Prognostic significance of interim18F-FDG PET/CT SUV reduction associated with Ki67 in patients with diffuse large B-cell lymphoma Postprint

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Abstract

To investigate the prognostic significance of interim 18F-FDG PET/CT SUV (standard uptake value) reduction (ΔSUVmax) associated with Ki67 in patients with diffuse large B-cell lymphoma (DLBCL). Forty-seven DLBCL patients who underwent PET/CT before treatment initiation and after 2–4 cycles of chemotherapy were included. The SUVmax of dominant lesions was calculated. Ki67 positive indices were determined by enzyme-labeled immunohistochemistry. SPSS 17.0 was used for statistical analysis. ΔSUVmax values of different groups were compared by t-test. Receiver operating characteristic analysis was performed to determine optimal cutoff values. Kaplan-Meier analyses of PFS (progression-free survival) were compared using the log-rank test. The average ΔSUVmax and ΔSUVmax% were 11.53 and 69.10%, respectively. The optimal cutoff values for ΔSUVmax and ΔSUVmax% were 11.45 and 82.92%, respectively. Higher ΔSUVmax and ΔSUVmax% indicated longer PFS ($p<0.001$). The optimal cutoff value for Ki67 was 55%. Ki67$ 55 $11.45 or Ki67>55% was defined as an indicator of poor outcome and assigned 1 point. The PFS rate was 100% in patients with a score of 0, yet 0% in patients with a score of 2. PFS tended to be shorter as the score increased ($p=0.006$). Both ΔSUVmax and Ki67 positive index had prognostic significance in DLBCL. The prognostic value may be confirmed when ΔSUVmax was concordant with Ki67.

Full Text

Abstract

Objective: To investigate the prognostic significance of interim 18F-FDG PET/CT SUV (standardized uptake value) reduction (ΔSUVmax) combined

with Ki67 expression in patients with diffuse large B-cell lymphoma (DLBCL).

Methods: Forty-seven DLBCL patients who underwent PET/CT scanning before treatment initiation and after 2–4 cycles of chemotherapy were included. The SUVmax of dominant lesions was calculated, and Ki67 positivity indices were determined by enzyme-labeled immunohistochemistry. Statistical analysis was performed using SPSS 17.0. The ΔSUVmax values across different groups were compared using t-tests. Receiver operating characteristic (ROC) analysis was employed to determine optimal cutoff values. Progression-free survival (PFS) was analyzed using Kaplan-Meier methods and compared with the log-rank test.

Results: The mean ΔSUVmax and ΔSUVmax% were 11.53 and 69.10%, respectively. ROC analysis identified optimal cutoff values of 11.45 for ΔSUVmax and 82.92% for ΔSUVmax% for predicting PFS. Higher ΔSUVmax and ΔSUVmax% were associated with longer PFS ($p < 0.001$). The optimal Ki67 cutoff value was 55%, with Ki67 $\geq$ 55% indicating shorter PFS ($p = 0.019$). Patients were assigned 1 point for either ΔSUVmax $\leq$ 11.45 or Ki67 $>$ 55% as indicators of poor outcome. The PFS rate was 100% in patients with a score of 0, but 0% in those with a score of 2. PFS decreased significantly as the score increased ($p = 0.006$).

Conclusion: Both ΔSUVmax and Ki67 positivity index are significant prognostic factors in DLBCL. The prognostic value may be enhanced when ΔSUVmax findings are concordant with Ki67 expression.

Keywords: Diffuse large B-cell lymphoma, Standardized uptake value, Ki67, Prognosis

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive non-Hodgkin lymphoma (NHL) in adults. Advances in chemotherapy, particularly the introduction of rituximab, and progress in autologous stem cell transplantation have enabled DLBCL patients to achieve relatively long-term remission. However, refractory disease and tumor relapse remain significant clinical challenges. Additionally, acute and long-term toxicities from chemotherapeutic agents contribute to patient mortality. These problems underscore the need for risk-adapted therapy, which requires early and accurate prognostic assessment.

18F-FDG PET/CT is a metabolic imaging modality that reflects glucose metabolism. Its value in staging, response assessment, prognosis, and follow-up of DLBCL has been well established and incorporated into NHL management guidelines for years [**?**]. While post-treatment PET/CT has proven valuable for prognostication, early assessment requires imaging after initial treatment phases, such as following 2 or 4 cycles of chemotherapy (interim PET/CT). Efforts to establish appropriate criteria for interim PET/CT interpretation

have revealed limitations in visual analysis, with several groups considering it insufficiently reliable [**?**, **?**]. Semi-quantitative analysis based on standardized uptake value (SUV) has been proposed to improve prognostic accuracy [**?**], particularly SUV reduction analysis [**?**, **?**].

