**“Is it time for PET-guided therapy in follicular lymphoma.”**

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**Word count:**

Currently 4355. Abstract 249.

Tables 3, Figures 3 or 4

**Acknowledgements**

**Abstract**

18F-fluorodeoxyglucose (FDG) Positron Emission Tomography-Computerised Tomography (PET) is now established as the gold-standard imaging modality for both staging and response assessment of follicular lymphoma (FL). In this Perspective, we propose where PET can, and cannot, guide clinicians in their therapeutic approach. PET at diagnosis/pre-treatment is important for staging, with greater sensitivity compared to standard CT and consequent improved outcomes in truly limited stage FL. Small datasets suggesting a high baseline SUVmax identifies de-novo histologic transformation (HT) are not corroborated by data from GALLIUM, the largest prospective study using modern therapies for FL. Nonetheless, the role of baseline quantitative PET measures requires further clarification.

The median survival of patients with newly diagnosed FL is now potentially beyond 20 years. Treatment of symptomatic FL aims to achieve remission and optimise quality of life for as long as possible, with many patients achieving a “functional cure” at the cost of unwanted treatment effects. Several studies have identified that end-of-induction (EOI) PET after initial chemoimmunotherapy for patients with high tumour burden is strongly predictive of both progression-free and overall survival, and EOI PET is being evaluated as a platform for response-adapted treatment. There remain unmet needs: improving the inferior survival for patients remaining PET-positive; and quantifying the PFS and time to next treatment advantage, and additional toxicity of anti-CD20 maintenance in patients achieving complete metabolic remission. In the absence of an overall survival advantage for frontline maintenance, the question of using PET to guide our therapeutic approach is more important than ever in the context of the COVID-19 pandemic.

**Introduction**

18Fluorine fluorodeoxyglucose (FDG) positron emission tomography combined with computerised tomography (PET-CT, hereafter cited as PET) is an important imaging modality in a range of FDG-avid lymphomas. Initially, with a focus on diffuse large B cell and Hodgkin lymphomas, PET was not considered central to staging and response assessment of the “incurable” indolent follicular lymphoma (FL). However, it became apparent that FL is universally, albeit not uniformly, FDG-avid.1-4 This Perspective will consider the current role of PET in the management of FL at key points in the patient pathway. We will also consider the potential role of PET in identifying/predicting high-grade transformation and/or selecting optimal biopsy sites. We seek to assist clinicians in deciding how to integrate PET scanning in their own practices for each individual patient.

**Search strategy and selection criteria.**

References for this perspective were identified through searches of Medline and EMBASE with the search terms ‘positron emission tomography’ and ‘follicular lymphoma’ from 2000 to January 2020. Articles were also identified through searches of the authors’ own files. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this perspective.

**Staging and prognostication in newly diagnosed patients**

While there are differences across health care systems, in the authors’ experience, a contrast enhanced computerised tomography (CT) scan is usually performed at the time a diagnosis of FL is made. Notwithstanding this, the 2014 Lugano Classification recommends PET for staging of all FDG-avid lymphomas based on the greater sensitivity of PET in detecting lymphoma in small nodes and extra-nodal sites compared with CT.5,6 This guidance is applicable to FL, which is FDG avid in almost all cases, albeit with variable FDG uptake between and within patients1-4. Additional sites are detected by PET in approximately two-thirds of cases, with upstaging estimated in 10-60%, especially those with apparently limited stage disease on CT.7,2,8,9 Retrospective reports suggest that PET scanning alters management in 5-25% of lymphoma patients.10-12 In FL, more sensitive staging could potentially lead to better informed treatment decisions, influencing both choice and timing of therapy.

