

**Bari, 17-18 febbraio 2023**

Sala "A. Leogrande"  
Centro Polifunzionale Studenti  
Università degli Studi di Bari "Aldo Moro"

# LATE EFFECTS GUARIRE DAL LINFOMA E VIVERE BENE

**La PET/CT come  
strumento di gestione  
clinica e predittività di  
lungovivenza a linfoma**

*Dott.ssa C. Ferrari*

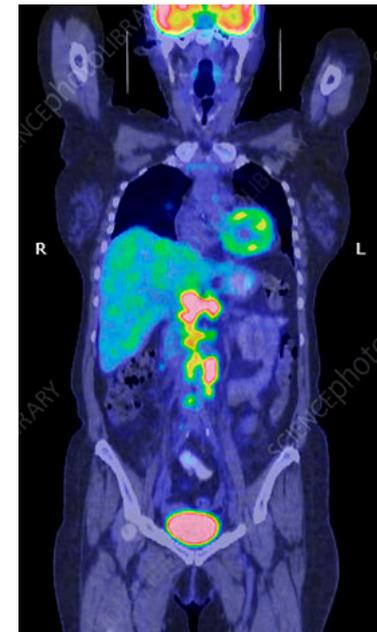
**Prof. G. Rubini**

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Dipartimento Interdisciplinare di Medicina (D.I.M.) – Sezione Diagnostica per Immagini  
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*Direttore: Prof. G. Rubini*

## Disclosures of Name Surname

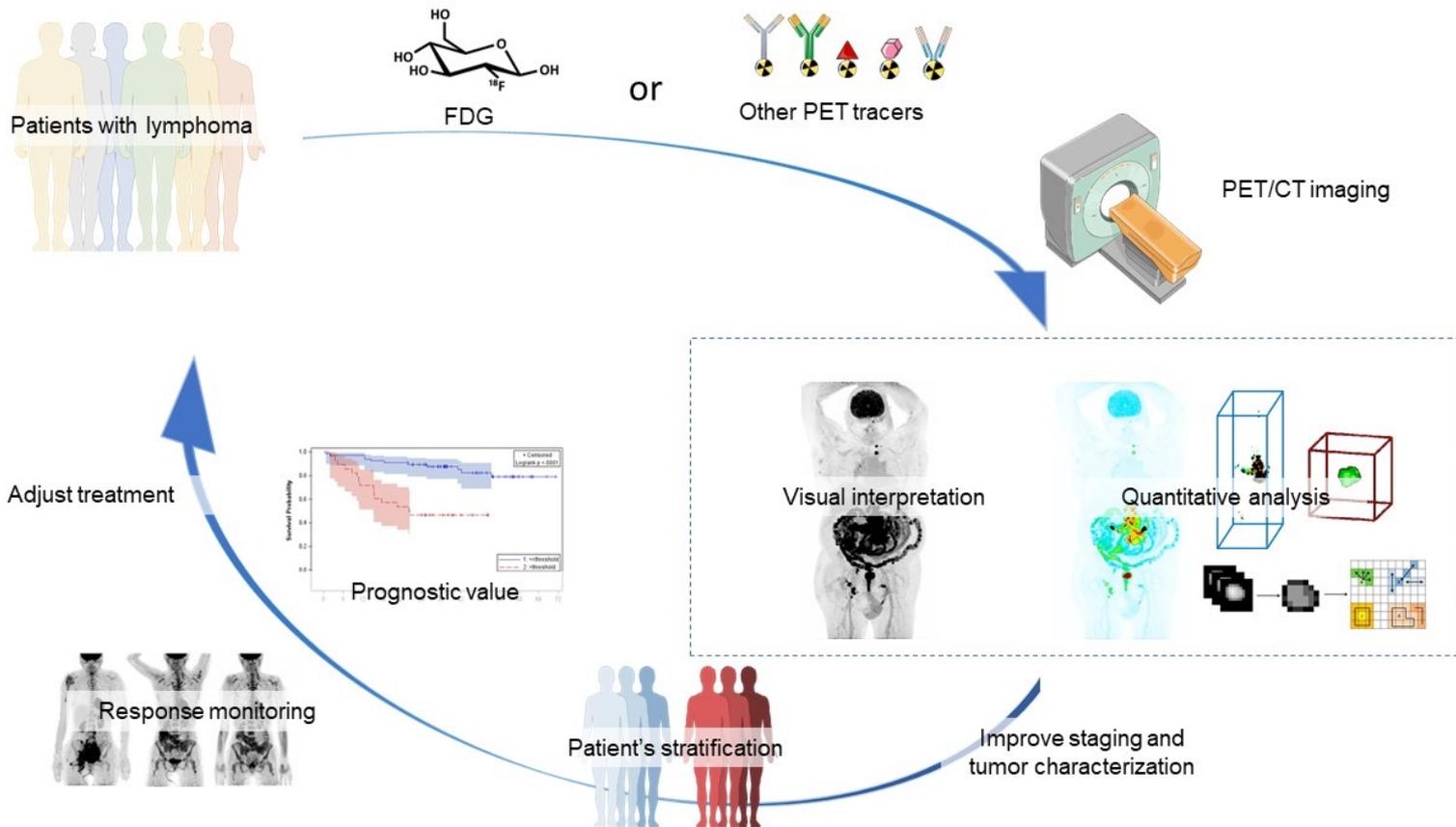
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
NOTHING TO DISCLOSE							

➤ 18FDG-PET/CT: Strumento di gestione clinica



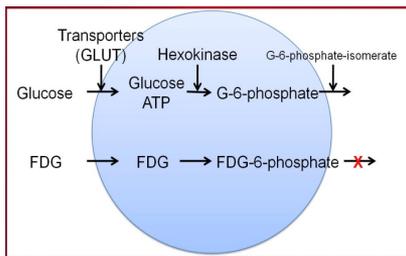
Grazie ad una migliore stadiazione e valutazione della risposta al trattamento e attraverso strategie terapeutiche precoci PET-guidate, ha aperto la strada alla medicina personalizzata e all'ottimizzazione del controllo della malattia e della tossicità

