

Update of the role of PET/CT and PET/MRI in the management of patients with cervical cancer

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Abstract

In cervical cancer (CC), fluorine-18-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography/computed tomography (PET/CT) has been proven to be beneficial for patient management. Positron emission tomography/CT is useful in pretreatment evaluation due to the ability to evaluate disease extent and to assess regional lymph nodes as well as distant sites for metastases. PET/CT has an impact on treatment planning as well as it is incorporated in radiation therapy planning, resulting in more appropriate and effective treatment with less cost and radiation dose to normal tissues. Positron emission tomography/CT is used to predict early treatment response and to assess treatment response after completion of concurrent chemoradiation therapy. PET/CT has been used for surveillance after treatment as well as for restaging in suspected recurrent or metastatic disease. Qualitative PET/CT imaging findings as well as quantitative parameters such as maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) are useful to predict prognosis and clinical outcome. Moreover, PET imaging using other radiotracers to detect and quantify hypoxia may help to identify aggressive tumors and predict treatment outcome even though it is not widely clinical used. Positron emission tomography/magnetic resonance imaging (PET/MRI) instruments are now available, which may potentially improve evaluation of primary tumors and metastatic sites given the improved soft tissue contrast resolution of MRI relative to CT. This article reviews the role of ¹⁸F-FDG PET/CT, hypoxia agent PET/CT, and ¹⁸F-FDG PET/MRI in the management of patients with CC.

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Introduction

Cervical cancer (CC) is one of the most common female cancers and the leading cause of female cancer-related death worldwide. This cancer is clinical staged by the International Federation of Gynecology and Obstetrics (FIGO) system. Patients with local disease (stage I) will be treated with surgery. Patients with locally advanced disease (stage II-IVA) will be treated with definitive chemoradiation, and patients with distant metastatic disease (stage IVB) will be treated with systemic chemotherapy or chemoradiation therapy. The major histopathologic types are squamous cell carcinoma (80%-85%) and adenocarcinoma/adenosquamous cell carcinoma (15%-20%) [1]. Patients with adenocarcinoma/adenosquamous cell carcinoma generally have a worse prognosis than patients with squamous cell carcinoma [2].

Radiologic imaging studies are important in the management of patients with CC. Computed tomography (CT) and magnetic resonance imaging (MRI) are useful for pretreatment planning. Computed tomography allows for assessment of regional lymph node and distant metastases, radiation therapy planning, and guidance for biopsy. However, CT has suboptimal soft tissue resolution, which limits evaluation of local tumor extension. Magnetic resonance imaging has superior soft tissue contrast resolution, which allows for accurate evaluation of local disease extension as well as for presence of regional lymph node and distant metastases. Both CT and MRI play a role in response assessment and detection of tumor recurrence. Transrectal ultrasonography (TRUS) may be of benefit in detecting tumor and parametrial invasion in early CC [3]. Transvaginal ultrasonography (TVU) has higher accuracy than CT or MRI to evaluate for the presence of bladder invasion [4]. Transvaginal ultrasonography can also be useful to help differentiate malignant from benign cervical lesions [5]. Ultrasonography (US) is also useful to evaluate for the presence of hydronephrosis in advanced CC.

Fluorine-18-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography/CT (PET/CT) is a molecular imaging technique, which is useful in the management of patients with CC.

It is particularly useful for pretreatment evaluation and post-treatment surveillance of patients [6, 7]. Recent studies [8, 9] reported more benefit for treatment response assessment and prognostic predictor. Moreover, non- ^{18}F -FDG PET radiotracers are available that allow for assessment of tumor hypoxia, which are useful for predicting treatment response and patient outcome.

Positron emission tomography/MRI is a new hybrid imaging modality that is promising for the optimized assessment of local tumor extension, given the high soft tissue contrast resolution of MRI, as well as of regional nodal and distant metastatic disease in pretreatment planning. Other roles of PET/MRI in the management of CC patients are not yet well established and require more investigation.

Fluorine-18-FDG can accumulate in both benign and malignant lesions, which may cause misinterpretation. Fluorine-18-FDG is a glucose analogue that accumulates in malignant lesions because of increased glucose metabolism. However, ^{18}F -FDG can accumulate in normal tissues, benign tumors of the pelvic area, as well as other non-neoplastic conditions in the pelvis. False positive ^{18}F -FDG uptake in pelvis may occur due to physiologic, inflammatory, infectious, benign neoplastic and post-treatment conditions. False negative ^{18}F -FDG uptake may occur when small tumor deposits or microscopic diseases-such as cervical-pelvic diseases-are present.

Physiologic increased ^{18}F -FDG uptake in bowel, uterus, ovary, bone marrow, bone, and urinary system may occur in the female pelvis [10]. Normal bowel activity may cause problems for the detection of peritoneal diseases. Functional increased ^{18}F -FDG uptake of the endometrium can normally be observed in pre-menopausal patients during the menstrual and ovulatory phases of the menstrual cycle [11, 12]. However, increased endometrial ^{18}F -FDG uptake in post-menopausal woman is suspicious for endometrial malignancy, and requires further assessment. Diffusely increase bone marrow ^{18}F -FDG uptake can occur following chemotherapy and/or colony-stimulating factor administration. Fluorine-18-FDG excretion into the urinary system commonly occurs, and may confound assessment of the female pelvis. Diuretics may be administered to reduce ^{18}F -FDG accumulation in the urinary tract, and patients are requested to void completely prior to PET/CT image acquisition. Positron emission tomography/CT is also typically acquired in the caudal to cranial direction to further reduce urinary bladder ^{18}F -FDG accumulation. Bladder catheterization or continuous bladder irrigation may also be used to reduce bladder activity or in patients who cannot urinate well [13].

Non-malignant ^{18}F -FDG uptake in the pelvis from inflammatory or infectious processes such as appendicitis, colitis, diverticulitis, pelvic inflammatory disease, and perianal fistula has been reported [13]. Post-treatment changes after surgery or radiation therapy such as incision site, ostomy site, urinary diversion, urinary bladder hernias, radiation-induced proctitis, and radiation-induced vasculitis can cause false positive findings. Bone lesions such as acute or healing bone fractures, inflammatory or degenerative bone di-

sease, active Paget's disease, and fibrous dysplasia [14] can also lead to false positive ^{18}F -FDG uptake. Acute deep vein thrombosis (DVT) and pulmonary embolism (PE) have been reported as other causes of non-malignant ^{18}F -FDG uptake [13, 15]. Radiation-induced insufficiency fractures can show increased ^{18}F -FDG uptake. Asymmetric ^{18}F -FDG uptake in muscles of the pelvis can be detected in patients with scoliosis and post-treatment changes [16]. Benign diseases such as leiomyomas, endometrial hyperplasia, endometriosis, endometritis, endometrial polyps, and pyometra can be causes of increased ^{18}F -FDG uptake in uterus [12]. Leiomyomas, which are common benign tumors of the uterus, show variable ^{18}F -FDG uptake [17]. Fluorine-18-FDG uptake in leiomyomas tends to be more commonly seen in premenopausal women than in post-menopausal woman. Also, ^{18}F -FDG uptake tends to be higher within leiomyomas during the luteal phase compared to uptake during menses and during the follicular and periovulatory phases [18].

False positive ^{18}F -FDG uptake may also be caused by attenuation (transmission) correction artifacts from high attenuation objects in the path of CT beam such as from indwelling hip prostheses [19]. Attenuation correction artifacts may also occur when high density oral or intravenous contrast agents are utilized [20]. Non-attenuation-corrected PET images may be helpful for interpretation in cases where there is a question of artifacts on attenuation-corrected PET images. Misregistration of fused PET and CT images can also cause artifacts. Bowel motility and urinary bladder distension are the most common causes for misregistration between PET and CT images in pelvis.

Positron emission tomography/CT has limited spatial resolution for the evaluation of subcentimeter tumor lesions or micro-metastases. Standardized uptake value (SUV) is underestimated in small lesions due to partial volume effects. These effects may lead to false negative results on PET/CT. Moreover, false negative results may occur when lymph nodes are necrotic. In this situation, diagnostic CT or MRI is useful.