Interestingly, the application of PET to clinical staging affects the performance of FL prognostic scoring systems.7 In a US SEER-Medicare database study of 5712 patients diagnosed from 2000 to 2009, the use of PET for staging was associated with more favorable overall survival (OS) (hazard ratio [HR] 0.75, 0.68-0.83) and lymphoma-specific survival (HR 0.69, 0.58-0.82).13 An analysis of the distribution of treatment strategies suggested that PET affects clinical staging, prognostic evaluation and treatment decisions. This observation was echoed in a National Comprehensive Cancer Network (NCCN) database analysis of 953 patients with grade 1-2 FL: the 532 (56%) patients who underwent staging by PET were more likely to receive early treatment and anthracycline-based chemotherapy.14

In keeping with this finding, a recent retrospective analysis from MSKCC, validated using an Italian FOLL05 trial cohort, compared patients staged by CT versus PET. Those staged by CT had an inferior OS despite a similar rate of PFS at 24 months (PFS24).15 The improvement in outcomes associated with PET staging likely resulted from multiple factors including the Will Rogers phenomenon associated with stage migration, as well as the availability of more effective treatments recently. In the discovery cohort, patients with progression of disease (POD) within 24 months of R-CHOP had a 5-year OS of 57.6% for CT-staged patients compared with 70.6% for PET-staged patients. In the validation cohort, the corresponding figures were 53.9% and 100%. Among patients with POD within one year of initiating therapy, the rate of histologic transformation (HT) was higher in CT-staged patients than in those staged by PET (16.7% versus 6.3%, respectively). The explanation for the observed association between PET imaging and reduced rates of HT in this retrospective study is unclear and may reflect confounding variables.

Directly demonstrating the clinical benefit of new imaging modalities presents major challenges due to many confounding factors that influence, or are influenced by, their application. Consequently, they are often adopted into routine practice based on improved sensitivity alone. The application of PET scanning to FL staging creates the specific challenge of knowing how best to manage patients with FL who have advanced-stage (AS) disease by PET and limited-stage (LS) disease by CT. Since the clinical course and optimal management of such patients has not been defined, caution should be exercised when extrapolating from data generated in patient cohorts staged by CT. Nonetheless (and abscopal effects notwithstanding), it is reasonable to assume that localised radiotherapy (RT) is unlikely to be curative in this setting. Conversely, in patients with LS disease defined by both imaging modalities, it is reasonable to assume that local RT may achieve better long-term disease control if the radiation field is based on PET rather than CT. In keeping with this idea, a recent study reported excellent outcomes for patients with LS using PET to select for radiotherapy.16 Five-year freedom from progression (FFP) was 68.9% (95% CI, 63.9-73.4) and 5y-OS was 96% (95% CI 93.2-97.6), better than in earlier series from the pre-PET era.17 Similarly, in the MSKCC cohort cited earlier, patients with stage I/II disease defined by PET demonstrated superior OS compared with those with stage I/II disease defined by CT. For patients with stage I disease, 10-year OS was 93% and 82%, respectively (log-rank P=0.005), while the corresponding figures for patients with stage II disease were 89% and 68%, (log-rank P=0.048).15 In contrast, the clinical impact of identifying more disease sites in patients who already have evidence of AS on conventional CT and bone marrow biopsy-based staging is limited, with only 4% of patients upstaged from stage III to IV in one series and no effect on management.2

In summary, for the patient with apparently localised disease on CT, PET may detect additional sites of disease with beneficial implications for therapeutic decision making. In contrast, for patients with asymptomatic AS disease identified on CT who do not meet criteria for commencing therapy, a PET scan can be deferred until treatment is required.

An important, but conceptually distinct, use of PET staging in treatment naive patients just prior to therapy is to provide a map of disease distribution to facilitate end-of-induction (EOI) response evaluation.5,6

**Role of bone marrow biopsy in the context of PET staging**

In diffuse large B-cell lymphoma (DLBCL), PET has effectively rendered the bone marrow biopsy (BMB) redundant owing to its greater sensitivity in detecting bone marrow involvement (BMI).18-20 PET is less sensitive at detecting BMI in FL which is usually more subtle with widespread but low-level paratrabecular involvement.2 That said, focal lesions are more likely to be detected by PET, therefore PET and BMB provide complementary information. Although both are required for accurate staging, the presence of bone marrow involvement in the GALLIUM trial, which was demonstrated by BMB in 613/1190 (51.5%) of patients, had no impact on PFS.21 In a recent retrospective study from MSKCC performed in 261 patients with newly diagnosed FL,22 BMI was found in 46 patients by both modalities, 35 by BMB only and 32 by PET only. The BMB was positive in 4/74, 2/26, 26/73 and 49/88 patients with PET stage I, II, III and IV disease, respectively. Conversely, PET upstaged 24 patients to stage IV, including 10 from stages I/II. BMI by PET but not BMB was an independent predictor of PFS and OS. Consequently, it may be reasonable to defer BMB in FL in patients who do not require immediate treatment or omit the pre-treatment BMB altogether where the results will not impact on the therapeutic approach.

