one of the most common sites for early extrathoracic spread. Some of these bony metastases are asymptomatic. The exclusion of bone metastases is important in the initial preoperative staging of lung cancer, although it is not clear from the literature whether bone scans should be performed routinely or only when clinical indicators suggest skeletal metastases [28-30]. The panel currently recommends a radionuclide bone scan of the skeleton in patients coming for staging after needle

Variant 6. Patient with known bone metastatic disease (carcinoma of the breast); presenting with pathologic fracture of left femur on radiography

Radiologic Procedure	Rating	Comments	RRL
^{99m}Tc bone scan whole body	9		Medium
FDG-PET whole body	5	If results of bone scan are negative and the results of the PET examination will influence the use of systemic treatment.	High
SPECT femur	1		Medium
X-ray radiographic survey whole body	1		Medium
CT femur without contrast	1		Low
MRI femur without contrast	1		None
X-ray femur	1		Minimal
Percutaneous biopsy femur	1		NS

Note: Rating scale: 1 = least appropriate, 9 = most appropriate. FDG = 2-[^{18}F]fluoro-2-deoxyglucose; NS = not specified; RRL = relative radiation level.

Variant 7. Prostate nodule on physical examination proven to be a well-differentiated or moderately differentiated carcinoma and prostate-specific antigen level < 20 mg/mL; patient asymptomatic

Radiologic Procedure	Rating	Comments	RRL
MRI area of interest without contrast	1		None
CT area of interest without contrast	1		NS
X-ray radiographic survey whole body	1		Medium
^{99m}Tc bone scan whole body	1		Medium
FDG-PET whole body	1		High

Note: Rating scale: 1 = least appropriate, 9 = most appropriate. FDG = 2-[^{18}F]fluoro-2-deoxyglucose; NS = not specified; RRL = relative radiation level.

biopsy of lung nodules revealed non-small-cell carcinomas (see Variant 9). However, in patients with non-small-cell carcinoma of the lung who have undergone or will be undergoing FDG-PET studies as part of their initial workup, radionuclide bone scanning is not necessary [1,2]. The current PET literature has significant variability due to differing study quality and imaging techniques used, but this technique has the potential to improve the accuracy of non-small-cell lung carcinoma tumor staging, especially for bone metastases [31].

Primary Bone Tumors

Bone metastases are very uncommon at initial presentation in patients with primary malignant bone tumors; therefore, radionuclide bone scanning is not indicated. Bone scanning has been shown not to be useful in differentiating between benign and malignant lesions or in defining the local extent of a malignant tumor reliably [32,33]. Osteosarcoma is probably the only exception; although the yield of imaging for metastases at the time of diagnosis is small, the presence of an occasional metastasis could substantially affect the treatment of the patient [34,35]. The panel concurs with these reports, and it recommends radionuclide bone scanning for patients with osteosarcoma at presentation for staging (see Variant 10). In patients with osteosarcoma who have received adjuvant chemotherapy, 16% may develop asymptomatic osseous metastasis before lung metastasis; therefore, some authors suggest bone scans for routine follow-up [34,35]. The panel concurs with these reports, and it recommends radionuclide bone scanning for patients with osteosarcoma at follow-up and after tumor resection with clear margins and chemotherapy (see Variant 11). FDG-PET has not been proven to replace chest CT and bone scanning as a staging modality for osteosarcoma [36].

Other Cancers

In patients with cancers that rarely metastasize to bone—such as cervical, endometrial, bladder, and gastrointestinal tract tumors—baseline scans are obtained only when the disease is advanced [37]. There is no consensus in the literature about the timing of follow-up scans in asymptomatic patients. Some authors have suggested bone scans every 6 months for 1 year and then every 2 years. In clinical practice, most medical and radiation oncologists request follow-up bone scans only (1) in asymptomatic patients with evidence of progressive disease (ie, rising carcinoembryonic antigen or alkaline phosphatase values), (2) for restaging the disease in patients with local recurrence, and (3) in patients with symptoms that are potentially of osseous origin [37].

Radiography is frequently used to screen for metastatic sites in multiple myeloma and Langerhans cell histiocytosis (histiocytosis X), but generally it is considered insensitive to screen for asymptomatic metastases [8-11]. In patients with multiple myeloma who present with acute low-back pain, the panel recommends radiography

Variant 8. Prostate nodule on physical examination proven to be a poorly differentiated carcinoma or prostate-specific antigen ≥ 20 mg/mL; patient asymptomatic

Radiologic Procedure	Rating	Comments	RRL
^{99m}Tc bone scan whole body	9		Medium
CT area of interest without contrast	1		NS
X-ray radiographic survey whole body	1		Medium
MRI area of interest without contrast	1		None
FDG-PET whole body	1		High

Note: Rating scale: 1 = least appropriate, 9 = most appropriate. FDG = 2-[^{18}F]fluoro-2-deoxyglucose; NS = not specified; RRL = relative radiation level.

