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FDG-PET Imaging in Cervical Cancer

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FDG-PET/CT has an established role in the initial staging of locally advanced cervical cancers, particularly in evaluation of nodal disease and distant metastases. It is common practice to perform FDG-PET/CT 3 months postcompletion of chemoradiotherapy as it can predict outcome and be used to tailor management, including adjuvant therapy and follow-up. It is also routinely used prior to pelvic exenterative surgery to ensure there is no disease outside the pelvis. There is growing evidence that FDG-PET-derived parameters are prognostic and could potentially be used to tailor therapy. This review outlines the use of FDG-PET/CT imaging in cervical cancer.
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Cervical cancer is the fourth most common cancer in women globally, with the fourth highest mortality.[1] It is the most common cause of death in the less than 35-year-old female population despite the development of screening and a vaccine, and remains the leading cause of cancer death in women in the majority of Sub-Saharan Africa and South-Eastern Asia.[1]

The vast majority of cervical cancers are attributable to persistent human papillomavirus infection (HPV). Primary prevention is possible via immunization with highly efficacious HPV vaccines and secondary prevention is improving with the advent of sensitive HPV DNA testing to improve the traditional Pap smear screening programmes.[2] Patients may present with vaginal bleeding, intermenstrual or postcoital bleeding or may be asymptomatic when cancer is detected early during screening. Late presentation with advanced disease and renal failure due to ureteric obstruction is occasionally seen but it is less frequent in countries with a screening program.

Microinvasive disease is usually managed by localized excision by laser loop excision, cold cautery or cone biopsy and followed up by regular colposcopy. Early stage organ-confined invasive disease is usually managed by radical surgery. Those with locally advanced disease are treated with chemoradiotherapy (external beam radiotherapy (EBRT) with concurrent cisplatin chemotherapy followed by intrauterine brachytherapy) as recommended by the American Society of Clinical Oncology, NCI, and European Society for Medical Oncology.[2,3] If para-aortic nodes are involved, the radiation field is extended.

Cervical cancer is often curable if detected early with 5-year survival rates of 92% in the United States. However, for locally advanced disease the recurrence rates are higher with 5-year survival rates of 56%. If there are distant metastases the 5-year survival rate drops to 17%.[4]

Recently the International Federation of Gynaecology and Obstetrics (FIGO) revised their cervix uteri cancer staging to include imaging and pathologic findings when assigning the stage.[5] A key change was the incorporation of nodal metastases into the staging system since this has a major impact on management and prognosis (Tables 1 and 2). This new FIGO staging system was validated in a retrospective United States SEER cohort, which reviewed cause-specific survival in 8909 patients with stage IB disease and 11,733 stage III patients and identified distinct characteristics and survival outcomes within the subdivisions of Stage IB and Stage III.[6] It showed an almost twofold increase in risk of cervical cancer mortality within the stage IB2 cohort (tumour > 4 cm) in comparison to stage IB1 (tumour < 4 cm) with an adjusted-hazard ratio of 1.98 (95% CI 1.62-2.41). Interestingly the stage III cohort had a diverse range of survival outcomes as women with stage IIIC1 (pelvic nodal disease) had superior cancer specific survival than those with stage IIIA-B disease (5-year survival rates of 46%, 42.6%, and 62.1% for stage IIIA, B, C1, respectively).

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Table 1 FIGO Staging of Cancer of the Cervix Uteri 2018[5]

Stage	Description
I	The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)
IA	Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion <5 mm
IA1	Measured stromal invasion <3 mm in depth
IA2	Measured stromal invasion ≥3 mm and <5 mm in depth
IB	Invasive carcinoma with measured deepest invasion ≥5 mm (greater than Stage IA, lesion limited to cervix uteri)
IB1	Invasive carcinoma ≥5 mm depth of stromal invasion, and <2 cm in greatest dimension
IB2	Invasive carcinoma ≥2 cm and <4 cm in greatest dimension
IB3	Invasive carcinoma ≥4 cm in greatest dimension
II	The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
IIA	Involvement limited to the upper two-thirds of the vagina without parametrial involvement
IIA1	Invasive carcinoma <4 cm in greatest dimension
IIA2	Invasive carcinoma ≥4 cm in greatest dimension
IIB	With parametrial involvement but not up to the pelvic wall
III	The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney and/or involves pelvic and/or paraaortic lymph nodes
IIIA	The carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney (unless known to be due to another cause)
IIIC	Involvement of pelvic and/or paraaortic lymph nodes, irrespective of tumour size and extent
IIIC1	Pelvic lymph node metastasis only
IIIC2	Para-aortic lymph node metastasis
IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. (A bullous oedema, as such, does not permit a case to be allotted to Stage IV)
IVA	Spread to adjacent pelvic organs
IVB	Spread to distant organs

However, survival within the stage IIIC1 cohort differed based on T-stage (5-years rates: 74.8% T1, 58.7% T2, 39.3% T3). This demonstrated a limitation of stage IIIC1, which did not account for inhomogeneity within the primary tumour in the presence of pelvic nodal metastasis. Information on the degree of lymph node metastasis ie, bulky vs microscopic in the stage IIIC1 group was unavailable, as was information on the presence or absence of para-aortic node metastasis (stage IIIC2).

Whilst prior versions of FIGO staging primarily utilized clinical examination to provide uniformity in staging in settings where imaging was not readily available, the new FIGO staging places increasing emphasis on the role of imaging.

Table 2 Changes in Cervical Cancer Staging System[6]

Characteristics	2014 FIGO System	2018 FIGO System
Stage IB1	Tumour size <4 cm	Tumour size <2 cm
Stage IB2	Tumour size >4 cm	Tumour size 2-3.9 cm
Stage IB3	n/a	Tumour size >4 cm
Stage IIIC1	n/a	Pelvic lymph node metastasis only
Stage IIIC2	n/a	Para-aortic lymph node metastasis

Imaging is important for accurate staging of invasive organ-confined, locally advanced, and metastatic disease and during relapse to direct appropriate management.

FDG-PET/CT imaging provides functional data about the glucose metabolism of the tumor, nodes, and metastases. It can be utilized at various time points of cervical cancer management including staging, response assessment, and restaging.

Staging

The appropriate management of cervical cancer is reliant on accurate staging to help determine the initial course of treatment (surgical vs. nonsurgical) and the patient's prognosis.

Primary tumour "T" staging in cervical cancer is predominantly carried out clinically and with pelvic MRI. The excellent soft tissue resolution of MRI allows for accurate assessment of tumour volume, tumour size, and extent of parametrial invasion.[7] Diffusion-weighted sequences are helpful in detection of smaller lesions that may not be visualized on standard sequences.[7]

Due to its limited spatial resolution, PET/CT does not play a role in characterization or T-staging of the primary cervical lesion, as it cannot accurately depict local spread such as parametrial extension and vaginal involvement. In addition, it cannot reliably differentiate between postcone biopsy inflammatory change and tumour.

Nodal staging is important as it impacts both prognosis and treatment planning. The role of FDG-PET/CT in staging in early stage disease which is typically treated with surgery is limited, since the prevalence of nodal disease in this group is low and, if present, it is often small volume micrometastases below the resolution of PET.[8] A prospective study of preoperative FDG-PET/CT in 159 patients demonstrated low sensitivity (32.1%) for detection of nodal disease in early stage (stage Ib1-IIa < 4 cm) cervical cancer.[9] Notably most nodal metastases were micrometastases with 34 out of the 61 metastatic nodes measuring <5 mm, hence below PET resolution.

