The role of FDG PETCT in cervical cancer

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Introduction
Cervical cancer is the third most common cancer to affect women worldwide. In 2008, 2,938 women were diagnosed with cervical cancer in the UK. It is the 12th most common malignancy in women, accounting for around 2% of all female cancers but it is the most common in women under 35 years old.

With the introduction of cervical screening and, more recently, human papilloma virus (HPV) vaccination, the incidence of cervical cancer and the mortality from invasive cervical carcinoma has continued to decrease in the UK, but it remains a significant cause of morbidity and mortality in the developing world. Traditionally, cervical cancer is staged clinically using the internationally accepted Fédération Internationale de Gynécologie et d’Obstétrique (FIGO) classification. This clinical staging system is known to be limited, particularly in the assessment of locally invasive disease and, furthermore, does not currently incorporate lymph node status, an important prognostic indicator. Due to these limitations and the need for accurate staging prior to selecting appropriate treatment and to help with prognosis, the addition of imaging in the pre-treatment staging has been instigated.

Treatment options vary according to the tumour stage and nodal status. Early stage disease is treated with surgery alone, with fertility sparing options, whereas more locally advanced disease or lymph node involvement is treated with chemoradiotherapy, typically external beam radiotherapy to the pelvis with weekly chemotherapy, followed by intracavitary brachytherapy. Stage IVB, with distant metastases, is currently not considered ‘curable’. Accurate pre-treatment staging and assessment of prognostic factors is vital for tailoring the correct therapeutic regime, particularly as cervical cancer affects women of child bearing age.

FDG PETCT
Positron emission tomography (PET) imaging involves the intravenous administration of small amounts of short-lived radioactive tracers that emit positrons. The most widely used tracer is F-18 2-deoxy-2-fluoro-D-glucose (FDG), a glucose analogue taken up by tumours with increased glycolytic activity. PETCT cameras permit functional PET images to be fused to CT acquired in the same sitting.

Imaging in cervical cancer and the use of FDG PETCT
Primary tumour staging
Currently, MRI is the best imaging modality available for initial primary tumour staging of cervical cancer due to the superb soft tissue contrast and spatial resolution for delineation of parametrial, pelvic sidewall and vaginal extension. Neither PET nor CT is accurate in the assessment of tumour size and extension into parametrium and surrounding tissues. However, the level of metabolic activity in the tumour (SUVmax tumour) has been shown to be a prognostic indicator and independent predictor of recurrence post-surgery or chemoradiotherapy. In future this could decide patients who may benefit from neo adjuvant treatment.

Nodal staging
Cervical cancer typically spreads to pelvic, paraaortic and supraclavicular lymph nodes, then extra nodal sites of distant metastases (figure 1). Nodal staging is one of the strongest prognostic factors. MRI and CT predominately rely on size criteria for nodal assessment with nodes greater than 10mm short axis or ≥8mm and round being considered involved. However, tumour may be present in non-enlarged nodes and enlarged nodes may be reactive. Although ultra small iron oxide contrast agents improve nodal detection rate they are not routinely available. FDG PETCT can detect disease in nodes that may not meet the size criteria of MRI or CT, both within the pelvis and in the paraaortic region and beyond, but can have false negative results in nodes found to have micrometastases on histology. Two recent meta analyses of CT, MRI and FDG PET for detection of metastatic lymph nodes in patients with cervical cancer have shown FDG PET to be more accurate than CT or MRI for N staging. The pooled sensitivity and specificity for detection of pelvic nodal metastases was 74.7 % and 97.6% for PET; 55.5 % and 99.2 % for MRI; and 57.5% and 92.3 % for CT.

