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PET and PET/CT of Cervical Cancer

By Lee P. Adler, M.D.

LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Describe the indications for cross-sectional imaging in patients with advanced cervical carcinoma.
- List the indications of PET and PET/CT for patients with newly diagnosed cervical cancer.
- Explain the advantages of PET and PET/CT for staging cervical cancer.
- Describe the most important prognostic factor among patients with newly diagnosed, locally advanced cervical carcinoma prior to and following therapy.

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Carcinoma of the cervix is the second most common malignancy among women worldwide, with an incidence of 500,000 new cases annually. In developed nations, routine screening for and aggressive treatment of cervical intraepithelial neoplasia has dramatically reduced both the incidence and the mortality rate from malignancies of the cervix. Within the U.S., more than 10,500 new cases of cervical carcinoma are expected to be diagnosed in 2004, in addition to 65,000 cases of premalignant disease. About 3900 women will succumb to the disease this year,^{1,2} making it the third most common and lethal gynecologic malignancy after uterine and ovarian carcinoma.

Staging is generally performed under the FIGO (International Federation of Gynecology and Obstetrics) classification system, based on clinical exam, chest x-ray, and intravenous pyelogram (see table). Although clinical staging is strongly correlated with prognosis, the presence or absence of para-aortic adenopathy in patients with advanced disease is by far the most important risk factor.³

Carcinoma of the cervix spreads predictably, with involvement of pelvic lymph node

chains occurring prior to para-aortic involvement, which in turn is generally present before either distant organ or lymph node metastases are seen. Para-aortic lymph node metastases are apparent in only a minority of patients with involvement. Patients with stage I or IIA disease are considered to be early stage and are amenable to surgical cure. Patients with more advanced disease generally receive primary radiotherapy.¹

The availability of more aggressive treatments such as extended field radiotherapy, brachytherapy,

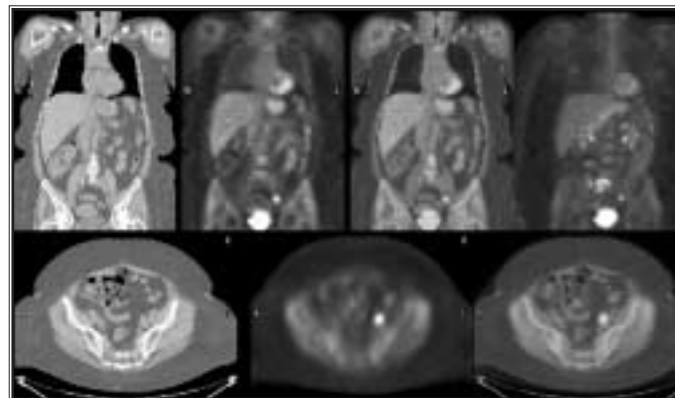


Figure 1. 49-year-old woman with newly discovered carcinoma of the cervix thought to be localized to the cervix on both physical exam and CT. Top row: Coronal CT, PET, fused, and MIP images. Bottom row: Transverse CT, PET, and fused images. In addition to demonstrating the primary tumor immediately rostral to the bladder, PET reveals a metabolically active left external iliac lymph node less than 1 cm in diameter. Radiation treatment planning field was extended to include this otherwise occult metastasis, and follow-up scan revealed complete response.

and intensity-modulated radiation therapy (IMRT), alone or in conjunction with surgery and adjuvant chemotherapy, has the potential to improve prognosis in patients with metastatic disease. Accurate pretreatment assessment is required to tailor the treatment to each patient, particularly in radiation therapy planning.

The success of therapy must be evaluated after treatment for advanced cervical carcinoma. Areas of residual viable tumor may warrant additional radiation therapy. Persistent and/or recurrent tumor of the cervix following radiation therapy can generally be detected by physical exam. Viable tumor following definitive therapy to a region is a poor prognostic sign. Evaluation of lymph node disease response is more difficult, as residual lymph nodes may be free of disease, while lymph nodes that are reduced to normal size can still be metastatic. With the availability of new treatment modalities, residual tumor may warrant additional therapy.

Recurrences may occur in previously uninvolved lymph nodes, lung, liver, and skeleton. The majority of recurrences manifest within two years. Spread to supraclavicular lymph nodes is an infrequent finding associated with a poor prognosis. Recurrences following surgery can be treated with chemoradiation with a 20% to 60% salvage rate.¹ In patients with pelvic recurrence following primary radiation treatment, care must be taken when applying radiation within the same fields. IMRT and dose painting can be used to limit the dose to radiosensitive normal tissue.

