Can we use pre-treatment Nuclear Medicine tests to predict outcome in Lymphoma?

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University of Miami Health System

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One of the many reasons I have moved to Miami!

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Disclosures

- **Research Funding: Merck, Seattle Genetics, BMS, ADC therapeutics**

- **SAB: Novartis, Seattle Genetics, Celgene, Merck, BMS, Astra-Zeneca, Takeda**

Definitions

- **SUV: ratio of the decay corrected FDG concentration in the volume of interest (VOI), to the injected dose normalized to patients body weight**
- **SUV max: maximum volume for SUV in VOI, highest metabolism in tumor; influenced by tumor heterogeneity and background noise since it is a single VOI**
- **SUV mean: average volume of different measurements of SUV within VOI**
- **SUV peak: maximum tumor intensity within 1 cm^3 VOI in hottest part of tumor volume (measurement proposed for PERCIST)**

Definitions

- **Metabolic tumor volume (MTV): total volume of metabolically active tumor in VOI, expressed in cm^3 or ml**
- **Total Lesion Glycolysis (TLG): multiplication of SUV mean of the VOI and MTV**

- **Most common ways to determine if a lesion should be used to determine MTV**
  - **Fixed threshold SUV: eg 2.5 or a value relative to mean liver uptake plus 2 standard deviations**
  - **Percentage threshold: of SUV max using a cutoff of 40-50% of its value**

Lymphoma docs vs. Nuclear medicine docs

- It is clear that quantitative metabolic imaging is a more objective surrogate marker than visual analysis for prognostication and prediction of outcome

- Visual assessment based upon Deauville score relies upon NM read
  - Standard for interim and end of treatment evaluation in the aggressive lymphomas
  - high false positive result because of variable hepatic uptake is concerning

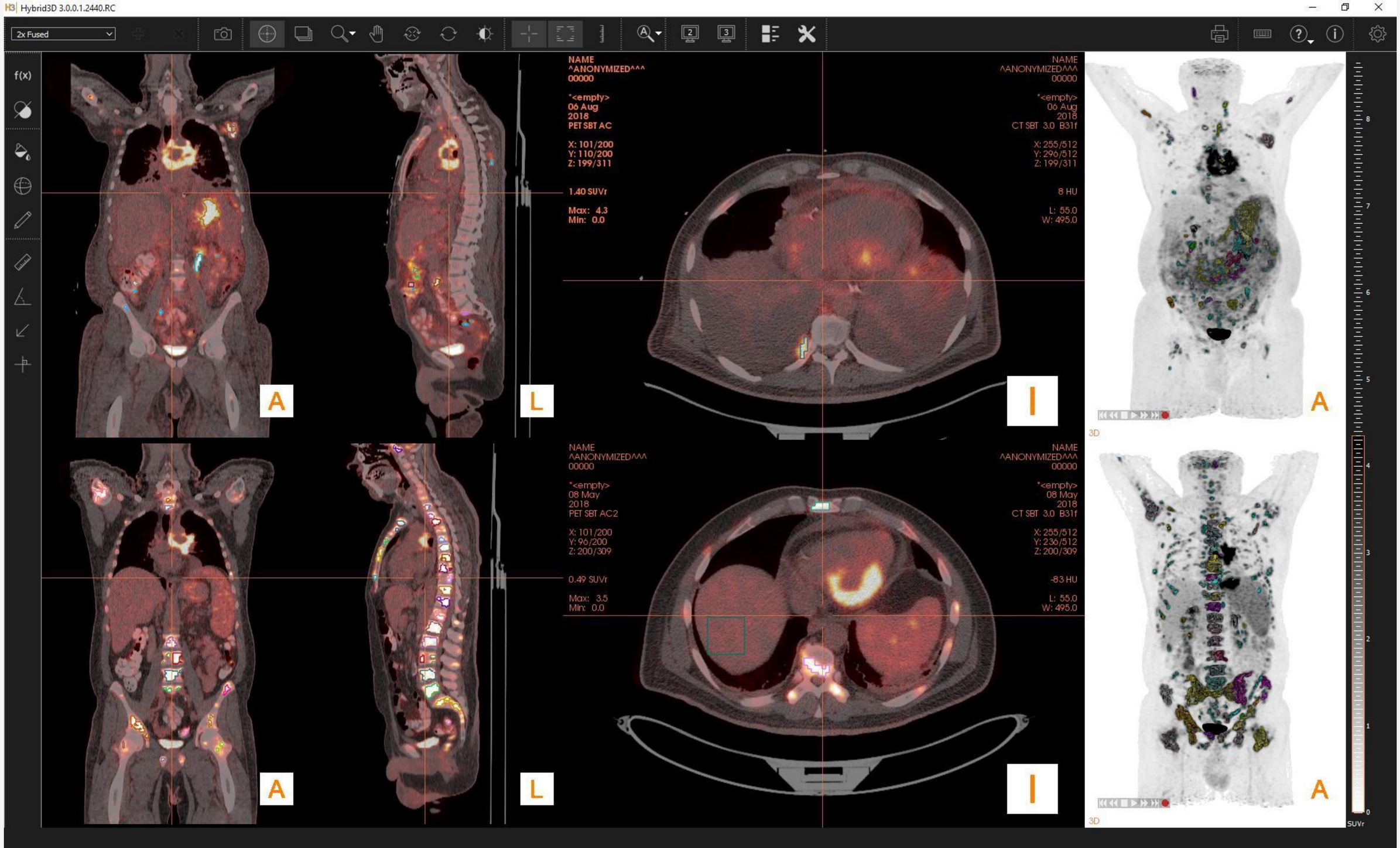
- Now there are computer algorithms and user friendly commercially available software packages that allows for multicenter investigational therapy using MTV easily

