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## REVIEW ARTICLE

# Radiotherapy response evaluation using FDG PET-CT—established and emerging applications

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## ABSTRACT

Radiation therapy is a common component of curative cancer treatment. However, there is a significant incidence of treatment failure. In these cases, salvage surgical options are sometimes appropriate. Accurate assessment of response and early recognition of treatment success or failure is therefore critical to guide treatment decisions and impacts on survival and the morbidity of treatment. Traditionally, treatment response has depended upon the anatomical measurement of disease. However, this may not correlate well with the presence of disease, especially after radiotherapy. Combined positron emission tomography (PET) and CT imaging employs radioactive tracers to identify molecular characteristics of tissues. PET imaging exploits the fact that malignancies have characteristic molecular profiles which differ compared with surrounding tissues. The complementary anatomical and functional information facilitates accurate non-invasive assessment of surrogate biomarkers of disease activity.

This article reviews the rationale for positron emission tomography (PET)-CT response assessment in radiation oncology, describing current uses of 2-<sup>18</sup>F-fluoro-2-deoxy-D-glucose (FDG) PET-CT in treatment response following radiotherapy in head and neck, oesophageal, rectal and brain tumours. Emerging applications of FDG PET-CT in cervical and lung carcinomas and hepato-pancreatico-biliary tumours, particularly pancreatic carcinoma and liver metastases (post-selective internal radiotherapy treatment), are reviewed. Finally, the limitations of FDG PET-CT are considered, highlighting areas for future development.

## THE RATIONALE FOR POSITRON EMISSION TOMOGRAPHY-CT RESPONSE ASSESSMENT IN RADIATION ONCOLOGY

In the UK, radiotherapy forms part of 40% of oncology treatment pathways and is the mainstay of 19% of curative treatment.<sup>1</sup> Intensity-modulated radiotherapy has become the standard of care for multiple malignancies by virtue of the ability to deliver highly conformal doses whilst minimizing damage to adjacent tissues.<sup>2</sup> Despite this, curative-intent radiotherapy has a significant risk of locoregional treatment failure.<sup>3</sup>

Accurate response assessment informs future treatment decisions and in some situations guides the need for potentially curative surgical salvage. Early recognition of treatment success or failure can therefore impact on patient survival. Traditionally, this assessment relied upon anatomical measurement of disease, such as CT evaluation using Response Evaluation Criteria in Solid Tumours (RECIST). However, such measurements are of inherently limited value following radiotherapy, as residual masses/tissue abnormalities are common post-treatment and do not necessarily infer the presence of viable clonogenic tumour cells.<sup>4</sup> For example, in head and neck cancer, residual lymph node masses are well recognized following radiotherapy and, particularly with human papilloma virus-related disease, can continue to regress many months following completion of treatment.<sup>5</sup> The challenge of determining the presence or absence of viable tumour within residual masses following radiotherapy provides a powerful rationale for the incorporation of functional imaging into response assessment protocols.

PET-CT employs radioactive tracers to assess molecular characteristics of tissues. Malignancies have distinctive molecular profiles, which differ compared with

surrounding normal tissue, and may therefore be exploited by PET-CT imaging with appropriate tracers. The use of FDG PET-CT to demonstrate altered cellular glucose metabolism is the most widely used application of molecular imaging. Complementary anatomical and functional information facilitates an accurate non-invasive assessment of surrogate biomarkers of disease activity.

PET-CT in radiotherapy response assessment is useful for several reasons. Firstly, molecular response to radiotherapy may precede anatomical response and PET-CT may allow a more accurate assessment at an earlier stage than standard cross-sectional imaging. Secondly, use of specific tracers, allows a more reliable discrimination of tumour from treatment-related inflammation or fibrosis. Thirdly, tumours respond heterogeneously during radiotherapy.<sup>6</sup> Although this may not be apparent on anatomical imaging, by using an appropriate molecular biomarker which changes at an early stage and correlates with response, this variability may be demonstrated with PET-CT and the treatment adapted accordingly. Finally, tumour cells may develop resistance to radiotherapy during treatment. This development of resistance may be predicted using PET tracers which demonstrate hypoxia<sup>7</sup> or assess cell proliferation, *e.g.* fluorothymidine.<sup>8</sup> The optimal clinical utilization of these tracers remains a focus of ongoing research and a detailed assessment is beyond the scope of this article.

PET-CT has potential utility at different stages of radiotherapy response. Firstly, a growing area of research focuses on employing PET-CT during radiotherapy; this can facilitate an adaptive individualized approach to treatment with potential for escalation or de-escalation strategies depending on the quality/speed of on-treatment response or switching of treatment approach, for example to surgery in the event of an absent early response to radiotherapy. This emerging aspect has been covered elsewhere in detail and will only be briefly mentioned in this article.<sup>9</sup> Secondly, imaging can be used after radiotherapy to stratify patients who are responding and conversely identify non-responders and discriminate this from treatment effects, allowing for early aggressive treatment of persistent or progressive disease.

In the era of precision medicine, PET-CT may become more routinely used to identify persistent tumour and for biological characterization of disease response facilitating adaptive radiotherapy<sup>10</sup> maximizing survival and minimizing morbidity.

