INTEGRATION OF [18F]FDG-PET RADIOMICS WITH LIQUID BIOPSY IMPROVES OUTCOME PREDICTION IN NEWLY DIAGNOSED DLBCL PATIENTS

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Introduction

Baseline circulating tumor DNA (ctDNA) levels, molecular clusters and PET/CT radiomics allow to identify DLBCL destined to early relapse, but their integration has not been extensively evaluated.

Aim

The aim of this study was to integrate the prognostic value of ctDNA levels, molecular clusters, and PET/CT variables to improve outcome prediction in DLBCL.

Methods

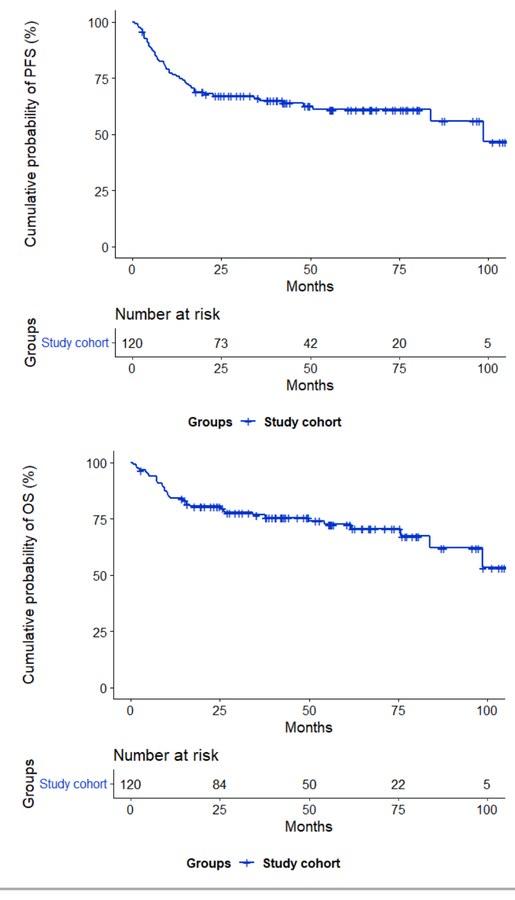
- ✓ Real-world cohort of **120 newly diagnosed DLBCL**
- ✓ **ctDNA levels** were reported as Log_{10}hGE/mL and **molecular clusters on ctDNA** were identified by LymphGen tool
- ✓ Using the standardized uptake value (SUV) threshold of 4.0, the following were collected: *i*) maximum SUV of the hottest lesion **(SUVmax)**; *ii*) total metabolic tumor volume **(tMTV)**; *iii*) total tumor lesion glycolysis **(tTLG)**; *iv*) maximum distance between the two farthest lesions **(Dmax)**
- ✓ The maximally selected rank statistics was used to identify the best cutoff values in **predicting PFS**

Results

1. PATIENT CHARACTERISTICS

Characteristics	Values
Median Age	67 (IQR 51-76)
Stage	
I-II	33 (27.5%)
III-IV	87 (72.5%)
IPI	
0-1	32 (26.7%)
2	20 (16.7%)
3	33 (27.5%)
4-5	35 (29.1%)
COO	
GC	40 (33.3%)
Non-GC	72 (60.0%)
Not available	8 (6.7%)
LDH above ULN	
Yes	69 (57.5%)
Extranodal sites	
Yes	66 (55.0%)
No	54 (45.0%)