RADIOLOGICAL EVALUATION

The potential role for imaging at the time of initial diagnosis includes improved delineation of the primary tumor and detection of spread within the pelvis to para-aortic lymph nodes and to distant lymph nodes and organs. For tumor staging, the excellent contrast resolution of MR makes it the method of choice for supplementing physical exam. Advances in spiral CT, however, which allow dynamic volume imaging following contrast administration, make CT a rival to MR for both tumor staging and parametrial invasion detection.⁴ Transrectal ultrasound has been shown to be accurate at tumor and parametrial staging. The ability to stage pelvic and para-aortic lymph nodes is limited by ultrasound's low contrast resolution, but contrast agents under development may increase the role of transvaginal and transabdominal ultrasound in staging cervical cancer.⁴

Lymphangiography requires direct cannulation of lymphatic vessels from the dorsi of both feet to administer contrast that opacifies normal lymph nodes in the pelvis and along the para-aortic chains. Lymph nodes that have been partially replaced by metastatic tissue show defects or distortions on lymphangiograms. Metastatic lymph nodes that are normal in size can therefore be detected by lymphangiography. Unfortunately, this expensive procedure is tedious, difficult to perform, and poorly tolerated by patients. The sensitivity of the procedure varies with technical expertise, and false positives occur frequently.⁵ For these reasons, lymphangiography is performed at a decreasing number of institutions.

In four studies of patients with untreated locally advanced cervical cancer, the primary carcinoma was identified with PET imaging in 184 of 186 patients (99%, range 94% to 100%).⁶⁻⁹ Variations in results were due in part to the care in clearing the urinary tract of intense, excreted activity. Because of limited spatial resolution and the absence of anatomic landmarks, PET is generally not used for tumor staging. PET/CT may provide the necessary anatomic and functional information to substitute for an MR of the pelvis.

REGIONAL STAGING

Although CT and MR are most commonly used for staging lymphatic spread, their sensitivity for detecting both pelvic and para-aortic adenopathy is compromised by their use of size criteria alone for determining the presence of lymphadenopathy,⁴ with sensitivities as low as 24% compared with surgical exploration. Improved pretreatment staging of patients presenting with advanced cervical carcinoma (stage IIB-IV) is needed.

Intense radiotracer activity in the ureters and bladder can sometimes obscure activity in malignant tissue. An early study of a group of patients with either newly diagnosed or recurrent cervical cancer found improved visualization of primary tumors when postvoid imaging was performed.⁷ Ureteral activity obscured an otherwise obvious lymph node metastasis in one patient and simulated metastases in two patients. The foci were transient on postvoid imaging, confirming their true nature.

PET/CT can help distinguish ureteral activity from metastatic lymph node, although to do so consistently requires either intravenous contrast or careful tracking of the unenhanced ureters from the renal pelvis. Figure 1 illustrates a newly discovered cervical cancer patient in whom a focus of intensely increased tracer activity could have represented an otherwise occult metastatic lymph node or physiologic activity in the ureter. Careful interpretation of the PET/CT confirmed that the focus was separate from the ureter, corresponding to a nearly 1-cm-diameter lymph node. This finding resulted in a change in the radiation treatment plan. The patient remains free of recurrence 23 months later.

In our study of 32 patients with locally advanced untreated cervical cancer,⁶ we used PET to prospectively evaluate the patients, who had no radiographic evidence of spread beyond the pelvis (negative CT of abdomen and pelvis, chest x-ray), prior to surgical staging lymphadenectomy. Among 17 patients

TABLE 1. STAGING OF CARCINOMA OF THE CERVIX

FIGO	DESCRIPTION	TNM
I	Cervical carcinoma confined to uterus	T1
II	Tumor invades beyond uterus but not to pelvic wall or lower third of vagina	T2a
IIA	Without parametrial invasion	T2b
III	Tumor extends to pelvic wall and/or involves lower third of vagina and/or causes hydronephrosis or non functioning kidney	T3
IVA	Tumor invades mucosa of bladder or rectum and/or extends beyond true pelvis	T4
IVB	Distant metastasis	M1

Adapted from International Federation of Gynecology and Obstetrics (FIGO) classification system (www.igo.com)
TNM= tumor, nodes, metastases