#### Key issues for the use of PET-CT for response assessment

There are several themes for each tumour site which need to be considered in determining the optimal use of PET-CT for response assessment following completion of (chemo)radiotherapy. Many of these issues remain unresolved in some tumour sites for which there are only limited data available regarding the use of PET-CT.

##### *Timing*

The timing of post-treatment response assessment represents a balance between allowing time for completion of tumour response and resolution of radiotherapy-related inflammation *vs*

the need to assess response early enough post-treatment to allow potential surgical intervention in the event of an incomplete response.

##### *Negative-predictive value*

A high negative-predictive value (NPV) of functional imaging is required to determine whether residual anatomical abnormalities can be safely monitored. Also, it is essential that a high NPV is demonstrated if response assessment PET-CT is used to guide a strategy of clinical follow-up over further investigation/treatment.

##### *Positive-predictive value*

(FDG) PET-CT can have a limited positive-predictive value (PPV) following radiotherapy owing to non-specific inflammatory changes showing FDG uptake. This does not preclude the use of (FDG) PET-CT, as a high NPV can still be valuable in guiding decision-making. However, it is essential that knowledge of the limited PPV is used to interpret imaging. For example, following (chemo)radiotherapy for head and neck squamous cell carcinoma (HNSCC), the PPV is reported in the order of 50%;<sup>11</sup> this is too low to embark upon surgical salvage, but may be used to guide the need for biopsy confirmation.

##### *Method of response assessment reporting*

There are different methods of reporting post-treatment PET-CT. These include qualitative methods which may incorporate the combined metabolic and anatomical response<sup>12</sup> or only metabolic response.<sup>13</sup> Qualitative interpretation raises the question of the optimal clinical interpretation of “equivocal” metabolic responses, *i.e.* low-grade residual uptake.<sup>14</sup> To the best of our knowledge, there are no established quantitative criteria in routine clinical practice for response assessment following radiotherapy.

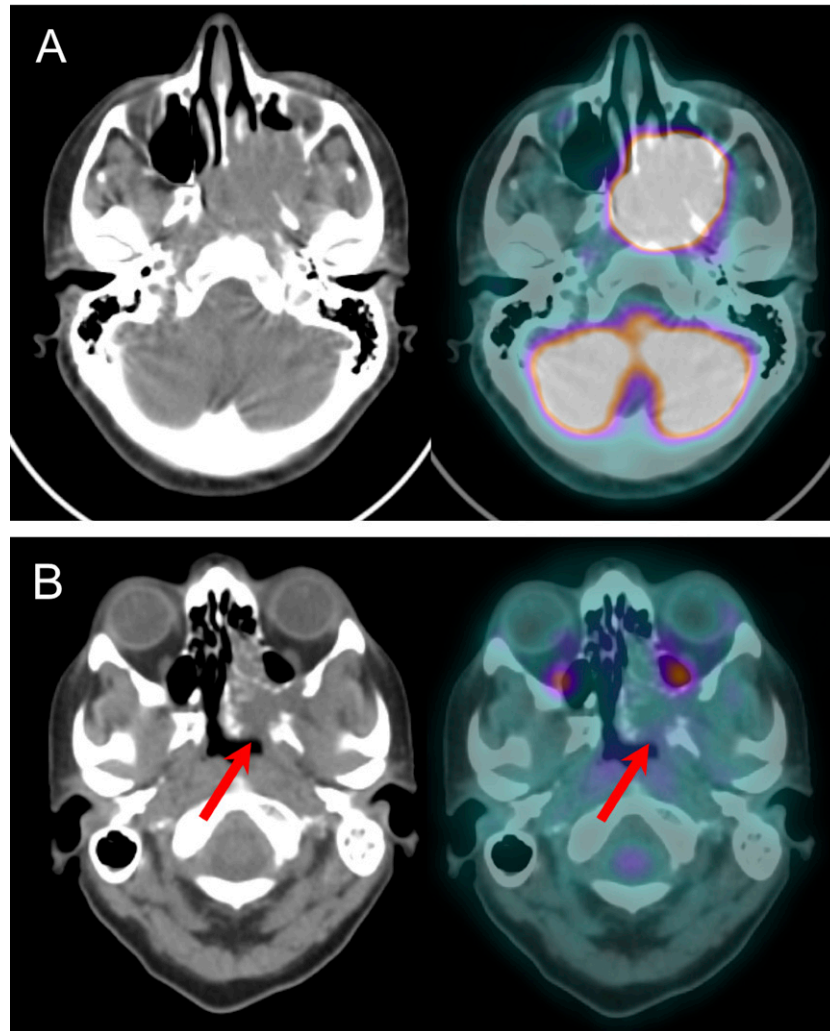
## **CURRENT USES OF FDG POSITRON EMISSION TOMOGRAPHY-CT IN TREATMENT RESPONSE FOLLOWING RADIATION THERAPY**

### Head and neck cancer

Head and neck cancer has an annual incidence of 550,000 worldwide.<sup>15</sup> Chemoradiotherapy (CRT) is the standard of care for locally advanced HNSCC for both unresectable disease<sup>16</sup> and to achieve organ preservation. The avoidance of unnecessary post-CRT neck dissection in complete responders depends on accurate post-treatment response assessment (Figure 1). Conventional imaging is hampered by treatment-related anatomical distortion and residual masses as well as the possibility of small occult deposits.