Integrated PET/CT imaging is more suitable to use in cancer management than isolated PET or CT alone. Computed tomography provides anatomic information and improves specificity, which helps one to identify normal variants, sites of physiologic ^{18}F -FDG uptake, hypometabolic malignant lesions, and hypermetabolic non-malignant lesions in the pelvis. The interpretation of combined PET and CT data in properly prepared patients can minimize these pitfalls and allow for optimal diagnostic assessment.

This review article emphasizes the value of ^{18}F -FDG PET/CT, non- ^{18}F -FDG PET/CT, and PET/MRI in the management of patients with CC as well as some non-malignant conditions that may be detected by ^{18}F -FDG PET/CT in the pelvic area.

Findings in the pelvic cavity

Detection of disease and screening

The diagnosis of CC is based on clinical examination and cervical biopsy. Fluorine-18-FDG PET is not used for screening because of low efficacy and high cost to detect early cervical carcinoma [21]. Positron emission tomography has limited spatial resolution to detect small lesions, including early cancer (Figure 1) [17] and is therefore mainly used to assess for regional extra-cervical spread of tumor and distant metastatic disease in CC.

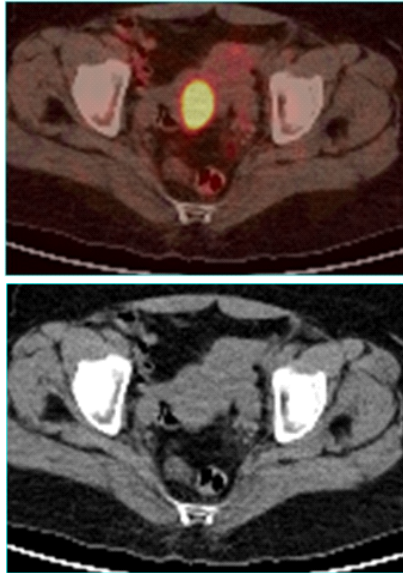


Figure 1. A 43 years old female with focal area of increased ^{18}F -FDG uptake in primary tumor in cervix. Computed tomography of corresponding images shows a mass in the cervix.

Lymph node assessment

It is important to consider nodal involvement in the pelvic area for treatment planning and for prognosticating patient outcome. The pattern of lymph node metastases in CC is generally predictable. Tumor tends to spread sequentially from primary tumor to pelvic, para-aortic, and supraclavicular lymph nodes (Figure 2). There is 10%-30% chance of lymph node metastases in early CC [22] and a 15%-30% chance of pelvic lymph node metastases in locally advanced CC [23]. Patients may suffer from post-surgical morbidity such as infection, lymphedema, vessel injury, or nerve injury following unnecessary lymphadenectomy. It is therefore beneficial to detect presence of lymph node metastases by non-invasive imaging prior to treatment. Fluorine- ^{18}F -FDG PET/CT is able to detect lymph node metastases and distant metastases; however, it does have some limitations. Firstly, ^{18}F -FDG uptake is not specific for cancer, as inflammatory lymph nodes can also take up ^{18}F -FDG. Second, ^{18}F -FDG uptake may not be apparent in small metastatic lymph nodes or when nodal micro metastases are present due to limited spatial resolution.

The diagnostic performance of ^{18}F -FDG PET/contrast-enhanced CT (ceCT) in detecting pelvic or para-aortic lymph node metastases was reported by Kitajima et al. (2009) [24] in 45 patients with uterine cancer (30 cases) and CC (15 cases). The overall sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy to

detect nodal metastases at the nodal level were 51.1%, 99.8%, 85.2%, 98.9% and 98.7%, respectively, and 50%, 90.9%, 66.7%, 83.3% and 80.0%, respectively, at the patient level.

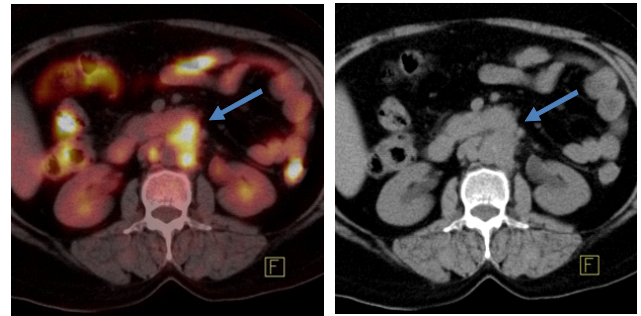


Figure 2. A 58 years old female with known case of CC, post-surgery, post chemotherapy presented with suspected recurrence on ultrasonography. PET/CT and CT images of abdomen show abnormal ^{18}F -FDG uptake suggestive of recurrence in retro-peritoneal lymph nodes.

For nodal assessment in CC, the accuracy of MRI to detect lymph node metastases has been reported to be 86% [25, 26]. Computed tomography showed a sensitivity of 43% to detect lymph node involvement by tumor [27]. Both CT and MRI have limitations to evaluate metastatic lymph nodes, as enlarged lymph nodes may sometimes be inflammatory in nature, and normal size lymph nodes may sometimes harbor micrometastatic disease. Positron emission tomography/CT is more accurate than CT or MRI to evaluate lymph node metastases [28, 29]. Choi et al. (2010) [29] reported the pooled sensitivity and pooled specificity of PET or PET/CT to detect metastatic lymph nodes as 82% and 95%, respectively, at the patient level and 54% and 97%, respectively, at the regional or nodal level. The patient level pooled sensitivity and specificity were 50% and 92%, respectively, for CT, and 56% and 91%, respectively for MRI. The regional or nodal level pooled sensitivity and specificity were 52% and 92%, respectively, for CT, and 38% and 97%, respectively, for MRI.

In early cervical carcinoma, the sensitivity of PET/CT for nodal assessment is fairly low at 32%-58% although the specificity is high at 93%-97%. Goyal et al. (2010) [30] reported that the sensitivity, specificity, PPV, and NPV of PET/CT for nodal assessment were 58.33%, 92.8%, 77.7%, and 83.8%, respectively in 80 clinically operable CC patients. Positron emission tomography/CT helped to reduce patients who require multimodality treatment from 30% to 12.5% ($P < 0.01$). Signorelli et al. (2011) [22] studied the diagnostic performance of PET/CT to detect nodal metastases in 159 stage IB1-IIA CC patients. The overall sensitivity, specificity, PPV, and NPV at the patient level were 32.1%, 96.9%, 69.2% and 87.0%, respectively. Positron emission tomography/CT had low sensitivity in detecting nodal metastases in early CC. Similar to pelvic lymph node assessment, Chung et al. (2009) [31] showed the diagnostic performance of ^{18}F -FDG PET/CT to detect pelvic lymph node metastases in 34 stage IA2-IIIB CC patients. The overall region-level sensitivity, specificity, PPV, NPV, and accuracy were 36.4%, 98.8%, 85.7%, 88.9% and 88.7%, respectively.

Positron emission tomography/CT shows limited sensitivity but high specificity to evaluate microscopic para-aortic lymph node involvement in locally advanced CC. Leblanc et al. (2011) [32] reported the accuracy of PET to detect para-aortic lymph node metastases in 125 locally advanced stage IB2-IVA CC patients with who had a negative morphologic (CT, MR) imaging results. The sensitivity, specificity, PPV, and NPV were 33.3%, 94.2%, 53.8% and 87.5%, respectively, to detect microscopic lymph node metastases. The result is similar to study by Ramirez et al. (2011) [33] that studied pretreatment ^{18}F -FDG PET/CT in 65 stage IB2-IVA CC patients without evidence of para-aortic lymphadenopathy on CT or MRI. The sensitivity, specificity, PPV, and NPV of PET/CT were 36%, 96%, 71%, and 83%, respectively.

Fluorine-18-FDG PET is useful to evaluate metastatic disease in supraclavicular lymph nodes. Lee et al. (2012) [34] showed the ^{18}F -FDG PET had a sensitivity of 74.4%, specificity of 78.6%, PPV of 95.5%, NPV of 33.3%, and accuracy of 75% to detect metastases in supraclavicular lymph nodes with $\text{SUV}_{\text{max}} > 3$. Ultrasound tests were added to ^{18}F -FDG PET to evaluate supraclavicular lymph nodes with $\text{SUV}_{\text{max}} \leq 3$. The overall sensitivity and accuracy were increased to 100% and 92%, respectively.

