

American College of Radiology ACR Appropriateness Criteria®

Clinical Condition: Pretreatment Planning of Invasive Cancer of the Cervix

Variant 1: FIGO stage Ib1, tumor size <4 cm.

Radiologic Procedure	Rating	Comments	RRL*
MRI pelvis without and with IV contrast	8	DWI improves interobserver agreement and accuracy and helps distinguish post biopsy change. MRI and FDG-PET/CT are complementary examinations.	O
FDG-PET/CT whole body	8	MRI and FDG-PET/CT are complementary examinations.	⚠⚠⚠⚠
MRI pelvis without IV contrast	6		O
CT abdomen and pelvis with IV contrast	5		⚠⚠⚠
X-ray chest	4		⚠
CT abdomen and pelvis without IV contrast	2		⚠⚠⚠
US abdomen	2		O
US pelvis transabdominal	2		O
US pelvis transvaginal	2		O
CT abdomen and pelvis without and with IV contrast	1		⚠⚠⚠⚠
X-ray IV contrast enema	1		⚠⚠⚠
Radiography intravenous urography	1		⚠⚠⚠
Bone scan whole body	1		⚠⚠⚠
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			*Relative Radiation Level

Clinical Condition: Pretreatment Planning of Invasive Cancer of the Cervix**Variant 2:** FIGO stage Ib2, tumor size >4 cm.

Radiologic Procedure	Rating	Comments	RRL*
MRI pelvis without and with IV contrast	9	DWI improves interobserver agreement and accuracy and helps distinguish post biopsy change. MRI and FDG-PET/CT are complementary examinations.	○
FDG-PET/CT whole body	9	MRI and FDG-PET/CT are complementary examinations.	☢☢☢☢
MRI pelvis without IV contrast	6		○
X-ray chest	5		☢
CT abdomen and pelvis with IV contrast	5		☢☢☢
CT abdomen and pelvis without IV contrast	2		☢☢☢
US pelvis transvaginal	2		○
US pelvis transabdominal	2		○
US abdomen	2		○
CT abdomen and pelvis without and with IV contrast	1		☢☢☢☢
X-ray IV contrast enema	1		☢☢☢
Radiography intravenous urography	1		☢☢☢
Bone scan whole body	1		☢☢☢
<u>Rating Scale:</u> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			*Relative Radiation Level

Clinical Condition: Pretreatment Planning of Invasive Cancer of the Cervix**Variant 3:** FIGO stage >Ib.

Radiologic Procedure	Rating	Comments	RRL*
MRI pelvis without and with IV contrast	9	DWI improves interobserver agreement and accuracy and helps distinguish post biopsy change. MRI and FDG-PET/CT are complementary examinations.	O
FDG-PET/CT whole body	9	MRI and FDG-PET/CT are complementary examinations.	⚠⚠⚠⚠
CT abdomen and pelvis with IV contrast	7		⚠⚠⚠
CT chest with IV contrast	6		⚠⚠⚠
MRI pelvis without IV contrast	6		O
CT chest without IV contrast	4		⚠⚠⚠
CT abdomen and pelvis without IV contrast	2		⚠⚠⚠
X-ray chest	2		⚠
US pelvis transabdominal	2		O
US abdomen	2		O
Bone scan whole body	2	This procedure is used with stages >II or with symptoms of bone metastases.	⚠⚠⚠
US pelvis transvaginal	2		O
CT abdomen and pelvis without and with IV contrast	1		⚠⚠⚠⚠
CT chest without and with IV contrast	1		⚠⚠⚠
Radiography intravenous urography	1		⚠⚠⚠
X-ray IV contrast enema	1		⚠⚠⚠
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			*Relative Radiation Level

PRETREATMENT PLANNING OF INVASIVE CANCER OF THE CERVIX

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Summary of Literature Review

Introduction/Background

Cervical cancer is the third most common gynecological malignancy in the United States. It is estimated that during 2015 there will be approximately 12,900 new cases of cervical cancer and 4100 deaths from this disease in the United States [1]. The American Cancer Society reports that the death rate from cervical cancer decreased 29% from 1991 to 2003 [1], but it did not significantly change from 2002 to 2012 [2]. This improvement in mortality has been attributed to a significant increase in detection of early-stage small cancers due to the development of the Papanicolaou smear. However, only minor improvement has been achieved in the survival rate for invasive cervical cancer [3]. Established risk factors for cervical cancer include early sexual activity, especially with multiple partners; cigarette smoking; immunosuppression; and infection with human papilloma viruses 16 and 18 and other high-risk serotypes. [4].