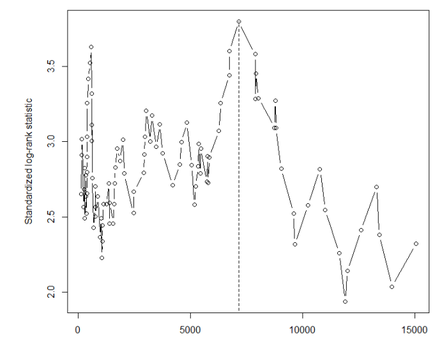
Median follow-up: 56 months

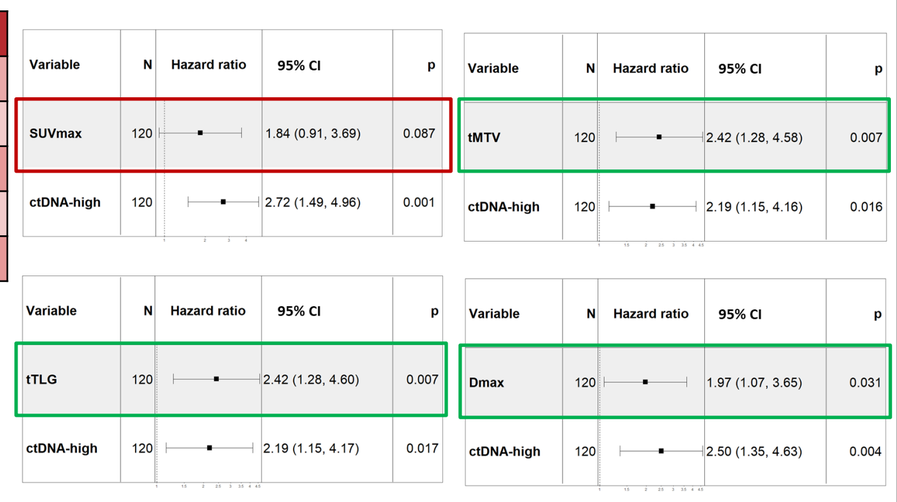


2. PROGNOSTIC VALUE OF PET/CT VARIABLES ADJUSTED FOR ctDNA LEVELS

Maxstat test

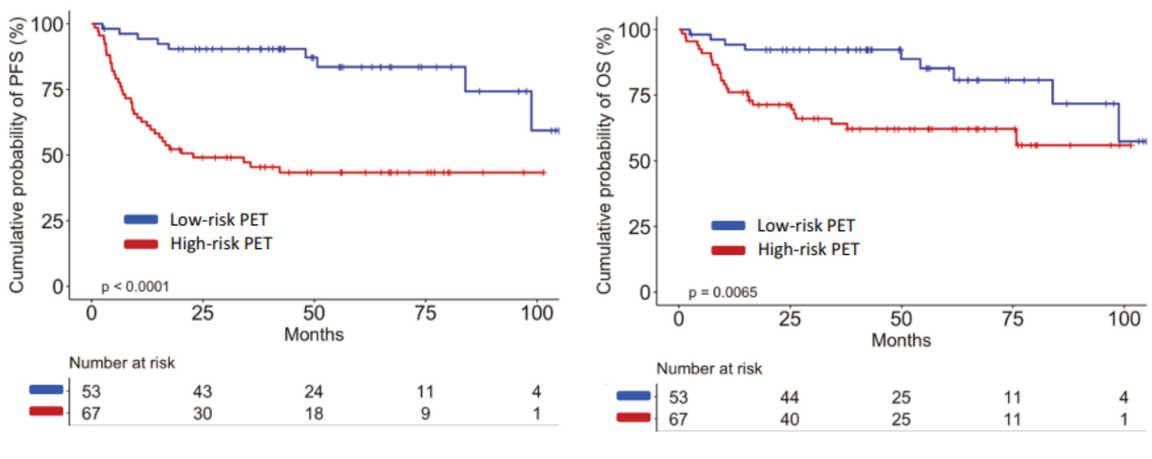
Parameter	Cutoff
SUVmax	17.66
tMTV	639.2 cm^3
tTLG	7138.34
Dmax	39 cm
ctDNA levels	2.68 Log_{10}hGE





3. HIGH-RISK PET PATIENTS HAVE WORSE OUTCOME

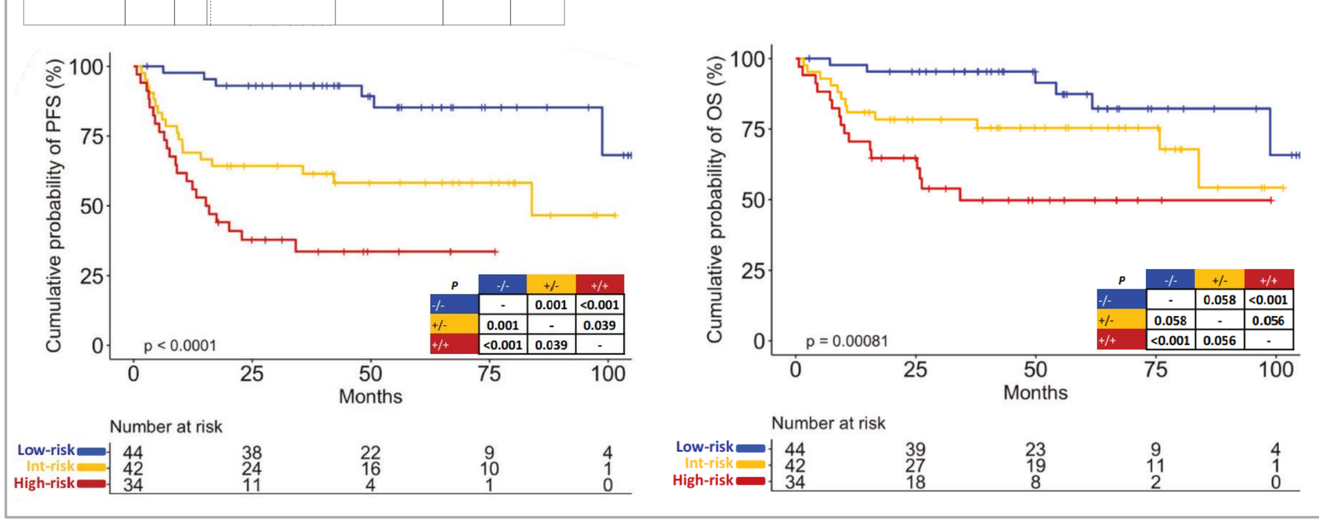
Patients with **at least one** PET/CT variable (among tMTV, tTLG or Dmax) above the respective cutoff were grouped as **high-risk PET patients**.



