Published in final edited form as:

PET Clin. 2018 April ; 13(2): 165–177. doi:10.1016/j.cpet.2017.11.004.

FDG-PET assessment of cervical cancer

Chitra Viswanathan, M.D. [Associate Professor],

1400 Pressler St., Unit 1473, Houston, TX 77030-4008, (713) 470-8440,

Chitra.Viswanathan@mdanderson.org

Silvana Faria, M.D., Ph.D. [Associate Professor],

1400 Pressler St., Unit 1473, Houston, TX 77030-4008, (713) 563-7832,

SCFaria@mdanderson.org

Catherine Devine, MD [Associate Professor],

1400 Pressler St., Unit 1473, Houston, TX 77030-4008, cdevine@mdanderson.org

Madhavi Patnana, MD [Associate Professor],

1400 Pressler St., Unit 1473, Houston, TX 77030-4008, mpatnana@mdanderson.org

Tara Sagebiel [Assistant Professor],

1400 Pressler St., Unit 1473, Houston, TX 77030-4008, tsagebiel@mdanderson.org

Revathy B. Iyer, M.D. [Professor], and

1400 Pressler St., Unit 1476, Houston, TX 77030-4008, (713) 792-5043, Rlyer@mdanderson.org

Priya R. Bhosale, M.D. [Professor]

1400 Pressler St., Unit 1473, Houston, TX 77030-4008, (713) 792-0221,

Priya.Bhosale@mdanderson.org

Synopsis

This paper will provide an overview of PET in cervical cancer, primarily with regard to the use of FDG PET/CT. A brief discussion of upcoming technologies, such as PET/MRI, will be presented.

Keywords

Cervical cancer; PET/CT; PET/MRI; Cancer staging; Treatment planning

Introduction

According to the American Cancer Society, there will be 12,280 new diagnoses and 4,210 deaths attributable to cervical cancer in 2017[1]. Worldwide, cervical cancer is the 4th most common cause of cancer with a disease incidence of approximately 520,000 cases per year with 265,000 deaths[2]. In the Western world, most cancers are now diagnosed in the

---

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

preclinical stage as a result of active screening with the Papanicolaou (Pap) test. This has reduced the incidence of cervical cancer significantly by over 50%. Additionally, Human Papilloma Virus (HPV) has been found to be a causal factor, with HPV subtypes 16 and 18 a cause in 99% of cervical tumors [3]. The implementation of the HPV vaccine has decreased disease incidence as well. Despite these measures, cervical cancer continues to be a major health issue worldwide.

The clinical staging system utilized worldwide is the International Federation of Gynecology and Obstetrics (FIGO). Where available, modalities such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography/computed tomography (PET/CT) that provide anatomic and metabolic information are highly useful and impact patient therapy and treatment. The treatment for most stages of cervical cancer is chemoradiation, and imaging helps guide the treatment planning. The goal of this review is to provide evidence of the utility of PET imaging, primarily PET/CT, in the diagnosis, staging, treatment planning, and evaluation of tumor recurrence in patients with cervical cancer.

Detection

In the western world, the use of active screening Papanicolaou (Pap) testing in women ages 21–70 allows early detection of pre-invasive and early stage cancers (stage 1) before patients present with symptoms and findings on clinical exam. Symptomatic patients with more advanced tumors may present with post-coital bleeding, intermenstrual and postmenstrual bleeding, foul-smelling discharge, chronic anemia, and mass [4].

Risk factors for cervical cancer include early age of sexual activity, genital warts, cigarette smoking, greater number of sexual partners, immunosuppression, human immunodeficiency virus (HIV) positive status, and HPV infection serotypes 16 and 18. With the strong causal relationship between HPV and cervical cancer, patients over 30 have HPV testing at the time of Pap smear [3].

Pathology

The World Health Organization (WHO) pathology classification includes squamous (epithelial), glandular (adenocarcinoma), and other epithelial tumors such as adenosquamous, neuroendocrine, and undifferentiated carcinoma. The majority of cervical cancer cases are of squamous cell histology, accounting for 70–80% of cases. Adenocarcinoma histologies account for 20–25% [5]. The non-squamous pathologies are associated with worse prognoses [3].

Staging

Cervical cancer first spreads locally to adjacent structures such as the vagina, bladder, ureters, and rectum. Then, spread occurs via the pelvic, para-aortic, and supraclavicular lymph nodes in a cephalad fashion. Hematogenous spread occurs to the non-nodal distal sites [6].

Cervical cancer is most commonly staged utilizing the International Federation of Gynecology and Obstetrics (FIGO) and the American Joint Committee on Cancer TNM systems (Table 1). FIGO is a clinical staging system that uses physical exam including examination under anesthesia (EUA), cystoscopy, colposcopy, proctoscopy, hysteroscopy, barium enema examination, intravenous urography (IVU), radiography of the chest and skeleton, and endocervical curettage and biopsy [7] The use of the FIGO system allows for uniform worldwide staging of patients, but the system is limited in that it does not account for information and factors that affect prognosis and management, such as lymph node status [3]

Anatomic Imaging

CT and MRI historically have been performed for anatomic assessment and locoregional involvement prior to the development of metabolic imaging. CT can assess for regional lymph nodes, distal metastases, and hydronephrosis; it has eliminated the need for lymphoscintigraphy and IVU in areas with access to CT. However, CT is limited in its soft tissue resolution and assessment of cervical tumor invasion, parametrial invasion, and pelvic sidewall involvement. In this regard, MRI is highly valuable in the evaluation of the primary tumor. MRI has close to 90% accuracy in the local staging of cervical cancer tumors > 1 cm. MRI is superior in the evaluation of tumor size, extension, and location. This is very helpful in treatment planning, in separating patients who can undergo surgical resection versus those who receive chemoradiation[8].