## ➤ 18FDG-PET/CT: Strumento di gestione clinica



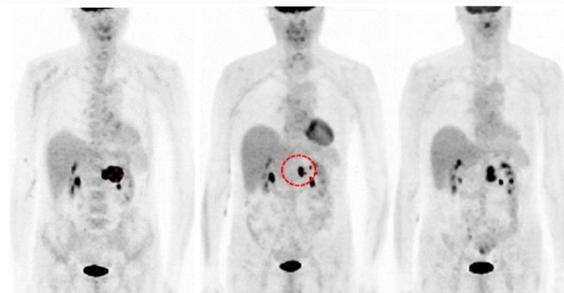
## ➤ Fattori prognostici e predittivi: SUV, iPET e DS

L'assorbimento di FDG è correlato alla de-differenziazione, all'aumento dell'aggressività e del tasso di proliferazione e alla prognosi infausta



DIAGNOSIS

INTERIM



STAGING

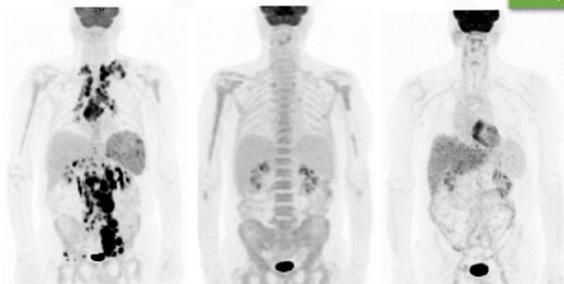
INTERIM

END-TREATMENT

Non-responder

Responder

STAGING



STAGING

INTERIM

END-TREATMENT

↑  
Linfomi aggressivi  
↓  
Linfomi indolenti



**HL** → iPET has shown a high prognostic value in several studies with a high NPV of 80–90% and a lower PPV of 50–55%.

**DLBCL** → iPET has been assessed as a potential biomarker of the early success or failure of R-CHOP. The combination of iPET2 and DSUVmax seemed preferable in NHL.

## ➤ Fattori prognostici e predittivi

- Most patients with classical Hodgkin lymphoma (cHL) will be cured with standard chemotherapy, and relapses occur in about 15–25% of the patients .
- Up to one third of DLBCL patients fail to achieve complete remission during first-line treatment or experience relapse, and salvage treatment regimens lead to modest cure rates

**Predictive biomarkers** are an essential tool of precision medicine and individualized treatment.



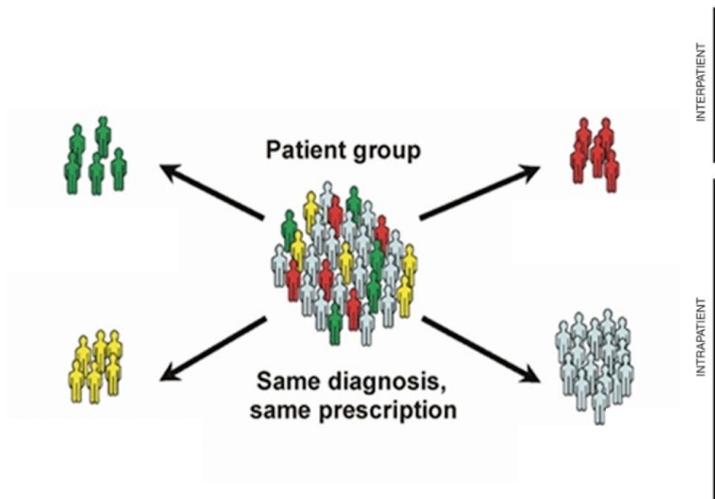
*Perspective*

### FDG-PET/CT in Lymphoma: Where Do We Go Now?

Yassine Al Tabaa <sup>1,\*</sup>, Clement Bailly <sup>2,3</sup> and Salim Kanoun <sup>4,5</sup>



## ➤ Fattori prognostici e predittivi: Medicina Personalizzata



INTERPATIENT

**1. Inter-patient Tumor Heterogeneity**  
(variazione delle caratteristiche del tumore tra i pazienti)

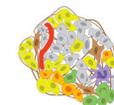


INTRAPATIENT

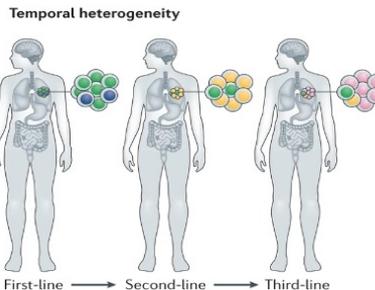
**2. Intra-patient Tumor Heterogeneity**  
(variazione delle caratteristiche del tumore tra le lesioni all'interno di un paziente)



**3. Intra-tumoral Heterogeneity**  
(differenze molecolari all'interno di un tumore)



Differenze fenotipiche e funzionali nelle cellule tumorali insorgono anche durante il decorso della malattia a causa di cambiamenti genetici e del perpetuo rimodellamento clonale sotto la pressione del microambiente e dei trattamenti.



## ➤ Fattori prognostici e predittivi: Medicina Personalizzata

La 18FDG-PET/CT rappresenta uno strumento ottimale, fornendo un **metodo non invasivo di tutto il corpo** per valutare l'eterogeneità della lesione target, e valutando l'intero carico di malattia, per aiutare il processo decisionale clinico.



