The Role and Prognostic Value of PET-CT in Patients with Cervical Cancer Treated with Definitive Radiotherapy

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INTRODUCTION

Cervical cancer is the second most common gynecological malignancy around the worldwide [1]. Nearly half of the patients present with advanced disease at the time of initial diagnosis [2]. Young age, initial FIGO stage, lymph node status are most important prognostic factors associated with clinical outcome [2]. Lymph node metastasis and stage also have a significant impact on treatment outcomes in cervical cancer patients. Squamous cell carcinoma accounts for 80-85% of all cases in cervical cancer. Adenocarcinoma and subtypes (adeno squamous carcinoma, clear cell and small cell) represents the rest with worse prognosis and clinical outcomes compared to squamous cell carcinoma [3-5].

18F-Fluorodeoxyglucose Positron-Emission Tomography **(FDG-PET)** integrated with Computed Tomography **(CT)** incorporates metabolic tumor function with anatomic localization. PET-CT has become an increasingly important component of staging tumor localization and assessing treatment response for many malignancies (Figure 1,Figure 2). Furthermore, some studies concluded that the efficacy of FDG uptake measured as the maximum standardized uptake value (SUVmax) was predictive of outcome [6-8]. With increasing use of FDG-PET-CT, many report describing the utility of FDG-PET for the staging, treatment planning, evaluation of

treatment response and prognostic importance have been published. The aim of this chapter is to review the role and prognostic value of PET-CT in patients with cervical cancer treated with Radiotherapy **(RT)**.

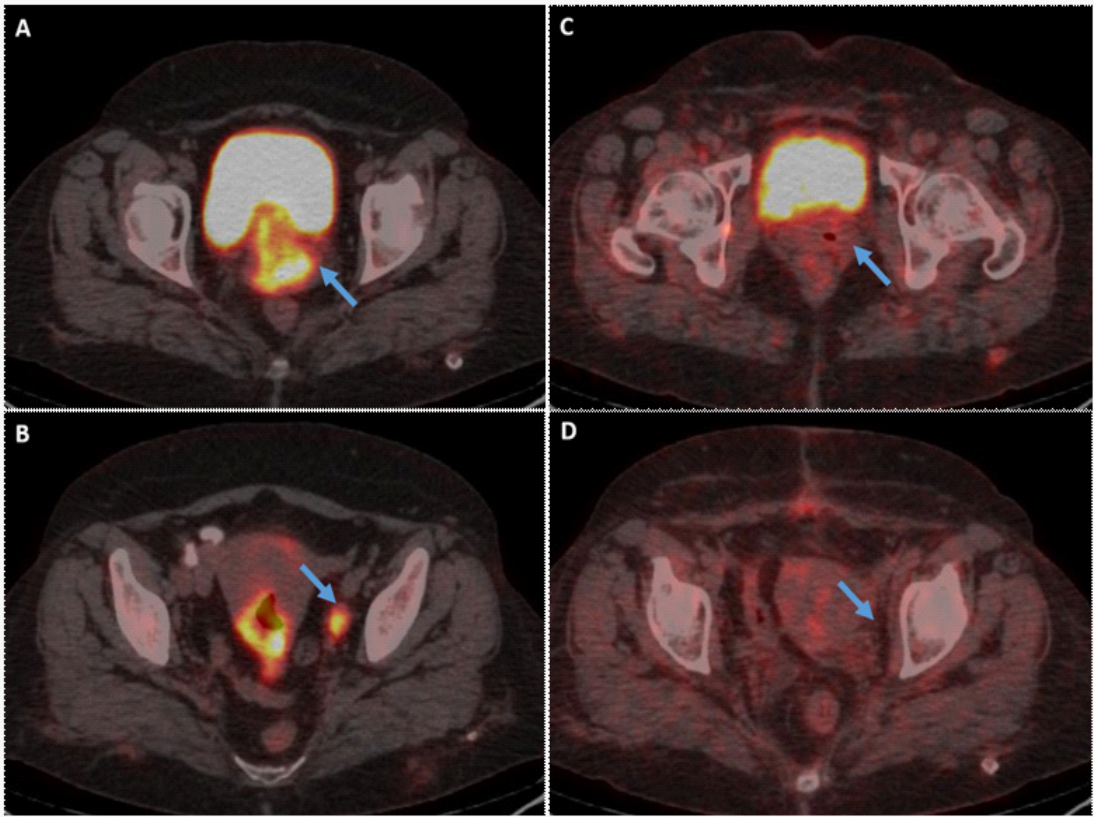

Figure 1: FDG-PET-CT images demonstrating (A) Cervical mass (arrow) infiltrating left parametrium (SUVmax = 24.2) and (B) Lymphadenopathy at left iliac region (arrow) (SUVmax = 9.4). (C-D) Complete metabolic response 3-months after completion of definitive chemoradiotherapy.