**Quantitative baseline PET measurements in FL**

The maximal standardised uptake value, (SUVmax) is a semi-quantitative measure of 18F-FDG metabolism that describes the radioactivity in a lesion corrected for dose of FDG and patient weight at a given time after FDG injection. Patients with aggressive B cell lymphomas generally have higher baseline SUVmax (bSUVmax) values than patients with FL, and earlier small single-institution studies suggested that bSUVmax could identify large-cell histologic transformation (HT).23,24 A recent large single institution analysis of bSUVmax in 346 patients with advanced stage grade 1-3a FL was reported. The median bSUVmax was 11 (range: 1.5-42) with a defined optimal cutoff for predicting PFS of >18. A biopsy of the most FDG-avid node in all 52 patients with an SUVmax >18 did not identify HT. In patients treated with CIT, SUVmax>18 correlated with inferior OS.25 In large prospective multicentre studies, the bSUVmax in newly diagnosed FL likewise ranged considerably, reflecting the biological heterogeneity of this lymphoma, where FDG uptake is likely affected by not only the lymphoma cells but also non-malignant cells in the tumour microenvironment. In the follicular lymphoma collaboration (FOLLCOLL) combined analysis, involving 181 patients from three prospective studies,3,26-28 median bSUVmax was 10 (range 3-35, IQR:7-14) with no correlation between bSUVmax and histological grade. Surprisingly, the 47% of patients with a bSUVmax ≤ 9.4 had an inferior 5-year PFS (47.4% vs. 62.4% [HR 1.62, p=0.032]). This finding was confirmed (HR 1.81, p = 0.044) on multivariate analysis, that took into account age, longest diameter of largest involved lymph node (LodLin) > 6cm, positive bone marrow biopsy and β2 microglobulin28. Although at first sight counterintuitive, it is possible that higher bSUVmax values reflect an immune microenvironment more conducive to rituximab-induced ADCC. 29 In support of this, a recent correlation between lesional SUV max and CD4 and CD8A gene expression suggests a strong influence of the intra-tumoral T cell component on bSUVmax.

The largest prospective dataset on bSUVmax30 comes from the phase III GALLIUM study31 where patients with HTB FL were treated with induction chemoimmunotherapy (CIT) containing either obinutuzumab or rituximab followed by antibody maintenance. Among 549 patients for whom PET data were available, bSUVmax values ranged from 3.1 to 64.4. After a median follow-up of 5 years, biopsy-confirmed HT occurred in 15 patients (2.7%). Median bSUVmax was 12.4 (range, 8.1-28.0) in those developing HT versus 11.8 (3.1-64.4) in those without HT. The SUVrange (difference between bSUVmax of the most and least 18F-FDG–avid lymphoma sites) was similar in both groups (median 8.0 [range, 1.08-23.91] versus 7.1 [0.00-59.81], respectively). Seventy-four of 549 (13.5%) patients had a bSUVmax of >20, with only 1/74 (1.4%) undergoing documented HT. No association with HT was observed with any specific chemotherapy regimen (CHOP, CVP, or bendamustine) or antibody, and SUVmax did not predict subsequent HT in patients treated with any specific regimen.30 Furthermore, baseline SUVmax did not correlate with PFS in the GALLIUM study (Barrington S, PET in Lymphoma and Myeloma Meeting, 2018). It is important to note that this is the only prospective data charting quantitative PET metrics in a bendamustine-treated population. Table 1 summarises the key studies correlating SUVmax with outcome in FL. These data suggest there is no clear benefit in biopsying or re-biopsying lesions on the basis of SUVmax alone, even if the area of maximum FDG uptake was not sampled. One possible caveat to making this conclusion is that some patients with high SUVmax values might have been excluded from the GALLIUM trial due to concerns about HT on the pre-treatment PET. However, there was a similarly low rate (25/653, 3.8%) of documented HT in the subset of GALLIUM patients without baseline PET performed, arguing against such a selection bias. Nonetheless, to directly investigate this possibility, the PETReA (PET-guided, Response-Adapted therapy) study (EudraCT number: 2016-004010-10) will include the collection of screening logs for all patients diagnosed with FL at participating institutions irrespective of trial enrollment. In this way, it should be possible to evaluate the clinical significance of bSUVmax without the potential confounding effects of patient exclusion due to high SUVmax values. Notwithstanding these data, the limited reproducibility of SUV measurements with the higher SUVmax charted by more modern PET scanners, will make standardisation challenging in future trials.