In locally advanced cervical cancer (LACC), the diagnostic performance of FDG-PET/CT for nodal disease is superior to standard MRI and contrast-enhanced CT using size criteria.[10,11] Selman et al. reported for nodal status pooled positive likelihood ratios (and 95% CI) of 15.3 (7.9-29.6) for PET, 6.4

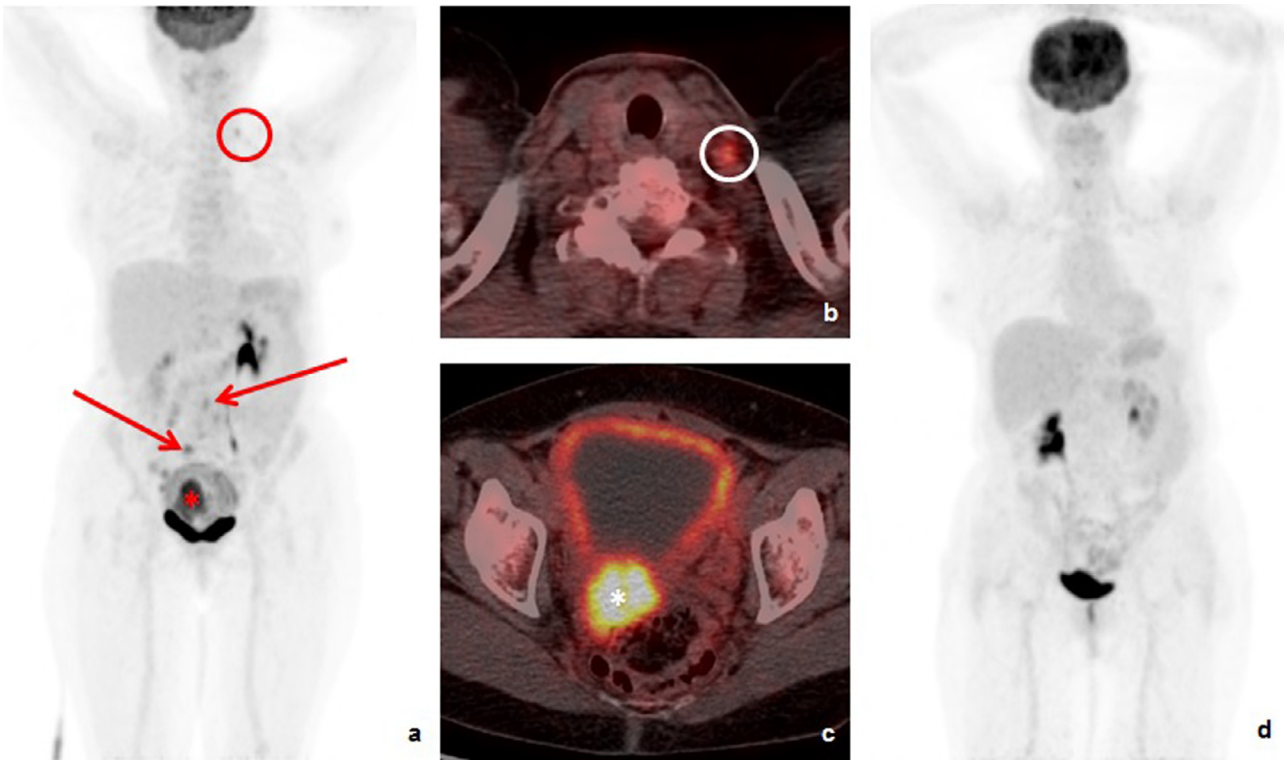

Figure 1 Cervical cancer staging: 64 year old with FIGO stage IIIb cervical carcinoma. Staging FDG PET/CT imaging (a-c) demonstrates the intensely avid primary cervical tumour (*) with a fluid-filled endometrial cavity and right hydronephrosis. There are moderately FDG avid small volume pelvic and para-aortic nodes (**arrows**) with a suspicious left supraclavicular node (**circle**) – stage IV disease. The para-aortic and supraclavicular nodal disease was not identified on CT or MRI. Biopsy of the supraclavicular node confirmed metastasis. The PET/CT changed the management plan and the patient was treated with chemoradiotherapy to include the aortic strip + brachytherapy. The repeat FDG-PET/CT 3 months after treatment (**d**) demonstrates complete metabolic response. The patient remains disease free 2 years following treatment.

(4.9-8.3) for MRI, and 4.3 (3.0-6.2) for CT with pooled negative likelihood ratios of 0.27 (0.11-0.66) for PET, 0.50 (0.39-0.64) for MRI, and 0.58 (0.48-0.70) for CT.[11]

A meta-analysis of 41 studies, total sample size of 4121 cases, assessing the diagnostic performance of FDG-PET/CT, MRI, and CT for the detection of metastatic lymph nodes showed PET had pooled sensitivity of 82% and specificity of 95% while CT had 50% and 92% and MRI 56% and 91%, respectively.[10] A more recent systematic review of the diagnostic performance of FDG-PET/CT for nodal staging included 27 studies, with total sample size of 8507 cases, with surgical pathology as the reference standard.[12] This demonstrated a pooled sensitivity of 72% and pooled specificity of 96% for PET/CT.

Para-aortic nodal disease detection is perhaps more important as it results in upstaging of the patient's disease and subsequent modification of treatment (extended field radiotherapy) (Fig. 1). The incidence of para-aortic nodal involvement increases with tumour "T" stage ranging from 5% in patients with stage I disease to 23% of those with stage III.[13]

A meta-analysis assessing the diagnostic performance of PET/CT in detection of para-aortic lymph node (PALN) metastasis in 10 studies with histology as the reference standard reported consistently high specificity (97%; 95% CI 93%-99%) but low and heterogeneous sensitivity (34%; 95% CI 10%-72%). However, subanalysis of studies with a higher prevalence of nodal disease (>15% prevalence) showed improved pooled sensitivity of 73% (95% CI, 53%-97%) and specificity of 93% (95% CI, 86%-97%).[14]

A recent multicenter prospective trial compared the diagnostic accuracy of combined FDG-PET/contrast-enhanced CT and contrast-enhanced CT alone with the reference standard of surgically removed lymph node pathology in 153 patients with LACC. It identified a borderline significant increase in sensitivity to detect lymph node metastasis in the abdomen with the addition of PET to CECT (50% vs. 42%), the specificity was comparable (85% vs. 89%).[15]

Given the suboptimal sensitivity of FDG-PET/CT for para-aortic nodal disease, there is debate regarding the best way to assess para-aortic nodes.[2] Some groups would advocate surgical PALN sampling especially if the pelvic nodes are PET positive and para-aortic PET negative. Others rely on PET and suggest if high pelvic nodes (common iliac) are PET positive and sampling is not performed, the radiotherapy field may be extended to the para-aortic chain.[16] A multicenter RCT assessed the impact of surgical PALN staging in patients with negative PET imaging of the para-aortic nodes.[17] Out of 237 patients, 12% had PALN involvement (12% false negative rate of PET). They reported the same survival rates in patients with PALN metastases ≤5 mm detected surgically and patients without PALN involvement.

