To PET or not to PET? That is the question. Staging in anal cancer


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Background: Anal cancer is a rare tumour accounting for ~2% of all colorectal cancers between 1997 and 2000 in the UK. Staging is still dominated by DRE (digital rectal examination), computed tomography (CT) and magnetic resonance imaging (MRI) imaging. The role of PET as a definitive modality is still emerging and there are relatively few adequate studies in the literature.

Methods: We looked at patients treated radically for anal cancer at Mount Vernon Cancer Centre (UK) between 2009 and 2010. Eighty-eight patients underwent treatment according to data-based coding records of which 46 had positron emission tomography (PET)/CT scans. Notes were unavailable for three patients. We compared staging following conventional modalities (DRE, MRI and CT) and PET/CT scans for these 43 patients.

Results: In 18 patients, the PET/CT stage differed from MRI. PET/CT altered the stage in 42% of patients but changes in subsequent management were not implemented.

Conclusions: Our data show that PET/CT does alter staging in a significant number of cases although it did not lead to change in management under the current guidelines. Furthermore, there is agreement that PET/CT shows greater sensitivity for detection of lymph nodes and our study has demonstrated a distinct trend towards upstaging of anal cancer with PET/CT.

Key words: anal, cancer, lymph nodes, PET/CT, staging

introduction

Anal cancer is a rare tumour with ~1000 new cases being diagnosed in the UK per year. This equates to 2% of all colorectal cancers between 1997 and 2000 [1]. Incidence is increasing although mortality still remains low. It is predicted to account for only 720 deaths in the United States in 2010 [2]. It still remains a curable disease and 5-year survival rates in the UK remain at 80% for stage 1 and stage 2 diseases and between 20% and 60% for stage 3 and stage 4 diseases [3]. Survival figures for the United States reflect those of the UK and little has changed in the last 30 years.

The anus is clearly delineated by the anal margin distally and the anorectal junction. The dentate line marks midway between these two points, where transition from squamous to mucosal, glandular epithelium occurs. The anal margin is visible as pigmented perianal skin immediately surrounding the exterior anal orifice. The anal canal is lined by non-keratinising squamous epithelium. Squamous cell carcinoma is the commonest histological type, although further subclassifications of basaloid, transitional, spheroidal and cloacogenic have been noted. Anal margin tumours are well differentiated unlike anal canal tumours. There are suggestions in the literature that basaloid tumours have a greater propensity to metastasise but histologic subtype, however, does not bear any influence on management.

Thirty percentage of patients will have lymph node involvement at presentation. Anatomically lymphatic drainage is as follows:

- Proximal: perirectal lymph nodes.
- Supra dentate: internal pudendal lymph nodes.
- Infra dentate/Perianal: inguinal, femoral and external iliac lymph nodes.

Treatment of anal cancer remains locoregional, as only a small proportion will have distal metastatic disease. In the 1980s, surgery was the mainstay of treatment and still remains the standard for small tumours (T1) at the anal margin. However, it was associated with high rates of local recurrence and involves loss of the anal sphincter and colostomy. Therefore, over the last three decades, treatment has moved on from primary surgery to organ-conserving treatment of which chemoradiation is the cornerstone for all T2–T4 and node-positive tumours.

Standard first-line treatment is chemoradiation with 5-fluorouracil and mitomycin C rather than radiation alone with guidelines based on several large phase II and randomised
phase III trials [4–6]. Due to the rarity of the tumour, the role of prognostic factors influencing survival and outcome has been difficult to evaluate but a small randomised study has reported that gender, nodal status and skin ulceration are all important but tumour size is not [7]. Accurate staging is crucial to facilitate assessment of local tumour extent, nodal spread and distal metastases. The TNM (tumour–node–metastasis) clinical staging system is used. A ‘T’ size of <4–5 cm is thought to be consistent with better prognosis and nodal status is dependant on distance from the primary site rather the absolute number involved.

