Expanding Role of Positron Emission Tomography in Cancer of the Uterine Cervix

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Key Words
PET, FDG, cancer cervix, molecular imaging

Abstract
Molecular imaging through positron emission tomography (PET) is playing a very important role in the management of several different cancers. Its noninvasive nature and ability to study biologic function are ideal for oncology practice. PET is establishing itself in staging, guiding therapy, and follow-up of patients with cervical cancer. The emergence and widespread availability of combined PET/computed tomography technology has further consolidated the role of molecular scanning in managing these patients. This technology is now accessible to every cancer center in the United States and is also available in most countries. Although it is approved for staging patients with cervical cancer, its use in other clinical management situations is being evaluated. The real power of molecular imaging will be to predict treatment response and guide therapy and applications of novel PET tracers for studying complex cellular functions that characterize the tumor for individualized treatment approaches. Although PET technology is beyond the reach of many developing countries, the experience gained in major centers would help devise more effective and simpler treatments that can be introduced. (JNCCN 2006;4:463–469)

Carcinoma of the uterine cervix (i.e., cervical cancer) affects approximately 12,000 women and causes approximately 4,000 deaths every year in the United States. Cervical cancer generally has greater prevalence in lower socioeconomic groups and thus poses unique challenges to the society at large. The overall incidence of invasive cancer has declined steadily since the mid-1940s. Outside of a screening program, many patients are still diagnosed in advanced stages, often resulting in poor response to treatment, higher rates of recurrence, and poorer overall survival. Locally advanced cervical cancer (LACC) often has poor outcomes because it frequently presents with regional metastatic spread.

Staging
Clinical methods currently predominate in staging cervical cancer and are based on the classification system of the International Federation of Gynecologic Oncology. However, the negative influence of pelvic para-aortic lymph node (PALN) disease is well recognized and has resulted in the introduction of surgical staging procedures.1,2 In cervical cancer, PALN metastasis has an estimated incidence of 30% to 40% and shows a steep increase associated with tumor stage and size and histologic differentiation.3 The presence and extent of metastases are highly predictive of survival in patients with LACC.4 The superiority of [18F]-fluorodeoxyglucose (FDG) positron emission tomography (PET) (sensitivity of 78% for PALN and 83%–100% for pelvic nodes) in staging has been established,5 particularly in terms of its noninvasiveness. Whole-body FDG-PET is useful for detecting extrapelvic metastases.6 PET alone, and PET/computed tomography (CT) in particular, is valuable in establishing the diagnosis of pelvis and abdominal lymph nodes.7 Positive predictive value of abnormal left supraclavicular nodes is 100% and is associated with poor survival after aggressive treatment.8 The ability to perform whole-body screening is the main advantage of using FDG-PET in cervical cancer, although magnetic resonance imaging (MRI) is more useful for staging locoregional disease (Figures 1 and 2). Combined use of morphologic and functional imaging with sentinel node identification improves diagnostic accuracy.9–11

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PALN Involvement

Although primary pelvic radiotherapy or radical hysterectomy is associated with good local control, many patients (up to 30%), particularly those with bulky stage I or II primary disease, have PALN disease and undergo failed treatment.\(^2\)\(^3\) FDG-PET is a more sensitive method for detecting PALN involvement\(^4\)\(^5\)\(^6\)\(^7\)\(^8\)\(^9\)\(^10\) and determining radiation field placement\(^10\) compared with CT and MRI. Dual-phase imaging has been shown to increase the sensitivity of PALN detection.\(^2\)\(^0\) Although rarely performed, when lymphangiography is also used for staging, it should be done after PET imaging to avoid interference.\(^2\)\(^1\)

Prognostication of Cervical Cancer

Current prognostic criteria, including tumor stage information, cannot effectively predict the clinical course for all patients because clinical stages comprise heterogeneous populations. Several molecular and serum markers have been used for this purpose, but their effectiveness is limited by sampling errors from a heterogeneous disease or lack of specificity.\(^2\)\(^2\)\(^3\)\(^4\) PET imaging satisfies the requirements of an ideal noninvasive prognostic method that can be used to identify patients at increased risk for failure and to select patients for optimal therapy. The standardized uptake value (SUV) from baseline FDG-PET has been used as a marker for tumor aggressiveness,\(^2\)\(^5\)\(^2\)\(^6\) whereas a change in the SUV with treatment can confidently establish response.\(^2\)\(^7\)\(^2\)\(^8\)\(^2\)\(^9\) Using FDG-PET, Miller et al.\(^3\)\(^0\) investigated the role of a simple visual analysis or tumor volume for determining prognosis for patients with cervical cancer.