4. HR PET AND ctDNA-HIGH INDEPENDENTLY PREDICT PFS: 2-FACTOR MODEL

Variable	Points	N	Hazard ratio	95% CI	β	p
ctDNA-high	+1	120		2.04 (1.10, 3.78)	0.711	0.02
High-risk PET	+2	120		3.84 (1.78, 8.28)	1.345	<0.001

Low risk	ctDNA-low and low-risk PET	0 point
Intermediate risk	ctDNA-high or high-risk PET	1 to 2 points
High risk	ctDNA-high and high-risk PET	3 points

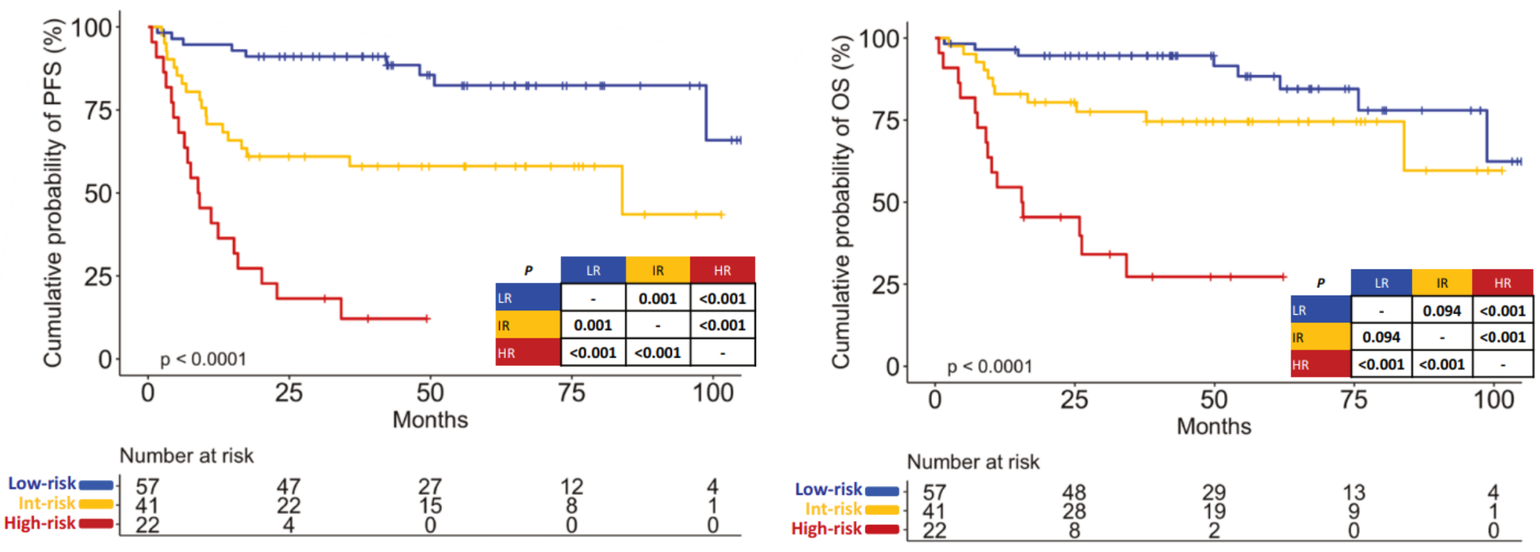


5. MOLECULAR CLUSTERS ON LIQUID BIOPSY IMPROVE OUTCOME PREDICTION: 3-FACTOR MODEL

Variable	Points	N	Hazard ratio	95% CI	β	p	HR	LCI	UCI	Bootstrapping selection
ctDNA-high	+1	120	2.77 (1.45, 5.27)		1.018	0.002	2.77	1.46	6.09	85.0%
High-risk PET	+1.5	120	3.90 (1.79, 8.48)		1.361	<0.001	3.90	1.60	8.63	96.4%
BN2/EZB/ST2	-1.5	120	0.27 (0.12, 0.62)		-1.310	0.002	0.27	0.10	0.69	91.5%

Bootstrapping validation

Low risk	-1.5 to 0.5 points
Intermediate risk	1 to 1.5 points
High risk	2.5 points



Prognostic model	C-index for PFS	C-index for OS
ctDNA-high	0.630	0.648
High-risk PET	0.685	0.645
2-FACTOR MODEL	0.712	0.696
3-FACTOR MODEL	0.745	0.746

Summary and Discussion

The integration of baseline PET/CT variables (tMTV, tTLG and Dmax), ctDNA levels and molecular clusters on liquid biopsy improves the outcome prediction of newly diagnosed DLBCL compared to PET/CT and ctDNA levels alone or both combined. If validated, the 3-factor prognostic model should be implemented within dedicated clinical trials during the first cycle of standard chemoimmunotherapy to identify high-risk DLBCL patients who may benefit from an early switch to bispecific monoclonal antibodies and/or CAR-T cell therapy.

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