Staging is still dominated by digital rectal examination, computed tomography (CT) and magnetic resonance imaging (MRI) imaging. The use of $[^{18}F]$2-fluoro-2-deoxy-D-glucose–positron emission tomography (PET)/CT (FDG–PET/CT) has a high sensitivity for lymph node involvement and is recommended in the most current National Comprehensive Cancer Network guidelines. In the UK, the ACT II trial recommends a two-phase protocol employing 50.4 Gy in 28 continuous fractions [8]. Standard radiotherapy fields should include the primary tumour and any likely involved nodes. The likelihood of nodal involvement increases with tumour size and the inguinal nodes are included in the radiation field in most cases even if not demonstrably involved. PET/CT can be used to help define dose delivery, especially as we move towards the use of more advanced radiotherapy such as conformal and even intensity modulated radiotherapy (IMRT). Although PET/CT will never replace MRI as the modality of choice for planning, as it cannot provide the necessary anatomical detail required, it does have the potential to reveal more information regarding tumour extent, nodal involvement and detection of distal deposits. Acute and late toxicity profiles can therefore be greatly influenced with more precise staging techniques. The aim of this study was to assess the usefulness of PET/CT in addition to standard imaging and evaluate its impact on staging and management of anal cancer.

methods

We carried out a retrospective study of all patients undergoing radical treatment for anal cancer at our centre [Mount Vernon Cancer Centre (MVCC), Middlesex, UK] between 2009 and 2010. Eighty-eight patients underwent this treatment within the time period. Patient details were retrieved from a coded database and of these, 43 patients underwent PET/CT scanning in addition to routine CT and MRI as part of their staging workup. All 43 patients had a clinical examination, CT scans of the chest, abdomen and pelvis, MRI scans of the pelvis and whole-body FDG–PET/CT scans. Tumour stage was determined according to the American Joint Committee classification of Cancer (AJCC). Patients treated included those initially seen at peripheral district general hospitals and treated at MVCC as the tertiary radiotherapy referral centre as well as those who initially presented to MVCC.

CT and MRI

Staging CT and MRI investigations were not carried out and/or interpreted in the same radiology departments but analysis was undertaken by experienced radiologists and reporting was consistent in that it followed standard protocols as issued by the Royal College of Radiologists’ training curriculum. Furthermore, the CT and MRI scanners used for scanning were all similar, minimising inconsistency in the data resulting from variations in equipment.

Watford General Hospital, Lister Hospital and Barnet Hospital: CT—Siemens Somatom Definition 16 slice scanner, MRI—Siemens Avanto 1.5T scanner; Luton and Dunstable Hospital: CT—GE Lightspeed 16 slice scanner, MRI—Philips Achiever 1.5T scanner; Paul Strickland Scanner Centre (MVCC): CT—Siemens Somatom Definition 64 slice scanner, MRI—Siemens Avanto 1.5T scanner.

$[^{18}F]$-fluorodeoxyglucose–positron emission tomography/computed tomography

All FDG/PET scans were carried out at the Paul Strickland Scanner Centre (MVCC) as per standard protocol. After 6 h of fasting, patients were injected with 4.5 MBq/kg body weight of FDG and imaged following a 60 min-uptake period on a Discovery ST (GE Medical Systems, Waukesha, Wisconsin) PET/CT using a standard skull base to pelvis protocol. The scanner included a four-detector row spiral CT with the following routine imaging parameters: 80 mA, 140 kVp, detector row configuration 4 × 2.5 mm, pitch 1.5, table speed 15 mm per gantry rotation, rotation time 0.8 sec. No i.v. contrast was administered and water was used to delineate bowel. On completion of CT, 2-D PET acquisition commenced utilising 4 min per multiple bed position over an axial field-of-view of 15.7 cm with a three-slice overlap. Transaxial images were reconstructed into a 128 × 128 matrix of 4.7 mm pixels with slice spacing of 3.27 mm. Total acquisition time was ~30 min per patient. Images were reported consistently within the same department.