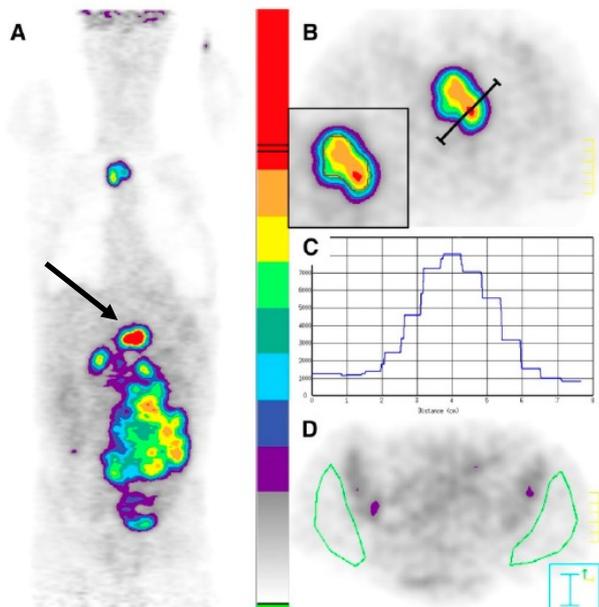
- Imaging Biometabolico
- Interpretazione semplice
- Whole Body
- Ibrido
- Quantizzazione
- Radiomica
- Intelligenza Artificiale

**Nuclear medicine** is one of the most dynamic medical fields, in constant evolution over the past decades.

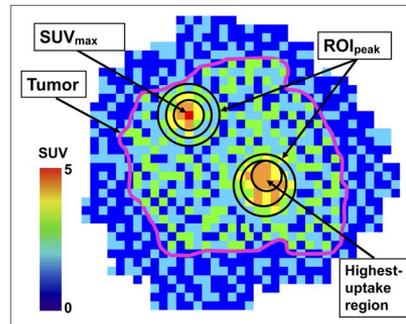
## ➤ Fattori prognostici e predittivi: Medicina Personalizzata

### Intra-patient Tumor Heterogeneity / Intra-tumoral Heterogeneity

(variazione delle caratteristiche del tumore tra le lesioni all'interno di un paziente e all'interno del tumore stesso)



- **Lesione target:** > SUVmax, > aggressività
- l'espressione del target in un sito, non garantisce la stessa espressione in tutti i siti



la distribuzione spaziale dei voxel di diversa intensità in una regione selezionata e quindi la distribuzione spaziale del 18FDG può essere estremamente eterogenea.

## ➤ Fattori prognostici e predittivi:

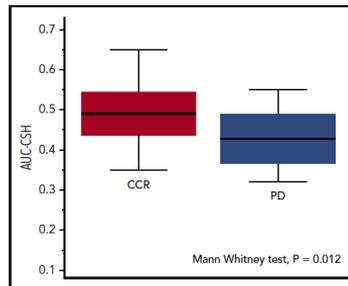
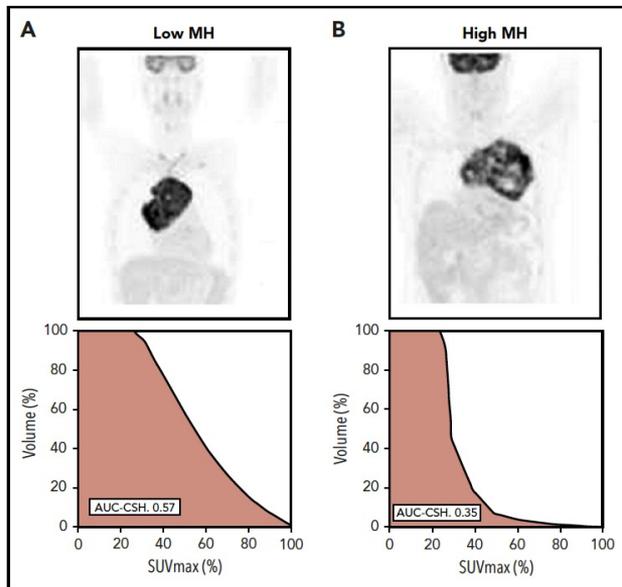
### 3. Intra-Tumor Heterogeneity

Metabolic heterogeneity on baseline 18FDG-PET/CT scan is a predictor of outcome in primary mediastinal B-cell lymphoma

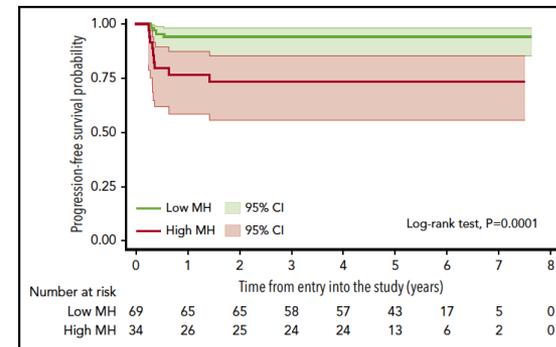
Luca Ceriani,<sup>1</sup> Lisa Milan,<sup>1</sup> Maurizio Martelli,<sup>2</sup> Andrés J. M. Ferreri,<sup>3</sup> Luciano Cascione,<sup>4</sup> Pier Luigi Zinzani,<sup>5</sup> Alice Di Rocco,<sup>2</sup> Annarita Conconi,<sup>4</sup> Anastasios Stathis,<sup>7</sup> Franco Cavalli,<sup>4</sup> Monica Bellei,<sup>8</sup> Kelly Cozens,<sup>9</sup> Elena Porro,<sup>4</sup> Luca Giovanella,<sup>1</sup> Peter W. Johnson,<sup>10,\*</sup> and Emanuele Zucca<sup>7,11,\*</sup>

blood 12 JULY 2018 |

- High heterogeneity of intratumoral 18FDG uptake distribution on PET/CT scans has been suggested as a possible marker of chemoresistance in solid tumors.
- In the present study, we investigated the prognostic value of metabolic heterogeneity (MH) in 103 patients with PMBCL prospectively enrolled in the International Extranodal Lymphoma Study Group (IELSG) 26 study, aimed at clarifying the role of PET in this lymphoma subtype.