However, the limitation of CT and MRI arises in the evaluation of metastatic nodal disease in the preoperative setting. CT and MRI are limited in the evaluation of micrometastatic disease in lymph nodes smaller than 1 cm. They also cannot reliably detect reactive nodes versus metastatic nodes greater than 1 cm.

FDG PET/CT

PET is most commonly performed with the radiotracer ^{18}F -2-fluoro-2-deoxy-D-glucose (FDG). FDG PET/CT is dependent upon physiologic changes and is based on the degree of uptake and metabolism of glucose, which is abnormal in tumors as compared to surrounding tissues. Historically, PET used to be performed as a standalone procedure. The use of FDG PET alone is an older technique recently replaced with FDG PET/CT given the value of hybrid metabolic and anatomic imaging.

Protocols

FDG PET/CT can be performed in two ways. CT can be performed with a low-dose radiation technique for coregistration and attenuation-correction, or contrast-enhanced (CE) CT can be performed with oral and intravenous contrast administration for diagnosis, attenuation-correction, and coregistration.

Patients are asked to fast for 6 hours prior to procedure. If diabetic, they are asked to hold their medication or insulin for 6 hours prior to study[8]. The intravenous injection of a weight-based amount of FDG (0.22 mCi/kg) is then given. If patient is receiving a CE

examination, oral contrast material is given at this time as well. After approximately 60–90 minutes to allow for the uptake of radiotracer, the combined PET/CT is obtained. PET acquisition from the proximal thighs to skull base occurs after the patient empties their bladder to avoid intense bladder activity. CT acquisition occurs after the administration of intravenous contrast material. PET imaging information is reconstructed and available with CT attenuation correction (AC) or without CT AC (NAC). The images are sent to a dedicated software platform and fused for image analysis[9].

Staging

Primary tumor

FDG PET/CT has been shown to be useful in the detection of the primary tumor and in the assessment of tumor volume. The normal cervix does not accumulate FDG much over the background tissue. The metabolic activity of the primary tumor, as measured by maximum standardized uptake value (SUVmax), has been shown in many studies to be a prognostic indicator in patients with cervical cancer (Figure 1). In their study of 59 patients with stage IA2–IIB cervical cancer who underwent PET/CT followed by surgery, Yagi et al found patients with higher SUVmax tumors have lower overall survival (OS) and progression-free survival (PFS). These higher SUVmax tumors are also associated with lymph node metastases, advanced stage, lymphovascular invasion, and larger tumors [10, 11]. Kidd et al found that SUVmax of the primary tumor also has other prognostic value, having a correlation with histology and differentiation[11]. Other quantitative data obtained from PET/CT have been shown to be helpful, such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) [12, 13]. Zhang et al compared the gross tumor volume (GTV) as assessed by CT, MRI, and PET/CT to pathologic volume in 10 patients with stages I-II cervical cancer, and found that PET/CT GTV determined under 40% SUVmax had the best correlation with pathology volume [14]. Yang and colleagues found that PET/CT better evaluates the depth of cervical stromal invasion than conventional methods using SUVmax = 7.83 or MTV = 8.76 ml, and may allow for better treatment planning[15].

Lymph Node Metastases

The lymph node status has been shown to be a significant prognostic indicator for survival. In cervical cancer, metastases can involve the pelvic and para-aortic lymph node chains (Figure 2). FDG PET/CT is valuable in detecting metastases in the typical distribution but also in identifying any other lymph nodes[16]. In their 2001 study, Grigsby et al showed in their retrospective study that FDG PET was superior to CT in the detection of abnormal nodes and prediction of treatment outcome[17]. Kidd et al showed in their larger patient prospective study that the frequency of FDG avid lymph nodes correlates with stage. Patients with FDG-avid lymph nodes have poorer outcomes as compared to patients without FDG-avid lymph nodes within the same stage[18]. In their additional study of 83 patients, Kidd and colleagues showed the SUVmax of the pelvic lymph node (PLN) is a prognostic biomarker for cervical cancer response, recurrence, and survival [19].

Onal et al recently studied 93 patients with pelvic and para-aortic lymph node metastases, and found patients with pelvic lymph node metastases SUVmax > 7.5 had larger lymph node

metastases, higher SUVmax primary tumor, higher rate of para-aortic lymph node involvement, and lower post-therapy complete response rates [20]. Rose et al showed that PET has high specificity and sensitivity for predicting pelvic and para-aortic lymphadenopathy and for showing the presence and absence of disease[21].

PET/CT may be of limited usefulness in the early stage cervical tumors. Driscoll et al found PET/CT to be of limited value in their cohort of patients with early stage (stages IA–IB1) MRI lymph node negative cervical cancer [22]. Signorelli et al evaluated 159 women with cervical cancer stages IB1 and IIA, and found that PET/CT had low sensitivity for lymph node involvement and did not change management in treatment planning[23].

Distal Metastatic Disease

FDG PET/CT is valuable in the assessment of distal metastatic disease. Tumors can spread hematogenously to the lungs, liver, and bone marrow (Figure 3). Liu et al studied patients with advanced stage disease, lymph node metastases, and suspected recurrent disease, and found PET/CT to be superior to MRI and CT for evaluation of osseous disease (Figure 4). They also found an association between lymph node metastases and osseous metastatic disease[24]. Loft and colleagues found metastatic disease in 10 of 119 patients and concluded PET/CT has a sensitivity 100%, specificity 94%, positive predictive value (PPV) 63%, and negative predictive value (NPV) 100% [25].

Treatment Planning

Treatment of cervical cancer includes surgery, radiation, chemotherapy, and/or a combination of these modalities. For the majority of the stages, chemoradiation is the primary mode of treatment. Aside from its diagnostic and prognostic factors, PET/CT is utilized for radiation treatment planning modeling and dose allocation.