The prognosis of cervical carcinoma has been strongly linked to lymph node involvement by tumor [5]. This, in turn, is predicted clinically and pathologically by the stage of disease, the volume of the primary tumor, and the histologic grade [6]. The current official staging system for cervical cancer is based on the International Federation of Gynecology and Obstetrics (FIGO) classification [7]. It defines the clinical staging system for cervical carcinoma based on clinical assessments including physical examination under anesthesia, colposcopy, endocervical curettage, hysteroscopy, cystoscopy, proctoscopy, intravenous urography, barium enema (BE), and radiographs of lungs and skeleton [8]. Although various imaging tests are selected, cross-sectional imaging with computed tomography (CT) or magnetic resonance imaging (MRI) is not essential. Errors in clinical FIGO staging have been consistently reported, with understaging of Ib–IIIb cancer varying from 20%–40%. Overstaging of FIGO IIIb cancer in up to 64% of patients has also been reported [9].

Inaccuracy in clinical staging is predominantly due to difficulties in evaluating parametrial and pelvic sidewall invasion, bladder or rectal wall invasion, and metastatic spread; in evaluating primary endocervical (endophytic) tumors; and in estimating primary tumor size, especially the craniocaudal dimension. Aside from the inaccuracies of clinical staging, evaluation of lymph node metastasis, which is an important prognostic factor and a determinant in treatment planning, is not included in the clinical staging system [8]. In spite of these limitations of clinical FIGO staging, modern cross-sectional imaging modalities such as ultrasound (US), CT, and MRI have not been incorporated into FIGO staging. Arguments against the use of CT and MRI as staging tools include their high cost and possible lack of availability, especially in the underdeveloped regions of the world where invasive cervical cancer is the most prevalent [8]. Because of the limitations of clinical staging, cross-sectional imaging is frequently used in the United States. The results are used for treatment planning but are not included in reporting the FIGO stage.

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Current Role of Imaging

The most important issue in treatment planning for cervical cancer is to distinguish early disease (stages Ia, Ib, and IIa) that can be treated with surgery from advanced disease that must be treated with radiation therapy or chemoradiation [10]. In addition, for those with advanced disease, imaging is used to define the radiation therapy fields by delineating the anatomical extent of disease [11,12]. Conventional radiological studies such as excretory urography, BE, and lymphangiography (LAG) are rarely, if ever, used today. There has been an increase in the use of cross-sectional imaging, particularly CT, MRI, and positron emission tomography (PET)/CT [13].

Radiographs

Chest radiographs are obtained as a staging procedure to identify pleural effusion or pulmonary metastasis, which occur in the late stages of cervical cancer. However, chest CT is superior to radiographs in both cases.

Excretory Urography

Although excretory urography is a sensitive test for detecting urinary obstruction, CT, MRI, and US reliably identify urinary tract obstruction. Excretory urography is not indicated in women with cervical cancer due to the limited information provided and ionizing radiation.

Ultrasound

Transabdominal US is a sensitive, noninvasive means of detecting hydronephrosis but has a limited role in evaluating the local extent of cervical cancer. Transrectal US (TRUS) and transvaginal US have been used in assessing local disease. The detection of parametrial disease and pelvic sidewall involvement can be achieved with TRUS. The accuracies of TRUS and MRI are similar for tumor detection and parametrial infiltration [14,15]. MRI has better soft-tissue contrast than US. TRUS is operator dependent and, due to the narrow field of view, gives no additional information on nodal status.