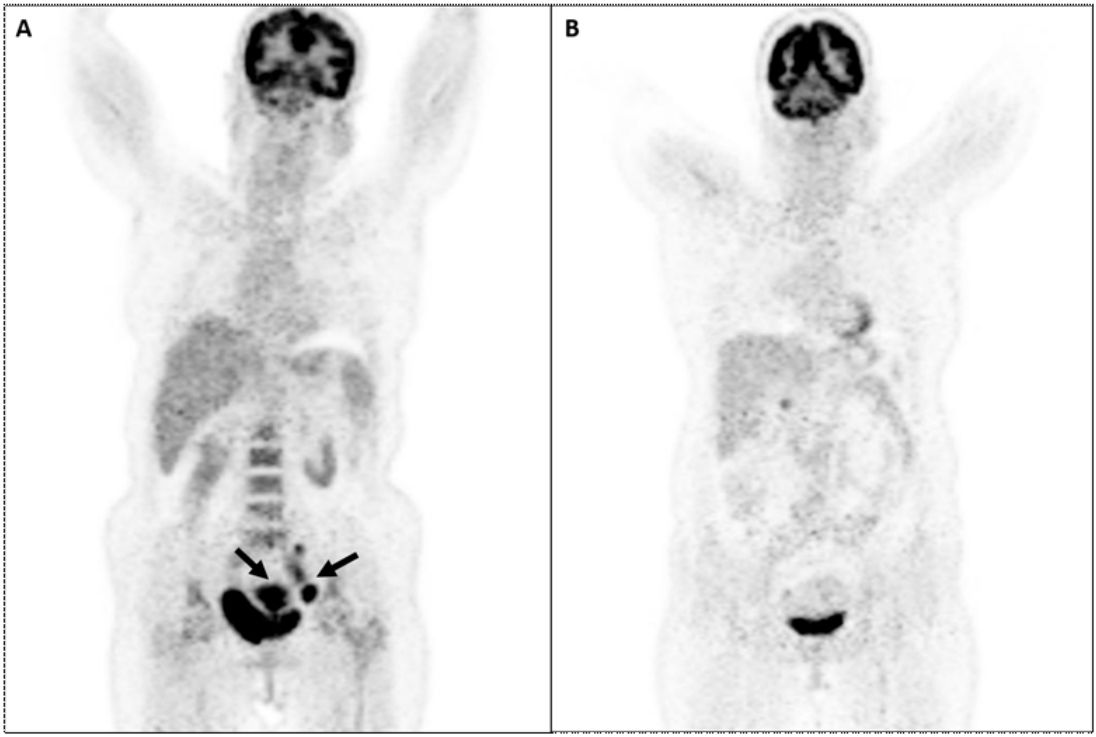

Figure 2: (A) FDG-PET image, demonstrating increased uptake in the cervix and left iliac lymph node region (arrows). (B) Complete metabolic response 3-months after completion of definitive chemo radiotherapy.

PET-CT

PET is a non-invasive molecular functional imaging modality that performed with the glucose analogue labeled with the positron emitter fluorine. PET-CT has been used as a useful imaging modality for many solid tumors [9-11]. PET-CT is most commonly used with the radiotracer FDG. FDG is a glucose analogue that especially accumulates in malignant tissues owing to their higher rates of glycolysis. Other potentially radiotracers are 11C-methione, 18F-Fluoro-17-Beta-Estradiol **(FES)**, 60Cu-diacetyl-bis and 64Cu-N4 methylthio-semicarba zone. PET-CT has become an essential modality for staging, treatment response assessment and detection of recurrences in patients with cervical carcinoma [12,13]. Especially combination of metabolic PET images with anatomic CT images provides better resolution and anatomical detection.

Protocols, Technique and Analysis

There are two main protocols that are adopted PET-CT for cervical cancer [14]. In principle PET protocols are the same but the doses of CT protocols re the main difference. Low dose or standard dose diagnostic CT images with or without contrast enhanced are used for attenuation correction, co-registration and diagnosis [14].

