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# Are Semiquantitative Methods Superior to Deauville Scoring in Monitoring Therapy Response of Pediatric Hodgkin Lymphoma?

**Firuz Ibrahim[1], Michela Gabelloni[2], Lorenzo Faggioni[2*], Subramanyam Padma[3], Arun R. Visakh[4], Dania Cioni[2] and Emanuele Neri[2]**

[1] Department of Nuclear Medicine and PET-CT, Burjeel Medical City, Abu Dhabi, United Arab Emirates; firuz.ibrahim@burjeelmedicalcity.com
[2] Academic Radiology, Department of Translational Research, University of Pisa, Italy; michela.gabelloni@unipi.it (M.G.), lorenzo.faggioni@unipi.it (L.F.), dania.cioni@unipi.it (D.C.), emanuele.neri@unipi.it (E.N.)
[3] Amrita Institute of Medical Sciences, Kochi, Kerala, India; padmasundaram@gmail.com
[4] Department of Nuclear Medicine, VPS Lakeshore Hospital, Kochi, Kerala, India; drvisakhrnair@gmail.com
* Correspondence: lorenzo.faggioni@unipi.it; Tel.: +39 050 992509

**Abstract:** Tailoring treatment in patients with Hodgkin lymphoma (HL) is paramount to maximize outcomes while avoiding unnecessary toxicity. We aimed to compare the performance of SUVmax reduction ($\Delta SUV_{max\%}$) versus Deauville score (DS) in assessing chemotherapy response in pediatric HL patients undergoing $^{18}$F-FDG PET-CT. Fifty-two patients with biopsy-proven HL (age 8-16 years) were enrolled at baseline, interim (after the 2$^{nd}$ or 3$^{rd}$ chemotherapy round), and post-therapy (upon completion of first-line chemotherapy) $^{18}$F-FDG PET-CT. Interim and post-therapy DS and $\Delta SUV_{max\%}$ were compared as response predictors. Patients were classified as responders and non-responders based on 24-month clinical follow-up. Interim DS showed a sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy of 100%, 80.4%, 100%, 40% and 82.7%, respectively in predicting response. Post-therapy DS showed a sensitivity, specificity, PPV, NPV and accuracy of 66.7%, 97.8%, 95.7%, 80% and 94.2%. Interim $\Delta SUV_{max\%}$ showed a sensitivity, specificity, PPV, NPV and accuracy of 83.3%, 82.6%, 97.4%, 38.5% and 82.7%, with a 56.3% cutoff. Post-therapy $\Delta SUV_{max\%}$ showed a sensitivity, specificity, PPV, NPV and accuracy of 83.3%, 84.8%, 97.5%, 41.7% and 84.6%, with a 76.8% cutoff. Sensitivity, specificity ($p<0.05$) and NPV ($p<0.01$) were significantly higher using DS than $\Delta SUV_{max\%}$. In conclusion, DS can predict chemotherapy response better than $\Delta SUV_{max\%}$ in pediatric HL patients.

**Keywords:** Hodgkin lymphoma; chemotherapy; positron emission tomography computed tomography (PET-CT); fluorodeoxyglucose F18 ($^{18}$F-FDG); Deauville score; standardized uptake value (SUV); response prediction

## 1. Introduction

Hodgkin lymphoma (HL) is now one of the most curable forms of neoplasms in children. Compared to the past, survivors have a longer post-exposure life expectancy and can experience long-term and latent side effects of cancer treatment in a non-negligible proportion of cases [1-6]. Therefore, optimizing treatment to minimize subsequent risks while maintaining the chance of cure without compromising long-term survival is of utmost importance.

Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography ($^{18}$F-FDG PET-CT) is a highly sensitive tool for HL staging and restaging and is routinely used for response assessment and treatment adaptation. Various studies have demonstrated its role in preventing unnecessary side effects and morbidity and reducing the cost of treatment, without compromising long-term survival [7-9].

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$^{18}$F-FDG uptake can be assessed using several approaches, including quantitative, semiquantitative and qualitative (i.e., visual) methods. While theoretically most accurate, the absolute quantification of $^{18}$F-FDG uptake is complex and impractical for routine clinical practice [10-11]. To mitigate this difficulty, semiquantitative approaches have been introduced and have become the standard of care in clinical practice [12]. The maximum standardized uptake value ($SUV_{max}$) is a semiquantitative representation of tumor $^{18}$F-FDG uptake and is the commonest method to assess the tumor $^{18}$F-FDG concentration at a single point in time. However, SUV measurements are affected by multiple technical, physical, and biological factors, e.g. the amount of radioactivity injected, tissue blood perfusion, blood sugar level, time of uptake, dose and PET-CT scanner calibrations [13-14].