Perhaps more importantly is the detection of paraaortic lymph nodes (figure 2), which occur in approximately 15-30% cases with locally advanced cervical cancer, as these patients will benefit from extended field radiotherapy protocols. A recent meta analysis of 385 patients in 10 studies with histopathology as the reference standard showed low and heterogenous sensitivity (5-73%) depending on the prevalence of paraaortic lymph nodes (PALN). In a study of 22 FIGO stage IB-Iva cervical cancer patients Choi and co-workers compared accuracy of PETCT and MRI for paraaortic nodal disease prior to retropelitoneal lymphadenectomy. PETCT identified metastatic involvement in 19 out of 33 nodes compared with only 10 using MRI (sensitivity 57.6% vs 30.3%). Boughanim and co-workers performed CRT and then surgery, including retropelitoneal lymphadenectomy in 38 patients of FIGO stage IB/II. Three out of 38 (8%) patients with no PALN uptake on PET had positive paraaortic nodes giving a NPV of 92% for FDG PET for paraaortic nodal involvement. Thus, a negative PET in the PALN cannot exclude micrometastases and some would advocate retropelitoneal lymphadenectomy if involved pelvic nodes and negative PALN on PET.

In summary, the greatest benefit of staging FDG PETCT is in women with inoperable disease who are potentially curable with chemoradiotherapy and who are statistically more likely to have nodal disease than women with early...
stage disease suitable for surgery. Thus, the Scottish Intercollegiate Guidelines Network (SIGN) and National Comprehensive Cancer Network (NCCN) guidelines currently recommend PET for staging in cancers >1B1 potentially curative by chemoradiotherapy.

Recurrence/pre-pelvic exenteration

Recurrence rate depends on stage with overall 20-30% patients relapsing, particularly in the first two years. Approximately 70% of recurrences are distant or a combination of distant and local recurrence.

Evidence for the effectiveness of post-treatment follow-up is inconsistent. Routine follow-up in the UK typically entails clinical follow-up at six weeks post-treatment, three months post-treatment and every three months for two years, and every six months for the third to fifth year post-treatment to detect both asymptomatic and symptomatic disease recurrence as well as treatment complications. Although FDG PET may detect recurrence earlier than conventional methods there is no routine role in follow-up at present.

FDG PET/CT is currently reserved for patients who have recurrent or persistent disease demonstrated on conventional CT or MRI in whom further salvage therapy is being considered (pelvic exenteration or radiotherapy). For example, prior to salvage pelvic exenteration, a major debilitating operation with significant morbidity, PET may detect distant disease beyond the pelvis and avoid futile surgery.

Radiotherapy planning

Individualised treatment planning, which aims to optimize dose to treatment areas without increasing radiation associated side effects to ultimately improve outcome, is gaining great interest. PET/CT may modify the treatment strategy by extending the radiation field and/or modifying doses by providing information about staging and viable tumour tissue important for intensity modulated radiation therapy (IMRT).

In a recent systematic review of use of PET for radiation therapy planning, Salem and co-workers assessed 10 studies looking at PET and PET/CT in external beam radiotherapy planning. Most of these studies were small, single centre series and in general reported that PET upstaged a proportion of patients, leading to extension of radiation fields to include metabolically active nodes including paraaortic, inguinal and supravacular nodes with encouraging post-treatment survival figures when available. FDG PET has been reported to alter the radiotherapy fields in 11-19% of cases.

Kidd and co-workers reported a group of 452 newly-diagnosed cervical cancer patients in whom 135 patients were treated by PET/CT-guided IMRT, compared to 317 patients who received conventional EBRT. The FDG PET-guided IMRT group showed better overall and cause-specific survivals (p<0.0001) and less treatment-related toxicity, compared with patients treated with non-IMRT radiotherapy. Esthappan and co-workers have reported their use of PET/CT in guiding IMRT of 60Gy to positive paraaortic lymph nodes, but outcome and toxicity data is still lacking. There is also future promise for FDG PET/CT in brachytherapy planning. FDG PET-based plans have the potential to improve target dose distribution without significantly increasing the dose to the bladder and rectum, but more work needs to be done to assess if it will have a clinical benefit.

Response assessment

FDG PET three months post-chemoradiotherapy can be predictive of tumour recurrence and overall survival. Grigsby and co-workers have shown that PET response three months after completion of chemoradiotherapy is predictive of progression-free survival (PFS) and a reliable surrogate marker of response. The three-year PFS according to metabolic response was 78% (for complete metabolic response), 33% (partial metabolic response) and 0% (progressive disease). In a multivariate analysis of factors known to be predictive of outcome for cervical cancer, only post-therapy PET status and pre-treatment nodal status (defined by FDG PET) predicted PFS.