Ki67 is a nuclear antigen expressed during the cell generation cycle that is absent in resting-phase cells, making it a reliable parameter for measuring tumor proliferation index. High Ki67 positivity has been demonstrated to predict poor outcomes in various malignancies [**?**], including lymphoma. Since SUV reduction reflects changes in glucose metabolism after therapy while Ki67 indicates tumor cell proliferation, integrating these parameters provides complementary biological information. This study aimed to evaluate the prognostic significance of interim 18F-FDG PET/CT SUV reduction in combination with Ki67 expression in DLBCL patients.

Materials and Methods

Patients

Forty-seven pathologically confirmed DLBCL patients who underwent PET/CT scanning between July 2007 and June 2011 were included. Patients with prior malignancies were excluded. All patients received first-line chemotherapy (CHOP, R-CHOP, or CHOPE) following diagnosis. Follow-up duration ranged from 14 to 52 months (median 34 months), with a follow-up rate of 95.7% (45/47). Patient characteristics are summarized in .

18F-FDG PET/CT Imaging

PET/CT scans were performed on a Discovery STE16 PET/CT scanner (GE Healthcare). The radiochemical purity of FDG exceeded 95%, meeting all quality requirements for radiopharmaceuticals. Patients underwent imaging before treatment initiation (baseline) and after 2–4 cycles of chemotherapy (interim). Patients fasted for 6 hours, and blood glucose levels were maintained below 7.8 mmol/L. Data acquisition was performed 50–60 minutes after intravenous injection of 0.12–0.15 mCi/kg 18F-FDG, consisting of 5–7 bed positions covering from the upper thigh to the skull. Emission scans lasted 3 minutes per bed position (5 minutes for the skull). A low-dose CT transmission scan (100 kV, 40 mAs, 5 mm slice thickness) was used for attenuation correction.

SUV-Based Assessment

For each PET dataset, the lesion with the most intense 18F-FDG uptake was identified as the dominant lesion. Regions of interest (ROIs) were drawn around dominant lesions, and SUVmax was calculated using a Xeleris workstation and normalized to body surface area (BSA) using Eqs. (1) and (2):

$$\text{SUV} = \frac{\text{Tissue activity (kBq/ml)}}{\text{Injected activity (MBq/ml)} \cdot \text{BSA}}$$

$$\text{BSA (Body Surface Area)} = 0.007184 \times \text{Height}^{0.725} \times \text{Weight}^{0.425}$$

In patients with complete lesion disappearance after chemotherapy, ROIs were drawn in the same anatomic location on interim PET images as on baseline images. ΔSUVmax and ΔSUVmax% were calculated as follows:

$$\Delta\text{SUVmax} = \text{SUVmax(initial)} - \text{SUVmax(interim)}$$

$$\Delta\text{SUVmax\%} = \frac{\text{SUVmax(initial)} - \text{SUVmax(interim)}}{\text{SUVmax(initial)}}$$

Ki67 Positivity Index

Ki67 positivity indices were determined by enzyme-labeled immunohistochemistry. PBS served as negative control, and known positive sections as positive controls. Positive results were defined as stained tumor cell nuclei. For each section, five high-power fields were selected, and 200 tumor cells were randomly counted per field. The Ki67 positivity index was calculated as the ratio of positive tumor cells per 1000 total tumor cells.

Statistical Analysis

SPSS 17.0 was used for statistical analysis. The primary endpoint was progression-free survival (PFS), defined as the interval from enrollment to first evidence of progression, relapse, or death from any cause. Data were censored for patients alive and progression-free at last follow-up. Independent samples t-tests compared SUVmax reduction across different stages, IPI scores, and outcomes. ROC analysis determined optimal cutoff values for ΔSUVmax, ΔSUVmax%, and Ki67 positivity index for predicting outcome (progression/death vs. progression-free). Kaplan-Meier survival curves were generated and compared using log-rank tests. Statistical significance was defined as two-sided $p < 0.05$.

Results

Patient Outcomes

During follow-up, 19 of 45 patients (42.2%) remained progression-free. The remaining 26 patients (57.8%) experienced disease progression at a median of 10.0 months.

Prognostic Significance of ΔSUVmax and ΔSUVmax%

Baseline SUVmax was 18.16 ± 6.54, decreasing to 5.20 ± 4.89 after 2–4 chemotherapy cycles. Mean ΔSUVmax and ΔSUVmax% were 11.53 ± 5.53 and (69.10 ± 27.90)%, respectively. presents ΔSUVmax and ΔSUVmax% across different groups.

Patients with high IPI scores and those who progressed during follow-up showed significantly lower ΔSUVmax and ΔSUVmax% ($0.001 \leq p \leq 0.008$). ΔSUVmax% was also significantly lower in stage IV patients. ΔSUVmax tended to be lower in stage IV patients, though this difference was not statistically significant.