The qualitative assessment of $^{18}$F-FDG uptake is based on the visual evaluation of PET images, which however relies on reader experience and knowledge of physiologic FDG distribution. The Deauville score (DS) is a visual method based on a five-point scale that is commonly used in routine $^{18}$F-FDG PET-CT clinical reporting and in clinical trials for response assessment in HL and certain non-HL tumors. For each patient, visual scoring is carried out by comparing the $^{18}$F-FDG uptake in pathological sites to that of two reference points (i.e., mediastinum and liver) [15-16].

SUV is routinely used in combination with visual assessment to assess chemotherapy response in patients with HL. Unlike in adults, in pediatric patients $^{18}$F-FDG uptake can be detected in normal tissues (such as brown fat or rebound thymic hyperplasia), potentially leading to errors when therapeutic response is evaluated using visual scoring methods [17]. Hence, in pediatric patients it is important to understand whether visual interpretation of $^{18}$F-FDG PET-CT images is adequate to reliably evaluate treatment response.

Our purpose is to develop a method that can assist deciding whether therapy regimens could be tapered to reduce the risk of toxicity.

## 2. Materials and Methods

### *2.1. Patient enrolment and $^{18}$F-FDG PET-CT image acquisition protocol*

This was a retrospective study involving 52 patients (male:female 26:26, age range 8-16 years, mean ± standard deviation 12 ± 2.4 years) with a histopathologic diagnosis of HL, who underwent $^{18}$F-FDG PET-CT at our referral center between January 2017 and January 2021. Written informed consent to PET-CT imaging was obtained from all patients, and institutional review board approval was waived due to the retrospective nature of our study. $^{18}$F-FDG PET-CT examinations performed at baseline, after the second or third cycle of chemotherapy (interim) and after completion of first-line chemotherapy (post-therapy) were examined. All examinations were carried out on a commercial 16-row PET-CT whole-body scanner (GE Discovery 610®, General Electric, Milwaukee, WI, USA). Patients fasted for 6–8 hours before intravenous administration of $^{18}$F-FDG (5.18–7.4 MBq/kg body weight) to reach a serum glucose level below 180 mg/dL. PET-CT images with a longitudinal coverage from the proximal thighs to the skull base were acquired 45 to 60 minutes after $^{18}$F-FDG injection. Images were reconstructed with a 128x128 matrix using an ordered subset expectation maximum iterative reconstruction algorithm, a 8mm Gaussian filter and a field of view of 50cm. CT, PET and coregistered PET-CT images were reviewed as source axial images, as sagittal and coronal reformations and using maximum intensity projection views by two nuclear medicine physicians with 20 and 4 years of experience. Any disagreement between the two readers was resolved in consensus. Patients' medical history and clinical lab results were accessed from our local hospital information system. HL staging was performed using the Ann Arbor staging system.

The distribution of patients according to HL subtype and stage is reported in Table 1 and Table 2, respectively. All patients received chemo- and/or radiotherapy depending on disease stage.

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**Table 1.** Percentage distribution of the patient sample according to HL subtype.

| HL subtype | Patients (N=) | Proportion (%) |
|---|---|---|
| Mixed cellularity | 9 | 17.3 |
| Nodular lymphocyte predominant | 8 | 15.4 |
| Nodular sclerosing | 35 | 67.3 |

**Table 2.** Percentage distribution of the patient sample according to HL stage.

| HL stage | Patients (N=) | Proportion (%) |
|---|---|---|
| 1A | 10 | 19.2 |
| 1B | 3 | 5.8 |
| 2A | 15 | 28.8 |
| 2B | 5 | 9.6 |
| 3A | 11 | 21.2 |
| 3B | 3 | 5.8 |
| 4A | 3 | 5.8 |
| 4B | 2 | 3.8 |

*2.2. Visual and quantitative assessment of $^{18}$F-FDG PET-CT images*

Increased $^{18}$F-FDG uptake in nodes or extranodal sites was considered as a positive $^{18}$F-FDG PET-CT finding. Care was taken to avoid areas of $^{18}$F-FDG uptake related to any physiological 8F-FDG activity. All positive $^{18}$F-FDG-avid lesions were annotated and followed up at interim and post-treatment PET-CT examinations. Interim and post-therapy PET-CT scans were evaluated visually using the Deauville 5-point scoring system and quantitatively in terms of percentage maximum SUV reduction ($\Delta SUV_{max}$) between baseline and interim PET-CT scans. For each lesion, the maximum DS was recorded.