External Beam Radiation Therapy

Studies have found that PET/CT is useful in radiation treatment planning to assess the treatment volume, treatment dose, and to direct therapy to lymph nodes. External beam radiation may be given to the pelvis only if patients have tumor in the pelvis and lymph nodes confined to pelvis. If there is para-aortic nodal involvement, then radiation will be given to the pelvis and para-aortic region. Radiation treatment planning contours can be made from the PET/CT images to specifically target the FDG-avid tumor regions and to decrease the dose to adjacent organs not involved with tumor[26]. The field may be extended to include nodal involvement[27].

Brachytherapy

Intracavitary brachytherapy can be performed using 2D techniques such as radiography and 3D techniques such as CT, MRI, and FDG PET/CT[28]. PET/CT has the advantage of not being dependent upon anatomic details like CT and MRI but rather dependent on changes in metabolic activity. The metabolic activity of the tumor on PET/CT can be directly overlaid upon the CT image of the intracavitary applicators, and dose calculations can be obtained

accordingly. Changes in metabolic activity can be monitored using PET/CT during the course of radiation therapy[27].

Evidence

Chung et al found a higher disease-free survival and overall better survival when PET/CT intensity-modulated radiation therapy (IMRT), image-guided radiation therapy (IGRT), and 3D brachytherapy treatment planning were used in their study set of 72 patients with advanced cervical cancer with pelvic, para-aortic, and supraclavicular nodes. The main causes of treatment failure were out-of-field disease at the junction of the treatment plan and distal metastatic disease[29]. The use of PET/CT in this regard can be very helpful in targeting the tumor and sparing normal adjacent tissues. Lazzari and colleagues reported that FDG PET/CT helps accurately determine tumor volumes, which enables higher dose to smaller areas and may allow for dose escalation[30]. This helps decrease patient morbidity from treatment and possible side effects.

Follow-up Evaluation

Response Assessment

PET/CT is usually performed 3–7 months after chemoradiation to determine the efficacy of treatment and to determine the follow-up interval required [28]. Response to therapy is related to prognosis (Figure 5). Kidd et al studied the SUVmax, MTV, and tumor heterogeneity in 25 patients with stages IA–IV cervical cancer at different time points after treatment. They found that SUVmax declines with treatment, and pretreatment and 4 week SUVmax measurements represent the best time points for assessment of response. There were 5 patients with persistent or new disease on 3 month follow-up FDG PET/CT, and these patients showed higher SUVmax and tumor heterogeneity at all time points[31]. Schwarz and colleagues did a retrospective analysis of 92 patients after external radiation, brachytherapy, and concurrent chemotherapy, and found that the 3 month post-therapy SUVmax is predictive of survival. 70% of the patients had a complete metabolic response (MR), 15% had a partial MR, and 6% had progressive disease (PD). The 3 year PFS rates were 78% for the complete MR group, 33% for the partial MR group, and 0% for the PD group[32]. Siva and colleagues examined 105 patients who underwent post-treatment PET/CT at 3–12 months (average 5 months), based on the discretion of the clinician. In the 73 patients with complete MR, only 1 had tumor recurrence, detected by clinical examination as the patient was asymptomatic. They concluded that the presence of complete MR is a strong predictor of survival. In the patients with complete MR post-treatment, conservative follow-up can be performed[33, 34]. Herrera et al found that the parameters of TLG, pretreatment mean standardized uptake value (SUVmean) ≥ 5 , and partial MR to be associated with unfavorable outcome[35].

Recurrence/Restaging

Tumor recurrence is the development of tumor at least 6 months after the initially treated disease has responded to therapy[9, 36] (Figure 6). As many as 1/3 of patients with locally advanced cervical cancer develop recurrent disease, usually within two years[35]. Wong et al found PET/CT to be an accurate tool in diagnosing local recurrence and distant metastases.

The sensitivity, specificity, and accuracy of PET/CT was 82%, 97%, and 92%, respectively, for local tumor recurrence, and 100%, 90%, and 94%, respectively, for distant metastatic disease[37]. Ryu and colleagues evaluated 249 patients with no evidence of cancer after treatment with surveillance PET. They found PET to be effective in detection of tumor recurrence, with a sensitivity of 90.3% and a specificity of 76.1%. 82% of the recurrent cases occurred within 6–18 months after therapy and 89% of recurrent cases occurred in patients with stage IIB and III disease[38]. Lee et al studied 51 patients with treated cervical cancer and found tumor recurrence or metastasis in 37. They found PET/CT to have a sensitivity of 97.3%, a specificity of 71.4%, and an accuracy of 90.2%[39]. PET/CT has been shown to detect metastases in asymptomatic patients and in patients with increasing tumor markers.

Brooks and colleagues performed a prospective study that followed asymptomatic patients who had complete response on their 3 month evaluation, and found that PET/CT detected tumor recurrence in patients who could potentially benefit from salvage therapy[40].

Chong and colleagues evaluated patients with unexplained tumor marker elevation following complete treatment response with PET/CT. These patients had elevation of carcinoembryonic antigen (CEA) or squamous cell carcinoma antigen (SCC-Ag), and PET/CT had high sensitivity and high negative predictive value [41].

PET/CT has been shown in studies to impact clinical management and change treatment plans. Chung and colleagues showed post-treatment PET/CT to have significant prognostic impact, showing patients with a negative PET/CT to have a better PFS and OS. In their study, PET/CT changed treatment plans in 24.2% of patients[42]. Recent meta-analyses performed in the United Kingdom found that PET/CT is not cost-effective for the evaluation of recurrent disease; however, the recommendations could change if the cost of PET/CT decreases and more studies show therapeutic impact in patients with recurrent or persistent disease [43, 44].