In cervical adenocarcinoma/adenosquamous cell carcinoma, PET/CT showed better diagnostic efficacy to detect para-aortic lymph node metastases than MRI ($P=0.039$). FIGO stage IIB, deep cervical stromal invasion, tumor size $\geq 4\text{cm}$ on MRI, primary tumor $\text{SUV}_{\text{max}} > 5.3$, and pelvic lymph node metastases were correlated with decreased overall survival (OS) [35]. However, another study showed different results. Chung et al. (2010) [36] reported MRI has higher sensitivity than PET/CT to detect metastatic lymph nodes ($P=0.006$). The sensitivity, specificity, and accuracy of MRI to detect lymph node metastases were 64.3%, 69.1% and 67.5%, respectively, compared to 28.6%, 83.6%, and 65.1%, respectively for PET/CT. The different results may have been due to use of thinner pathology sections compared to the conventional method and use of a size threshold of 0.5cm to detect metastatic lymph nodes.

Many studies have mentioned that ^{18}F -FDG PET/CT cannot be used to replace surgical lymphadenectomy. There is low sensitivity in detecting pelvic and para-aortic lymph node metastases in early CC. Wright et al. (2005) [37] reported the diagnostic performance of ^{18}F -FDG PET in detecting lymph node metastases compared with pathology in 59 stage IA-IIA cervical carcinoma patients. The sensitivity to detect pelvic and para-aortic lymph node metastases were 53% and 25%, respectively. Similar results were demonstrated by Margulies et al. (2013) [38]. There was no significant difference between the risk of para-aortic lymph node metastases in patients with negative ^{18}F -FDG uptake in the pelvic area (8%) and with positive ^{18}F -FDG uptake in pelvic area (18%). Kitajima et al. (2012) [39] compared diffusion-weighted MR imaging (DWI) and PET/CT for preoperative evaluation of pelvic lymph node metastases in uterine cancer. Positron emission tomography/CT had a lower sensitivity compared to DWI (38.9% vs. 83.3%, respectively, at the nodal level; 44.4% vs. 88.9% respectively, at the patient level) but higher specificity (96.3% vs. 51.2% respectively, at the nodal level; 93.8% vs. 43.8% respectively, at the patient

level) to detect lymph node metastases. However, neither PET/CT nor DWI was accurate enough to replace surgical lymphadenectomy. In the addition, the false negative rate of PET for para-aortic lymph node assessment was 5%-17% [40, 41]. Therefore, surgical staging is important for accurate evaluation. Parez-Medina et al. (2013) [42] recommended that para-aortic lymph node dissection should be part of pre-treatment staging in locally advanced CC because of the limited sensitivity and specificity and low negative likelihood ratio of ^{18}F -FDG PET/CT. Patients with a para-aortic nodal metastases $> 5\text{mm}$ had poorer survival rate than patients without para-aortic nodal involvement or patients with a para-aortic nodal metastases $\leq 5\text{mm}$ ($P < 0.001$). Moreover, isolated mediastinal lymph nodes uptake in CC is possibly due to granulomatous change. Therefore, histopathologic confirmation is required for accurate staging [43]. Kim et al. (2014) [44] used PET findings combined with other variables to create a predictive model. The three variables age, tumor size assessed by MRI, and lymph nodes metastases determined by PET/CT were used to obtain a nomogram that can define a low risk of lymph nodes metastases in early CC patients in order to avoid lymphadenectomy.

The correlation of parameters measured on PET images with lymph node metastases is controversial. Fluorine-18-FDG uptake heterogeneity was not correlated with pelvic lymph nodes involvement in FIGO stage IIB CC [45]. However, metabolic tumor volume (MTV) and total lesional glycolysis (TLG) of the primary tumor were significantly associated with nodal metastases in early stage cervical patients [46].

Distant metastases assessment

Positron emission tomography/CT is able to evaluate for presence of distant metastases to sites such as lymph nodes, lung, liver, or bone marrow due to whole-body evaluation (Figures 3 and 4). Previous studies [47, 48] reported a high sensitivity of ^{18}F -FDG PET/CT to detect metastases in advanced CC. Onal et al. (2013) [43] have reported that PET/CT detected disseminated disease in 29 of 228 patients (17%). Wong et al. (2004) [49] reported a sensitivity of 100%, specificity of 90%, and accuracy of 94% of PET to evaluate distant metastases. Liu et al. (2009) [50] studied the diagnostic performance of CT, MRI, and ^{18}F -FDG PET to detect bone marrow metastases in patients with FIGO stage III/IV disease or positive lymph nodes metastases and suspected recurrent disease. Positron emission tomography had higher sensitivity than CT ($P=0.004$) and higher specificity than MRI ($P=0.04$). Overall, PET had higher accuracy than CT and MRI ($P=0.006$ and 0.003 , respectively). The extent of lymph nodes metastases was an independent risk factor for presence of osseous metastases ($P=0.025$).

Treatment planning

Pretreatment phase planning

Computed tomography and MRI play a role in the evaluation of local disease extension. Magnetic resonance imaging is su-

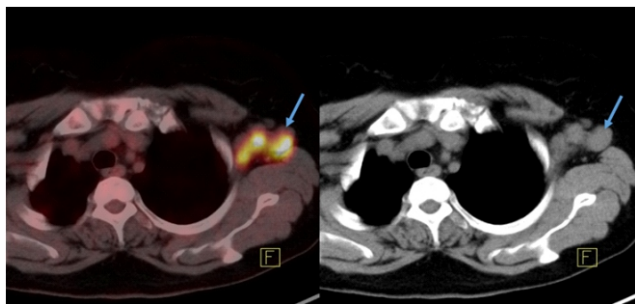


Figure 3. A 56 years old female with known case of CC, post-surgery, post chemotherapy presented with suspected recurrence on clinical examination. Positron emission tomography/CT and CT images of thorax show abnormal ^{18}F -FDG uptake suggestive of recurrence in left axillary lymph nodal metastases.

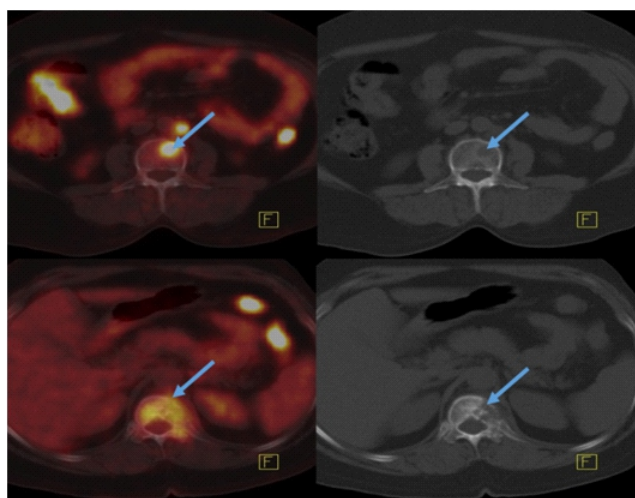


Figure 4. A 45 years old female treated with radical radiotherapy for carcinoma cervix presented with low back pain. Fluorine-18-FDG PET/CT revealed lytic skeletal metastases with increased ^{18}F -FDG uptake.

rior to CT for tumor visualization and parametrial involvement [51]. Sala et al. (2007) [52] reported the sensitivity and specificity of MRI for assessment of parametrial invasion as 69% and 93%, respectively. The sensitivity and specificity to evaluate bladder and rectal invasion were 71%-100% and 88%-91%, respectively. Even though CT has some limitations for assessment of local disease extent, CT can be useful to assess for regional nodal and distant metastatic disease.

Fluorine-18-FDG PET/CT is also useful for pretreatment evaluation. Positron emission tomography showed accurate evaluation for tumor size. Showalter et al. (2009) [53] found that the tumor diameter measured by pretreatment ^{18}F -FDG PET significantly correlated with pathologic tumor diameter ($P < 0.0001$) in early stage CC. Fluorine-18-FDG PET/CT was reported to be better than CT and MRI to detect lymph node and distant metastases [50, 54, 55]. Akkas et al. (2012) [54] found that PET/CT was superior to MRI in detecting lymph node and distant metastases in locally advanced cervical carcinoma, resulting in modification of radiation fields and changes to patient treatment plans.

