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Lymphoma and Chronic Lymphocytic Leukemias

The Role of Functional Imaging in Lymphoma: Current Controversies and Future Directions

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ABSTRACT: Fluorodeoxyglucose positron emission tomography (FDG-PET)/computerized tomography (CT) has revolutionized the management of several lymphoma subtypes, yet controversy remains regarding its cost-effectiveness and the appropriate interpretation of equivocal or false-positive PET scans. In this review, we examine the current evidence base informing the management of these controversial aspects of PET, and look ahead to the emerging uses of PET imaging and the application of novel tracers and quantification tools.

KEYWORDS: FDG-PET, lymphoma, cost-effectiveness, false-positive PET, equivocal PET

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Introduction

Functional imaging has proven to be one of the most vibrant fields in applied lymphoma research of the past decade. Although there has been a significant expansion in the use of functional imaging in lymphoma patients, the evidence base struggled to keep pace with clinical demand for this new imaging modality. In this review, we first examine some of the most pressing controversies currently surrounding the use of fluorodeoxyglucose positron emission tomography (FDG-PET) imaging in lymphoma, including its interpretation, and then explore the evidence base for its cost-effectiveness. We also look ahead to potential roles for functional imaging in the future and examine novel tracer and quantification tools.

FDG-PET Scanning

PET scanning is a functional imaging technique by which the accumulation of specific radioisotopic tracers can be imaged by detecting the radiation signatures of positron emitting isotopes. The most commonly used tracer is 18F-flurodeoxyglucose, a glucose analog that is avidly taken up by metabolically active tissues such as cancer or inflammation. PET scanning can be combined with computerized tomography (CT) to produce a combination of functional and anatomical information that is well suited to cancer staging. The scans are visually interpreted, with the FDG-uptake often reported as a standardized uptake value (SUV), which is the tracer activity corrected for patient weight and administered dose. For further background information, the reader is directed to recent comprehensive reviews of the field.[1,2]

Current Controversies

Equivocal and false-positive FDG-PET results. PET is recommended to assess the response to therapy of FDG-avid lymphomas treated with curative intent.[3–5] Clinical decisions

are made based on the binary distinction of a scan being either positive or negative, whereas nuclear medicine physicians recognize a continuum of uptake, with persistent disease more likely at higher levels of activity. Furthermore, the time course of resolution of FDG avidity following successful treatment is also variable depending on lymphoma subtype and treatment modality. Using a snapshot measurement of the continuous variable of FDG-uptake to make a binary decision generates the common problem of an equivocal PET result (Fig. 1). A significant advance in dealing with this problem has been the adoption of the five-point Deauville criteria for reporting PET.[6] These criteria have high inter-observer agreement and allow different thresholds to be set depending on the clinical circumstances such as lymphoma subtype, scan timing, and the therapeutic decision required (eg, treatment escalation or de-escalation), and have recently been recommended as standard practice in international consensus guidelines.[4]

A further problem with FDG-PET imaging in lymphoma is that the glucose analog used in this technique is not specific for lymphoma, resulting in a consistently high rate of false positivity (FP). Inflammation, infection, and concurrent malignancy all result in FDG avidity that can be misinterpreted as lymphoma. Other well-documented factors also influence the level of uptake, eg, blood sugar levels, time between injection and scanning, delay between treatment (chemotherapy and radiotherapy) and scanning, and reconstruction parameters. In addition, lymphoma and its treatment can result in a number of benign sources of FDG avidity that can be falsely interpreted as sites of disease. Reactive bone marrow changes are frequently seen in Hodgkin's lymphoma (HL), but this is usually in advanced-stage patients, and biopsy rarely changes management.[7,8] Chemotherapy, radiotherapy, and colony-stimulating factor treatment can all result in FDG-avid inflammatory or reactive changes requiring PET scans to be deferred until after treatment has been completed.[9] Immunotherapy, such as rituximab, can be particularly problematic; a retrospective study of 137 diffuse large B-cell lymphoma (DLBCL) patients treated with either CHOP or Rituximab, Cyclophosphamide, Hydroxydaunomycin (doxorubicin), Oncovin® (vincristine), Prednisolone (R-CHOP) chemotherapy and monitored by surveillance PET scanning showed a markedly high FP rate in the rituximab-treated patients compared to those receiving just CHOP (77 vs. 26%, $P < 0.0001$). Importantly, this effect lasted for up to three years following treatment. Multivariate analysis showed rituximab administration was the most significant predictor of FP PET.[10] Guidelines state that PET should be avoided within 10 days of chemotherapy, 2 weeks of

