FDG PET-CT in follicular lymphoma: a case-based evidence review

Stephen D. Smith,[1] Mary Redman,[2] and Kieron Dunleavy[3]

[1]Division of Medical Oncology, Department of Medicine, University of Washington School of Medicine, Seattle Cancer Care Alliance, Seattle, WA; [2]Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA; and [3]Lymphoid Malignancies Branch, National Cancer Institute, Bethesda, MD

Case

A 52-year-old woman develops right neck lymphadenopathy in the absence of systemic symptoms. Excisional biopsy specimen shows grade 1-2 follicular lymphoma (FL). Physical examination reveals a cluster of 1- to 2-cm right cervical nodes but no other abnormalities. Lactate dehydrogenase is 400 U/L (normal: 140-210 U/L), β-2 microglobulin is 4.1 μg/mL (normal: 0-2.5 μg/mL), and a complete blood count with differential is normal.

18-Fluorodeoxyglucose (FDG) positron emission tomography (PET) with computed tomography (CT) is performed, showing FDG-avid lymphadenopathy above and below the diaphragm, ranging in size from 1.2 to 6 cm. Three FDG-avid lymph nodes measure more than 3 cm. A single 6-cm pelvic node has a maximum standardized uptake value (SUVmax) of 22, and other SUVs range from 6 to 8. An absence of FDG marrow uptake is noted.

How should these PET-CT findings be integrated into further evaluation, prognostication, and treatment recommendations for this patient with FL? Should repeat PET-CT be performed on completion of therapy?

Background

The use of PET-CT in oncology is increasing, and its role in the assessment and management of lymphoma has evolved.[1-4] Given the variable glucose avidity and heterogeneous behavior of lymphomas, it is not surprising that histology, timing in relation to therapy, and interpretation methods influence PET-CT findings. Indolent lymphomas, characterized by variable FDG avidity and often a prolonged natural history, represent a unique context for assessing the merits of PET-CT. Prior consensus guidelines in 2007, reflecting a paucity of data, recommended PET-CT in restricted fashion for indolent lymphomas, such as clinical trials incorporating response rate as a primary end point.[5] However, increasing evidence supports its role in FDG-avid indolent non-Hodgkin lymphoma (NHL) subtypes, particularly FL, a histology in which PET-CT is frequently performed in both community and academic settings.[6,7] Recently, formal guidelines for the use of PET-CT in FL have shifted, recommending its use for initial staging, evaluation for transformation, and response assessment after first-line therapy.[3,4,8] PET imaging offers several benefits, including the potential for improved staging accuracy and evaluation of large cell transformation, which may optimize selection of first-line therapy. In the posttreatment setting, accurate identification of patients at highest risk of early relapse and mortality may inform surveillance methods or the need for additional therapy. Nonetheless, until prospective studies are available, the impact of PET-CT on outcomes in FL remains to be defined, and integration into clinical management will require nuanced judgment based primarily on retrospective data. We present an evidence-based, focused review of the role of PET-CT in follicular lymphoma, identifying relevant references through PubMed searches, existing review articles, and expert sources. A pooled analysis was undertaken to assess the impact of PET-based imaging compared with conventional CT on initial stage. Recommendations for the use of PET-CT in FL are provided and rated in terms of strength according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group system.[9]

PET-CT for initial staging of FL

Historically, a number of studies have demonstrated that PET-based imaging is sensitive for staging FL irrespective of grade.[10-14] PET-based imaging (and more recently, combined PET-CT) identifies a greater extent of nodal and extranodal disease sites than standard staging including CT.[12-17] A study published in 2008 by Janikova and colleagues found that among 62 newly diagnosed FL patients, PET-based staging identified a different disease distribution (compared with conventional CT) in 29 patients, and changed the stage in 6 of the 62 patients (10%).[16] Another retrospective study restricted to patients with early-stage FL by conventional staging including CT found that among 42 patients, PET results were projected to alter stage designation in 13 patients (31%) and management in 19 (45%).[13] To elucidate the impact of PET-based staging on management, Scott and colleagues performed a prospective study in which clinicians devised treatment plans for 74 patients with indolent NHL before and after PET imaging.[18] The addition of PET to staging led to a revised treatment plan in 25 patients (34%), including a shift to palliative-intent therapy in 7 patients. Patients with stage I-II indolent NHL defined by PET imaging (treated primarily with radiotherapy) had excellent outcomes, superior to patients with stage III-IV disease.