Patients with progression or relapse had significantly lower AUC-CSH (corresponding to higher MH) than those remaining in continuous remission

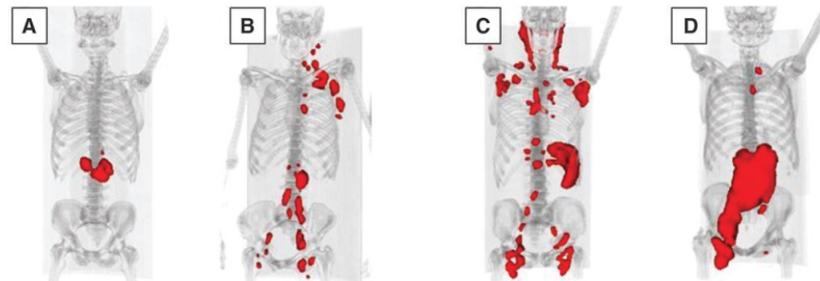
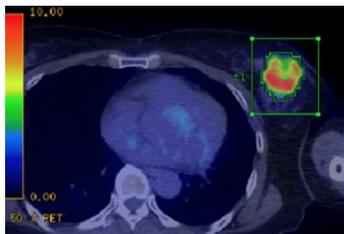


In univariate analysis of dichotomized parameters, PFS at 5 years was 94% (95% CI, 85%-98%) for patients with low MH and 73% (95% CI, 55%-85%) for those with high MH

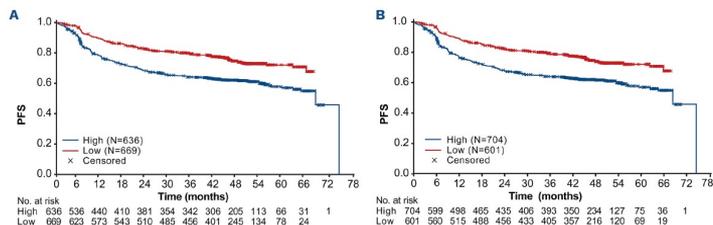
## ➤ Fattori prognostici e predittivi: Tumor Burden e Total Metabolic Tumor Volume

### 2. Intra-patient Tumor Heterogeneity

- quantificazione del carico tumorale di tutto il corpo
- si basa sulla segmentazione di ciascuna lesione metabolicamente attiva
- parametro prognostico in vari sottotipi di linfoma



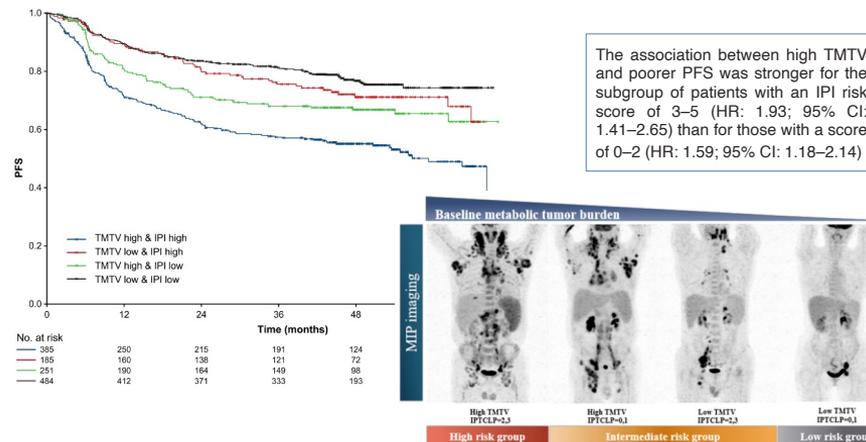
**Total metabolic tumor volume as a survival predictor for patients with diffuse large B-cell lymphoma in the GOYAN study** L. Kostakoglu et al. *Haematologica* | 107 July 2022



4-year PFS rates lower for patients with baseline TMTV  $\geq 366$  cm<sup>3</sup> compared with  $<366$  cm<sup>3</sup> (4-year rate: 59.7% vs. 74.7%)

4-year OS poorer in patients with high versus low TMTV, based on the tumor volume cut-off of 366 cm<sup>3</sup> (stratified HR: 1.76; 95% CI: 1.34–2.30;  $P < 0.0001$ ; 4-year OS rate: 74.5% vs. 86.6%) and the 300 cm<sup>3</sup> cut-off

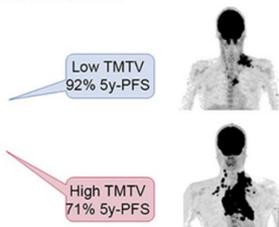
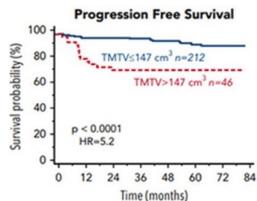
**Figure 1.** Examples of patients with low TMTV; patient A (137 cm<sup>3</sup>), patient B (280 cm<sup>3</sup>), and patients with high TMTV; patient C (1,103 cm<sup>3</sup>), patient D (1,363 cm<sup>3</sup>).



## ➤ Fattori prognostici e predittivi: Issue to solve

➤ TMTV: grande variabilità tra gli istotipi di linfoma

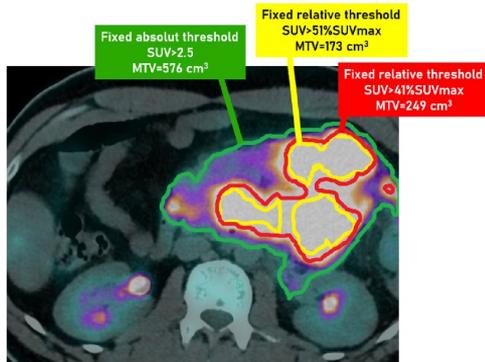
**Total Metabolic Tumor Volume** measured on baseline PET :  
a new prognosticator of PFS and OS in early stage HL  
from the standard arm of the H10 trial



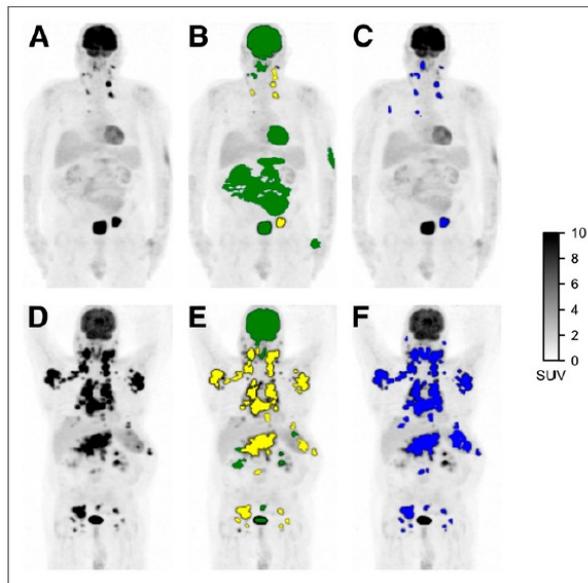
have a lower PFS/OS:

- early stage HL: TMTV > 147 mL
- advanced HL: TMTV > 268 mL
- DLBCL: TMTV > 328 ml
- FL: TMTV > 510 mL

➤ TMTV: metodologia di segmentazione consensuale

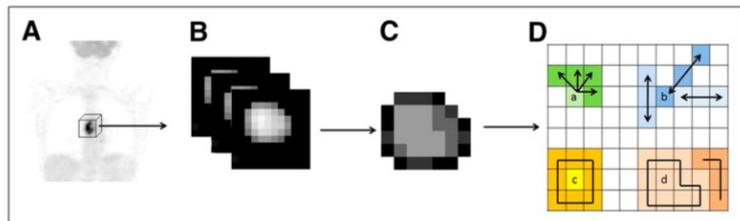
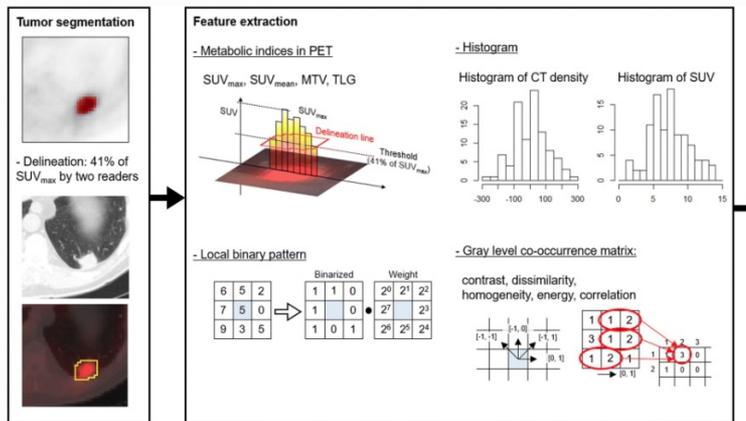


➤ TMTV: automatizzazione del calcolo. notevolmente migliorato grazie ai nuovi algoritmi di *deep learning* che stanno mostrando un'ottima accuratezza nel riprodurre la segmentazione manuale dell'utente



## ➤ Fattori prognostici e predittivi: Radiomica applicata a PET e TC

### 3. Intra-Tumor Heterogeneity



**TEXTURE ANALYSIS:** gruppo di metodi computazionali in grado di estrarre le caratteristiche della trama utilizzando la relazione tra pixel adiacenti da una data immagine

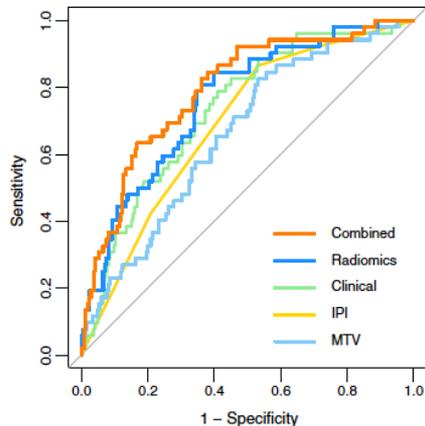
Order	Matrix	Name of the Parameter	Description of the Parameter	
First Order		SUVmax	SUV value of the maximum intensity voxel within a region of interest (ROI)	
		SUVpeak	Average SUV within a small ROI (usually, a 1-cm <sup>3</sup> spherical volume)	
		SUVmean	Average measure of SUV within a defined ROI	
		Metabolic tumor volume (MTV)	Volume of a defined ROI	
		Total lesion glycolysis (TLG)	Product of SUVmean × MTV	
Second Order	Grey-Level Co-Occurrence Matrix (GLCM)	Contrast	Local variations in the GLCM	
		Correlation	Joint probability occurrence of the specified pixel pairs	
		Entropy	Texture randomness or irregularity	
		Energy	Sum of squared elements in the GLCM	
		Homogeneity	Closeness of the distribution of elements to the diagonal	
		Short run emphasis (SRE)	Distribution of short runs	
		Long run emphasis (LRE)	Distribution of long runs	
High Order	Grey-Level Run-Length Matrix (GLRLM)	High gray level run emphasis (HGRE)	Distribution of high grey level values runs	
		Grey-level non-uniformity (GLNU)	Similarity of grey level values throughout the image	
		Run percentage (RP)	Homogeneity and distribution of runs of an image in a specific direction	
		High gray-level zone emphasis (HGZE)	Distribution of high grey level values zones	
		Zone length non uniformity (ZLNU)	Similarity of zone length throughout the image	
		Zone percentage (ZP)	Homogeneity and distribution of zones of an image in a specific direction	
		Short zone emphasis (SZE)	Distribution of small zones	
		Neighborhood Grey Tone Difference Matrix (NGTDM)	Coarseness	Granularity within an image.