FDG PET-CT has an established role in post-CRT assessment in locally advanced HNSCC. Post-treatment FDG PET-CT has an NPV up to 99% for nodal disease (when performed at 4 months),<sup>17</sup> benefit over conventional assessment (anatomical imaging and clinical examination)<sup>18</sup> and a high probability of long-term regional control (2.3% regional failure rate at 36 months).<sup>19</sup> A recent randomized controlled trial, the UK PET-NECK study, demonstrated that PET-CT surveillance had equivalent survival outcome at lower overall cost, when compared with routine neck dissection for N2/3 nodal disease post-CRT for advanced nodal disease.<sup>12</sup> In this study, PET-CT took place 12 weeks following CRT. In line with this, a prior meta-analysis had shown that diagnostic accuracy was improved when

Figure 1. Use of fluorodeoxyglucose (FDG) positron emission tomography (PET)-CT for response assessment following chemoradiotherapy (CRT) for head and neck cancer: (a) axial panel of CT and fused PET-CT images in a patient with a left paranasal sinus squamous cell carcinoma pre-treatment. (b) Axial panel of CT and fused PET-CT images in the same patient 14 weeks following CRT is showing a residual FDG-negative mass (arrows). The patient has remained disease free for 3 years following treatment. See online version with colour rendering available.



response assessment was performed more than 12 weeks post-treatment.<sup>20</sup> Some groups have adopted a policy of response assessment at least 4 months post-treatment.<sup>17,21</sup> The clinical management of equivocal results remains problematic.<sup>12,14,17</sup> The majority of published data relate to the use of response assessment PET-CT following CRT for oropharyngeal carcinoma; the test characteristics of PET-CT for other head and neck tumour sites and following the use of radiotherapy alone remain less clear. Future work includes the incorporation of standardized qualitative interpretative response assessment criteria, *e.g.* Hopkins Criteria,<sup>13</sup> which may help stratify management and the use of FDG PET-CT during radiotherapy to optimize the therapeutic ratio.<sup>22</sup>

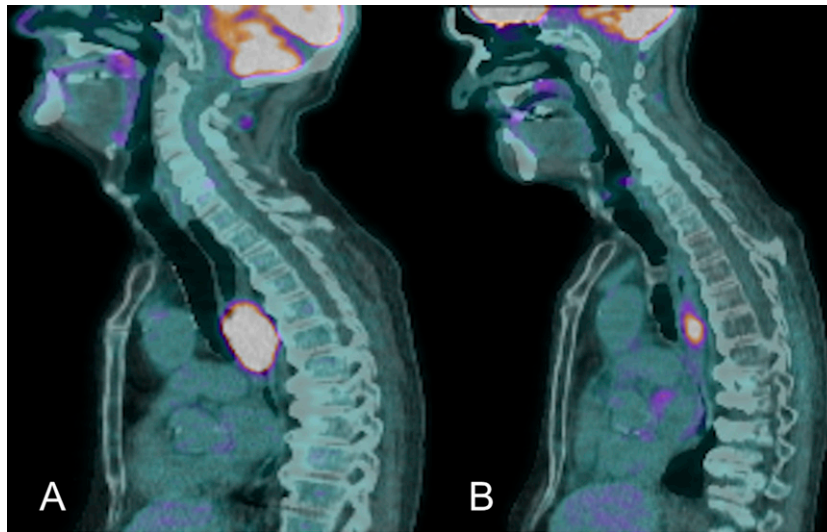
#### Oesophageal carcinoma

Oesophageal carcinoma has poor survival rates. Neoadjuvant CRT is a standard of care for locally advanced disease, but responders and non-responders have a significantly differing prognosis.<sup>23</sup> Use of interim post-CRT FDG PET-CT prior to surgery can help guide appropriate further management

(Figure 2), specifically by identifying interim metastatic disease (which may occur in up to 17%) preventing futile surgery.<sup>24,25</sup>

The added benefit of surgery for those with complete metabolic response (CMR) is less well defined. A substantial minority (20–30%) of patients with resectable disease have a complete pathologic response (CPR) to CRT.<sup>26</sup> Multiple groups have described the correlation between CMR on post-CRT FDG PET-CT, CPR and survival benefit.<sup>27</sup> Monjazebl et al<sup>28</sup> suggested patients with CMR may be spared surgery. Cervino et al<sup>29</sup> described a 91% 18-month disease-free survival for patients with a negative FDG PET-CT, who did not undergo surgery post-neoadjuvant treatment. However, the reported data are heterogeneous; for example, Elliot et al<sup>30</sup> found that CMR on post-CRT FDG PET-CT and CPR did not correlate. This may partly relate to study timing, as radiation-induced oesophagitis can mimic residual active disease and limit the utility of interim and post-treatment PET-CT. Many advocate surgery for even complete responders post-CRT and consider the role of FDG

Figure 2. Use of FDG positron emission tomography (PET)-CT to assess treatment response to radiotherapy in oesophageal cancer: (a) sagittal fused PET-CT image pre-treatment in a patient with a locally advanced oesophageal tumour. (b) Sagittal fused PET-CT image in the same patient performed after completion of treatment showing partial metabolic response within the primary tumour. See online version with colour rendering available.