Based on current Lugano Criteria, complete response is defined as complete normalization of $^{18}$F-FDG uptake (DS from 1 to 3) [18]. Patients with increased $^{18}$F-FDG uptake of pathological lesions compared to the liver (Deauville scores more than 3) were considered as poor responders based on visual scoring. To measure $SUV_{max}$, a volume of interest was drawn semiautomatically on each node or extra nodal site with pathologically increased $^{18}$F-FDG uptake using the following formula:

$$SUV_{max}\ (g/ml) = \frac{maximum\ tumor\ activity\ concentration\ (mCi/ml) \times body\ weight\ (g)}{injected\ dose\ (mCi)}$$

For each patient, the lesion with the highest $SUV_{max}$ was recorded, and the follow-up value for the same lesion was used to calculate the percentage change in $SUV_{max}$ ($\Delta SUV_{max}$) using the formula:

$$\Delta SUV_{max\%} = 100 \times \frac{highest\ SUV\ (PET_{baseline}) - highest\ SUV\ (PET_{interim})}{highest\ SUV\ (PET_{baseline})}$$

$\Delta SUV_{max}$ was used to predict clinical outcome and tumor response to treatment. For each patient, prediction of response using the DS and $\Delta SUV_{max}$ was compared and correlated with disease-free survival. Unlike for adults, to our knowledge $\Delta SUV_{max}$ cut-off values validated from large trials for differentiating good from poor pediatric responders are currently unavailable, with some data having only been provided by a few studies based on small patient cohorts [19-20]. During clinical follow-up, those patients who had a recurrence/disease progression after completion of therapy were considered as non-responders, and the remaining were deemed as responders. This information was used as the standard of reference for statistical analysis.

Patients were classified as true positive at follow-up if they had evidence of disease at interim imaging, followed by persistent disease and/or evidence of recurrence at the end of therapy. True negative patients were defined as those with no evidence of disease

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and complete remission at follow-up. False positive patients showed evidence of disease at interim PET-CT imaging, but remained in remission during follow-up. Finally, false negative patients showed no residual disease at interim PET-CT, but showed evidence of disease at follow-up.

*2.3. Statistical analysis*

Data were analyzed using the SPSS software package, version 20.0 (https://www.ibm.com/products/spss-statistics). Categorical and quantitative variables were expressed as frequency (percentage) and mean ± standard deviation, respectively. Receiver operating characteristic (ROC) curves were generated, and the area under the ROC curve was calculated to assess the diagnostic accuracy of $\Delta SUV_{max\%}$ in detecting positive response, along with the corresponding cut-off scores. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy were calculated as indicators of the performance of DS and $\Delta SUV_{max\%}$ in predicting positive response. The Spearman rank test was used to find a correlation between DS and $\Delta SUV_{max\%}$. Finally, the z-test was used to compare the performance of DS and $\Delta SUV_{max\%}$ in predicting positive response in all patients. A p-value less than 0.05 was set as threshold for statistical significance.

## 3. Results

*3.1. Baseline $SUV_{max}$ in predicting positive response*

Of 52 patients, 46 (88.5%) showed a complete therapy response at follow-up and were classified as responders, whereas the remaining ones had disease progression and/or recurrence. Baseline $SUV_{max}$ was 12.3 ± 5.7 g/ml (mean ± standard deviation; range 3.2 – 29.8 g/ml. Interim $SUV_{max}$ was 3.8 ± 4.4 g/ml (range 1.2 – 21.6 g/ml), and post-therapy $SUV_{max}$ was 2.1 ± 1.9 g/ml (range 1.2 – 9.0 g/ml).

Using a cut-off of 15.5g/ml, baseline $SUV_{max}$ for predicting positive response to therapy at 24 months showed a sensitivity of 80.4%, specificity of 66.7%, PPV of 94.9%, NPV of 30.8 %, and accuracy of 78.8% (Figure 1).