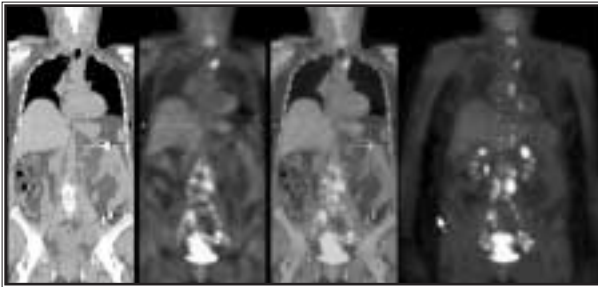


Figure 2. 47-year-old woman with bladder wall invasion, hydronephrosis, extensive pelvic adenopathy, and a possible para-aortic adenopathy. Coronal CT, PET, fused, and MIP images from the patient's PET/CT show unsuspected retrocrural, mediastinal, and left hilar adenopathy as well as intense activity in primary tumor extending well into the uterus and known and suspected para-aortic pelvic lymph node metastases.

who underwent pelvic node resection, pelvic adenopathy was detected in 11/11 patients (100%) with a specificity of 100% (six/six). Only five/11 patients (45%) with pelvic adenopathy were detected by CT. Para-aortic adenopathy was detected in six/eight patients (75%), confirmed at the time of retroperitoneal lymphadenectomy, with a specificity of 92%.

To achieve high sensitivity in the pelvis using older reconstruction techniques, we followed an aggressive protocol for bladder irrigation and drainage and for hydration.¹⁰ With modern iterative reconstruction algorithms, routine hydration and normal voiding are generally all that is necessary to evaluate the abdomen and most of the pelvis, although small obturator lymph nodes may be missed if bladder activity is intense.

Several other investigators have shown PET to be superior to conventional imaging at nodal staging. Among 35 patients with stage IB or II cervical cancer, the sensitivity and specificity of PET was 91% and 100% compared with 73% and 83%, respectively, for MR.⁹ This trend of PET's greater sensitiv-

ity relative to MR for staging lymph nodes was confirmed by a study of 42 women with stage IB or greater cervical cancer and negative abdominal MR examinations.¹¹ PET correctly identified 10 of 12 patients (83%) with positive para-aortic lymph nodes at subsequent lymphadenectomy with one false positive (specificity, 97%). In a subsequent paper, the same group evaluated 50 patients with advanced cervical cancer and negative abdominal CT and found a sensitivity

of 86% and specificity of 94% when compared with surgical staging.¹²

Grigsby et al retrospectively reviewed 101 newly diagnosed cervical cancer patients who were referred for definitive irradiation.⁸ All patients received CT of the abdomen and pelvis and a whole-body PET scan prior to therapy, with follow-up performed for 2.5 to 30 months. PET detected 100 of the 101 primary tumors (99%), while CT found 77 of those same tumors (76%). Specificity for both procedures was 100%. PET detected adenopathy in 67 patients (67%), and CT detected lymph node involvement in 21 patients (20%). The authors used progression-free survival as the outcome variable for comparing the modalities. PET detected supraclavicular lymph nodes in eight patients; all eight succumbed to their disease and were excluded from analysis. Multivariate analysis of six prognostic variables, including CT nodal status, demonstrated PET lymph node status as the only significant prognostic variable ($p = 0.01$), validating the meaningfulness of PET nodal staging. Figure 2 graphically demonstrates the increased sensitivity of PET for

detecting nodal metastases in this patient, whose disease was thought to be largely limited to the pelvis.

RESPONSE AND/OR RECURRENCE TO THERAPY

Because nearly half of patients with advanced disease at the time of diagnosis will ultimately recur, surveillance of patients following successful therapy is performed, usually by CT and/or MR. Systemic therapy alone is generally not a curative option for patients with recurrent disease; the five-year survival rate for patients treated with chemotherapy alone is less than 5%.

Patients with recurrence may be candidates for salvage with either radiation therapy or pelvic exenteration.¹ Early detection of recurrent disease is difficult, due to scarring and radiation changes that sometimes mimic the infiltrative spread of recurrent malignancy. Improved means of detecting residual or recurrent tumor would yield more accurate prognostic information and help select the optimal treatment regimen.

Grigsby et al retrospectively reviewed 76 patients with cervical cancer referred for definitive RT who received both pre- and post-treatment PET scans.⁸ Treatment consisted of pelvic irradiation and para-aortic radiation therapy when there was evidence of para-aortic adenopathy. The post-treatment scans were performed for routine follow-up in asymptomatic patients. Patients then received clinical follow-up for three to 44 months. The post-treatment PET results were found to be the most significant prognostic variable on multivariate analysis, regardless of location.