The patients fasted for at least 6 hours before administration of intravenous 370 to 555 MBq (10-15 mCi) FDG. Blood glucose levels are measured before this injection and it is expected that they were below 150 mg/dl. The first phase is the distribution phase. In this phase patients lay in a quiet room in supine position. Combined image acquisition begins 60 minutes after first FDG injection. Patients lie on a flat carbon fiber composite panel for scanning. Firstly, an unenhanced CT scans with 5 mm slice thickness were acquired from the base of the skull to inferior border of the pelvis. 140 kV and 80 Ma were used for this standardized protocol. Secondly, subsequent PET scan was acquired in 3-dimensional mode from the base of skull to the inferior border of pelvis. In this protocol patient's position on the table were not changed by technician, the scans were acquired in 6-7 bed position change over 3 minutes per position. The patient breathes shallowly during the acquisition of CT and PET images. Attenuation was corrected using the CT images. Areas of FDG uptake were categorized as malignant based on location, intensity, shape, size and visual correlation with CT images to differentiate physiologic from pathological uptake. If the lymph nodes FDG uptake is greater than blood pool or surrounding tissues, this node considered as PET positive.

Visual qualitative and quantitative analysis of the tumor can be performed with PET-CT. The quantitative analysis of SUVmax values may be utilized for initial diagnosis and treatment response. A threshold value according to blood glucose level or an arbitrary cut off (generally 2.5) may be used to differentiate the malignant uptake from physiologic or inflammatory uptake [15]. However, an absolute SUVmax threshold for cervical cancer has not been yet identified.

Total Lesion Glycolysis **(TLG)** and Metabolic Tumor Volume **(MTV)** are other quantitative metabolic parameters in PET-CT. MTV is defined as the tumor that uptakes FDG and TLG is a parameter which is calculated by software and related to MTV and SUVmean. During MTV measurement, a volume of interest is placed over the lesion with an automated segmentation software system to detect the threshold level that separates the target volume from the background tissue by weighting of the SUVmax and the SUVmean within the target volume with a specified weighting factor.

The methods for determining gross tumor volume are inherently different for MRI and PET-CT. Ma et al. [16] compared MRI gross tumor volume contoured manually on axial T2-weighted images with MTV contoured with a 40% SUV automatic threshold. The MRI and FDG PET tumor volumes were similar, but the tumor location varied significantly, especially for small tumor volumes. MRI was better in showing larger tumors compared to PET-CT.

Initial Staging

The staging of cervical cancer is performed clinically. Accurate staging, the evaluation of lymph node involvement and primary tumor extension are essential to deliver appropriate treatment. In order to assess tumor extension and lymph node involvement, together with physical examination

findings, some imaging methods are important. The most common preferred imaging modalities are CT, Magnetic Resonance Imaging **(MRI)** and for functional imaging FDG-PET. MRI provides anatomical information for accurate evaluation of the tumor size, parametrial and pelvic sidewall involvement, and vaginal invasion. Also diffusion-weighted MRI provides additional functional images, such as detecting tiny lesions and disseminated lesions [17].

The presence of FDG activity has been found almost in all cervical cancers ≥7 mm in size. It is usually not appreciated in the necrotic component of the tumoror within the uterine cavity distended by the accumulation of blood, serous fluid, or pussecondary to obstruction of the endocervical canal by the tumor. Because of limited spatial resolution of milimetric lesions and partial volume effect, small lesions and micrometa static deposits can be missed with PET, resulting in false-negative findings [18]. However, even though use of imaging does not appear to improve survival, PET-CT maximizes patient triage to correct therapy, and the combination of MRI and PET-CT spares most patients unnecessary trimodality therapy [19]. Sala et al. [20] stated that MRI is the best single imaging investigation for accurately determining tumor location, tumor size, depth of stromal invasion, and extension into the lower uterine segment. The authors also reported that MRI is accurate for evaluation of tumor size, usually within 0.5 cm of the surgical size, in 70–90% of cases. The sensitivity of MRI in the evaluation of bladder and rectal invasion of 71–100% and specificity of 88–91%. However, MRI may overestimate the parametrial invasion in larger tumors compared with small ones on T2-weighted images which may be due to stromal edema caused by tumor compression or inflammation [20].