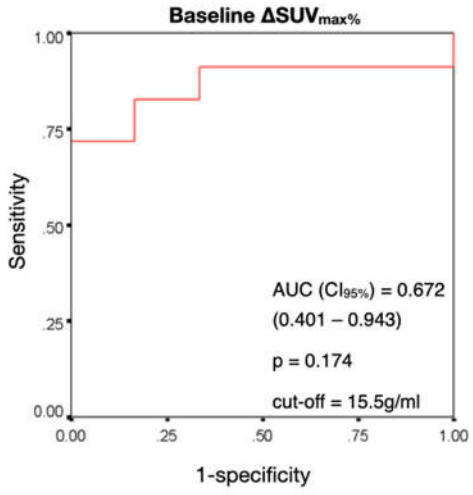


**Figure 1.** ROC curve for $SUV_{max}$ prediction of response at 24 months at baseline $^{18}$F-FDG PET-CT. AUC = area under the ROC curve. CI95% = 95% confidence interval.

Using the DS method, 31 (71.1%) patients were classified as responders (DS 1, 2 and 3) at interim PET-CT, whereas 47 (90.4%) were classified as responders at post-therapy PET-CT. No patients had a DS of 5 at either interim or post-therapy PET-CT. 5 (9.6%) patients had a DS of 4 after completion of therapy and were treated more aggressively with a change in chemotherapy regimen and/or field radiotherapy.

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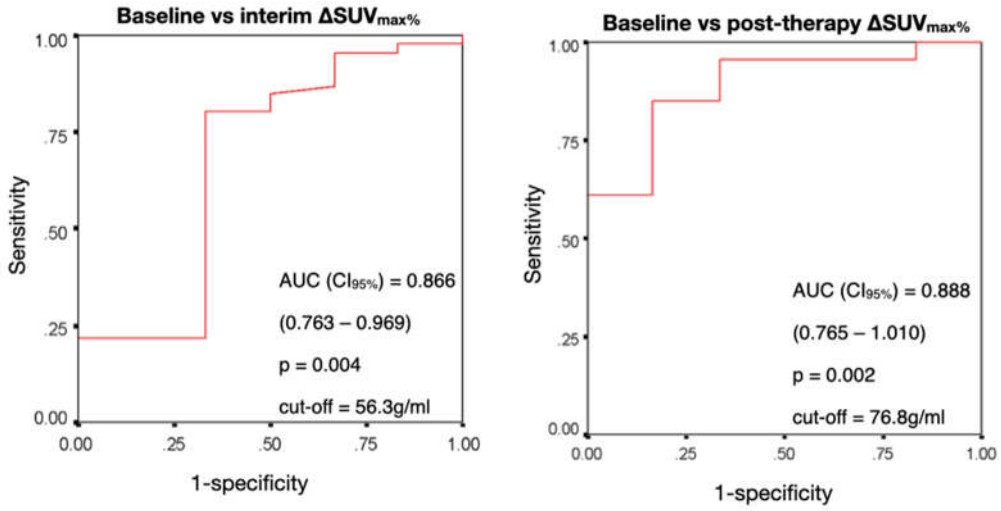
Using the semiquantitative method, interim $\Delta SUV_{max\%}$ was 69.1 ± 24.8 g/ml, whereas post-therapy $\Delta SUV_{max\%}$ was 81.7 ± 11.4 g/ml.

*3.2. Performance of $\Delta SUV_{max\%}$ in predicting therapy response at 24 months*

For $\Delta SUV_{max\%}$ at interim and post-therapy PET-CT, an optimal cut-off of 56.3% and 76.8% were found, respectively (Figure 2).




(**a**) (**b**)

**Figure 2.** ROC curves for therapy response prediction at 24 months based on $\Delta SUV_{max\%}$ at interim (a) and post-therapy PET-CT (b).

The sensitivity, specificity PPV, NPV and accuracy of interim $\Delta SUV_{max\%}$ in predicting therapy response at 24 months were 83.3%, 82.6%, 97.4%, 38.5% and 82.7%, respectively.

The sensitivity, specificity PPV, NPV and accuracy of post-therapy $\Delta SUV_{max\%}$ in predicting therapy response at 24 months were 83.3%, 84.8%, 97.5%, 41.7% and 84.6%, respectively.

*3.3. Diagnostic accuracy of prognostication by Deauville criteria (visual assessment) at different intervals of time in prediction of response at 24 months*

The sensitivity, specificity, PPV, NPV and accuracy of interim DS in predicting therapy response at 24 months were 100.0%, 80.4%, 100.0%, 40.0% and 82.7%, respectively.

The sensitivity, specificity, PPV, NPV and accuracy of post-therapy DS in predicting therapy response at 24 months were 66.7%, 97.8%, 95.7%, 80.0% and 94.2%, respectively.