Interestingly, CT, MRI, and PET/CT imaging findings are not utilized to determine disease stage in patients with CC, but are instead used for pretreatment planning purposes.

Radiation therapy planning

Fluorine-18-FDG PET/CT aids radiation therapy planning in patients with CC. Fluorine-18-FDG PET/CT provides information to modify radiation treatment volumes and radiation dose to positive lymph nodes, and allows for image-guided brachytherapy. It enables the use of higher radiation doses to tumor but lower radiation doses to normal tissue. In comparison with conventional planning techniques, PET/CT planning is better for target coverage [56, 57]. The gross tumor volume (GTV) based on ^{18}F -FDG PET/CT was similar to pathologic volume without a significant difference ($P = 0.512$). In addition, GTVs based on CT or MRI were statistically significantly greater than pathologic volume ($P < 0.05$) [58]. In the study performed by Ciernik et al. (2003) [59] using PET resulted in $\geq 25\%$ increase of GTV in 17% of patients with head-and-neck cancer, 17% of patients with lung cancer and 33% of patients with cancer of the pelvis. Also, GTV reduced $\geq 25\%$ in 33%, 67% and 19% of patients with head-and-neck cancer, lung cancer and cancer of the pelvis, respectively. The modification of GTV resulted in altered PTV changes more than $>20\%$ in 46% of patients. Using PET resulted in a decrease of volume delineation variability between two independent oncologists from a mean volume difference of 25.7cm^3 to 9.2cm^3 . Moreover, this was associated with a significant reduction of the standard deviation from 38.3cm^3 to 13.3cm^3 ($P = 0.02$). Positron emission tomography/CT also revealed distant metastases in 16% of cases which led to a change of treatment plan from curative to palliative.

Fluorine-18-FDG PET/CT is useful to guide intensity modulated radiation therapy (IMRT) effectively. Esthappan et al. (2008) [60] used ^{18}F -FDG PET/CT guided IMRT modified target coverage in positive para-aortic lymph nodes and spared normal tissues. Kidd et al. (2010) [61] reported the treatment outcome in patients treated with IMRT and non-IMRT treatment, where IMRT was performed based on ^{18}F -FDG PET/CT simulation. Patients treated with IMRT had better OS and cause-specific survival ($P < 0.0001$) and less treatment related toxicity compared to patients treated with non-IMRT. Fluorine-18-FDG PET has also been used in brachytherapy treatment planning. Malyapa et al. (2002) [62] compared three dimensional (3D) brachytherapy treatment planning based on ^{18}F -FDG PET with two-dimensional (2D) brachytherapy treatment planning based on orthogonal radiography in 11 patients with CC. Fluorine-18-FDG PET brachytherapy treatment planning is feasible and accurate compared to conventional 2D treatment planning. Malyapa et al. (2002) showed that ^{18}F -FDG PET brachytherapy treatment planning has potential to improve isodose tumor coverage while sparing critical organs.

Fluorine-18-FDG PET/CT is of benefit to evaluate lymph node involvement in locally advanced CC patients who underwent chemoradiation with IMRT and simultaneous integrated boost. The treatment is effective with acceptable toxicity [63].

Treatment response assessment

Tumor response assessment after treatment is not only important for clinicians to determine further treatment but

also is predictive for tumor recurrence and death in CC patients [64, 65]. To assess response to therapy, clinical examination and MRI are performed 3-6 months after completion of concurrent chemoradiation therapy. However, it is sometimes difficult to differentiate between recurrent tumor and post-treatment change on MRI [66, 67].

The preoperative PET tumor size is highly correlated with pathologic tumor measurement [53]. Kidd et al. (2007) [68] showed pretreatment ^{18}F -FDG uptake (SUVmax) of primary CC predicted treatment response and prognosis. The intratumoral ^{18}F -FDG metabolic heterogeneity of primary tumor predicted lymph node involvement at diagnosis, treatment response, local recurrence, and progression-free survival (PFS) [69].

Positron emission tomography/CT has been used to monitor treatment response in CC patients [8]. Positron emission tomography/CT has potential to predict early treatment response prior to morphologic changes have occurred, as ^{18}F -FDG uptake decreases earlier than tumor volume decreases [70]. Positron emission tomography/CT performed too soon after treatment may be affected by treatment related metabolic change and cannot be accurately interpreted [71]. The optimal timing to obtain ^{18}F -FDG PET/CT to assess for treatment response is at least 6 weeks after surgery and 3 months after completion of concurrent chemoradiation therapy [72].

Previous studies [65, 73, 74] reported the role of ^{18}F -FDG PET/CT in evaluating treatment response after definite chemoradiation treatment. Fluorine-18-FDG PET/CT findings are associated with survival outcome. Kunos et al. (2011) [74] reported that the three month post-therapy ^{18}F -FDG PET/CT can predict response to chemoradiation therapy. The ratio of SUVmax at post-therapy to SUVmax at pre-therapy of <0.33 correlated with tumor pathologic response (AUC of 0.955, $P<0.001$) and a 35% improvement of 6 month PFS ($P=0.004$) in advanced stage IB2-IVA CC patients. Schwarz et al. (2007) [65] evaluated metabolic response 3 months after treatment. The metabolic response determined by ^{18}F -FDG PET was categorized into 3 groups: complete metabolic response, partial metabolic response, and progressive disease. The cause-specific survival and PFS rates were different among the 3 groups ($P<0.001$ and $P<0.001$, respectively). Progressive disease (HR 32.57, 95% CI 10.22-103.82) was the most significant predictor for PFS. Another study by Schwarz et al. (2012) [73] reported that post-therapy ^{18}F -FDG PET can be used to evaluate metabolic response and the pattern of treatment failure in CC treated with definitive radiotherapy. Complete metabolic response, partial metabolic response, and progressive disease groups determined by ^{18}F -FDG PET 8-16 weeks after completion of radiotherapy were significant differences in the OS ($P<0.0001$). Positron emission tomography response predicted PFS ($P<0.0001$) and cause-specific survival ($P<0.0001$). Partial metabolic response correlated with isolated local tumor recurrence. Siva et al. (2011) [75] studied post-therapy ^{18}F -FDG PET in 105 stage IB-III CC patients treated with chemoradiation therapy. Fluorine-18-FDG PET was performed between 3-12 months after chemoradiation therapy and categorized into complete metabolic response, partial metabolic response, and progressive metabolic response. Patients with partial

metabolic response had distant failure 36-fold higher than that in patients with complete metabolic response ($P<0.0001$). Patients with partial metabolic response had nodal failure 51-fold higher than that in patients with complete metabolic response ($P=0.0061$).

Fluorine-18-FDG PET or PET/CT can be used to monitor treatment response during treatment [76]. Kidd et al. (2013) [77] showed change in ^{18}F -FDG uptake during chemoradiation therapy is associated with response to treatment. Fluorine-18-FDG PET/CT images were performed pretreatment, weeks 2 and 4 of treatment with concurrent cisplatin and radiation therapy, and 3 months after completing chemoradiation therapy. Non-responders had higher SUVmax, larger MTV, and greater tumor heterogeneity compared with responders. SUVmax at week 4 was correlated with post-treatment PET response ($P=0.037$). In addition, tumor heterogeneity and MTV at all times were significantly correlated with post-treatment PET response. Pretreatment and week 4 of chemoradiation were the best times to early predict treatment response. Lee et al. (2013) [78] showed that the mid-treatment percent volume reduction measured by ^{18}F -FDG PET/CT was significantly greater than the percent volume reduction calculated from MRI ($P=0.024$). Lin et al. (2006) [79] found a significant tumor volume reduction evaluated by ^{18}F -FDG PET within 20 days of starting chemoradiation treatment. Bjurberg et al. (2009) [80] reported that visual complete metabolic response was detected after mean radiation therapy dose of 23Gy. The ability of ^{18}F -FDG PET/CT to early predict response during and after completion of treatment may be used to consider additional therapy and provide prognostic information. Fluorine-18-FDG PET/CT can be used to evaluate treatment response and predict survival time in recurrent CC. Dhull et al. (2014) [81] have found that metabolically progressive disease after treatment in recurrent CC is significantly associated with shorter PFS ($P<0.0001$).