FDG-PET shows metabolic tumor function and integration of Pet with Computerized Tomography **(PET-CT)** is much better for detecting anatomic localization rather than PET alone. Its ability to identify lymph node involvement, distant disease and recurrences has been shown in various studies in cervical cancer patients. Cervical cancer is typically has high levels of FDG uptake. PET-CT can be used for initial evaluation of primary tumor, local extension of disease, lymph node involvement and distant metastasis. National Comprehensive Cancer Network **(NCCN)** recommends PET-CT imaging as part of pretreatment assessment of cervical cancer [21].The sensitivity of MRI and CT is very low and the reported sensitivity of MRI was 31 - 37%, whereas in surgically staged patients the specificity was 93 - 94% [22]. MRI and CT uses size of the lymph node as metastasis criteria, however FDG-PET-CT is a functional method based on the increased glucose metabolism of cancer cells, regardless of node size, and PET-CT can often detect tiny metastatic lymph nodes from 5 to 9 mm in size. The usefulness of pretreatment FDG-PET in evaluating the extent of disease in patients with newly diagnosed carcinoma of the cervix has been well established. In these patients, the sensitivity and specificity of PET/CT for detection of pelvic lymph nodes metastasis were in range of 36% to 88% and 44% to 99%, respectively, which are higher than those of CT and MRI [22-29] (Table 1). Grigsby et al. [30] retrospectively compared the results of CT lymph node staging and whole body FDG PET in the care of 101 consecutively registered patients with carcinoma of the cervix. PET showed abnormal

FDG uptake in pelvic lymph nodes in 67 (67%) of the patients, in Para aortic lymph nodes in 21 (21%), and in supraclavicular lymph nodes in eight (8%). Lee et al. [31] assessed the diagnostic accuracy of FDG PET in the detection of metastatic supraclavicular lymph nodes and found a high incidence of metastasis in PET-detected supraclavicular lymph nodes in cancer patients. One hundred supraclavicular nodes detected with FDG PET alone were biopsied, and 86 were found to be malignant. With application of the cutoff value obtained by receiver operating characteristic analysis (SUVmax, 3.0), the diagnostic accuracy of FDG PET was 75.0% with sensitivity of 74.4% and specificity of 78.6%. For supraclavicular lymph nodes with a SUVmax of >3.0, FDG PET had a positive predictive value of 95.5%. For supraclavicular lymph nodes with a SUVmax of ≤3, sonographic findings excluded all false-negative FDG PET cases and had a high negative predictive value of 100%. Choi et al. [22] compared the accuracy of PET/CT and MRI for detecting pelvic and para-aortic lymph node metastasis in 154 regions in 22 patients with FIGO IB – IVA cervical cancer patients and the authors demonstrated that PET-CT was more sensitive than MRI (58% vs. 30%) but there were no statistically significant differences noted with regard to specificity (93% vs. 93%) and accuracy (85% vs. 73%). Sironi et al. [21] evaluated 1081 regional lymph nodes in 47 patients with early stage cervical cancer and demonstrated that the sensitivity, specificity, and accuracy of overall node-based analysis of PET-CT were 72%, 100%, and 99%, respectively. The authors also reported that the sensitivity and specificity for PET-CT-based diagnosis of lymph nodes >5 mm in diameter was 100% and 100%, respectively. In another study, Yildirim et al. [25] demonstrated that the sensitivity, specificity, and accuracy of detecting para-aortic lymph node metastasis in 16 patients with negative conventional CT findings were 50%, 84%, and75%, respectively, and the treatment was modified in four of 16 patients (25%). Wright et al. [32] determined the sensitivity and specificity of PET in detecting lymph node metastasis in women with early-stage cervical carcinoma. The authors concluded that PET had sensitivity of 53% and specificity of 90% in the detection of lymph node metastasis in patients with early-stage cervical carcinoma. FDG PET played a more valuable role in more advanced disease (stage IIB–IVB), in which lymph node involvement is more prevalent. In a meta-analysis, the reported sensitivity and specificity of PET for the detection of aortic node metastasis were 84% 95%, respectively.

Generally, the role of FDG-PET-CT has mainly been to assess lymph Nodes **(N)** and distant Metastasis **(M)**, rather than to determine local tumor extension (T) [24]. However, PET-CT has effective role instaging patients with extensive stage, which provides information on extra-pelvic sites, such as supraclavicular lymph nodes, para-aortic lymph node metastasis, peritoneum, omentum, bone, and soft tissues.

Table 1: The studies using FDG-PET-CT in the evaluation lymph node metastases of cervical cancer.

Study (year)	Patient number	Stage	Sensitivity (%)	Specificity (%)	Accuracy (%)	Imaging modality
Lin et al. (2003)	50	IIB - IVA			86	PET
Choi et al. (2006)	22	IB - IVA	77	56	68	PET-CT
			39	44	41	MRI
Sironi et al. (2006)	47	IA - IB	72	99	99	PET-CT
Amit et al. (2006)	75	I - IV	60	94		PET-CT
Loft et al. (2007)	27	IB - IVA	75	96	93	PET-CT
Yildirim et al. (2008)	16	IIB - IVA	50	84	75	PET-CT
Chung et al. (2009)	34	IA2 - IIB	41	94	68	PET-CT
			36	99	89	
Leblanc et al. (2011)	182	IB2 - IVA	40	63		PET-CT
Ramirez et al. (2011)	53	IB2 - IVA	80	95	90	PET-CT

Prognostic Value of FDG-PET Parameters

PET-CT has become an increasingly important component of staging tumor localization and assessment of treatment response in many malignancies. Furthermore, some studies draw the conclusion that the efficacy of FDG uptake measured as SUVmax is predictive of outcome [7,33,34]; however, other studies do not agree [35]. Although some studies have assessed the relationship between FDG uptake and outcome in cervical cancer, the number of these articles is relatively small, and the predictive value of FDG uptake remains unclear.

