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Predictive Value of Metabolic and Tumor Dissemination Parameters in Diffuse Large B-Cell Lymphoma: Can Relapse Be Predicted Despite Adequate Interim PET Response?

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Abstract

Objective:
To evaluate the association between baseline and interim 18F-FDG PET/CT parameters and early clinical outcomes in patients with Diffuse Large B-Cell Lymphoma, and to identify potential prognostic and predictive biomarkers. We also assessed whether baseline clinical and metabolic parameters could predict outcomes in cases with discordant interim PET findings and clinical course.

Methods:
A total of 112 patients with DLBCL were retrospectively analyzed. Baseline clinical and biochemical data, along with metabolic parameters derived from staging PET (sPET) and interim PET (iPET), were recorded. Delta (Δ) parameters were calculated to reflect interval changes. Interim PET findings were categorized according to Deauville criteria as adequate or inadequate response. Based on clinical follow-up, patients were classified as remission or refractory/progressive disease. Group comparisons were performed using appropriate parametric or non-parametric tests. Discriminative performance was assessed using receiver operating characteristic (ROC) analysis.

Results:
Interim PET demonstrated a sensitivity of 79%, specificity of 71%, and accuracy of 74% for predicting outcomes, with a negative predictive value of 82% and a positive predictive value of 66%. Baseline tumor dissemination parameters derived from sPET, namely DmaxPET and DmaxVoxPET, were significantly higher in patients who developed relapse/progression despite adequate interim PET response (AUC: 0.81 and 0.77).

Among evaluated variables, DmaxVox from sPET showed limited but significant discriminative ability. In contrast, iPET-derived metabolic parameters—including SUVmax, SUVmean, SUVpeak, lesion-to-liver ratio (RLL), and total lesion glycolysis (TLG)—as well as selected delta parameters (ΔSUVmax, ΔSUVmean, ΔSUVpeak, ΔRLL), demonstrated significant predictive value for remission (AUC: 0.70–0.79), with overall superior performance compared to baseline parameters. SUV-based indices and RLL outperformed volumetric TLG, while SUV-derived metrics showed comparable performance. Among clinical and biochemical variables, only ferritin demonstrated significant predictive value (AUC: 0.79).

Conclusion:
Interim PET is a robust tool for early response assessment and risk-adapted management in DLBCL. While staging PET provides prognostic information related to tumor burden and dissemination, interim PET offers stronger predictive value through metabolic response assessment. SUV-based parameters and RLL derived from iPET are particularly effective in predicting early clinical outcomes. Baseline dissemination metrics may further identify patients at increased risk of relapse despite favorable interim PET findings, supporting closer clinical surveillance.

INTRODUCTION

Non-Hodgkin lymphoma (NHL) represents a heterogeneous group of malignancies originating from lymphoid cells, including B lymphocytes, T lymphocytes, and natural killer (NK) cells. Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of NHL in adults [1]. R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) is the standard first-line treatment regimen. Although durable remission is achieved in approximately 60–70% of patients, 30–40% exhibit refractory disease or relapse [2]. In such cases, salvage chemotherapy followed by high-dose chemotherapy and autologous stem cell transplantation is commonly applied. Additionally, novel treatment strategies, including immunotherapies, CAR-T cell therapy, and bispecific antibodies, have demonstrated promising outcomes [3].

The NCCN-IPI has been shown to outperform the traditional IPI in predicting prognosis and improving risk stratification in DLBCL [4]. However, clinical scoring systems based solely on baseline parameters remain insufficient for accurately identifying high-risk patients [5, 6]. Therefore, there is a growing need to develop more robust prognostic biomarkers incorporating imaging-derived parameters. 18F-FDG PET/CT is widely used in lymphoma management for staging, restaging, and post-treatment evaluation. Interim PET (iPET), performed during treatment, enables early assessment of chemosensitivity and identification of patients with favorable or poor prognosis [7]. In DLBCL, iPET is typically recommended after 2–4 cycles of R-CHOP chemotherapy [8].

Several studies have demonstrated the prognostic significance of metabolic PET parameters such as SUVmax, MTV, and TLG in DLBCL [9–12]. However, the optimal metabolic biomarker for clinical use remains controversial. Cui et al. introduced the concept of metabolic tumor area (MTA), initially applied in prostate cancer, and demonstrated its independent prognostic value for progression-free survival (PFS) and overall survival (OS) in DLBCL patients treated with R-CHOP, particularly in high-risk groups defined by NCCN-IPI ≥ 4 [13]. In another study evaluating the prognostic value of combined metabolic and anatomical changes, ΔSUVmax and the composite parameter ΔSUVmax × ΔSLD were reported as significant predictors of survival outcomes, with optimal cutoff values of 74% and 30%, respectively [14].

Spatial dissemination parameters have also gained attention. DmaxVoxMIP, representing the maximum distance between the outermost voxels of the two most distant lesions on MIP images, has been shown to correlate with survival outcomes [15]. Gao et al. demonstrated that the lesion-to-liver SUVmax ratio (RLL) and bone marrow involvement on interim PET were independent prognostic factors for treatment outcomes, with defined cutoff values for RLL [16]. Similarly, Ferrari et al. reported that the lesion-to-liver ratio showed a stronger correlation with PFS and OS compared to the Deauville score [17].

In this context, the present study aimed to evaluate the predictive value of clinical and metabolic PET/CT parameters for treatment response in newly diagnosed DLBCL patients. Additionally, we sought to identify biomarkers capable of explaining discordance between interim PET findings and clinical outcomes and to determine the most relevant parameters for predicting remission versus refractory/progressive disease.