- Is MTV ready for primetime?

HERMES MEDICAL SOLUTIONS

3 to 4 mins per PET timepoint

- Create a VOI in the right liver lobe called BG
- Perform a global threshold using (>= 3 * Mean BG)
- Perform clustering to isolate all lesions and filter out anything to small (<0.5ml)
- Remove bladder and myocardium VOIs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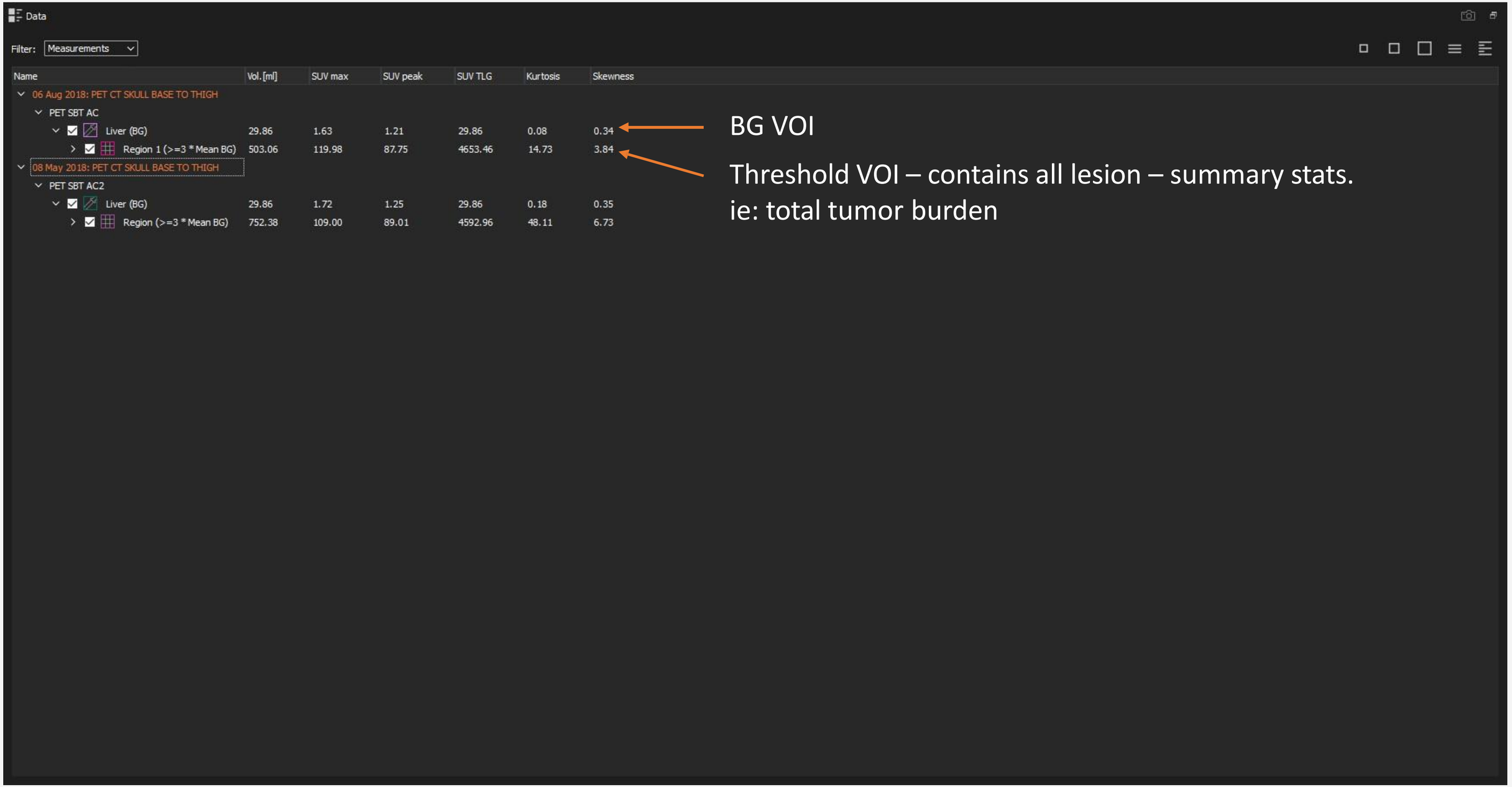
Data
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Vol. [ml]
SUV max
SUV peak
SUV TLG
Kurtosis
Skewness
06 Aug 2018: PET CT SKULL BASE TO THIGH
PET SBT AC
Liver (BG) 29.86 1.63 1.21 29.86 0.08 0.34
Region 1 (>=3 * Mean BG) 503.06 119.98 87.75 4653.46 14.73 3.84
08 May 2018: PET CT SKULL BASE TO THIGH
PET SBT AC2
Liver (BG) 29.86 1.72 1.25 29.86 0.18 0.35
Region (>=3 * Mean BG) 752.38 109.00 89.01 4592.96 48.11 6.73
BG VOI
Threshold VOI – contains all lesion – summary stats.
ie: total tumor burden