The Lymphadenectomy in Locally Advanced Cervical Cancer (LiLACS) Study phase III clinical trial is recruiting patients with LACC and randomizing those with PET/CT positive pelvic nodes and negative para-aortic nodes into two treatment groups: whole pelvic chemoradiation therapy vs laparoscopic extraperitoneal para-aortic lymphadenectomy and tailored chemoradiation. Given the moderate sensitivity of PET/CT in previously published studies they are expecting to show a 9% benefit in overall survival at 3 years in patients that undergo lymphadenectomy and tailored chemoradiation.[18]

A recent retrospective single center study assessing the detection of distant metastatic disease by FDG-PET/CT at the time of staging in 1158 consecutive subjects reported 6.2% to have metastases with the lung being the most common site (35% cases) followed by omentum, bone, and liver.[19] A further study reported a prevalence of distant metastases of 13.7% in 153 cervical cancer patients with high specificity (97.7%) and positive predictive value (79.3%) of FDG-PET/CT for detecting distant metastases.[20]

The use of staging FDG-PET/CT for LACC has been shown to have a major impact in the initial management in approximately one-third of patients by altering treatment intent and/or radiotherapy planning.[21] A systematic review published in 2011 by Salem et al. analyzed 10 studies that addressed the role of PET/CT in planning for EBRT and found that 11%-19% of patients were upstaged following PET/CT with resultant modification radiotherapy treatment field.[22]

Several national and international guidelines recommend the use of FDG-PET/CT in the staging of locally advanced cervical cancer. The American National Comprehensive Cancer Network (NCCN) guidelines currently recommend PET/CT in FIGO (2014) stage IB2 and state that it is the preferred modality for staging FIGO stage II-IV.[23]

The Royal College of Radiologists UK recommends PET/CT in staging or restaging of patients being considered for exenterative surgery as well as those with locally advanced cervical cancer being considered for radical chemoradiotherapy.[24] PET/CT can also be utilized in response assessment for locally advanced cervical cancer after chemoradiotherapy.[24]

The European Society of Gynaecological Oncology (ESGO), European Society of Radiotherapy and Oncology (ESTRO) and European Society of Pathology (ESP) recommend use of PET/CT or chest/abdomen CT for assessment of nodal and distant disease in locally advanced cervical cancer.[25]

As recommended by these guidelines, imaging prior to radiotherapy planning is a mainstay in patient management. ESGO guidelines suggest the use of external beam radiotherapy to the level of the renal vessels in cases of pelvic nodal involvement indicating a high risk of para-aortic nodal involvement.[25] Image-guided brachytherapy requires good primary tumour spatial resolution and therefore utilizes MRI. However, as will be discussed later, PET/CT plays a key role in radiotherapy planning, especially with the development of new techniques to delineate metabolic tumour volume and reduce interobserver variability in identifying target volume boundaries.

Several interpretative pitfalls exist in FDG-PET/CT imaging of the pelvis which can lead to potential false positives and false negatives. Physiological FDG uptake within the ovaries and endometrium during menstruation and ovulation as well as within benign uterine fibroids or endometriotic cysts can mimic disease. Focal ureteric or bladder activity and physiological bowel activity can also be mistaken for pathologic uptake or lead to masking of serosal, peritoneal, or nodal disease. Some mucinous or necrotic tumours may show low-level FDG uptake and therefore can be less readily detected. Small lymph nodes or small volume peritoneal deposits may be below the resolution of PET/CT and therefore not identified as FDG avid.[26]

Baseline PET-Derived Prognostic Factors

A number of FDG-PET-derived baseline prognostic factors have been reported to predict tumour response to therapy, the risk of nodal disease, and overall survival. These include tumour SUV_{max}, metabolic tumour volume (MTV) and total lesion glycolysis (TLG).

Several studies have demonstrated that SUV_{max} of the primary tumour at baseline can predict outcome. The largest retrospective study of 287 patients with stage IA2-IVB disease established three prognostic groups based on SUV_{max} with 5-year overall survival rates of 95% for $SUV_{max} \leq 5.2$, 70% for SUV_{max} between 5.2 and 13.3 and 44% for $SUV_{max} > 13.3$. In multivariate analysis of histology, nodal status, tumour volume, and tumour SUV_{max}, SUV_{max} was the only significant independent predictor.[27] A further study by Onal et al. of 149 patients demonstrated a significantly lower baseline tumour SUV_{max} in patients achieving complete remission compared to those with partial response or progressive disease, SUV_{max} 15.6 vs SUV_{max} 28.0 respectively. It also identified a 4-year actuarial overall survival and disease-free survival for $SUV_{max} < 15.6$ to be 85% compared to 34% for $SUV_{max} > 15.6$.[28]

However, other studies have demonstrated that SUV_{max} is a poor independent predictor of disease progression, recurrence, and overall survival. A study of 53 patients with FIGO stage IB1 to IVA with FDG-PET/CT prior to treatment demonstrated no significant correlation between tumour SUV_{max} and FIGO stage with an area under curve of 0.67 for SUV_{max} in predicting recurrence or progression. The optimal SUV_{max} cut off was determined to be 16.0, however, this did not significantly predict progression or recurrence-free survival.[29] SUV_{max} suffers from several limiting factors including, the limitation of representing the highest metabolic voxel but not the metabolic activity of the entire tumour. It is reliant on technical factors including the type of scanner, reconstruction algorithm, and biological factors like weight and blood glucose level. More recent studies have suggested reviewing serial SUV_{max} values during and following treatment to predict response to therapy.[30]

In addition, assessment of the whole tumour volume may be more valuable than SUV_{max} alone. Volume-based FDG-PET/CT parameters such as MTV and TLG have been shown to be of prognostic value in a number of studies. A recent systematic review and meta-analysis of 12 studies including 660 patients that evaluated pretreatment MTV or TLG as a

prognostic factor reported that high baseline MTV and TLG were predictive of higher risk of adverse events or death.[31]

Lymph node status on FDG-PET has also been shown to predict disease recurrence and survival outcomes. A prospective cohort study of 560 patients with pretreatment FDG-PET/CT staging demonstrated that patients with PET-positive lymph nodes had significantly worse disease-specific survival compared to those with PET-negative nodes. The hazard ratios for disease recurrence increased incrementally based on the most distant level of PET positive nodal disease: pelvic 2.40 (95%CI, 1.65-3.52), para-aortic 5.88 (95%CI, 3.80-9.09), and supraclavicular 30.27 (95%CI 16.56-55.34).[32]

It has also been documented that the level of metabolic activity (SUV_{max}) within nodes correlates with outcome. Onal et al. reported that patients with highly avid pelvic nodes (SUV_{max} >7.5) had a higher risk of disease recurrence and worse OS and a nonsignificant trend for a higher risk of failure within boosted nodes.[28] Ramlov et al. showed a significant correlation between nodal SUV max and failure in boosted nodes.[33] Nodal SUV_{max} was a stronger negative prognostic factor for nodal failure than size or volume of nodes. This suggests that dose escalation or surgical removal of nodes may be relevant in patients with high nodal SUV_{max}.

A retrospective study published in 2013 reviewed the pretreatment PET/CT in 58 cases of FIGO stage IIB-IVB cervical cancer who underwent chemoradiotherapy. It reviewed baseline first order textural features on initial PET/CT imaging and follow up of patients with their clinical examination findings and imaging post treatment. It identified advanced FIGO stage and presence of PALN avidity on PET/CT to be independent predictors of persistent disease and decreased overall survival post treatment.[34]

Multiple textural analysis features have been assessed on recent studies including those looking at metabolic tumour volume, total lesion glycolysis, and tumour heterogeneity. This is discussed further in future directions.