Recently Kidd et al. [33] evaluated pre-treatment SUVmax and its association with treatment response and prognosis in 287 patients with stage IA2 -IVB cervical cancer. In multivariate analysis, SUVmax was the only significant independent factor ($p = 0.003$). The overall 5 year survival rates were 95% for SUVmax<5.2, 70% for a SUVmax ranging 5.2 - 13.3, and 44% for a SUVmax>13.3 ($p< 0.0001$). A higher SUVmax was associated with an increased risk of lymph node metastasis at diagnosis ($p=0.0009$). Lee et al. [36] analyzed the pre-treatment SUVmax and its association with other prognostic factors in 44 early stage cervical cancer patients. The SUVmax was significantly higher in patients with deep stromal invasion, lymphovascular space invasion and large tumor size. Multivariate analysis demonstrated that a higher SUVmax (>13.4) of the primary tumor was a significant independent predictor of recurrence after treatment with surgery and/or adjuvant therapy.

Some studies also inferred about relationship between FDG uptake and outcome in cervical cancer patients [7,8,37]. In our previous studies, we found that the maximum standardized uptake value (SUVmax) for the primary tumor was correlated with increased tumor size and lymph node metastasis, persistence of residual tumor after treatment and worse overall survival [7,37]. Not only the tumor but also the regional lymph node FDG uptake has a prognostic value in cervical cancer patients. According to some authors the predictive value of FDG uptake in pelvic or Para aortic lymph nodes remains unclear [38,39]. In our recent study, we sought to evaluate the prognostic significance, treatment response, local control and overall survival of the pelvic lymph node SUVmax in cervical cancer patients. We found that the pelvic lymph node SUVmax is strongly correlated with both treatment response and overall survival [6].

Treatment Outcome

It has been demonstrated that metabolic response determined by FDG-PET performed within 8–16 weeks after the completion of therapy can be used to predict outcome [34,37,40]. Schwarz et al. [34] reported 3-year cause-specific survival rates of 100 % in patients with Complete Metabolic Responses **(CMRs)**, 51 % for patients with Partial Responses **(PRs)** and 17% for patients with Progressive Disease **(PD)**. In this study, the majority (85 %) of patients who relapsed had distant failures. In another study, Beriwal et al. [41] reported 3-year actuarial Disease-Free Survival **(DFS)** and Overall Survival **(OS)** rates of 79 and 88 %, respectively, in patients with CMR after a median follow-up of 15 months. Furthermore, Onal et al. [7] previously reported that the primary tumor pretreatment SUVmax for patients with CMR was significantly lower than that of patients with PR or PD (15.6±5.7 vs 28.0±9.9, respectively; $p<0.001$).

Local failure can be defined by either clinical examination or serial imaging studies. However, clinical examination in some cases under assesses the local disease response and it does not account for nodal response or any new onset metastatic disease [26,42]. It has been demonstrated that metabolic response demonstrated by post-therapy PET-CT has utility in predicting long-term outcome [34,41]. The metabolic CMR rate on PET-CT after definitive ChRT in cervical cancer patients is 70–80 % [7,41]. Grigsby et al. [17] reported a 2-year PFS rate of 86%for patients with no abnormal FDG uptake at any site on post treatment PET and 40 % for those with persistent abnormal up take. In a prospective study of 92 patients imaged with FDG-PET, Schwarz et al. [2] reported 3-year PFS rates of 78, 33, and 0 % for patients with CMRs, PRs, and PD, respectively. Similarly Beriwal et al. [7] reported 3-year DFS rates of 78, 31 and 0% for patients with CMRs, PRs, and PD, respectively. In study by Onal et al. [37] reported that the 2-year and 3-year DFS rates were 84 and 75 %, after CMR respectively.

Tumor Recurrence

Recurrent cervical cancer is defined as the tumor development at least 6 months after regression of the initial treatment [43]. If the patient had stage IIB or more disease (parametrial involvement) or para aortic lymph node metastasis, recurrences rates are up to 35%. Local

recurrences mainly occur in vaginal vault but subsequently more advanced recurrences may be seen. Synchronous distant metastasis is frequent in recurrent cases and it is nearly 70% [44].

