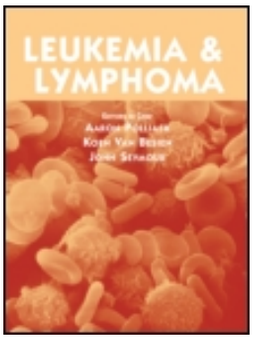

Leukemia & Lymphoma

ISSN: 1042-8194 (Print) 1029-2403 (Online) Journal homepage: informahealthcare.com/journals/ilal20

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To cite this article: John F. Seymour, Judith Trotman & Michael S. Hofman (2013) Evaluating the place of 18-fluoro-2-deoxy-d-glucose positron emission tomography scanning in primary staging and beyond in patients with follicular lymphoma, Leukemia & Lymphoma, 54:10, 2093-2095, DOI: 10.3109/10428194.2013.800201

To link to this article: https://doi.org/10.3109/10428194.2013.800201

Leukemia & Lymphoma, October 2013; 54(10): 2093–2095

ISSN: 1042-8194 print / 1029-2403 online
DOI: 10.3109/10428194.2013.800201

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COMMENTARY

Evaluating the place of 18-fluoro-2-deoxy-D-glucose positron emission tomography scanning in primary staging and beyond in patients with follicular lymphoma

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18-Fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) is a highly sensitive and reasonably specific imaging modality with a clearly established place in the initial staging, response assessment and likely interim response assessment of patients with aggressive non-Hodgkin lymphomas (NHLs) and Hodgkin lymphoma [1–3]. Despite early reports of lower FDG-PET avidity in follicular lymphoma (FL), larger more recent studies with modern co-registered PET/computed tomography (CT) equipment consistently report almost universal, albeit heterogeneous, FDG avidity in $>95\%$ of patients presenting with FL [4,5]. Uncommon localizations such as skin constitute many of the reported "non-FDG-avid" cases. The revised 2013 National Comprehensive Cancer Network (NCCN) guidelines advocate FDG-PET/CT in selected cases [6], but most other current guidelines and consensus statements generally do not recommend the use of PET scanning in FL; is this justified and appropriate?

In this issue of the journal, Abou-Nassar *et al*. employ the large NCCN NHL outcomes database to explore the utilization and perceived impact of PET scanning in the initial staging of patients with FL on their treatment and outcome [7]. Data from seven large institutions between 2001 and 2009 were evaluated, finding 953 patients with newly diagnosed grade 1–2 FL and >6 months' follow-up. They observed marked inter-institutional variation in the rate of utilization of PET scanning (25–76%; $p<0.0001$) and an association between PET scanning and the earlier initiation of therapy ($p<0.0001$). Given that treatment strategies also varied markedly across FL international prognostic index (FLIPI) score and institutions (rates of observation and utilization of anthracycline-based chemo-immunotherapy both ranged from $<10\%$ to $>50\%$), it is likely that other prognostic factors and, in particular, institutional policies and practitioner attitudes were strong determinants of treatment selections, and that PET utilization rates were a correlate of these factors, despite an attempt to tease out these separate effects in a multivariate analysis. In part, the variation may also represent increased availability of PET over the course of the study period, as accessibility was limited in 2001 but more widespread by 2009. The increased utilization of PET also correlates with an expanding evidence base on the use of PET in follicular lymphoma [5]. Although guidelines were not being followed, in an area of rapidly evolving literature it takes time to reach consensus. Some features of the inclusion criteria and staging conventions used by Abou-Nassar *et al*. may have influenced these conclusions. First, the allocated stage and prognostic score for the patient utilized all staging investigations, including the PET scan. Thus, those patients "up-staged," as discussed above, had their disease stage (and derived prognostic score) determined based on the PET data.

Surprisingly, they describe that PET scanning was not more frequently used in patients with stage I FL, although this varied markedly between institutions (range 33–100%; $p<0.003$). Only 47% of patients with stage I disease were treated with radiation therapy (RT) (range 17–100%), echoing the surprising results reported by the US National LymphoCare Study where only 27% of patients with stage I FL were treated with RT alone, and overall only 40% received RT-containing therapy [8]. There is a large and consistent literature confirming the ability of involved field RT (IFRT) to cure 40–50% of patients with stage I–II FL [9], but radiation cannot be directly effective against disease not included within the irradiated field. Accurate determination of disease location and extent is particularly important for those patients where IFRT is included in their management, as most guidelines currently recommend for stage I–II disease. Recent series have consistently shown that patients with apparent stage I–II FL after completion of "conventional" staging procedures have their disease status "up-staged" to stage III–IV disease

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This commentary accompanies an article to be published in *Leukemia & Lymphoma*. Please refer to the table of contents of the print issue in which this commentary appears.

in 28–62% following PET imaging [10–14]. Importantly, patients upstaged with PET in a prospective multicenter trial had a significantly inferior progression-free survival, confirming the prognostic significance of PET-identified disease [13]. This is discordant with Abou-Nassar *et al.*'s assertion that "no studies to date have reported clinical outcomes following the changes in staging and initial treatment strategies resulting from the use of FDG-PET in FL." If RT is to be utilized in a patient with stage I–II FL (and we support the existing consensus guidelines that recommend this approach), then it is appropriate that loco-regional disease is confirmed by PET scanning prior to implementation of RT.