MATERIALS AND METHODS

Patient Selection

This retrospective study included patients diagnosed with DLBCL between 2012 and 2024 who underwent baseline staging 18F-FDG PET/CT imaging. A total of 112 patients aged ≥ 18 years with available staging PET (sPET) and interim PET (iPET) scans were included. Patients with a history of another malignancy or active significant infection were excluded.

All patients received standard first-line R-CHOP chemotherapy following staging PET. Interim PET imaging was performed after 2–4 cycles of treatment. Metabolic parameters were extracted from both sPET and iPET scans. Clinical and laboratory data were retrieved from medical records and the institutional database.

Clinical outcomes were determined based on post-treatment PET findings, histopathological confirmation (when available), and clinical follow-up of up to two years. Patients with shorter follow-up (6–12 months) were included if they had biopsy-proven relapse, refractory disease, early progression, or death. Outcomes were categorized as remission (Outcome 1) or refractory/progressive disease (Outcome 2).

The study protocol was approved by the institutional review board, and informed consent was waived due to the retrospective design and anonymized data analysis (2025/395).

FDG PET/CT Acquisition and Image Analysis

All patients underwent 18F-FDG PET/CT imaging using a high-resolution scanner equipped with an integrated 16-slice CT system (Biograph 16 PET/CT, Siemens, Chicago, IL, USA). Patients fasted for at least 4 hours prior to imaging, and blood glucose levels were confirmed to be below 150 mg/dL before tracer injection.

An intravenous dose of 18F-FDG (296–555 MBq) was administered, followed by an uptake period of 45–60 minutes in a resting state. Imaging was performed from the vertex to the upper thigh. Low-dose CT was acquired for attenuation correction and anatomical localization, followed by PET acquisition with approximately 3 minutes per bed position. Images were reconstructed using an ordered-subset expectation maximization algorithm.

All images were reviewed by two experienced nuclear medicine physicians. Metabolic and volumetric parameters were calculated using LIFEx software (v25.06.1, https://www.lifexsoft.org) [18].

The following parameters were recorded:

* SUV-based metrics: SUVmax, SUVmean, SUVpeak

* Tumor burden parameters: MTVd, TMTV, TLG

* Spatial dissemination metrics: Dmax, DmaxVox

* Morphological parameter: longest diameter of dominant lesion (LDD)

* Other parameters: MTA and lesion-to-liver ratio (RLL)

Delta (Δ) values representing changes between sPET and iPET were calculated for all parameters. Additionally, derived composite indices (“double products”) such as ΔSUVmax × ΔLDD, DmaxVoxi × SUVmaxi, and DmaxVoxs × TLGi were generated.

Clinical Parameters

Baseline clinical and laboratory variables included ECOG performance status, B symptoms, NCCN-IPI and R-IPI scores, cell-of-origin classification (GCB vs non-GCB), bone marrow involvement, hematological parameters (neutrophils, lymphocytes, platelet count, N/L ratio), ferritin, CRP, albumin, CRP/albumin ratio, LDH, Ki-67 proliferation index, MYC/BCL2/BCL6 status, Ann Arbor stage, bulky disease, and extranodal involvement.

Study Design

Patients were initially classified into two groups based on iPET findings using Deauville criteria: * **Group 1**: adequate response (DS 1–3) and * **Group 2**: inadequate response (DS 4–5).

In the second step, patients were categorized according to clinical outcomes: * **Outcome 1**: remission and * **Outcome 2**: refractory disease, relapse, progression, or death.

The diagnostic performance of iPET was assessed by comparing Group 1 and Group 2 with clinical outcomes. Subsequently, baseline PET, interim PET, delta parameters, and clinical variables were analyzed to identify predictors of clinical outcomes.

Finally, discordant cases were specifically evaluated: * patients with favorable iPET but poor clinical outcomes and * patients with unfavorable iPET but favorable outcomes, to identify parameters associated with this mismatch.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation or median (range), while categorical variables were presented as frequencies and percentages. Normality was assessed using the Shapiro–Wilk test.

Group comparisons were performed using the Mann–Whitney U test or independent samples t-test. Categorical variables were analyzed using Pearson's chi-square, Fisher's exact test, or Fisher–Freeman–Halton test.

Receiver operating characteristic (ROC) analysis was used to evaluate discriminative performance, and area under the curve (AUC) values were reported with standard errors. Optimal cut-off values were determined using Youden's index.

All analyses were conducted using SPSS (version 28.0) and MedCalc (version 19.6.1), with a significance level set at $p < 0.05$.

RESULTS

The study population consisted of 112 patients (56 females and 56 males) with a mean age of 55.4 years (range: 18–87). Based on interim PET evaluation, 65 patients were classified as Group 1 and 47 as Group 2.

During clinical follow-up, 56 patients achieved remission (Outcome 1), while 56 experienced refractory or progressive disease (Outcome 2). Among Group 1 patients, 46 (71%) remained in remission, whereas 19 (29%) developed relapse, progression, or death. In Group 2, 37 patients (79%) experienced disease progression or death, while 10 (21%) achieved remission (Fig. 1). The baseline clinical characteristics of the study population are presented in table 1.

Interim PET demonstrated a sensitivity of 79%, specificity of 71%, accuracy of 74%, NPV of 82%, and PPV of 66% in predicting clinical outcomes.

ROC analysis revealed that baseline spatial dissemination parameters derived from sPET—specifically DmaxPET and DmaxVoxPET—were significantly higher in patients who later developed relapse or progression despite an adequate interim PET response (AUC: 0.81 and 0.77, respectively). A patient with extensive baseline tumor burden and dissemination who subsequently exhibited disease progression despite a favorable interim PET response is illustrated in (Fig. 2). Among biochemical markers, ferritin also showed significant discriminative ability in this subgroup (AUC: 0.81) (Fig. 3).

