American College of Radiology
ACR Appropriateness Criteria®

Clinical Condition: **Screening for Pulmonary Metastases**

Variant 1:   **Primary malignancy: bone and soft tissue sarcoma.**

Radiologic Procedure	Rating	Comments	RRL*
CT chest	9	Initial evaluation or surveillance.	Med
X-ray chest	9	If performed as a baseline.	Min
FDG-PET whole body	5		High
MRI chest	2		None
Rating Scale: 1=Least appropriate, 9=Most appropriate			***Relative Radiation Level**

Variant 2:   **Primary malignancy: renal cell carcinoma.**

Radiologic Procedure	Rating	Comments	RRL*
X-ray chest	8		Min
CT chest	7	Depends on the stage of the disease.	Med
MRI chest	2		None
FDG-PET whole body	1		High
Rating Scale: 1=Least appropriate, 9=Most appropriate			***Relative Radiation Level**

Variant 3:   **Primary malignancy: testicular cancer.**

Radiologic Procedure	Rating	Comments	RRL*
X-ray chest	8		Min
CT chest	7	Recommended if abdominal disease is present.	Med
MRI chest	3		None
FDG-PET whole body	3		High
Rating Scale: 1=Least appropriate, 9=Most appropriate			***Relative Radiation Level**

An ACR Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). 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 exams generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent 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 FDA have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.

Clinical Condition: **Screening for Pulmonary Metastases**

Variant 4: **Primary malignancy: malignant melanoma.**

Radiologic Procedure	Rating	Comments	RRL*
X-ray chest	9	If performed as a baseline.	Min
CT chest	8	Initial evaluation or surveillance.	Med
FDG-PET whole body	5		High
MRI chest	2		None
Rating Scale: 1=Least appropriate, 9=Most appropriate			***Relative Radiation Level**

Variant 5: **Primary malignancy: head and neck carcinoma.**

Radiologic Procedure	Rating	Comments	RRL*
X-ray chest	9	If performed as a baseline.	Min
CT chest	9	Initial evaluation or surveillance.	Med
FDG-PET whole body	5		High
MRI chest	2		None
Rating Scale: 1=Least appropriate, 9=Most appropriate			***Relative Radiation Level**

SCREENING FOR PULMONARY METASTASES

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Summary of Literature Review

The incidence of pulmonary metastatic disease in patients who have died of an extrathracic malignancy (ETM) is reported as 20%-54% [1,2]. The indications for chest radiography, computed tomography (CT), magnetic resonance imaging (MRI), and scintigraphic imaging have been discussed in the literature. Since the last update of the ACR Appropriateness Criteria® on screening for pulmonary metastatic disease in 1999, there have been improvements in CT imaging quality and scan time, as well as advances in the field of nuclear medicine and MRI. In particular, there have been more studies on the use of positron emission tomography (PET) CT in the evaluation of patients with metastatic pulmonary disease.

In determining the specific imaging modality that should be performed, authors conclude that several factors should be taken into consideration: 1) the biological behavior of the tumor, 2) the sensitivity and specificity of the imaging modality, 3) radiation dose, and 4) cost effectiveness. The relative indications for chest radiography, CT, MRI, and scintigraphy have been evaluated for various primary malignancies. Detection of pulmonary nodules, lymphangetic spread, endobronchial lesions, intravascular metastatic pulmonary disease, nodal disease, and chest wall lesions have all been discussed in the literature.

Chest Radiography
It is generally accepted that chest radiography, with posteroanterior (PA) and lateral views, should be the initial imaging test in patients without known or suspected thoracic metastatic disease [1-3]. If the chest radiograph demonstrates obvious multiple pulmonary nodules, further imaging beyond follow-up chest radiography may not be indicated unless biopsy is planned, or unless precise quantification of disease is required in the preoperative evaluation for metastasectomy or the assessment of response to systemic radiation therapy or chemotherapy.