Total metabolic tumour volume (TMTV) was conceived as a way of measuring the overall tumour burden and in doing so integrating several elements of the FLIPI and FLIPI2 indices: (longest diameter of the largest involved node, number of nodal sites, LDH and stage). It was originally measured using a semi-automated method with lesions initially identified by visual assessment of PET images scaled to a fixed SUV display and color table, followed by calculation of TMTV using 41% of the SUVmax as a threshold value. A cut-off of ≥ 510 cm3 was confirmed as predictive of inferior PFS in the FOLLCOLL analysis.32 However, irrespective of whether the tumour threshold was set at 41% SUVmax or a fixed SUVmax of ≥2.5, TMTV did not clearly correlate with either PFS or OS in 522 patients with baseline PET data in the GALLIUM study, (Barrington S, PET in Lymphoma and Myeloma meeting 2018). One possible explanation for these contradictory findings is that the adverse prognostic effect of high TMTV was overcome by the more intensive therapeutic approach in GALLIUM, where the majority of patients received induction with bendamustine and all were assigned to antibody maintenance for 2 years.33 In a later effort to simplify TMTV measurement, the GALLIUM investigators developed a fully automated method, using a novel deep learning-based approach to calculate whole-body TMTV in <5 minutes and achieving excellent correlation with the manually calculated TMTV.34 Applying this new method to a cohort of 541 GALLIUM patients showed that the 193 (35.7%) with high TMTV had an inferior PFS (HR 1.59, p=0.05). The improved predictive value of automated TMTV requires further validation. Other aspects of TMTV measurement requiring additional work include the criteria for defining splenic involvement, the optimisation and standardisation of TMTV measurement in clinical trials, and the development of simple software solutions suitable for clinical practice.35 Until this work has been done and the prognostic value of TMTV validated in other trials, it is premature to use TMTV for prognostication or patient stratification, either on its own on in combination with clinical features and/or metabolic/molecular response to therapy.

**Response assessment by PET-CT**

PET has also emerged as the imaging modality of choice for response evaluation at end-of-induction (EOI). The 2014 ICML (Lugano) response criteria recommend assessing metabolic response using a 5-point scale (5-PS) which measures residual FDG uptake relative to the mediastinum and liver, (Table 2). To mitigate the possibility of optical illusion, the reporter’s qualitative assessment is confirmed by documenting the SUVmax of lymphoma lesions relative to that of these reference organs.36,37 There is ongoing clarification in the distinction between scores 4 and 5, which require lesional SUVmax to be moderately (score 4) and markedly (score 5) higher than that of the liver. It has been suggested to assign score 5 not just to the occurrence of new lesions but also where the lesional SUVmax is greater than two or three times (depending on the research group) that of the liver.38 In FL, it has been demonstrated that applying a cut-off of score ≥ 4 rather than ≥ 3 provided both better reporter concordance and greater separation of PFS and OS curves.4,39 Therefore scores 1-3 are considered to represent a complete metabolic response (CMR) and scores 4 or 5 to represent an inadequate EOI response. Unlike in DLBCL and HL, there are no published data in FL showing that score 5 is associated with a worse outcome compared to score 4.