More recently, Luminari and colleagues reported on 142 FL patients with available pretreatment PET-CT imaging who were included in the FOLL05 trial, a prospective 3-arm comparison of first-line chemoimmunotherapy regimens.[14] Forty-three percent of the patients had a different number of nodal sites (including 34% showing more sites) than were visualized with conventional CT. PET-CT upstaged 15 patients and downstaged 5. Analogous to

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the findings of Wirth and colleagues,[13] most patients (15 of 24) previously classified as having early-stage disease by CT were found to have advanced-stage disease using PET-CT. Frequent bone, spleen, and gastrointestinal tract extranodal sites were also visualized. PET was insensitive for detecting marrow involvement (identifying 43% of patients with histologically confirmed disease), a consistent finding in indolent NHL.[19]

Using data from 6 studies,[12-17] we calculated a pooled proportion of FL patients in whom stage would be altered if PET-based imaging were employed instead of CT. A weighted average was calculated, based on data from a total of 252 patients, using the Freeman-Tukey transformation (arcsine square root transformation).[20] This analysis indicates that the estimated proportion of FL patients whose stage is altered by PET-based staging is 19%, with a 95% confidence interval of 14% to 23%. The increased accuracy of PET-CT staging may hold the most clinical relevance in the management of early-stage FL. Exclusion of occult, distant disease using PET-CT—as was observed in historical FL cohorts staged with laparotomy—may translate to improved disease control and survival rates for such patients.[18,21] Even when stage designation is unchanged, PET-CT may assist in defining margins of the radiation field. In modern practice and in clinical trials, routine application of PET-CT staging in FL is likely to cause stage migration, introducing bias in survival outcomes. Overall, the recommendation for routine use of PET-CT for FL staging is tempered by limitations of the available data, which are generally retrospective, and lack routine histologic confirmation of suspected distant sites or long-term follow-up. False-positive results with PET are well described and occur with normal physiologic processes, additional malignancy, and inflammatory and benign lesions.[22] Thus, single PET imaging findings that may influence management should be confirmed with biopsy.[23]

PET-CT and prognosis in FL

Because PET-CT regularly identifies additional disease sites in FL, some impact on the Follicular Lymphoma International Prognostic Index (FLIPI)—incorporating number of nodal sites and disease stage on the basis of conventional imaging—would be anticipated.[24] In a descriptive study of PET-CT staging in FL patients at National Comprehensive Cancer Network centers, no difference in FLIPI distribution was seen between those staged with or without PET.[6] However, in an analysis of a group of patients enrolled in a prospective trial and who had a FLIPI score calculated using both CT and PET-CT at staging, Luminari and colleagues found that PET-CT resulted in a different FLIPI risk group in 24% of patients.[14] In 2011, Le Dortz and colleagues showed that bone uptake and the presence of 6 or more nodal sites on staging PET imaging predicted poor outcomes following chemoimmunotherapy.[17] In that study, a PET-based prognostic score was developed but has yet to be validated in prospective trials. Given the sensitivity of PET-CT, the value of the FLIPI must be reassessed, and new prognostic models incorporating number, intensity, and location of FDG-avid sites should be explored. Interestingly, Abou-Nassar and colleagues found that patients undergoing PET staging at National Comprehensive Cancer Network centers were treated earlier and more frequently with an anthracycline, but the significance of this observation, derived from an uncontrolled setting, is unclear.[6] Alteration of content or timing of first-line therapy for FL on the basis of PET-CT findings alone cannot be recommended according to the data available.

PET-CT in evaluation of HT

The presence of histologic transformation (HT; or discordant presentation, used synonymously in this review) carries implications for prognosis and first-line therapy. Biopsy evidence of HT requires consideration of anthracycline-based therapy and is predicted by clinical factors including elevated lactate dehydrogenase, poor performance status, and adverse risk group according to standard prognostic models.[25,26] Early reports of PET imaging in NHL noted higher SUVs in aggressive NHL than in indolent forms, although with wide variation and overlap.[27-29] In 2005, Schöder and colleagues confirmed that in 97 NHL patients, SUVs were lower in indolent lymphomas, and that an SUVmax >10 at a given biopsy site was 81% specific for an aggressive histology.[30] Subsequently, investigators have described the SUVmax of biopsy-proven HT sites, as well as the highest SUVmax on a given scan and its variation between nodal sites, as predictors of HT.[31-34]