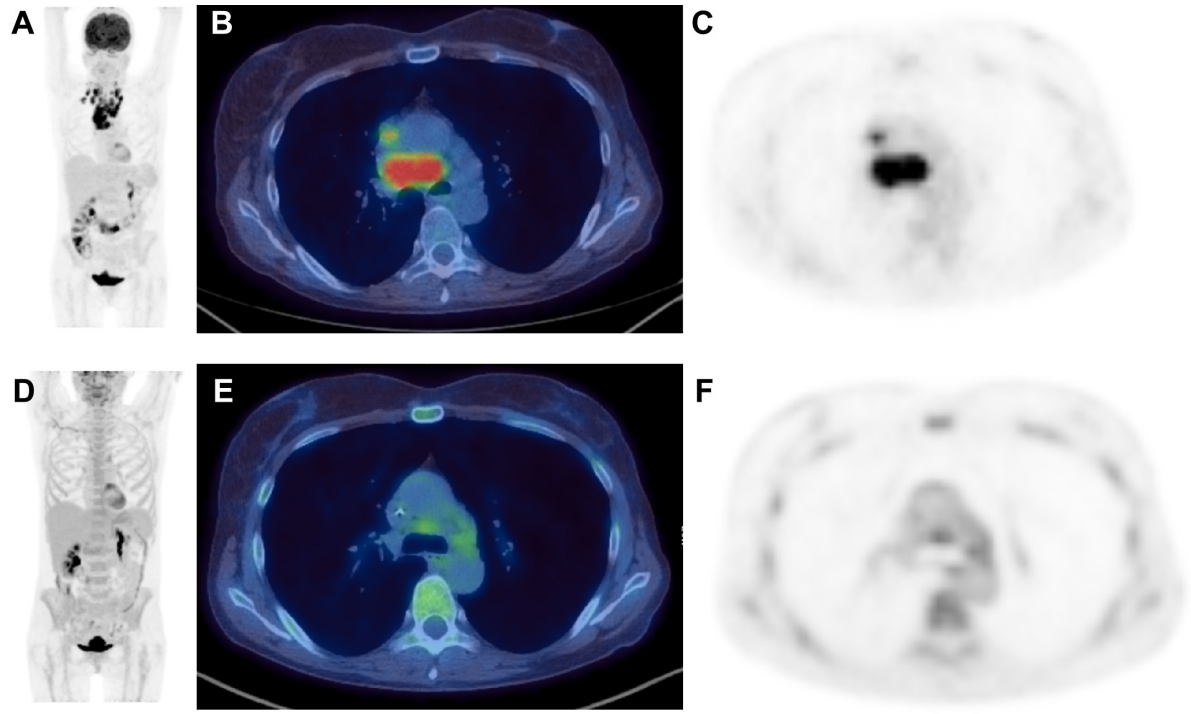

Figure 1. Baseline and post-treatment PET-CT in a patient with Hodgkin lymphoma. PET demonstrated very good partial metabolic response with residual low-grade uptake in mediastinal nodes. The intensity of uptake was slightly greater than liver background, classified as Deauville score 3. The patient was asymptomatic and therefore serial PET imaging was used to monitor the equivocal uptake, which resolved despite the absence of anti-lymphoma treatment. The residual low-grade uptake therefore most likely represents post-treatment inflammatory changes. (**A**) Baseline MIP shows intense uptake in cervical and mediastinal nodes. (**B**) Transverse fused image shows intense uptake in enlarged pretracheal nodes. (**C**) Transverse PET only image shows intense uptake in enlarged pretracheal nodes. (**D**) Post-treatment MIP shows resolution of the areas of intense uptake. (**E**) Transverse fused image shows residual lowgrade uptake in pretracheal nodes. (**F**) Transverse PET only image shows residual lowgrade uptake in pretracheal nodes.

granulocyte-colony stimulating factor (G-CSF) treatment, or 3 months of radiotherapy in order to minimize false positives.[9]

Allogeneic stem cell transplantation (alloSCT) can also result in persistent reactive FDG positivity. A retrospective analysis of 107 patients treated with alloSCT showed that only 29 of 50 positive PET scans represented lymphoma. FDG positive nodes tended to appear after three months post transplant and often persisted. Nodes measuring ≤1.5 cm did not result in an inferior outcome, and 21/22 of these were demonstrated to be benign. In contrast, FDG positive lymph nodes following autologous SCT were strongly associated with malignant pathology.[11] The Deauville criteria can help to reduce FP by using higher thresholds than the mediastinal blood pool in differentiating response. However, in a successful international validation study of concordance in reporting the Deauville score in Adriamycin (doxorubicin), Bleomycin, Vinblastine, Dacarbazine (ABVD)-treated advanced-stage HL, the positive predictive value (PPV) was only 0.73.[12]

Recent studies that employed a program of biopsy of avid lesions, or serial scanning and patient follow-up, suggest poor PPV of end-of-treatment PET (endPET) scans in some lymphoma subtypes.[13] Significant work has been undertaken to strengthen the prognostic role and validity of the assessment methodology for the interpretation of interim PET (intPET) scans in patients with HL who are treated with ABVD chemotherapy.[14] Earlier reports in HL suggested a proportion of scans with minimal residual uptake (MRU) that was regarded as equivocal for the presence of disease, often manifesting as faint residual uptake in a site of previous disease bulk. The outcome for this group, however, was found to be similar to that of patients with a negative interim scan. Using the Deauville criteria, patients with MRU are assigned a score of 3, equivalent to a negative scan with MRU likely representing non-specific inflammatory change secondary to chemotherapy.

The non-specific nature of FDG underlines the importance of careful review of patients with persistent low-grade uptake at the end of treatment, where decisions about further toxic therapies are made. Prior to committing to further therapy, the significance of residual PET positivity must be clinically evaluated, and serial scanning and/or biopsy, wherever possible, should be recommended. Harmonization across future clinical trials on this issue will be a major achievement.

Is PET cost-effective? Although many studies have demonstrated that functional imaging can improve diagnostic accuracy and even change management in lymphoma, there is limited evidence to support a benefit on patient outcomes or cost-effectiveness. Indeed across all malignancies, only in the evaluation of non-small cell lung cancer and solitary pulmonary nodule has PET proven unequivocally cost-effective.[15–17]

The main benefit of functional imaging is to improve the accuracy of anatomical staging and response assessment. In contrast with other solid malignancies, staging of lymphoma is combined with other data to define clinical risk groups, and thus, changing stage often does not alter management. Scenarios where precise anatomical localization of disease may radically alter treatment include the initial staging of limited stage disease and the identification of residual disease after first-line treatment, where localized radiotherapy may form an important part of management. The costs of PET/CT are well documented. A single scan costs between £325 and £1300.[18] Furthermore, PET/CT is associated with a radiation dose of 11–17 mSv, the equivalent of five to eight years of background radiation or that of a whole-body contrast-enhanced CT.

Crucially, the clinical effectiveness and cost-effectiveness of PET depend on the subtype of lymphoma and the timing in relation to treatment. The majority of reports supporting the clinical efficacy of PET scanning in lymphoma relate to the common B-cell lymphomas: HL, DLBCL, and follicular lymphoma (FL). T-cell malignancies are heterogeneous with respect to FDG avidity, often related to the proliferation fraction or site of disease,[19,20] and the smaller number of patients with T-cell lymphomas and the relatively limited treatment modalities available have further limited studies. The metabolic changes detected by functional imaging usually precede change in nodal size, with kinetics varying depending on disease subtype. This can facilitate early changes of management based on intPET scanning, which have the potential for greatest clinical impact in aggressive lymphomas that are treated with curative intent.

Pre-treatment staging PET. There is some evidence that PET is cost-effective in the initial staging of lymphoma. Baseline scanning has a number of clinical benefits including improving the accuracy and inter-reporter agreement of subsequent scans,[6] and planning for involved site/involved node radiotherapy. A systematic review has shown that pre-treatment PET staging can change treatment in a median of 14% (0–25%) of patients with 14.5% (11–55%) upstaged and 7% (0–28%) downstaged.[21] In limited stage, FL PET scanning can potentially upstage as many as 60% of patients, radically changing management,[22–24] but the long-term effect of these changes on patient outcomes are unknown. Furthermore, the increased sensitivity of PET compared to CT alone can obviate the need for additional staging investigations, such as routine bone marrow biopsy in HL.[8,25] Thus, the potential for cost savings is high, but accurately quantifying these savings can be difficult.