CT and MRI have difficulty in discriminating areas of treatment related changes from recurrences. PET-CT, as a functional imaging, has advantages over these conventional technics and it has been shown to be effective in detecting recurrent tumor [45-47] (Table 2). Chu et al, reported meta-analysis about diagnostic value of PET-CT in recurrent cervical cancer and they reported that the pooled sensitivity and specificity of PET and PET-CT were 0.87 (95% Confidence Interval **(CI)**: 0.80-0.92) and 0.97 (95% CI: 0.96-0.98), respectively. The pooled sensitivity and specificity for local regional recurrence were 0.82 (95% CI: 0.72-0.90) and 0.98 (95% CI: 0.96-0.99), respectively [46]. Meads et al concluded that evidence to support additional PET-CT is scarce, of average quality and does not distinguish between application for surveillance and diagnosis [45]. But they are criticized about older CT or MRI studies or poor quality studies. Also therapeutic strategies may even change about 25% patients after PET-CT imaging and more aggressive/curative treatment options may be enforced [48,49].

Table 2: Recurrence rates after definitive treatment detected with PET or PET-CT.

Author	Year	PET or PET-CT	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
Ryu	2003	PET	90	76	5	98
Van der Veldt	2008	PET	92	93	96	87
Mittra	2009	PET-CT	93	93	86	96
Meads	2014	PET-CT	95	87		

CONCLUSION

PET-CT has become an increasingly important non-invasive diagnostic tool for staging, radiotherapy planning and detection of recurrence disease in cervical cancer. Also the FDG PET derived markers SUVmax, TLG and MTV are predictive for treatment response and survival. Identification of the population with high risk of disease recurrence or worse survival may permit the evaluation of clinical benefits of additional local or systemic treatments for individual patients with cervical cancer.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005; 55: 74-108.
2. Atahan IL, Onal C, Ozyar E, Yiliz F, Selek U. Long-term outcome and prognostic factors in patients with cervical carcinoma: a retrospective study. Int J Gynecol Cancer. 2007; 17: 833-842.
3. Chaturvedi AK, Kleinerman RA, Hildesheim A, Gilbert ES, Storm H. Second cancers after squamous cell carcinoma and adenocarcinoma of the cervix. J Clin Oncol. 2009; 27: 967-973.
4. Imadome K, Iwakawa M, Nakawatari M, Fujita H, Kato S. Subtypes of cervical adenosquamous carcinomas classified by EpCAM expression related to radiosensitivity. Cancer Biol Ther. 2010; 10: 1019-1026.
5. Vizcaino AP, Moreno V, Bosch FX, Muñoz N, Barros-Dios XM. International trends in incidence of cervical cancer: II. Squamous-cell carcinoma. Int J Cancer. 2000; 86: 429-435.

6. Onal C, Guler OC, Reyhan M, Yapar AF. Prognostic value of 18F-fluorodeoxyglucose uptake in pelvic lymph nodes in patients with cervical cancer treated with definitive chemoradiotherapy. Gynecol Oncol. 2015; 137: 40-46.

7. Onal C, Reyhan M, Parlak C, Guler OC, Oymak E. Prognostic value of pretreatment 18F-fluorodeoxyglucose uptake in patients with cervical cancer treated with definitive chemoradiotherapy. Int J Gynecol Cancer. 2013; 23: 1104-1110.

8. 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: 55-62.

9. Dibble EH, Alvarez AC, Truong MT, Mercier G, Cook EF. 18F-FDG metabolic tumor volume and total glycolytic activity of oral cavity and oropharyngeal squamous cell cancer: adding value to clinical staging. J Nucl Med. 2012; 53: 709-715.

10. Sacks A, Peller PJ, Surasi DS, Chatburn L, Mercier G. Value of PET/CT in the management of liver metastases, part 1. AJR Am J Roentgenol. 2011; 197: W256-259.

11. Subramaniam RM, Wilcox B, Aubry MC, Jett J, Peller PJ. 18F-fluoro-2-deoxy-D-glucose positron emission tomography and positron emission tomography/computed tomography imaging of malignant pleural mesothelioma. J Med Imaging Radiat Oncol. 2009; 53: 160-169.

12. Park W, Park YJ, Huh SJ, Kim BG, Bae DS. The usefulness of MRI and PET imaging for the detection of parametrial involvement and lymph node metastasis in patients with cervical cancer. Jpn J Clin Oncol. 2005; 35: 260-264.