In 2008, Bodet-Milin identified 38 indolent NHL patients with clinical or laboratory signs of HT and performed a prospective study using PET-CT imaging to guide biopsies that were performed at sites with highest SUVmax.[31] Seventeen patients were diagnosed with HT by biopsy (45%), with a median SUVmax of 18.5 (range: 11.7-41.2) compared with 8.6 (range: 1.7-17.0) in nontransformed cases. All patients with an SUVmax >17 showed HT on biopsy of that site. Using a cutoff SUVmax of 14 in this group that had clinical risk factors for transformation, the positive predictive value for HT was 94%.

Noy and colleagues reported a group of patients with indolent NHL who developed biopsy-proven HT and underwent PET imaging at time of transformation.[32] Of 33 patients with evaluable data, the mean SUVmax at the site of HT was 14, with a range of 3 to 38 (standard deviation 8.7, calculated for this review). Among 12 patients with available paired PET scans (from diagnosis of both indolent NHL and HT), 8 showed a $>50\%$ increase in highest scan SUVmax at time of HT.

Karam and colleagues reported PET-CT findings in 29 patients with HT compared with 40 patients with indolent NHL.[33] PET-CT and biopsy were not performed in a standardized manner; the study reflected heterogeneous clinical practice. The mean highest SUVmax was 20.4 (standard deviation 9.5) in HT but was 6.5 (standard deviation 4.4) in indolent histologies. The authors described significantly higher SUVs in areas of HT compared with indolent NHL (11.8 vs 2.3), in a subset of patients in whom 2 biopsies were performed. Based on a small sample of patients and without adjustment for clinical risk factors, the authors concluded that a threefold higher SUV (in a given scan, or increasing over time) should warrant suspicion for HT.

Blase and colleagues reported staging PET findings of 88 indolent lymphoma patients, 5 of whom were diagnosed with HT at a median of 8 months later.[34] The odds ratio for developing HT was 1.25 (95% confidence interval: 1.024-1.513) for each unit of SUVmax, and remained elevated when corrected for lactate dehydrogenase. Baseline SUVmax measurements ranged from 4.2 to 19.6, but PET imaging was not repeated at time of HT. In 4 of the 5 cases, the site of highest SUVmax on staging PET-CT was used to direct biopsy and successfully identify HT.

Limitations of these data are several-fold and warrant caution in applying these findings to routine clinical practice. Standard PET-CT acquisition and interpretation criteria were not applied, and SUV

measurements are known for variability and limited reproducibility.[35] With the exception of the study by Bodet-Milin et al,[31] data are retrospective, include varying indolent NHL subtypes, and do not report or adjust for known clinical risk factors for HT. Although SUV cutoffs of 10, 14, and 17 have been proposed to signify high likelihood of HT, the standard deviation of highest SUVs observed in biopsy-proven HT is wide, and a significant proportion of HT (45% in the study by Noy et al[32]) is associated with an SUV of 10 or under.

Finally, in initial staging of FL and in the absence of risk factors for HT,[25,26] the overall prevalence of HT (or discordant, aggressive NHL) is likely to be low. Even with reasonable specificity at a given SUV cutoff (such as 10), the positive predictive value of PET-CT for detecting true HT will be limited. Therefore, overreliance on SUVs in asymptomatic or low-risk FL patients at initial staging may expose patients to unnecessary biopsies and excess risk. Until more data are available, clinical factors should drive suspicion for HT, which may subsequently be confirmed by biopsy.

PET-CT for response evaluation in FL

Although survival rates in FL have improved in the last 2 decades, a continual pattern of relapse is observed.[36,37] Consolidation of first remission using high-dose chemotherapy and autologous stem cell transplant, and maintenance using scheduled rituximab, improve disease control but not overall survival.[38,39] Nonetheless, certain high-risk subgroups may achieve greater benefit with postinduction therapy, including transplant, rituximab maintenance, or incorporation of novel agents, and are a high-priority group for inclusion in prospective clinical trials.