The best evidence of cost-effectiveness of PET in pre-treatment staging is in HL. Cerci et al prospectively analyzed 210 patients with HL and compared conventional CT-based staging with metabolic staging by PET or PET/CT. The incremental cost-effectiveness ratio (ICER) for PET/CT was $16,215 per patient with modified treatment compared to conventional staging (the WHO guidelines state <$19,016 for this Brazilian population to be very effective). The addition of PET/CT to initial staging was estimated to add 2% to the overall cost of treating HL.[26]

FDG-PET activity correlates with proliferation fraction suggesting an ability to differentiate sites of transformation in low-grade lymphomas.[27] In a study of 97 patients with non-Hodgkin's lymphoma (NHL), an SUVmax <13 was able to accurately exclude aggressive lymphoma; conversely, using an SUVmax ≥10 could differentiate aggressive lymphoma from indolent with 81% specificity and 71% sensitivity.[28] PET is, therefore, recommended to target biopsy in low-grade NHL suspected of transformation,[4] and this approach is likely to be highly cost-effective when used in the appropriate clinical context.

Interim PET. Despite exciting data demonstrating the powerful prognostic value of intPET scanning in predicting progression-free survival (PFS) in advanced HL, there is as yet no randomized controlled trial outcome data to support its routine use in determining subsequent management, although the results of several large randomized controlled trials are awaited.[29] One study predicted substantial savings by discontinuing R-CHOP treatment in patients with DLBCL intPET-positive scans after three cycles, but there is an absence of clear evidence that intPET is predictive of PFS in DLBCL treated with immunochemotherapy.[30] IntPET does not appear to be predictive of outcome in FL, which follows a slower course.[31] Thus, there is no current evidence to support intPET as either clinically effective or cost-effective in any lymphoma subtype. Nevertheless, the results of several prospective trials investigating the clinical benefit of intPET in high-grade B-cell lymphoma are awaited; given the high negative predictive value (NPV) anticipated at this stage, there may be significant cost savings through minimizing further treatment and imaging.

Post-treatment PET. Evidence exists that appropriately timed endPET is cost-effective in HL and DLBCL. Post-treatment PET is associated with a high NPV (>90%) with a PPV of 50–82%, because of false-positive PET findings related to residual inflammatory change.[32,33] The benefit of PET in remission assessment led to its incorporation in the 2007 international working group (IWG) criteria.[34] Residual masses that are PET negative can be safely considered to be complete remission (CR), whereas patients with residual PET-positive lesions should proceed to biopsy wherever possible.

One of the earliest models of the cost-effectiveness of PET predicted that it could reduce the rate of post-treatment radiotherapy to 6% compared to 36% restaged by CT alone.[35] More recently, the German Hodgkin Study Group (GHSG) HD15 trial has demonstrated that directing consolidation radiotherapy only to HL patients who were endPET positive gave similar outcomes to those endPET negative avoiding both unnecessary biopsy and empirical radiotherapy.[36]

In a prospective study of 130 patients with HL, CT staged 40% as either unconfirmed complete remission (CRu) or partial remission (PR) after first-line treatment. In these patients, PET had a 100% NPV, reducing the need for biopsy cutting restaging costs by 19%. This was calculated to give a significant ICER of $3268 to detect one case of persistent disease and was simulated to provide a 1% cost saving to HL management if applied across the Brazilian healthcare system.[33]

Given the high NPV of intPET, the rates of intPET-negative patients progressing through chemotherapy to become endPET positive are very low. Thus, endPET can be safely excluded in patients who were negative at intPET.[29,37] A Swiss study further demonstrated the high NPV of intPET in 68 patients with HL/high-grade NHL. The authors calculated that endPET could be safely omitted in this group, reducing imaging costs by 27% or a total of $102,600 in the study population.[38]

PET after first-line treatment. It is clear that post-remission surveillance PET is not clinically effective or cost-effective, with a cost of $100,000 to detect a single event.[5,39] The use of PET in directing salvage and transplantation approaches is an area of intense clinical interest.[40,41] Of note, given the high costs of these treatment modalities, it is likely that where PET is proven to alter clinical management, it will also be highly cost-effective.

In conclusion, the literature supporting the cost-effectiveness of PET in lymphoma is limited. There is reasonable evidence of cost-effectiveness in response assessment at the end of treatment for HL, at least in patients in PR/CRu on CT. There is also limited evidence for cost-effectiveness in the initial staging of high-grade B-cell lymphomas and in ruling out advanced-stage disease in otherwise limited FL planned for radical treatment. The clinical utility and cost-effectiveness of PET is highly related to the precise lymphoma subtype, the timing in relation to therapy, and the availability and cost of alternative treatments. The clinical indications for PET scanning in lymphoma based on recent guidelines are summarized in Table 1.[4,5] In an era of spending restraint, large-scale clinical studies will increasingly be required to provide economic analysis to justify the expansion of functional imaging in lymphoma.

Future Directions

The use of PET in lymphomas other than DLBCL and HL. The value of PET in the setting of many lymphoma subtypes remains controversial. The management of patients with FL and other low-grade lymphomas differs from those with DLBCL and HL. Treatment is generally withheld unless patients have localized disease where long-term disease control might be achieved by involved field radiotherapy (IFRT) or patients have advanced-stage disease where they are symptomatic and require therapy. Patients with FL who remain PET positive following rituximab-containing chemotherapy have been reported to demonstrate inferior PFS compared to those patients who were PET negative following treatment.[42] These data have been recently updated with central review and the inclusion of a larger patient cohort. With follow-up of more than four years and conventional description of a positive scan, PET was highly predictive of PFS and overall

Table 1. Indications for PET scanning during treatment depending on lymphoma subtype. PET scanning is recommended for the initial staging and remission assessment of FDG-avid lymphomas. intPET scanning is an active research question in HL and DLBCL. Surveillance PET is generally not indicated.