13. Son H, Kositwattanarerk A, Hayes MP, Chuang L, Rahaman J. PET/CT evaluation of cervical cancer: spectrum of disease. Radiographics. 2010; 30: 1251-1268.

14. Antoch G, Freudenberg LS, Beyer T, Bockisch A, Debatin JF. To enhance or not to enhance? 18F-FDG and CT contrast agents in dual-modality 18F-FDG PET/CT. J Nucl Med. 2004; 45 Suppl 1: 56S-65S.

15. Lin LL, Yang Z, Mutic S, Miller TR, Grigsby PW. FDG-PET imaging for the assessment of physiologic volume response during radiotherapy in cervix cancer. Int J Radiat Oncol Biol Phys. 2006; 65: 177-181.

16. Ma DJ, Zhu JM, Grigsby PW. Tumor volume discrepancies between FDG-PET and MRI for cervical cancer. Radiother Oncol. 2011; 98: 139-142.

17. Namimoto T, Awai K, Nakaura T, Yanaga Y, Hirai T. Role of diffusion-weighted imaging in the diagnosis of gynecological diseases. Eur Radiol. 2009; 19: 745-760.

18. Gouy S, Morice P, Narducci F, Uzan C, Gilmore J. Nodal-staging surgery for locally advanced cervical cancer in the era of PET. Lancet Oncol. 2012; 13: e212-220.

19. Pandharipande PV, Choy G, del Carmen MG, Gazelle GS, Russell AH, et al. MRI and PET/CT for triaging stage IB clinically operable cervical cancer to appropriate therapy: decision analysis to assess patient outcomes. AJR Am J Roentgenol. 2009; 192: 802-814.

20. Sala E, Wakely S, Senior E, Lomas D. MRI of malignant neoplasms of the uterine corpus and cervix. AJR Am J Roentgenol. 2007; 188: 1577-1587.

21. Sironi S, Buda A, Picchio M, Perego P, Moreni R. Lymph node metastasis in patients with clinical early-stage cervical cancer: detection with integrated FDG PET/CT. Radiology. 2006; 238: 272-279.

22. Choi HJ, Roh JW, Seo SS, Lee S, Kim JY. Comparison of the accuracy of magnetic resonance imaging and positron emission tomography/computed tomography in the presurgical detection of lymph node metastases in patients with uterine cervical carcinoma: a prospective study. Cancer. 2006; 106: 914-922.

23. Amit A, Beck D, Lowenstein L, Lavie O, Bar Shalom R. The role of hybrid PET/CT in the evaluation of patients with cervical cancer. Gynecol Oncol. 2006; 100: 65-69.

24. Loft A, Berthelsen AK, Roed H, Ottosen C, Lundvall L. The diagnostic value of PET/CT scanning in patients with cervical cancer: a prospective study. Gynecol Oncol. 2007; 106: 29-34.

25. Yildirim Y, Sehirali S, Avci ME, Yilmaz C, Ertopcu K. Integrated PET/CT for the evaluation of para-aortic nodal metastasis in locally advanced cervical cancer patients with negative conventional CT findings. Gynecol Oncol. 2008; 108: 154-159.

26. Chung HH, Park NH, Kim JW, Song YS, Chung JK. Role of integrated PET-CT in pelvic lymph node staging of cervical cancer before radical hysterectomy. Gynecol Obstet Invest. 2009; 67: 61-66.

27. Leblanc E, Gauthier H, Querleu D et al. Accuracy of 18-fluoro-2-deoxy-D-glucose positron emission tomography in the pretherapeutic detection of occult para-aortic node involvement in patients with a locally advanced cervical carcinoma. Ann Surg Oncol. 2011; 18: 2302-2309.

28. Ramirez PT, Jhingran A, Macapinlac HA, Euscher ED, Munsell MF. Laparoscopic extraperitoneal para-aortic lymphadenectomy in locally advanced cervical cancer: a prospective correlation of surgical findings with positron emission tomography/computed tomography findings. Cancer. 2011; 117: 1928-1934.

29. Lin WC, Hung YC, Yeh LS, Kao CH, Yen RF, et al. Usefulness of (18)F-fluorodeoxyglucose positron emission tomography to detect para-aortic lymph nodal metastasis in advanced cervical cancer with negative computed tomography findings. Gynecol Oncol. 2003; 89: 73-76.

30. 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.

31. Lee JH, Kim J, Moon HJ, Cho A, Yun M. Supraclavicular lymph nodes detected by 18F-FDG PET/CT in cancer patients: assessment with 18F-FDG PET/CT and sonography. AJR Am J Roentgenol. 2012; 198: 187-193.

