

# Imaging in Cervical Cancer

Michele Follen, M.D., Ph.D.<sup>1</sup>  
 Charles F. Levenback, M.D.<sup>1</sup>  
 Revathy B. Iyer, M.D.<sup>2</sup>  
 Perry W. Grigsby, M.D.<sup>3</sup>  
 Erik A. Boss, M.D.<sup>4</sup>  
 Ebrahim S. Delpassand, M.D.<sup>5</sup>  
 Bruno D. Fornage, M.D.<sup>2</sup>  
 Elliot K. Fishman, M.D.<sup>6</sup>

<sup>1</sup> Department of Gynecologic Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas.

<sup>2</sup> Department of Diagnostic Radiology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas.

<sup>3</sup> Department of Radiation Oncology, Washington University School of Medicine, St. Louis, Missouri.

<sup>4</sup> Department of Gynecology and Obstetrics, University Medical Center St. Radboud Nijmegen, Nijmegen, The Netherlands.

<sup>5</sup> Department of Nuclear Medicine, The University of Texas M. D. Anderson Cancer Center, Houston, Texas.

<sup>6</sup> Department of Radiology, The Johns Hopkins University School of Medicine, Baltimore, Maryland.

Presented at the Second International Conference on Cervical Cancer, Houston, Texas, April 11–14, 2002.

Address for reprints: Michele Follen, M.D., Ph.D., Center for Biomedical Engineering, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 193, Houston, TX 77030; Fax: (713) 792-4856; E-mail: mfollen@mdanderson.org

Received October 31, 2003; accepted February 7, 2003.

Cervical cancer traditionally has been staged clinically. Advances in imaging could improve the staging of cervical cancer by facilitating the detection of lymph node metastases and micrometastases in distant organs. Such progress could lead to improvements in treatment selection and therefore increase overall survival rates. At the Second International Conference on Clinical Cancer (Houston, TX, April 11–14, 2002), a panel composed of gynecologic oncologists, radiation oncologists, and diagnostic radiologists reviewed relevant technologies. Advances in lymphangiography, ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and lymphatic mapping were reviewed, along with the impact of these advances on the diagnosis, treatment, and survival of patients with cervical cancer. Few cancer centers still use lymphangiography, but the sensitivity of this method ranges from 28% to 83%, with specificity ranging from 47% to 100%. The roles of transabdominal and transvaginal ultrasonography in evaluating cervical cancer are expected to expand when new contrast agents increase the sensitivity of these techniques to parametrial invasion and lymph node metastases; meanwhile, ultrasonography's most significant contributions may involve the identification of uterine and cervical leiomyomas and the evaluation of urinary tract obstruction. Advances in CT have made it a rival technique to MRI, but limitations prevent CT from providing definitive information on certain parameters. MRI, which is valuable because of its superior soft tissue contrast resolution, multiplanar capabilities, and cost-effectiveness, is used to determine the size of the cervix and to detect certain types of invasion, characteristics of lymph nodes, and the presence of disease in the ureter, lung, and liver. PET with 2-[fluorine-18]fluoro-2-deoxy-D-glucose has been found to detect abnormal lymph node regions better than CT does but PET can also be used in conjunction with CT to measure tumor dimensions. PET also has become a method for identifying tumors that are unresponsive to chemoradiation. When used together with immunohistochemical and molecular techniques as well as conventional stains, sentinel lymph node mapping, an important development in the surgical management of solid tumors, is expected to improve gynecologic cancer management. Advances in imaging methods and in contrast agents, along with advances in the combined use of the two, are expected to make imaging technologies more valuable in cervical cancer assessment. *Cancer* 2003;98(9 Suppl):2028–38. © 2003 American Cancer Society.

**KEYWORDS:** staging, imaging, cervical cancer, lymphography, ultrasonography, computed axial tomography, magnetic resonance imaging, positron emission tomography.

**T**reatment for cervical cancer has improved vastly over the past few decades, in no small part because of the increased accuracy of cervical cancer staging. Cervical cancer typically is staged clinically, but clinical staging, while accurate in diagnosing localized disease, does not detect lymph node metastases or micrometastases in distant organs. Imaging technologies, especially computed tomography (CT)

**TABLE 1**  
**TNM and International Federation of Gynecology and Obstetrics**  
**Clinical Classifications of Cervical Cancer<sup>a</sup>**

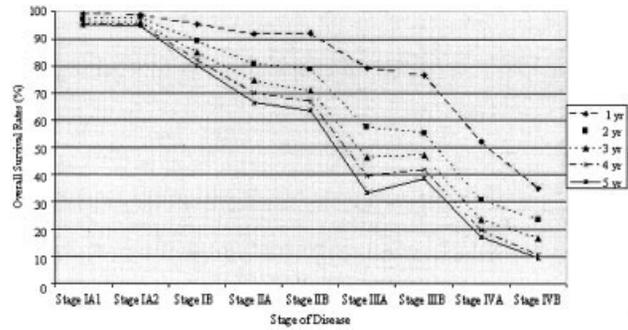
TNM <sup>b</sup>	Description	FIGO
T	Tumor classification	
Tis	In situ	0
T1	Confined to uterus	I
T1a	Diagnosed only by microscopy	IA
T1a1	Depth ≤ 3 mm, horizontal spread ≤ 7 mm	IA1
T1a2	Depth 3–5 mm, horizontal spread ≤ 7 mm	IA2
	Clinically visible or microscopic lesion, greater than T1a2	
T1b	Beyond uterus but not pelvic wall or lower third of vagina	IB
T1b1	≤ 4 cm	IB1
T1b2	>4 cm	IB2
T2	Lower third of vagina/parametrium	II
T2a	No parametrium	IIA
T2b	Parametrium	IIB
T3	Lower third of vagina/pelvic wall/hydronephrosis	III
T3a	Lower third of vagina	IIIA
T3b	Pelvic wall/hydronephrosis	IIIB
T4	Mucosa of bladder/rectum; beyond true pelvis	IVA
N	Regional lymph nodes	—
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Regional lymph node metastasis	
M	Distant metastasis	IVB
MX	Distant metastasis cannot be assessed	
M0	No distant metastasis	
M1	Distant metastasis	

FIGO: International Federation of Gynecology and Obstetrics.  
<sup>a</sup> Sobin LH, Wittekind C, editors. TNM classification of malignant tumours, 6th edition. New York: John Wiley & Sons, 2002.<sup>8</sup>  
<sup>b</sup> Staging method of the American Joint Committee on Cancer and the International Union Against Cancer.

and magnetic resonance imaging (MRI), have the potential to make a significant impact in determining the proper treatment for patients with cervical cancer and in improving overall survival rates. Positron emission tomography (PET), in conjunction with 2-[fluorine-1]fluoro-2-deoxy-D-glucose (FDG), has been used in cervical cancer staging and follow-up,<sup>1–5</sup> and it has been valuable in accurately assessing lymph node and distant metastases.<sup>6</sup> Newer, copper-labeled tracers also are expanding the range of uses of PET. In the current report, after a brief discussion of staging, we discuss new developments and their contributions toward improved delineation of tumors and metastases using lymphangiography, ultrasonography, CT, MRI, PET, and lymphatic mapping.

