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Additional value of volumetric and texture analysis on FDG PET assessment in paediatric Hodgkin lymphoma: an Italian multicentric study protocol

Egesta Lopci ,[1] Roberta Burnelli,[2] Caterina Elia,[3] Arnoldo Piccardo,[4] Angelo Castello,[1] Eugenio Borsatti,[5] Pietro Zucchetta,[6] Angelina Cistaro,[4] Maurizio Mascarin,[3] AIEOP Hodgkin Lymphoma Study Group

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For numbered affiliations see end of article.

Correspondence to
Dr Egesta Lopci;
egesta.lopci@gmail.com

ABSTRACT

Introduction Assessment of response to therapy in paediatric patients with Hodgkin lymphoma (HL) by 18F-fluorodeoxyglucose positron emission tomography/CT has become a powerful tool for the discrimination of responders from non-responders. The addition of volumetric and texture analyses can be regarded as a valuable help for disease prognostication and biological characterisation. Based on these premises, the Hodgkin Lymphoma Study Group of the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) has designed a prospective evaluation of volumetric and texture analysis in the Italian cohort of patients enrolled in the EuroNet-PHL-C2.

Methods and analysis The primary objective is to compare volumetric assessment in patiens with HL at baseline and during the course of therapy with standard visual and semiquantitative analyses. The secondary objective is to identify the impact of volumetric and texture analysis on bulky masses. The tertiary objective is to determine the additional value of multiparametric assessment in patients having a partial response on morphological imaging.

The overall cohort of the study is expected to be round 400–500 patients, with approximately half presenting with bulky masses. All PET scans of the Italian cohort will be analysed for volumetric assessment, comprising metabolic tumour volume and total lesion glycolysis at baseline and during the course of therapy. A dedicated software will delineate semiautomatically contours using different threshold methods, and the impact of each segmentation techniques will be evaluated. Bulky will be defined on contiguous lymph node masses ≥200 mL on CT/MRI. All bulky masses will be outlined and analysed by the same software to provide textural features. Morphological assessment will be based on RECIL 2017 for response definition.

Ethics and dissemination The current study has been ethically approved (AIFA/SC/P/27087 approved 09/03/2018; EudraCT 2012-004053-88, EM-04). The results of the different analyses performed during and after study completion the will be actively disseminated through peer-reviewed journals, conference presentations, social media, print media and internet.

Strengths and limitations of this study

- This study will represent the largest analysis on volumetric and semiquantitative parameters in paediatric Hodgkin lymphoma (HL) undergoing a therapeutic trial.
- The dedicated evaluation of texture features in HL bulky masses will allow for a solid definition of the impact of radiomics in this large paediatric population.
- Thanks to a comparative disease evaluation with both metabolic (Positron Emission Tomography) and morphological (CT/MRI) parameters, we will be able to assess the added value of the technique in paediatric patients with HL presenting with a partial response to therapy.
- The segmentation used for volumetric analyses can be considered a limit, since the predefined threshold methods might not be applicable for all lesions, particularly during response assessment; hence, a preliminary validation study will be performed.
- Data extraction for radiomic features will be necessarily performed in PET exams obtained from different scanners and undergoing different reconstruction algorithms, although harmonisation based on EANM (European Association of Nuclear Medicine) guidelines is recommended for the trial.

INTRODUCTION

18F-fluorodeoxyglucose positron emission tomography (FDG PET) has become a standard diagnostic procedure for the assessment of response to therapy in adults and children with Hodgkin lymphoma (HL). International guidelines recommend the using of Deauville five-point scale as a visual method for discriminating responders from non-responder patients.[1 2] In 2014, the paediatric German group proposed the use of qPET with the intent to extend the Deauville score to a continuous scale and limit visual misinterpretation due to the influence of background

activity.[3 4] This quantitative method is being applied in the current EuroNet-PHL-C2 clinical trial, in which adapted therapy is based on quantitative FDG avidity of tumour masses on PET evaluation after two cycles of OEPA (Vincristine, Etoposide, Prednisone, Doxorubicin).[5 6] This approach, however, postpones risk stratification at interim evaluation; therefore, the definition of imaging baseline predictors is highly desirable.