data analysis

Staging was compared following conventional techniques alone (DRE/CT/MRI) and following FDG–PET/CT. The primary tumour was assessed for size and invasion into surrounding structures. Nodal status was assessed according to the UK ACT II trial protocol. FDG–PET/CT underestimated disease. MRI and FDG–PET/CT results were available for all 43 patients. The scan reports were all looked at in detail and AJCC TNM staging data were logged into a Microsoft Excel spreadsheet. Concordance or discordance between conventional staging and FDG–PET/CT staging was documented in a separate column. Furthermore, the clinical notes were examined and any changes to the original management plan following FDG–PET/CT staging were also highlighted. First-line radical treatment of anal cancer at MVCC is a combination of chemotherapy and radiation according to the UK ACT II trial protocol.

results

primary tumour

By MRI, T staging was as follows; Tx ($n = 1$), T0 ($n = 2$), T1 ($n = 2$), T2 ($n = 16$), T3 ($n = 10$), T4 ($n = 9$). Discordance on FDG–PET/CT was found in three patients. For these discordant results, taking MRI as the reference standard, FDG–PET/CT underestimated the MRI findings in one patient but upstaged the MRI findings in the other two patients. Where the only difference in staging was the T stage, FDG–PET/CT upgraded staging from T2 to T4 and T2 to T3, respectively. In the case where FDG–PET/CT underestimated the T stage as T2 (but T3 on MRI), the nodal staging was increased on FDG–PET/CT.
nodal metastases
By MRI, N staging was as follows; N0 (n = 12), N1 (n = 7), N2 (n = 16), N3 (n = 5). Disconcordance on FDG–PET/CT was found in 14 patients. For these discordant results, 13 showed a change in N staging alone and in 1, an upstaging in nodal status (N2–N3) was accompanied by a downgrading in T stage. FDG–PET/CT identified bilateral regional inguinal and iliac nodes, a presacral node and nodes above the diaphragm in four patients that were not seen on MRI, upstaging these cases to N3 disease. In three patients, FDG–PET/CT demonstrated unilateral inguinal nodal metastases not picked up on MRI, upstaging to N2 disease from N1 or N0. In two cases, N0 disease on MRI was upstaged to N1 disease on FDG–PET/CT with the revelation of small volume adjacent nodes in both. However, in five patients, FDG–PET/CT actually led to a downstaging of nodal status with involved nodes by MRI criteria not metabolically active on FDG–PET/CT. Two of these cases included a change from bilaterally enlarged inguinal nodes on MRI to unilateral nodes on FDG–PET/CT (N3 to N2). In a further two cases, FDG–PET/CT found no macroscopic/avid nodal metastases, whereas MRI demonstrated adjacent mesorectal and iliac lymph nodes (N1 and N2 to N0, respectively). The fifth case was shown to have small mesorectal and bilateral inguinal lymph nodes present on MRI (N3) but in fact, there was no evidence of nodal disease reported on FDG–PET/CT (N0).

distant metastases
By MRI, M staging was as follows; Mx (n = 1), M0 (n = 35), M1 (n = 4). Disconcordance on FDG–PET/CT was found in two patients. In both cases, FDG–PET/CT found distant metastatic deposits, not described on previous CT or MRI imaging, including distant pelvic and right supraclavicular nodal involvement.

overall results
In 18 patients, the PET/CT stage differed from MRI. Of these, 2 cases showed differences in ‘T’ staging alone (both upstaged), 13 showed a change in ‘N’ staging alone (8 upstaged, 5 downstaged), 1 showed a change in ‘T’ and ‘N’ staging (T downstaged, N upstaged) and 2 showed a change in ‘M’ staging alone (upstaged) (Figure 1). PET/CT altered the stage in 42% of patients but changes in subsequent management were not implemented. All patients still underwent radical chemoradiotherapy according to the planned protocol. The majority of changes involved upstaging disease.