PET-CT to be guiding biopsy and highlighting patients requiring escalation of treatment.<sup>31</sup>

#### Rectal carcinoma

Neoadjuvant CRT prior to resection is the standard of care for locally advanced rectal cancer (LARC). Early evidence of treatment response can alter surgical management, and accurate restaging is critical (Figure 3).

MRI is the mainstay of radiological staging of rectal cancer, but has limited value in response assessment following CRT.<sup>32</sup> International guidelines do not yet reflect a role for FDG PET-CT in the post-CRT restaging of LARC. However, several small studies have indicated a correlation between metabolic and pathologic response and demonstrated a superior NPV (up to 95.5%) of FDG PET-CT for CPR compared with MRI in LARC restaging.<sup>33–35</sup> Furthermore, a recent systematic review combining results of over 1500 patients found a high pooled accuracy for early PET restaging post-CRT for LARC.<sup>36</sup>

The role of PET-CT should not be overstated. Two systematic reviews of post-CRT FDG PET-CT suggest the main role for functional imaging was in identification of non-responders rather than selection for organ-sparing strategies.<sup>37,38</sup> However, post-CRT FDG PET-CT has a role in early outcome prediction with markers for metabolic response correlating with overall survival and disease-free survival.<sup>39</sup>

#### Brain tumours

Following radiotherapy for brain tumours, radiation necrosis can occur and mimic tumour progression or recurrence on conventional imaging.

FDG PET-CT has an established role in differentiating radiation necrosis from tumour progression. Stereotactic radiotherapy can result in apparent expansion and increased enhancement of

treated lesions. FDG PET has a reported sensitivity of 75% and specificity of 81% for distinguishing radiation necrosis from recurrent tumour at sites of radiosurgery.<sup>40</sup>

Distinction of radiation necrosis from residual tumour after fractionated radiotherapy can be problematic (Figure 4). The two often coexist, radiation necrosis may be hypermetabolic and local seizure activity may falsely increase uptake.<sup>41</sup> Increased uptake relative to contralateral grey matter has been demonstrated to have 68% accuracy in the diagnosis of recurrent tumour.<sup>42</sup>

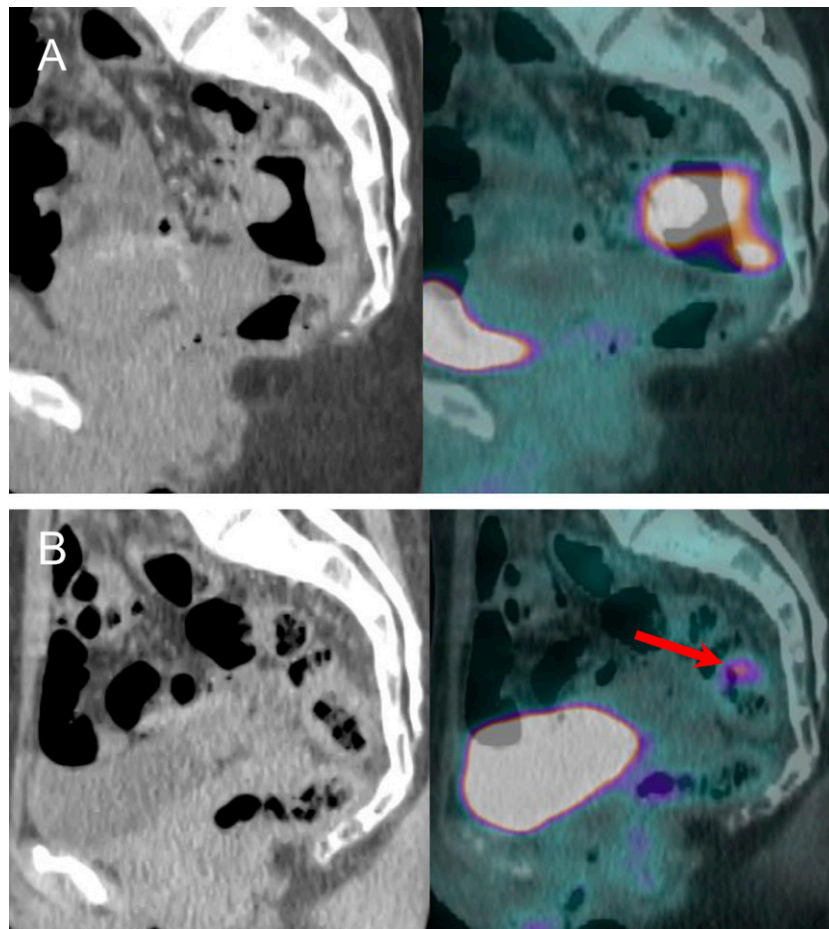
The role of FDG PET-CT post-radiotherapy is largely problem-solving and biopsy guidance in combination with MRI and other advanced imaging techniques. However, owing to the sub-optimal sensitivity and specificity of FDG-PET, other PET tracers may have superior accuracy.<sup>43</sup> Fluorine-18 fluoro-ethyl tyrosine is an amino acid analogue with improved tumour-to-background contrast compared with FDG and higher sensitivity for detection of recurrent glioma.<sup>44</sup> Fluoro-ethyl tyrosine does not require an onsite cyclotron and cost-effectiveness has been reported in diagnostic and recurrent indications,<sup>45</sup> although not yet specifically for post-radiosurgery indications.