## ➤ Fattori prognostici e predittivi:

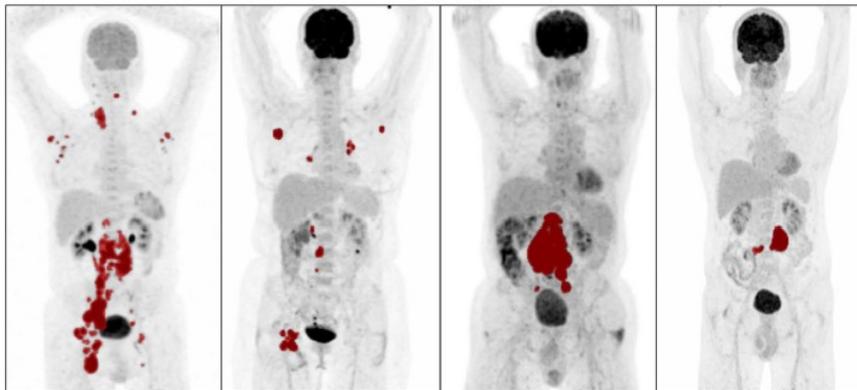
Parameter	Events (n=52)		Non-events (n=265)	
	Median (IQR)	Range	Median (IQR)	Range
MTV (ml)	652.2 (322.6–1363.2)	13.7–5598.5	351.4 (115.9–842.1)	0.8–2827.3
SUV <sub>max</sub>	20.4 (15.2–27.7)	5.4–48.3	22.6 (16.8–29.3)	4.1–56.9
SUV <sub>peak</sub>	16.4 (12.1–21.8)	4.1–34.8	17.8 (13.8–24.3)	2.5–47.7
SUV <sub>mean</sub>	8.4 (6.0–9.8)	4.2–13.6	8.7 (6.9–10.6)	4.1–21.5
TLG	6030.9 (2446.1–10,571.8)	59.3–47,965.7	3216.1 (1041.5–7091.3)	0.3–25,776.8
Number of lesions	19 (6–35)	1–143	8 (4–16)	1–55
Dmax <sub>patient</sub> (cm)	63.9 (43.4–70.3)	0–114.2	40.8 (15.9–58.3)	0–126.1
Dmax <sub>bulk</sub> (cm)	44.4 (32.6–54.2)	0–110.8	29.4 (13.1–43.0)	0–87.0
spread <sub>patient</sub> (cm)	7482.3 (734.0–37,496.1)	0–968,211	607.6 (108.0–4995.9)	0–175,968
spread <sub>bulk</sub> (cm)	604.3 (156.1–1193.0)	0–6067.6	148.1 (46.3–429.5)	0–4406.9
sphericity	0.31 (0.23–0.42)	0.13–0.68	0.39 (0.29–0.53)	0.08–1.0

Abbreviations: *MTV*, metabolic tumor volume; *SUV*, standardized uptake value; *TLG*, total lesion glycolysis; *Dmax*, maximum distance

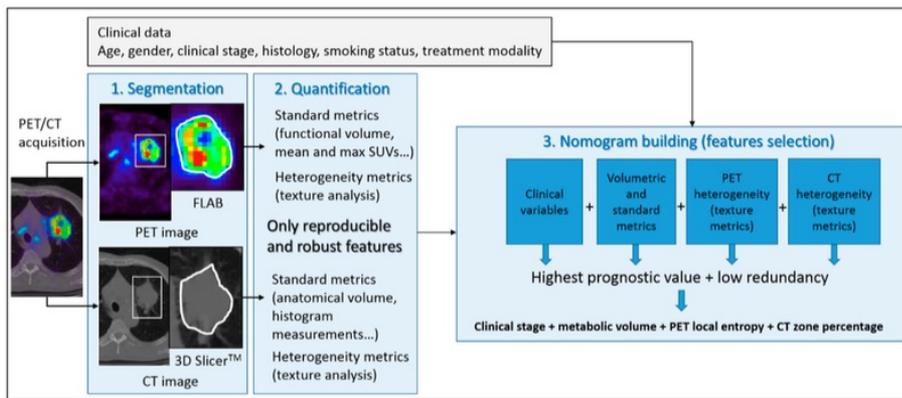


## <sup>18</sup>F-FDG PET baseline radiomics features improve the prediction of treatment outcome in diffuse large B-cell lymphoma

European Journal of Nuclear Medicine and Molecular Imaging (2022) 49:932–942



Da sinistra a destra:  
 - alto MTV e alta diffusione,  
 - basso MTV e alta diffusione,  
 - alto MTV alto e bassa diffusione  
 - basso MTV e bassa diffusione



## ➤ Fattori prognostici e predittivi: Sarcopenia

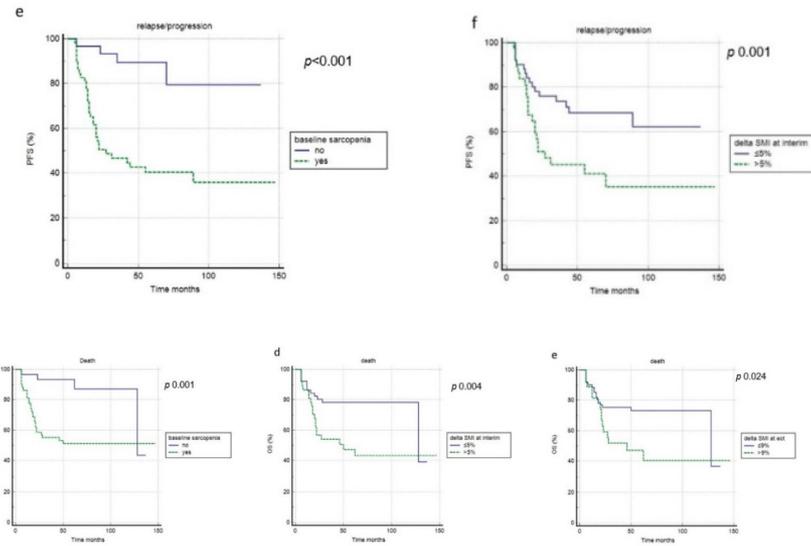
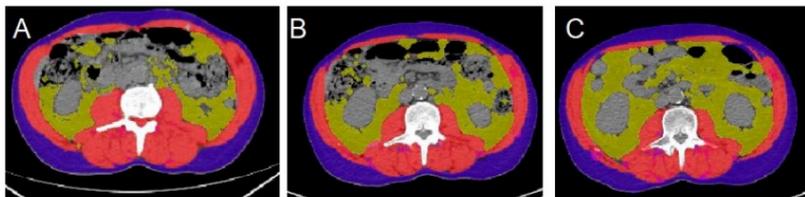
Article *Cancers* 2022, 14, 5147. <https://doi.org/10.3390/cancers14205147>