Variant 9. 1-cm lung nodule; non–small-cell at needle biopsy; now presenting for staging and resection

Radiologic Procedure	Rating	Comments	RRL
FDG-PET whole body	9		High
^{99m}Tc bone scan whole body	9	Not needed if PET imaging performed for initial nodule workup.	Medium
MRI chest without contrast	1		None
X-ray radiographic survey whole body	1		Medium
CT chest without contrast	1		Medium

Note: Rating scale: 1 = least appropriate, 9 = most appropriate. FDG = 2-[^{18}F]fluoro-2-deoxyglucose; RRL = relative radiation level.

of the lumbosacral spine or bone survey if the interval since the last bone survey is long (see Variant 12). Magnetic resonance imaging is useful in patients with neurologic findings or to better characterize the bone marrow. The panel believes that the only time when radionuclide bone scanning (with or without SPECT) would be needed in cases of multiple myeloma is when ^{89}Sr treatment is being considered.

Vertebral Column

The vertebral column deserves special consideration. It is the most common site of skeletal metastasis, and cord compression from metastasis is among the most dreaded complications of cancer [12]. Magnetic resonance imaging has proven advantages over all other imaging modalities, including myelography and CT myelography [6,16] (see Variant 13). One limitation of MRI has been its inability to consistently differentiate an acute traumatic or acute osteopenic compression fracture from a pathologic fracture. The use of diffusion-weighted MRI has been shown to be effective in differentiating benign osteopenic vertebral collapse from malignant collapse, but the efficacy of this technique is still controversial, and it has not gained widespread use [38-42]. The role of FDG-PET and FDG-PET/CT has been assessed in metastatic disease of the spine. In patients with lung cancer, studies have shown that FDG-PET has better specificity than bone scans using ^{99m}Tc methylene diphosphonate tracer but similar sensitivity for detecting osseous metastatic disease [1,2]. Additionally, FDG-PET/CT has better specificity for detecting metastatic involvement of the spine than FDG-PET. FDG-PET/CT allows precise localization of bone lesions and associated soft-tissue involvement with potential neurologic significance [4].

As MRI sequences continue to become faster, there is emerging evidence showing that whole-body MRI is feasible and that it can replace bone scintigraphy for detecting metastatic bone disease. Proponents of this technique indicate that whole-body MRI is more sensitive and more specific than bone scintigraphy or PET [43,44]. In addition to bone metastases, whole-body MRI can demonstrate silent metastases in the brain, lungs, and liver

Variant 10. Young patient with osteosarcoma of long bone presenting for staging; results of chest CT normal; looking for bone metastases

Radiologic Procedure	Rating	Comments	RRL
^{99m}Tc bone scan whole body	9		Medium
MRI area of interest with or without contrast	9	MRI of surrounding region to evaluate for small skip metastases. See statement regarding contrast in text under “Anticipated Exceptions.”	None
FDG-PET whole body	5	If results of bone scan are negative and MRI is equivocal, and if results of the PET examination will influence the use of systemic treatment.	High
^{99m}Tc bone scan with SPECT area of interest	1	SPECT added to nuclear medicine in equivocal lesions.	Medium
CT area of interest without contrast	1		NS
X-ray radiographic survey whole body	1		Medium

Note: Rating scale: 1 = least appropriate, 9 = most appropriate. FDG = 2-[^{18}F]fluoro-2-deoxyglucose; NS = not specified; RRL = relative radiation level.

Variant 11. Osteosarcoma, resected clear margins; chemotherapy, asymptomatic; 6-month follow-up after treatment to rule out bone metastases

Radiologic Procedure	Rating	Comments	RRL
^{99m}Tc bone scan whole body	9		Medium
CT area of interest with or without contrast	1		NS
X-ray radiographic survey whole body	1		Medium
MRI area of interest with or without contrast	1		None
^{99m}Tc bone scan with SPECT area of interest	1		Medium
FDG-PET whole body	1		High

Note: Rating scale: 1 = least appropriate, 9 = most appropriate. FDG = 2-[^{18}F]fluoro-2-deoxyglucose; NS = not specified; RRL = relative radiation level.

[45]. Whole-body MRI is also comparable in cost to bone scintigraphy [46]. No ionizing radiation is involved with whole-body MRI, making it especially suited for pregnant patients with suspected bony metastasis [3] (see Variant 14).

Depending on whether the lesion is lytic, blastic, or associated with a soft-tissue mass, fine-needle aspiration or core biopsy can be used to arrive at a definitive diagnosis in patients suspected of having metastasis of known or unknown origin. Needle biopsy is also helpful in suspected tumor recurrence and to differentiate metastasis from osteonecrosis in previously irradiated bone [47-50].

SUMMARY

- Radionuclide bone scanning is the most widely used primary imaging examination for detecting osseous metastasis.
- After an abnormality has been detected, radiographs should be obtained to make sure the abnormality does not represent a benign process.
- If radiography is not diagnostic, additional lesion workup with MRI, CT, SPECT, or FDG-PET/CT is highly variable and should be based on the clinical situation and lesion location.