The potential for PET-CT to identify FL subsets at high risk of relapse following rituximab-containing chemoimmunotherapy has been consistently observed in recent reports. Analyses of FL patients enrolled in the PRIMA[39] and FOLL05[40] trials, who had PET performed off-trial and interpreted locally within 3 months of completing therapy, found that a positive posttreatment PET scan was seen in about 25% of patients and predicted poor progression-free survival (PFS).[41,42] In both analyses, more than half of patients previously classified as having a partial response by CT-based imaging were reclassified to complete response by PET, and PET-defined complete response was a more powerful prognostic indicator than the FLIPI score. A prospective study by Dupuis and colleagues enrolled 121 high-tumor-burden FL patients from 2007-2009, performing PET imaging before treatment with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; after 4 cycles; and after treatment and outcomes, with the primary objective to determine PFS according to PET findings.[43] Maintenance therapy was not given. Standard PET acquisition parameters and central review according to the 5-point, visual Deauville scale[44] were undertaken; the best discrimination and interobserver concordance was achieved using a Deauville cutoff of 3 or lower to define a negative PET scan result. At 23 months of follow-up, a negative posttreatment PET scan was seen in 76% of patients, which predicted a superior 2-year PFS rate (87% vs 51% for those with a positive PET scan, $P < .001$) and overall survival rate (100% vs 88% for those with a positive PET scan, $P = .01$). The predictive value of interim PET was less powerful, and similar to retrospective studies, posttreatment PET was a more powerful predictor than FLIPI score on multivariate analysis. A recent pooled analysis of these 3 studies[41-43] conducted independent analyses of available PET scans using the Deauville scale, and showed that patients with a positive PET scan (score of 4 or 5) following completion of therapy (occurring in 17%) had a poor PFS (23% at 4 years vs 63% for those with a negative PET scan).[45]

The prognostic role of PET-CT has yet to be formally compared with that of minimal residual disease (MRD) in FL. MRD detected by polymerase chain reaction—and more recently, tumor-specific DNA identified and monitored by next-generation sequencing—predicts relapse in FL and aggressive NHL.[46-50] Therefore, although a positive PET-CT scan result predicts poor PFS in high-tumor-burden FL after chemoimmunotherapy, how to ameliorate this course and to define the value of PET with respect to molecular techniques for MRD monitoring remain to be determined by prospective trials.

Case conclusion, summary, and general recommendations

An additional biopsy of the 6-cm mass with an SUV of 22 was undertaken, which showed diffuse large B-cell lymphoma. Bone marrow aspirate and the biopsy specimen showed 30% involvement by grade 1-2 FL. Following complete pretreatment evaluation, anthracycline chemoimmunotherapy was initiated.

In light of evolving data, national trends, and recent clinical guidelines, PET-CT is poised for increasing integration into routine FL management.[3,4,6-8] Nonetheless, prospective data defining its role are scant. Retrospective studies suggest that PET-CT increases accuracy of initial staging, with implications for patients under consideration for localized radiotherapy; routine use in such patients is recommended (grade 1C). Evaluation for transformation should not be determined solely by PET-CT results including SUV but should incorporate known risk factors for transformation to limit the risk of false discovery and unnecessary biopsies. PET-CT can be used to direct the site of biopsy in FL patients with existing clinical risk factors for HT (grade 1B). The sensitivity of PET-CT is relatively low for bone marrow involvement. Although PET-CT does not impact the FLIPI prognostic group in most patients, the relevance of the FLIPI requires reassessment, and functional imaging may offer novel prognostic information that is best defined in the context of prospective trials. After standard chemoimmunotherapy treatment, PET discriminates prognosis among high-tumor-burden FL patients when visual interpretation methods are employed. Nonetheless, the role of posttreatment PET-CT alongside emerging MRD assays, and its potential to meaningfully inform surveillance or treatment decisions, remain to be defined. Thus, although PET-CT is useful for specific purposes in FL, clinical judgment, use of standardized acquisition and interpretation methods,[4,51] and judicious use of confirmatory biopsy are required. With a shift toward novel, noncytotoxic treatments for FL, the role of PET-CT in FL is likely to require continual reassessment.

Authorship

Contribution: S.D.S. and K.D. developed the concept for this review; S.D.S. conducted the literature search and wrote the first draft; M.R. designed and performed the pooled analysis. All authors provided input and critical review of the manuscript.

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Correspondence: Stephen D. Smith, Seattle Cancer Care Alliance, Box G3-200, Seattle, CA 98109; e-mail: ssmith50@u.washington.edu.

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