**STAGING**

In the United States, cervical cancer staging is governed by three separate bodies: the International Federation of Gynecology and Obstetrics (FIGO), the

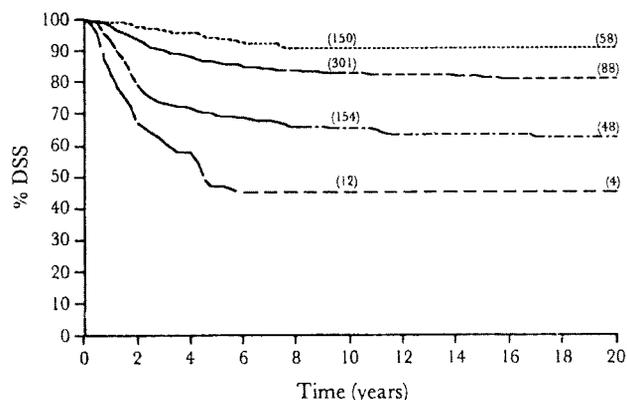


**FIGURE 1.** Survival by disease stage (International Federation of Gynecology and Obstetrics) for patients with carcinoma of the cervix uteri who were treated between 1990 and 1992. Reprinted from Benedet et al.<sup>7</sup> (Carcinoma of the cervix uteri. *J Epidemiol Biostat.* 2001;6:7–43) with permission from Taylor & Francis Ltd. (Abingdon, United Kingdom; <http://www.tandf.co.uk/journals>) and J. Benedet.

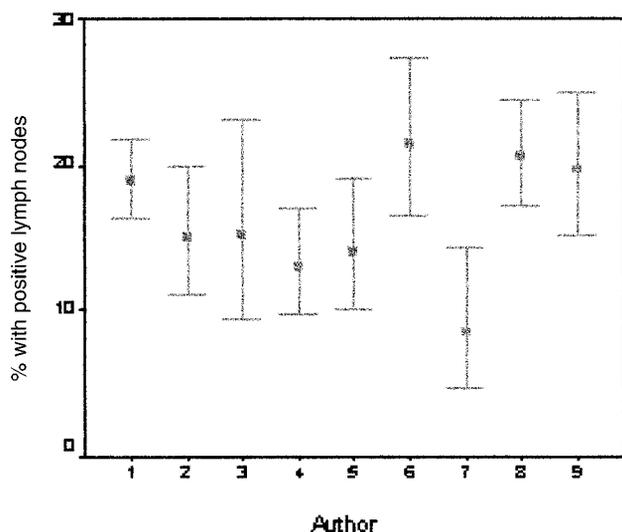
American Joint Committee on Cancer (AJCC), and the International Union Against Cancer (UICC). FIGO developed one system of staging, and the UICC and AJCC together developed another cancer staging classification, known as the TNM system (Table 1).<sup>7,8</sup> In the TNM system, cancer is staged according to the extent of the primary tumor (T), lymph node metastasis (N), and distant metastasis (M). The critical staging variables include depth and width of invasion, tumor size, extension into the upper two-thirds of the vagina or into the parametrium, extension into the lower third of the vagina or into the pelvic sidewall, invasion of the bladder or rectum, and spread to distant organs.

Clinical staging entails a detailed history and a physical examination involving inspection and palpation of the pelvic organs and rectum. Common laboratory tests include the evaluation of hemoglobin levels, liver function, and renal function. Standard chest radiographs and intravenous pyelograms are used to evaluate the lungs for metastases and the kidneys for ureteral obstruction. Cystoscopy and proctoscopy are used to evaluate the patient for the presence of tumor invasion into the bladder and rectum. Barium enemas and X-rays are allowed in staging but typically are performed in patients with bulky tumors as part of treatment planning. Clinical stage is an important predictor of survival (Fig. 1).<sup>9</sup>

Aside from staging variables, prognostic factors that have been found by many investigators to have an impact on survival include clinical tumor diameter (Fig. 2),<sup>10</sup> lymph node metastasis (Figs. 3, 4; Table 2),<sup>11,12</sup> lymphatic vascular space invasion (Table 3),<sup>13–20</sup> deep stromal invasion (Table 4),<sup>21–26</sup> microscopic evidence of parametrial extension, cell type

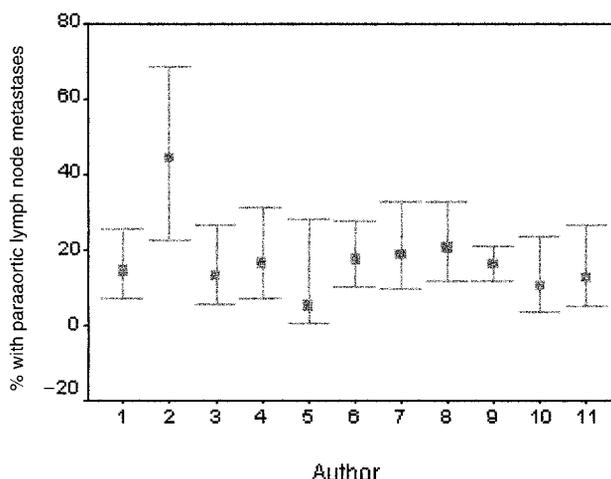


**FIGURE 2.** Disease-specific survival (DSS) by clinical tumor diameter for patients with cervical cancer. Patients with tumors that had the most favorable prognosis are represented by the top line, and patients with the largest tumors (diameter  $\geq 8$  cm) are represented by the bottom line. Numbers of patients alive at 10 and 20 years are displayed in parentheses. Reprinted from Eifel et al.<sup>10</sup> (The influence of tumor size and morphology on the outcome of patients with FIGO Stage IB squamous cell carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys.* 1994;29:9–16) with permission from Elsevier (Oxford, United Kingdom) and P. Eifel.



**FIGURE 3.** Incidence of pelvic lymph node metastases in Stage IB cervical cancer. Each square represents the percentage (with 95% confidence intervals) of positive lymph nodes reported by 1 of 9 investigators. The  $9 \times 2$  table had a chi-square value of 25.63 ( $P = 0.0012$ ; 8 degrees of freedom). Adapted from Hacker.<sup>12</sup>

(Fig. 5),<sup>27</sup> and hemoglobin level. Other prognostic factors that have been studied by fewer investigators but also have been found to be correlated with poorer survival include patient age, intratumoral oxygenation, tumor vascularity, DNA ploidy, and human papillomavirus infection.



**FIGURE 4.** Incidence of paraaortic lymph node metastases in patients with Stage II cervical cancer. Each square represents the percentage (with 95% confidence intervals) of paraaortic lymph node metastases reported by 1 of 11 investigators. The associated  $11 \times 2$  table had a chi-square value of 11.95 ( $P = 0.2885$ ; 10 degrees of freedom). Adapted from Hacker.<sup>12</sup>

**TABLE 2**  
Parameters for Evaluation of Enlarged Lymph Nodes on Ultrasonography, Computed Tomography, and Magnetic Resonance Imaging<sup>a</sup>

PARAMETERS COMMON TO ULTRASONOGRAPHY, CT, AND MRI

1. Axial diameter of lymph node
2. Roundness index
3. Irregular contours
4. Extracapsular spread

ULTRASONOGRAPHY-ASSOCIATED PARAMETERS

5. Presence/absence of hilar structures of lymph node
6. Relationship between the hilar and cortical structure of lymph node
7. Alterations of cortical structure (microcalcification, necrotic areas)

CT PARAMETERS

8. Presence of necrosis (hypodense areas)
9. Lower fat amount verified with densitometry
10. High density after intravenous contrast administration inhomogeneous enhancement

MRI PARAMETERS

11. Presence of necrosis (hyperintense areas in T2-weighted sequences)
12. Inhomogeneous signal in T2-weighted sequences
13. Unchanged intensity after contrast medium (USPIO) administration in T2, T2-weighted sequences
14. Inhomogeneous enhancement after contrast medium (gadolinium) administration

CT: computed tomography; MRI: magnetic resonance imaging; USPIO: ultrasmall superparamagnetic iron oxide.