The implementation of metabolic tumour volume (MTV), as a sum of areas with an increased SUV inside the tumour, as well as the characterisation of the heterogeneity of tumour metabolic patterns on FDG PET has become an emerging topic in nuclear medicine.[7] Several studies[8–11] have shown that the addition of volumetric and textural parameters can be a valuable help for disease prognostication and biological characterisation of many tumour types, thus suggesting a similar implication for paediatric HL.[12] Not forgetting the concept of 'Radiomics', which has gained a proper place in predicting outcome and metabolic response in malignant lymphoma.[13 14] The scientific background and the results obtained from our previous studies in the context of the Italian AIEOP-LH2004 trial[15 16] suggest an additional impact of FDG PET in patients with or without bulky disease presenting with residual masses on morphological evaluation with CT.

Given the above-mentioned premises, the Hodgkin Lymphoma Study Group of the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) has planned to perform in the Italian cohort of patients treated according to the EuroNet-PHL-C2 trial additional volumetric analyses, to improve the evaluation of tumour burden computed at baseline FDG PET and to identify prognostic factors suitable for predicting early metabolic response to therapy in paediatric HL. In case of bulky disease, further textural and shape analysis will be performed to evaluate macroscopic and microscopic heterogeneity of tumour masses, as reflection of their aggressiveness and different chemotherapy sensitivity.

METHODS AND ANALYSIS

Study objectives

This is a prospective observational multicentric cohort study. The primary objective of the study is to compare the diagnostic and prognostic role of volumetric assessment in patients with HL at baseline and during the course of therapy with standard visual (Deauville score) and semiquantitative (ie, SUVmax, SUVmean, SUVpeak, total lesion glycolysis (TLG), and MTV) analyses.

The secondary objective of the study is to identify the diagnostic and prognostic impact of texture analyses and the other metabolic parameters on bulky masses.

The tertiary objective of the study is to determine the additional predictive and prognostic value of multiparametric assessment (ie, SUVmax, SUVmean, SUVpeak, MTV, TLG and texture analysis) in patients with HL having a partial response on morphological imaging.

Eligibility criteria

In accordance to the EuroNet-PHL-C2 trial, the population of our study will include paediatric patients of the Italian cohort, aged <25 years, with histologically confirmed primary diagnosis of classical HL, who will undergo FDG PET at baseline (PET1), after two cycles of induction OEPA therapy (PET2) and after the end of chemotherapy (PET3), in case of PET2-positive patients.[17] Patients will be stratified at baseline in one of the three treatment levels (TLs) on basis of stage and risk factors, confirmed by central review: TL-1, TL-2 and TL-3 for low, intermediate and advanced HL, respectively.[6 17]

Study timeline

The protocol herein illustrated represents a parallel study on PET imaging performed after the EuroNet-PHL-C2 trial amendment (Amendment Nr. 04, dated 31 July 2017) on the Italian cohort of patients. The study has been also submitted and approved by the Italian authority (Agenzia Italiana del Farmaco) the date 9 March 2018. Consequently, the timeline of the protocol will be as follows: (1) enrolment period will start from the 10 March 2018 until 31 December 2020; (2) follow-up period will last 5 years after last enrolment day; and (3) study completion is planned before 31 December 2025.

METHODOLOGY

Whole body assessment of HL

All FDG PET scans performed in the Italian cohort of patients undergoing the EuroNet-PHL-C2 trail will be analysed with additional volumetric assessment comprising MTV and TLG at baseline and during the course of therapy.