ANTICIPATED EXCEPTIONS

Nephrogenic systemic fibrosis is a disorder with a scleroderma-like presentation and a spectrum of manifestations that can range from limited clinical sequelae to fatality. It seems to be related to both underlying severe renal dysfunction and the administration of gadolinium-based contrast agents. It has occurred primarily in patients on dialysis, rarely in patients with very limited glomerular filtration rates (ie, $<$30 mL/min/1.73 m^2), and almost never in other patients. There is growing literature regarding nephrogenic systemic fibrosis. Although some controversy and lack of clarity remain, there is a consensus that it is advisable to avoid all gadolinium-based contrast agents in dialysis-dependent patients unless the possible benefits clearly outweigh the risk and to limit the type and amount in patients with estimated glomerular filtration rates $<$30 mL/min/1.73 m^2. For more information, please see the ACR's *Manual on Contrast Media* [51].

Variant 12. Patient with multiple myeloma presenting with acute low back pain

Radiologic Procedure	Rating	Comments	RRL
X-ray lumbar spine	9		Medium
MRI lumbar spine without contrast	8	Important if neurologic symptoms are present. Better defines lesion characteristics and adjacent marrow.	None
X-ray radiographic survey whole body	2	If long interval since last bone survey.	Medium
^{99m}Tc bone scan whole body	1		Medium
CT lumbar spine without contrast	1		Medium
MRI lumbar spine with contrast	1		None
FDG-PET whole body	1		High

Note: Rating scale: 1 = least appropriate, 9 = most appropriate. FDG = 2-[^{18}F]fluoro-2-deoxyglucose; RRL = relative radiation level.

Variant 13. Patient with known malignancy, with back pain and partially collapsed vertebra on radiography; otherwise healthy

Radiologic Procedure	Rating	Comments	RRL
MRI spine without contrast	9	To differentiate osteoporotic collapse from destructive lesion.	None
^{99m}Tc bone scan whole body with SPECT spine	8	To detect additional lesions.	Medium
FDG-PET whole body	5	If results of bone scan are negative and the results of the PET examination will influence the use of systemic treatment.	High
MRI spine with contrast	1		None
CT spine without contrast	1		Medium
Percutaneous biopsy spine	1		NS
X-ray radiographic survey whole body	1		Medium

Note: Rating scale: 1 = least appropriate, 9 = most appropriate. FDG = 2-[^{18}F]fluoro-2-deoxyglucose; NS = not specified; RRL = relative radiation level.

RELATIVE RADIATION LEVEL INFORMATION

Potential adverse health effects associated with radiation exposure are an important factor to consider when selecting the appropriate imaging procedure. Because there is a wide range of radiation exposures associated with different diagnostic procedures, a relative radiation level indication has been included for each imaging examination. The relative radiation levels are based on effective dose, which is a radiation dose quantity that is used to estimate population total radiation risk associated with an imaging procedure (Table 1). Additional information regarding radiation dose assessment for imaging examinations can be found in *ACR Appropriateness Criteria®: Radiation Dose Assessment Introduction* [52].

Disclaimer: *The ACR Committee on Appropriateness Criteria® and its expert panels have developed criteria for determining appropriate imaging examinations for the diagnosis and treatment of specified medical conditions. These criteria are intended to guide radiologists, radiation oncologists, and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for the evaluation of a patient's condition are ranked. Other imaging studies necessary to evaluate other coexistent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the US Food and Drug Administration have not been considered in developing these criteria, but the study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be*

Variant 14. Woman, 8 weeks pregnant, with known primary, now suspected of having bone metastasis; patient wants to continue with the pregnancy

Radiologic Procedure	Rating	Comments	RRL
MRI whole body without contrast	9	Should be done first due to lack of ionizing radiation.	None
X-ray area of interest	9	With appropriate shielding. Helpful to evaluate risk of pathologic fracture.	NS
CT area of interest without contrast	2	If involving an extremity. With appropriate shielding.	NS
^{99m}Tc bone scan whole body	2		Medium
X-ray radiographic survey whole body	1		Medium
FDG-PET whole body	1		High

Note: Rating scale: 1 = least appropriate, 9 = most appropriate. FDG = 2-[^{18}F]fluoro-2-deoxyglucose; NS = not specified; RRL = relative radiation level.

Table 1. Relative radiation level designations

Relative Radiation Level*	Effective Dose Estimate Range (mSv)
None	0
Minimal	<0.1
Low	0.1-1
Medium	1-10
High	10-100

*The relative radiation level assignments for some examinations cannot be made, because the actual patient doses in these procedures vary as a function of a number of factors (eg, the region of the body exposed to ionizing radiation, the imaging guidance that is used). The relative radiation levels for these examinations are designated as "NS" (not specified).

made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.

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