Received:
16 May 2014

Revised:
16 July 2014

Accepted:
23 July 2014

doi: 10.1259/bjr.20140360

Cite this article as:

Metser U, Hussey D, Murphy G. Impact of ^{18}F -FDG PET/CT on the staging and management of follicular lymphoma. *Br J Radiol* 2014;87: 20140360.

PICTORIAL REVIEW

Impact of ^{18}F -FDG PET/CT on the staging and management of follicular lymphoma

U METSER, MD, D HUSSEY, BSc, RTNM and G MURPHY, MBBCh, BAO

Joint Department of Medical Imaging, University Health Network, Mount Sinai Hospital and Women's College Hospital, University of Toronto, Toronto, ON, Canada

Address correspondence to: Dr Ur Metser

E-mail: ur.metser@uhn.ca

ABSTRACT

Follicular lymphoma (FL) is the most common indolent lymphoma. Despite the evidence-based utilization of fluorine-18 fludeoxyglucose positron emission tomography (^{18}F -FDG PET)/CT in aggressive lymphomas, the utility of PET in FL remains controversial and varies across different jurisdictions. The management of patients with FL differs from aggressive lymphomas and is usually reserved for patients with localized disease in whom long-term control may potentially be achieved by involved field radiotherapy, or for symptomatic patients with advanced-stage disease in whom systemic therapy is indicated. There is a growing body of literature supporting the use of PET/CT in initial staging of FL to guide management decisions. In this review, we summarize the existing literature and present cases from our experience to illustrate current knowledge on the potential role of ^{18}F -FDG PET/CT in FL.

Follicular lymphoma (FL) is the second most common form of non-Hodgkin's lymphoma accounting for 20–25% of adult non-Hodgkin's lymphomas worldwide and is the most common low-grade lymphoma. It has a variable course, usually indolent, with some patients experiencing a complete response, while others relapse or transform to aggressive lymphoma. Up to 23% may spontaneously regress.¹ Treatment varies depending on the stage and clinical presentation. Durable remissions have been attained in 30–35% of patients with early (Stages I–II) FL treated with involved field radiotherapy (IFRT) alone; however, more extensive disease in the absence of B symptoms would be better managed with watchful waiting.² Therefore, accurate staging is crucial for appropriate management.

Although the impact of positron emission tomography (PET)/CT on the staging and assessment of treatment response in potentially curable, high-grade lymphomas is well established, its role in indolent, low-grade disease such as FL is more controversial.³ This is owing to the biological behaviour of the tumour and the treatment algorithm, which is limited to localized or systemic symptomatic disease. Furthermore, the correlation between response to therapy and overall survival in FL is not as strong as for aggressive lymphoma.

In this pictorial review, we present the available evidence in the literature for the use of PET/CT in FL and provide

multiple case examples illustrating the significant impact of PET/CT findings on therapy planning and patient management.

STAGING AND PROGNOSTICATION OF FOLLICULAR LYMPHOMA

FL is staged according to the Cotswolds modification of the Ann Arbor staging system,⁴ presented in [Table 1](#). This classification scheme takes into account the number of nodal groups involved, their location and the presence or absence of extranodal disease. The prognostic index for FL [termed the FL International Prognostic Index (FLIPI)] includes five variables that have been shown to be strong and independent predictors of poor outcome. These include age >60 years, Ann Arbor Stages III–IV, haemoglobin level <12 g dl⁻¹, elevated lactate dehydrogenase level and >4 nodal sites of disease. Patients with ≤1, 2 or ≥3 of these factors have low-, intermediate- or high-risk disease, respectively.⁵ Therefore, improved staging and accurate determination of nodal and extranodal involvement may impact staging and prognostication of patients with FL.

Determining disease extent and stage is essential in planning appropriate management. Studies have shown that FL is almost always fluorine-18 fludeoxyglucose (^{18}F -FDG) avid, regardless of tumour grade, and PET may identify further findings in 18–29% of cases. Therefore, there is a

Table 1. Cotswolds modification of Ann Arbor staging system

Stage	Area of involvement
I	One lymph node group
II	Multiple lymph node groups on the same side of the diaphragm
III	Multiple lymph node groups on both sides of the diaphragm
IV	Multiple extranodal sites or lymph nodes and extranodal disease

X denotes bulky disease measuring >10 cm.

E denotes extranodal extension or single isolated site of extranodal disease.