The prognostic value of EOI PET in prospective clinical trials is summarised in Table 3. An exploratory analysis performed as part of the PRIMA trial,26 provided the first hypothesis-generating data suggesting PET might be better than CT at prognostication based on therapeutic response to CIT (Figure 1). The sub-study showed that the 32/122 (26%) patients remaining EOI PET-positive after rituximab-chemotherapy had a significantly (P<0.001) inferior 42-month PFS of 32.9% (95% CI, 17.2% to 49.5%) compared with 70.7% (95% CI, 59.3% to 79.4%) in those who became PET-negative. The risk of death was also increased in EOI PET-positive patients (HR 7.0; P< 0.001).1 The same findings were obtained when the PET scans were centrally reviewed using the 5-PS with a cutoff of ≥4, with a HR for progression or death in the PET-positive group of 3.1 (95% CI 1.2-7.8 p = 0.01).40 This study was followed by a similar analysis of EOI PET scans in 202 patients with HTB FL in the Fondazione Italiana Linfomi FOLL05 trial. Forty-nine (24%) had positive EOI PET scans7 with a 3-year PFS of 35% compared to 66% for patients with negative scans (P<0.001). EOI-PET predicted outcome independently of anatomical response, FLIPI and treatment arm (HR 2.57, 95% CI 1.52-4.34, P<0.001). In the LYSA prospective PET-Folliculaire study,3 121 patients with previously untreated HTB FL were treated with six cycles of R-CHOP plus two additional cycles of rituximab induction. PET was performed before treatment, after four cycles of R-CHOP (interim PET), and at the end of treatment. With a median follow-up of 23 months, 2-year PFS rates were 51% for EOI PET-positive patients versus 87% for EOI PET-negative (P < 0.001), respectively. Two-year OS also significantly differed at 88% versus 100%, respectively (P = 0.0128).

To provide more robust survival estimates and longer-term follow-up using the 5-PS as the emerging standard for PET-based response assessment, a pooled analysis was conducted of the combined PET data from all three studies (Figure 2). EOI PET scans available for central review were scored independently by three reviewers, with 41/246 (17%) remaining PET-positive (Score ≥4) after CIT induction. With a median follow-up of 54.8 months, the HR was 3.9 (95% CI 2.5-5.9; p<0.0001) for PFS, and 6.7 (2.4-18.5; p=0.0002) for OS. Among patients with a positive EOI PET, 23.2% (95% CI 11.1-37.9) were progression free at 4 years compared with 63.4% (55.9-70.0) of those with a negative EOI PET (p<0.0001); 4-year OS was 87.2% (95% CI 71.9-94.5) versus 97.1% (93.2-98.8), respectively (p<0.0001). In contrast, conventional CT-based response (i.e. complete response or unconfirmed complete response vs partial response) was only weakly predictive of progression-free survival (HR 1.7 [95% CI 1.1-2.5]; p=0.017).

A landmark analysis of 508 patients with advanced FL in the GALLIUM study (in which all patients received CIT induction followed by antibody maintenance) confirmed that EOI PET was superior to CT for response assessment 4 Patients obtaining CMR (PET score 1-3) had a PFS at 2.5 years of 87.4% (95% CI 83.7 – 90.2) compared to 54.9% (95% CI 40.5 - 67.3); HR 0.2 (CI 0.1 – 0.3, p<0.0001) for patients who failed to achieve CMR. Crucially, achieving CMR was the only independent predictor of OS (HR 0.2, 95% CI 0.1 - 0.5, p <0.0001) on multivariate analysis including FLIPI score and type of chemotherapy and antibody administered. In a recent update with a median follow-up of 77 months, patients who remained PET positive at EOI had a 5-year PFS of 29.4% (95% CI: 17.8–42.0) versus 70.0% (95% CI: 65.2–74.2) for those in CMR (HR 3.40; 95% CI: 2.33–4.97, p<0.0001). 5 year OS was 79.6% (95% CI: 68.0–87.4) versus 92.0% (95% CI: 89.0–94.2), respectively (HR 3.34; 95% CI: 1.81–6.17, p<0.0001) 41 (Figure 3). Furthermore, updated abstract data from GALLIUM (Mir F, PET in Lymphoma Meeting, Menton 2018) identified that POD24 occurred in 31/69 (44.9%) patients in the PET-positive group compared with 38/450 (8.4%) of patients obtaining a CMR; odds ratio 8.84 (95% CI 4.96-15.78).

Persisting bone marrow involvement on BMB was clearly identified in only 2.3% (5/213) of patients obtaining CMR at EOI in the GALLIUM study, suggesting limited additional value of EOI BMB in these patients.21 In patients failing to achieve a CMR, repeat BMB adds even less relevant information for therapeutic decision making and is likely redundant outside of clinical trials. There is a paucity of data on the clinical significance of changes in quantitative PET measurements (SUVmax and TMTV) in FL response assessment, as well as likely challenges in analysing such data given the often low baseline SUV in FL lesions and the heterogeneity of FDG uptake within individual patients.