In contrast, no PET-derived parameter was able to distinguish patients with poor interim PET response who subsequently achieved remission. However, ferritin and albumin levels demonstrated discriminative value in this subgroup (AUC:0.78 and 0.70).

We systematically examined the discriminative capacity of clinical and biochemical variables—including PET-derived metrics, iPET, and ΔPET—between patients who achieved remission and those who did not. As presented in table 2, mean values of these parameters differed between the remission and non-remission cohorts.

Furthermore, as summarized in table 3, assessment of predictors of remission revealed that, among sPET-derived metrics, DmaxVox demonstrated statistically significant discriminative performance. In contrast, several iPET-derived SUV-based parameters (SUVmax, SUVmean, SUVpeak), as well as RLL and TLG, exhibited significant predictive utility. Likewise, selected delta parameters (ΔSUVmax, ΔSUVmean, ΔSUVpeak, and ΔRLL) were also associated with meaningful predictive performance, with AUC values ranging from 0.70 to 0.79. Notably, iPET-derived parameters yielded the highest overall predictive performance among the evaluated variables. A case characterized by an insufficient reduction in ΔSUVmax and persistently elevated interim SUVmax, subsequently demonstrating marked disease progression, is presented in Fig. 4.

SUV-based parameters and RLL outperformed volumetric TLG, while SUV-based metrics showed comparable performance among themselves. Among clinical variables, only ferritin demonstrated significant predictive value (AUC: 0.79) (Fig. 5). Table 4 summarizes the differences in the mean values of clinical and biochemical parameters between patients who remained in remission and those who did not.

Derived composite parameters (double products) were also evaluated. Both DmaxVoxi × SUVmaxi and DmaxVoxs × TLGi demonstrated moderate discriminative ability (AUC: 0.742 and 0.758, respectively). Optimal cut-off values determined by Youden's index were 0.31 (sensitivity 87.5%, specificity 52%) and 7.49 (sensitivity 91%, specificity 54%), respectively.

DISCUSSION

Interim 18F-FDG PET/CT is widely recognized as a valuable tool for early assessment of treatment response and prognostication in patients with Diffuse Large B-Cell Lymphoma. Owing to the ability of metabolic imaging to identify chemosensitive tumors at an early stage, several studies have demonstrated that patients achieving a metabolic response on interim PET exhibit significantly higher progression-free survival and overall survival rates [19–21]. In line with the literature, our cohort showed a remission rate of 71% in patients with favorable iPET response, compared with only 21% in those with inadequate response.

Based on clinical follow-up, the sensitivity, specificity, and overall accuracy of iPET for predicting early remission/progression-free survival were 79%, 71%, and 74%, respectively, with a negative predictive value (NPV) of 82% and a positive predictive value (PPV) of 66%. These findings are broadly consistent with previously reported data. Systematic reviews and meta-analyses evaluating the prognostic value of interim PET in DLBCL have demonstrated a wide range of sensitivity and specificity values. For instance, a large meta-analysis reported sensitivity ranging from 33% to 87%, specificity from 49% to 94%, PPV from 20% to 74%, and NPV from 64% to 95%, with particular emphasis on the consistently high NPV, often exceeding 80% [22]. Similarly, a more recent study evaluating interim PET parameters reported a sensitivity of 73.3% and specificity of 72% when using a semiquantitative threshold [16]. These values

closely parallel our findings (79% sensitivity and 71% specificity), further supporting the moderate-to-high diagnostic performance of interim PET in early response assessment.

Notably, interim PET has been consistently characterized by a high NPV. Negative interim PET findings are strongly associated with favorable prognosis, with NPV exceeding 80% in most studies [22]. The NPV of 82% observed in our study corroborates these findings and underscores the reliability of negative interim PET in predicting favorable treatment response. In contrast, PPV is generally lower and more variable, largely due to false-positive findings caused by inflammation or treatment-related metabolic activity. Consequently, several studies have emphasized that PPV alone may be insufficient to justify treatment modification [22]. The PPV of 66% in our study lies at the upper end of reported ranges, suggesting that positive interim PET may still represent a meaningful indicator of disease progression risk. Overall, the diagnostic performance metrics observed in our study are consistent with the literature and support the clinical utility of interim PET in evaluating early treatment response in DLBCL.

In our analysis, parameters reflecting tumor dissemination derived from baseline PET—namely DmaxPET and DmaxVoxPET—were significantly higher in patients who experienced relapse/progression during follow-up despite an adequate response on interim PET. This finding suggests that spatial distribution metrics obtained from baseline PET/CT may provide important prognostic information regarding tumor biology and clinical behavior. Studies by Cottereau et al. have demonstrated that Dmax (maximum tumor dissemination) measured on baseline PET is significantly associated with both progression-free and overall survival in DLBCL, and that its combination with metabolic tumor volume (MTV) improves risk stratification [23]. These results indicate that the spatial distribution of disease, independent of tumor burden, carries prognostic significance. Similarly, a systematic review by Albano et al. (2023) identified high Dmax values as adverse prognostic factors for both progression-free and overall survival [24]. Consistent with our findings, these data suggest that early metabolic response alone may not fully capture tumor biology, and that patients with extensive spatial tumor dissemination at baseline may harbor minimal residual disease or microscopic spread influencing clinical outcomes. Therefore, integrating tumor dissemination parameters from baseline PET/CT with interim PET findings may improve identification of patients at high risk of relapse.