Computed Tomography

CT has staging accuracy ranging from 32%–80% in cervical cancer [16,17]. The sensitivity for parametrial invasion ranges from 17%–100%, with an average of 64% [16,17]. There is a consensus in the literature that CT is most valuable in patients with advanced disease and that it has limited value (a positive predictive value of 58%) in evaluating early parametrial invasion [16,17]. CT has been reported to have a high accuracy in depicting advanced disease. However, an ACRIN[®] trial reported that CT had a sensitivity of only 42% for detecting advanced disease (>IIB), with a sensitivity and specificity for detecting lymph node involvement of 31% and 86%, respectively [13,18].

The major limitation of CT in local staging is the inadequate differentiation between tumor and normal cervical stroma or parametrial structures [19]. Therefore, CT is mainly used in advanced disease and in the assessment of lymph nodes. The positive predictive value of CT for nodal involvement ranges from 51%–65%, with negative predictive value ranging from 86%–96% [16,17,20] and with sensitivities reported recently to range from 31%–65% [13,20]. CT detection of lymph node metastasis has a pooled sensitivity and specificity of 50% and 92%, respectively, on meta-analysis [21]. The reliance on size criterion alone (>1 cm) for diagnosing malignant lymphadenopathy on CT is believed to account for the low sensitivity because micrometastases will be missed. CT shows distant metastases for radiation therapy planning and can be used to guide interventional procedures [22].

Magnetic Resonance Imaging

MRI is very accurate in determining tumor size, especially the craniocaudal extent, and tumor location (exophytic or endocervical). MRI is helpful in assessing the depth of stromal invasion to assess parametrial tumor extension and further local extension of the tumor. MRI is superior to clinical evaluation in assessing tumor size. MRI measurements are within 0.5 cm of the surgical size in 70%–94% of cases [6,17,19,23,24]. However, an ACRIN[®] trial reported that neither MRI nor CT was accurate for evaluating the cervical stroma [19]. The use of endovaginal coils has been reported to be helpful in assessing small-volume disease [25]. MRI after cone biopsy has significantly lower sensitivity and specificity for tumor detection [26].

The staging accuracy of MRI ranges from 75%–96% [16,17,27,28]. The sensitivity of MRI in evaluating parametrial invasion ranges from 40%–57%, with a specificity of 77%–80% [16-18,27,28]. In studies that compare MRI and CT for evaluating parametrial invasion, MRI was superior to CT [16,17,27,28]. Use of 3.0T MRI does not provide improvement in accuracy [29]. The apparent diffusion coefficients (ADCs) calculated in

cervical cancer are lower than those of normal cervical stroma, providing increased contrast between the normal cervical stroma and tumor. The diffusion sequences require no intravenous contrast and add approximately 2 minutes to the MR protocol [30]. The addition of diffusion-weighted imaging (DWI) improves interobserver agreement and is helpful, especially when the T2-weighted images are equivocal [31]. In assessing local tumor invasion, T2-weighted and contrast-enhanced T1-weighted images are helpful. Small tumors may be better defined with postcontrast imaging [32,33]. Lymph node metastases also show significantly decreased ADC values when compared to benign lymph nodes. Abnormal nodes as small as 5 mm can be detected with DWI [34,35]. MR spectroscopy with choline measurements provides no additional benefit [30]. In evaluating nodal disease, the sensitivity and specificity of MRI are 30%–73% and 69%–95%, respectively. These findings are similar to those of CT [16,17,20,27,28,36,37]. Like CT, MRI also relies on size criteria for assessing lymph nodes and thus misses microscopic disease [38]. The sensitivity of MRI in detecting lymph node metastases is reported to be both higher [36] and lower [39] than that of PET/CT in different studies. MRI had greater accuracy in detecting lymph node metastases in patients with tumors >4 cm in size [40].