In each patient, HL lesions will be identified by visual analysis, and corresponding SUVmax, SUVmean and SUVpeak[18] will be determined as the pixel with the highest value of uptake, the mean value of uptake and the average value of uptake in a volume of interest (VOI) of 1 mL that surrounds the voxel with the highest activity, respectively. A dedicated software will be used to delineate, semiautomatically, contours of the lesions using different threshold methods, and the impact of segmentation technique will be evaluated (figure 1). More specifically, four threshold methods will be used based on previously reported methodologies[19–22]:

- Fixed 41% threshold of the SUVmax within the respective lymphoma site.
- Fixed absolute SUV threshold of 2.5.
- SUVmax(lesion)/SUVmean liver >1.5.
- Adaptative method: I(threshold)= [0.15× I(mean)]+I(background). I(mean) is calculated as the mean intensity of all pixels surrounded by the 70% Imax isocontour within the tumour; I(background) is defined as a SUVmean of liver.[23]

After delineation of all individual lesions, patient MTV will be estimated as the sum of voxels with suprathreshold

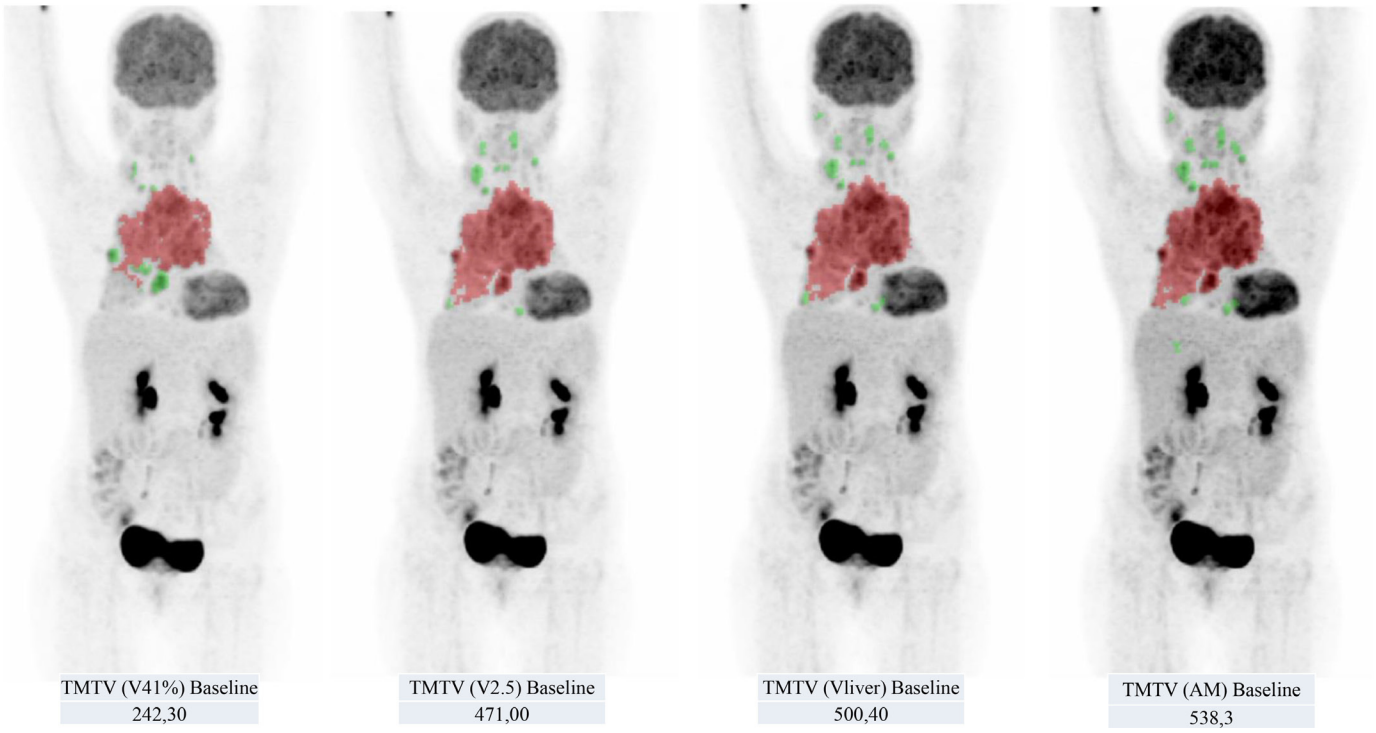

Figure 1 Comparative representation of the four segmentation techniques applied in our study protocol illustrated from left to right: fixed 41% threshold (V41%); fixed absolute SUV threshold of 2.5 (V2.5); SUVmax(lesion)/SUVmean liver >1.5 (Vliver); and adaptative method (AM). The same patient with Hodgkin lymphoma has been analysed according to the above-mentioned techniques and corresponding total metabolic tumour volumes (TMTVS) at baseline have been displayed for comparison.

uptake, reported in millilitres, and TLG will be calculated as [MTV × SUVmean].