discussion
The role of PET as a definitive modality is still emerging. An Italian group looked at the impact of PET/CT in stage definition and target volume delineation when comparing CT-GTV + CT-CTV and PET-GTV + PET-CTV; finding a clinical stage difference in 18.5% of the 27 cases studied and leading to a change in treatment intent in 3.7% [9]. The largest published series to date on the use of PET in squamous cell carcinoma of the anus from the UK looked at 61 patients and staged them both conventionally and with PET. Changes in staging and management were recorded in a significant number of the cases studied, especially in tumours >2 cm in size. PET/CT led to a change in stage in 23% of patients. The sensitivity of PET was also found to be superior for detection of regional nodal metastases; 89% versus 62% and overall PET changed management in 16% of cases [10]. Trautmann et al. [11] looked at 21 patients in a prospective study between 1999 and 2002 and assessed the usefulness of pre- and post-treatment PET scanning. The results correlate with de Winton’s more recently published data in that PET scanning provides useful and complementary pre-treatment staging information in 10%–24% of cases but has little value after treatment.

Figure 1. Change in Staging of Anal Cancer using PET/CT at Mount Vernon Cancer Centre 2009-2010.
At present, PET/CT is not part of routine staging and is mainly used as a reassurance and to confirm the absence of metastatic disease to justify a radical treatment aim. Despite the PET/CT findings and changes in staging, all patients in this study still underwent radical chemoradiation without any alterations in planned treatment. Multiple randomised controlled trials tell us that this combination of radiotherapy, mitomycin C and 5-fluorouracil does result in excellent local control, disease-free survival as well as high rates of sphincter preservation. However, conventionally planned external beam radiotherapy used in anal cancer is also associated with high morbidity and significant treatment-related toxicity. This in itself may compromise our ability to deliver optimal doses and so impact on therapeutic success due to missed fractions, treatment breaks and incomplete treatment courses.

Our study found that PET/CT altered staging in 42% of patients overall and in 5% previously unobserved distal metastatic disease was demonstrated. In these two patients, intensive chemoradiation with radical intent should have been avoided along with the associated morbidity had the PET/CT findings been acknowledged during staging and before treatment. Nodal staging altered in 32% and of these 14 patients, 9 had upstaging of nodal involvement and 5 were downstaged (Table 1).

It is impossible to confirm the absolute specificity of these PET/CT findings without surgical nodal staging but these results do concur with several studies, which describe PET to be highly specific for nodal spread in other pelvic malignancies such as vulva and cervix [12, 13]. It is important to note, however that the reporting of lymph nodes on CT and MRI scans used in this study consistently described size only and did not comment on other morphological features. The use of size alone limits sensitivity to 60%–70%. Furthermore, PET/CT itself has a limitation for lymph nodes <8 mm in size but this is also below the positive size limit for CT and MRI and thus, a false negative will be a false negative in all three modalities.

The addition of other descriptive features, such as heterogeneity, may improve sensitivity of CT and MRI to 80%–90% and therefore bear influence on nodal staging and our analysis of concordance between imaging modalities. The advantage of PET, however, is its sensitivity to detect uptake in non-enlarged involved nodes with a high-positive predictive value. In the ACT II protocol, phase I of treatment is the same for node-negative and node-positive diseases and includes large parallel-opposed fields to prophylactically include the inguinofemoral regions at risk of microscopic spread. The justification for this is that larger (>T2) tumours have a high risk of nodal involvement (45%–50%) and even in smaller T1 tumours, this risk remains at 10%–15%. In ACT II phase II, the treatment fields differ depending on nodal involvement or not. Therefore, volumes treated may be manifestly larger or smaller if based on PET/CT staging information. Given this, if the information provided by PET/CT is used to change the phase II treatment volume, the associated morbidity would be impacted greatly. However, the problem is that, this and most other studies describe PET/CT as a more sensitive detector of involved lymph nodes, i.e. it mostly upstages disease and in doing so would lead to larger phase II treatment volumes. Failure to treat these sites of active disease would, of course, be detrimental but intuitively this would also mean greater treatment-induced toxicity.