PET Principles

FDG has a structure similar to that of glucose and is readily taken up and phosphorylated in cells but cannot chemically proceed past hexose-6-phosphate and becomes trapped inside the cell. Uptake and use of FDG reflects the rate of glycolysis and thus the rate of glucose metabolism in tumors. Although no single explanation is available for the increased glycolysis seen in neoplastic tissues, cancer cells in general have increased aerobic glycolysis (Warburg effect).\(^3\)\(^1\) Increased expression of glucose transporter receptors has been seen in cancer cells and can be further augmented under hypoxia. This fact, combined with a higher concentration and density of neoplastic cells in a tumor, results in a greater tumor-to-background ratio, providing for the successful use of FDG in tumor imaging. For this reason, patients with diabetes mellitus must have a blood glucose level of 150 mg or less. The use of insulin to lower the blood sugar before FDG scan is generally not advisable because it would push FDG into the muscles and cause difficulties with interpretation. Catheterization and drainage of the urinary bladder are necessary to reduce the influence of radioactive urine on interpretation of pelvic and abdominal sites.\(^3\)\(^2\) Some patients may also require lorazepam or similar drugs.

FDG uptake has been expressed in several ways, with SUV the most common. It is the ratio of FDG concentration in a region of interest to its concentration in the whole body. Several factors affect the
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calculated SUV, including body surface area, partial volume effect, and time after tracer injection. Commercial availability of FDG radiopharmaceuticals from centralized sources and dedicated PET scanners have resulted in the popularity and widespread clinical use of PET imaging.

The popularity of PET in general has recently increased significantly, with predicted future annual revenues approaching approximately $1 billion. Innovative commercial ventures in marketing PET tracers (FDG) from a nationwide network of radiopharmacies seem to have been highly successful in obviating the need for on-site cyclotrons in PET facilities. The Center for Medicare & Medicaid Services approved and provides coverage for FDG-PET for staging as adjunct to conventional imaging. For other indications, including diagnosis, restaging, and monitoring, coverage is based on evidence development.

Greater resolution of modern PET scanners allows detection of tumors as small as 4.5 to 8 mm. However, because of the influence of partial volume effects, smaller lesions should be interpreted cautiously, particularly when semiquantitative methods such as SUV are used to corroborate malignancy. Several authors have attempted to improve the accuracy of SUV by making adjustments/corrections.

Combined PET/CT is fast becoming the standard technology in the clinic because of its distinct advantages over PET and CT alone. PET/CT imaging is generally performed with noncontrast CT for attenuation correction. Also, a diagnostic-quality full contrast CT scan might be done at the same session. In addition to reducing the overall imaging time, PET/CT reduces the number of equivocal interpretations, which is particularly useful in evaluating peritoneal disease. Use of PET/CT is also helpful in interpreting normal physiologic activity in the body, such as in the bowels, endometrium, and ovaries. Coregistration of PET images with anatomic imaging such as CT or MRI is extremely useful for this purpose.

Treatment Approaches for Cervical Cancer

Current management strategies for cervical cancer involve surgery and radiation therapy in different combinations with chemotherapy. Radiation therapy and surgery are the mainstays of treatment. Radiotherapy typically involves a combination of external beam radiation therapy and brachytherapy. Use of concurrent chemotherapy has significantly improved the results but can be associated with higher toxicity. After radiotherapy, up to 25% of patients typically experience treatment failure at the primary site. Disease recurrence rate has been correlated with the stage of the primary disease.

PET-Directed Treatment

Use of biologic information to decide target volume is very attractive and has been approached in many ways. High sensitivity and negative predictive value of FDG-PET can be used to select the appropriate treatment or to define fields and dose intensity for radiation therapy. A negative PET finding in the para-aortic region has a high negative predictive value for nodal disease and can be used to de-escalate the volume of normal tissue included in radiation treatment. Fusion of PET and CT images and the use of intensity modulated radiotherapy (IMRT) allow for dose modulation with lower toxicity while maintaining an optimal therapeutic ratio. FDG-PET has been investigated in selecting the target volume and guiding radiation therapy for the primary disease and PALN.

Evaluation of Treatment Response

The SUV measurements from FDG-PET have been used to predict response to therapy. Tumors with a high initial SUV tend to show greater local failure after treatment and greater metastatic disease. SUV measurements can also be used to decide the intensity of treatment. Several studies have shown that patients with tumors that show a reduction in SUV experience a favorable response to therapy. Both the absolute pretreatment SUV and its change on serial FDG scans can be used as prognostic indicators, measures of response in patients undergoing radiation therapy or chemotherapy, and measures of greater metastatic disease. Studies have shown that patients with tumors that show a reduction in SUV as a result of therapy have experienced a favorable response to therapy. The practical implications of this approach would be enormous. This approach would provide the oncologist with an opportunity to tailor therapy or modify it based on the presence or lack of treatment response. FDG-PET has been found to be very useful during follow-up of patients with rising tumor markers or equivocal CT or MR imaging. In a retrospective review of 152 patients, Grigsby et al. concluded that persistence of FDG uptake post-therapy might be predictive of tumor recurrence.
Recurrent or Persistent Disease
Post-Chemotherapy/Radiation Therapy