A or B denotes absence or presence of B symptoms, which include weight loss >10%, fever, drenching night sweats.

rationale for using PET to stage patients with FL. The greatest potential clinical benefit in more accurate initial staging of FL with PET may be in patients with presumed localized early stage disease being considered for potentially curative IFRT.^{6,7} For these patients, identification of more extensive local disease may impact the scope of radiation field and identification of multifocal disease may make IFRT futile (Figure 1). A study by Wirth *et al*⁶ evaluating only patients with early stage FL (Stages I–II) showed an enhanced impact for PET in

this subgroup of patients. The authors presented data on 42 patients with presumed early stage disease per conventional staging procedures. After PET/CT, 31% were upstaged to Stages III or IV and for an additional 14% of patients, the radiation field was altered. More recently, a larger scale study investigated the role of PET in the initial staging of 142 FL patients enrolled in the FOLL05 Phase III trial, which compared various first-line regimens. PET identified a larger number of nodal areas in 32% of patients and more extranodal sites than CT. In addition, the FLIPI score was increased in 18% of patients and decreased in 6% after PET because of downstaging of disease (Figure 2). Overall, the impact of PET on modifying the stage was highest in patients with limited stage, although the number of patients in this group was exceedingly small ($n = 24$). In this limited subgroup, 62% were upstaged with PET.⁷ That study also showed that PET identified more extranodal sites than CT (Figure 3). Not surprisingly, in this study, the greatest contribution of PET was in identification of lesions in the bone, spleen, gastrointestinal tract and skin; although it appeared limited in detecting bone marrow infiltration and may not replace bone marrow biopsy in the work up of these patients.⁸ In our experience, PET may also have higher specificity than that of CT for extranodal involvement, and it may be worthwhile to further evaluate equivocal CT findings or confirm or exclude extranodal involvement with PET in patients with otherwise early stage or localized disease (Figures 4 and 5).

Figure 1. A 55-year-old female referred for radiotherapy to presumed Stage 1 follicular lymphoma (FL) of the right groin as per CT staging. (a) Maximum-intensity projection fluorine-18 fludeoxyglucose positron emission tomography (¹⁸F-FDG PET)/CT image shows multiple foci of abnormal ¹⁸F-FDG uptake in several nodes below and above the diaphragms (arrows). (b) Axial ¹⁸F-FDG PET/CT images (CT left, fused PET/CT middle, PET right) revealed ¹⁸F-FDG -avid nodes in the right groin (row i, arrow), retroperitoneum (row ii, arrow), mesentery (row iii, arrow) and right axilla (row iv, arrow). The right axillary node was biopsied and shown to represent FL. The patient was deemed unsuitable for radiotherapy and is undergoing watchful waiting.

Figure 2. A 53-year-old male with left neck lymphadenopathy (grade 2 follicular lymphoma). Staging CT demonstrated an equivocal right pelvic node. Axial fluorine-18 fludeoxyglucose positron emission tomography (PET)/CT images (CT left, fused PET/CT middle, PET right) show metabolically active left neck nodes (arrows in rows i and ii) but did not show uptake in the questionable right external iliac node (arrow on CT image in row iii). Patient was deemed suitable for radiotherapy and is disease free 2 years after completion of involved field radiotherapy.

The ramification of more accurate staging and PET-directed management on outcome of patients with FL is unknown. Currently, a prospective provincial registry is underway in Ontario (Canada) to assess the effect of PET on staging and management of presumed early stage FL according to conventional CT staging. When it becomes available, the data from this registry may provide further evidence for the use of PET in the management of patients with early stage disease. These data may then be linked to outcome parameters and may shed further light on the long-term impact of utilization of PET in the diagnostic algorithm of patients with early stage FL.

RESPONSE ASSESSMENT WITH FLUORINE-18 FLUDEOXYGLUCOSE POSITRON EMISSION TOMOGRAPHY-CT

The utility of ^{18}F -FDG PET/CT in response assessment at the end of induction therapy is well documented in Hodgkin's and diffuse large B-cell lymphomas, but its role in FL is not as well established. In fact, the International Harmonization Project⁹ recommends PET imaging for response assessment at the end of therapy for aggressive lymphomas but not for FL, outside clinical trials. Recently, a retrospective analysis of a subset of 122 patients with FL in the Primary Rituximab and Maintenance (PRIMA) study after first-line therapy showed that PET performed at the end of immunochemotherapy induction is a significant