Other significant variables were post-treatment supraclavicular lymph nodes and any new metastatic sites on PET. Figure 3 illustrates a patient with recurrent cervical cancer to the pelvic side wall who was studied before

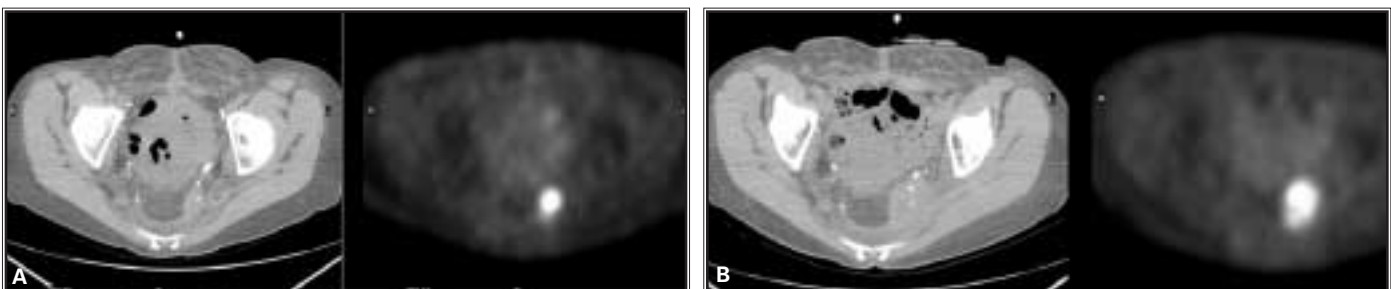


Figure 3. 44-year-old woman previously status post radical hysterectomy, para-aortic lymph node dissection treated with 5080 cGy to pelvis for poorly differentiated squamous cell carcinoma of the cervix with extensive lymphatic invasion (FIGO stage IB2, TNM T1b2 N0 M0). A: PET/CT follow-up 15 months later demonstrates highly metabolically active left pelvic/obturator sidewall recurrence without evidence of additional sites. Patient received combined modality therapy with cisplatin and defini-

itive local pelvic irradiation (5940 cGy) to biologic tumor volume as defined by pre-treatment PET/CT. B: PET/CT performed six weeks after therapy demonstrates increased tumor size on both CT and PET, thought to be nonspecific. Although the normalized FDG accumulation or SUV decreased from 10 to 7, the mass remained markedly hypermetabolic. The patient received additional cisplatin in combination with Taxotere but died five months later.

and after definitive radiation to the recurrence. Unfortunately, marked metabolic activity was only minimally decreased following therapy, which is strongly predictive of a poor prognosis. Despite combined therapy with cisplatin and Taxotere, the patient died five months later.

A retrospective evaluation of 249 patients treated for cervical cancer without evidence of recurrence according to pelvic imaging and routine clinical parameters found 28 of 31 early recurrences on PET prior to CT or MR (sensitivity, 90%). There were 52 false-positive PET interpretations (specificity, 76%), half of which were attributable to chest lesions.¹³ This lower specificity may be due at least in part to differences in the incidence of granulomatous disease in Korea versus many Western nations.

Yen et al looked at early and delayed imaging in 94 patients with either untreated locally advanced cervical cancer or suspected recurrence, using PET performed at both 40 minutes and three hours postinjection as part of a comparison between MR/CT and dual-time-point PET.¹⁴ The authors found dual-time-point PET significantly better than MR/CT at detecting metastatic lesions but similar in accuracy for evaluating primary tumors. Delayed PET imaging was more sensitive than early PET imaging, detecting 134 of 148 malig-

nant lesions, compared with 116 for early imaging, with no loss in specificity.

PET/CT has been shown to offer superior staging and restaging for a variety of malignancies including non-small cell lung cancer, colorectal cancer, and ovarian cancer.¹⁵⁻¹⁸ This is due in large part to the synergies of anatomic and functional information. Suspicious foci that are precisely localized to lymph node that does not meet size criteria for malignancy are interpreted as definitively positive. Those that localize to normal or benign structures known to exhibit focal FDG activity (ureters, arterial plaque, fat, muscle) can be confidently excluded. As experience grows with this rapidly emerging modality, PET/CT will likely be associated with an overall improvement in staging/restaging accuracy similar to that found with other malignancies (10% to 20%). PET/CT is already being used to assist in radiation treatment planning by combining the registered data set with the CT simulation study. This combined approach is routinely leading to changes in radiation treatment planning.