Response Assessment

Therapy response assessment helps alter and adapt a patient's management plan and tailor treatment to tumour behavior. In patients with locally advanced cervical cancer the typical regime consists of 5 weeks of EBRT with concurrent cisplatin chemoradiotherapy followed by intracavitary brachytherapy. MRI is now recommended for image-guided adaptive brachytherapy enabling dose optimization and/or dose escalation leading to superior local control rates (>90%) particularly for large tumours, lower toxicity rates, and an approximately 10% increase in survival.[35] The use of PET for radiotherapy planning is covered in a later chapter.

FDG -PET/CT response, usually 3 months post completion of CRT has been shown by a number of groups to be a surrogate biomarker of response and prognosis (Fig. 1). The Mallinkrodt group reported in an initial retrospective series and then in a subsequent prospective cohort that visual analysis of the PET data into three categories (complete metabolic response (CMR), partial metabolic response (PMR), and progressive disease (PD)) predicts survival.[36,37] The 3-year PFS rate was 78% for CMR, 33% for PMR, and 0% for PD.[36] A further study by the same group assessing the ability of post-therapy PET to predict patterns of failure following radiotherapy in 238 patients with LACC reported that although the CMR group had a lower failure rate, 23% of patients in this group subsequently relapsed.[38] In addition, the PMR group had a high false positive rate as only 26 out of 40 patients considered to have PMR on PET had biopsy proven disease. In summary, post CRT PET has higher NPV than PPV. Other studies have reported significantly higher OS rates in the CMR group compared to PMR/PD group.[39,40] However, recurrence still occurred in the CMR group in 21%-23% cases with baseline tumour size, a predictive factor for tumour recurrence in the CMR group.

More recently, a 5-point qualitative visual response assessment scoring system on 3-months post-therapy FDG-PET/CT ((1) No residual FDG uptake consistent with CMR, (2) focal uptake less than mediastinal blood pool activity, (3) focal uptake greater than mediastinal blood pool, but less than liver activity classified as indeterminate (ID). (4) Focal uptake greater than liver activity consistent with PMR. (5) Focal, intense uptake greater than twice background hepatic activity or new foci not present on baseline imaging PD has been shown to predict PFS and OS.[41]

A further study assessed the prognostic value of the 3-month post-CRT FDG-PET/CT using the European Organization for Research and Treatment of Cancer criteria which uses changes in SUV_{max} to designate responders and nonresponders.[42] Their results showed FDG-PET/CT response using the European Organization for Research and Treatment of Cancer criteria reliably predicts OS.

Several guidelines, including NCCN, suggest that PET/CT can be performed 3-6 months postcompletion of treatment in FIGO stage IB2 patients or in those with high risk factors requiring adjuvant chemoradiation (Fig. 2). PET/CT is the preferred method of surveillance in FIGO stage II-IV disease and should be performed within 3-6 months of completion of therapy.[5] The European Society of Medical Oncology recommended CT or PET/CT imaging to be carried out as clinically indicated, with a clinical follow-up schedule that involves review every 3-6 months for the first 2 years followed by 6-12 months for year 3-5.[2]

MRI can be performed 3-6 months postcompletion of therapy to assess for residual signal changes and abnormalities.[43] Interpretation with standard MRI sequences can be difficult due to presence of post-therapy inflammation or scarring,[44] although the addition of diffusion-weighted imaging in this scenario may help.[45]

The use of PET/CT early during CRT treatment, typically prior to brachytherapy, is not routine but has been explored. As mentioned, MRI is the modality of choice for brachytherapy planning but PET at this time point could be prognostic and delineate disease (tumour and nodes) for improved target dose. Bjurberg et al. assessed FDG-PET/CT at baseline, third week of treatment, and at 3 months after the completion of treatment in 32 patients with LACC. Visual CMR at 3 weeks during treatment occurred in 7 patients, who did not