Recurrent cancer can be difficult to diagnose using conventional imaging studies, mainly because of treatment-induced changes in normal tissues. Post-radiotherapy fibrosis produces problems in interpreting CT images and confounds active residual disease. A negative FDG-PET scan can obviate biopsy of suspicious findings after radiotherapy. FDG-PET is effective in restaging patients after treatment, and delayed FDG imaging can play an important role in diagnosing recurrences. Serial FDG-PET scans used in the follow-up of patients undergoing radiotherapy have indicated a mixed advantage for using the SUV to diagnose recurrence. Many authors have used the SUV to differentiate between recurrence and inflammatory lesions. A value higher than the threshold range of 2 to 3.5 is usually used to diagnose malignant disease. Dual-time-point imaging has been recommended as a means to differentiate neoplastic conditions from inflammation. FDG-PET has an overall sensitivity of 85% and specificities of 90% and close to 100% for detecting local and para-aortic nodal recurrence, respectively. FDG-PET has been found to be a useful tool in diagnosing recurrence and outcome after therapy, with a sensitivity of 90% and a specificity as high as 76%. Yen et al. created a scoring system that can be used effectively to select the optimal therapy for recurrent tumors.

Novel Tracers for Evaluating the Biology of Cervical Cancer

Several biologic factors are known to characterize cancer and predict treatment response and patient outcome, including information on tumor microenvironment (e.g., pH, hypoxia) and altered gene expression and physiologic function, such as proliferation and glucose metabolism. Identification of tumor hypoxia helps experts make sound treatment decisions based on tumor microenvironment.

Many solid tumors develop regions of hypoxia as they outgrow their blood supply. Tumor hypoxia induces biologic changes through hypoxia-inducible factor and negatively impacts treatment response, resulting in poor survival. Hypoxia in cervical cancer has been investigated using F-18 fluoro-romisonidazole and Cu-64 ATSM PET imaging. Similarly, cellular proliferation can be investigated with labeled thymidine analogues as early indicators of treatment response.

Torizuka et al. investigated the role of (11)C-choline in imaging gynecologic cancer, noting the lack of urinary activity to be an advantage over FDG. However, the presence of nonspecific uptake in the intestines and routine availability of (11)C-labeled compounds might limit its role.

Pitfalls

With high sensitivity of FDG-PET, nonspecific uptake can occur in sites of inflammation or infection and in certain normal organs or sites that may pose difficulties in interpretation. Although FDG-PET has a high level of sensitivity, a few pitfalls are associated with this imaging. For example, FDG uptake occurs in the menstruating endometrium of normal premenopausal women. Increased FDG uptake close to the cervix can be confusing but does not necessarily reflect endometrial spread. Likewise, increased ovarian uptake in premenopausal women is likely normal but in postmenopausal women is a strong indicator of malignancy. PET/CT would be helpful in these situations. Uptake of FDG in the rectum and bladder might pose difficulties in identifying smaller primary tumors, but the use of bladder catheterization and hybrid PET/CT is expected to play a crucial role in this respect. Experts must be cognizant of the inherent artifacts involved with PET/CT; for example, its limitations in detecting microscopic and small-volume disease (< 0.5 cm). These limitations are caused by the simultaneous use of contrast, presence of metallic prosthesis and implants, and breathing type and movements. CT-based attenuation correction also makes semiquantitative measurements somewhat difficult. SUV must be measured carefully because active bleeding in a tumor might give a slightly higher value. Inflammatory reactions induced by radiation therapy dictate that follow-up scans be sufficiently delayed for the uptake to normalize. Adequate patient preparation, clear knowledge of patient history, and correlation with anatomic imaging are vital for minimizing false-positive interpretation. Despite these pitfalls, the role of PET/CT will most likely escalate in clinical practice with the judicious application of sound principles.
Conclusions

In summary, functional imaging using PET is rapidly changing clinical practice for many gynecologic cancers, including those of the uterus. Its sensitivity and accuracy in detecting nodal disease makes it an effective tool in staging and characterizing these cancers. Semi-quantitative measures of FDG uptake can be reliably used to evaluate treatment response and diagnose recurrent disease. Use of PET/CT further increases the accuracy of localization and provides a tool for guiding radiation treatment. Novel PET tracers provide a complete range of molecular imaging tools to study functions other than glucose metabolism.

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References