PET2 scans will be evaluated by visual analysis on the basis of Deauville 5-point scale assigning inadequate response (IR) when at least one site shows FDG uptake higher than liver uptake (scores 4 and 5). Additionally, the variation of SUVmax, determined as the percentage reduction between the SUVmax in the tumour site with the most intense uptake on PET1 and the SUVmax in the tumour site with the most intense uptake on PET2 (ΔSUVmax),[9] will be computed. Similarly, will be calculated the variation of SUVmean, SUVpeak, MTV and TLG, respectively.

Assessment of bulky masses and radiomics analyses

The definition of bulky masses will be determined as specified in EuroNet-PHL-C2.[17] More specifically, a volume of a contiguous lymph node mass ≥200 mL, measured by the three largest diameters on CT/MRI, will be considered as bulky. All bulky masses will be outlined using different threshold methods, as explained previously, and analysed on dedicated software for semiquantitative and volumetric parameters. The same software will provide textural and shape features for radiomics analyses. The entire feature extraction will be performed using the freeware Local Image Features Extraction (LIFEx) software (http://www.lifexsoft.org).[24 25]

SUVmax will be defined as the maximum uptake in the segmented tumour. SUVmean will be measured as the average uptake in the tumour burden. SUVpeak will be computed as the average SUV in a 1 mL region of tumour burden around the maximal SUV voxel. MTV will be the volume of the segmented tumour. TLG will be calculated as the product of SUVmean by MTV.

Among shape parameters, asphericity, convexity and three-dimensional (3D) fractal dimensions will be computed.[15 18 26 27] For the characterisation of tumour texture, two methods will be used as previously reported[11 28 29]: analysis of the histogram of the voxel values within the tumour and the method accounting for the spatial arrangement of voxel values. On first-order statistics, will be computed SD, entropy, energy, kurtosis and skewness. To define the spatial arrangement of the voxel values within the tumour, four matrices will be computed from each VOI: grey-level co-occurance matrix, neighbourhood grey-level different matrix, grey-level zone length matrix and grey-level run length matrix. All parameters obtainable by the software and possible limitations are better detailed at http://www.lifex soft.org.[24 25]

Definition of morphological response

In paediatric patients with HL presenting with morphological partial response on bulky masses and/or residual lymph nodes with largest diameter ≥2 cm, a multiparametric assessment (ie, SUVmax, SUVmean, SUVpeak, MTV, TLG and texture analysis) will be performed. For this purpose, the International Working Group consensus response evaluation criteria in lymphoma, RECIL 2017,

will be used when necessary.[30] In particular, we will include in the analysis all cases with:

- Poor bulk response: <50% vol reduction and/or at least one nodal site with largest diameter of ≥2 cm and non-assessable qPET value due to brown fatty tissue.[17]
- Partial response: ≥30% decrease in the sum of longest diameters of target lesions but no complete response; positive PET (DS 4–5); any bone marrow involvement, no new lesions.[30]
- Minor response: ≥10% decrease in the sum of longest diameters of target lesions but not a partial response.[30]

Sample size calculation

Given the limited number of robust data for volumetric and texture analysis in paediatric HL population, we considered adequate a sample size comprising all eligible patients. In the current study, we expect to enrol a minimum of 50 patients per year from the Italian Hodgkin Lymphoma Group out for the different AIEOP Italian Centers. Based on the data derived from the previous AIEOP-LH2004 trial, the estimated number of bulky masses is quoted around 50% of the enrolled cases. Consequently, the overall cohort to be included in the study is expected of round 400–500 patients, with half presenting with bulky masses, eligible for dedicated analyses.

Patient and public involvement

No patient involved.