<sup>a</sup> Reprinted, with permission, from De Gaetano et al.<sup>11</sup> (The role of diagnostic imaging in abdominal lymphadenopathy. *Rays.* 2000;25:463–484).

The standard imaging methods acceptable for staging are chest radiography, intravenous pyelography, and barium enema. The field of diagnostic imaging has evolved and presents many new modalities

**TABLE 3**  
**Relation of Lymphatic Vascular Space Invasion to Pelvic Lymph Node Involvement and Recurrence Rate in Patients Treated with Radical Hysterectomy<sup>a</sup>**

References	Positive lymph nodes (%)		Recurrence rate (%)	
	LVSI	No LVSI	LVSI	No LVSI
Chung et al. <sup>14</sup>	63	13	50	6
Fuller et al. <sup>15</sup>	40	14	—	—
Nahhas et al. <sup>16</sup>	22	8	20	12
Boyce et al. <sup>17</sup>	32	6	36	4
Burke et al. <sup>18</sup>	—	—	38	9
Delgado et al. <sup>19</sup>	—	—	23	11
Kamura et al. <sup>20</sup>	—	—	18	9

LVSI: lymphatic vascular space invasion.

<sup>a</sup> Reprinted from Eifel et al.<sup>13</sup> (Cancer of the cervix, vagina, and vulva. In: DeVita VT, Hellman S, Rosenberg SA, editors. Cancer: principles and practice of oncology. Philadelphia: Lippincott Williams & Wilkins, 1997:1441-1478) with permission from Lippincott Williams & Wilkins (Philadelphia, PA) and P. Eifel.

**TABLE 4**  
**Incidence of Lymph Node Metastases with 3–5 mm Stromal Invasion<sup>a</sup>**

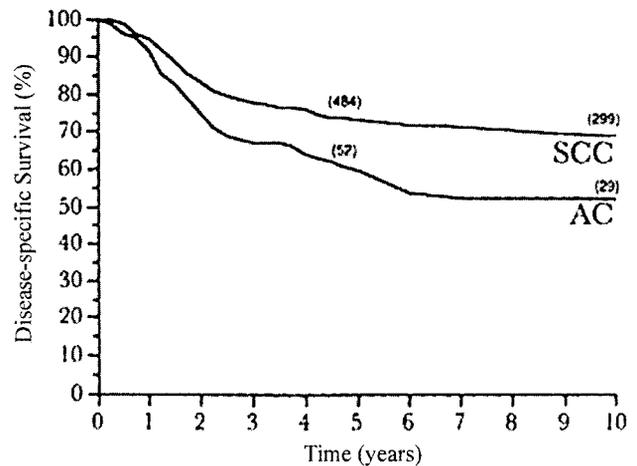
Author	N	Nodal Metastases	Invasive Recurrences	Dead of Disease
Van Nagell et al. <sup>21</sup>	32	3 (9.4%)	3	2
Hasumi et al. <sup>22</sup>	29	4 (13.8%)	NS	NS
Simon et al. <sup>23</sup>	26	1 (3.8%)	0	0
Maiman et al. <sup>24</sup>	30	4 (13.3%)	0	0
Buckley et al. <sup>25</sup>	94	7 (7.4%)	5	4
Creasman et al. <sup>26</sup>	51	0 (0.0%)	0	0
Total	262	19 (7.3%)	8 (3.1%)	6 (2.3%)

NS: not stated.

<sup>a</sup> Reprinted from Hacker<sup>12</sup> (Cervical cancer. In: Berek JS, Hacker NF. Practical gynecologic oncology [3rd edition]. Philadelphia: Lippincott Williams & Wilkins, 2000:357-405) with permission from Lippincott Williams & Wilkins (Philadelphia, PA) and N. Hacker.

that can aid the clinician in both diagnosis and prognosis. Studies comparing multiple imaging techniques with surgical staging offer the most rigorous test of the additional value of these techniques. Surgical staging allows the clinician to obtain histologic samples, which can be used as a gold standard (Table 5).<sup>1,3-5,28-36</sup>

The imaging modalities that have the potential to provide valuable information regarding the diagnosis and prognosis of cervical cancer are lymphangiography; ultrasonography; CT, including helical or spiral CT scanning; MRI; PET; lymphatic mapping; and functional imaging using contrast agents. Lymphangiography has been evaluated extensively for its ability to detect lymph node metastases in comparison with other modalities, all of which are considered emerging



**FIGURE 5.** Survival rates for patients with adenocarcinoma (AC) of the cervix compared with patients with squamous cell carcinoma (SCC) of the cervix. Reprinted from Eifel et al.<sup>27</sup> (Adenocarcinoma as an independent risk factor for disease recurrence in patients with Stage IB cervical carcinoma. *Gynecol Oncol.* 1995;59:38-44) with permission from Elsevier (Oxford, United Kingdom) and P. Eifel.

technologies for diagnosing and determining prognoses for cervical cancer (Table 6).

Technology assessment is a critical part of the evaluation of diagnostic imaging techniques and should be performed before a technique is introduced into clinical use. Rigorous assessment of emerging technologies involves the evaluation of five features: biologic plausibility, technical efficacy, clinical effectiveness, patient satisfaction, and cost-effectiveness.<sup>37</sup> Biologic plausibility refers to the existence of a biologic rationale for the use of a given technology for a particular disease. Evaluation of technical efficacy involves determination of whether the technology can be used safely and reliably at multiple sites. Clinical effectiveness refers to the performance of the technique as measured by the sensitivity, specificity, positive and negative predictive values, likelihood ratios, and receiver operating characteristic curves. Assessment of patient satisfaction involves evaluation of a technique's benefit as perceived by the patient. Cost-effectiveness studies measure dollars spent in terms of life years saved and lead to recommendations regarding how dollars should be spent to ensure the best use of scarce resources. The current review summarizes the state of technology assessment (as it relates to the diagnostic and prognostic factors mentioned earlier) for lymphangiography, ultrasonography, CT, MRI, PET, lymphatic mapping, and functional imaging with contrast agents (Table 7).