PET/CT Pitfalls

Benign conditions

There are potential imaging pitfalls that can occur with PET/CT. One is FDG uptake in brown fat, which can be distinguished from lymphadenopathy by its characteristic distribution in the neck and thorax and absence of lymph nodes in the areas of uptake. It can be prevented by use of blankets or with anxiolytics in the case of anxiety as tolerated by the patient[8]. Physiologic uptake in the endometrium and ovaries can occur in younger patients due to the menstrual cycle. Physiologic uptake in the ureter can mimic a lymph node. Infection or inflammation can also have FDG uptake and mimic malignancy.

Post-therapy Changes

The inflammatory response at the primary site caused by radiation therapy can be hypermetabolic. Therefore, follow-up PET/CT is generally performed 8–12 weeks after radiation therapy has been completed to allow these changes to abate[45]. However, in some cases, they may persist for months, and biopsy may be required for further evaluation.

Gastrointestinal side effects of radiation and chemotherapy such as enteritis, proctitis, fistulas, and strictures can also cause findings at PET/CT that should not be confused as progression of disease[46].

Post-therapeutic changes in the osseous structures can also be hypermetabolic or hypometabolic. Causes of increased metabolic uptake include bone marrow stimulation, inflammatory change due to radiation, or post-radiation fractures. Decreased metabolic uptake may be seen in delayed reactions such as bone marrow suppression[46].

Tumor Hypoxia

Hypoxic tumors have decreased response to chemotherapy and radiation therapy, and assessing the presence of hypoxia would be helpful to alter therapy. Hypoxia may be a significant prognostic factor, given that patients with hypoxic tumors have worse outcomes than patients who do not, and may be a factor in resistance to therapy[47]. Hypoxia studies have been performed with the copper-labeled dithiosemicarbazone radiotracers ^{60}Cu -diacetyl-bis (N^4 -methylthiosemicarbazone) (^{60}Cu -ATSM) and ^{64}Cu -diacetyl-bis (N^4 -methylthiosemicarbazone) (^{64}Cu -ATSM) along with ^{18}F -fluoromisonidazole (^{18}F -FMISO) PET/CT. Studies by Dehdashti et al with use of ^{60}Cu -ATSM in pretreatment planning concluded that tumor uptake, specifically tumor-to-muscle uptake of 3.5, was correlated to recurrent disease along with shorter PFS and cause-specific survival[48]. Lewis et al did a comparison of ^{60}Cu -ATSM and ^{64}Cu -ATSM and concluded ^{64}Cu -ATSM is a safe radiotracer for producing high quality PET images in the evaluation of hypoxia[49]. There is currently an ongoing American College of Radiology Imaging Network (ACRIN) clinical trial to study how well ^{64}Cu -ATSM PET performs in predicting disease progression in patients with cervical cancer[47, 50].

FDG PET/MRI

PET/MRI is coming now to the forefront as a new diagnostic tool in the treatment of cervical cancer, after some initial technical challenges. PET/MRI systems can either operate simultaneously or sequentially. In the simultaneous model, PET and MRI elements are housed in the same gantry, with simultaneous acquisition of data from the same body section. In the sequential model, the MRI and PET elements are connected via a moving table [51–54].

Study results are very promising. Kitajima et al evaluated 30 patients with PET/CT, MRI, non-fused PET and MRI, and fused PET/MRI. In evaluation of the primary tumor, PET/MRI detected tumor in 100% of the cases versus 93.3% with PET/CT. CE fused PET/MRI has the advantage of more detailed assessment of the extension of the primary tumor and spread into the parametrium, vagina, pelvic sidewall, and bladder due to a small field-of-view (FOV) (Figure 8). However, the difference between the two modalities was not statistically significant. In the evaluation of the primary tumor, PET/MRI is significantly more accurate, with accuracy of 83.3% versus PET/CT accuracy of 53.3%. For assessment of the lymph nodal stage, PET/MRI and PET/CT showed similar sensitivity, specificity, and accuracy of 92.3%, 88.2%, and 90.0%, respectively[55]. Grueneisen and colleagues showed PET/MRI to

have excellent performance in the evaluation of T stage, regional nodal involvement, and metastatic disease.

Functional and multiparametric techniques used in MRI may also allow greater quantitative assessment with new biomarkers [56]. Grueneisen and colleagues found that pathologic grade and tumor size were significantly correlated with SUVmax and apparent diffusion coefficient (ADC)[57]. Surov and colleagues performed PET/MRI on 21 patients, and found a statically significant correlation between the proliferation index Ki67 and SUV, minimum ADC (ADCmin), and SUVmax/ADCmin[58].

PET/MRI has advantages in follow-up after radiation treatment planning. In post-treatment evaluation, PET/MRI may be better able to detect radiation changes from recurrent tumor, such as post-therapeutic scarring[59]. Furthermore, the reduced radiation exposure in PET/MRI is an advantage in cancer patients who undergo multiple serial exams. As the current recommendation by most governing bodies such as the National Comprehensive Cancer Network (NCCN), American College of Radiology (ACR), and European Society of Gynecologic Oncology (ESGO) is to obtain PET/CT and MRI, this obviates the need for two exams as well[34, 47, 56, 60].