Very few integrated PET/MRI scanners are in operation, and to date there have been no studies performed to detect or stage cervical cancer. The theoretical advantage of PET/MRI over PET/CT is the improved soft-tissue contrast, yielding better tissue characterization with MR. One study involved patients who had both a PET/CT examination and an MRI examination. The MR images were fused with the PET/CT images using a Windows workstation, and the alignment was verified in 3 planes. This study found an improved sensitivity with PET/MRI when compared to PET/CT (54% versus 44%, respectively) for metastatic lymph node detection. [41]. No diffusion sequences were used in this protocol.

MRI can be a cost-effective staging technique. In a study of patients with Ib cervical cancer, those who underwent MRI as the initial imaging procedure for staging required fewer examinations and procedures compared with those who underwent tests such as BE, intravenous urogram, CT scan, cystogram, and proctoscopy [33,42]. Tumor size >4 cm, cervical stromal invasion, and parametrial extension are correlated with increased risk of lymphadenopathy, which significantly affects patient management and prognosis for survival [6,20,25]. Because these predictive criteria for the primary tumor are best evaluated radiologically, routine use of MRI has been recommended.

Lymphangiography and Lymphoscintigraphy

LAG has technical limitations such as incomplete opacification of lymph node chains, occasional inability to cannulate 1 side, and lack of assessment of internal iliac nodes. For the pretreatment evaluation of lymph node metastases, LAG has been replaced by CT, MRI, and PET imaging. Preoperative lymphoscintigraphy can be used in patients undergoing sentinel node biopsy. Patients have Bleu Patente V injected in the cervix at the time of laparoscopy. The bleu stained lymph nodes excised are correlated with lymph node radioactivity from a Tc-99m cervical injection on the day of or day prior to laparoscopy. This is used to aid the surgeon in the operating room. High sensitivity (92%) and negative predictive value (98%) have been shown [43].

Positron Emission Tomography and Positron Emission Tomography/Computed Tomography

PET imaging is superior to CT and LAG in assessing pelvic and extrapelvic lymph nodes and organ involvement by cervical cancer [44]. In the detection of metastatic lymph nodes in patients with cervical cancer, PET has been reported to have a sensitivity of 78%–91% and a specificity of 94%–100%. These values are higher than those for MRI and CT [45,46], although microscopic metastases may still be missed [47]. Accuracy rates for lymph node metastases are reportedly higher for PET imaging than for MRI (78% versus 67%) [48]. Another study demonstrated that prognosis was best when patients had both PET-negative and CT-negative lymph node status and that the presence of PET-positive para-aortic lymph nodes was the most significant negative prognostic factor for progression-free survival [49,50]. This same study found that PET using the tracer fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG) to assess lymph node status was the best predictor of overall survival in women with cervical cancer [50].

Hybrid PET/CT combines the functional metabolic imaging capabilities of PET with the spatial resolution of CT. Survival from cervical cancer can be stratified based on the level of lymph node metastases detected on FDG-PET. Lymph node involvement in pelvic, para-aortic, and supraclavicular nodes is associated with increasingly poor prognosis [63]. Recent studies report a sensitivity of 58%–82%, specificity of 93%–99%, and accuracy of 85%–99% for PET/CT in detecting metastatic lymph nodes from cervical cancer [21,39]. Another study showed that when abdominal CT is negative, PET has a sensitivity of 85.7%, a specificity of 94.4%, and an accuracy of

92% for detecting para-aortic lymph node metastasis in patients with advanced cervical cancer [51], prompting some to advocate routine PET imaging in such cases [52]. In patients with early-stage cervical cancer (stages Ib–IIa, <4 cm), the value of FDG-PET for lymph node metastasis is decreased, with a sensitivity of 32% [53,54]. A meta-analysis of imaging options found that FDG-PET/CT is the best predictor of lymph node status [55]. The overall sensitivity of FDG-PET/CT is variable by stage and improves with higher-stage disease, likely because of the increased prevalence of lymph node–positive disease in higher-staged tumors. Lymph node status and maximum standardized uptake value (SUV_{max}) of the tumor were found to be the 2 top indicators of poor prognosis [56].