However, ^{18}F -FDG PET after surgery in stage I CC was not shown to be beneficial as the recurrence rate in early stage CC after surgery is low. Bjurberg et al. (2007) [82] reported there is no benefit of ^{18}F -FDG PET performed 6 months after surgery in early stage CC. Moreover, Vandecasteele et al. (2012) [83] showed a higher specificity and NPV of MRI compared to PET/CT to identify tumor pathologic response. The ability of MRI and ^{18}F -FDG PET/CT to predict resectability and pathologic response after intensity-modulated arc therapy (IMAT) and cisplatin treatment in primary locally advanced CC was compared. A negative MRI result had 100% NPV for negative surgical margins. Ferrandina et al. (2012) [84] reported a sensitivity, specificity, and accuracy of PET/CT to detect residual disease of 28.6%, 97.8% and 88.7%, respectively, compared to 35.7%, 95.9% and 88.0%, respectively, for MRI. Magnetic resonance imaging and PET/CT are not accurate enough to detect residual disease for locally advanced CC patients triaged to radical surgery after neoadjuvant treatment.

Restaging

Early detection of recurrent CC correlates with improved sur-

vival [85]. Fluorine-18-FDG PET/CT may be utilized for surveillance in patients at high risk for locoregional failure. Fluorine-18-FDG PET/CT is useful to detect local recurrence and distant metastases with high diagnostic performance. Havrilesky et al. (2003) [6] reported a sensitivity, specificity, PPV, and NPV of ^{18}F -FDG PET in detecting recurrent CC of 85.7%, 86.7%, 85.7% and 86.7%, respectively. Chung et al. (2007) [86] showed a sensitivity, specificity, and accuracy of PET/CT of 90.3%, 81.0%, and 86.5%, respectively, to detect suspected tumor recurrence in CC patients. Mitra et al. (2009) [87] reported a patient level sensitivity, specificity, accuracy, PPV, and NPV of ^{18}F -FDG PET/CT to detect local recurrence at the primary site of 93% (95% CI 76%-99%), 93% (95% CI 84%-96%), 93% (95% CI 81%-97%), 86% (95% CI 71%-92%), and 96% (95% CI 87%-99%), respectively. Furthermore, the patient level sensitivity, specificity, PPV, NPV and aCCuracy to detect distant metastases were 96%, 95%, 95, 96%, and 95% respectively. All patients had a change in management based on PET/CT findings. Similar results have been found in other studies. Chung et al. (2012) [88] reported an overall sensitivity, specificity, PPV, NPV, and accuracy of post-treatment PET/CT to detect tumor recurrence of 94.7%, 87.8%, 80.4%, 97%, and 90.2%, respectively. Positron emission tomography/CT impacted clinical management in 24.2% of patients. Bhoil et al. (2013) [89] reported a sensitivity, specificity, PPV, and NPV of PET/CT, 97.5%, 63.6%, 90.9% and 87.5%, respectively, in detecting tumor recurrence in 53 CC patients with suspicion for recurrent disease based on clinical assessment or conventional imaging. Chu et al. (2014) [90] performed a meta-analysis to determine diagnostic accuracy of ^{18}F -FDG PET or PET/CT in recurrent CC. The pooled sensitivity and specificity to detect local recurrence were 82% (95% CI 0.72%-0.90%) and 98% (95% CI 0.96%-0.99%), respectively. The pooled sensitivity and specificity to detect distant metastases were 87% (95% CI 0.80%-0.92%) and 97% (95% CI 0.96%-0.98%), respectively.

Previous studies [91, 92] showed that PET/CT had higher diagnostic accuracy than PET or CT alone to detect tumor recurrence. Positron emission tomography/CT also had higher rate of associated management plan change, resulting more appropriate treatment than with use of other imaging modalities. Kitajima et al. (2008) [91] compared diagnostic performance of ^{18}F -FDG PET with ^{18}F -FDG PET/CT in 52 CC patients with suspected tumor recurrence. The sensitivity, specificity, and accuracy of PET/CT were 92.0%, 92.6%, and 92.3%, respectively, compared to 80%, 77.8% and 78.8%, respectively, for PET. Fluorine-18-FDG PET/CT reduced the false positive and false negative rates of ^{18}F -FDG uptake, compared to previous conventional imaging. Another study by Kitajima et al. (2010) [92] compared the diagnostic performance of PET/CT, PET, and contrast-enhanced CT in patients with uterine cervical and endometrial cancers [93, 94]. The sensitivity, specificity, and accuracy were 90.9%, 93.5% and 92.2%, respectively, for PET/CT, 79.5%, 73.9%, and 76.7% respectively, for PET, and 68.2%, 87.0%, and 77.8% respectively, for CT. Positron emission tomography/CT changed management in 42% of patients, whereas CT and PET changed management in 14% and 16%, respectively. In integrated PET/CT investigation, ceCT showed higher sensi-

tivity, specificity, and accuracy at the patient level compared to low dose non-enhanced CT (IdCT) for restaging uterine cervical or endometrial cancer. The sensitivity, specificity, and accuracy of PET/ceCT were 90%, 97%, and 95%, respectively, while those of PET/IdCT were 83%, 94%, and 91%, respectively. Even though the differences were not statistically significant, PET/ceCT may be more useful in equivocal cases [92].

Positron emission tomography/CT has an impact on management plan in patients with recurrent CC. Chung et al. (2007) [86] reported a change in patient management in 23.1% of 52 CC patients with suspected tumor recurrence. Patients with negative PET/CT for recurrence had a significantly better 2-year disease-free survival (DFS) rate compared to patients with positive PET/CT (85.0% vs. 10.9%, respectively, $P=0.002$). Similar results were reported by Bjurberg et al. (2013) [95] In their study, PET detected more metastatic sites compared to CT in 56% of patients. Positron emission tomography had high impact (led to a change or withholding of treatment) in 33% of patients and medium impact (altered planned procedure, treatment dose, or mode of delivery) in 22% of patients. The intention of treatment was changed in 30% of patients.

Burger et al. (2013) [96] reported that ^{18}F -FDG PET/CT is useful to determine local disease extension in recurrent gynecologic malignancies including CC before pelvic exenteration. The area under the curves (AUC) to detect pelvic organ and pelvic sidewall invasion was reported from the several studies 0.74 to 0.91. Moreover, MTV significantly correlated with OS ($P<0.001$) and PFS ($P=0.001$). TLG also correlated with OS ($P=0.022$). FDG PET has ability to detect extra-pelvic metastases in recurrent CC prior to plan pelvic exenteration [97, 98].

Fluorine-18-FDG PET/CT can be used to detect recurrence in either asymptomatic patients or patients with rising tumor markers. Brooks et al. (2009) [98] assessed the ability of ^{18}F -FDG PET to detect tumor recurrence in asymptomatic patients. Fluorine-18-FDG PET was performed in 103 stages IB-IIIB patients treated with definitive chemoradiation therapy. Positron emission tomography detected 9 tumor recurrences in 78 asymptomatic patients. Those patients with asymptomatic recurrences detected by ^{18}F -FDG PET had a significantly better 3-year cause-specific survival compared to patients with symptomatic recurrences confirmed by ^{18}F -FDG PET (59% vs. 19%, respectively, $P=0.09$). Chong et al. (2013) [99] studied ^{18}F -FDG PET/CT for restaging treated squamous cell CC in patients with unexplained tumor marker (squamous cell carcinoma antigen (SCC Ag) or carcinoembryonic antigen (CEA)) elevation following complete remission of tumor. Positron emission tomography/CT showed a sensitivity of 100%, specificity of 83.3%, PPV of 82.4%, and NPV of 100% to detect tumor recurrence. Positron emission tomography/CT had more accuracy in the setting of SCC Ag elevation (100%) than in the setting of CEA elevation (66.7%) ($P=0.0169$). Squamous cell carcinoma Ag correlates with disease recurrence, and can be used as a part of surveillance after treatment [100]. Chang et al. (2004) [101] reported that PET detected tumor recurrence in CC patients with prior complete response to treatment when serum SCC Ag levels were $\geq 2.0\text{ng/mL}$ but when no disease

was evident by conventional methods.