**TABLE 5**  
**Assessment of Lymph Node Positivity in Patients with Cervical Cancer Using Surgery as a Gold Standard**

Clinical effectiveness parameter	Lymphangiography	CT	MRI	PET	Lymphatic mapping
Sensitivity (%)	28–83 (Lewis, 1987 <sup>28</sup> ) 77 (Piver et al., 1971 <sup>29</sup> )	24 (Kim et al., 1997 <sup>30</sup> )	24 (Kim et al., 1997 <sup>30</sup> )	75 (Grigsby et al., 1999 <sup>1</sup> ) 75 (Rose et al., 1999 <sup>2</sup> ) 91 (Reinhardt et al., 2001 <sup>3</sup> ) 86 (Sugawara et al., 1999 <sup>4</sup> )	87.5 (Levenback et al., 2002 <sup>31</sup> ) 83 (Malur et al., 2001 <sup>32</sup> )
Specificity (%)	47–100 (Lewis, 1987 <sup>28</sup> ) 98 (Piver et al., 1971 <sup>29</sup> )	93 (Kim et al., 1997 <sup>30</sup> )	99 (Kim et al., 1997 <sup>30</sup> )	92 (Grigsby et al., 1999 <sup>5</sup> ) 92 (Rose et al., 1999 <sup>5</sup> ) 100 (Reinhardt et al., 2001 <sup>3</sup> )	
Accuracy (%)	87 (Piver et al., 1971 <sup>29</sup> )	86 (Janus et al., 1989 <sup>33</sup> ) 77 (Kim et al., 1993 <sup>34</sup> ) 83 (Kim et al., 1993 <sup>34</sup> ) 86 (Subak et al., 1995 <sup>35</sup> ) 91 (Yang et al., 2000 <sup>36</sup> )	86 (Janus et al., 1989 <sup>33</sup> ) 78 (Kim et al., 1993 <sup>34</sup> ) 88 (Kim et al., 1993 <sup>34</sup> ) 86 (Subak et al., 1995 <sup>35</sup> ) 86 (Yang et al., 2000 <sup>36</sup> )		
Positive predictive value (%)		39 (Kim et al., 1997 <sup>30</sup> )	78 (Kim et al., 1997 <sup>30</sup> )	75 (Rose et al., 1999 <sup>2</sup> ) 100 (Reinhardt et al., 2001 <sup>3</sup> )	
Negative predictive value (%)		88 (Kim et al., 1997 <sup>30</sup> )	88 (Kim et al., 1997 <sup>30</sup> )	92 (Rose et al., 1999 <sup>2</sup> ) 96 (Reinhardt et al., 2001 <sup>3</sup> )	97 (Levenback et al., 2002 <sup>31</sup> ) 97 (Malur et al., 2001 <sup>32</sup> )
Area under receiver operating characteristic curve (%)		86 (Yang et al., 2000 <sup>36</sup> )	84 (Yang et al., 2000 <sup>36</sup> )		

CT: computed tomography; MRI: magnetic resonance imaging; PET: positron emission tomography.

**TABLE 6**  
**Ability of Diagnostic Imaging Studies to Address Diagnostic and Prognostic Factors in Cervical Carcinoma**

Diagnostic or prognostic factor	Lymphangiography	Ultrasonography	CT	MRI	PET	Lymphatic mapping
Depth and width of invasion				✓		
Tumor size		✓	✓	✓	✓	
Extension into parametria			✓	✓		
Extension into vagina			✓	✓	✓	
Invasion of bladder or rectum			✓	✓		
Metastases to distant organs			✓	✓	✓	
Lymph node metastases	✓		✓	✓	✓	✓
Intratumoral oxygenation				✓ (contrast)	✓	
Tumor vascularity				✓ (contrast)	✓	

CT: computed tomography; MRI: magnetic resonance imaging; PET: position emission tomography.

**LYMPHANGIOGRAPHY**

Lymphangiography is performed by direct cannulation of the lymphatic ducts with injection of contrast agents that penetrate lymph nodes and make normal lymph nodes appear opaque on film. Neoplastic cells are carried through the lymphatic ducts to specific lymph nodes, and lymph nodes that harbor metastatic cells typically do not become opaque after the injection of contrast material. Lymphangiography has been used to diagnose lymph node metastases in patients with cervical cancer since 1961, when Wallace et al.<sup>38</sup> demonstrated that Lipiodol showed the structure of metastatic nodes. Lymphangiography reviews report sensitivities ranging from 28% to 83% and specificities ranging from 47% to 100%.<sup>11,29,39</sup> The procedure is

difficult to perform, and its results are difficult to read accurately. A limited number of cancer centers with adequate numbers of patients still use lymphangiography; hospitals that are unable to perform lymphangiography may use CT or MRI to assess pelvic lymph nodes.

Both the internal architecture and the size of a lymph node can be determined by lymphangiography; consequently, it is the only technique that can detect abnormalities within a normal-sized lymph node. False-negative interpretations may occur in the presence of microscopic metastases; false-positive interpretations often result from fatty infiltration and inflammatory processes. The cervix has predictable drainage to the parametrial, obturator internal iliac,

**TABLE 7**  
**Technologic Assessment of Imaging Modalities for Cervical Cancer<sup>a</sup>**

Parameter	Lymphangiography	Ultrasonography	CT	MRI	PET	Lymphatic mapping
Biologic plausibility	✓	✓	✓	✓	✓	✓
Technical efficacy	✓	✓	✓	✓	✓	✓
Clinical effectiveness	✓	✓	✓	✓	✓	✓
Cost-effectiveness				✓		

CT: computed tomography; MRI: magnetic resonance imaging; PET: positron emission tomography.

<sup>a</sup>Imaging modalities cannot assess patient satisfaction.

external iliac, sacral, perirectal, common iliac, and paraaortic nodes. As a result, cervical cancer is well suited to bipedal lymphangiography, in which the external iliac, common iliac, and retroperitoneal lymph nodes become opaque. The additional advantage of lymphangiography is that the contrast material remains in the lymph nodes for several months, allowing the lymph nodes to be used for radiation treatment planning.<sup>40</sup>

In a study performed at The University of Texas M. D. Anderson Cancer Center (Houston, TX) involving 103 patients with advanced carcinoma of the cervix, 42 patients were determined by lymphangiography to have metastatic disease. Exploratory laparotomy confirmed the presence of metastases. Surgical staging of these patients had a sensitivity of 77%, a specificity of 98%, and an overall accuracy of 87%. The high percentage of false-negative results was attributed to microscopic neoplastic foci in pelvic and paraaortic lymph nodes that did not become opaque.<sup>28,41,42</sup>

### ULTRASONOGRAPHY

Ultrasound is generated by piezoelectric materials, which experience a change in thickness when a voltage is applied across them. Ultrasound is a coherent, mechanical vibration of sound at high frequencies in real time. Transabdominal and transvaginal ultrasonography are used widely in gynecologic practice. In patients with cervical cancer, ultrasonography is useful for quantifying cervical size and identifying enlarged pelvic or paraaortic lymph nodes. Advances in ultrasonography, including color velocity imaging, involve the use of time shift rather than Doppler frequency shift to measure blood flow velocity. Echo-enhancing contrast agents that may provide additional information on tumor vascularity currently are being developed.

Transrectal ultrasonography (TRUS) has been used by several investigators to evaluate tumor size and parametrial involvement. Innocenti et al.<sup>43</sup> reported an accuracy of 83% for staging performed with

TRUS, compared with 79% for staging via physical examination. Similarly, in patients who underwent surgical staging for parametrial involvement, researchers reported sensitivity, specificity, and accuracy rates of 52%, 92%, and 84%, respectively, compared with 78%, 89%, and 87% for patients who were staged with TRUS. Magee et al.<sup>44</sup> evaluated correlations between TRUS findings (primarily tumor size) and survival. Gitsch et al.<sup>45</sup> reported the high specificity of diagnosing parametrial invasion based on sonographic features of stromal reaction. Cobby et al.<sup>46</sup> reported accuracy rates of 95% for ultrasonography, 85% for clinical examination, and 90% for MRI for local staging or evaluation of parametrial involvement; not all patients in that study underwent surgical staging.