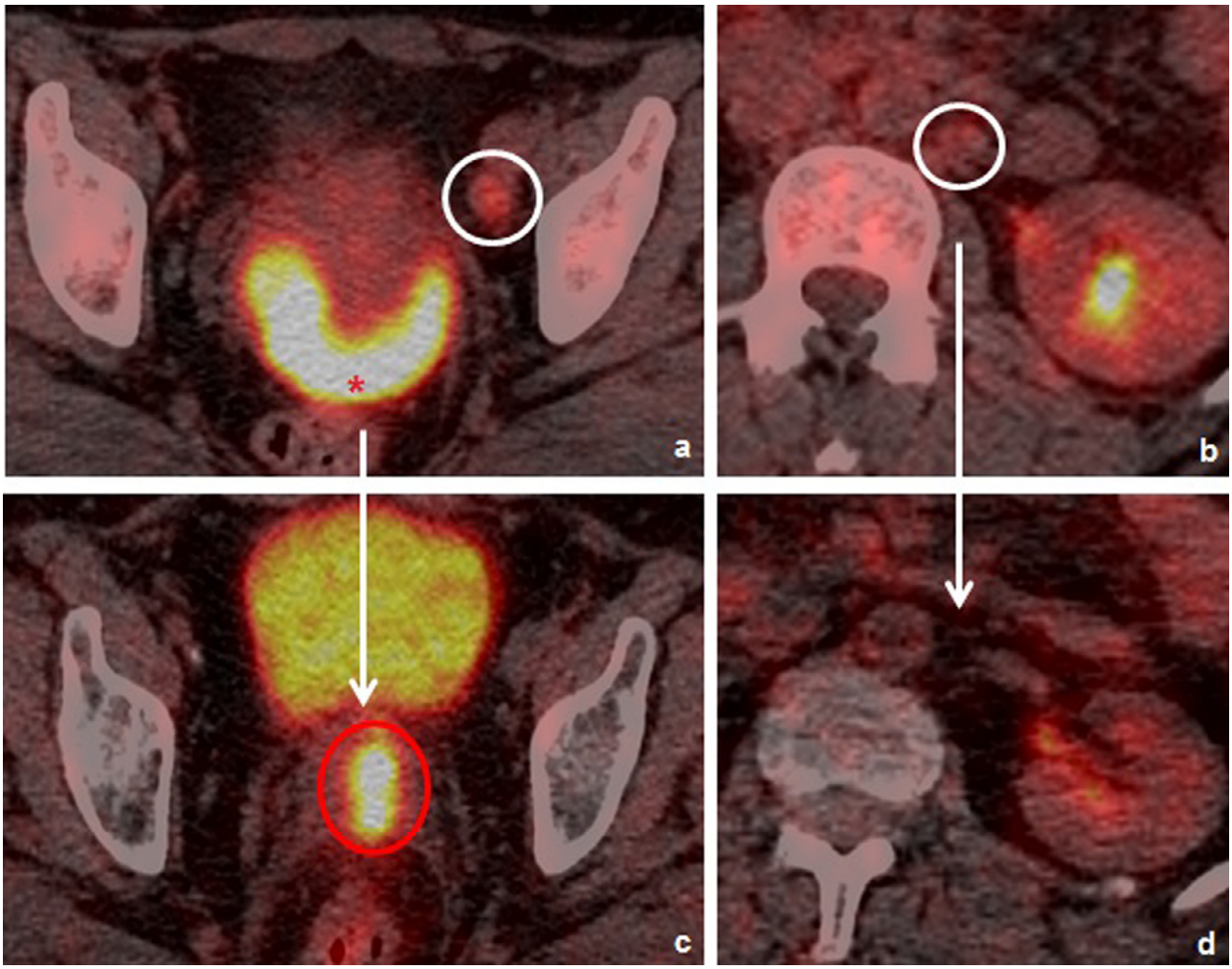

Figure 2 Recurrence post chemoradiotherapy – for consideration of exenteration: 52-year-old (stage IIa) T2 N1 M1 cervical carcinoma (*) with suspicious pelvic and para-aortic nodes (**white circles**) on staging FDG PET/CT (a,b). The patient underwent chemoradiotherapy including the pelvic and aortic strip + brachytherapy and the 3 month follow-up MRI study (not shown) demonstrated only a small volume of residual signal abnormality within the cervix. A subsequent FDG PET/CT performed 6 months following treatment (c,d) demonstrates local recurrence within the cervix (**red circle**) but resolution of the pelvic and para-aortic nodal disease with no evidence of metastases. The patient underwent subsequent pelvic exenteration.

demonstrate relapse (mean 28-months follow-up). However, the outcome of those with PMR or stable disease could not be accurately predicted.[46]

Kidd et al. performed baseline, 2-week and 4-week PET/CT imaging in patients with LACC and reported that tumour SUV_{max} and tumour heterogeneity at week 4 were significantly associated with post-treatment PET response and a better predictor than the 2-week scan.[30]

Yoon et al. assessed the use of FDG-PET/CT immediately post-nodal radiotherapy (median 63 Gy to gross nodes) in 48 patients with FDG avid nodal disease at baseline.[47] The disease-free survival for patients with nodal CMR was significantly better than those with non-CMR (71% vs 18% respectively; $P < 0.001$).

Overall, whilst patients who achieve CMR early during CRT carry an excellent prognosis, the PPV of patients with PMR/SD on early PET is unreliable and thus the utility of early PET imaging during therapy for response prediction is limited (Table 3).

Relapse/Pre-exenteration

Disease recurrence within 2 years is high with approximately one-third of patients with LACC developing recurrence at least 6 months after regression of treated disease[48] (Fig. 3). Despite some improvement in overall survival and progression-free survival with the addition of concurrent chemotherapy to radiotherapy, the 5-year OS rates for stage II, III, and IV are 64%, 40%, and 15%, respectively.[49]

Survival rates following recurrence of cervical cancer are low and the secondary cure efficacy is minimal. Improved survival and outcomes require early detection of recurrence and the localization of sites of disease.

As with initial staging imaging, MRI and CT imaging in the post-therapy setting can be limited in identifying lymph node metastases and extra pelvic metastases. Therapy related scarring or inflammation can also be difficult to differentiate from disease.

Table 3 FDG-PET/CT Biomarkers in Cervical Cancer Response Assessment

Time Point	FDG-PET/CT Response Predictors
Baseline	• PET nodal status is prognostic of DFS, OS and disease recurrence[32] • Baseline SUV_{max} predicts OS and outcome[27,28,30] • Nodal SUV_{max} [28,33] • Baseline MTV, TLG predicts DFS, PFS and OS[31] • Textural features[54,56-58]
Response assessment early during CRT	• Early FDG-PET/CT during CRT can identify a subgroup with CMR who have an excellent prognosis[30,47]
End of treatment (3 mo post CRT)	• CMR at 3 mo is an indicator of good overall survival[36,37] • Metabolic response[38,47]

CMR, complete metabolic response; CRT, chemoradiotherapy; DFS, disease free survival; MTV, metabolic tumour volume; OS, overall survival; SUV_{max}, maximum standardized uptake value; TLG, total lesion glycolysis.

There is no definitive evidence to support the routine use of FDG-PET/CT in follow-up of patients postcervical cancer treatment. PET/CT has a role in cases of suspected recurrence where MRI or CT imaging is equivocal, as suggested by the Royal College of Radiologists guidelines[24] and in cases of local vaginal recurrence seen on CT or MRI as per the Cancer Care Ontario guidelines.[50] Updated NCCN guidelines, however state PET/CT as the preferred modality for surveillance imaging in stage II-IV disease and recommend consideration of PET/CT in suspected recurrence or metastasis.[23] A prospective study of 40 patients with recurrent cervical carcinoma who underwent restaging PET/CT identified significant superiority of PET/CT imaging compared to CT/MRI in detection of metastatic lesions (sensitivity 92% vs. 60%).[51] 55% of patients underwent changes to their management plan following PET/CT.

A systematic review and meta-analysis by Chu et al. confirmed the diagnostic value of PET and PET/CT imaging with pooled sensitivity and specificity of 0.87 and 0.97, respectively in detecting distant metastasis in recurrent cervical cancer. Pooled sensitivity and specificity for local regional recurrence was 0.82 and 0.98 for PET and PET/CT

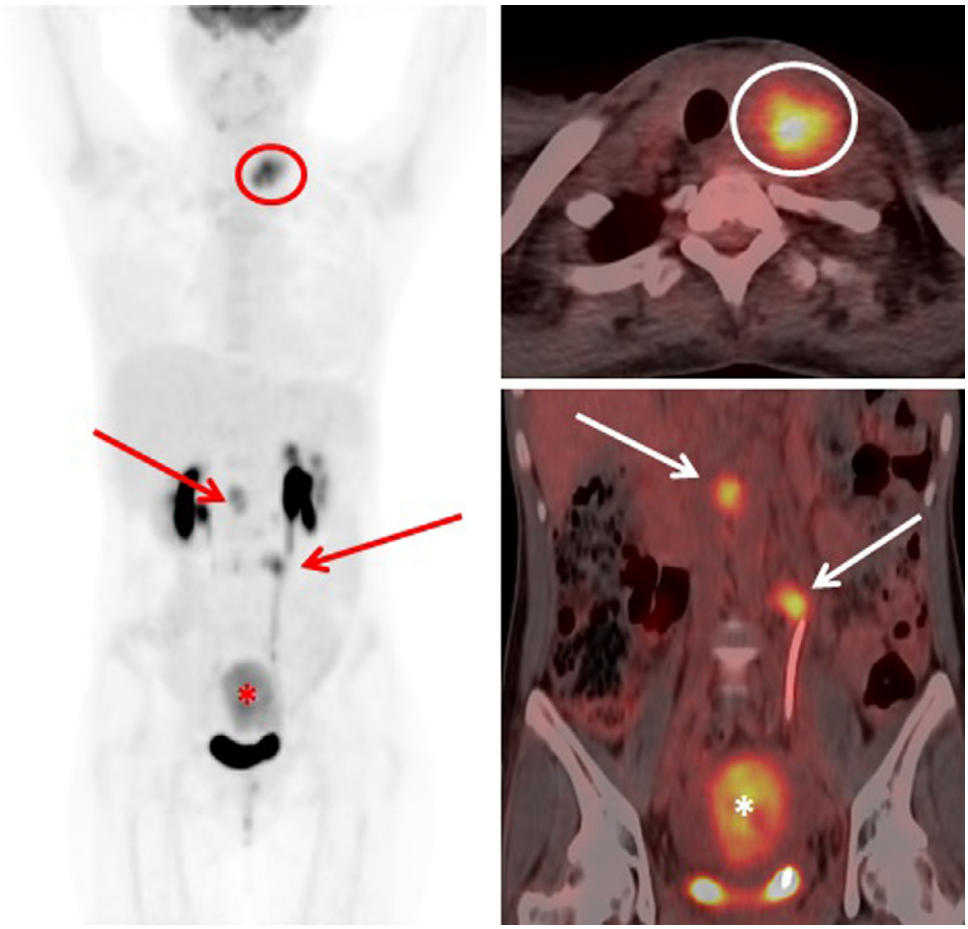

Figure 3 Recurrence post chemotherapy: 40 year old with previous locally advanced cervical cancer, treated with chemoradiotherapy, presented 1-year post treatment with new palpable left supraclavicular nodes. An FDG PET/CT performed for restaging confirms intensely metabolically active left supraclavicular nodal disease (**circle**) but in addition new local recurrence at the cervix (*) with multiple avid retroperitoneal and pelvic nodes (**arrows**). FDG PET/CT can be utilized in re-staging/recurrence imaging to assess extent of disease to help guide subsequent treatment options in cases when surgery would be futile.