Do we need Quantitative PET?

- **There is a clear clinical need to identify high risk patients, pre-treatment, where alternative therapy should be considered; standard therapy is suboptimal**

  - **Thus far the IPI, RIPI, HLIPI, Cell of origin analyses, mutational analyses, FISH data are unable to find a patient population that clearly needs alternative treatment**

  - **Patients with unfavorable risk factors still have reasonable cure rate; and standard therapy is fine**

  - **What is the data with pre-treatment MTV is various lymphoma studies?**

DLBCL

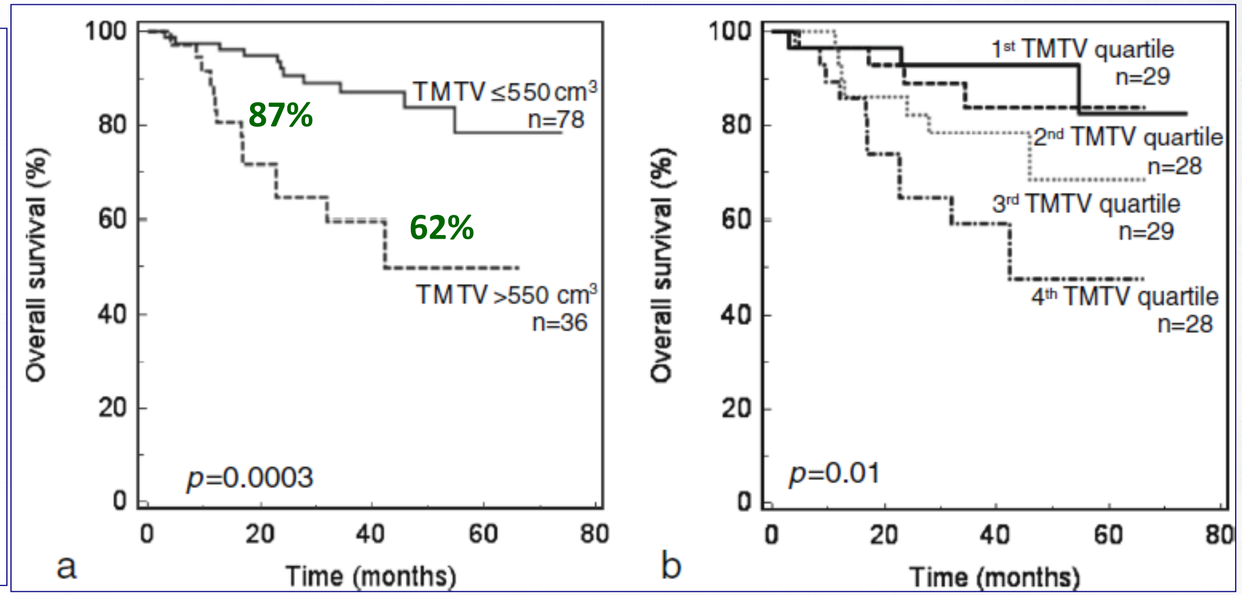
Pretherapy MTV is an independent predictor of outcome in DLBCL