In contrast, no PET-derived parameter demonstrated a significant ability to distinguish patients with inadequate interim PET response who subsequently achieved remission. Current evidence indicates that while interim PET has a high NPV, its PPV is more limited and may be affected by false-positive findings. Increased FDG uptake related to treatment-induced inflammation, infection, or immune activation within the tumor microenvironment may mimic residual disease. As a result, some patients classified as interim PET-positive may still achieve complete remission with continued therapy [16, 25–27]. These observations highlight the importance of interpreting interim PET findings in conjunction with clinical, biochemical, and baseline imaging parameters to improve prognostic accuracy.

In addition to imaging biomarkers, ferritin emerged as a significant biochemical parameter in our study. Elevated ferritin levels were observed in patients who developed relapse/progression despite adequate

interim PET response. As an acute-phase reactant involved in iron metabolism, ferritin has been associated with tumor burden, inflammation, and immune activation in malignancies. Previous studies in DLBCL have reported that elevated ferritin levels may reflect tumor-associated inflammation and macrophage activation, correlating with more aggressive disease biology and poorer prognosis [28, 29]. Furthermore, in patients with inadequate interim PET response who subsequently achieved remission, both ferritin and albumin demonstrated discriminatory value. Lower ferritin and higher albumin levels in this subgroup suggest that inflammatory status and nutritional condition may influence disease behavior. These readily accessible biochemical markers may provide additional prognostic insight, particularly in cases where metabolic response appears suboptimal [30].

When evaluating the discriminatory performance of baseline PET, interim PET, ΔPET parameters, and clinical-biochemical variables, only DmaxVox derived from baseline PET demonstrated significant predictive value for remission. This finding aligns with literature indicating that spatial tumor dissemination parameters reflect biological aggressiveness and prognosis [15, 23, 31, 32], whereas metabolic and volumetric PET parameters have shown more heterogeneous results depending on patient population, segmentation methodology, and threshold selection [19, 33, 34].

At interim PET, SUV-based metabolic parameters (SUVmax, SUVmean, SUVpeak), along with RLL and TLG, demonstrated significant predictive value for remission. These findings are consistent with reports indicating that semiquantitative metabolic PET parameters correlate with progression-free survival and may provide more accurate prognostic information than baseline PET [16, 19, 20]. Additionally, several delta parameters (ΔSUVmax, ΔSUVmean, ΔSUVpeak, and ΔRLL) were also found to have significant discriminatory power [14, 26, 35], with the highest predictive performance observed for parameters derived from interim PET. Among clinical-biochemical variables, only ferritin showed significant predictive value.

Li et al., in a study of 129 newly diagnosed DLBCL patients, reported that a composite parameter reflecting both tumor size and metabolic change (ΔSUVmax × ΔSLD) had significant predictive value for both overall and progression-free survival [14]. In our analysis, we explored whether derived composite PET parameters (“double products”) could enhance prognostic performance. We found that DmaxVoxi × SUVmaxi and DmaxVoxs × TLGi demonstrated discriminatory ability between patients achieving and not achieving remission. Optimal cut-off values determined by the Youden index were 7.49 (sensitivity 91%, specificity 54%) for DP_DmaxVoxs × TLGi and 0.31 (sensitivity 87.5%, specificity 52%) for DP_DmaxVoxi × SUVmaxi. Both parameters exhibited moderate discriminative performance, with slightly higher results for the TLG-based model (AUC: 0.758 vs. 0.742). However, these composite measures did not substantially outperform their individual components. These findings suggest that more complex and time-consuming volumetric or anatomical analyses may not provide meaningful incremental clinical benefit over simpler SUV-based metrics.

One limitation of our study is the relatively short duration of clinical follow-up. By focusing on outcomes within a maximum follow-up period of two years, we aimed to evaluate early treatment response.

However, longer follow-up may reveal changes in the number of patients achieving sustained remission or experiencing disease progression.

In conclusion, interim PET remains a critical tool for early response assessment and for guiding risk-adapted treatment strategies. Baseline PET appears to provide prognostic information primarily through tumor burden and spatial dissemination, whereas interim PET offers predictive value based on metabolic response. SUV-based parameters and RLL derived from interim PET demonstrate superior predictive performance in identifying patients likely to achieve remission during early clinical follow-up. Furthermore, baseline PET parameters reflecting tumor dissemination, such as DmaxPET and DmaxVoxPET, retain prognostic significance even in patients with favorable interim PET response, indicating an increased risk of relapse/progression in cases with extensive disease spread. These findings underscore the importance of close monitoring in patients with high baseline tumor dissemination, even when early metabolic response appears favorable.

Abbreviations

18F
FDG–Fluorine–18 fluorodeoxyglucose
AUC
Area under the curve
ASCT
Autologous stem cell transplantation
CRP
C–reactive protein
CT
Computed tomography
DLBCL
Diffuse large B–cell lymphoma
DS
Deauville score
ECOG
Eastern Cooperative Oncology Group
FDG
Fluorodeoxyglucose
GCB
Germinal center B–cell subtype
iPET
Interim positron emission tomography
IPI
International Prognostic Index
LDH

Lactate dehydrogenase
LDD
Longest diameter of dominant lesion
MBq
Megabecquerel
MIP
Maximum intensity projection
MTA
Metabolic tumor area
MTV
Metabolic tumor volume
MTVd
Metabolic tumor volume of dominant lesion
NHL
Non–Hodgkin lymphoma
NPV
Negative predictive value
OS
Overall survival
PET/CT
Positron emission tomography/computed tomography
PFS
Progression–free survival
PPV
Positive predictive value
R
CHOP–Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
R
IPI–Revised International Prognostic Index
RLL
Lesion–to–liver SUVmax ratio
ROC
Receiver operating characteristic
sPET
Staging positron emission tomography
SUV
Standardized uptake value
SUVmax
Maximum standardized uptake value
SUVmean

Mean standardized uptake value
SUVpeak
Peak standardized uptake value
TLG
Total lesion glycolysis
TMTV
Total metabolic tumor volume
Dmax
Maximum distance between the two most distant lesions
DmaxVox
Maximum distance between the outermost voxels of the two most distant lesions

Declarations

Acknowledgments

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Tables

Tables are available in the Supplementary Files section.