respectively. This study also confirmed the diagnostic superiority of PET/CT compared to PET alone.[52]

In the context of recurrent cervical cancer detected on follow-up MRI or CT in patients who may benefit from salvage therapy in the form of pelvic exenteration, a PET/CT may help identify presence of distant disease that would make extensive pelvic surgery futile[43] (Fig. 4). This is confirmed by the ESGO/ESTRO/ESP guidelines.[25]

Future Directions

Whilst various PET-derived parameters have been shown to be prognostic in cervical cancer at baseline, during and post-therapy (Table 3), we may be able to derive more detailed individual prognostic data from PET images, perhaps in combination with MRI. Biomarkers and textural/functional parameters derived from this imaging are being demonstrated to play a key role in understanding tumour aggressiveness and predicting outcome with the goal of precision medicine to ultimately improve outcomes.

Radiomics is the use of quantitative measures and features derived from medical images to help stage, plan management, and assess response in malignant disease.[53]

Yang et al. in a pilot study of 20 LACC patients with pre-treatment, 2 and 4-week treatment and 12-week post-treatment FDG-PET/CT studies demonstrated that reduction in regional features of heterogeneity, rather than baseline

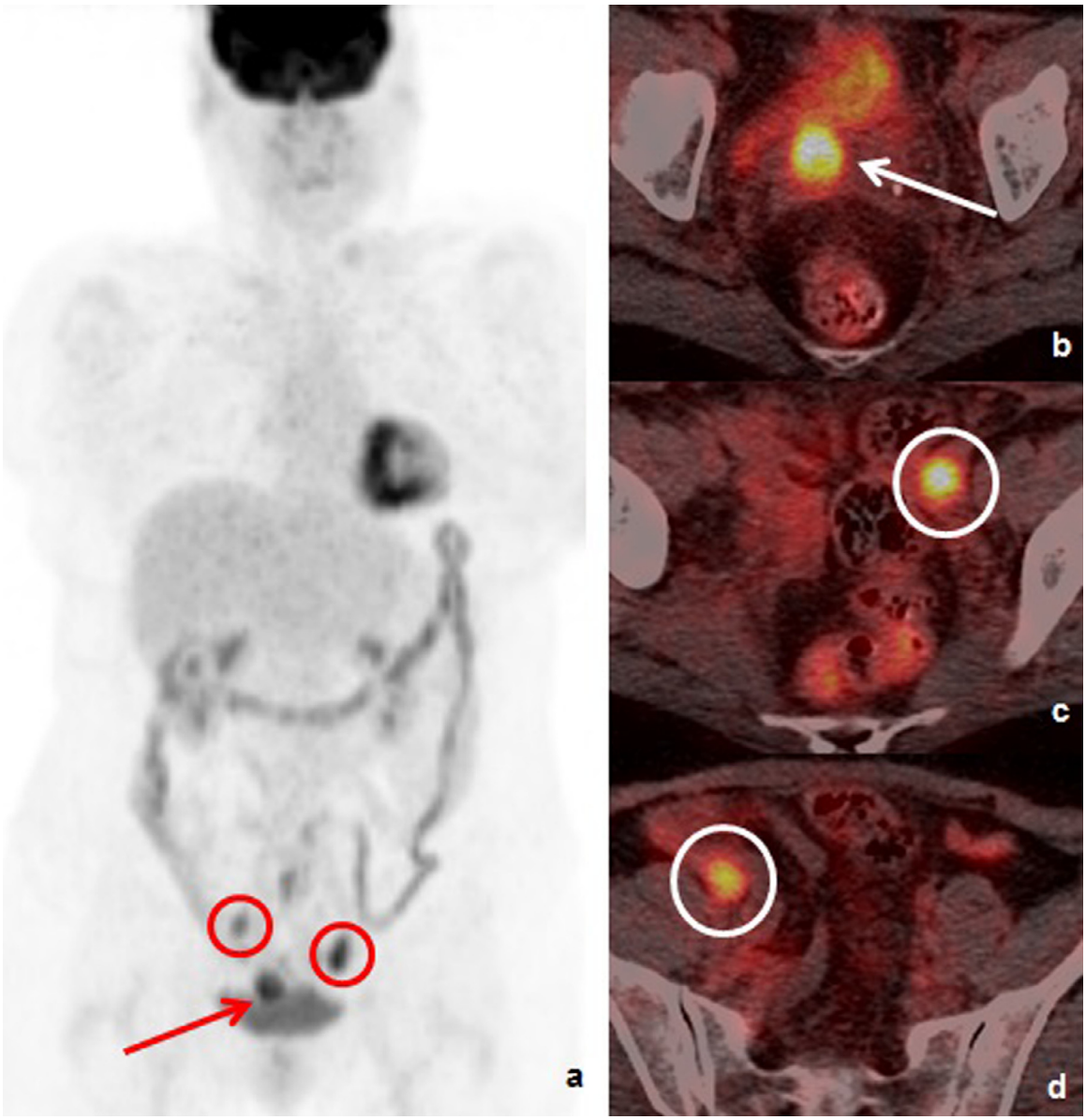

Figure 4 Pre-exenteration imaging: 55 year old with stage Ib1 cervical carcinoma treated with radiotherapy followed by TAH and BSO. Follow-up MRI imaging (not shown) demonstrated bulky vaginal vault recurrence. An FDG PET/CT was performed to re-stage disease and assess if suitable for exenteration. The vaginal vault recurrence (**arrow**) is demonstrated with bilateral pelvic lymph nodes (**circles**). The disease was limited to the pelvis and therefore a pelvic exenteration was performed.

features, were predictive of CMR.[54] Tsujikawa et al. reported FDG-PET-derived textural features might reflect differences in histologic architecture between cervical cancer subtypes.[55]

Kung-Chu et al. assessed intratumoral metabolic heterogeneity in 44 patients with <4-cm cervical tumours treated with CRT. By combining TLG and a textural feature assessing lesion uniformity, they were able to divide patients into high risk and low risk groups with a 5-year OS of 42% in the high risk group and 81% in the low risk group, $P = 0.001$.[56]

More recently, a study by Lucia et al. of 102 patients (69 training and 33 testing) with LACC assessed if radiomics features on FDG-PET/CT and diffusion-weighted imaging-MRI could predict prognosis.[57] Two textural features, $GLNU_{GLRLM}$ extracted from FDG-PET and $Entropy_{GLCM}$ from ADC maps derived from diffusion-weighted imaging MRI were powerful predictors of efficacy of CRT in LACC with higher accuracy than standard post-treatment metabolic response assessment.[57] They have subsequently validated these radiomics features in two external validation cohorts.[58] They proposed identification of high risk patients at diagnosis could permit tailored therapy strategies such as higher doses of radiation boost, consolidation chemotherapy, and /or hysterectomy. The proposed management of patients based on the radiomics models will be further assessed in prospective multicenter trials.