### EMERGING APPLICATIONS OF FDG POSITRON EMISSION TOMOGRAPHY-CT

#### Cervical carcinoma

Cervical cancer is the third most common malignancy worldwide.<sup>46</sup> Locally advanced disease is treated with CRT (typically external beam radiotherapy plus cisplatin with subsequent intrauterine brachytherapy), but 20–40% of patients suffer disease persistence or recurrence.<sup>47</sup> Pre-existing methods of assessment such as International Federation of Gynaecology and Obstetrics stage do not reliably predict early treatment response or outcome.<sup>48</sup> Hence, the development of non-invasive surrogate biomarkers to predict poor treatment response and facilitate treatment escalation is of clinical pertinence. Opportunities to

Figure 3. Use of FDG positron emission tomography (PET)-CT to assess treatment response to radiotherapy in rectal cancer: (a) sagittal panel of CT and fused PET-CT images pre-treatment in a patient with a locally advanced upper rectal carcinoma. (b) Sagittal panel of CT and fused PET-CT images in the same patient performed after completion of chemoradiotherapy showing a good partial metabolic response within the primary tumour (arrow). See online version with colour rendering available.



use PET-CT for this purpose may exist both during and after completion of treatment.

Evidence suggests that early treatment (pre-brachytherapy) FDG PET-CT may be used to delineate metabolically active disease, allowing treatment field adaptation.<sup>49</sup> Furthermore, CMR predicts end of treatment response; Kidd et al<sup>50</sup> found that maximum standardized uptake values (SUV<sub>max</sub>) and FDG heterogeneity at 4 weeks during treatment correlated with 3-month post-treatment PET response. Yoon et al<sup>51</sup> reported that, in patients with FDG-avid pelvic nodal disease, failure to achieve nodal CMR correlated with a markedly reduced disease-free survival (71% with CMR vs 18%;  $p < 0.001$ ). Whilst such use remains experimental, this may represent a method to flag those in need of treatment escalation.

A number of trials have demonstrated that FDG PET-CT at 3 months post-CRT predicts prognosis. Persistent abnormal or new FDG activity post-CRT (Figure 5) represented the most important predictor of disease-related death by 5 years in one study.<sup>52</sup> However, post-therapy PET biomarkers remain of uncertain value in assessing long-term treatment success; one study suggested that  $\Delta \text{SUV}_{\text{max}} > 60\%$  predicted disease-free survival and<sup>49</sup> another study reported a limited NPV with 21% of patients with CMR on

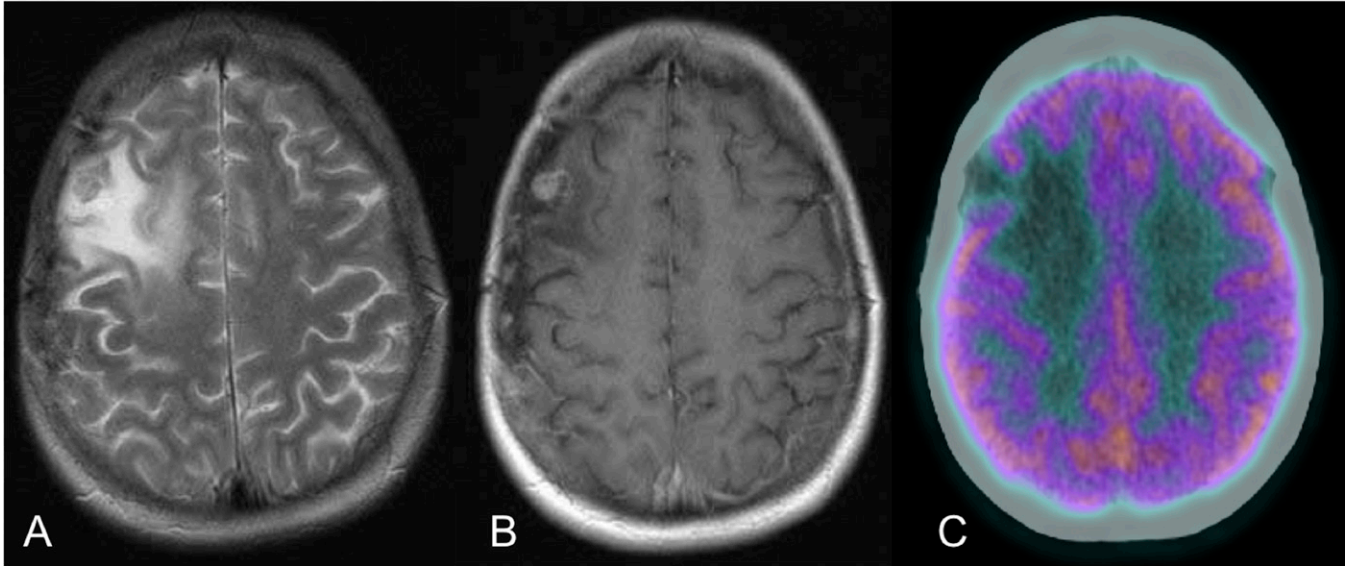
post-treatment FDG PET-CT developing disease recurrence during the median 28-month follow-up,<sup>53</sup> with tumour size and stage acting as predictors for recurrent disease. Furthermore, a systematic review suggests that although more accurate than MRI, PET-CT is less cost-effective in post-treatment surveillance<sup>54</sup> than standard follow-up. Therefore, whilst PET-CT offers promise in post-treatment assessment of cervical cancer, its potential to add value to the treatment pathway remains to be fully realized.