Conclusion

Cervical cancer continues to be a significant worldwide health issue. The use of PET/CT has continued to evolve and the modality has significant use in the detection of disease, prognosis and treatment planning. The NCCN, American College of Radiology and United States Center for Medicare and Medicaid Services (CMS) all acknowledge the utility of PET/CT in the initial evaluation of cervical cancer [61, 62]. Radiation treatment planning can be better performed with more targeted therapy and less effect on adjacent structures with the use of PET/CT. The use of tumor values from PET such as SUVmax, MTV and TLG, in combination with the parameter ADC from PET/MRI, continues to enhance the impact of these imaging modalities on disease prognostication and treatment planning.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA: A Cancer Journal for Clinicians. 2017; 67(1):7–30. [PubMed: 28055103]
2. Bruni LB-RL, Albero G, Serrano B, Mena M, Gomez D, Munoz J, Bosch FX, de Sanjose S. ICO Information Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and Related Diseases in the World. Summary Report.
3. Marth C, Landoni F, Mahner S, et al. Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Annals of Oncology. 2017; 28(suppl_4):iv72–iv83. [PubMed: 28881916]
4. Comprehensive Cervical Cancer Control: A Guide to Essential Practice. 2. Geneva: World Health Organization; 2014. Annex 10, Cervical cancer treatment by FIGO stage. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK269617/>
5. Howlader, NNA.Krapcho, M.Miller, D.Bishop, K.Kosary, CL.Yu, M.Ruhl, J.Tatalovich, Z.Mariotto, A.Lewis, DR.Chen, HS.Feuer, EJ., Cronin, KA., editors. National Cancer Institute. Bethesda, MD: Apr, 2017 SEER Cancer Statistics Review, 1975–2014. https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER web site

6. Benedetti-Panici P, Maneschi F, Scambia G, et al. Lymphatic Spread of Cervical Cancer: An Anatomical and Pathological Study Based on 225 Radical Hysterectomies with Systematic Pelvic and Aortic Lymphadenectomy. *Gynecologic Oncology*. 62(1):19–24.
7. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynaecol Obstet*. 2009; 105:103. [PubMed: 19367689]
8. Kusmirek J, Robbins J, Allen H, et al. PET/CT and MRI in the imaging assessment of cervical cancer. *Abdominal Imaging*. 2015; 40(7):2486–2511. [PubMed: 25666968]
9. Mirpour S, Mhlana JC, Logeswaran P, et al. The Role of PET/CT in the Management of Cervical Cancer. *American Journal of Roentgenology*. 2013; 201(2):W192–W205. [PubMed: 23883234]
10. Yagi S, Yahata T, Mabuchi Y, et al. Primary tumor SUVmax on preoperative FDG-PET/CT is a prognostic indicator in stage IA2–IIB cervical cancer patients treated with radical hysterectomy. *Mol Clin Oncol*. 2016; 5(3):216–222.
11. Kidd EA, Siegel BA, Dehdashti F, et al. The standardized uptake value for F-18 fluorodeoxyglucose is a sensitive predictive biomarker for cervical cancer treatment response and survival. *Cancer*. 2007; 110(8):1738–1744. [PubMed: 17786947]
12. Hong JH, Jung US, Min KJ, et al. Prognostic value of total lesion glycolysis measured by 18F-FDG PET/CT in patients with locally advanced cervical cancer. *Nucl Med Commun*. 2016; 37(8):843–8. [PubMed: 27058362]
13. Hong JH, Min KJ, Lee JK, et al. Prognostic Value of the Sum of Metabolic Tumor Volume of Primary Tumor and Lymph Nodes Using 18F-FDG PET/CT in Patients With Cervical Cancer. *Medicine (Baltimore)*. 2016; 95(9):e2992. [PubMed: 26945420]
14. Zhang Y, Hu J, Li J, et al. Comparison of imaging-based gross tumor volume and pathological volume determined by whole-mount serial sections in primary cervical cancer. *OncoTargets and therapy*. 2013; 6:917–923. [PubMed: 23888117]
15. Yang Z, Xu W, Ma Y, et al. 18F-FDG PET/CT can correct the clinical stages and predict pathological parameters before operation in cervical cancer. *European Journal of Radiology*. 2016; 85(5):877–884. [PubMed: 27130046]
16. Fontanilla HP, Klopp AH, Lindberg ME, et al. Anatomic distribution of [18F] fluorodeoxyglucose-avid lymph nodes in patients with cervical cancer. *Practical Radiation Oncology*. 2013; 3(1):45–53. [PubMed: 24674263]
17. Grigsby PW, Siegel BA, Dehdashti F. Lymph Node Staging by Positron Emission Tomography in Patients With Carcinoma of the Cervix. *Journal of Clinical Oncology*. 2001; 19(17):3745–3749. [PubMed: 11533097]
18. Kidd EA, Siegel BA, Dehdashti F, et al. Lymph Node Staging by Positron Emission Tomography in Cervical Cancer: Relationship to Prognosis. *Journal of Clinical Oncology*. 2010; 28(12):2108–2113. [PubMed: 20308664]
19. Kidd EA, Siegel BA, Dehdashti F, et al. Pelvic lymph node F-18 fluorodeoxyglucose uptake as a prognostic biomarker in newly diagnosed patients with locally advanced cervical cancer. *Cancer*. 2010; 116(6):1469–75. [PubMed: 20108309]
20. Onal C, Guler OC, Reyhan M, et al. Prognostic value of 18F-fluorodeoxyglucose uptake in pelvic lymph nodes in patients with cervical cancer treated with definitive chemoradiotherapy. *Gynecol Oncol*. 2015; 137(1):40–6. [PubMed: 25641567]
21. 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. *Journal of Clinical Oncology*. 1999; 17(1):41–41. [PubMed: 10458216]
22. Driscoll DO, Halpenny D, Johnston C, et al. 18F-FDG-PET/CT is of limited value in primary staging of early stage cervical cancer. *Abdom Imaging*. 2015; 40(1):127–33. [PubMed: 25015401]
23. Signorelli M, Guerra L, Montanelli L, et al. Preoperative staging of cervical cancer: is 18-FDG-PET/CT really effective in patients with early stage disease? *Gynecol Oncol*. 2011; 123(2):236–40. [PubMed: 21855972]
24. Liu FY, Yen TC, Chen MY, et al. Detection of hematogenous bone metastasis in cervical cancer: 18F-fluorodeoxyglucose-positron emission tomography versus computed tomography and magnetic resonance imaging. *Cancer*. 2009; 115(23):5470–80. [PubMed: 19739235]