ROC analysis identified optimal cutoff values of 11.45 for ΔSUVmax and 82.92% for ΔSUVmax% for PFS prediction [Figure 1: see original paper]. The predictive accuracies were 84.4% (area under curve [AUC] 0.842) and 80% (AUC 0.889), respectively. shows PFS rates and predictive values for each group. Kaplan-Meier analysis demonstrated that patients with higher ΔSUVmax and ΔSUVmax% had significantly longer PFS [Figure 2: see original paper]. PFS data are detailed in .

Prognostic Significance of Ki67 Positivity Index

ROC analysis identified an optimal Ki67 cutoff of 55% [Figure 3: see original paper]. PFS data are presented in . The accuracy for predicting 2-year PFS was 80% (positive predictive value [PPV] = 77.8%, negative predictive value [NPV] = 81.2%). Kaplan-Meier analysis showed that Ki67 > 55% predicted shorter PFS ($p = 0.019$) [Figure 4: see original paper].

Combined Prognostic Significance of ΔSUVmax and Ki67

Both ΔSUVmax and Ki67 data were available for 20 patients. Based on the established prognostic values, we developed an integrated scoring system: ΔSUVmax ≤ 11.45 and Ki67 > 55% were each assigned 1 point as indicators of poor outcome. shows the distribution of scores and outcomes. Patients with a score of 0 ("double positive") had 100% PFS (5/5), while those with a score of 2 ("double negative") had 0% PFS (0/7). This yielded 100% PPV for the 0-score group and 100% NPV for the 2-score group. Concordance between ΔSUVmax and Ki67 appeared to confirm prognostic predictions. Kaplan-Meier analysis based on this integrated scoring system showed that PFS decreased significantly as scores increased ($p = 0.006$) [Figure 5: see original paper].

Discussion

Since the International Harmonization Project incorporated PET/CT into NHL response criteria in 2007 [**?**], the value of PET/CT in lymphoma management has been well established. A systematic review by Terasawa et al. [**?**] of 19 studies including 474 Hodgkin lymphoma and 254 NHL patients

confirmed PET/CT's utility in identifying necrosis and residual tumors post-chemotherapy. However, earlier assessment is necessary to optimize treatment and minimize toxicity. While the International Prognostic Index (IPI) provides population-based risk stratification, metabolic imaging offers potential for individualized prognosis. In a study of 8 aggressive NHL patients, SUVmax decreased by 60% one week after the first chemotherapy dose [**?**], confirming PET/CT's potential for early prognostication. Currently, early (after 2 cycles) and interim (after 4 cycles) PET/CT assessments are actively investigated in NHL [**?**, **?**].

The prognostic accuracy of early or interim PET/CT using visual analysis alone has been suboptimal across various criteria [**?**, **?**, **?**], prompting interest in SUV-based analysis to improve precision [**?**]. SUV is a semi-quantitative parameter with advantages of being non-invasive, easily calculated, and widely applicable. However, its susceptibility to technical factors has generated controversy. To minimize variability, we standardized imaging conditions: all scans were performed on the same scanner at the same institution, imaging was conducted 50–60 minutes post-injection (when FDG uptake plateaus), and SUVmax rather than SUVmean was used to reduce partial-volume effects. Under these controlled conditions, SUVmax demonstrated good reproducibility [**?**].

Nevertheless, SUV calculations remain influenced by unavoidable factors. SUV reduction analysis using the same scanner, acquisition parameters, and normalization method may be more reliable. In studies of 92 DLBCL patients, optimal SUVmax reduction cutoffs after 2 and 4 chemotherapy cycles were 65.7% and 72.9%, respectively [**?**, **?**], with PPVs of 81.3% and 70.6% and NPVs of 76.1% and 79.4%, respectively. These studies also noted that SUVmax reduction analysis showed similar prognostic value after 2 versus 4 cycles, whereas visual analysis demonstrated higher prognostic accuracy after 4 cycles. Our study similarly confirmed the prognostic significance of SUVmax reduction in DLBCL, though our "interim" PET/CT timing was heterogeneous (4 patients scanned after 2 cycles, 1 after 3 cycles) due to limited sample size.

Ki67 positivity index is a well-established proliferation marker, with high Ki67 indicating poor prognosis across various malignancies [**?**], including lymphoma [**?**]. In a study of 58 DLBCL patients receiving R-CHOP chemotherapy, Ki67 $>$ 80% predicted shorter PFS and overall survival [**?**]. Shou et al. [**?**] demonstrated a positive correlation between Ki67 and FDG uptake in NHL, showing significantly higher SUVave in large cell lymphoma versus small cell lymphoma with minimal overlap.