CONCLUSION

PET is sensitive and specific for detection of both treated and untreated tumor in patients with locally advanced cervical carcinoma. Although MR remains the study of

choice for tumor staging, PET/CT may provide satisfactory locoregional and distant staging in a single test. PET contributes information on the status of para-aortic nodes that would otherwise require surgical lymphadenectomy to obtain reliably. The presence of para-aortic adenopathy represents a strong prognostic indicator of recurrence in patients with untreated cervical cancer. Among patients who have been treated, PET provides the best means of detecting residual or recurrent disease. The presence of abnormal FDG activity is a strong negative prognostic indicator that will often predate evidence of recurrence by CT or MR.

PET/CT is expected to improve the overall accuracy of PET staging/restaging as it has for other malignancies. PET/CT is used routinely to determine the biological tumor volume in patients with cervical carcinoma as an integral part of the radiation therapy planning process. At press time (July 2004), the Centers for Medicare and Medicaid Services is considering a national coverage determination request for PET in the evaluation of cervical cancer. Third-party payers often approve PET for their patients with advanced or recurrent cervical cancer based on documentation of a potential for management change. ■

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REFERENCES

- Perez CA, Grigsby PW, Mutch DG, et al. Gynecologic tumors. In: Rubin P, ed. Clinical oncology. A multidisciplinary approach for physicians and students. Philadelphia: WB Saunders, 2001:462-521.
- Jemal A, Tiwari RC, Murray T, et al. Cancer statistics, 2004. *CA Cancer J Clin* 2004;54(1):8-29.
- Stehman FB, Bundy BN, DiSaia PJ, et al. Carcinoma of the cervix treated with radiation therapy. I. A multi-variate analysis of prognostic variables in the gynecologic oncology group. *Cancer* 1991;67(11):2776-2785.
- Follen M, Levenback CF, Iyer RB, et al. Imaging in cervical cancer. *Cancer* 2003;98(9 suppl):2028-2038.
- Lewis E. The use and misuse of imaging in gynecologic cancer. *Cancer* 1987; 60:1993-2009.
- Rose PG, Adler LP, 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(1):41-44.
- Sugawara Y, Eisbruch A, Kosuda S, et al. Evaluation of FDG PET in patients with cervical cancer. *J Nucl Med* 1999;40(7):1125-1131.
- Grigsby PW, Siegel BA, Dehdashti A. Lymph node staging by positron emission tomography in patients with carcinoma of the cervix. *J Clin Oncol* 2001;19(17):3745-3749.
- Reinhardt MJ, Ehrhart-Braun C, Vogelgesang D, et al. Metastatic lymph nodes in patients with cervical cancer: detection with MR imaging and FDG PET. *Radiology* 2001;218(3):776-782.
- Leisure GP, Vesselle HJ, Faulhaber PF, et al. Technical improvements in fluorine-

- 18-FDG PET imaging of the abdomen and pelvis. *J Nucl Med Technol* 1997;25(2):115-119.
- Yeh LS, Hung YC, Shen YY, et al. Detecting para-aortic lymph nodal metastasis by positron emission tomography of 18F-fluorodeoxyglucose in advanced cervical cancer with negative magnetic resonance imaging findings. *Oncol Rep* 2002; 9(6):1289-1292.
- Lin EC. Thyroid nodule mimicking cervical adenopathy on FDG positron emission tomographic imaging. *Clin Nucl Med* 2002;27(9):656-657.
- Ryu SY, Kim MH, Choi SC, et al. Detection of early recurrence with 18F-FDG PET in patients with cervical cancer. *J Nucl Med* 2003;44(3):347-352.
- Yen TC, Ng KK, Ma SY, et al. Value of dual-phase 2-fluoro-2-deoxy-d-glucose positron emission tomography in cervical

- cancer. *J Clin Oncol* 2003;21(19):3651-3658.
- Antoch G, Stattaus J, Nemat AT, et al. Non-small cell lung cancer: dual-modality PET/CT in preoperative staging. *Radiology* 2003;229(2):526-533.
- Cohade C, Osman M, Leal J, et al. Direct comparison of (18)F-FDG PET and PET/CT in patients with colorectal carcinoma. *J Nucl Med* 2003;44(11):1797-1803.
- Lardinois D, Weder W, Hany TF, et al. Staging of non-small-cell lung cancer with integrated positron-emission tomography and computed tomography. *NEJM* 2003;348(25):2500-2507.
- Pannu HK, Bristow RE, Cohade C, et al. PET-CT in recurrent ovarian cancer: initial observations. *Radiographics* 2004;24(1):209-223.



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