25. Loft A, Berthelsen AK, Roed H, et al. The diagnostic value of PET/CT scanning in patients with cervical cancer: A prospective study. *Gynecologic Oncology*. 2007; 106(1):29–34. [PubMed: 17482666]
26. Haynes-Outlaw ED, Grigsby PW. The Role of FDG-PET/CT in Cervical Cancer: Diagnosis, Staging, Radiation Treatment Planning and Follow-Up. *PET Clinics*. 2010; 5(4):435–446. [PubMed: 27157971]
27. Grigsby PW. PET/CT imaging to guide cervical cancer therapy. *Future Oncology*. 2009; 5(7):953–958. [PubMed: 19792965]
28. Mackay HJ, Wenzel L, Mileskin L. Nonsurgical Management of Cervical Cancer: Locally Advanced, Recurrent, and Metastatic Disease, Survivorship, and Beyond. American Society of Clinical Oncology educational book / ASCO. American Society of Clinical Oncology. Meeting. 2015:e299–e309.
29. Chung Y-L, Horng C-F, Lee P-I, et al. Patterns of failure after use of 18F-FDG PET/CT in integration of extended-field chemo-IMRT and 3D-brachytherapy plannings for advanced cervical cancers with extensive lymph node metastases. *BMC Cancer*. 2016; 16(1):179. [PubMed: 26940959]
30. Lazzari R, Cecconi A, Jereczek-Fossa BA, et al. The role of [(18)F]FDG-PET/CT in staging and treatment planning for volumetric modulated Rapidarc radiotherapy in cervical cancer: experience of the European Institute of Oncology, Milan, Italy. *ecancermedicallscience*. 2014; 8:409.
31. Kidd EA, Thomas M, Siegel BA, et al. Changes in Cervical Cancer FDG Uptake During Chemoradiation and Association With Response. *International Journal of Radiation Oncology*Biophysics*. 2013; 85(1):116–122.
32. Schwarz JK, Siegel BA, Dehdashti F, et al. Association of posttherapy positron emission tomography with tumor response and survival in cervical carcinoma. *JAMA*. 2007; 298(19):2289–95. [PubMed: 18029833]
33. Siva S, Herschtal A, Thomas JM, et al. Impact of post-therapy positron emission tomography on prognostic stratification and surveillance after chemoradiotherapy for cervical cancer. *Cancer*. 2011; 117(17):3981–3988. [PubMed: 21365626]
34. Zola P, Macchi C, Cibula D, et al. Follow-up in Gynecological Malignancies: A State of Art. *Int J Gynecol Cancer*. 2015; 25(7):1151–64. [PubMed: 26207784]
35. Herrera FG, Breuneval T, Prior JO, et al. [18F]FDG-PET/CT metabolic parameters as useful prognostic factors in cervical cancer patients treated with chemo-radiotherapy. *Radiation Oncology*. 2016; 11(1):43. [PubMed: 26984385]
36. Heron CW, Husband JE, Williams MP, et al. The value of CT in the diagnosis of recurrent carcinoma of the cervix. *Clin Radiol*. 1988; 39(5):496–501. [PubMed: 3053000]
37. Wong TZ, Jones EL, Coleman RE. Positron emission tomography with 2-deoxy-2-[(18)F]fluoro-D-glucose for evaluating local and distant disease in patients with cervical cancer. *Mol Imaging Biol*. 2004; 6:55. [PubMed: 15018829]
38. Ryu S-Y, Kim M-H, Choi S-C, et al. Detection of Early Recurrence with 18F-FDG PET in Patients with Cervical Cancer. *Journal of Nuclear Medicine*. 2003; 44(3):347–352. [PubMed: 12620999]
39. Lee M, Lee Y, Hwang KH, et al. Usefulness of F-18 FDG PET/CT in Assessment of Recurrence of Cervical Cancer After Treatment. *Nuclear Medicine and Molecular Imaging*. 2011; 45(2):111–116. [PubMed: 24899989]
40. Brooks RA, Rader JS, Dehdashti F, et al. Surveillance FDG-PET Detection of Asymptomatic Recurrences in Patients with Cervical Cancer. *Gynecologic oncology*. 2009; 112(1):104–109. [PubMed: 18929403]
41. Chong A, Ha J-M, Jeong SY, et al. Clinical Usefulness of 18F-FDG PET/CT in the Detection of Early Recurrence in Treated Cervical Cancer Patients with Unexplained Elevation of Serum Tumor Markers. *Chonnam Med J*. 2013; 49(1):20–26. [PubMed: 23678473]
42. Hoon Chung H, Kim JW, Kang KW, et al. Predictive role of post-treatment [18F]FDG PET/CT in patients with uterine cervical cancer. *European Journal of Radiology*. 2012; 81(8):e817–e822. [PubMed: 22595504]
43. Meads C, Davenport C, Matysiak S, et al. Evaluating PET-CT in the detection and management of recurrent cervical cancer: systematic reviews of diagnostic accuracy and subjective elicitation.