However, recent studies have reported that ^{18}F -FDG PET/CT for routine surveillance and follow up in recurrent or persistent CC patients is not cost-effective. Auguste et al. (2014) [103] performed a cost-effectiveness analysis for PET/CT in routine surveillance and follow up after treatment. The model-based economic evaluation was based on the UK National Health Service for assessment of recurrent or persistent CC in patients at least 3 months after completed treatment. Positron emission tomography/CT for diagnosis of recurrent or persistent CC is not cost-effective when compared between standard practice (clinical examination, MRI and/or CT) and PET/CT together with standard practice. Meads et al. (2013) [104] perform a meta-analysis and cost-effectiveness analysis to determine whether PET/CT should be used as an adjunct to standard practice in patients with recurrent or persistent CC. From eligible 12 test accuracy studies, the sensitivity and specificity of PET/CT were 92.2% and 88.1%, respectively; where as those of MRI were 82%-100% and 78%-100%, and those of CT were 78%-93% and 0-95%, respectively. Some studies showed that PET/CT was not cost-effective. These cost-ineffectiveness results may be due to the lack of good quality evidence of diagnostic and therapeutic impact ^{18}F -FDG PET/CT on patients with recurrent or persistent disease, asymptomatic patients, and the high cost of PET/CT.

Prognosis assessment

The evaluation of prognosis in patients with CC is important. Care providers can tailor the treatment for an individual patient by using information about risk assessment. There are several prognostic factors in CC such as age, bulky tumor size, tumor stage, histological type, lymph node involvement, vessel invasion, parametrial involvement, and lymphovascular space invasion [105-107]. Lymph node metastases are the most important prognostic factor in CC [108, 109]. The presence of nodal metastases decreased 5-year survival from 85% to 50% [110]. Positron emission tomography/CT is able to predict prognosis and treatment response. Positron emission tomography derived metabolic tumor parameters in term of SUVmax, MTV, and TLG as well as PET response are predictors of patient outcome.

Previous studies showed that the degree of ^{18}F -FDG uptake within tumor sites on ^{18}F -FDG PET/CT during pretreatment evaluation correlated with outcome. High SUV of primary tumor and regional lymph nodes is strongly associated with poor clinical outcome. SUVmax of primary CC correlated with other worse prognosis factors such as pathologic features, tumor size, and lymph node metastases. The pretreatment SUVmax in poorly-differentiated cervical tumors was seen to be the highest and significantly different compared to well-differentiated cervical tumors (12.23 vs. 8.58, $P=0.474$) [111]. SUVmax correlated with depth of tumor invasion and histologic tumor grade. SUVmax helps to identify early stage patients who will need post-operative adjuvant treatment [112]. Nakamura et al. (2010) [113] re-

ported that the SUVmax of primary tumors is significantly associated with tumor maximum size and pelvic lymph node metastases ($P=0.027$ and 0.039 , respectively). The SUVmax significantly correlated with presence of bilateral pelvic lymph node metastases ($P=0.034$). A high SUVmax of the primary tumor with lymph node metastases (short axis diameter $>1\text{cm}$ and $\text{SUVmax} \geq 3.5$) is a significant predictor for worse OS ($P=0.0211$). SUVmax of primary tumor was associated with risk of lymph node metastases ($P=0.0009$). Kidd et al. (2009) found that SUVmax of pretreatment cervical tumor was the only independent prognostic factor ($P=0.0027$) [68]. Yilmaz et al. (2010) [114] found a correlation between high SUVmax (≥ 13.5) of the primary tumor and lymph node metastatic rate ($P=0.03$). Close follow up is recommended in patient with high SUV uptake due to the high potential risk of lymph node metastases. Nakamura et al. (2012) [115] compared the prognostic value between SUVmax from pretreatment PET/CT and minimum apparent diffusion coefficient (ADCmin) from MRI in CC. The cut-off values of SUVmax and ADCmin were 15.55 and 0.61, respectively. High SUVmax of the primary tumor was associated with a significantly shorter DFS ($P=0.0171$) and OS ($P=0.0367$) than a low SUVmax of primary tumors. High SUVmax with low ADCmin of primary tumor was an independent predictive factor for DFS and OS ($P=0.003$ and 0.0036 , respectively). Chung et al. (2010) [116] reported that preoperative SUVmax of primary tumor (HR 1.178, 95% CI 1.034-1.342), age (HR 0.87, 95% CI 0.772-0.980), and parametrial involvement (HR 27.974, 95% CI 1.156-677.043) were independent predictors for disease recurrence.

Many studies have shown that the SUVmax of primary CC and the change in SUVmax following treatment is associated with disease recurrence and survival time. Xue et al. (2006) [117] reported a significant difference of 5-year DFS in patients with $\text{SUVmax} < 10.2$ and ≥ 10.2 ($P=0.0289$). Lymph node metastases seen on PET were an independent predictor for DFS ($P < 0.0001$). Kidd et al. (2007) [68] studied pretreatment SUVmax in 287 stage IA2-IVB CC patients. A higher primary tumor SUVmax correlated with an increased risk of lymph node metastases ($P=0.0009$). SUVmax was an independent predictor for death ($P=0.0027$). When pretreatment SUVmax was categorized into three patient groups, namely $\text{SUVmax} \leq 5.2$, $\text{SUVmax} > 5.2$ and ≤ 13.3 , and $\text{SUV} > 13.3$, the 5-year OS was shown to be significantly different among these three groups ($P < 0.0001$). SUVmax was also correlated with persistent tumor 3 months after completed chemoradiation treatment ($P=0.0472$). Moreover, SUVmax correlated with pelvic recurrence ($P=0.0232$), cause-specific survival ($P=0.0126$) and OS ($P=0.0119$). Lee et al. (2009) [118] reported that patients with a high SUVmax (≥ 13.4) of primary tumor had significantly lower DFS than patients with a low SUVmax ($P=0.021$). High SUVmax was an independent predictive factor for disease recurrence in patients treated with surgery with or without adjuvant therapy ($P=0.0207$). Oh et al. (2013) [119] reported on the use of ^{18}F -FDG PET/CT performed before treatment, during concurrent chemoradiation therapy (CCRT) at 4 weeks, and 1 month post CCRT. They showed that the percentage change in SUVmax (ΔSUVmax) of the primary cervical tumor between pretreatment PET/CT and during CCRT PET/CT of

≥59.7% predicted complete response on post concurrent chemoradiation therapy PET/CT ($P < 0.001$). The Δ SUVmax ≥60% and post-CCRT response were independent predictive factors for PFS ($P = 0.045$ and 0.012 , respectively). Moreover, the combination of ^{18}F -FDG uptake with other factors has predictive value. Miller et al. (2003) [120] evaluated ^{18}F -FDG PET images in patients with CC for tumor size, shape, heterogeneity of ^{18}F -FDG uptake, and lymph node involvement via grading and scores to categorize patients into those with good or bad prognosis. The cut-off value 4 from total score of 8 was able to differentiate good and bad prognosis patients. Patients with a total score < 4 had significant better PFS (likelihood ratio (LR) 5.3, $P < 0.0001$) and OS (LR 9.5, $P < 0.0001$) than patients with a total score ≥ 4 . Moreover, lymph node status predicted PFS ($P = 0.04$) and OS ($P = 0.03$). Pan et al. (2012) [121] reported that a higher pretreatment SUVmax of primary tumor ≥ 11.2 with pelvic lymph node metastases was a significant predictor for worse OS ($P = 0.0099$). Moreover, higher pretreatment SUVmax with higher serum SCC Ag $\geq 6.4\text{ng/ml}$ (normal level $< 1.6\text{ng/ml}$) was a significant predictor for poor OS ($P = 0.0020$) in patients with cervical squamous cell carcinoma [121].