32. Wright JD, Dehdashti F, Herzog TJ, Mutch DG, Huettner PC. Preoperative lymph node staging of early-stage cervical carcinoma by [18F]-fluoro-2-deoxy-D-glucose-positron emission tomography. Cancer. 2005; 104: 2484-2491.

33. Kidd EA, Siegel BA, Dehdashti F, Grigsby PW. The standardized uptake value for F-18 fluorodeoxyglucose is a sensitive predictive biomarker for cervical cancer treatment response and survival. Cancer. 2007; 110: 1738-1744.

34. Schwarz JK, Siegel BA, Dehdashti F, Grigsby PW. Association of posttherapy positron emission tomography with tumor response and survival in cervical carcinoma. JAMA. 2007; 298: 2289-2295.

35. Hoang JK, Hoagland LF, Coleman RE, Coan AD, Herndon JE 2nd. Prognostic value of fluorine-18 fluorodeoxyglucose positron emission tomography imaging in patients with advanced-stage non-small-cell lung carcinoma. J Clin Oncol. 2008; 26: 1459-1464.

36. Lee YY, Choi CH, Kim CJ, Kang H, Kim TJ, et al. The prognostic significance of the SUVmax (maximum standardized uptake value for F-18 fluorodeoxyglucose) of the cervical tumor in PET imaging for early cervical cancer: preliminary results. Gynecol Oncol. 2009; 115: 65-68.

37. Onal C, Reyhan M, Guler OC, Yapar AF. Treatment outcomes of patients with cervical cancer with complete metabolic responses after definitive chemoradiotherapy. Eur J Nucl Med Mol Imaging. 2014; 41: 1336-1342.

38. Kidd EA, Siegel BA, Dehdashti F, Grigsby PW. Pelvic lymph node F-18 fluorodeoxyglucose uptake as a prognostic biomarker in newly diagnosed patients with locally advanced cervical cancer. Cancer. 2010; 116: 1469-1475.

39. Yen TC, See LC, Lai CH, Tsai CS, Chao A, et al. Standardized uptake value in para-aortic lymph nodes is a significant prognostic factor in patients with primary advanced squamous cervical cancer. Eur J Nucl Med Mol Imaging. 2008; 35: 493-501.

40. Chung HH, Kim JW, Kang KW, Park NH, Song YS. Predictive role of post-treatment [18F]FDG PET/CT in patients with uterine cervical cancer. Eur J Radiol. 2012; 81: e817-822.

41. Beriwal S, Kannan N, Sukumvanich P, Richard SD, Kelley JL, et al. Complete metabolic response after definitive radiation therapy for cervical cancer: patterns and factors predicting for recurrence. Gynecol Oncol 2012; 127: 303-306.

42. Narayan K, Fisher RJ, Bernshaw D, Shakher R, Hicks RJ. Patterns of failure and prognostic factor analyses in locally advanced cervical cancer patients staged by positron emission tomography and treated with curative intent. Int J Gynecol Cancer. 2009; 19: 912-918.

43. Heron CW, Husband JE, Williams MP, Dobbs HJ, Cosgrove DO. The value of CT in the diagnosis of recurrent carcinoma of the cervix. Clin Radiol. 1988; 39: 496-501.

44. Fulcher AS, O'Sullivan SG, Segreti EM, Kavanagh BD. Recurrent cervical carcinoma: typical and atypical manifestations. Radiographics. 1999; 19 Spec No: S103-116.

45. Meads C, Davenport C, MaÅ‚ysiak S, Kowalska M, Zapalska A. Evaluating PET-CT in the detection and management of recurrent cervical cancer: systematic reviews of diagnostic accuracy and subjective elicitation. BJOG. 2014; 121: 398-407.

46. Chu Y, Zheng A, Wang F, Lin W, Yang X. Diagnostic value of 18F-FDG-PET or PET-CT in recurrent cervical cancer: a systematic review and meta-analysis. Nucl Med Commun. 2014; 35: 144-150.

47. van der Veldt AA, Buist MR, van Baal MW, Comans EF, Hoekstra OS. Clarifying the diagnosis of clinically suspected recurrence of cervical cancer: impact of 18F-FDG PET. J Nucl Med. 2008; 49: 1936-1943.

48. Havrilesky LJ, Kulasingam SL, Matchar DB, Myers ER. FDG-PET for management of cervical and ovarian cancer. Gynecol Oncol. 2005; 97: 183-191.

49. Nakamoto Y, Saga T, Fujii S. Positron emission tomography application for gynecologic tumors. Int J Gynecol Cancer. 2005; 15: 701-709.