#### Lung carcinoma

Non-small-cell lung cancer (NSCLC) is the leading cause of cancer-related mortality.<sup>55</sup> FDG PET-CT is well established as a cost-effective staging tool prior to radical treatment. CRT is the standard treatment in locally advanced disease, but locoregional treatment failure rates are 15–40% and treatment escalation can cause morbidity.<sup>56</sup> Anatomical imaging response assessment post-CRT does not correlate well with histopathological response and distinction of post-treatment fibrosis from residual tumour is problematic. Therefore, the use of non-invasive surrogate biomarkers to flag non-responders early in treatment is crucial.

Studies suggest that surrogate PET biomarkers such as total lesion glycolysis<sup>57</sup> and SUV<sub>max</sub><sup>58</sup> may predict treatment response

Figure 4. Limited utility of FDG positron emission tomography (PET)-CT for assessment of treatment response following radiotherapy for brain malignancy: (a) an axial  $T_2$  weighted MR image in a young female patient with previous right frontal glioblastoma treated with surgery and adjuvant chemoradiotherapy showing a residual focal nodule and surrounding oedema. (b) Axial  $T_1$  weighted MR image following i.v. contrast (gadolinium) showing nodular enhancement. (c) Axial fused FDG PET-CT image showing photopenia at the site of the residual nodule—the patient underwent further surgical resection, which confirmed necrotic high-grade glioma. See online version with colour rendering available.



during CRT. However, the applicability of metabolic markers in predicting long-term outcomes post-CRT in NSCLC remains unclear. One study suggested that FDG PET post-stereotactic radiotherapy did not reliably predict long-term outcome.<sup>59</sup> More recently, Ding *et al*<sup>60</sup> found that metabolic tumour volume (MTV) at FDG PET-CT post-CRT was predictive of recurrence-free survival post-CRT at 2 years.

Surgical resection post-CRT is a potential curative treatment option for selected patients with Stage IIIA NSCLC and the high NPV of FDG PET-CT may aid interim treatment decisions post-CRT. Kim *et al*<sup>61</sup> demonstrated improved disease-free survival and overall survival in patients who demonstrated CMR.

FDG PET-CT may also have a role in adaptive radiotherapy planning in NSCLC, with changes in MTV<sup>62</sup> and gross tumour

volume<sup>60</sup> being used to adapt treatment. The use of FDG PET-CT to distinguish tumour recurrence from fibrosis has been reported to guide post-treatment problem-solving,<sup>63</sup> but can be challenging (Figure 6).

Hepato-pancreatico-biliary tumours, particularly pancreatic carcinoma and liver metastases (post-selective internal radiotherapy treatment) CRT is a standard of care for locally advanced pancreatic cancer. However, local relapse rates are high (42–68%) and distant recurrence is common.<sup>64</sup>

FDG PET-CT performed 12 weeks post-CRT demonstrated that increased delta  $SUV_{max}$  predicts overall survival and progression-free survival.<sup>57</sup> The use of FDG PET-CT during CRT is limited by the inflammation caused by bile duct

Figure 5. Use of FDG positron emission tomography (PET)-CT for assessment of treatment response following chemoradiation therapy in locally advanced cervical carcinoma: (a) axial fused PET-CT image pre-treatment in a patient with Stage 2b cervical carcinoma showing a bulky FDG-avid primary tumour. (b) Axial fused PET-CT image in the same patient obtained 3 months following completion of chemoradiotherapy showing a partial metabolic response to treatment with a residual FDG-positive tumour. The patient underwent salvage surgery. See online version with colour rendering available.