LYMPHOMA	INITIAL STAGING	INTERIM	END OF TREATMENT	SURVEILLANCE
HL	I	RQ	I	NI
DLBCL	I	RQ	I	NI
FL	I	NI	I/RQ*	NI
MCL	I	NI	I	NI
BL	I	NI	I	NI
Indolent/Marginal zone	RQ	NI	RQ	CD§
CLL/SLL	RQ	NI	RQ	NI
Aggressive T	I	NI	I	NI
Cutaneous T	RQ	NI	RQ	NI
High-grade transformation	I	NI	I	NI

Notes: *Post-treatment PET is predictive in FL, but lack data following rituximab maintenance. §International guidelines suggest judicious use of CT or PET scanning in the monitoring for relapse of low-grade lymphomas in clinically silent sites such as intra-abdominal or retroperitoneal disease.
Abbreviations: I, indicated; NI, not indicated; RQ, research question; CD, clinically directed; HL, Hodgkin's lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; BL, Burkitt's lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma.

survival (OS).[43] The hazard ratio (HR) for PFS and OS of PET+ vs. PET– patients was 3.9 (95% CI 2.5–5.9, $P < 0.0001$) and 6.7 (95% CI 2.4–18.5, $P = 0.0002$), respectively. In contrast, assessment based on CT (CR vs. PR) was only weakly predictive of PFS (HR 1.7, $P = 0.02$) but not OS. Although the authors of this study claim that PET is the standard for response assessment, the impact of this result on patient care is unclear from the available evidence base.

In contrast, the ability of PET to predict outcome in patients with mantle cell lymphoma (MCL) is unclear. A retrospective review of 58 MCL patients undergoing rituximab and chemotherapy studied the value of post-therapy PET scans.[44] There were no differences in OS or PFS between PET-positive and PET-negative patients both for interim and post-therapy scans. The authors conclude that there is no role for post-therapy PET in MCL. The role of FDG-PET scanning in lymphoma practice is constantly being questioned. How newer applications of this technology will influence clinical practice must be assessed using well-designed clinical trials.

PET scanning has also been studied in the setting of diagnosing lymphoma. It is well described that patients with lymphoma may present with a fever of unknown origin (FUO); once common infectious causes have been excluded, lymphoma becomes an important consideration in adult patients. PET scanning is non-invasive, scans a large proportion of the body, and may help identify targets for biopsy in patients who do not have palpable adenopathy.[45] The cost-effectiveness of such an approach and its benefit compared to conventional anatomical imaging are currently unknown.

Improving decision making using novel tracers and quantification tools. Efforts to improve the prognostic value of FDG-PET–CT at baseline, interim, and end of treatment have mostly focused on quantitative methods. New tracers with potentially higher specificity have also been investigated.

Novel tracers in lymphoma. FDG-PET has a relatively poor PPV for interim and end-of-treatment assessments and is not specific for malignancy, with positive results in inflammatory and infectious lesions, eg, tuberculosis (TB) and sarcoidosis. New imaging probes with potential higher specificity for malignant disease are currently being investigated. 3′-Deoxy-3′-^{18} F-fluorothymidine (FLT) is the most widely studied PET tracer of cellular proliferation. FLT is a pyrimidine analog and reflects the activity of a thymidine-kinase-1 during the S phase of DNA synthesis.[46] It accumulates in proliferating tissues and malignant tumors, and is a very good marker of cellular proliferation.[47] FLT is reported to have higher specificity than FDG to distinguish inflammation or infection from cancer, as FLT is not taken up in inflammatory reactions.[46] In a preclinical mouse model of high-grade lymphoma, early response to dose-dependent anti-proliferative treatment was more accurately visualized with FLT than with FDG.[47] In patients with indolent and aggressive lymphomas, FLT uptake in disease was lower than FDG-uptake, suggesting a lower sensitivity than FDG. FLT-PET missed three bone lesions compared to conventional staging, which could be explained by the high background uptake in the bone marrow. FLT had higher uptake in aggressive than indolent lymphoma with a cut-off value of 3 for FLT-SUV and seems to perform better than FDG to differentiate aggressive lymphoma from indolent lymphoma.[48]

A study of FLT and FDG-PET in residual masses in HL and NHL patients showed that patients with positive FLT or FDG-PET have lower survival than patients with negative PET. FLT did not perform better than FDG, and the latter was slightly better than FLT for the detection of residual active masses.[49]

Baseline FLT uptake was lower in DLBCL patients in CR at the end of treatment and was higher in patients with

lymphoma-associated deaths compared to patients with non-lymphoma-associated deaths or in all included patients.[50]

In MCL, FLT uptake was higher than FDG-uptake and was strongly correlated to Ki67 proliferation index.[51] FLT SUVmax was significantly higher in DLBCL than in MCL. There was no significant correlation between FDG and FLT-SUV values in most lymphoma subtypes studied in 114 lymphoma patients.[52]

Lee et al prospectively investigated the value of FLT at baseline, interim, and end of treatment in 75 patients with newly diagnosed NHL. There was a reduction in the SUV between baseline and interim scans, and a further reduction at the end of treatment. FLT SUVmax was predictive of disease progression and death. Interim FLT positivity was associated with worse five-year PFS and OS.[53]

Quantitative methods. FDG-PET–CT has a relatively poor PPV at interim and end of treatment. Recent studies have suggested that measurement of metabolic tumor volume (MTV) at baseline and of ΔSUVmax could improve specificity (Fig. 2). The ΔSUVmax is the decrease in percentage between the most intense site of uptake on the baseline scan and the most intense site of uptake on the interim scan. Measurement of MTV consists of drawing a volume of interest with a predefined threshold around the areas of active disease identified on FDG-PET. The sum of all volumes is sometimes called total metabolic tumor volume (TMTV). The tumor lesion glycolysis (TLG) is the product of the MTV and the mean SUV in that volume.

ΔSUVmax.

NHL. In 92 patients with aggressive NHL, the measurement of ΔSUVmax was better than visual analysis for predicting shorter event-free survival (EFS) in patients with a positive interim scan after two cycles of chemotherapy.[54] In the same cohort of patients, the measurement of ΔSUVmax after four cycles of chemotherapy was as well as visual analysis to predict two-year EFS.[55] The measurement of ΔSUVmax was better than visual analysis using the Deauville score[56] and the International Harmonisation Project (IHP) criteria[3] for predicting