Until contrast agents that increase the sensitivity of detection of parametrial invasion and lymph node metastases are developed, transabdominal and transvaginal ultrasound probably will play only a limited role in the evaluation of cervical cancer.<sup>47,48</sup> Because ultrasonography has low contrast resolution, it is difficult to directly visualize tumors and to differentiate between tumor tissue and adjacent normal tissue using ultrasonography. Ultrasonography is useful, however, in the identification of uterine and cervical leiomyomas, which may enlarge the cervix and not be part of the tumor. Ultrasonography also is useful for evaluating obstruction of the urinary tract in patients with advanced disease.<sup>47</sup>

### COMPUTED TOMOGRAPHY

Since the development of CT in the late 1970s, its range of uses has expanded in many areas of medicine. CT makes use of X-ray images obtained across a 360-degree diameter in serial fashion every few millimeters. Algorithms recombine the data into detailed slices of the human body. *Helical* or *spiral CT* refers to the collection of CT data as the patient moves through a rotating, continuous fan-beam exposure, which yields a corkscrew-shaped block of data. Depending on technique and technology, images with fine reso-

lution can be obtained using intravenous contrast. Advances in CT have made it a rival technique to MRI. In cervical cancer staging, CT is used primarily to evaluate the size of the cervix and to detect enlarged lymph nodes, obstruction of the ureter, and lung or liver metastases.

Some consider the value of CT in the assessment of cervical cancer to be limited by the obtainable resolution, but the tissue discriminator may be the actual limiting factor. The use of intravenous contrast media can make the tumor appear as a soft tissue mass that may enlarge the cervix, and areas of necrosis and ulceration can produce hypodense areas within the tumor. Published studies have reported mixed results regarding the reliable detection of tumor invasion into the parametrium and vagina using CT. Irregularity of the lateral cervical margins, obliteration of periureteral fat planes, and prominent parametrial soft tissue masses suggest invasion but are not definitive indicators. CT can detect lymph nodes that are enlarged by more than 1 cm but cannot determine lymph node architecture.<sup>40</sup> Subak et al.<sup>35</sup> reviewed studies comparing the accuracy of CT and MRI in the preoperative evaluation of parametrial invasion, disease stage, and lymph node involvement. Yang et al.<sup>36</sup> compared helical CT and dynamic MRI, evaluating their sensitivity (64.7% vs. 70.6%), specificity (96.6% vs. 89.9%), positive predictive value (84.6% vs. 66.7%), negative predictive value (90.5% vs. 91.4%), and accuracy (89.5% vs. 85.5%).

## **MRI**

MRI is a noninvasive method for mapping internal structures that does not rely on ionizing radiation. MRI employs radiofrequency pulses or signals in the presence of carefully controlled magnetic fields to portray the distribution of hydrogen nuclei in different tissues and other parameters related to the motion of hydrogen nuclei in water and lipids. Technical advances include improvements in spatial resolution, contrast agents, and in particular, speed of imaging. MRI, with its superior soft tissue contrast resolution and multiplanar capabilities, has proved to be useful in determining the size of the cervix and in detecting parametrial invasion, bladder and rectal invasion, the presence and consistency of enlarged lymph nodes, obstruction of the ureter, and lung or liver metastases.

T2-weighted MRI provides excellent detail of normal uterine and cervical anatomy and also detects the primary tumor and provides information on its extent. The normal cervical stroma has low signal intensity on T2-weighted images, and cervical tumors typically have greater T2 signal intensity compared with the surrounding stroma. Endocervical tumors may be dif-

ficult to evaluate clinically, but they are well characterized by MRI. Stromal invasion by the primary tumor also is well delineated by MRI, especially when the primary tumor is covered by epithelium that has a normal appearance. The reported overall accuracy of T2-weighted MRI in predicting tumor size is 93%.<sup>49</sup> The absence of parametrial invasion holds great importance in determining whether a patient is a surgical candidate. The reported negative predictive value of MRI in detecting parametrial invasion is approximately 95%<sup>35</sup>; when the fibrocervical stroma surrounding the tumor is seen as intact on imaging, the possibility of parametrial spread can be readily excluded. In contrast, the positive predictive value for parametrial invasion is considerably lower, because imaging cannot easily distinguish the occurrence of peritumoral reactive changes from the presence of invasive tumor.<sup>50</sup>

The utility of gadolinium contrast media for the staging of cervical cancer with MRI is not entirely clear. Most agree that delayed contrast-enhanced images provide little advantage over noncontrast images unless adjacent organ invasion is suspected. Dynamic gadolinium-enhanced images may be useful for detecting small cervical lesions, detecting or confirming invasion of adjacent organs, and identifying fistulous tracts. The reported overall accuracy for determination of bladder wall invasion status is approximately 90%.<sup>30</sup> The overall accuracy of MRI staging of cervical cancer is reported to be approximately 90%.<sup>35,49</sup> Dynamic imaging also has been advocated as an aid in predicting tumor response to radiotherapy.<sup>51-53</sup>

MRI also has been shown to be a cost-effective staging technique. Hricak et al.<sup>54</sup> reported that patients with cervical cancer who underwent MRI as the initial imaging procedure for staging required fewer tests and procedures compared with those who underwent standard clinical staging. The resultant cost savings was significant, not only in terms of the cost of saved procedures but also in terms of the overall cost of treatment when treatment was altered based on MRI findings. The cost-effectiveness of MRI also was evident in the fact that an MRI urogram (to exclude ureteral obstruction) could be obtained during the session in which MRI staging was performed.

The presence of lymph node metastases is not incorporated into the clinical staging system; nonetheless, it is an important factor in determining prognosis. Cross-sectional imaging techniques such as CT and MRI rely on lymph node size as the primary criterion for determining the presence of metastatic disease within a lymph node. Lymph nodes larger than 1 cm in the short-axis dimension are considered abnormal. It is well known, however, that size is not an

ideal criterion for determining the presence or absence of disease within a lymph node. Enlarged lymph nodes may be hyperplastic, and tumors smaller than 1 cm may contain metastatic disease. Central necrosis within a lymph node is a useful predictor of metastatic disease. The overall accuracy rates of MRI and CT in determining lymph node metastasis status in patients with cervical carcinoma range from 85% to 90%.<sup>36</sup> Exciting advances in novel combinations of contrast agents and techniques, such as iron oxide-enhanced MRI lymphography, may allow internal structure to be seen in normal-sized lymph nodes. These advances may make MRI as sensitive and specific as conventional lymphangiography.

### PET

PET with FDG rapidly is emerging as a technique for evaluating metabolic activity. PET imaging in oncology has made tremendous advancements over the past few years. Many positron-emitting isotopes are available for the evaluation of biologic processes; however, FDG-PET is the most common type of PET used in oncologic imaging. Imaging with FDG-PET relies on physiologic processes rather than on the anatomic changes detected by conventional imaging techniques.<sup>1,3-5</sup>

A limited number of surgical staging studies have been performed in patients with carcinoma of the cervix and have indicated that FDG-PET has high sensitivity and specificity in detecting lymph node metastases.<sup>5,55</sup> The status of the pelvic, paraaortic, and supraclavicular lymph nodes, as determined by radiologic imaging studies, is not considered part of the clinical staging system. An analysis of prognostic variables in 626 patients enrolled in clinical trials by the Gynecologic Oncology Group (GOG) revealed that in patients with Stage I-IVA cervical cancer who underwent surgical staging, the most significant prognostic factor was the status of the paraaortic lymph nodes; the second most significant prognostic factor was tumor size  $\geq 10$  cm (relative risk, 3.9).<sup>56</sup> Several different imaging methods have been used to assess pelvic and retroperitoneal lymph nodes in patients with cervical carcinoma. The results of the GOG study demonstrate that FDG-PET detects abnormal lymph node regions more frequently than CT does and that PET findings are a better predictor of survival than are CT findings in patients with carcinoma of the cervix.