Some authors have questioned the role of "routine" chest radiographs. In one study, a review of "routine" chest radiographs obtained in the evaluation of patients with breast cancer revealed that fewer than 0.93% of these radiographs demonstrated previously undiagnosed pulmonary metastases [4]. In another study, 876 asymptomatic patients with localized cutaneous (stage I or intermediate thickness stage II) malignant melanoma had initial staging chest radiographs; 130 (15%) had "suspicious" findings, but on further follow-up, only 1 (0.1%) of these patients had a true-positive study for pulmonary metastasis [5]. Another study analyzed the overall cost-effectiveness of chest radiographs in the life-long screening of patients with intermediate-thickness cutaneous melanoma. It was concluded that significant cost savings may be possible by decreasing the frequency of screening in the first 2 years and limiting screening to the first 5 to 10 years after diagnosis [6]. Patients with higher probability of pulmonary metastatic disease should be screened more frequently or with a more sensitive imaging modality such as CT.

Computed Tomography
Compared with chest radiography, CT is much more sensitive for detecting pulmonary nodules, because of its lack of superimposition and its high contrast resolution [1-3]. Other abnormalities, such as lymphadenopathy, pleural involvement, chest wall lesions, endobronchial lesions, intravascular pulmonary involvement, or incidental findings in the upper abdomen, may also be revealed or better demonstrated. In patients with known ETM, chest CT is recommended if the initial chest radiograph reveals an apparent solitary pulmonary nodule or an equivocal finding. If the chest radiograph is negative, CT is recommended if the underlying ETM is one that has a high propensity for dissemination to the lungs, such as breast, renal cell, colon, and bladder carcinoma. As noted in the preceding section, CT is indicated even with multiple pulmonary nodules on the chest radiograph if biopsy or definitive treatment by metastasectomy or systemic therapy is planned.

It is now well known that spiral CT scanning is more sensitive than conventional CT, allowing the detection of a significantly larger number of nodules and also a larger number of small nodules <5 mm in diameter [7]. With

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further developments in technology, it is likely that the sensitivity of CT scanning will continue to improve while the radiation dose associated with scanning may be lowered. Nevertheless, a few studies that have correlated CT findings with surgical or pathologic findings offer some sobering results. In a retrospective review, McCormack et al [8] found that CT underestimated the surgical pathologic findings in 25% of cases. More thorough detection of metastatic nodules is possible at thoracotomy by means of manual palpation of the entire collapsed lung [9,10].

It has been suggested that the greater sensitivity of CT for detecting pulmonary nodules, as compared with chest radiography, is associated with diminished specificity [2]. Nevertheless, it is increasingly recognized that even small pulmonary nodules may represent malignant lesions. In a series of patients undergoing video-assisted thoracoscopic resection of small (≤1 cm) pulmonary nodules, 28 malignant lesions were diagnosed in 27 patients with a history of previous malignancy; 23 lesions (84%) were malignant, including 15 metastases (54%) and eight new lung carcinomas (29%), and five nodules (18%) were benign [11]. The specificity of CT in any given series depends on several variables: 1) the propensity of the underlying ETM to disseminate to the lungs; 2) the stage of the ETM; 3) selection factors for the study population; and 4) patient age, smoking history, history of prior treatment for the ETM, and likelihood of prior granulomatous disease. In addition, it has been reported that intraoperative palpation of the lungs is still warranted to detect metastatic lesions not detected by spiral CT. In one study, 22% (9/41) more malignant nodules were found intraoperatively than were detected by helical CT [12].

Recently the utility of CT for evaluating intravascular pulmonary metastatic disease has also been described. Liver, kidney, stomach, and breast carcinoma as well as sarcomas have been reported to embolize to the pulmonary vasculature [13]. Differentiation between metastatic disease and thromboembolic disease can be difficult. Ting et al [13] describe morphological features such as tubular and beaded appearance to help distinguish between the two. With improvement of CT resolution, such intravascular metastatic disease will be more readily detectable [14].

Recommendations for the use of CT in detecting pulmonary metastases must be tailored for each ETM. Even for an individual ETM, however, it may still be difficult to arrive at a consensus for the optimal application of CT. Some guidelines for chest CT surveillance in a few common primary tumors, as determined from review of the recent literature, are summarized below.

Bone and Soft Tissue Sarcomas
Despite multi-agent chemotherapy regimens and radical resection of the primary tumor, a large number of patients with bone and soft tissue sarcomas will have relapse, manifested by dissemination of disease to the lungs as the first site of metastasis. One review of the published literature for osteosarcoma recommends aggressive surgical resection of synchronous and metachronous pulmonary metastases, even if multiple thoracotomies are required [15]. These authors state that CT is the preferred study in the screening for such metastases, although up to twice as many lesions may be found at thoracotomy.