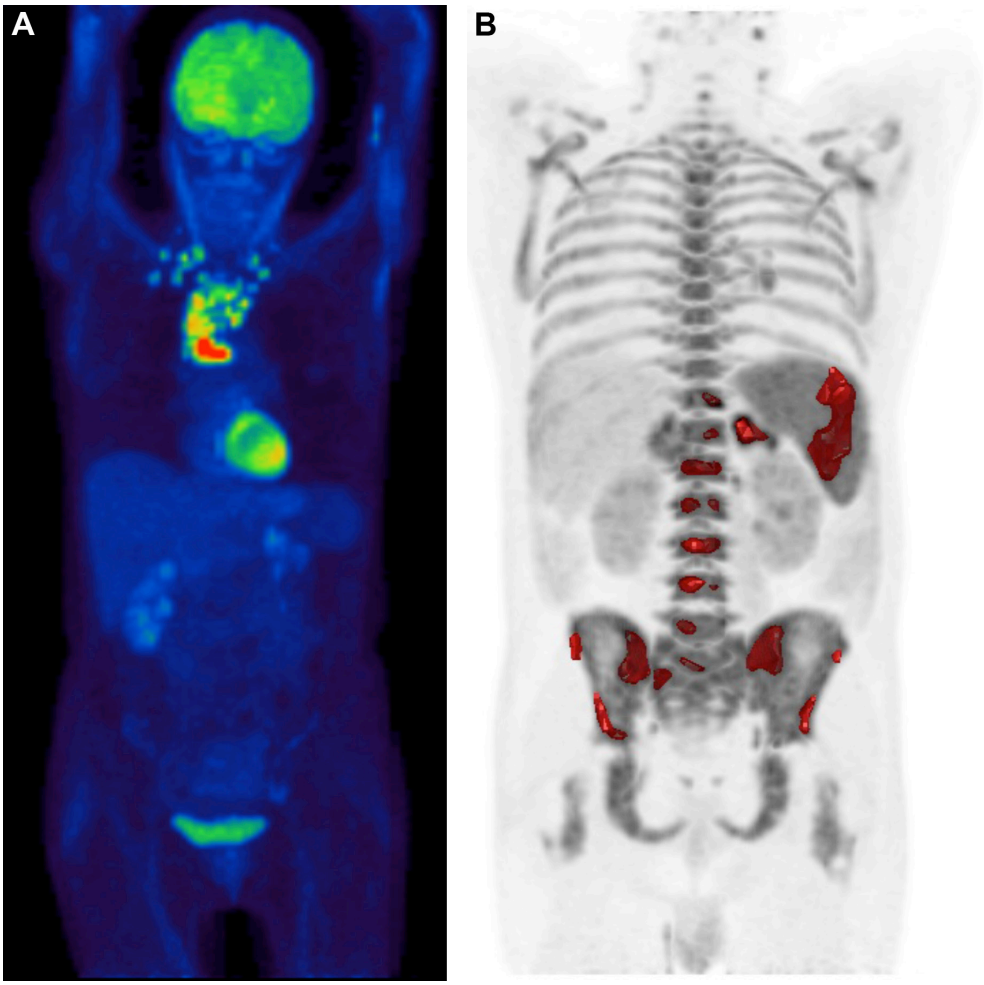

Figure 2. (**A**) **Maximum Intensity Projection (MIP) view displayed with a colour scale to identify the highest SUVmax.** By displaying the MIP using a colour scale rather than the standard gray scale, it is easier to identify the area of most intense uptake in order to calculate the ΔSUVmax. (**B**) **Image of metabolic tumour volume in a patient with diffuse large B-cell lymphoma.** Areas of uptake as defined by SUVmax above a predefined threshold are highlighted in red and superimposed over a MIP view. Acknowledgments to Helena McMeekin, nuclear medicine physicist, Royal Free London.

PFS and OS after two and four cycles of chemotherapy in 102 patients with DLBCL.[57] These results were confirmed in another study of 114 patients with DLBCL where ΔSUVmax was better than the Deauville score to predict three-year PFS and had better inter-observer reproducibility.[58]

HL. In 59 patients with HL, ΔSUVmax had a higher PPV than visual analysis. Patients with a visually positive PET and ΔSUVmax >71% had a similar outcome to patients with a visually negative PET.[59]

MTV and TLG. Meignan et al investigated the reproducibility and limitations of different methodologies of measuring MTV in patients with HL and DLBCL. They demonstrated that a fixed 41% SUVmax threshold is appropriate to define TMTV with excellent inter-observer reproducibility.[60]

In three studies investigating MTV in a total of over 400 patients with DLBCL, it was found that a high MTV was associated with worse OS and PFS[61–63] and that MTV was an independent prognostic factor of PFS and OS by multivariate analysis.[61,62] TLG failed to predict PFS and was less predictive of OS than TMTV in 114 patients with DLBCL.[62]

In 51 patients with high-grade NHL, the volume of uptake greater than the liver (functional volume, FV) and TLG predicted death and progression. Patients with a high FV had shorter OS. A high TLG was associated with poorer PFS. FV was an independent prognostic factor by multivariate analysis.[64]

Conversely, two studies did not find a predictive role for MTV in over 70 DLBCL patients. SUVmax was a predictor of survival.[65,66] One study did not find a predictive value for TLG,[66] whereas the other study did.[65]

High MTV was a better predictor of survival than SUVmax in 165 patients with Ann Arbor stage IE or IIE primary gastrointestinal DLBCL and was an independent prognostic factor for PFS and OS in multivariate analysis.[67]

In HL, high MTV was independently associated with PFS and OS in multivariate analysis in 127 patients with stages I and II HL. Baseline MTV was predictive of patient outcomes in 59 consecutive patients with HL. Baseline MTV was an independent predictor of PFS by multivariate analysis. The prognostic value of baseline MTV was higher than tumor bulk.[68]

Three-year PFS and OS were higher in the low MTV group than in the high MTV group in 80 patients with stage IE/IIE upper aerodigestive tract Extranodal Natural Killer/T cell (ENKTC) lymphoma. High MTV was an independent prognostic factor in multivariate analysis.[69]

Kim et al investigated the MTV and TLG in 20 patients with extranodal Natural Killer (NT)/T-cell lymphoma. MTV and TLG were higher in the group of patients who died than in the group of patients who survived. Higher values of MTV and TLG were associated with disease progression and higher mortality. High TLG and high MTV were significant predictors of PFS and OS. The best prognostic factor for OS by multivariate analysis was high MTV.[70]

SUVmax, SUVmean, tumor volume using a 30% fixed threshold of peak activity, and TLG were calculated in 35 NHL patients treated with radioimmunotherapy. These four functional parameters were significantly different between responders and non-responders in either one or both of two patient groups treated with two different radioimmunotherapy regimens.[71]

Although these new methods are promising, it is still early stage for new tracers, which are not widely available and expensive. Quantitative methods are available in software packages, but there are issues with strict adherence to Quality Control (QC) required, the level of reproducibility between centers, and the thresholds for metabolic volumes and ΔSUVmax needing consensus agreement within the nuclear medicine community.