Volume-based metabolic parameters have prognostic value in CC. Miller et al. (2002) [122] reported that tumor volume and lymph node disease determined by PET-predicted survival time. Tumor volume were significantly predictors for PFS ($P = 0.005$) and OS ($P = 0.003$). Patients with tumor volume $> 60\text{cm}^3$ had a worse PFS ($P = 0.007$) and OS ($P = 0.003$) than patients with tumor volume $\leq 60\text{cm}^3$. Patients with tumor volume $\leq 60\text{cm}^3$ and negative lymph nodes had a significantly better PFS ($P = 0.01$) than patients with tumor volume $> 60\text{cm}^3$ and/or positive lymph nodes. Chung et al. (2011) [123] found age and MTV $\geq 23.4\text{mL}$ were independent predictive factors of DFS in stage IB-IIA CC patients treated primarily with radical hysterectomy. Yoo et al. (2012) [124] reported that prognostic factors in 73 CC patients were age, cell type, disease stage, primary tumor size, lymph node status on PET, lymph node status on CT/MRI, treatment modalities, SUVmax, SUVaverage, MTV, and TLG. Among these factors, lymph node status on PET ($P < 0.001$) and TLG ($P < 0.05$) were independent predictive factors for DFS or PFS. However, some studies [125, 126] have not found associations between MTV and TLG and survival time. Akkas et al. (2013) [125] showed MTV, TLG, and SUVmax were not correlated with patient prognosis on multivariate analysis in inoperable CC patients. Maharjan et al. (2013) [126] reported that the aggressiveness of tumor measured by SUVmax, but not tumor size, is the most prognostic factor for PFS in recurrent CC.

Lymph node status determined by PET/CT and the degree of ^{18}F -FDG uptake in lymph node metastases has predictive role. Kidd et al. (2010) [108] reported that presence of lymph node metastases on ^{18}F -FDG PET predicted worse disease-specific survival ($P < 0.001$). Yen et al. (2008) [127] studied PET parameters in untreated squamous carcinoma CC patients. FIGO stage \geq III was an independent predictor for relapse-free survival ($P = 0.008$) and OS ($P = 0.008$) while SUVmax of para-aortic lymph nodes ≥ 3.3 was an independent predictor for OS ($P = 0.012$). Patients with SUVmax of para-aortic

lymph nodes ≥ 3.3 or FIGO stage \geq III had a significantly worse recurrence-free survival (HR 4.52, 95% CI 1.73-11.80) and OS (HR 6.04, 95% CI 1.97-18.57) than patients with SUVmax < 3.3 and FIGO stage \leq II. Narayan et al. (2009) [128] reported that lymph node status was a predictor of patient outcome. Patients with negative lymph nodes on PET had better OS than patients with positive lymph nodes on PET ($P < 0.0001$). Adenocarcinoma histology (HR 3.08, $P = 0.001$), FIGO stage (HR 1.73, $P = 0.002$) and positive nodes (HR 2.24, $P = 0.002$) were independent predictor for OS. Akkas et al. (2013) [125] studied pre-treatment ^{18}F -FDG PET/CT in 58 inoperable stage IIB-IVB CC patients who were treated with chemoradiation therapy. Advanced FIGO stage, frequency of ^{18}F -FDG avid pelvic and/or para-aortic lymph nodes, and lymph node SUVmax were correlated with persistent disease. The presence of ^{18}F -FDG avid para-aortic lymph node and stage IV disease were independent prognostic factors for persistent disease, OS, and DFS. Nakamura et al. (2014) [129] showed that the SUVmax of lymph nodes predicted recurrence and survival time in CC patients with lymph nodes confined to the pelvis. A SUVmax of lymph nodes ≥ 2.100 was used as a cut-off value to predict recurrence with sensitivity of 80% and specificity of 64.8%. SUVmax of lymph nodes ≥ 2.225 was used as a cut-off value to predict survival with a sensitivity of 80.0% and a specificity of 63.3%. Patients with higher SUVmax of lymph nodes had significantly shorter DFS ($P = 0.003$) and OS ($P = 0.019$) than patients with lower SUVmax of lymph nodes. High SUVmax of lymph nodes was an independent prognostic factor for DFS ($P = 0.0231$) and OS ($P = 0.0146$). Chung et al. (2014) [130] showed that preoperative ^{18}F -FDG uptake in pelvic lymph nodes was associated with recurrent CC. SUVmax of lymph nodes ≥ 2.36 was significantly associated with a better PFS (HR 15.20, $P < 0.001$). SUVmax of lymph nodes (HR 4.447, 95% CI 1.379-14.343) and parametrial invasion (HR 6.728, 95% CI 1.497-30.235) were independent prognostic factors for disease recurrence. Similarly, Kidd et al. (2010) [131] found that higher SUVmax of pelvic lymph nodes is associated with an increased risk of persistent disease after therapy ($P = 0.0025$) and an increased risk of persistent disease in pelvic lymph nodes ($P = 0.0003$). Increased SUVmax of pelvic nodes was the only independent factor for risk of pelvic disease recurrence ($P = 0.0035$). An elevated SUVmax of pelvic lymph nodes correlated with worse disease-specific survival ($P = 0.023$) and OS ($P = 0.0378$).

Positive pelvic nodes on PET/CT correlated with disease recurrence and worsened survival. Kang et al. (2011) [132] developed a predictive model to predict risk of distant recurrence in locally advanced CC patients treated with concurrent chemoradiation treatment. Positive pelvic nodes on PET predicted distant recurrence with a sensitivity of 100%, negative likelihood ratio of 0, and NPV of 100%. Moreover, DFS and distant recurrence-free survival was significantly lower than in patients with negative pelvic nodes on PET image ($P = 0.0016$ and 0.0006 , respectively). Yoon et al. (2012) [133] assessed PET/CT in 48 CC patients who had positive pelvic lymph nodes immediately after radiation therapy (median 63Gy to gross lymph nodes). Patients with a complete metabolic response of positive lymph node

(LNCMRI) had significantly better 3-year OS ($P=0.038$), DFS ($P<0.001$), and distant metastases free survival rates ($P<0.001$) compared to patients with non-LNCMRI. Im et al. (2014) [134] reported on the prognostic factors for PFS in CC patients who were treated with concurrent chemoradiation therapy. Among others, ^{18}F -FDG positive para-aortic (HR 6.05, 95% CI 2.18-16.81), retrocrural (HR 17.05, 95% CI 5.34-54.44), and supraclavicular (HR 19.56, 95% CI 7.15-53.54) lymph nodes were most significant. Para-aortic lymph node involvement was prognostic for disease progression [135]. Para-aortic lymph node metastases detected by PET was a better prognostic factor than that detected by CT to predict PFS [135].

Post-treatment ^{18}F -FDG PET/CT has a predictive role as well. Chung et al. (2012) found that $\text{SUV}_{\text{max}} \geq 5.25$ is associated with poor OS ($P=0.001$). Patients with positive PET/CT for recurrence had worse 5-year PFS ($P<0.0001$) and OS ($P=0.0015$) compared to those with a negative PET/CT. Ho et al. (2011) [136] reported on the benefit of ^{18}F -FDG PET to predict prognosis in 31 CC patients with evidence of supraclavicular lymph node recurrence. Patients with limited supraclavicular lymph node recurrence by ^{18}F -FDG PET had better 3-year OS rates than patients with disease extension beyond the supraclavicular lymph nodes ($P=0.031$). Patients with SUV_{max} of lymph node between 4.3 and 8 had significant better OS than patients with SUV_{max} of lymph node <4.3 or >8 ($P=0.004$). It is hypothesized that this is in part because tumors with low SUV may be resistant to chemotherapy due to hypoxia. Sharma et al. (2012) [137] reported that ^{18}F -FDG uptake predicts outcome in recurrent CC after radiation therapy. Patients with $\text{SUV}_{\text{max}} > 5.8$ had significant lower 1-year PFS than patients with $\text{SUV}_{\text{max}} < 5.8$ ($P=0.01$). However, MTV was not correlated with PFS.

Fluorine-18-FDG PET response predicts outcome after chemoradiation. Schwarz et al. (2007) reported that 3 month post-treatment ^{18}F -FDG uptake predicted survival outcome. Post-treatment PET response was an independent predictor for PFS ($P<0.001$). Beriwal et al. (2012) [138] reported good local disease control in patients with complete metabolic response after concurrent chemoradiation therapy. The 3-year DFS of complete metabolic response patients was 78%, and only tumor size was an independent predictor for local recurrence ($P \leq 0.025$). However, age, stage, histology, and nodal positivity were not significant predictors for recurrence. Siva et al. investigated ^{18}F -FDG PET that was obtained 3-12 months after chemoradiation therapy. Complete metabolic response and pretreatment tumor volume were independent predictors for OS ($P<0.0001$ and $P=0.041$, respectively). The number of lymph nodes involved and FIGO stage were associated with relapse-free survival.