Other authors, in a study of 5-year survival after pulmonary metastasectomy for soft tissue sarcoma, determined through multivariate analysis that the number of nodules detected by preoperative CT has prognostic value, and they recommend routine use of CT [16]. In another study of patients with high-grade soft tissue sarcomas undergoing metastasectomy, a specific protocol for follow-up is described: routine chest radiographs and chest CT are performed for the first 5 years, with a plain film obtained at each visit and chest CT performed every 3 months for the first year, every 4 months for the second year, every 6 months for the third year, and once yearly thereafter [17].

Renal Cell Carcinoma
Pulmonary metastases from renal cell carcinoma are seen in 25%-30% of patients at the time of initial diagnosis, and in 30%-50% of patients at a later time [18]. In patients with metastases to the lungs, surgical resection may provide the only effective treatment, in light of the fact that 5-year survival rate is < 5% for stage IV disease [19]. Based on their own experience and a review of the literature, Lim and Carter [19] recommended PA and lateral chest radiographs as an initial test. In patients with low-stage (T1) disease and a normal chest radiograph, CT is not necessary; if the chest radiograph demonstrates multiple nodules, CT is not necessary unless it is required as part of the protocol for systemic therapy. The authors proposed that indications for chest CT should include: 1) a solitary pulmonary nodule on the chest radiograph; 2) symptoms suggestive of endobronchial metastasis; 3) extensive regional disease; and 4) presence of other extrathoracic metastases that might be amenable to resection. Other authors advocate a more aggressive approach, with biannual chest radiographs and chest CT examinations [18]. They recommend that such surveillance be life-long, in view of the possibility of delayed recurrent pulmonary metastases.

Testicular Cancer
See and Hoxie [20] suggest that the risk of intrathoracic metastases is correlated with the presence of abnormal findings on abdominal CT. In their study, 74 of 155

patients with seminomatous or nonseminomatous testicular germ cell tumors had imaging by both chest radiographs and chest CT scans concurrently at the time of initial staging. Findings were compared to those of patients having negative or abnormal abdominal CT scans. For the group of 42 patients with negative abdominal CT scans, results of chest CT did not increase the yield for diagnosis of metastases as compared with the chest radiograph; a 2.3% chest CT false-positive rate is in fact cited as a potential source of morbidity in the workup of patients. For the group of 32 patients with abnormal abdominal CT, however, chest CT allowed detection of pulmonary metastases not seen on the chest radiograph in 12.5% of cases. For initial staging workup, the authors therefore recommend chest radiographs for patients with a negative abdominal CT and chest CT for patients with an abnormal abdominal CT.

Malignant Melanoma
Recommendations for chest CT scanning in malignant melanoma appear to be largely determined by the stage of the primary tumor. Buzaid et al [21] retrospectively assessed the role of CT (neck, chest, abdomen, and pelvis) in detecting occult distant metastases in 89 asymptomatic patients with local-regional melanoma who had normal chest radiographs and serum lactate dehydrogenase levels. In only one case was there evidence of disease on chest CT not seen on the chest radiograph, and the authors concluded that chest CT may not be indicated. A large retrospective study of asymptomatic patients with stage III melanoma, assessing the role of CT (head, chest, abdomen, pelvis), suggests that chest CT should be used selectively in patients with cervical adenopathy [22]. In a review of the role of surgical resection for melanoma metastatic to the lung, Ollila and Morton [23] emphasized that metastasectomy may represent the only potentially curative treatment modality in stage IV disease. While noting that metastasectomy is believed to improve survival in patients with one or two pulmonary nodules, they cautioned that the number of lesions should not represent an absolute contraindication to surgery. They recommended that preoperative evaluation of patients for pulmonary metastasectomy should include not only chest CT to determine the number of nodules but also whole-body imaging to exclude other extrapulmonary stage IV disease.