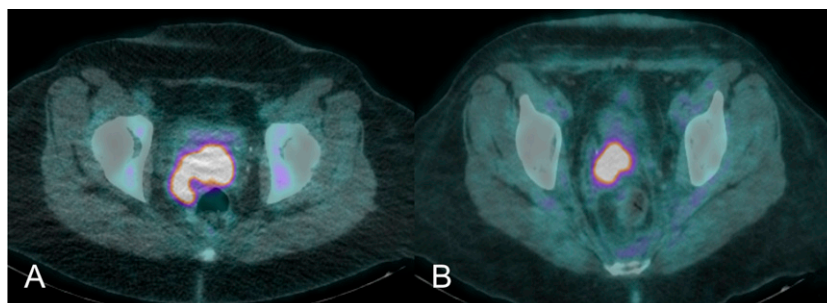
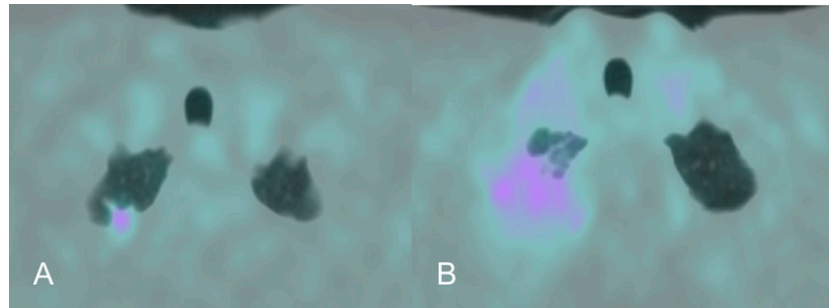


Figure 6. Use of FDG positron emission tomography (PET)-CT for monitoring treatment response following radiotherapy in non-small-cell lung cancer: (a) axial fused FDG PET-CT image showing a T1a NO M0 right apical lung tumour prior to treatment with stereotactic radiotherapy. (b) Axial fused FDG PET-CT image in the same patient 4 months after completion of radiotherapy showing diffuse low-grade FDG uptake at the site of treatment, which is non-specific. Subsequent follow-up confirmed no evidence of disease relapse. See online version with colour rendering available.



occlusion. Allowing for this, in the future, integration of PET-CT as a response assessment tool may help define futility owing to interim distant metastatic disease and allow adaptation of the therapy field and selection for aggressive treatment.<sup>65</sup>

Selective internal radiotherapy treatment is an important palliative treatment for unresectable metastatic liver disease. Early assessment of treatment response can help guide further treatment.<sup>66</sup> FDG PET-CT can provide an earlier and more accurate assessment of response to 90-Yttrium microsphere therapy than CT imaging alone (Figure 7).<sup>67</sup> MTV and total lesion glycolysis are reported to be the best predictors of survival in colorectal metastatic disease.<sup>68</sup> However, recent evidence suggests that diffusion-weighted MRI may be the superior modality with an NPV of 92% vs 56% for FDG PET-CT<sup>69</sup> and further investigation is required for clarification.

Limitations of FDG positron emission tomography-CT and the emergence of alternative tracers

FDG PET-CT has many potential benefits in assessing radiation response and shaping the treatment pathway; however, there are important limitations to be aware of to help limit misuse and misinterpretation.

Although molecular imaging may detect anatomically occult disease, sensitivity for detection decreases when the lesion size is <1 cm and superficial tumours and perineural spread are often FDG-negative.

Certain tumour types including mucoepidermoid, adenoid cystic and mucinous primaries have a low metabolic activity, which limits the utility of FDG PET-CT. There has been extensive interest in development of non-FDG tracers, and some

Figure 7. Use of FDG positron emission tomography (PET)-CT in response assessment following selective internal radiotherapy (SIRT) treatment for liver metastases: (a) axial panel of CT and fused PET-CT images in a patient with FDG-avid colorectal liver metastases pre-treatment. (b) Axial panel of CT and fused PET-CT images in the same patient 3 months following SIRT showing a partial response. In particular, a left lobe liver metastasis (arrows) has not changed in size but has shown a significant metabolic response to treatment. See online version with colour rendering available.

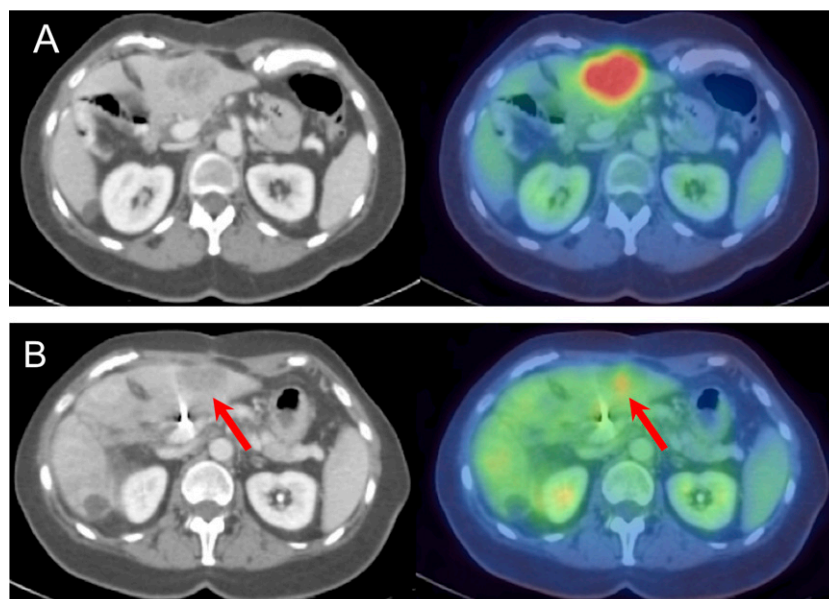
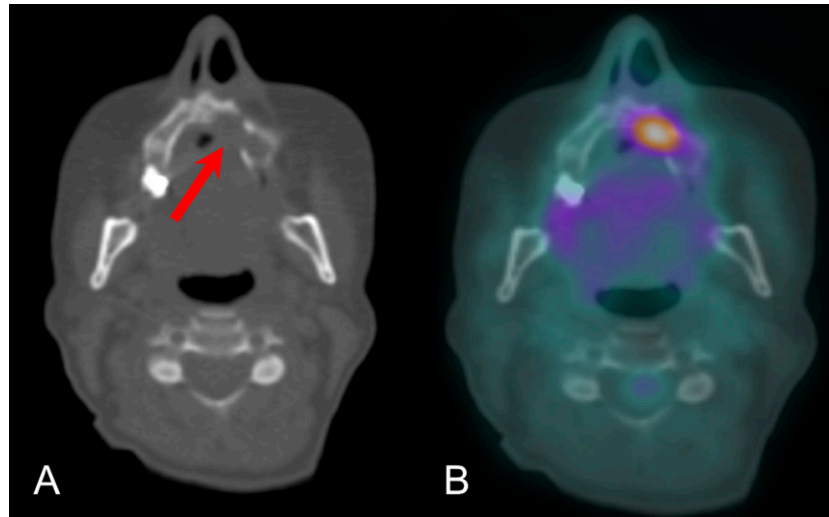


