The use of PETCT in Hodgkin’s lymphoma

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Background

Lymphoma is a haematological malignancy that affects both old and young. It is the most common indication for PETCT in the young adult. Lymphoma is the fifth commonest malignancy in the UK after breast, lung, colorectal and prostate cancer, accounting for 11,861 cancer cases in 2008 (4%). The current conventional treatments provide good cure rates, with overall 10-year survival rates of 51%. The use of PETCT helps with staging, monitoring and tailoring of therapies, in part to avoid the long-term morbidity and mortality associated with treatment of the young.

Lymphoma is subdivided into Hodgkin’s (20% of all lymphomas) and non-Hodgkin’s (80% of all lymphomas). Hodgkin’s disease is characterised by the presence of Reed Sternberg cells and is a relatively aggressive malignancy that affects a younger population than the NHL group. It has a bimodal distribution presenting commonly between the ages of 15 and 35, with a second peak in the over 50s.

The non-Hodgkin’s group is a heterogeneous set of conditions that are grouped together. The average age of diagnosis is 65. There are many sub-types of non-Hodgkin’s lymphoma, but they can all be put into one of two broad categories, high grade and low grade. This can be problematic in predicting response to treatment and interpreting imaging findings on PETCT, as the subtypes have a wide spectrum of natural histories reacting differently to treatments. This makes the use of PETCT in NHL more controversial and difficult to have confidence in its findings.

In general, lymphoma does not obey the same rules as other malignancies discussed elsewhere. It often has a large inflammatory soft tissue component that is not part of the active disease. The active disease can be confined to a small number of cells that phosphorylate and accumulate FDG. This produces imaging problems as active disease and quiescent disease look morphologically similar and monitoring response to treatment is not as clear cut as in malignancies that produce high SUV values.

Thus, interpreting these PETCT scans becomes difficult and poorly reproducible limiting, among other things, further standardised research. With this in mind, a European congress met to decide on a method that was reproducible and reliable in assessing response and progression of the disease. The semi-quantitative method they decided upon was the Deauville criteria (Table 1). These have shown good inter-observer concordance in HL. As standardised uptake values (SUVs) are calculated for each individual based on injected activity, weight, height, etc, they are prone to variation. To combat this, reference points are used; these are the background uptake in the mediastinum and liver. This reduces some of the variation between patients and is more reproducible.

These criteria will not exclude microscopic disease, so there will be a small number of false negatives, but the aim is to prevent a larger number of false positives. As you will read, this high negative predictive value (NPV) and poor positive predictive value (PPV) is the main limiting factor in the use of FDG PETCT.7

The consequences of treatment can produce significant morbidity and mortality. The patient group is generally younger so the identification of early disease is important as it is eminently treatable with conventional therapies. Over-treating will lead to a cure but produce delayed morbidity and mortality from cardiac damage and radiation-induced cancers. So, it is important to differentiate early on those with more benign disease who could be cured with less aggressive therapy and those whose only chance is the aggressive therapies.

Having a test with high false positives (or a poor PPV) exposes a group of cured patients to unnecessary and potentially damaging treatments. A systematic review looking at post-treatment assessment gave PETCT a pooled negative predictive value of 96% (84-100%) and a positive predictive value of 77% (60-100%).

FDG PETCT has proved to be a highly sensitive and specific tool and is a mainstay of current imaging. Several studies have shown that progression-free survival (PFS) when using CT alone can vary little from those with positive or negative post-therapy CT scans. FDG PETCT has a high sensitivity for nodal staging, performing particularly well in accurately identifying mediastinal nodes, peripheral nodes and extra nodal disease often overlooked in conventional imaging.

Pre-treatment staging

Pre-treatment staging with PET/CT has shown an upstaging of 10-25% when compared to conventional imaging.17 This can be due to the superior identification of involved nodes and the detection of extra nodal disease such as splenic metastases or marrow involvement. These pre-treatment scans also provide a baseline from which to assess response of the treatments. This allows the de-escalation of more toxic therapies.