Analysis of the posttreatment survival of patients with cervical cancer who were treated at the Mallinckrodt Institute of Radiology (St. Louis, MO) indicates the presence of a strong correlation between FDG-PET lymph node findings and patient survival.<sup>1,2</sup> Tumor volume, which also is correlated with survival, can be

directly assessed with FDG-PET.<sup>6</sup> Miller and Grigsby examined 51 patients who underwent PET studies before treatment. Using correlational CT scans from 13 patients in preliminary studies, they identified a fixed threshold fraction of the peak activity in the tumor and by simple count thresholding were able to identify tumor boundaries. The target-to-background ratio generally was 10:1 or greater. Follow-up FDG-PET evaluation of patients with cervical cancer indicated that persistent abnormal FDG uptake and the development of new abnormal FDG uptake are robust predictors of poor survival outcome. Areas of research on the use of FDG-PET for patients with cervical cancer encompass treatment planning for intensity-modulated radiotherapy, brachytherapy, and external irradiation.<sup>6,57</sup>

<sup>60</sup>Cu-diacetyl-bis(N<sup>4</sup>-methylthiosemicarbazone) (<sup>60</sup>Cu-ATSM), a recently developed copper-labeled tracer, contains a positron-emitting isotope that can be imaged with PET and appears to be highly specific for hypoxic cells. (<sup>60</sup>Cu is one of four positron-emitting copper nuclides, the others being <sup>61</sup>Cu, <sup>62</sup>Cu, and <sup>64</sup>Cu.) The uptake of <sup>60</sup>Cu-ATSM is entirely dependent on oxygen concentration.<sup>58,59</sup> <sup>60</sup>Cu-ATSM has been used in patients with cervical cancer to identify hypoxic tumors, which respond poorly to concurrent radiotherapy and chemotherapy and overexpress tumor markers.<sup>60</sup> The growing availability of the copper radionuclides, three of which can be produced by all biomedical cyclotrons, is matched by the growing interest in their use.<sup>58-61</sup> Early reports from studies at the Mallinckrodt Institute of Radiology using <sup>60</sup>Cu-ATSM to evaluate hypoxia in cervical and lung cancer currently are beginning to appear.<sup>60,62</sup>

For patients with new diagnoses of carcinoma of the cervix, PET has become the standard method of pretreatment imaging evaluation at some centers. Research areas involving PET for patients with cervical cancer include monitoring of response to therapy, treatment planning, and evaluation of tumor hypoxia. Researchers hope that these efforts will improve the therapeutic process and yield better survival results.

### LYMPHATIC MAPPING

Cutaneous lymphoscintigraphic mapping and lymphatic mapping use contrast agents and dyes that are able to identify the areas of primary drainage of the lymph nodes that surround the malignancy of interest. First used in melanoma, the concept has been validated in breast cancer, penile cancer, vulvar cancer, and, recently, in cervical cancer.

Lymphatic mapping and sentinel lymph node identification represent noteworthy recent advances in the surgical management of solid tumors. Gould et

al.<sup>63</sup> first used the term *sentinel lymph node* in 1960 to describe a lymph node that was the first to drain the parotid gland. In 1977, Cabanas et al.<sup>64</sup> were the first to describe a technique for lymphatic mapping (specifically, lymphography of the penis). In 1992, Morton et al.<sup>65</sup> described a simple and practical technique for lymphatic mapping and sentinel lymph node identification in patients with cutaneous melanoma. They demonstrated in their report that a false-negative sentinel lymph node is very rare. The report by Morton et al. introduced modern surgical oncologists to a new surgical technique with a wide range of applications. The sentinel lymph node currently is defined as the first draining lymph node of a solid tumor and the most likely site of metastasis.

Lymphatic mapping is a technique used to identify the sentinel lymph node and usually involves a peritumoral injection of blue dye or of a short-lived radioactive nuclide that is transported by the lymphatic channels to the sentinel lymph node. The blue dye is visible in the operating room on macroscopic inspection. The radionuclide can be detected with a gamma camera, which obtains images called lymphoscintigrams. In addition, small, portable gamma probes for use in the operating room now are available; these hand-held devices do not produce images but can be used to localize 'hot' sentinel lymph nodes.

Over the last 10 years, numerous articles have described the results of sentinel lymph node identification studies involving thousands of patients with breast cancer or melanoma, for whom sentinel lymph node identification has become standard practice. The false-negative rate for sentinel lymph node identification is low (< 5% when the procedure is performed by an experienced surgeon). Phase III studies comparing the safety of sentinel lymph node biopsy alone with that of regional lymphadenectomy currently are underway.

The first mapping study involving patients with vulvar cancer was published in 1994.<sup>66</sup> Since then, several studies appear to have validated the sentinel lymph node concept in patients with vulvar cancer.<sup>67-69</sup> The number of cases examined still is small. A large validation trial is underway in North America under the auspices of the GOG. In addition, an observational study is underway in the Netherlands. Vulvar cancer is an interesting target for mapping, because the majority of patients with Stage I-II disease have negative lymph nodes and the risk of lymphedema remains significant.

There is a small but growing amount of interest in lymphatic mapping of the cervix. An excellent target for mapping, the cervix is a midline structure with complex lymphatic drainage. Extensive dissection is

required to complete a pelvic lymphadenectomy. Lymph node status is the most important prognostic factor in patient evaluation and determines treatment selection. Early published results are encouraging,<sup>32,33,70</sup> and the GOG is planning a large validation trial involving patients with Stage IB1 disease. Of special interest is that mapping can be performed during laparoscopy, the ideal combination of two minimally invasive surgical concepts. A report by van Trappen et al.<sup>71</sup> indicates that molecular techniques can be used to identify 'biologic' metastases in patients with cervical cancer. In the future, sentinel lymph nodes are likely to be studied with conventional stains as well as with immunohistochemical and molecular techniques.

In summary, lymphatic mapping and sentinel lymph node identification are likely to alter the management of gynecologic cancer, much as they have altered the management of solid tumors.

## CONCLUSIONS

Accurate evaluation is necessary for successful treatment; therefore, researchers seek to exploit every benefit of every modality, every combination of methods, and every available enhancement, including the use of immunohistochemical and molecular techniques. The development of novel contrast agents promises to increase understanding of cancer biology and should make the future of evaluation technologies quite exciting; however, new agents are likely to appear and surpass older agents before studies necessary to validate the older agents are complete and government approval is in hand.

Because little has been done to assess patient satisfaction or the cost-effectiveness of any of these technologies, well-designed studies comparing surgical evaluation of lymph nodes and evaluation with multiple imaging modalities are necessary; one ongoing reevaluation, comparing CT and MRI with surgical staging, is being performed by the American College of Radiology Imaging Network. Furthermore, interobserver and intraobserver studies among radiologists are imperative. Currently, MRI appears to provide information on most diagnostic and prognostic factors for cervical carcinoma. Other techniques may show similar promise as new contrast agents are developed.