Figure 8. Limitations of the use of FDG positron emission tomography (PET)-CT in response assessment: (a) axial CT in a patient with oropharyngeal head and neck squamous cell carcinoma treated with chemoradiation showing a lytic soft-tissue deposit in the left maxilla (arrow) distant from the treated primary tumour. (b) Axial fused FDG PET-CT showing corresponding avid tracer uptake suspicious of tumour—this area was biopsied, no malignancy was demonstrated—the appearances were due to radiation-induced osteonecrosis. See online version with colour rendering available.



have already translated into routine clinical practice. For example, choline PET-CT has high specificity and sensitivity<sup>70</sup> and is recommended<sup>71</sup> in the reassessment of biochemically relapsed prostate cancer after local curative treatment (including radiotherapy). Gallium-68-labelled somatostatin receptor PET-CT has emerged as the new gold standard for imaging of neuroendocrine tumours<sup>72</sup> and may provide a potential non-invasive molecular biomarker for assessment of early response to peptide receptor-targeted radiotherapy<sup>73</sup> in gastrointestinal neuroendocrine malignancy. There is a significant false-positive rate in post-radiotherapy assessment owing to treatment-related inflammation. This is particularly pertinent in cervical and oesophageal malignancy. Radiation complications such as osteoradionecrosis may mimic disease (Figure 8) and PET imaging should always be interpreted in the context of anatomical imaging findings and clinical examination.<sup>74</sup>

The imperfect specificity of FDG PET-CT in the post-treatment setting has stimulated interest in the use of alternative tracers, which correlate more closely with mechanisms involved in tumour treatment response or radiotherapy resistance. Tumour hypoxia is known to promote radiotherapy resistance.<sup>75</sup> Fluorine-18 fluoromisonidazole has been widely researched and demonstrated to accumulate in hypoxic cells in head and neck,<sup>76</sup> brain<sup>77</sup> and lung<sup>78</sup> tumours, but its clinical application is limited by a high signal-to-noise ratio. Alternative tracers which act as surrogates for hypoxia include fluorine-18 fluoroazomycin-arabino-furanoside and copper-64 diacetyl-bis(N4-methylthiosemicarbazone). Both tracers have more favourable pharmacokinetics than fluoromisonidazole and hold promise for further research (an overview can be seen in the study of Feling *et al* 2015<sup>79</sup>). Cellular mechanisms involved in tumour response to treatment include a reduction in cell proliferation, which can be assessed using fluorothymidine PET-CT and an increase in apoptosis, which could be evaluated

using a specialized tracer such as fluorine-18 2-(5-fluoro-pentyl)-2-methyl-malonic acid, as a surrogate biomarker. At the present time, use of these tracers for response evaluation after radiation treatment remains in the research domain.<sup>80</sup>

In many tumour types, standardized metabolic parameters and appropriate timing of imaging are yet to be agreed in consensus and currently act as a barrier to more widespread clinical adoption of FDG PET-CT for radiotherapy response assessment. Progress in implementation of PET-CT-guided response evaluation post-radiotherapy requires both progression in the evidence basis, particularly around standardization and validation of the technique in various tumour types, and assessment of cost-effectiveness. These aspects warrant consideration when designing future clinical trials in radiotherapy.

## CONCLUSION

Radiation therapy is an increasingly common component of curative cancer treatment pathways, but is associated with a significant risk of heterogeneous and/or incomplete response or disease recurrence. PET-CT provides accurate non-invasive assessment surrogate biomarkers of tumour response to therapy, facilitating early adaptation, switching or termination of treatment in order to maximize cure rates and minimize morbidity. Currently, FDG PET-CT has a role in treatment response assessment following radiotherapy in a variety of tumour types and can help guide patient management. Whilst there are limitations of FDG PET-CT, ongoing research suggests that a range of non-FDG tracers show promise in a range of applications.

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