Figures

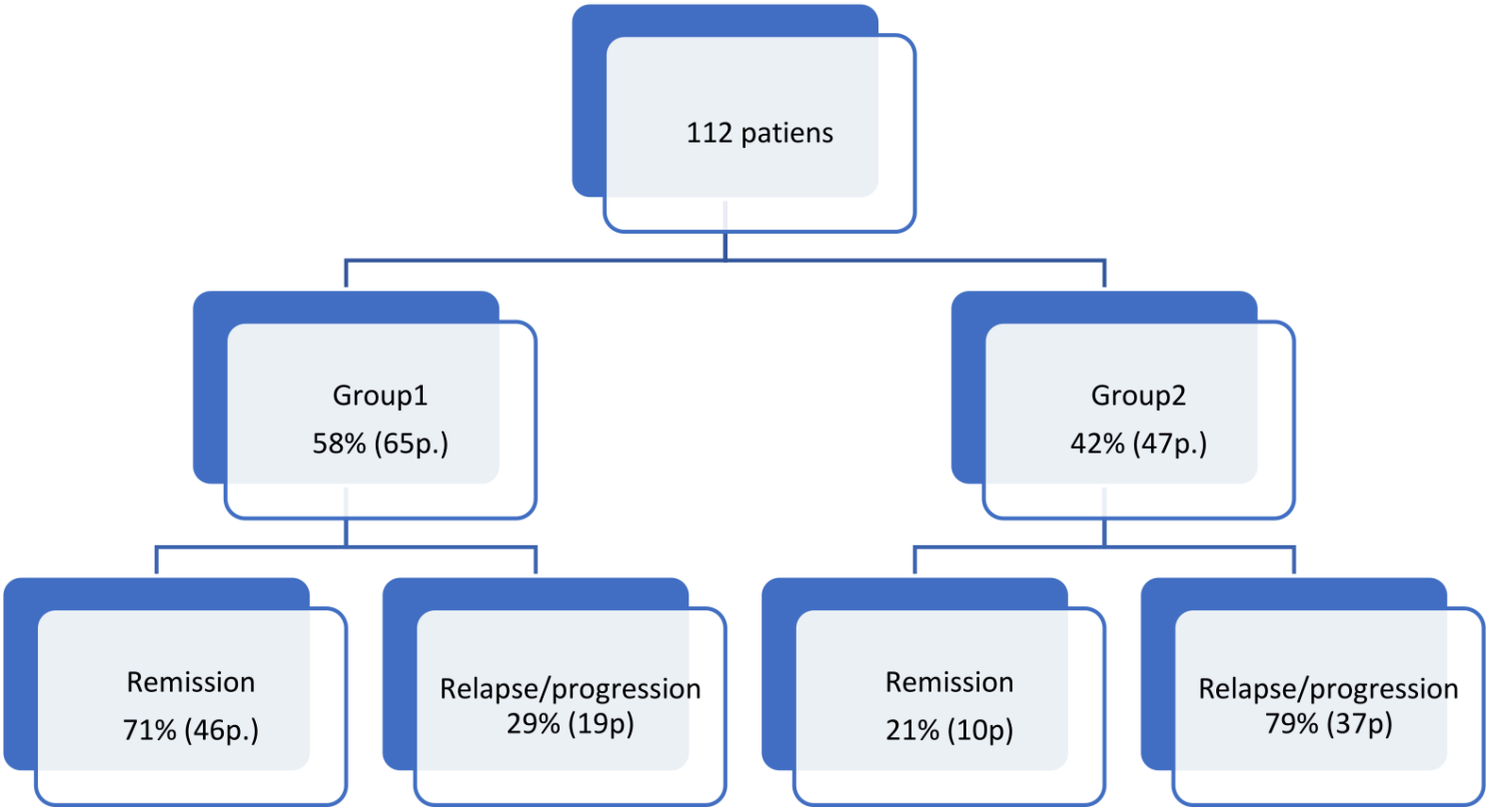


Figure 1

Clinical follow-up flowchart of treatment response groups according to interim PET.