These EOI PET data have set the scene for testing response-adapted approaches in FL: exploring the balance between the beneficial and unwanted effects of maintenance therapy in patients achieving CMR following CIT, and studying treatment escalation in patients with an inadequate response. Preliminary data from the first trial to address these questions, FOLL12,42 suggest that rituximab maintenance prolongs PFS even in patients who achieve a CMR. This finding is not unexpected given the magnitude of the PFS advantage of rituximab maintenance in the PRIMA trial,26 and highlights the need for even more sensitive measures of complete response than PET alone. The current UK/Australian PETReA study43 is seeking to directly quantify both the beneficial effect of rituximab maintenance (in terms of PFS and time to next lymphoma treatment), as well as its unwanted effects in patients who achieve a CMR following frontline CIT. The current COVID-19 pandemic highlights the importance of balancing safety, quality of life and long-term disease control in patients with FL, and moving beyond the restricted paradigm of focusing on PFS as the sole endpoint of importance. In addition to addressing risk:benefit considerations of anti-CD20 maintenance in good-risk patients achieving CMR, it is also important to evaluate approaches to improve the poor outcome in the minority who remain EOI PET-positive, e.g. by adding (90)Y ibritumomab tiuxetan (FOLL12)42 or lenalidomide (PETReA)43. It is also important to appreciate that the prognostic value of EOI PET may depend on the therapeutic context, and that EOT-PET-based outcomes following rituximab and lenalidomide have not yet been reported in a large cohort. To that end, data from the RELEVANCE study44 will be important.

**Use of PET for interim response assessment and remission surveillance**.

An interim PET scan after 4 cycles of R-CHOP was shown to be predictive of response in the PET Folliculaire study,3 but did not discriminate between responders and non-responders as effectively as the EOI PET. Similarly, as with all lymphoma histologies, there is no demonstrated role for surveillance PET imaging in FL. Indeed, surveillance imaging is discouraged owing to a risk of false positive scans leading to unnecessary biopsies, expense, patient anxiety and radiation exposure. Nonetheless, we acknowledge that in patients with residual abdominal disease concerns for asymptomatic progression may warrant judicious use of surveillance CT scanning, dependent on the likely therapeutic approach in the event of significant progression. Importantly, studies in FL have shown a significant delay between PFS (a primarily CT-based endpoint) and time to next lymphoma therapy (TNLT), with an interval of 2 years in patients undergoing observation in the PRIMA study.45 While PFS is a key endpoint for drug development phase III trials in FL, TNLT is the endpoint arguably of greatest significance to patients in an era where an OS advantage is not easily demonstrated. Consequently, imaging is not required to confirm disease progression outside of a clinical trial unless further treatment is indicated. Once there are concerns for symptomatic relapse requiring therapy, we recommend re-staging with PET and repeat biopsy to exclude HT before re-treatment. As is the case at diagnosis, the relationship between SUVmax and subsequent HT is unclear. Consequently, although it is reasonable to use PET to select a representative biopsy site, it should be noted that the SUVmax of abdominal disease in FL is commonly higher than that of involved peripheral lymph nodes37 and obtaining a large biopsy from an accessible site may be more informative than attempting a technically challenging biopsy from the site with the highest SUVmax.

**Future directions**

With prolonged survival of most patients with FL in the modern era, and with median PFS after frontline FL therapy and maintenance estimated to be approximately 10 years45, PFS is becoming an increasingly impractical endpoint in clinical trials. With EOI PET status predictive of both PFS and OS, it is appropriate that the Follicular Lymphoma Analysis of Surrogacy Hypothesis (FLASH) consortitium have begun analysing individual patient data from a few clinical trials to conduct a meta-analysis to evaluate EOI PET as a surrogate endpoint after firstline therapy, but a larger dataset is likely necessary. Such an analysis would be essential before EOI PET could be accepted by licensing agencies as an early surrogate endpoint beyond early phase trials to accelerate testing of novel approaches. Furthermore, given the potential for novel agents to affect FDG uptake independently of cytoreduction, the correlation between PET-response and PFS would need to be validated for specific classes of drugs before relying on PET as the primary outcome measure.