Advances in PET technology with digital PET scanners which have superior spatial resolution may improve the diagnostic performance of PET/CT for detecting small volume nodal disease and metastases.

Future developments of new PET/CT tracers and the role of PET/MRI in cervical cancer are further discussed in subsequent chapters. ADC = apparent diffusion coefficient; NCI = National Cancer Institute; SUV = standardized uptake value; NPV = negative predictive value; PPV = positive predictive value; TAH = total abdominal hysterectomy; BSO = bilateral salpingo-oopherectomy.

Summary

FDG-PET/CT has an established role in the staging and therapy planning of LACC particularly for the assessment of nodal disease and distant metastases.

FDG-PET/CT is increasingly used 3-months post CRT for response assessment and prognosis and also routinely used prior to pelvic exenteration.

The rapidly evolving field of radiomics offers future potential to subselect patients with poor prognostic features for a more personalized therapeutic approach with the ultimate goal of improving outcomes.

References

1. Bray F, Ferlay J, Soerjomataram I, et al: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68:394-424, 2018
2. Marth C, Landoni F, Mahner S, et al: Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol Off J Eur Soc Med Oncol 28:iv72-iv83, 2017
3. Chuang LT, Temin S, Camacho R, et al: Management and care of women with invasive cervical cancer: American Society of Clinical Oncology Resource-Stratified Clinical Practice Guideline. J Glob Oncol 2:311-340, 2016
4. https://www.cancer.net/cancer-types/cervical-cancer/statistics.
5. Bhatla N, Aoki D, Sharma DN, et al: Cancer of the cervix uteri. Int J Gynaecol Obstet 143(suppl):22-36, 2018
6. Matsuo K, Machida H, Mandelbaum RS, et al: Validation of the 2018 FIGO cervical cancer staging system. Gynecol Oncol 152:87-93, 2019
7. Khan SR, Rockall AG, Barwick TD: Molecular imaging in cervical cancer. Q J Nucl Med Mol Imaging 60:77-92, 2016
8. Nogami Y, Banno K, Irie H, et al: The efficacy of preoperative positron emission tomography-computed tomography (PET-CT) for detection of lymph node metastasis in cervical and endometrial cancer: Clinical and pathological factors influencing it. Jpn J Clin Oncol 45:26-34, 2015
9. Signorelli M, Guerra L, Montanelli L, et al: Preoperative staging of cervical cancer: Is 18-FDG-PET/CT really effective in patients with early stage disease? Gynecol Oncol 123:236-240, 2011
10. Choi HJ, Ju W, Myung SK, et al: Diagnostic performance of computer tomography, magnetic resonance imaging, and positron emission tomography or positron emission tomography/computer tomography for detection of metastatic lymph nodes in patients with cervical cancer: Meta-analysis. Cancer Sci 101:1471-1479, 2010
11. Selman TJ, Mann C, Zamora J, et al: Diagnostic accuracy of tests for lymph node status in primary cervical cancer: A systematic review and meta-analysis. CMAJ 178:855-862, 2008
12. Ruan J, Zhang Y, Ren H: Meta-analysis of PET/CT detect lymph nodes metastases of cervical cancer. Open Med 13:436-442, 2018
13. Berman ML, Keys H, Creasman W, et al: Survival and patterns of recurrence in cervical cancer metastatic to periaortic lymph nodes (a Gynecologic Oncology Group study). Gynecol Oncol 19:8-16, 1984
14. Kang S, Kim SK, Chung DC, et al: Diagnostic value of (18)F-FDG PET for evaluation of paraaortic nodal metastasis in patients with cervical carcinoma: A meta-analysis. J Nucl Med 51:360-367, 2010
15. Atri M, Zhang Z, Dehdashti F, et al: Utility of PET-CT to evaluate retroperitoneal lymph node metastasis in advanced cervical cancer: Results of ACRIN6671/GOG0233 trial. Gynecol Oncol 142:413-419, 2016
16. Vargo JA, Kim H, Choi S, et al: Extended field intensity modulated radiation therapy with concomitant boost for lymph node-positive cervical cancer: Analysis of regional control and recurrence patterns in the positron emission tomography/computed tomography era. Int J Radiat Oncol Biol Phys 90:1091-1098, 2014
17. Gouy S, Morice P, Narducci F, et al: Prospective multicenter study evaluating the survival of patients with locally advanced cervical cancer undergoing laparoscopic para-aortic lymphadenectomy before chemoradiotherapy in the era of positron emission tomography imaging. J Clin Oncol 31:3026-3033, 2013
18. Frumovitz M, Querleu D, Gil-Moreno A, et al: Lymphadenectomy in locally advanced cervical cancer study (LiLACS): Phase III clinical trial comparing surgical with radiologic staging in patients with stages IB2-IVA cervical cancer. J Minim Invasive Gynecol 21:3-8, 2014
19. Lin A, Ma S, Dehdashti F, et al: Detection of distant metastatic disease by positron emission tomography with (18)F-fluorodeoxyglucose (FDG-PET) at initial staging of cervical carcinoma. Int J Gynecol Cancer 29:487-491, 2019
20. Gee MS, Atri M, Bandos AI, et al: Identification of distant metastatic disease in uterine cervical and endometrial cancers with FDG PET/CT: Analysis from the ACRIN 6671/GOG 0233 Multicenter Trial. Radiology 287:176-184, 2018
21. Fleming S, Cooper RA, Swift SE, et al: Clinical impact of FDG PET-CT on the management of patients with locally advanced cervical carcinoma. Clin Radiol 69:1235-1243, 2014
22. Salem A, Salem AF, Al-Ibraheem A, et al: Evidence for the use PET for radiation therapy planning in patients with cervical cancer: A systematic review. Hematol Oncol Stem Cell Ther 4:173-181, 2011
23. Koh WJ, Abu-Rustum NR, Bean S, et al: Cervical cancer, Version 3.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Cancer Netw 17:64-84, 2019
24. Evidence-based indications for the use of PET-CT in the United Kingdom 2016. Clin Radiol 71:e171-e188, 2016