- BJOG: An International Journal of Obstetrics & Gynaecology. 2014; 121(4):398–407. [PubMed: 24299154]
44. Auguste P, Barton P, Meads C, et al. Evaluating PET–CT in routine surveillance and follow-up after treatment for cervical cancer: a cost-effectiveness analysis. *BJOG: An International Journal of Obstetrics & Gynaecology*. 2014; 121(4):464–476. [PubMed: 24299112]
  45. Ulaner GA, Lyall A. Identifying and Distinguishing Treatment Effects and Complications from Malignancy at FDG PET/CT. *RadioGraphics*. 2013; 33(6):1817–1834. [PubMed: 24108564]
  46. Viswanathan AN, Lee LJ, Eswara JR, et al. Complications of pelvic radiation in patients treated for gynecologic malignancies. *Cancer*. 2014; 120(24):3870–3883. [PubMed: 25056522]
  47. Khiewvan B, Torigian DA, Emamzadehfard S, et al. Update of the role of PET/CT and PET/MRI in the management of patients with cervical cancer. *Hell J Nucl Med*. 2016; 19(3):254–268. [PubMed: 27824966]
  48. Dehdashti F, Grigsby PW, Lewis JS, et al. Assessing tumor hypoxia in cervical cancer by PET with ⁶⁰Cu-labeled diacetyl-bis(N4-methylthiosemicarbazone). *J Nucl Med*. 2008; 49:201. [PubMed: 18199612]
  49. Lewis JS, Laforest R, Dehdashti F, et al. An imaging comparison of ⁶⁴Cu-ATSM and ⁶⁰Cu-ATSM in cancer of the uterine cervix. *J Nucl Med*. 2008; 49:1177. [PubMed: 18552145]
  50. ACRIN. [cited 2017 August 13] Available from: https://www.acrin.org/6682_protocol.aspx
  51. Lee SI, Catalano OA, Dehdashti F. Evaluation of Gynecologic Cancer with MR Imaging, ¹⁸F-FDG PET/CT, and PET/MR Imaging. *Journal of Nuclear Medicine*. 2015; 56(3):436–443. [PubMed: 25635136]
  52. Zaidi H, Ojha N, Morich M, et al. Design and performance evaluation of a whole-body Ingenuity TF PET-MRI system. *Phys Med Biol*. 2011; 56(10):3091–106. [PubMed: 21508443]
  53. Delso G, Fürst S, Jakoby B, et al. Performance Measurements of the Siemens mMR Integrated Whole-Body PET/MR Scanner. *Journal of Nuclear Medicine*. 2011; 52(12):1914–1922. [PubMed: 22080447]
  54. Torigian DA, Zaidi H, Kwee TC, et al. PET/MR Imaging: Technical Aspects and Potential Clinical Applications. *Radiology*. 2013; 267(1):26–44. [PubMed: 23525716]
  55. Kitajima K, Suenaga Y, Ueno Y, et al. Fusion of PET and MRI for staging of uterine cervical cancer: comparison with contrast-enhanced (18)F-FDG PET/CT and pelvic MRI. *Clin Imaging*. 2014; 38(4):464–9. [PubMed: 24642250]
  56. Ponisio MR, Fowler KJ, Dehdashti F. The Emerging Role of PET/MR Imaging in Gynecologic Cancers. *PET Clin*. 2016; 11(4):425–40. [PubMed: 27593247]
  57. Grueneisen J, Schaarschmidt BM, Heubner M, et al. Integrated PET/MRI for whole-body staging of patients with primary cervical cancer: preliminary results. *European Journal of Nuclear Medicine and Molecular Imaging*. 2015; 42(12):1814–1824. [PubMed: 26199113]
  58. Surov A, Meyer HJ, Schob S, et al. Parameters of simultaneous (18)F-FDG-PET/MRI predict tumor stage and several histopathological features in uterine cervical cancer. *Oncotarget*. 2017; 8(17):28285–28296. [PubMed: 28423698]
  59. Nie J, Zhang J, Gao J, et al. Diagnostic role of ¹⁸F-FDG PET/MRI in patients with gynecological malignancies of the pelvis: A systematic review and meta-analysis. *PLOS ONE*. 2017; 12(5):e0175401. [PubMed: 28481958]
  60. Gaffney DK, Erickson-Wittmann BA, Jhingran A, et al. ACR Appropriateness Criteria on Advanced Cervical Cancer Expert Panel on Radiation Oncology&Gynecology. *International Journal of Radiation Oncology • Biology • Physics*. 81(3):609–614.
  61. Siegel CL, Andreotti RF, Cardenes HR, et al. ACR Appropriateness Criteria Pretreatment Planning of Invasive Cancer of the Cervix. *Journal of the American College of Radiology*. 9(6):395–402.
  62. 2013 NCCN Clinical Practice Guidelines in Oncology™ Cervical Cancer v.2.2013. http://www.nccn.org/professionals/physician_gls/PDF/cervical.pdf.

Key Points

- PET/CT is a highly valuable imaging modality in the assessment of patients with cervical cancer, providing prognostic and staging information.
- The metabolic parameters of the primary tumor (SUVmax, MTV, and TLG) have been shown to correlate with patient outcome and survival.
- The presence of lymph node involvement and the SUVmax of the lymph nodes are significant prognostic factors.
- By combining metabolic imaging with anatomic detail of the primary tumor, PET/MRI enhances treatment and care for patients with cervical cancer with decreased radiation dose.

Figure 1.
PET/CT in initial evaluation of cervical cancer primary tumor. 46-year-old female with stage IIB squamous cell carcinoma of cervix.
A–C. Axial (A), coronal (B), and sagittal (C) fused PET/CT images show an intensely FDG-avid cervical mass with SUVmax 15.5, MTV 70.64 ml, and TLG 623 ml.

Figure 2.

PET/CT in initial evaluation of cervical cancer primary tumor and lymph nodes. 57-year-old female with stage IV squamous cell carcinoma of the cervix.

A. Axial fused FDG PET/CT shows cervical tumor (T) with posterior bladder (B) involvement along with anterior rectal invasion and extension to bilateral uterosacral ligaments and upper 1/3 of vagina. Also note left pelvic sidewall lymphadenopathy (N).

B. Axial fused PET/CT shows bilateral pelvic sidewall lymphadenopathy (N), consisting of 2.7 cm left external iliac node and 2.8 cm right external iliac node.

C. Axial fused PET/CT shows 1 cm left common iliac node (N). As a result of the PET/CT findings, the patient will be treated with definitive chemoradiation to include the pelvis and retroperitoneum.