Conclusion

The use of functional imaging in lymphoma has extended beyond anatomical staging and is becoming established as a tool for response assessment and risk stratification. Nevertheless, there are ongoing concerns regarding equivocal and false-positive results, and the impact of PET scanning on prognosis and its cost-effectiveness. Meanwhile, the routine use of PET is expanding into unconventional lymphoma subtypes, often with a limited evidence base. The role of FLT-PET, at the moment, is still unclear: it seems to be inferior to FDG-PET for baseline staging, but may add value in assessing early response to chemotherapy and to distinguish post-treatment inflammatory changes from residual disease. Currently, FLT-PET should be restricted to research studies, and comprehensive studies comparing FLT and FDG will hopefully shed light on how to make the best use of each tracer. Novel tracers or quantification tools are likely to advance the field considerably in the short to medium term, but will need to be carefully validated in multicenter prospective studies. Although the technology remains nascent, diagnostic or serial tumor biomarkers may in the future provide cheaper and more convenient ways of defining risk, measuring disease burden, and monitoring response or relapse. A potential example of such a biomarker is that of the chemokine Thymus and activation-regulated chemokine (TARC), where early phase evidence suggests that it can significantly contribute to a multivariate model of prognostic risk in HL.[72] In the meantime, PET should be used within its established evidence base or prospective clinical trials.

Author Contributions

Conceived the concepts: SER, TW, CM. Analyzed the data: SER, TW, CM. Wrote the first draft of the manuscript: SER, TW, CM. Contributed to the writing of the manuscript: SER, TW, CM. Agree with manuscript results and conclusions: SER, TW, CM. Jointly developed the structure and arguments for the paper: SER, TW, CM. Made critical revisions and approved final version: SER, TW, CM. All authors reviewed and approved of the final manuscript.