Recent meta-analysis study was performed by Zhao et al. (2013) [139] to determine the association between ^{18}F -FDG PET/CT or PET findings and survival outcomes. From 16 studies and 1854 patients, positive pretreatment ^{18}F -FDG PET findings were associated with poor event-free survival (pooled HR 2.681, 95% CI 2.059-3.490) and OS (pooled HR 2.063, 95% CI 1.023-4.158). Post-treatment ^{18}F -FDG PET significantly predicted event-free survival (pooled HR 2.030, 95% CI 1.537-2.681) and OS (pooled HR 2.322, 95% CI 1.485-3.630).

Tumor hypoxia

Hypoxic tumor tissue is a well-known factor for resistance to radiation therapy and chemotherapy. As the effectiveness to radiation and chemotherapy treatment is reduced in hypoxic cells, knowledge of presence of tumor hypoxia can allow for adaptive modification of the treatment plan to improve treatment response. Hypoxia PET imaging studies such as with ^{18}F -fluoromisonidazole (FMISO) or copper (II)-diacetyl-bis (N4-methylthiosemicarbazone) (^{60}Cu -ATSM) have been used in various cancers to predict patient prognosis [140-143].

Grigsby et al. (2007) [144] showed the correlation between ^{60}Cu -ATSM uptake in hypoxic tissue and molecular markers in CC. ^{60}Cu ATSM uptake in tumor on PET imaging is significantly associated with overexpression of carbonic anhydrase IX ($P=0.02$) and presence of apoptosis ($P=0.005$). ^{60}Cu -ATSM uptake was an independent predictive factor for recurrence ($P=0.0287$). Dehdashti et al. (2003) [145] reported preliminary data on pretreatment ^{60}Cu -ATSM PET in 14 locally advanced CC patients to predict treatment response. Tumor radiotracer uptake was inversely correlated with PFS ($P=0.0005$) and OS ($P=0.015$). A tumor-to-muscle uptake ratio of >3.5 was associated with disease recurrence. There was no correlation between ^{18}F -FDG uptake and ^{60}Cu -ATSM uptake. Another study by Dehdashti et al. (2008) [143] reported on 38 CC patients who underwent pretreatment ^{60}Cu -ATSM PET imaging. Higher ^{60}Cu -ATSM uptake was associated with shorter PFS ($P=0.006$) and cause-specific survival ($P=0.04$). Tumor-to-muscle activity ratio >3.5 correlated with recurrent cases. The data confirm that ^{60}Cu -ATSM PET imaging predicted prognosis in CC patients. Lewis et al. (2008) [146] compared the image quality between ^{64}Cu -ATSM PET images and ^{60}Cu -ATSM PET images. The image quality by ^{64}Cu -ATSM was better than that of ^{60}Cu -ATSM because of lower noise. Tumor uptake of ^{64}Cu -ATSM and ^{60}Cu -ATSM appeared to be similar. Vercellino et al. (2012) [147] studied the use of ^{18}F -fluroerythronitroimidazole (^{18}F -FETNIM) PET/CT in CC. High ^{18}F -FETNIM tumor uptake was correlated with a worse PFS and OS.

PET/MRI and fusion of PET and MRI

Positron emission tomography/MRI is beneficial for accurate target volume delineation [148]. Positron emission tomography/MRI reduces radiation exposure when compared with PET/CT [149]. Positron emission tomography/MRI detects CC with high sensitivity because it gives improved detail regarding local tumor extension and parametrial invasion which is difficult to evaluate on PET/CT. The fusion of ^{18}F -FDG PET and MRI data sets may be of benefit for pretreatment assessment of the primary tumor. Kitajima et al. (2014) [150] reported that fused PET/MRI detected 100% of primary CCs in 30 patients. Fused PET/MRI had an accuracy of 83.3% for primary tumor (T) staging, which was significantly more accurate than the accuracy of 53.3% of PET/contrast-enhanced CT (ceCT) ($P=0.0077$). Even though the sensitivities of fused PET/MRI were higher

than those of PET/ceCT to detect parametrial (85.7% vs. 53.8%, respectively), vaginal (100% vs. 33.3%, respectively), pelvic side wall (100% vs. 75.0%, respectively), and bladder invasion (100% vs. 0%, respectively), the differences were not statistically significant. The sensitivity, specificity, and accuracy for regional nodal (N) staging at the patient level were 91.3%, 88.2%, and 90%, respectively, for both fused PET/MRI and PET/ceCT. However, Kim et al. (2009) [151] showed the benefit of fused PET/MRI in detecting lymph node metastases. The sensitivity, specificity, PPV, and NPV of PET/CT and fused PET/MRI were 44.1%, 93.9%, 46.4%, 93.4% and 54.2%, 92.7%, 47.1%, 94.4%, respectively. The ROC analysis showed a higher diagnostic performance of fused PET/MRI than PET/CT in detecting lymph node metastases ($P=0.0259$). There was no evidence of benefit of PET/MRI to detect distant metastases, for restaging, or for assessing treatment response. Further studies to assess the added value of fused or integrated PET/MRI imaging compared to currently available diagnostic techniques in patients with CC is warranted. Table 1 showed summarized roles of PET/CT and PET/MRI in CC patients.

Table 1. Summarized roles of PET/CT and PET/MRI in CC patients

Imaging technique	Clinical applications
¹⁸F-FDG PET/CT	
1. Pretreatment evaluation	Detection of metastatic disease in locally advanced disease. Optimization of treatment (including radiation therapy) planning to increase tumor coverage and decrease toxicity to normal tissues.
2. Surveillance after treatment/restaging	Detection of tumor recurrence (especially in asymptomatic patients) and localization of sites of recurrence.
3. Assessment treatment response	Determination of treatment response during radiation therapy and 3 months after chemoradiation in locally advanced CC. Complete metabolic response is associated with a better survival outcome than partial metabolic response or progressive disease.
4. Prognosis	Increased pretreatment SUVmax of primary tumor is associated with decreased survival. Lymph node involvement determined by PET/CT predicts outcome. SUVmax of pelvic node metastases predict prognosis. MTV, TLG, and lymph node status are independent predictive factors. Post-treatment ¹⁸ F-FDG uptake predicts survival time.

Hypoxia PET/CT

- | | |
|---------------------------|---|
| 1. ⁶⁰ Cu ATSM | Prediction of treatment response. Prediction of local tumor control, PFS, and OS. |
| 2. ¹⁸ F-FETNIM | Prediction of survival time. |

PET/MRI

- | | |
|-----------------|---|
| 1. Pretreatment | Improved evaluation of tumor extent. |
| 2. Treatment | Improved tumor delineation for radiation therapy treatment. |

MTV=metabolic tumor volume, TLG=total lesional glycolysis, OS=overall survival, DFS=disease-free survival, PFS=progression free survival

Appropriate use criteria for CC: NCCN, ACR, CMS guidelines

The National Comprehensive Cancer Network (NCCN) guidelines recommend that clinicians have the discretion to use PET/CT in the initial work up in CC [122]. Positron emission tomography/CT is optional in stage IB and higher patients with positive para-aortic nodal involvement at surgery or surveillance after treatment.

The American College of Radiology (ACR) Appropriateness Criteria suggests the usefulness of PET/CT in early and advanced CC. In early cases, PET/CT is favored to evaluate lymph node status and distant metastases before treatment and extent of residual disease at 3 months [152]. In advanced cases, PET/CT plays an important role in evaluating disease extent before and 3 months after treatment as well as detecting persistent or recurrent disease [153]. SUVmax is also useful to predict patient outcome [152].

The United States Center for Medicare and Medicaid Services (CMS) covers ¹⁸F-FDG PET for use in newly diagnosed CC patients where conventional imaging is negative for extrapelvic metastases [154].

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