D. Axial T2-weighted MRI better shows the rectal and bladder involvement by cervical tumor (T).

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 3.

PET/CT in evaluation of metastatic disease. 46-year-old female with stage IVB poorly differentiated cervical carcinoma.

- A. Axial fused FDG PET/CT shows primary cervical tumor (arrow).
- B. Axial fused PET/CT shows FDG-avid left common iliac node (arrow).
- C. Axial fused PET/CT through upper pelvis shows stranding in left omental fat with mild FDG uptake (arrow), in keeping with peritoneal disease.
- D. Axial fused PET/CT shows an FDG-avid left lung nodule (arrow).
- E. Axial fused PET/CT shows an FDG-avid left supraclavicular node (arrow).

Figure 4.

PET/CT in evaluation of osseous metastatic disease. 40-year-old female with stage IIA poorly differentiated adenocarcinoma of the cervix.

A. Axial fused FDG PET/CT shows primary cervical tumor (arrow).

B. Axial fused PET/CT shows FDG-avid right rib lesion (arrow).

C. Coronal PET maximum intensity projection (MIP) image shows multiple FDG-avid osseous lesions compatible with widespread bone marrow metastases.

Figure 5.

PET/CT in tumor response: complete metabolic response to therapy. 47-year-old female with stage IIB squamous cell carcinoma of the cervix.

A–B. Axial (A) and coronal (B) fused FDG PET/CT images show mass with intense FDG uptake in the cervix with SUVmax 19.6 (arrow).

C–E. Follow-up axial (C) and coronal (D) fused PET/CT images after treatment with definitive chemoradiation using external beam radiation therapy and brachytherapy show complete metabolic and anatomic response after therapy (SUVmax 3.4) with radiation

fiducial marker in place (arrow). Coronal (E) fused PET/CT shows FDG uptake in brown fat in the neck and chest (arrows).

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 6.

PET/CT in recurrent cervical cancer. 39-year-old female with FIGO stage IB adenocarcinoma of the cervix initially diagnosed 2 years prior and treated with radical hysterectomy and bilateral pelvic lymph node dissection. Although the lymph nodes were negative, there was deep cervical involvement and radiation therapy was implemented. Follow-up PET/CT was obtained due to symptoms and elevated CEA levels.

A. Axial fused FDG PET/CT shows an FDG avid focus in the left pelvis in the region of the radiation marker, representing recurrent disease (arrow).

B. Axial fused PET/CT also shows an FDG-avid left supraclavicular lymph node (arrow) suspicious for metastasis. Biopsy was obtained to exclude metastatic disease, with no evidence of malignancy noted on pathology.

Figure 7.

PET/MRI in primary evaluation. 53-year-old female with stage IVA squamous cell carcinoma of the cervix.

A. Axial fused FDG PET/MRI shows FDG-avid large circumferential cervical tumor involving the left parametrium (arrow), lower one third of vagina, uterus, and urinary bladder (B). Significant thickening is seen in the distal portions of bilateral ureters (right ureter labeled U), likely representing tumor extension. The patient had bilateral ureteral stents in place.

B. Axial T2-weighted MRI at the same level of fused PET/MRI shows the primary cervical tumor and local extension into the surrounding tissues as described in (A) with improved conspicuity, demonstrating the value of MRI in local tumor evaluation.

C. Sagittal T2-weighted MRI shows the full extent of cervical tumor, along with extension into the posterior urinary bladder and into the vagina.

D. Sagittal ADC map MRI reveals low signal intensity of the primary cervical tumor, in keeping with restricted diffusion.

Table 1

FIGO and TNM Staging Classifications of Cervical Cancer

FIGO	TNM	Tumor characteristics	Therapy
	TX	Primary tumor not detectable	
	T0	No evidence of primary tumor	
	Tis	Carcinoma in situ (pre-invasive carcinoma)	Surgery
I	T1	Carcinoma confined to the cervix (disregard extension to uterine corpus)	Surgery
IA	T1a	Invasive carcinoma diagnosed by microscopy. Stromal invasion with max depth of 5 mm from base of epithelium and horizontal spread 7.0 mm	Surgery
IA1	T1a1	Stromal invasion > 3.0 mm in depth and 7.0 mm in horizontal spread	Surgery
IA2	T1a2	Stromal invasion 3 mm and 5 mm with horizontal spread 7.0 mm	Surgery
IB	T1b	Clinical lesion confined to cervix or microscopic lesion > T1a/IA2	Surgery
IB1	T1b1	Clinical visible lesion 4 cm in greatest dimension	Surgery
IB2	T1b2	Clinical visible lesion > 4 cm in greatest dimension	Surgery
II	T2	Extension beyond uterus but not to pelvic wall or lower 1/3 rd of vagina	Surgery
IIA	T2a	Tumor without parametrial invasion	Surgery
IIA1	T2a1	Clinical visible lesion 4 cm in greatest dimension	Chemoradiation (CRT) ± Surgery
IIA2	T2a2	Clinical visible lesion > 4 cm in greatest dimension	CRT ± Surgery
IIB	T2b	Tumor with parametrial invasion	CRT
III	T3	Tumor extends to pelvic wall and/or involves lower 1/3 rd of vagina and/or causes hydronephrosis or nonfunctional kidney	CRT
IIIA	T3a	Tumor involves lower 1/3 rd of vagina, no extension to pelvic wall	CRT
IIIB	T3b	Tumor extends to pelvic wall and/or causes hydronephrosis or nonfunctional kidney	CRT
IV	T4	Tumor invades bladder or rectum and/or extends below true pelvis	CRT
IVA	T4a	Tumor invades bladder or rectum	CRT
IVB	T4b	Tumor extends beyond true pelvis	CRT/Chemotherapy