REFERENCES

1. Barrington SF, Mikhaeel NG. When should FDG-PET be used in the modern management of lymphoma? *Br J Haematol*. 2014;164(3):315–328.
2. Kostakoglu L, Cheson BD. Current role of FDG PET/CT in lymphoma. *Eur J Nucl Med Mol Imaging*. 2014;41(5):1004–1027.
3. Juweid ME, Stroobants S, Hoekstra OS, Imaging Subcommittee of International Harmonization Project in Lymphoma, Imaging Subcommittee of International Harmonization Project in Lymphoma, 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(5):571–578.
4. Barrington SF, Mikhaeel NG, Kostakoglu L, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the international conference on malignant lymphomas imaging working group. *J Clin Oncol*. 2014 Aug 11. pii: JCO.2013.53.5229. [Epub ahead of print] PMID: 25113771.
5. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014 Aug 11. pii: JCO.2013.54.8800. [Epub ahead of print] PMID: 2511375.
6. Meignan M, Itti E, Bardet S, et al. Development and application of a real-time on-line blinded independent central review of interim PET scans to determine treatment allocation in lymphoma trials. *J Clin Oncol*. 2009;27(16): 2739–2741.
7. Elstrom RL, Tsai DE, Vergilio JA, Downs LH, Alavi A, Schuster SJ. Enhanced marrow [18F]fluorodeoxyglucose uptake related to myeloid hyperplasia in Hodgkin's lymphoma can simulate lymphoma involvement in marrow. *Clin Lymphoma*. 2004;5(1):62–64.
8. Richardson SE, Sudak J, Warbey V, Ramsay A, McNamara CJ. Routine bone marrow biopsy is not necessary in the staging of patients with classical Hodgkin lymphoma in the 18F-fluoro-2-deoxyglucose positron emission tomography era. *Leuk Lymphoma*. 2012;53(3):381–385.
9. Boellaard R, O'Doherty MJ, Weber WA, et al. FDG PET and PET/CT: EANM procedure guidelines for tumour PET imaging: version 1.0. *Eur J Nucl Med Mol Imaging*. 2010;37(1):181–200.
10. Avivi I, Zilberlicht A, Dann EJ, et al. Strikingly high false positivity of surveillance FDG-PET/CT scanning among patients with diffuse large cell lymphoma in the rituximab era. *Am J Hematol*. 2013;88(5):400–405.
11. Ulaner GA, Lilienstein J, Gonen M, Maragulia J, Moskowitz CH, Zelenetz AD. False-Positive [18F]fluorodeoxyglucose-avid lymph nodes on positron emission tomography-computed tomography after allogeneic but not autologous stem-cell transplantation in patients with lymphoma. *J Clin Oncol*. 2014;32(1): 51–56.
12. Biggi A, Gallamini A, Chauvie S, et al. International validation study for interim PET in ABVD-treated, advanced-stage Hodgkin lymphoma: interpretation criteria and concordance rate among reviewers. *J Nuclear Med*. 2013;54(5): 683–690.
13. Dunleavy K, Pittaluga S, Maeda LS, et al. Dose-adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma. *N Engl J Med*. 2013;368(15): 1408–1416.
14. Gallamini A, Barrington SF, Biggi A, et al. The predictive role of interim positron emission tomography for Hodgkin lymphoma treatment outcome is confirmed using the interpretation criteria of the Deauville five-point scale. *Haematologica*. 2014;99(6):1107–1113.
15. Nguyen VH, Peloquin S, Lacasse Y. Cost-effectiveness of positron emission tomography for the management of potentially operable non-small cell lung cancer in Quebec. *Can Respir J*. 2005;12(1):19–25.
16. van Loon J, Grutters JP, Wanders R, et al. 18FDG-PET–CT in the follow-up of non-small cell lung cancer patients after radical radiotherapy with or without chemotherapy: an economic evaluation. *Eur J Cancer*. 2010;46(1):110–119.
17. Lejeune C, Al Zahouri K, Woronoff-Lemsi MC, et al. Use of a decision analysis model to assess the medicoeconomic implications of FDG PET imaging in diagnosing a solitary pulmonary nodule. *Eur J Health Econ*. 2005;6(3):203–214.
18. Facey K, Bradbury I, Laking G, Payne E. Overview of the clinical effectiveness of positron emission tomography imaging in selected cancers. *Health Technol Assess*. 2007;11(44):iii-iv, xi-267.
19. Feeney J, Horwitz S, Gonen M, Schoder H. Characterization of T-cell lymphomas by FDG PET/CT. *AJR Am J Roentgenol*. 2010;195(2):333–340.
20. Zinzani PL, Gandolfi L, Broccoli A, et al. Midtreatment 18F-fluorodeoxyglucose positron-emission tomography in aggressive non-Hodgkin lymphoma. *Cancer*. 2011;117(5):1010–1018.
21. Kirby AM, Mikhaeel NG. The role of FDG PET in the management of lymphoma: what is the evidence base? *Nucl Med Commun*. 2007;28(5):335–354.
22. Karam M, Novak L, Cyriac J, Ali A, Nazeer T, Nugent F. Role of fluorine-18 fluoro-deoxyglucose positron emission tomography scan in the evaluation and follow-up of patients with low-grade lymphomas. *Cancer*. 2006;107(1):175–183.
23. Luminari S, Biasoli I, Arcaini L, 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(8):2108–2112.
24. Wirth A, Foo M, Seymour JF, Macmanus MP, Hicks RJ. Impact of [18f] fluorodeoxyglucose positron emission tomography on staging and management of early-stage follicular non-Hodgkin lymphoma. *Int J Radiat Oncol Biol Phys*. 2008;71(1):213–219.
25. El-Galaly TC, d'Amore F, Mylam KJ, et al. Routine bone marrow biopsy has little or no therapeutic consequence for positron emission tomography/computed tomography-staged treatment-naive patients with Hodgkin lymphoma. *J Clin Oncol*. 2012;30(36):4508–4514.
26. Cerci JJ, Trindade E, Buccheri V, et al. Consistency of FDG-PET accuracy and cost-effectiveness in initial staging of patients with Hodgkin lymphoma across jurisdictions. *Clin Lymphoma Myeloma Leuk*. 2011;11(4):314–320.
27. Watanabe R, Tomita N, Takeuchi K, et al. SUVmax in FDG-PET at the biopsy site correlates with the proliferation potential of tumor cells in non-Hodgkin lymphoma. *Leuk Lymphoma*. 2010;51(2):279–283.
28. Schöder H, Noy A, Gönen M, et al. Intensity of 18fluorodeoxyglucose uptake in positron emission tomography distinguishes between indolent and aggressive non-Hodgkin's lymphoma. *J Clin Oncol*. 2005;23(21):4643–4651.
29. Gallamini A, Hutchings M, Rigacci L, et al. Early interim 2-[18F]fluoro-2-deoxy-d-glucose positron emission tomography is prognostically superior to international prognostic score in advanced-stage Hodgkin's lymphoma: a report from a joint Italian-Danish study. *J Clin Oncol*. 2007;25(24):3746–3752.
30. Moulin-Romsee G, Spaepen K, Stroobants S, Mortelmans L. Non-Hodgkin lymphoma: retrospective study on the cost-effectiveness of early treatment response assessment by FDG-PET. *Eur J Nucl Med Mol Imaging*. 2008;35(6): 1074–1080.
31. Dupuis J, Berriolo-Riedinger A, Julian A, 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(35):4317–4322.
32. Spaepen K, Stroobants S, Dupont P, et al. Prognostic value of positron emission tomography (PET) with fluorine-18 fluorodeoxyglucose ([18F]FDG) after first-line chemotherapy in non-Hodgkin's lymphoma: is [18F]FDG-PET a valid alternative to conventional diagnostic methods? *J Clin Oncol*. 2001;19(2):414–419.
33. Cerci JJ, Trindade E, Pracchia LF, et al. Cost effectiveness of positron emission tomography in patients with Hodgkin's lymphoma in unconfirmed complete remission or partial remission after first-line therapy. *J Clin Oncol*. 2010;28(8): 1415–1421.
34. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol*. 2007;25(5):579–586.
35. Bradbury I BE, Boynton J, Cummins E, Facey K, Iqbal K, Laking G, McDonald C, Parpia T, Sharp P, Single A, Walker A. Health Technology Assessment Report 2: positron emission tomography (PET) imaging in cancer management. Report No. 1903961319. 2002.
36. Engert A, Haverkamp H, Kobe C, et al. Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial. *Lancet*. 2012;379(9828):1791–1799.
37. Hutchings M, Loft A, Hansen M, et al. FDG-PET after two cycles of chemotherapy predicts treatment failure and progression-free survival in Hodgkin lymphoma. *Blood*. 2006;107(1):52–59.
38. Strobel K, Schaefer NG, Renner C, et al. Cost-effective therapy remission assessment in lymphoma patients using 2-[fluorine-18]fluoro-2-deoxy-d-glucose-positron emission tomography/computed tomography: is an end of treatment exam necessary in all patients? *Annals Oncol*. 2007;18(4):658–664.
39. Lee AI, Zuckerman DS, Van den Abbeele AD, et al. Surveillance imaging of Hodgkin lymphoma patients in first remission: a clinical and economic analysis. *Cancer*. 2010;116(16):3835–3842.
40. Moskowitz CH, Matasar MJ, Zelenetz AD, et al. Normalization of pre-ASCT, FDG-PET imaging with second-line, non-cross-resistant, chemotherapy programs improves event-free survival in patients with Hodgkin lymphoma. *Blood*. 2012;119(7):1665–1670.
41. Thomson KJ, Kayani I, Ardeshna K, et al. A response-adjusted PET-based transplantation strategy in primary resistant and relapsed Hodgkin lymphoma. *Leukemia*. 2013;27(6):1419–1422.
42. Trotman J, Fournier M, Lamy T, 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(23):3194–3200.
43. Trotman J, Luminari S, Boussetta S, et al. Prognostic value of PET–CT after frontline therapy in follicular lymphoma: a pooled analysis of central review in three multicenter studies. *J Clin Oncol*. 2014;32((5s):suppl; abstr):8502.