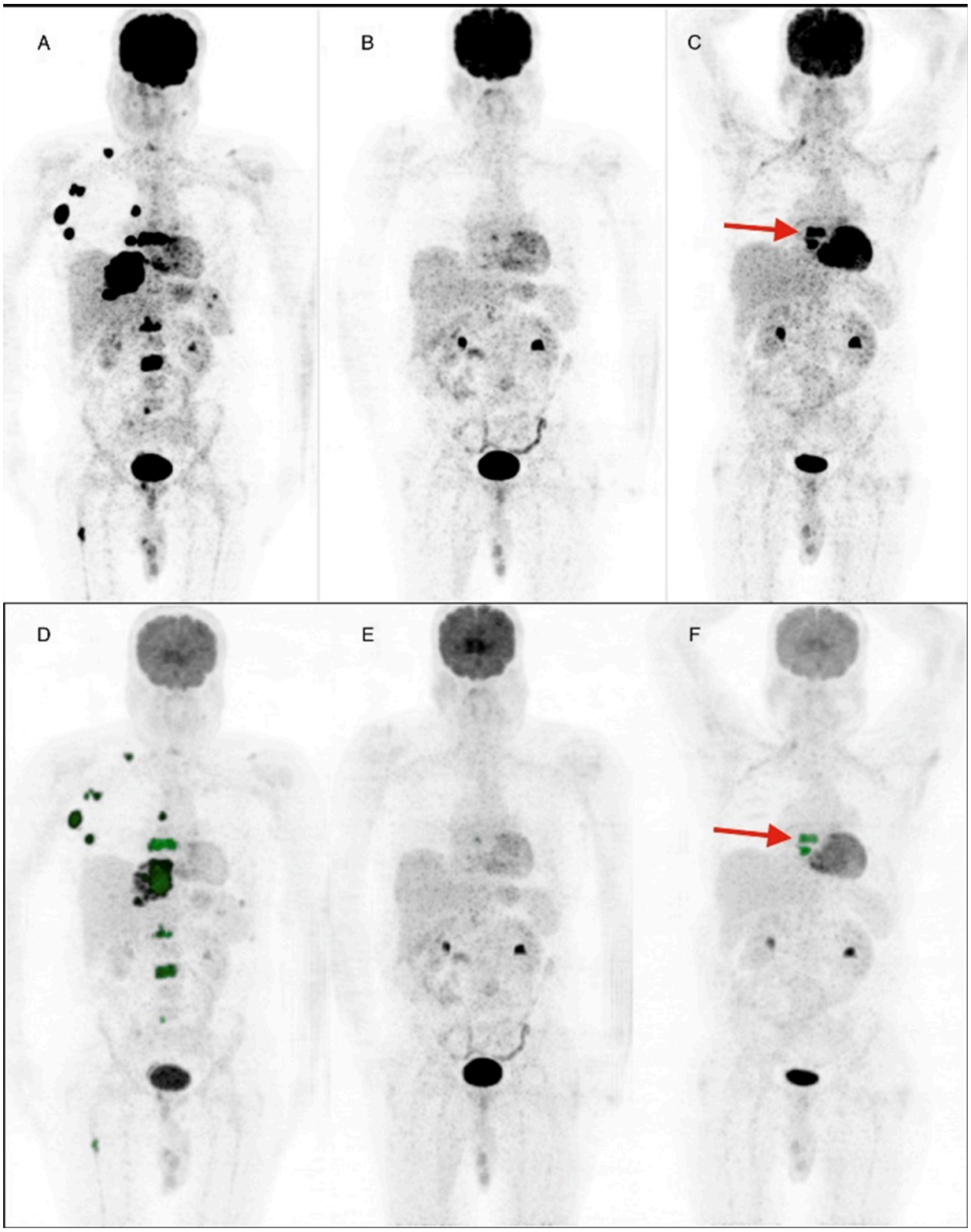
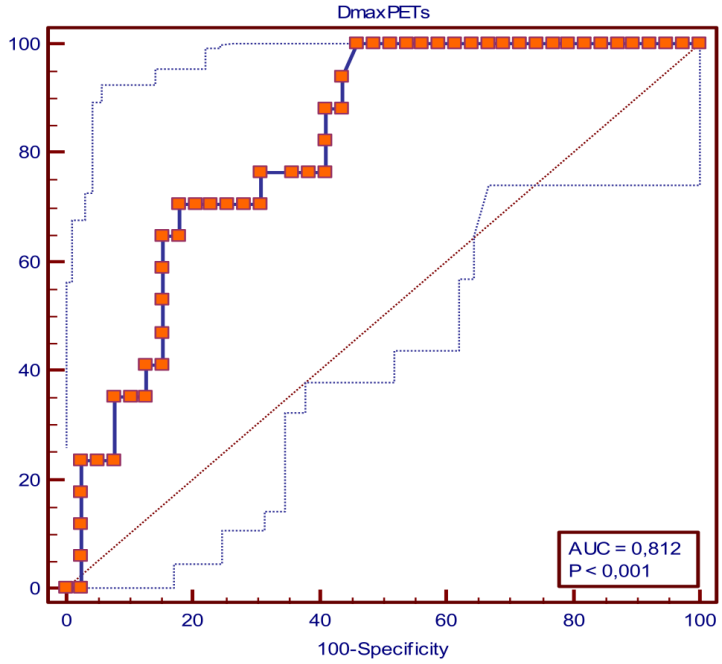
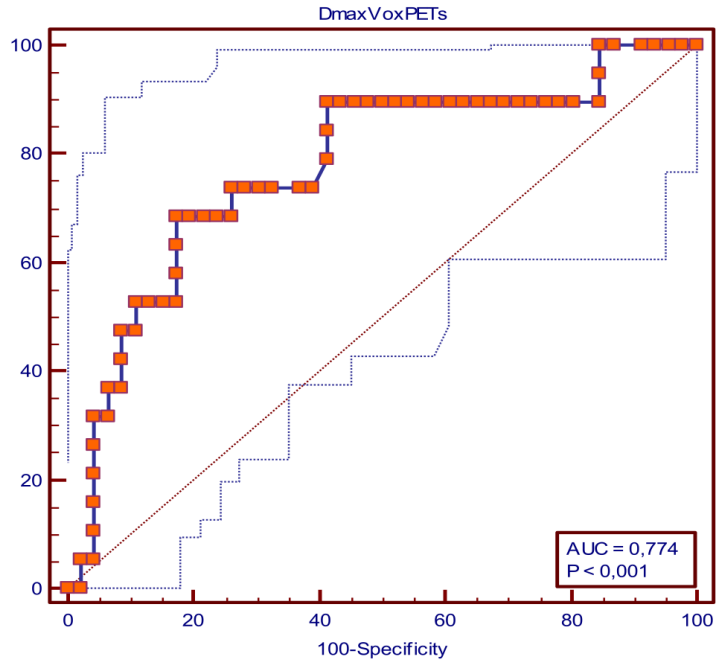