### Longitudinal Body Composition Changes Detected by [<sup>18</sup>F]FDG PET/CT during and after Chemotherapy and Their Prognostic Role in Elderly Hodgkin Lymphoma

Domenico Albano <sup>1,2,\*</sup>, Francesco Dondi <sup>1</sup>, Giorgio Treglia <sup>3,4,5</sup>, Alessandra Tucci <sup>6</sup>, Marco Ravaneli <sup>7</sup>, Davide Farina <sup>7</sup> and Francesco Bertagna <sup>1,2</sup>

- Now, CT is considered the best tool for the non-invasive assessment of muscle and fat quantity/mass.
- There are also preliminary data concerning the possibility to measure muscle and fat areas with the low-dose CT component of PET/CT scan with high accuracy and reproducibility
- To define the muscular mass, conventionally, we measure a cross-sectional area of specific muscle groups located at the third lumbar vertebra defined as skeletal muscle index (SMI).

baseline                      interim                      end-of-treatment



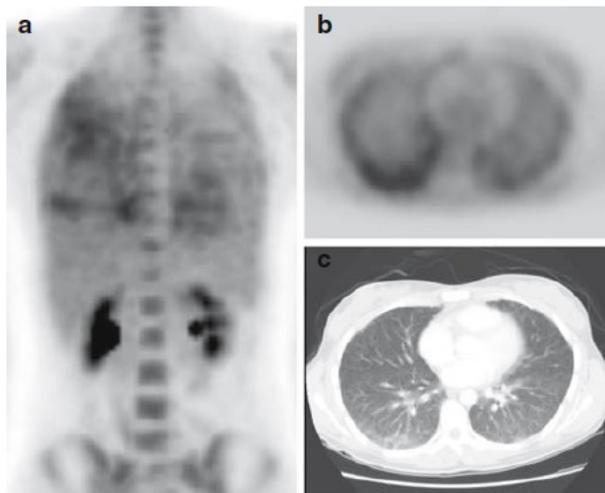
- baseline sarcopenia, and interim-D SMI end of treatment-D SMI were significantly associated with outcome
- baseline sarcopenia, and body composition changes during chemotherapy may have a prognostic role.

➤ **Valutazione della tossicità:**

Ann Nucl Med (2008) 22:111–114

**Pulmonary drug toxicity: FDG-PET findings in patients with lymphoma**

Toshiki Kazama · Silvana C. Faria · Yoshitaka Uchida  
Hisao Ito · Homer A. Macapinlac

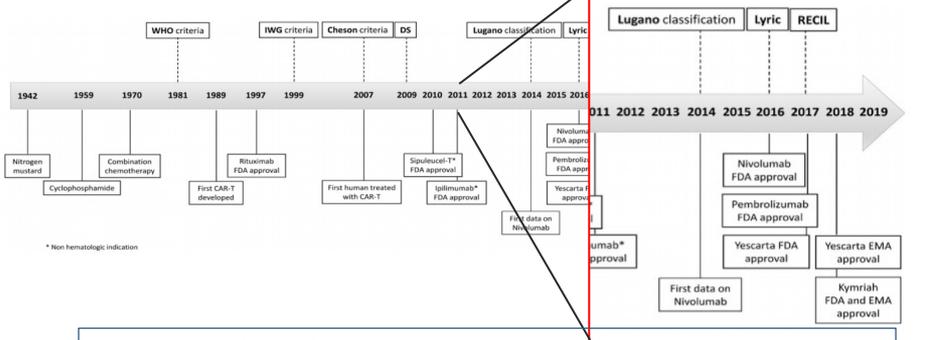


Lung toxicity in chemotherapy patients is not uncommon, especially when bleomycin is used

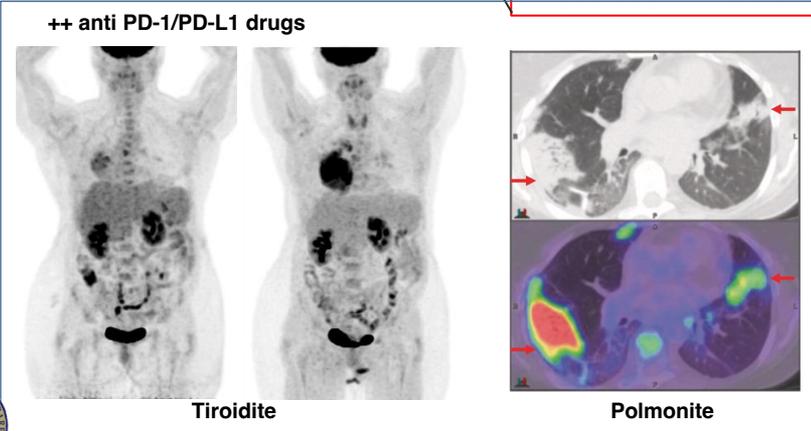
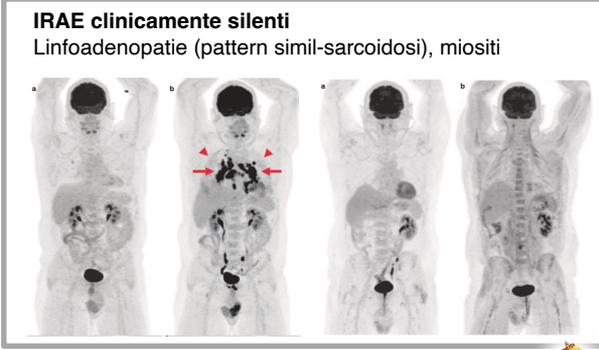
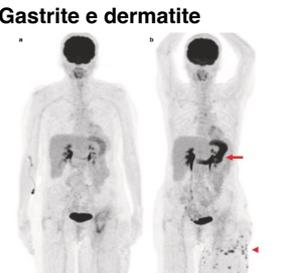
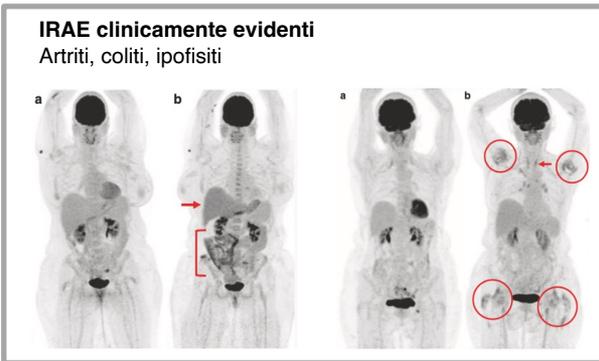
## ➤ Valutazione della tossicità: Immunoterapia e Immune-Related Adverse Events