44. Kedmi M, Avivi I, Ribakovsky E, et al. Is there a role for therapy response assessment with 2-[fluorine-18] fluoro-2-deoxy-d-glucose-positron emission tomography/computed tomography in mantle cell lymphoma? *Leuk Lymphoma*. 2014:;55(11):2484–2489.
45. Sheng ZK, Ye J, Li JJ, Zhao K, Sheng JF. Utility of fluorodeoxyglucose positron emission tomography/computed tomography in patients with fever of unknown origin diagnosed as lymphoma. *Med Princ Pract*. 2014;23:437–442.
46. Kostakoglu L. Novel PET radiotracers for potential use in management of lymphoma. *PET Clinics*. 2012;7:83–117.
47. Graf N, Herrmann K, Numberger B, et al. [18F]FLT is superior to [18F]FDG for predicting early response to antiproliferative treatment in high-grade lymphoma in a dose-dependent manner. *Eur J Nucl Med Mol Imaging*. 2013;40(1):34–43.
48. Buck AK, Bommer M, Stilgenbauer S, et al. Molecular imaging of proliferation in malignant lymphoma. *Cancer Res*. 2006;66(22):11055–11061.
49. Kasper B, Egerer G, Gronkowski M, et al. Functional diagnosis of residual lymphomas after radiochemotherapy with positron emission tomography comparing FDG- and FLT-PET. *Leuk Lymphoma*. 2007;48(4):746–753.
50. Herrmann K, Buck AK, Schuster T, et al. Predictive value of initial 18F-FLT uptake in patients with aggressive non-Hodgkin lymphoma receiving R-CHOP treatment. *J Nucl Med*. 2011;52(5):690–696.
51. Herrmann K, Buck AK, Schuster T, et al. A pilot study to evaluate 3′-deoxy-3′-18F-fluorothymidine pet for initial and early response imaging in mantle cell lymphoma. *J Nucl Med*. 2011;52(12):1898–1902.
52. Wang R, Zhu H, Chen Y, et al. Standardized uptake value based evaluation of lymphoma by FDG and FLT PET/CT. *Hematol Oncol*. 2013;32:126–132.
53. Lee H, Kim SK, Kim YI, et al. Early determination of prognosis by interim 3′-deoxy-3′-18F-fluorothymidine PET in patients with non-Hodgkin lymphoma. *J Nucl Med*. 2014;55(2):216–222.
54. Lin C, Itti E, Haioun C, et al. Early 18F-FDG PET for prediction of prognosis in patients with diffuse large B-cell lymphoma: SUV-based assessment versus visual analysis. *J Nucl Med*. 2007;48(10):1626–1632.
55. Itti E, Lin C, Dupuis J, et al. Prognostic value of interim 18F-FDG PET in patients with diffuse large B-Cell lymphoma: SUV-based assessment at 4 cycles of chemotherapy. *J Nucl Med*. 2009;50(4):527–533.
56. Meignan M, Gallamini A, Haioun C. Report on the First International Workshop on Interim-PET-Scan in Lymphoma. *Leuk Lymphoma*. 2009;50(8):1257–1260.
57. Casasnovas RO, Meignan M, Berriolo-Riedinger A, Groupe d'étudedeslympho mesdel'adulte(GELA), Groupe d'étude des lymphomes de l'adulte (GELA), et al. SUVmax reduction improves early prognosis value of interim positron emission tomography scans in diffuse large B-cell lymphoma. *Blood*. 2011;118(1):37–43.
58. Itti E, Meignan M, Berriolo-Riedinger A, et al. An international confirmatory study of the prognostic value of early PET/CT in diffuse large B-cell lymphoma: comparison between Deauville criteria and DeltaSUVmax. *Eur J Nucl Med Mol Imaging*. 2013;40(9):1312–1320.
59. Rossi C, Kanoun S, Berriolo-Riedinger A, et al. Interim 18F-FDG PET SUVmax reduction is superior to visual analysis in predicting outcome early in Hodgkin lymphoma patients. *J Nucl Med*. 2014;55(4):569–573.
60. Meignan M, Sasanelli M, Casasnovas RO, et al. Metabolic tumour volumes measured at staging in lymphoma: methodological evaluation on phantom experiments and patients. *Eur J Nucl Med Mol Imaging*. 2014;41(6):1113–1122.
61. Kim TM, Paeng JC, Chun IK, et al. Total lesion glycolysis in positron emission tomography is a better predictor of outcome than the International Prognostic Index for patients with diffuse large B cell lymphoma. *Cancer*. 2013;119(6):1195–1202.
62. Sasanelli M, Meignan M, Haioun C, et al. Pretherapy metabolic tumour volume is an independent predictor of outcome in patients with diffuse large B-cell lymphoma. *Eur J Nucl Med Mol Imaging*. 2014;41:2017–2022.
63. Song MK, Chung JS, Shin HJ, et al. Clinical significance of metabolic tumor volume by PET/CT in stages II and III of diffuse large B cell lymphoma without extranodal site involvement. *Ann Hematol*. 2012;91(5):697–703.
64. Manohar K, Mittal BR, Bhattacharya A, Malhotra P, Varma S. Prognostic value of quantitative parameters derived on initial staging 18F-fluorodeoxyglucose positron emission tomography/computed tomography in patients with high-grade non-Hodgkin's lymphoma. *Nucl Med Commun*. 2012;33(9):974–981.
65. Esfahani SA, Heidari P, Halpern EF, Hochberg EP, Palmer EL, Mahmood U. Baseline total lesion glycolysis measured with (18)F-FDG PET/CT as a predictor of progression-free survival in diffuse large B-cell lymphoma: a pilot study. *Am J Nucl Med Mol Imaging*. 2013;3(3):272–281.
66. Gallicchio R, Mansueto G, Simeon V, et al. F-18 FDG PET/CT quantization parameters as predictors of outcome in patients with diffuse large B-cell lymphoma. *Eur J Haematol*. 2014;92(5):382–389.
67. Song MK, Chung JS, Shin HJ, et al. Prognostic value of metabolic tumor volume on PET/CT in primary gastrointestinal diffuse large B cell lymphoma. *Cancer Sci*. 2012;103(3):477–482.
68. Song MK, Chung JS, Lee JJ, et al. Metabolic tumor volume by positron emission tomography/computed tomography as a clinical parameter to determine therapeutic modality for early stage Hodgkin's lymphoma. *Cancer Sci*. 2013;104(12):1656–1661.
69. Song MK, Chung JS, Shin HJ, et al. Clinical value of metabolic tumor volume by PET/CT in extranodal natural killer/T cell lymphoma. *Leuk Res*. 2013;37(1):58–63.
70. Kim CY, Hong CM, Kim DH, et al. Prognostic value of whole-body metabolic tumour volume and total lesion glycolysis measured on (1)(8)F-FDG PET/CT in patients with extranodal NK/T-cell lymphoma. *Eur J Nucl Med Mol Imaging*. 2013;40(9):1321–1329.
71. Cazaentre T, Morschhauser F, Vermandel M, et al. Pre-therapy 18F-FDG PET quantitative parameters help in predicting the response to radioimmunotherapy in non-Hodgkin lymphoma. *Eur J Nucl Med Mol Imaging*. 2010;37(3):494–504.
72. Sauer M, Plütschow A, Jachimowicz RD, et al. Baseline serum TARC levels predict therapy outcome in patients with Hodgkin lymphoma. *Am J Hematol*. 2013;88(2):113–115.