Testing of response-adapted approaches following CIT in FL will determine whether EOI PET can be used to guide subsequent therapy.42,43 This is particularly important in the current pandemic when the balance between the beneficial effects (improved PFS but not OS) and unwanted effects (increased susceptibility to infection) of continued therapy with anti-CD20 maintenance is being re-evaluated. In the meantime, while patients who fail to achieve a CMR have a sufficiently poor prognosis to warrant testing of PET-guided intensification of treatment, improvements in the positive predictive value of EOI PET imaging are needed. To this end, analysis of the characteristics of residual FDG uptake and outcomes in patients who fail to achieve CMR in the GALLIUM study is ongoing. Likewise, further studies are necessary to confirm if EOI PET status in the modern therapeutic era overrides the prognostic value of pre-treatment risk scores. Furthermore, if TMTV is confirmed to have prognostic value, standardisation and optimisation of TMTV measurement is required with software solutions for semi-automated measurements that will be suitable for everyday practice. Finally, if additional studies confirm the findings in GALLIUM that EOI PET and PCR-based EOI minimal residual disease (MRD) status (with a clonal t(14;18) translocation and/or Ig variable domain rearrangement detectable in 75% of patients), are each independently predictive of outcome,46 this may create a platform for striving for both CMR and MRD negativity as a necessary first step in a potentially curative approach for younger patients with FL who might not otherwise achieve a “functional cure”. Improvements in MRD sensitivity and the evolution of next generation sequencing techniques using universal primers will advance circulating tumor (DNA as another biomarker in FL reflecting intratumor spatial heterogeneity. With harmonisation of techniques to detect the often-low levels of circulating tumor DNA found in FL and panel consensus this may in the future be combined with PET to enhance our prognostic modelling and response assessment for patients.

**Conclusion**

This perspective charts the role of PET as the gold standard imaging modality for staging and response assessment of FL. The sensitivity of PET supports a PET-guided approach to initial therapy with supplementary BMB in selected cases. There is no confirmed correlation between high bSUVmax and risk of HT or inferior PFS , and exposing patients to repeat biopsy in search of HT should not be prompted solely by this semi-quantitative measure of FDG-uptake. After first-line CIT, EOI PET status is strongly predictive of outcome. Achieving CMR provides patients with greater confidence of a prolonged first remission and can assist patients and clinicians in making decisions on the trade-off between the PFS advantage and toxicity of further treatment with antibody maintenance – a dilemma that has been thrown into sharp focus by the current COVID pandemic. There are currently no data to support pre-emptive intervention in patients who remain PET-positive and particularly for this poor risk population, the results of current trials involving EOI PET-adapted approaches are awaited with interest.

**Declaration of interests**

JT reports institutional research funding from Beigene, Roche, Takeda, Celgene, Janssen and PCYC, outside the submitted work.

AP reports institutional research funding from Celgene, Gilead, GSK/Novartis, Chugai, Napp and Roche outside the submitted work

**Author contributions**

JT performed the literature search, interpreted data and wrote the first draft of the manuscript.

AP edited the manuscript and both authors approved the manuscript.

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**Table 1. Key studies relating baseline SUVmax with outcome in follicular lymphoma.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Reference** | **Patients n** | **Median baseline SUVmax (range)** | **Histologic transformation (HT)** | **PFS** |
| PET in PRIMA  Tychyj-Pinel C, 2014  Retrospective | 58 | 11.7 (4.6 – 35.6) | No patients with HT | No association of bSUVmax with PFS (p=0.53).  ROC analysis did not  identify an optimal pre-treatment SUVmax cut-off with a significant impact on PFS |
| FOLLCOLL  Cottereau AS,  ASH 2016  Retrospective | 181 | 10 (3-35) (IQR 7-14)  No correlation with histologic grade, p=0.66.  Best cut-off on ROC and X-tile analysis SUVmax 9.4 | 2 patients with HT | SUVmax >9.4: 5yr PFS 62%, median PFS 78.7 months.  SUVmax <9.4: 5yr PFS 47%, median PFS 48.7 months.  p=0.0318  No difference in OS,  93.7% vs 88.4%, p 0.15 |
| GALLIUM Mir F, Blood 2020  Prospective  Barrington PiLM 2018 | 549 | Range 3-64.  median 12.4 (8.1 – 28.0) in HT  median 11.8 (3.1-64.4) in non HT | 15 patients (2.7%) with HT at 5 years | No association of bSUVmax with PFS, Q1 vs. Q4, HR 1.14 (0.72 – 1.81), p=0.58 |
| Strati, P  Haematologica 2020.  Retrospective | 346 | 11 (1.5 – 42)  52 patients (15%) with SUVmax >18 | HT excluded from study population | No effect on PFS if treated with R-CHOP or other chemoimmunotherapy.  Inferior 8-year OS if SUVmax >18 (65% vs. 89%, P=0.001). |