predictor of outcome. Patients who remained PET positive had inferior progression-free survival at 42 months as compared with those who became PET negative (32.9% vs 70.7%, respectively).¹⁰ A recently published prospective study evaluating 121 patients with high tumor burden FL, evaluated the predictive value of PET after four cycles of therapy (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) and at the end of therapy. The investigators used the Deauville criteria with ^{18}F -FDG uptake graded on a five-point scale. Lesions categorized as Score 4 or 5 (uptake above physiological liver uptake) were considered positive for residual disease. The 2-year progression-free survival was better for interim PET-negative vs PET-positive cases (86% and 61%, respectively; $p = 0.0046$). This correlation was stronger for end-of-therapy PET (with 2-year progression-free survival of 87% and 51% for end-of-therapy PET-positive and PET-negative cases, respectively; $p < 0.001$). The application of these results for patients treated with other chemotherapy regimens should be performed with caution. Only end-of-therapy scans were predictive of 2-year overall survival (88% for PET-positive and 100% for PET-negative studies; $p = 0.0128$). As change in the management of patients in FL is likely to occur only after completion of induction immunochemotherapy, and given the better predictive value of PET after completing course of treatment, assessment of response to therapy with PET should probably be reserved for the end of therapy¹¹ (Figure 6).

Figure 3. A 46-year-old male with biopsy-proven follicular lymphoma (grade 1-2) from left Level I neck node, presumed Stage IA per conventional staging. (a) Maximum intensity projection fluorine-18 fludeoxyglucose positron emission tomography (^{18}F -FDG PET)/CT image shows abnormal uptake of ^{18}F -FDG in left Level I node (arrow), biopsy-proven follicular lymphoma. There were two additional foci of abnormal ^{18}F -FDG uptake in spine (dashed arrows). (b) Sagittal PET/CT images show focal uptake of ^{18}F -FDG in T10 and L2 vertebral bodies (arrows), with no definite abnormality in the bone on CT, suggestive of bone marrow involvement. (c) Sagittal T_1 weighted MR shows bone marrow infiltration in the same location (arrows). Biopsy subsequently performed from L2 vertebra was suggestive of lymphoma.

POSITRON EMISSION TOMOGRAPHY IN TRANSFORMATION TO AGGRESSIVE LYMPHOMA

Histological transformation of FL occurs in 5–10% of patients and carries a poor prognosis. Early identification of recurrence is beneficial as intensified therapy regimens may result in complete response and prolonged survival. Several authors have suggested that ^{18}F -FDG PET can be used to direct site of biopsy in patients showing clinical, biochemical or anatomical signs of transformation to aggressive disease.¹²

Nonetheless, there exists a significant overlap in uptake values between indolent and aggressive lymphoma, and there is no consensus on optimal standardized uptake value cut-off to detect transformation. These preliminary results should be confirmed

prospectively to determine whether PET significantly impacts the management of patients with suspected transformation.

In summary, the current literature suggests that initial staging of presumed early-stage FL with PET may change management in a significant number of patients. PET can also be used as a problem-solving tool to confirm the extent of disease for equivocal CT findings, especially when these would determine early stage vs advanced-stage disease. Since long-term control can be achieved with IFRT in localized disease, accurate delineation of the extent of disease may improve patient selection for therapy and better define the radiation field. Further studies are needed to determine the impact of PET-guided therapy on patient outcome.

Figure 4. A 42-year-old female with follicular lymphoma of the upper lip excised. (a) Staging contrast-enhanced CT shows a few low-attenuation lesions in the spleen (arrow), concerning for involvement. (b) Axial fluorine-18 fludeoxyglucose positron emission tomography (^{18}F -FDG PET)/CT (CT left, fused PET/CT middle, PET right) images show that the lesions were not ^{18}F -FDG avid (arrow) and therefore likely not representing lymphomatous infiltration of the spleen. The disease was confirmed to be localized.