**Anti-PD1** (Nivolumab e Pembrolizumab)

- Refractory HL and NHL



Nuovi QUADRI di:  
**TOSSICITA'**  
**Eventi avversi immuno-relati**



Atlas of Response to Immunotherapy, Springer



## ➤ Valutazione della tossicità: Immunoterapia e Immune-Related Adverse Events

**CAR-T** (terapia approvata da FDA nel 2017)

- Refractory DBCL, MCL, FL, MM
- assenza di marcatore tumore-specifico, > rischio di tossicità

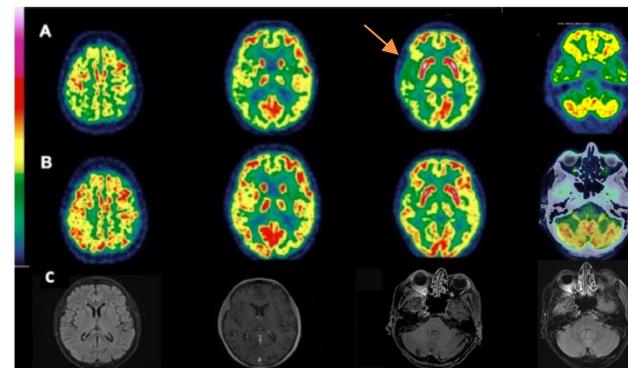
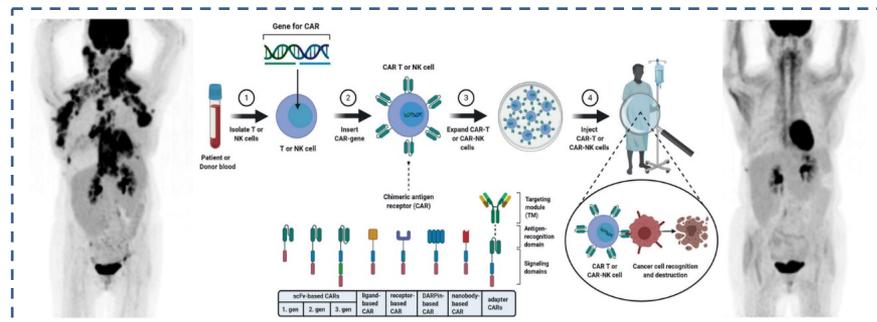
Review

Cancers 2022, 14, 4700. <https://doi.org/10.3390/cancers14194700>

### Metabolic Imaging in B-Cell Lymphomas during CAR-T Cell Therapy

Flavia Linguanti <sup>1</sup>, Elisabetta Maria Abenavoli <sup>1</sup>, Valentina Berti <sup>1</sup> and Egesta Lopci <sup>2</sup>\*

- [...] patients with **high SUVmax** and potential aggressive lymphoma, may be particularly inclined to the manifestation of toxicity
- the tumor burden was strictly correlated with CRS's severity
- staging PET/CT with a **high tumor burden**, reflected by SUV average (SUVavg), MTV, and TLG, was a significant risk factor to develop any grade of CRS

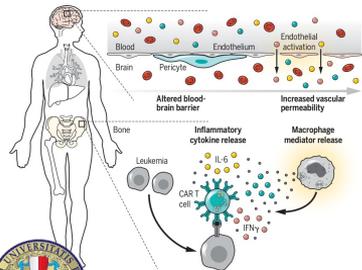


Vernier V, et al. Hypometabolism on brain FDG-PET as a marker for neurotoxicity after CAR T-cell therapy: A case report. *Revue neurologique* (2021)

pz con DLCBL: dopo 2 giorni dall'infusione di cellule CAR-T presentava CRS seguita da sindrome da neurotossicità, con anomalie EEG diffuse non associate ad alterazioni RM.

**A.** Al 14° giorno dall' infusione, 18FDG-PET/TC cerebrale mostrava un ipometabolismo bilaterale e diffuso, prevalentemente nella corteccia parietale e temporale.

**B.** 4 mesi dopo, nuova 18FDG-PET/TC cerebrale ha mostrato miglioramento.



### ➤ Cytokine release syndrome (CRS)

### ➤ Neurotossicità

perdita temporanea della memoria, delirio, convulsioni raramente, edema cerebrale acuto



## ➤ Conclusioni: 18FDG PET/CT

- Fornisce una valutazione **total body** del carico di malattia
- Risponde e risolve il problema **ETEROGENEITA'** (inter-paziente, intra-paziente, intra-tumorale e temporale)
- **Imaging ibrido** multimodale: aspetti biometabolico e morfologico in grado di fornire numerosissime informazioni
- Analisi quantitativa: permette di andare **oltre il SUV**.
- la quantificazione accurata del **carico tumorale (TMTV)** mediante 18FDG-PET/CT è un metodo importante per la valutazione e la previsione della risposta terapeutica
- 18FDG PET/CT integrata **all'Intelligenza Artificiale e analisi radiomica**, permetterà di estrarre in modo efficiente informazioni preziose sulla biologia del tumore e di avere a breve nuovi biomarcatori e metodi di standardizzazione dell'analisi quantitativa
- I **biomarcatori predittivi** sono uno strumento essenziale della medicina di precisione e del trattamento individualizzato.
- Permette di valutare la **tossicità** alle diverse terapie e, in alcuni casi, di prevederla.

La **18FDG PET/CT** permette sia la valutazione panoramica di tutto il pz e dello stato di malattia sia la valutazione precisa e dettagliata della biologia della singola lesione e del singolo voxel



# *Grazie per l'attenzione*