Figure 2

A staging PET (sPET) of a 64-year-old male patient diagnosed with DLBCL reveals tumoral foci with intense FDG uptake localized in multiple bones, multiple lymphatic stations, and a bulky mass on the chest wall (A). In this case with extensive tumor burden on sPET, the Dmax was measured as 84.8 cm and the SUVmax as 30. Despite a significant reduction in tumor burden on interim PET (iPET) (SUVmax:

5.9, DS: 4, ΔSUVmax: 80%) (B), progression was observed on the end-of-treatment PET (DS: 5) (C). The painted tumor areas of the same MIP images are shown in the bottom row, respectively (D, E, F).





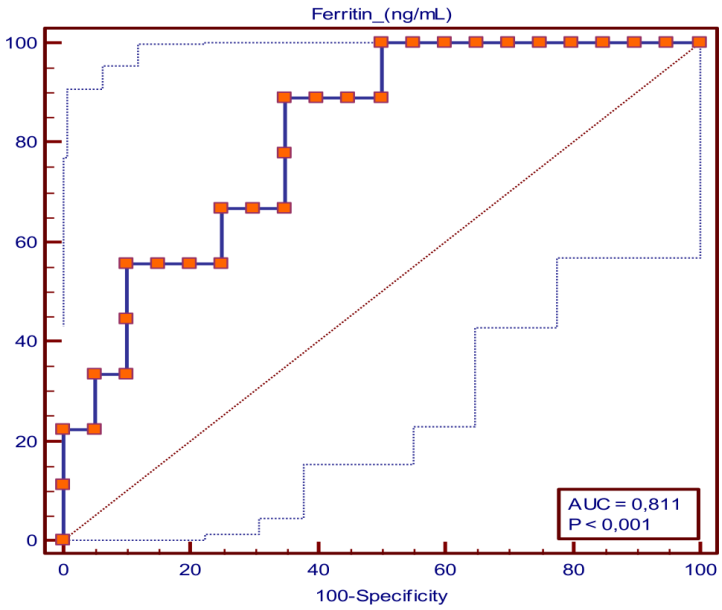


Figure 3

Despite an adequate response on interim PET, DmaxPET, DmaxVoxPET, and ferritin levels were significantly higher in patients who developed relapse/progression during clinical follow-up.