25. Cibula D, Potter R, Planchamp F, et al: The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology Guidelines for the Management of Patients With Cervical Cancer. Int J Gynecol Cancer 28:641-655, 2018
26. Lakhani A, Khan SR, Bharwani N, et al: FDG PET/CT pitfalls in gynecologic and genitourinary oncologic imaging. Radiographics 37:577-594, 2017
27. Kidd EA, Siegel BA, Dehdashti F, et al: The standardized uptake value for F-18 fluorodeoxyglucose is a sensitive predictive biomarker for cervical cancer treatment response and survival. Cancer 110:1738-1744, 2007
28. Onal C, Guler OC, Reyhan M, et al: Prognostic value of 18F-fluorodeoxyglucose uptake in pelvic lymph nodes in patients with cervical cancer treated with definitive chemoradiotherapy. Gynecol Oncol 137:40-46, 2015
29. Bollineni VR, Ytre-Hauge S, Gulati A, et al: The prognostic value of preoperative FDG-PET/CT metabolic parameters in cervical cancer patients. Eur J Hybrid Imaging 2:24, 2018
30. Kidd EA, Thomas M, Siegel BA, et al: Changes in cervical cancer FDG uptake during chemoradiation and association with response. Int J Radiat Oncol Biol Phys 85:116-122, 2013
31. Han S, Kim H, Kim YJ, et al: Prognostic value of volume-based metabolic parameters of 18F-FDG PET/CT in uterine cervical cancer: A systematic review and meta-analysis. Am J Roentgenol 211:1112-1121, 2018
32. Kidd EA, Siegel BA, Dehdashti F, et al: Lymph node staging by positron emission tomography in cervical cancer: Relationship to prognosis. J Clin Oncol 28:2108-2113, 2010
33. Ramlov A, Kroon PS, Jurgenliemk-Schulz IM, et al: Impact of radiation dose and standardized uptake value of (18)FDG PET on nodal control in locally advanced cervical cancer. Acta Oncol 54:1567-1573, 2015
34. Akkas BE, Demirel BB, Dizman A, et al: Do clinical characteristics and metabolic markers detected on positron emission tomography/computerized tomography associate with persistent disease in patients with inoperable cervical cancer? Ann Nucl Med 27:756-763, 2013
35. Potter R, Georg P, Dimopoulos JCA, et al: Clinical outcome of protocol based image (MRI) guided adaptive brachytherapy combined with 3D conformal radiotherapy with or without chemotherapy in patients with locally advanced cervical cancer. Radiother Oncol 100:116-123, 2011
36. Schwarz JK, Siegel BA, Dehdashti F, et al: Association of posttherapy positron emission tomography with tumor response and survival in cervical carcinoma. JAMA 298:2289-2295, 2007
37. Grigsby PW, Siegel BA, Dehdashti F, et al: Posttherapy [18F] fluorodeoxyglucose positron emission tomography in carcinoma of the cervix: Response and outcome. J Clin Oncol 22:2167-2171, 2004
38. Schwarz JK, Siegel BA, Dehdashti F, et al: Metabolic response on posttherapy FDG-PET predicts patterns of failure after radiotherapy for cervical cancer. Int J Radiat Oncol Biol Phys 83:185-190, 2012
39. Onal C, Reyhan M, Guler OC, et al: Treatment outcomes of patients with cervical cancer with complete metabolic responses after definitive chemoradiotherapy. Eur J Nucl Med Mol Imaging 41:1336-1342, 2014
40. Beriwal S, Kannan N, Sukumvanich P, et al: Complete metabolic response after definitive radiation therapy for cervical cancer: Patterns and factors predicting for recurrence. Gynecol Oncol 127:303-306, 2012
41. Scarsbrook A, Vaidyanathan S, Chowdhury F, et al: Efficacy of qualitative response assessment interpretation criteria at 18F-FDG PET-CT for predicting outcome in locally advanced cervical carcinoma treated with chemoradiotherapy. Eur J Nucl Med Mol Imaging 44:581-588, 2017
42. Lima GM, Matti A, Vara G, et al: Prognostic value of posttreatment (18)F-FDG PET/CT and predictors of metabolic response to therapy in patients with locally advanced cervical cancer treated with concomitant chemoradiation therapy: An analysis of intensity- and volume-based PET parameters. Eur J Nucl Med Mol Imaging 45:2139-2146, 2018
43. Papadopoulou I, Rockall AG, Taylor A, et al: Functional imaging for measuring the response to treatment. In: Ayhan A (ed): Textbook of Gynaecological Oncology, Turkey: Gunes Publishing, 143-157, 2016
44. Vincens E, Balleyguier C, Rey A, et al: Accuracy of magnetic resonance imaging in predicting residual disease in patients treated for stage IB2/II cervical carcinoma with chemoradiation therapy : Correlation of radiologic findings with surgicopathologic results. Cancer 113:2158-2165, 2008
45. Schreuder SM, Lensing R, Stoker J, et al: Monitoring treatment response in patients undergoing chemoradiotherapy for locally advanced uterine cervical cancer by additional diffusion-weighted imaging: A systematic review. J Magn Reson Imaging 42:572-594, 2015
46. Bjurberg M, Kjellen E, Ohlsson T, et al: Prediction of patient outcome with 2-deoxy-2-[18F]fluoro-D-glucose-positron emission tomography early during radiotherapy for locally advanced cervical cancer. Int J Gynecol Cancer 19:1600-1605, 2009
47. Yoon MS, Ahn SJ, Nah BS, et al: Metabolic response of lymph nodes immediately after RT is related with survival outcome of patients with pelvic node-positive cervical cancer using consecutive [18F]fluorodeoxyglucose-positron emission tomography/computed tomography. Int J Radiat Oncol Biol Phys 84:e491-e497, 2012
48. Heron CW, Husband JE, Williams MP, et al: The value of CT in the diagnosis of recurrent carcinoma of the cervix. Clin Radiol 39:496-501, 1988
49. Green JA, Kirwan JM, Tierney JF, et al: Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: A systematic review and meta-analysis. Lancet 358:781-786, 2001
50. Milosevic M, Murphy J, Elit L, et al.: Cancer Care Ontario: Cervical cancer disease pathway management. 2018.
51. Lai CH, Huang KG, See LC, et al: Restaging of recurrent cervical carcinoma with dual-phase [18F]fluoro-2-deoxy-D-glucose positron emission tomography. Cancer 100:544-552, 2004
52. Chu Y, Zheng A, Wang F, et al: Diagnostic value of 18F-FDG-PET or PET-CT in recurrent cervical cancer: A systematic review and meta-analysis. Nucl Med Commun 35:144-150, 2014
53. Lambin P, Rios-Velazquez E, Leijenaar R, et al: Radiomics: Extracting more information from medical images using advanced feature analysis. Eur J Cancer 48:441-446, 2012
54. Yang F, Thomas MA, Dehdashti F, et al: Temporal analysis of intratumoral metabolic heterogeneity characterized by textural features in cervical cancer. Eur J Nucl Med Mol Imaging 40:716-727, 2013
55. Tsujikawa T, Rahman T, Yamamoto M, et al: (18)F-FDG PET radiomics approaches: Comparing and clustering features in cervical cancer. Ann Nucl Med 31:678-685, 2017
56. Ho KC, Fang YHD, Chung HW, et al: A preliminary investigation into textural features of intratumoral metabolic heterogeneity in (18)F-FDG PET for overall survival prognosis in patients with bulky cervical cancer treated with definitive concurrent chemoradiotherapy. Am J Nucl Med Mol Imaging 6:166-175, 2016
57. Lucia F, Visvikis D, Desseroit MC, et al: Prediction of outcome using pretreatment (18)F-FDG PET/CT and MRI radiomics in locally advanced cervical cancer treated with chemoradiotherapy. Eur J Nucl Med Mol Imaging 45:768-786, 2018
58. Lucia F, Visvikis D, Vallieres M, et al: External validation of a combined PET and MRI radiomics model for prediction of recurrence in cervical cancer patients treated with chemoradiotherapy. Eur J Nucl Med Mol Imaging 2018. https://doi.org/10.1007/s00259-018-4231-9