## REFERENCES

1. Grigsby PW, Dehdashti F, Siegel BA. FDG-PET evaluation of carcinoma of the cervix. *Clin Positron Imaging*. 1999;2:105-109.
2. Grigsby PW, Siegel BA, Dehdashti F. Lymph node staging by positron emission tomography in patients with carcinoma of the cervix. *J Clin Oncol*. 2001;19:3745-3749.

3. Reinhardt M, Ehrhrit-Braun D, Vogelgesang D, et al. Metastatic lymph nodes in patients with cervical cancer: detection with MR imaging and FDG PET. *Radiology*. 2001;218:776–782.
4. Sugawara A, Eisbruch S, Kosuda S, Recker BE, Kison PV, Wahl RL. Evaluation of FDG-PET in patients with cervical cancer. *J Nucl Med*. 1999;40:1125–1131.
5. Rose P, Adler L, Rodriguez M, et al. Positron emission tomography for evaluating para-aortic nodal metastasis in locally advanced cervical cancer before surgical staging: a surgicopathologic study. *J Clin Oncol*. 1999;17:41–45.
6. Miller TR, Grigsby PW. Measurement of tumor volume by PET to evaluate prognosis in patients with advanced cervical cancer treated by radiation therapy. *Int J Radiat Oncol Biol Phys*. 2002;53:353–359.
7. Benedet JL, Odicino F, Maisonneuve P, et al. Carcinoma of the cervix uteri. *J Epidemiol Biostat*. 2001;6:7–43.
8. Sobin LH, Wittekind C, editors. TNM classification of malignant tumours, 6th edition. New York: John Wiley & Sons, 2002.
9. Benedet J, Odicino F, Maisonneuve P, et al. Carcinoma of the cervix uteri. Annual report on the results of treatment in gynecological cancer. *J Epidemiol Biostat*. 1998;3:5–34.
10. Eifel PJ, Morris M, Wharton JT, Oswald MJ. The influence of tumor size and morphology on the outcome of patients with FIGO Stage IB squamous cell carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys*. 1994;29:9–16.
11. De Gaetano AM, Vecchioli A, Minordi M, et al. Role of diagnostic imaging in abdominal lymphadenopathy. *Rays*. 2000;25:463–484.
12. Hacker NF. Cervical cancer. In: Berek JS, Hacker NF. Practical gynecologic oncology, 3rd edition. Philadelphia: Lippincott Williams & Wilkins, 2000:345–405.
13. Eifel PJ, Berek JS, Thigpen JT. Cancer of the cervix, vagina, and vulva. In: DeVita VT, Hellman S, Rosenberg SA, editors. Cancer: principles and practice of oncology. Philadelphia: Lippincott Williams & Wilkins, 1997:1433–1478.
14. Chung CK, Nahhas WA, Stryker JA, Curry SL, Mortel R. Analysis of factors contributing to treatment failures in Stages IB and IIA carcinoma of the cervix. *Am J Obstet Gynecol*. 1980;138:550–556.
15. Fuller AF, Elliott N, Kosloff C, Lewis JL. Lymph node metastases from carcinoma of the cervix, Stages IF and IIA: implications for prognosis and treatment. *Gynecol Oncol*. 1982;13:165–174.
16. Nahhas WA, Sharkey FE, Whitney CW, et al. The prognostic significance of vascular channel involvement and deep stromal penetration in early cervical carcinoma. *Am J Clin Oncol*. 1983;6:259–264.
17. Boyce JG, Fruchter RG, Nicastrì AD, et al. Vascular invasion in Stage I carcinoma of the cervix. *Cancer*. 1984;53:1175–1180.
18. Burke TW, Hoskins WF, Heller PB, Bibro MC, Weiser EB, Park RC. Prognostic factors associated with radical hysterectomy failure. *Gynecol Oncol*. 1987;26:153–159.
19. Delgado G, Bundy B, Zaino R, et al. Prospective surgical-pathological study of disease-free interval in patients with Stage IB squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. *Gynecol Oncol*. 1990;38:352–357.
20. Kamura T, Tsukamoto N, Tsuruchi N, et al. Multivariate analysis of the histopathologic prognostic factors of cervical cancer in patients undergoing radical hysterectomy. *Cancer*. 1992;69:181–186.
21. Van Nagell JR, Breenwell N, Powell DF, et al. Microinvasive carcinoma of the cervix. *Am J Obstet Gynecol*. 1983;145:981–989.
22. Hasumi K, Sakamoto A, Sugano H. Microinvasive carcinoma of the uterine cervix. *Cancer*. 1980;45:928–931.
23. Simon NL, Gore H, Shingleton HM, et al. Study of superficially invasive carcinoma of the cervix. *Am J Obstet Gynecol*. 1983;145:981–991.
24. Maiman MA, Fruchter RG, Di Maio TM, Boyce JG. Superficially invasive squamous cell carcinoma of the cervix. *Obstet Gynecol*. 1988;72:399–403.
25. Buckley SL, Tritz DM, van Le L, et al. Lymph node metastases and prognosis in patients with Stage IA2 cervical cancer. *Gynecol Oncol*. 1996;63:4–9.
26. Creasman WT, Zaino RJ, Major FJ, et al. Early invasive carcinoma of the cervix (3 to 5 mm invasion): risk factors and prognosis. A Gynecologic Oncology Group study. *Am J Obstet Gynecol*. 1998;178:62–65.
27. Eifel PJ, Burke TW, Morris M, Smith TL. Adenocarcinoma as an independent risk factor for disease recurrence in patients with Stage IB cervical carcinoma. *Gynecol Oncol*. 1995;59:38–44.
28. Lewis E. The use and abuse of imaging in gynecologic cancer. *Cancer*. 1987;60:1993–2009.
29. Piver MS, Wallace D, Castro JR. The accuracy of lymphangiography in carcinoma of the uterine cervix. *AJR Am J Roentgenol*. 1971;111:278–283.
30. Kim SH, Han MC. Invasion of the urinary bladder by uterine cervical carcinoma: evaluation with MR imaging. *AJR Am J Roentgenol*. 1997;168:393–397.
31. Levenback C, Coleman RL, Burke TW, et al. Lymphatic mapping and sentinel node identification in patients with cervix cancer undergoing radical hysterectomy and pelvic lymphadenectomy. *J Clin Oncol*. 2002;20:688–693.
32. Malur S, Krause N, Kohler C, Schneider A. Sentinel lymph node detection in patients with cervical cancer. *Gynecol Oncol*. 2001;80:254–257.
33. Janus CL, Mendelson DS, Moore S, et al. Staging of cervical carcinoma: accuracy of magnetic resonance imaging and computed tomography. *Clin Imaging*. 1989;13:114–116.
34. Kim SH, Choi BI, Han JK, et al. Preoperative staging of uterine cervical carcinoma: comparison of CT and MRI in 99 patients. *J Comput Assist Tomogr*. 1993;17:633–640.
35. Subak LL, Hricak H, Powell CB, Azizi L, Stern JL. Cervical carcinoma: computed tomography and magnetic resonance imaging for preoperative staging. *Obstet Gynecol*. 1995;86:43–50.
36. Yang WT, Lam WW, Yu MY, Cheung TH, Metreweli C. Comparison of dynamic helical CT and dynamic MR imaging in the evaluation of pelvic lymph nodes in cervical carcinoma. *AJR Am J Roentgenol*. 2000;175:759–766.
37. Littenberg B. Technology assessment in medicine. *Acad Med*. 1992;67:424–428.
38. Wallace S, Jackson L, Schaffer B, et al. Lymphangiograms, their diagnostic and therapeutic potentials. *Radiology*. 1961;76:179–199.
39. Macis G, Cina A, Pedicelli A, Resaino G, Molinari F. Lymph node imaging: from conventional radiology to diagnostic imaging. *Rays*. 2000;25:399–417.
40. Hricak H. Role of imaging in the evaluation of pelvic cancer. *Important Adv Oncol*. 1991:103–133.
41. LeGasse LD, Gresman WT, Shingleton HM, Ford JH, Blessing JA. Results and complications of operative staging in cervical cancer: experience of the Gynecologic Oncology Group. *Gynecol Oncol*. 1980;9:90–98.