Further, it is also not possible to know how many patients with a histologic diagnosis of grade I–II FL had a subsequent PET scan which revealed features suggestive of a more aggressive disease histology based on an elevated maximum standardized uptake value (SUV_{max}), prompting an additional targeted biopsy [15–17]. A major advantage of PET is its ability to characterize disease activity, resulting in a paradigm shift from conventional imaging that principally identifies sites of disease and measures their size [18]. In FL, FDG-PET frequently demonstrates disease heterogeneity, with varying intensities of glycolytic activity at different sites. Whilst biopsy is traditionally directed to a site that easiest and safest, it is possible that using histology from a "random" site may be misrepresentative. Reported SUV_{max} thresholds have varied, but one large study suggested that values >10 were associated with a sensitivity and specificity of 71% and 81%, respectively, for transformed disease [16]. If such a biopsy revealed transformed disease/diffuse large cell lymphoma, such patients would have been excluded from this analysis.

Also, given the retrospectively applied inclusion window of ± 90 days for initial staging tests, any patients who manifested features of disease progression or developed concerning symptoms prompting re-evaluation with PET scanning during that period would have had their PET scan considered part of their initial staging evaluation.

Although beyond the scope of the current article by Abou-Nassar *et al.*, there are also recent data from two large series demonstrating that residual PET-positivity after completion of frontline chemo-immunotherapy identifies a small subset of patients at risk of early disease progression and impaired overall survival [19,20]. The first of these studies was a retrospective subset analysis of 122 patients from the large prospective PRIMA study [20,21], with the inherent limitations of such a retrospective multicenter cohort. PET-based response assessment was more predictive than conventional response assessment using the 1999 International Workshop Criteria (IWC), and identified persisting PET avidity in 18% of patients otherwise considered to have achieved a complete response or complete response unconfirmed (CR or CRu). The second post-treatment evaluation was prospectively conducted [19] and utilized standardized methods for PET acquisition and interpretation with centralized reporting, using the increasingly widely adopted five-point scale (5PS) in which the level of any residual FDG uptake is compared with the uptake in reference sites of normal mediastinum and liver [22]. This more rigorous study largely confirmed the earlier observational findings, in that end-of-treatment scans (with a cut-off ≥ 4 on the 5PS) were predictive of inferior 2-year progression-free survival (PFS), with rates of 51% vs. 87% ($p < 0.001$). End-of-treatment scan results were also predictive of 2-year overall survival (OS), with rates of 88% vs. 100% ($p = 0.0128$). While application of the 5PS in itself does not require a pretreatment scan, the availability of a baseline PET/CT increases the accuracy of a subsequent response assessment. The emerging data on the utilization of post-treatment PET scanning are very exciting, and have the potential to be used as a robust surrogate marker for long-term treatment outcomes that would allow far more rapid evaluation of the efficacy of new therapies, accelerating clinical trial progress in this increasingly prevalent disease.

The current analysis is a very useful and illuminating description of the marked variation in current utilization patterns of PET. As this is a retrospective study, the findings are associative and correlative, even though they may hint at causality. The increasing utilization of PET, despite lack of support in guidelines, likely reflects that clinicians are finding the modality beneficial for guiding management in individual patients. Whilst there is evidence that PET changes management in a high proportion of up-staged patients, currently accruing and future studies must further examine the potential contribution of PET scanning in follicular lymphoma on overall patient population outcomes and system resource utilization. Diagnostic procedures including PET, however, constitute less than 6% of expenditure in cancer patient-care [23]. There is some irony that so-called "expensive" imaging forms the cornerstone for directing therapies that are far more costly [24]. FDG-PET/CT can reduce utilization of other tests with mounting evidence that, for many patients, routine additional contrast-enhanced CT (CECT) is redundant, particularly in follow-up, and can be used selectively in patients with equivocal PET/CT findings [25]. Low-dose CT also bears merit in follicular lymphoma imaging, as it provides ample image quality whilst reducing the cumulative radiation exposure in a population subjected to serial imaging. Given the benefits of PET/CT [26] in staging, directing biopsy and response assessment, it is timely to ask whether PET/CT should be the first rather than the last test performed.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

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