An earlier biomarker of response during chemoradiotherapy could potentially tailor brachytherapy treatment regimes and requires further study with FDG and other tracers targeting hypoxia, for example. Functional MRI is developing in parallel with PET and a recent feasibility study of diffusion weighted MRI at two weeks during chemoradiotherapy in 20 patients showed changes in apparent diffusion coefficient values (ADC) correlated with final MRI response, and was reproducible. In the future early PET derived metabolic or hypoxia data combined with functional MRI in PET/MRI systems may show promise.

Conclusion

Currently the main indications for FDG PET/CT in cervical cancer are staging of locally advanced cervical cancer patients (>1B1) undergoing potentially curative chemoradiotherapy and the assessment pre-salvage pelvic exenteration or radiotherapy outside the surgical radiotherapy field. There are emerging roles for FDG PET/CT in IMRT and brachytherapy planning and also as an early biomarker of treatment response.

References

<table>
<thead>
<tr>
<th>TNM categories</th>
<th>FIGO stages</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>TX</td>
<td></td>
<td>Primary tumour cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td></td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>Tis</td>
<td></td>
<td>Carcinoma in situ (pre-invasive carcinoma)</td>
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<tr>
<td>T1</td>
<td></td>
<td>Cervical carcinoma confined to uterus (extension to corpus should be disregarded)</td>
</tr>
<tr>
<td>T1a</td>
<td>A</td>
<td>Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximum depth of 5.0mm measured from the base of the epithelium and a horizontal spread of ≤7.0mm. Vascular space involvement, venous or lymphatic, does not affect classification</td>
</tr>
<tr>
<td>T1a1</td>
<td>IA1</td>
<td>Measured stromal invasion ≤3.0mm in depth and ≤7.0mm in horizontal spread</td>
</tr>
<tr>
<td>T1a2</td>
<td>IA2</td>
<td>Measured stromal invasion &gt;3.0mm and ≤5.0mm with a horizontal spread of ≤7.0mm</td>
</tr>
<tr>
<td>T1b</td>
<td>IB</td>
<td>Clinically visible lesion confined to the cervix or microscopic lesion &gt;T1a/IA2</td>
</tr>
<tr>
<td>T1b1</td>
<td>IB1</td>
<td>Clinically visible lesion ≤4.0cm in greatest dimension</td>
</tr>
<tr>
<td>T1b2</td>
<td>IB2</td>
<td>Clinically visible lesion &gt;4.0cm in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>II</td>
<td>Cervical carcinoma invades beyond uterus but not to pelvic wall or to lower third of vagina</td>
</tr>
<tr>
<td>T2a</td>
<td>IIA</td>
<td>Tumour without parametrial invasion</td>
</tr>
<tr>
<td>T2a1</td>
<td>IIA1</td>
<td>Clinically visible lesion ≤4.0cm in greatest dimension</td>
</tr>
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<td>IIA2</td>
<td>Clinically visible lesion &gt;4.0cm in greatest dimension</td>
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<tr>
<td>T2b</td>
<td>IIB</td>
<td>Tumour with parametrial invasion</td>
</tr>
<tr>
<td>T3</td>
<td>III</td>
<td>Tumour extends to pelvic wall and/or involves lower third of vagina, and/or causes hydronephrosis or nonfunctioning kidney</td>
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<tr>
<td>T3a</td>
<td>IIIA</td>
<td>Tumour involves lower third of vagina, no extension to pelvic wall</td>
</tr>
<tr>
<td>T3b</td>
<td>IIIB</td>
<td>Tumour extends to pelvic wall and/or causes hydronephrosis or nonfunctioning kidney</td>
</tr>
<tr>
<td>T4</td>
<td>IVA</td>
<td>Tumour invades mucosa of bladder or rectum, and/or extends beyond true pelvis (bullous oedema is not sufficient to classify a tumour as T4)</td>
</tr>
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**TABLE 1**
**FIGURE 1**
Coronal MIP, axial CECT and fused PETCT show cervical primary (*), bilateral pelvic nodes and retroperitoneal nodes (arrow) not enlarged by size criteria.

**FIGURE 2**
Coronal MIP and axial fused PETCT images showing cervical primary (*), right common iliac (long arrow) and left supraclavicular adenopathy (short arrow).