The tumor size, lymph node status, stage, and SUV_{max} are all important in predicting outcome. The SUV predicts metabolic activity and tumor proliferation and is associated with tumor size and lymph node metastasis. High SUV_{max} with lymph node disease indicates a poor prognosis [57,58]. Another study compared a low- SUV_{max} group of cervical cancer patients ($SUV_{max} = 9.6 \pm 2.6$) with a high- SUV_{max} group ($SUV_{max} = 19.9 \pm 4.9$). A higher rate of pelvic/para-aortic lymph node disease (73% versus 38%) was found in the high- SUV_{max} cohort [59]. A study by Xue et al [60] found that a low SUV_{max} was associated with a better outcome in women treated with radiation therapy or concurrent chemotherapy. In addition to SUV_{max} tumor, standardized uptake value in pelvic lymph nodes (SUV_{PLN}) is an additional independent marker for prognosis [77]. The SUV_{PLN} was not strongly correlated with SUV_{max} of the index tumor or to lymph node size but was predictive of patient survival. In addition to lymph node status, total lesion glycolysis (a volume-based parameter) may prove to be an additional independent predictor of prognosis [61].

FDG-PET/CT may alter cervical cancer treatment plans. In one study, 4 of 15 patients had significant changes of radiation therapy treatment plans after review of the FDG-PET/CT [78].

Nuclear Medicine Bone Scan

Bone scans do not seem warranted for initial screening in asymptomatic patients with stages 0, I, or II cervical carcinoma. Bone scintigraphy may be useful in patients with advanced disease (stages III and IV) who are symptomatic for bone metastases, such as with pain or hypercalcemia, and may not have access to PET/CT imaging. PET/CT did outperform CT and MRI in detecting hematogenous bone metastasis from cervical cancer [62]. FDG-PET is more sensitive in detecting bone metastases in cancer patients than is bone scintigraphy [63].

Trachelectomy Assessment

Women with invasive cervical cancer stage Ia or small stage Ib who wish to retain fertility can be evaluated for trachelectomy, which is removal of the cervix, parametrial tissue, and cuff of the vagina. During the surgery, a cerclage suture is placed across the uterine isthmus to maintain uterine competency in the event of a future pregnancy. Staging based on FIGO is not sufficient for these women, and precise identification of tumor extent up to, including, and beyond the internal os is essential. MRI will aid in assessment of patients wishing to preserve fertility, evaluating these inclusion criteria [64]:

- 1) Tumor confined to the cervix; no tumor beyond the cervix or into the uterine body
- 2) No pelvic lymph node metastases
- 3) No evidence of impaired fertility
- 4) Tumor size <2 cm (some centers will go up to 4 cm)

These women will require a careful evaluation to assess tumor size and the distance from the tumor to the internal os. One centimeter of preserved healthy cervical stroma is preferred; some surgeons will accept as little as 5 mm. Tumors ≤ 2 cm in size are associated with increased likelihood of trachelectomy surgery [65].

MRI is good at accurately measuring the distance of the tumor to the internal os. Nine of 9 patients with a ≤ 5 -mm distance and 3 of 5 patients with a 6- to 9-mm distance required a radical hysterectomy because intraoperative assessment revealed a positive tumor resection margin [65]. Unfortunately, small-volume cervical cancer tumor and post biopsy inflammatory changes may be indistinguishable on T2-weighted images. Recent studies of endovaginal MRI with DWI show promise. The DWI in conjunction with the T2-weighted images provided increased accuracy. Restricted diffusion was shown in the cervical cancer tumor and helped distinguish post biopsy changes [31].

Tumor Stage Ib

Women with stage Ib1 who do not wish fertility preservation are also best evaluated with MRI as tumor visualization, tumor size accuracy and parametrial invasion are all best assessed on MRI when compared to CT

[18]. Nodal metastatic disease ranges from 10%–30% in stage Ib1 disease, depending on the tumor grade and volume and the presence or absence of lymph/vascular space invasion [54]. It is essential to exclude lymph node metastatic disease in this group because curative surgery is not an option in the setting of lymph node metastatic disease. MRI had a sensitivity and specificity of 64% and 69%, respectively, for lymph node metastases in a cohort of 83 patients with FIGO stages Ib–II [66]. FDG-PET/CT has a sensitivity ranging from 29%–75% in early-stage cervical cancer [36,67]. The specificity of FDG-PET/CT is high, ranging from 84%–97% [68]. The PET/CT sensitivity and specificity are 29% and 84%, respectively. MRI is more sensitive and FDG-PET is more specific. Overall accuracies are similar for the 2 tests: 65% and 68% for FDG-PET and MRI, respectively.