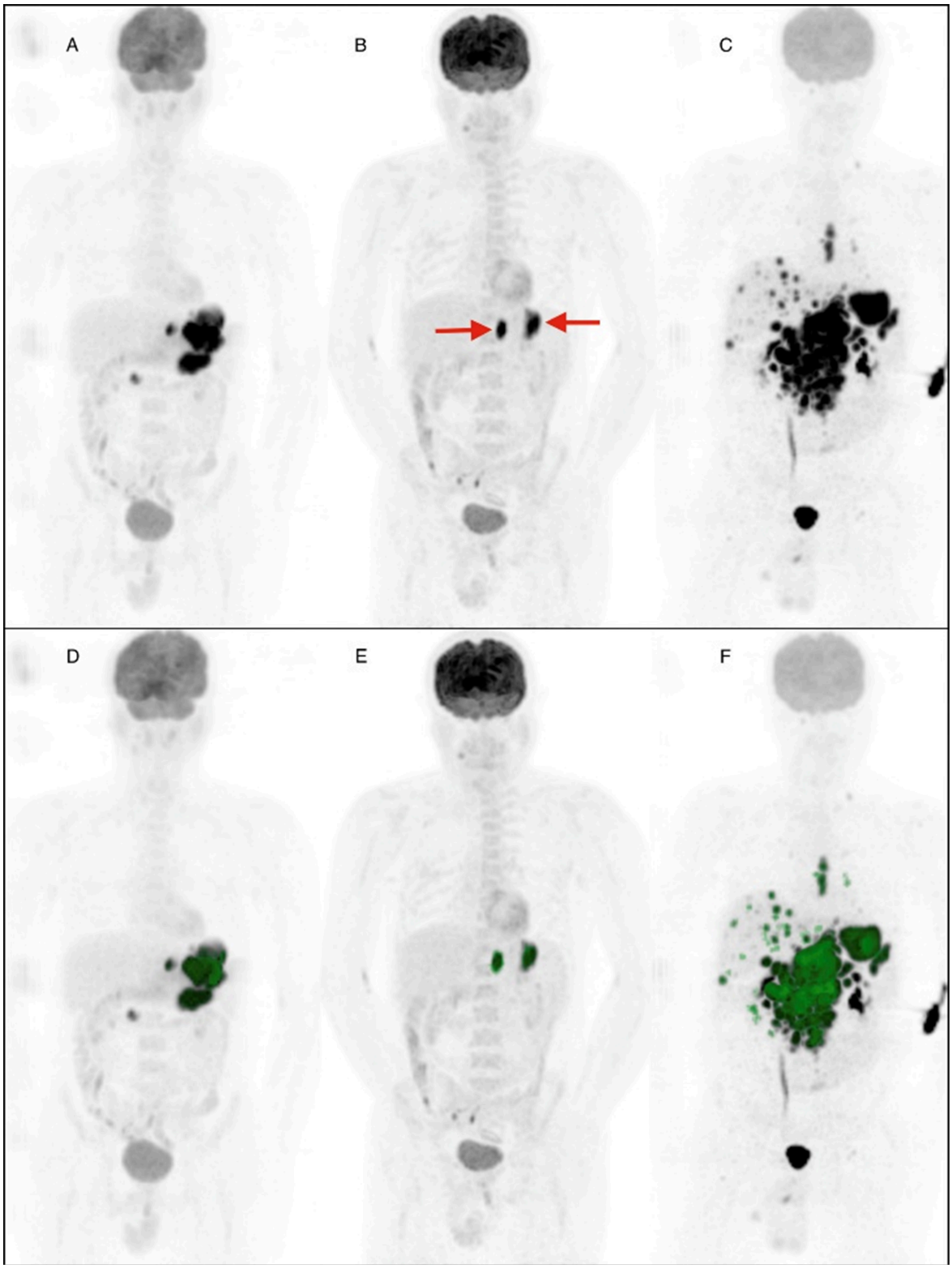


Figure 4

The sPET of a 45-year-old male patient diagnosed with DLBCL showed lymphoma involvement with diffuse, intense FDG uptake in the gastric walls (sPET Dmax: 6.5 cm, SUVmax: 44) (A). On the subsequent iPET, although the tumor area had significantly decreased in size, only slight metabolic regression was observed in the residual mass (SUVmax: 36, ΔSUVmax: 18%) (B). Progression with newly

developed diffuse tumoral foci was observed on the end-of-treatment PET (C). The painted tumor areas of the same MIP images are shown in the bottom row, respectively (D, E, F).

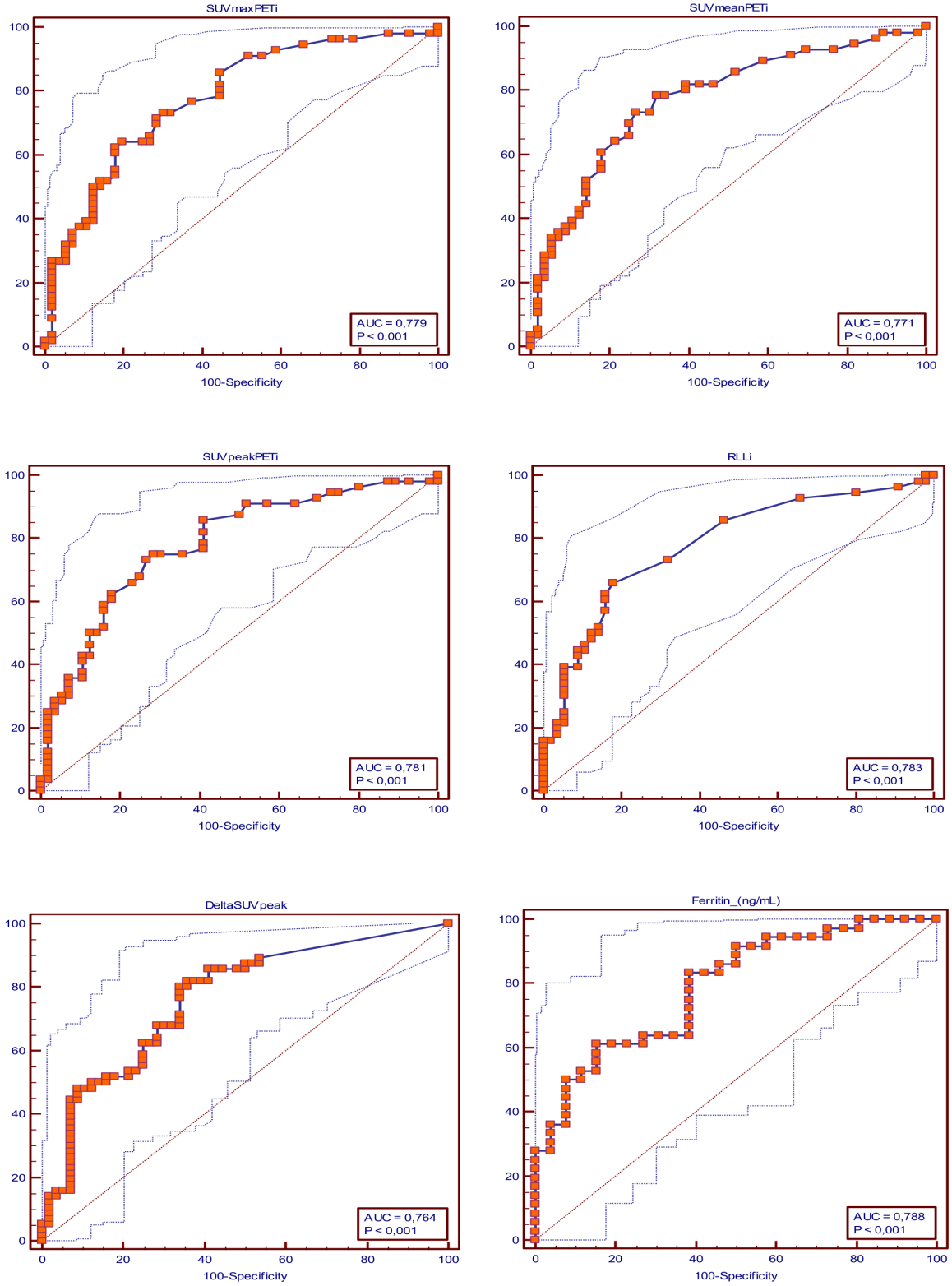


Figure 5

Receiver operating characteristic (ROC) curves comparing selected parameters with clinical follow-up outcomes.

Supplementary Files

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- Table1.docx
- Table2.docx
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- Table4.docx