Several groups have proposed integrating SUV analysis with clinical risk factors to improve prognostic accuracy. Nguyen et al. [**?**] defined "SIMaxSUV" (SUVmax multiplied by maximal lesion diameter) as an independent PFS predictor. Lanic et al. [**?**] developed a scoring system integrating SUVmax reduction, age-adjusted IPI, and DLBCL molecular subtype that predicted overall survival.

Inflammatory response post-therapy represents a major cause of false-positive

results on FDG PET/CT [**?**]. While 18F-FLT (a thymine analog reflecting proliferation) can reduce inflammatory false-positives, it is not routinely used clinically. Fortunately, Ki67, widely used to assess tumor proliferation, also provides prognostic information.

Our study evaluated the combined prognostic significance of interim SUV reduction and Ki67 positivity. No significant difference was found between ΔSUVmax and ΔSUVmax% prognostic values ($p = 0.970$ and 0.318, respectively) when comparing their PPVs and NPVs using two-dimensional cross-tabulation. Notably, the PPV for 0-score patients and NPV for 2-score patients both reached 100%. This scoring system integrates two key aspects of tumor biology—glucose metabolism and cellular proliferation—potentially enhancing prognostic capacity. Despite the small sample size, concordance between these parameters appeared to confirm prognosis, particularly in the 0-score group [Figure 6: see original paper], suggesting that low Ki67 may help identify a subset of patients where marked FDG uptake reduction predicts excellent outcomes.

Limitations include the lack of post-treatment Ki67 data, which might correlate more closely with SUVmax reduction and improve outcome prediction. Additionally, potential therapeutic modifications based on interim PET/CT results were not accounted for, which could have influenced outcomes. Future prospective studies with larger samples should standardize SUV measurement conditions and control for treatment changes.

Conclusion

In summary, both ΔSUVmax and Ki67 positivity index are significant prognostic factors in DLBCL. Prognostic accuracy may be enhanced when ΔSUVmax findings are concordant with Ki67 expression, particularly for identifying patients with excellent outcomes. Further prospective studies with larger cohorts are warranted.

References

[1] Cheson B, Pfstner B, Juweid M, et al. J Clin Oncol, 2007, 25: 579-586. [2] Pregno P, Chiappella A, Bellò M, et al. Blood, 2012, 119: 3263-3268. [3] Cox M C, Ambrogi V, Lanni V et al. Leukemia Lymphoma, 2012, 53: 263-269. [4] Casasnovas R O, Meignan M, Berriolo-Riedinger A, et al. Blood, 2011, 118: 37-43. [5] Lin C, Itti E, Haioun C, et al. J Nucl Med, 2007, 48: 1626-1632. [6] Broyde A, Boycov O, Strenov Y, et al. Am J Hematol, 2009, 84: 338-343. [7] Bryant R J, Banks P M, O'Malley D P, et al. Histopathology, 2006, 48: 505-515. [8] Szczuraszek K, Mazur G, Jelen M, et al. Anticancer Res, 2008, 28: 1113-1118. [9] Kim S J, Kim B S, Choi C W, et al. Ann Oncol, 2007, 18: 1252-1257. [10] Terasawa T, Nihashi T, Hotta T, et al. J Nucl Med, 2008, 49: 8-15. [11] Wu X, Dastidar P, Pertovaara H, et al. Mol Imaging Biol, 2011, 13: 785-792. [12] Itti E, Lin C, Dupuis J, et al. J Nucl Med, 2009, 50: 527-533. [13] Itti E, Juweid M E, Haioun C, et al. J Nucl Med, 2010, 51: 1347-1350. [14]

Nahmias C and Wahl L M. J Nucl Med, 2008, 49: 1804-1808. [15] Han B, Lin S, Yu L J, et al. Nucl Med Commun, 2009, 30: 831-837. [16] Ueda S, Tsuda H, Saeki T, et al. Breast Cancer, 2011, 18: 299-304. [17] Tang B, Malysz J, Douglas-Nikitin V, et al. Mol Imaging Biol, 2009, 11: 296-302. [18] Gaudio F, Giordano A, Perrone T, et al. Acta Haematol, 2011, 126: 44-51. [19] Shou Y, Lu J, Chen T, et al. J Cancer Res Ther, 2012, 8: 96-100. [20] Nguyen X C, Lee W W, Amin A M, et al. Nucl Med Mol Imaging, 2010, 44: 39-44. [21] Lanic H, Mareschal S, Mechken F, et al. Leukemia Lymphoma, 2012, 53: 34-42. [22] Herrmann K, Buck A K, Schuster T, et al. J Nucl Med, 2011, 52: 690-696.

Note: Figure translations are in progress. See original paper for figures.