Patients with stage Ib2 tumors >4 cm are best evaluated with MRI because MRI assessment is better than CT assessment for tumor visualization, accuracy of tumor size, and parametrial invasion [18]. FDG-PET/CT remains the best imaging test to assess lymph node metastases [55].

Tumor Stage >Ib

Tumors beyond stage Ib have spread beyond the confines of the cervix. Tumors spread to the upper vagina, stage IIa, can be surgically resected, whereas stage IIb tumors have invaded the parametrium and are treated not with surgery but rather with chemoradiation. These patients benefit from MRI evaluation of the index tumor for size and local invasion. FDG-PET/CT is beneficial in identifying metastatic disease and planning external radiation therapy [69].

Summary of Recommendations

- Imaging plays an essential role in pretreatment evaluation of women with invasive cervical cancer. It is used to assess tumor size and location; to detect involvement of the parametrium, pelvic sidewall, and adjacent organs; and to search for lymph node metastases.
- MRI provides the best visualization of the primary tumor, estimation of tumor size and volume, and extent of soft-tissue disease in the central pelvis.
- FDG-PET is the best modality in assessing nodal, extrapelvic, and bone metastasis and is also helpful in predicting patient outcome when SUV_{max} and SUV_{PLN} are incorporated into the assessment.
- Future studies may use the best of both techniques with MRI/PET fusion imaging.

Summary of Evidence

Of the 69 references cited in the *ACR Appropriateness Criteria® Pretreatment Planning of Invasive Cancer of the Cervix* document, 63 are categorized as diagnostic references including 1 well designed study, 21 good quality studies, and 24 quality studies that may have design limitations. Additionally, 4 references are categorized as therapeutic references including 1 good quality study. There are 20 references that may not be useful as primary evidence. There are 2 references that are meta-analysis studies.

The 69 references cited in the *ACR Appropriateness Criteria® Appropriateness Criteria® Pretreatment Planning of Invasive Cancer of the Cervix* document were published from 1991-2015.

While there are references that report on studies with design limitations, 23 well designed or good quality studies provide good evidence.

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 (RRL) indication has been included for each imaging examination. The RRLs 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. Patients in the pediatric age group are at inherently higher risk from exposure, both because of organ sensitivity and longer life expectancy (relevant to the long latency that appears to accompany radiation exposure). For these reasons, the RRL dose estimate ranges for pediatric examinations are lower as compared to those specified for adults (see Table below). Additional information regarding radiation dose assessment for imaging examinations can be found in the *ACR Appropriateness Criteria® [Radiation Dose Assessment Introduction](#)* document.

Relative Radiation Level Designations		
Relative Radiation Level*	Adult Effective Dose Estimate Range	Pediatric Effective Dose Estimate Range
○	0 mSv	0 mSv
⊗	<0.1 mSv	<0.03 mSv
⊗⊗	0.1-1 mSv	0.03-0.3 mSv
⊗⊗⊗	1-10 mSv	0.3-3 mSv
⊗⊗⊗⊗	10-30 mSv	3-10 mSv
⊗⊗⊗⊗⊗	30-100 mSv	10-30 mSv
*RRL assignments for some of the examinations cannot be made, because the actual patient doses in these procedures vary as a function of a number of factors (eg, region of the body exposed to ionizing radiation, the imaging guidance that is used). The RRLs for these examinations are designated as “Varies”.		

Supporting Documents

For additional information on the Appropriateness Criteria methodology and other supporting documents go to www.acr.org/ac.

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The 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 examinations 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.