Head and Neck Carcinoma
Although the lungs are the most common site of distant metastases in squamous cell carcinoma (SCCA) of the head and neck, there is no clear consensus as to the optimal imaging modality for surveillance. An issue of particular importance in this population is the known increased incidence (15%-30%) of second primary malignancies, including neck, lung, and esophageal cancers [24]. In one retrospective study, only two of 57 patients with head and neck SCCA (stage not specified) had malignancy in the form of synchronous tumors identified on routine chest CT, and these lesions were also evident on chest radiographs [25]. Other authors, however, have observed that chest CT demonstrates a high number of malignancies, including both pulmonary metastases and additional thoracic malignancies, in patients with advanced SCCA [24]. Among 93 patients undergoing chest CT at the time of initial presentation, during routine follow-up or at the time of local-regional neck recurrence, a total of 24 (25.8%) had identification of thoracic malignancy, including 14 (15%) with pulmonary metastases, 5 (5.4%) with lung carcinoma, and 1 (1.1%) with esophageal carcinoma. Except for two patients with initial stage I or II disease and local-regional neck recurrence, these patients all had stage III or IV disease.

Magnetic Resonance Imaging
MRI has been considered an alternative to CT for detecting pulmonary metastases, primarily because exposure to ionizing radiation would be avoided, an issue of particular concern with young patients undergoing multiple follow-up examinations. Nevertheless, it is generally accepted that MRI does not currently have a role in screening of patients for pulmonary metastases [3,26]. Motion-related artifacts, a lower spatial resolution than CT, and an inability to detect calcification within lesions all represent limitations of MRI [26]. A recent study comparing turbo-spin echo MRI with spiral CT as a gold standard demonstrated a lower sensitivity for MRI in detecting pulmonary metastases; for 340 metastases identified on CT, the overall sensitivity of MRI was 84%, but for nodules <5 mm in diameter, sensitivity was only 36% [26].

Scintigraphy
The use of scintigraphy in conjunction with tumor-seeking agents may offer significant incremental information, enhancing the specificity of diagnosis, as compared with conventional morphologic imaging techniques. There are preliminary reports of results for a variety of scintigraphic techniques applied to a number of different malignancies, but the ultimate role of such imaging has yet to be established.

Imaging with ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) is increasingly being used in the staging of patients with bronchogenic carcinoma, not only for nodal involvement but also for possible distant metastases. Its role in detecting pulmonary metastases from known ETM is well established. One study demonstrated the utility of FDG-PET in detecting occult extrapulmonary disease in patients with pulmonary metastatic melanoma [27]. In particular, it was determined to be useful in excluding extrapulmonary

metastatic melanoma prior to surgery, and the authors concluded that PET scanning should be used in patients with pulmonary metastatic melanoma prior to metastectomy [27]. Use of FDG-PET in the staging of malignant melanoma has also been investigated, but it is acknowledged that this technique has limited sensitivity for small pulmonary nodules, and that false-positive results may occur because of inflammatory processes [28]. Use of FDG-PET alone does not negate the need for spiral CT in evaluating pulmonary metastatic disease. A negative FDG-PET exam cannot exclude metastatic disease [29]. This is thought to be due to small metastatic nodules.

Other radiopharmaceuticals have also been used. In one study, encouraging results were reported for the use of ^{99m}Tc-methoxyisobutylisonitrile scintigraphy in 81 patients with a history of previously excised malignant melanoma [30]. Such whole-body scanning correctly detected 92% of 74 metastatic lesions at various sites, including 8 lung lesions ranging from 1.2 to 6.0 cm in size, two of which were not previously diagnosed. Use of an indium-111-labeled monoclonal antibody (CCR 086) for detecting colorectal metastases at various sites, including lung lesions as small as 1 cm, has been reported [31]. In patients with osteosarcoma, bone scintigraphy with single photon emission computed tomography (SPECT) has been compared with chest CT for detecting pulmonary metastases [32]. In eight patients with pulmonary metastases, bone SPECT and CT results were both positive, but bone SPECT showed additional lesions initially missed on CT in two patients; in the other four patients, bone SPECT was negative for lesions (1.0-1.5 cm) that were detected by CT. In 19 patients without pulmonary metastases, bone SPECT results were negative; chest CT revealed lesions in seven patients, but these were eventually proved to be benign. The authors concluded that negative findings on a bone SPECT study do not exclude the possibility of pulmonary metastases, but that positive findings on a bone SPECT study may lead to earlier surgical resection of small pulmonary nodules seen on CT, or may even reveal subtle lesions not detected by CT. More recently, ^{99m}Tc-depreotide has shown promise in detecting pulmonary metastasis from renal cell carcinoma that is somatostatin receptor-positive [33].

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