REFERENCES

1. Horning SJ, Rosenberg SA. The natural history of initially untreated low-grade non-Hodgkin's lymphomas. *N Engl J Med* 1984; **311**: 1471–5. doi: [10.1056/NEJM198412063112303](https://doi.org/10.1056/NEJM198412063112303)
2. Guadagnolo BA, Li S, Neuberg D, Ng A, Hua L, Silver B, et al. Long-term outcome and mortality trends in early-stage, Grade 1–2 follicular lymphoma treated with radiation therapy. *Int J Radiat Oncol Biol Phys* 2006; **64**: 928–34. doi: [10.1016/j.ijrobp.2005.08.010](https://doi.org/10.1016/j.ijrobp.2005.08.010)
3. Podaloff DA, Advani RH, Allred C, Benson AB 3rd, Brown E, Burstein HJ, et al. NCCN task force report: positron emission tomography (PET)/computed tomography (CT) scanning in cancer. *J Natl Compr Canc Netw* 2007; **5**(Suppl. 1): S1–22; quiz S23–22.
4. Lister TA, Crowther D, Sutcliffe SB, Glatstein E, Canellos GP, Young RC, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. *J Clin Oncol* 1989; **7**: 1630–6.
5. Solal-Céligny P, Roy P, Colombat P, White J, Armitage JO, Arranz-Saez R, et al. Follicular lymphoma international prognostic index. *Blood* 2004; **104**: 1258–65.
6. Wirth A, Foo M, Seymour JF, Macmanus MP, Hicks RJ. Impact of [^{18}F] fluorodeoxyglucose positron emission tomography on staging and management of early-stage follicular non-hodgkin lymphoma. *Int J Radiat Oncol Biol Phys* 2008; **71**: 213–19. doi: [10.1016/j.ijrobp.2007.09.051](https://doi.org/10.1016/j.ijrobp.2007.09.051)
7. Luminari S, Biasoli I, Arcaini L, Versari A, Rusconi C, Merli F, et al. The use of FDG-PET in the initial staging of 142 patients with follicular lymphoma: a retrospective study from the FOLL05 randomized trial of the Fondazione Italiana Linfomi. *Ann Oncol* 2013; **24**: 2108–12. doi: [10.1093/annonc/mdt137](https://doi.org/10.1093/annonc/mdt137)
8. Meignan M, Barrington S, Itti E, Gallamini A, Haioun C, Polliack A. Report on the 4th International Workshop on Positron Emission Tomography in Lymphoma held in Menton, France, 3–5 October 2012. *Leuk Lymphoma* 2014; **55**: 31–7. doi: [10.3109/10428194.2013.802784](https://doi.org/10.3109/10428194.2013.802784)
9. Juweid ME, Stroobants S, Hoekstra OS, Mottaghy FM, Dietlein M, Guermazi A, et al. Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. *J Clin Oncol* 2007; **25**: 571–8.
10. Trotman J, Fournier M, Lamy T, Seymour JF, Sonet A, Janikova A, et al. Positron emission tomography-computed tomography (PET-CT) after induction therapy is highly predictive of patient outcome in follicular lymphoma: analysis of PET-CT in a subset of PRIMA trial participants. *J Clin Oncol* 2011; **29**: 3194–200.
11. Dupuis J, Berriolo-Riedinger A, Julian A, Brice P, Tychy-Pinel C, Tilly H, et al. Impact of [^{18}F] fluorodeoxyglucose positron emission tomography response evaluation in patients with high-tumor burden follicular lymphoma treated with immunochemotherapy: a prospective study from the Groupe d'Etudes des Lymphomes de l'Adulte and GOELAMS. *J Clin Oncol* 2012; **30**: 4317–22.
12. Bodet-Milin C, Kraeber-Bodéré F, Moreau P, Campion L, Dupas B, Le Gouill S. Investigation of FDG-PET/CT imaging to guide biopsies in the detection of histological transformation of indolent lymphoma. *Haematologica* 2008; **93**: 471–2. doi: [10.3324/haematol.12013](https://doi.org/10.3324/haematol.12013)

Figure 5. A 64-year-old female with left breast follicular lymphoma. Involved field radiotherapy planned. Staging CT (not shown) demonstrated equivocal pulmonary nodules. (a) Maximum intensity projection fluorine-18 fludeoxyglucose positron emission tomography (^{18}F -FDG PET)/CT image shows no abnormal uptake of ^{18}F -FDG in the chest; however, unexpected ^{18}F -FDG uptake is identified in the right groin (arrow). (b) Axial ^{18}F -FDG PET/CT (CT left, fused PET/CT middle, PET right) images show metabolically active right groin node (arrow). Biopsy-confirmed disease was not localized to the breast and management was changed to watchful waiting.

Figure 6. A 75-year-old male with Stage III follicular lymphoma. (a) Axial images from staging fluorine-18 fludeoxyglucose positron emission tomography (^{18}F -FDG PET)/CT showed ^{18}F -FDG-avid subcarinal, retroperitoneal and mesenteric nodes (arrows). (b) Post-chemotherapy follow-up PET/CT axial images acquired at same levels show residual masses on CT (white arrows on CT images) but no abnormal ^{18}F -FDG uptake, indicating complete metabolic response. The patient has been in remission for 4 years without clinical or imaging evidence of recurrence.