Table 3 shows the comparison of diagnostic performance of $\Delta SUV_{max\%}$ and DS at interim PET-CT in predicting therapy response at 24 months. Interim DS yielded a significantly higher specificity and lower false-positive ratio compared with interim $\Delta SUV_{max\%}$ (p=0.002).

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**Table 3.** Comparison of diagnostic performance of $\Delta SUV_{max\%}$ and DS at interim PET-CT in predicting therapy response at 24 months.

| | $\Delta SUV_{max\%}$ | DS | z (p) |
|---|---|---|---|
| Sensitivity | 82.6 | 80.4 | 0.286 (0.779) |
| Specificity | 83.3 | 100.0 | 3.075 (0.002) |
| False negative ratio | 17.4 | 19.6 | 0.286 (0.779) |
| False positive ratio | 16.7 | 0.0 | 3.075 (0.002) |
| PPV | 97.4 | 100.0 | 1.162 (0.246) |
| NPV | 38.5 | 40.0 | 0.161 (0.873) |
| Positive likelihood ratio | 5.0 | - | - (-) |
| Negative likelihood ratio | 0.2 | 0.2 | 0.015 (0.992) |
| Accuracy | 82.7 | 82.7 | 0 (1) |

Post-therapy DS yielded a higher sensitivity ($p=0.018$), specificity ($p<0.05$), NPV ($p<0.001$) and lower false positive ($p<0.05$) and false negative ratios ($p=0.018$) compared to post-therapy $\Delta SUV_{max\%}$ (Table 4).

**Table 4.** Comparison of diagnostic performance of $\Delta SUV_{max\%}$ and DS at post-therapy PET-CT in predicting therapy response at 24 months.

| | $\Delta SUV_{max\%}$ | DS | z (p) |
|---|---|---|---|
| Sensitivity | 84.8 | 97.8 | 2.36 (0.018) |
| Specificity | 83.3 | 66.7 | 1.963 (0.049) |
| False negative ratio | 15.2 | 2.2 | 2.36 (0.018) |
| False positive ratio | 16.7 | 33.3 | 1.963 (0.049) |
| PPV | 97.5 | 95.7 | 0.495 (0.624) |
| NPV | 41.7 | 80.0 | 4.004 (0.001) |
| Positive likelihood ratio | 5.1 | 2.9 | 0.559 (0.582) |
| Negative likelihood ratio | 0.2 | 0.0 | 0.233 (0.818) |
| Accuracy | 84.6 | 94.2 | 1.594 (0.112) |

## 4. Discussion

Hodgkin lymphoma is the third most common childhood malignancy. It usually responds well to combination therapy, justifying the need for clinicians to know when to intensify therapy in poor responders, or to maintain or reduce it in responders. For this reason, it is also important to identify non-responders earlier during treatment course to optimize the therapeutic strategy. To this purpose, the role of $^{18}$F-FDG PET-CT in the management of adult HL patients is well known and widely accepted [21-22].

We enrolled 52 patients, which is a relatively large number for a single center study carried out in a high-volume referral center, given that HL incidence is lower in our region compared to other regions of our country (BLINDED) [23]. When compared to other studies conducted on the same subject, sample size was generally lower, ranging from 30 to 54 [10,19,24-25].

Accurate HL staging is the most important factor for setting prognosis and deciding treatment options. The addition of $^{18}$F-FDG PET-CT can help identify disease locations that could be missed by CT alone [19]. In our study, most patients had stage 2A (28.8%) and stage 3A (21.2%) categories, with the commonest histopathologic type being the nodular sclerosing variant (63.4%).

### *4.1. Semiquantitative assessment*

Based on our findings, we recommend that pediatric patients with $SUV_{max}$ higher than 15.5g/ml at baseline $^{18}$F-FDG PET-CT should undergo a stricter follow-up. However,

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it is known that SUV measurements can be affected by several factors that may result in considerable variations of accuracy and reproducibility, including alterations in the calibration of the PET scanner or dose calibrator, tracer extravasation at the injection site, elevated blood glucose levels or patient motion (leading to SUV measurement errors up to 50%), and partial volume effect (which may lead to SUV underestimation in smaller tumors) [11,26-27]. Additional studies with a larger sample size should be conducted to corroborate our findings.