Newer radiotherapy planning techniques such as IMRT enable us to address this balance by allowing accurate and optimal dose target conformity while minimising acute and late toxicity as well allowing safe dose escalation. The value of ‘dose painting’ in IMRT is very encouraging. Pepek at al. [14] looked at 47 patients with anal cancer treated with IMRT-based chemoradiation and compared them with historical controls treated conventionally. Significantly reduced rates of acute toxic effects were seen in the IMRT treatment arm. These advances should test the hypothesis that improved outcomes can be achieved in those whose treatment has been manipulated on the basis of PET/CT imaging and includes IMRT compared with the current UK standard ACT II regimen.

### Table 1. Nodal staging discordance; MRI vs. PET/CT

<table>
<thead>
<tr>
<th>PET/CT</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral inguinal nodes. N3</td>
<td>Inguinal node. N2</td>
</tr>
<tr>
<td>Bilateral internal/external iliac nodes. N3</td>
<td>Abnormal left inguinal node. N2</td>
</tr>
<tr>
<td>Metastatic focus in right groin node. N2</td>
<td>Adjacent perirectal nodes. N1</td>
</tr>
<tr>
<td>Metastatic node left inguinal region. N2</td>
<td>Perirectal nodes. N1</td>
</tr>
<tr>
<td>No macroscopic/FDG avid metastases seen. N0</td>
<td>3 mm mesorectal lymph node. N1</td>
</tr>
<tr>
<td>No macroscopic/FDG avid metastases seen. N0</td>
<td>Mesorectal node and solitary inguinal node. N2</td>
</tr>
<tr>
<td>Single nodal metastasis in the left groin. N2</td>
<td>Bilateral inguinal nodes. N3</td>
</tr>
<tr>
<td>Small volume adjacent nodes. N1</td>
<td>No significant lymph nodes. N0</td>
</tr>
<tr>
<td>Presacral node. N3</td>
<td>Mesorectal and pelvic lymphadenopathy. N2</td>
</tr>
<tr>
<td>Bilateral inguinal nodes. N3</td>
<td>Mesorectal nodes. N1</td>
</tr>
<tr>
<td>No evidence of nodal disease. N0</td>
<td>Mesorectal and bilateral inguinal lymph nodes. N3</td>
</tr>
<tr>
<td>Adjacent regional nodes. N1</td>
<td>No enlarged nodes/metastatic disease. N0</td>
</tr>
<tr>
<td>Small left groin node. N2</td>
<td>No significant pelvic lymphadenopathy. N0</td>
</tr>
<tr>
<td>Enlarged left inguinal node. N2</td>
<td>Bilateral inguinal nodes. N3</td>
</tr>
</tbody>
</table>

FDG, 18fluoroxyglucose; PET/CT, positron emission tomography/ computed tomography.

### conclusion

This study shows us that PET/CT does alter staging for anal cancer in a significant proportion of cases. As we have seen in previously published studies, this is not a new finding and helps to confirm the argument that PET/CT should be increasingly utilised in standard staging protocols. With the advent of advanced planning techniques such as IMRT, altered radiotherapy treatment volumes based on PET/CT imaging may lead to potentially lower toxicity, improved dose accuracy and a paradigm shift away from therapeutic techniques dependant on the assumption of malignant involvement to
those in which we can be more confident of optimal target delineation.

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disclosure

The authors declare no conflicts of interest.

references


Zoledronic acid in patients with stage IIIA/B NSCLC: results of a randomized, phase III study


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Background: Bone metastases are common in patients with advanced non-small-cell lung cancer (NSCLC) and can have devastating consequences. Preventing or delaying bone metastases may improve outcomes.

Patients and methods: This study evaluated whether zoledronic acid (ZOL) delayed disease progression or recurrence in patients with controlled stage IIIA/B NSCLC after first-line therapy. Patients received vitamin D and

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