Monitoring

The timing of the scan during therapy is still debatable. There are many papers and trials in progress looking for the optimum time to rescan. The ideal timing would be after an interval that would identify a definite response, allowing one to alter treatments with confidence, but not so delayed that

1. No uptake
2. Uptake less than mediastinum
3. Uptake more than the mediastinum but less than the liver
4. Uptake moderately increased above liver at any site
5. Markedly increased uptake at any site including new sites of disease

TABLE 1
Deauville PETCT five-point scale.

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>No uptake</td>
</tr>
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the benefits of a limited treatment cannot be reaped in those responding well. This can differ with different chemotherapy agents, timing, use of radiotherapy and the histological subtype of the tumour. Most studies are after two cycles, but between one and three cycles has been shown to be predictive of final treatment response and progression free survival.\(^6\)\(^-\)\(^9\)

A general conclusion that can be drawn is that a negative interim scan has a good negative predictive value. Some studies suggest that a negative interim scan correlates with such a good prognosis that there is no need to get a post-treatment scan\(^7\)\(^-\)\(^9\) and is a prognostic factor for failure-free survival (FFS).

Post-treatment scanning is the most accepted use for PETCT. In recognition of this it now forms part of the international working groups response criteria.\(^7\) Again, a negative scan has a good NPV. It also adds value when looking at residual masses, a particular problem in lymphoma. As mentioned previously there is often a large soft tissue component with two-thirds of patients having a residual mass at the end of treatment.\(^7\) Identifying those where the soft tissue mass is part of active disease and those where it is simply inflammatory is key. This is one area where PETCT and its molecular, functional basis far outperforms CT alone, but it will still only be positive in two-thirds of the patients with active disease in the residual mass. This means that to avoid potentially harmful further treatments, these post-therapy patients require biopsy and tissue diagnosis to confirm the presence of disease.

The consistently lower PPV will hopefully be limited in the future by the careful timing of scans in relation to their treatment. The International Harmonisation Project (IHP) suggests scanning three weeks after cessation of chemotherapy and 10-12 weeks after finishing radiotherapy, limiting any false positives from treatment-related inflammatory responses. It has also been suggested that this is particularly the case in Hodgkin’s lymphoma where patients get more radiotherapy and so fibrosis and inflammation.

The accurate early detection of recurrence using PETCT suffers from the same problems as post-treatment scans and evaluation of residual masses. The main difficulty is deciding if low grade uptake represents new disease. The Deauville criteria help with the assessment of low grade uptake, but the continuing message is that if it is a completely negative scan or a strongly positive scan a decision can be made on the scan alone. If there is any doubt a tissue diagnosis is required.

Pitfalls

Lymphoma in the brain, testis and stomach are difficult to assess on PETCT due to physiological marrow activation because of anaemia, marrow reactivation due to treatment and the administration of GCSF (a stimulating factor used in chemotherapy regimes). When evaluating PETCT in lymphoma patients, opportunistic infections should always be considered as an alternative cause for uptake in this potentially immune compromised group of patients.

Conclusion

FDG PETCT is proving to be a useful tool in the assessment and treatment of Hodgkin’s lymphoma disease. It provides better staging and gives a more sensitive idea of how the treatment is progressing. This allows tailoring of the therapy to provide the best chance of cure and the least chance of treatment side effects. A negative scan at any stage of the disease is accurate and provides a good chance of PFS. There continues to be research on the relative value of a positive scan at the various stages of disease. Use of the Deauville criteria will hopefully improve confidence in a positive result but the current evidence is that there is a poor positive predictive value and as such patients will often need tissue diagnosis for confirmation.

References

FIGURE 1
Marked resolution of disease on post-treatment scanning.

FIGURE 2
Despite treatment progressing well, the final scan shows recurrence.