The best cut-off for interim $\Delta SUV_{max\%}$ was 56.3%, yielding a sensitivity, specificity, PPV, NPV, and accuracy of 82.6%, 83.3%, 97.4%, 38.5% and 82.7%, respectively. In a prospective study by Furth et al on pediatric HL, a similar cut-off (58%) for $\Delta SUV_{max\%}$ was used for predicting disease relapse by means of interim $^{18}$F-FDG PET-CT, showing a sensitivity, specificity, NPV and accuracy of 100%, 97%, 100% and 97%, respectively [19]. Based on these findings, patients with $\Delta SUV_{max\%}$ less than 56% at interim $^{18}$F-FDG PET-CT are more likely to be non-responders or at a higher risk of relapse at follow-up.

The usefulness of interim PET-CT in predicting treatment response is underscored by its high PPV. Based on our findings, patients with interim $\Delta SUV_{max\%}$ lower than 56% should be followed up more aggressively. Of note, the fact that all parameters that can affect SUV calculation will also affect the $\Delta SUV_{max\%}$ calculation should be considered.

### *4.2. Deauville scoring*

Our findings showed that DS at interim PET-CT had a specificity and PPV of 100% in predicting treatment response at 24 months, higher than previous studies [19,24,27]. One explanation could be that the older studies followed heterogeneous visual criteria, which might have affected the prognostic accuracy of interim PET-CT, as pointed out by Terasawa et al [28]. Our finding that DS at both interim and post-therapy PET-CT can predict response with a high PPV seems to suggest a more aggressive treatment for patients with a score higher than 3, as opposed to those with a lower score. This is in line with the results by Ilivitzki et al, who found that visual interpretation has a higher PPV in the early evaluation of chemosensitivity in pediatric HL patients [29].

Care must be taken when DS is performed, as $^{18}$F-FDG distribution in pediatric patients is slightly different compared to adults. It is known that pediatric patients may show a thymic rebound at post-therapy PET-CT, which can be misleading. Moreover, liver tissue in pediatric patients is less affected by fatty changes than in adults, and it has been proven that $^{18}$F-FDG metabolism may be altered in patients with liver cirrhosis, potentially affecting both visual scoring and SUV measurements [15]. Thermogenic brown adipose tissue, which is commonly seen in pediatric patients, can affect the quality of PET images, and the knowledge of its normal distribution can help avoid false positive findings [34].

It has been found that liver and mediastinal blood pool SUVs were both predicted by patient weight [31]. Malladi et al proved that liver SUV was affected by gender, whereas mediastinal SUV was dependent on the uptake time [36]. Moreover, in children aged between 6 and 8 years, intense $^{18}$F-FDG uptake can be seen within pharyngeal and palatine tonsils, potentially causing difficulties in interpretation [32]. New, diffuse $^{18}$F-FDG uptakes in bone marrow and spleen can also be seen after chemotherapy. The aforementioned factors were considered when interpreting interim PET-CT scans.

### *4.3. Comparison of DS and $SUV_{max\%}$ reduction*

For interim PET-CT, a statistically significant association was found in the specificity and false positive rates when $\Delta SUV_{max\%}$ and DS were compared, and the latter showed a better performance (83.3% vs 100% and 16.7% vs 0%, respectively), whereas the remaining parameters were concordant. This finding reflects the superiority of DS at interim PET-CT. In contrast, a similar retrospective study by Ferrari et al found DS to be inferior to $\Delta SUV_{max\%}$, but it was based on a lower sample size (N=30) [24]. The main reason for this was the higher false positive rate for DS, due to the presence of inflammatory cells in the tumor microenvironment and the factors that affect background $^{18}$F-FDG uptake [24,35].

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Moreover, a fixed $\Delta SUV_{max\%}$ cannot always be used when baseline $SUV_{max}$ is low (e.g., <10g/ml), or when $SUV_{max}$ in the residual lesion is >5g/ml. In such instances, both the DS and quantitative $\Delta SUV_{max\%}$ methods are needed, as suggested at the Third International Workshop on Interim Positron Emission Tomography in Lymphoma [16].

## 5. Conclusions

Compared to the $\Delta SUV_{max\%}$ method, Deauville scoring is an easier method yielding better specificity and positive predictive value at interim PET-CT imaging for the assessment of treatment response in pediatric patients with HL, justifying its preferred use in clinical practice. Patients with higher Deauville scores at interim and post-therapy PET-CT should undergo a stricter follow-up, as they are at a higher chance of treatment failure or disease relapse. Conversely, $\Delta SUV_{max\%}$ should be used in patients classified as Deauville score 4 or 5 at interim PET-CT. In such instances, patients with a $SUV_{max\%}$ reduction less than 56% should be treated more aggressively. The issue of a low negative predictive value for $\Delta SUV_{max\%}$ should be evaluated in a larger multicenter trial.

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