Statistical analysis

Descriptive statistics will be performed using conventional metrics (mean, median and range). All metabolic and heterogeneity parameters will be correlated with each other and with the disease outcome, and their diagnostic and prognostic role will be investigated. For continuous data, differences between groups will be compared by the t-test or the Wilcoxon test, when appropriate. For rank correlation, we will use Spearman's correlation coefficient (rho). The different threshold methods used to outline all individual lesions will be compared by the Pearson correlation coefficient, linear regression, Bland-Altmann and logistic regression. Optimal cut-off values of the metabolic parameters and, in patients with bulky mass, also of textural/radiomics parameters for distinguishing IR from adequate response to therapy will be defined by receiver operating characteristic curves with respective areas under the curve. Patients with or without bulky mass will be divided into groups of complete metabolic response, partial metabolic response, no metabolic response and progressive metabolic disease and differences in metabolic and textural parameters will be investigated by analysis of variance. Linear regression will be applied to determine the relationship between response and all other variables. Statistical significance will be set for $p<0.05$.

DISCUSSION

In literature, there is evidence that metabolically active tumour volume determined by PET/CT is more advantageous than tumour volume measured by CT or MRI for predicting response to treatment in various malignancies afflicting both adult and paediatric population. More specifically, in adult population, recent publications have demonstrated that the measurement of 3D disease volume (MTV) and metabolic activity (TLG)[14] can help predict outcomes in patients with HL.[8 9 14 30–32] This might suggest a similar implication also in paediatric HL, where the tumour volume may not change because of overlapping inflammatory processes correlated to therapy, while early changes of metabolic activity are most frequently reported.

Along with the abovementioned semiquantitative parameters, it is possible to extract other quantitative features from PET-CT images, including intensity, heterogeneity and shape within the tumour, potentially reflecting underlying biological characteristics.[14] These characteristics are embedded in the so called 'Radiomics', a translational field of research aiming to extract high-dimensional data from clinical images to predict underlying biological characteristics of the disease.[33] Radiomic features are correlated to prognostic markers in cancer (ie, hypoxia, angiogenesis, proliferation and so on) and might be used for tumour response prediction and outcome prognostication. In paediatric population, especially in case of advanced stage disease, high-dose therapeutic regimens represent the standard to cure, yet at the expense of early and delayed side effects.[34] In this context, it becomes even more important to identify those factors capable of limiting the doses to the necessary therapeutic effect while reducing at maximum the undesirable consequences. These prerogatives have guided in the last decades clinical research in adult[35 36] and paediatric HL.[6 17]

In the present study, we aim to identify prospectively the role of volumetric and texture (radiomic) characteristics better fulfilling the need for predictive and prognostic factors in paediatric HL. Thanks to a large sample size and to a preliminary methodological validation, we expect to obtain significant data on the added value of volumetric and texture analysis on FDG PET assessment in paediatric HL.

ETHICS AND DISSEMINATION

The current study has been approved by Agenzia Italiana del Farmaco (AIFA) on 9 March 2018 (EudraCT 2012-004053-88, EM-04; AIFA/SC/P/27087 approved 09/03/2018). All procedures involving human participants will be performed in accordance with the ethical standards of the institutional and/or national research committee and with the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. All patients will sign a written informed consent to participate in the study. The results

of the different analyses performed during and after study completion will be actively disseminated through peer-reviewed journals, conference presentations, social media, print media and internet.

Author affiliations
[1]Nuclear Medicine Department, IRCCS - Humanitas Research Hospital, Rozzano, Italy
[2]Pediatric Onco-hematologic Unit, University Hospital Arcispedale Sant'Anna of Ferrara, Ferrara, Italy
[3]AYA Oncology and Pediatric Radiotherapy Unit, Centro di Riferimento Oncologico, Aviano, Italy
[4]Nuclear Medicine Department, Ente Ospedaliero Ospedali Galliera, Genova, Italy
[5]Nuclear Medicine Department, Centro di Riferimento Oncologico, Aviano, Italy
[6]Nuclear Medicine Department, Padua University Hospital, Padova, Italy

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Competing interests None declared.

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ORCID iD
Egesta Lopci http://orcid.org/0000-0001-9732-1094

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