42. Ginaldi S, Wallace S, Jing BS, et al. Carcinoma of the cervix: lymphangiography and computed tomography. *AJR Am J Roentgenol.* 1982;136:1087–1091.
43. Innocenti P, Pulli F, Savino L, et al. Staging of cervical cancer: reliability of transrectal US. *Radiology.* 1992;185:201–205.
44. Magee BJ, Logue JP, Swindell R, McHugh D. Tumor size as a prognostic factor in carcinoma of the cervix: assessment by transrectal ultrasound. *Br J Radiol.* 1991;64:812–815.
45. Gitsch G, Deutinger J, Renthaller A, Breitenecker G, Bernaschek G. Cervical cancer: the diagnostic value of rectosonography for the judgment of parametrial invasion in regard of inflammatory stromal reaction. *Br J Obstet Gynaecol.* 1993;100:696–697.
46. Cobby M, Browning J, Jones A, Whipp E, Goddard P. Magnetic resonance imaging, computed tomography and endosonography in the local staging of carcinoma of the cervix. *Br J Radiol.* 1990;63:673–679.
47. Hricak H, Yu KK. Radiology in invasive cervical cancer. *AJR Am J Roentgenol.* 1996;167:1101–1108.
48. Carter J, Carson LF, Elg S. Transvaginal sonography as an aid in the clinical staging of carcinoma of the cervix. *J Clin Ultrasound.* 1992;20:283–287.
49. Hricak H, Lacey CG, Sandles LG, et al. Invasive cervical carcinoma: comparison of MR imaging and surgical findings. *Radiology.* 1988;166:623–631.
50. Ascher SM, Takahama J, Jha RC. Staging of gynecologic malignancies. *Top Magn Reson Imaging.* 2001;12:105–129.
51. Yamashita Y, Baba T, Baba Y, et al. Dynamic contrast-enhanced MR imaging of uterine cervical cancer: pharmacokinetic analysis with histopathologic correlation and its importance in predicting the outcome of radiation therapy. *Radiology.* 2000;216:803–809.
52. Boss EA, Massuger LE, Pop LA, et al. Post-radiotherapy contrast enhancement changes in fast dynamic MRI of cervical carcinoma. *J Magn Reson Imaging.* 2001;13:600–606.
53. Boss EA, Barentsz JO, Massuger LF, Boonstra H. The role of MR imaging in invasive cervical carcinoma. *Eur Radiol.* 2000;10:256–270.
54. Hricak H, Powell CB, Yu KK, et al. Invasive cervical carcinoma: role of MR imaging in pretreatment work-up—cost minimization and diagnostic efficacy analysis. *Radiology.* 1996;198:403–409.
55. Narayan K, Hicks RJ, Jobling T, Bernshaw D, McKenzie AF. A comparison of MRI and PET scanning in surgically staged loco-regionally advanced cervical cancer: potential impact on treatment. *Int J Gynecol Cancer.* 2001;11:263–271.
56. Stehman FB, Bundy BN, DiSaia PJ, et al. Carcinoma of the cervix treated with radiation therapy. I. A multivariate analysis of prognostic variables in the Gynecologic Oncology Group. *Cancer.* 1991;67:2776–2785.
57. Mutic S, Malyapa RS, Grigsby PW, et al. PET-guided IMRT for cervical carcinoma with positive para-aortic lymph nodes—a dose-escalation treatment planning study. *Int J Radiat Oncol Biol Phys.* 2003;55:28–35.
58. Lewis JS, McCarthy DW, McCarthy TJ, et al. The evaluation of <sup>64</sup>Cu-ATSM in vitro and in vivo in a hypoxic tumor model. *J Nucl Med.* 1999;40:177–183.
59. Lewis JS, Sharp TL, Laforest R, et al. Tumor uptake of copper-diacetyl-bis(N4-methylthiosemicarbazone): effect of changes in tissue oxygenation. *J Nucl Med.* 2001;42:655–661.
60. Dehdashti F, Grigsby PW, Mintun MA, et al. Assessing tumor hypoxia in cervical cancer by positron emission tomography with (60)Cu-ATSM: relationship to therapeutic response—a preliminary report. *Int J Radiat Oncol Biol Phys.* 2003;55:1233–1238.
61. McCarthy DW, Shefer RE, Klinkowstein RE, et al. Efficient production of high specific activity <sup>64</sup>Cu using a biomedical cyclotron. *Nucl Med Biol.* 1997;24:35–43.
62. Dehdashti F, Mintun MA, Lewis JS, et al. In vivo assessment of tumor hypoxia in lung cancer with (60)Cu-ATSM. *Eur J Nucl Med Mol Imaging.* 2003;30:844–880.
63. Gould EA, Philbin WT, Hyland PH, Kerr H. Observations on a “sentinel node” in cancer of the parotid. *Cancer.* 1960;13:77–78.
64. Cabanas RM. An approach for the treatment of penile carcinoma. *Cancer.* 1977;39:456–466.
65. Morton DL, Wen DR, Wong JH, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg.* 1992;127:392–399.
66. Levenback C, Burke TW, Bershenson DM, Morris M, Malpica A, Ross MI. Intraoperative lymphatic mapping for vulvar cancer. *Obstet Gynecol.* 1994;84:163–167.
67. Levenback C, Coleman RL, Burke TW, Bodurka-Bevers D, Wolf JK, Gershenson DM. Intraoperative lymphatic mapping and sentinel node identification with blue dye in patients with vulvar cancer. *Gynecol Oncol.* 2001;83:276–281.
68. de Hullu JA, Hollema H, Piers DA, et al. Sentinel lymph node procedure is highly accurate in squamous cell carcinoma of the vulva. *J Clin Oncol.* 2000;18:2811–2816.
69. De Cicco C, Sideri M, Bartolomei M, et al. Sentinel node biopsy in early vulvar cancer. *Br J Cancer.* 2000;82:295–299.
70. Dargent D, Martin X, Mathevet P. Laparoscopic assessment of the sentinel lymph node in early stage cervical cancer. *Gynecol Oncol.* 2000;79:411–415.
71. van Trappen PO, Gyselman VG, Lowe DG, et al. Molecular quantification and mapping of lymph-node micrometastases in cervical cancer. *Lancet.* 2001;357:15–20.