**Table 2. Lugano response criteria based on the 5 Point Scale (Deauville score).**

|  |  |
| --- | --- |
| Deauville score | Definition |
| 1 | No uptake |
| 2 | Uptake ≤ mediastinum |
| 3 | Uptake > mediastinum but ≤ liver |
| 4 | Uptake moderately higher than liver |
| 5 | Uptake markedly higher than liver and/or new lesions\* |
| X | New areas of uptake unlikely to be related to lymphoma |

\*Suggested to assign score 4 as FDG uptake above liver, and score 5 as 2 or 3x higher than liver (according to research group), or the presence of new lesions.

**Table 3. Prognostic value of EOI PET in prospective clinical trials.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study**  **Reference** | **Patients n** | **PET response criteria** | **PET+ or**  **non-CMR patients**  **n (%)** | **Median follow-up** | **PFS**  **PET+ or**  **non-CMR**  **vs PET- or CMR**  **(95% CI)** | **OS**  **PET+ or non-CMR**  **vs PET- or CMR (95% CI)** |
| PET in PRIMA,  Trotman J,  JCO 2010 | 122 | Local assessment | 32 (26%) | 42 months | 3.5 yr PFS 32.9% (17.2% - 49.5%) vs. 70.7% (59.3% - 79.4%); HR 3.3 (1.9 - 5.9). p<0.001 | 3.5 yr OS 78.5% (57.6% -  89.9%) vs. 96.5% (89.7% - 98.9%)  HR 7.0 (1.8 - 27.0).  P=0.0011 |
| PET in PRIMA Central Review  Tychyj-Pinel C,  EJNMMI 2014 |  | 5PS with cut-off ≥4, |  | 42-month | 3.5 yr PFS 25.0%, (3.7-55.8%) vs 61.4% (45.4% -74.1%), p=0.01; HR 3.1 (1.2-7.8) |  |
| FOLL05  Luminari S,  Ann Oncol, 2014 | 202 | Local assessment | 49 (24%) | 34 months | 3 yr PFS 35% (18%–52%);  vs 66% (57%–74%)  HR 2.59, (1.59–4.24] (P < 0.001). | Overall 3 yr OS 99% (94-100%).  3 deaths in PET+ 3 deaths in PET- groups. |
| PET Folliculaire  Dupuis J,  JCO 2012 | 121 | DS ≥4 | 15 (12%) | 23 months | 2yr PFS 61% vs 86%, p=0.0046. | 2yr OS 88% vs. 100%, p=0.0128. |
| FOLLCOLL,  (central review of PRIMA, FOLL05 and PET Folliculaire patients)  Trotman J,  The Lancet Haematology, 2014 | 246 | DS ≥4 | 41 (17%) | 55 months. | 4 yr PFS 23.2%  (11.1–37.9) vs. 63.4% (55.9–70.0), HR 3.9 (2.5–5.9), p<0.0001 | 4 yr OS 87.2% (71.9–94.5) vs 97.1% (93.2–98.8), p<0.0001. |
| GALLIUM,  Trotman J,  The Lancet Oncology, 2018 | 508 | Lugano 2014 criteria  (incorporating DS ≥4) | 58 (25%) | 43 months | 2.5 yr from end of induction,  87.3% (83.7-90.2) vs 54.9% (40.5-67.3), HR 5.0 (3.3-10)\* | 2.5 yr from end of induction,  84·0% (95% Cl 72·9–90·8) vs. 96·6% (95% CI 94·4–97·9), HR 5 (2.0 – 10.0)\* p<0.0001. |

\* The HRs for the GALLIUM study are presented as the reciprocal of the values originally reported [PFS 0.2 (95% CI 0.1-0.3), and OS 0.2 (95% CI 0.1-0.5)] to align its directionality with the other studies.