Sasanelli M, Eur J Nucl Med 2014:41:2017

segmentation threshold
41% SUV_{max}

MTV is the only independent predictor of

- OS (p = 0.002)
- PFS (p=0.03)
- other pre-therapy indices fared worse; tumor bulk (≥10 cm), LDH, stage and aaIPI



N=114, retrospective, R-CHOP, med fu 39mo

	low MTV group	high MTV group	
3y PFS	77%	60%	p=0.04
3y OS	87%	62%	p =0.0003

Cox regression showed independence of TMTV for OS prediction (p=0.002) compared with other pretherapy indices of tm burden, i.e. bulk and the IPI

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PET/CT functional parameters in defining prognosis of PMBCL (IELSG trial)

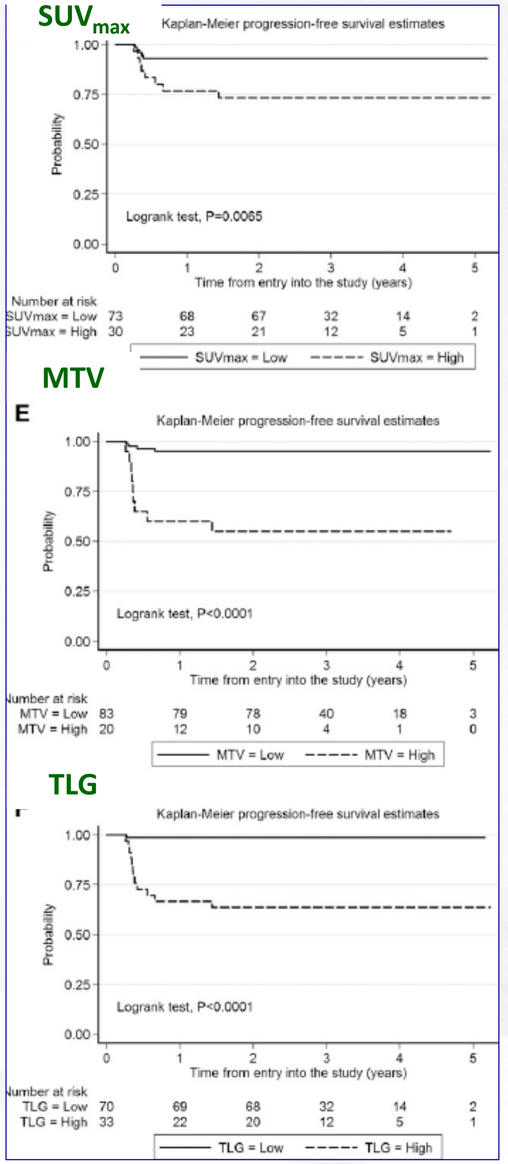
N=103, median fu 36 months

	5y PFS	5y OS
low TLG	99%	100%
high TLG	64% (P < .0001)	80% (p< .0001)

multivariate - only TLG retained statistical significance for both OS (P<.001) & PFS (P < .001)

- Baseline TLG appeared to be a powerful predictor of outcomes
- May be used as a a better selection tool for high-risk pts before an intensive rx decision is made

Segmentation threshold 25% SUV_{max}



Ceriani L, et al. Blood 2015;126:950

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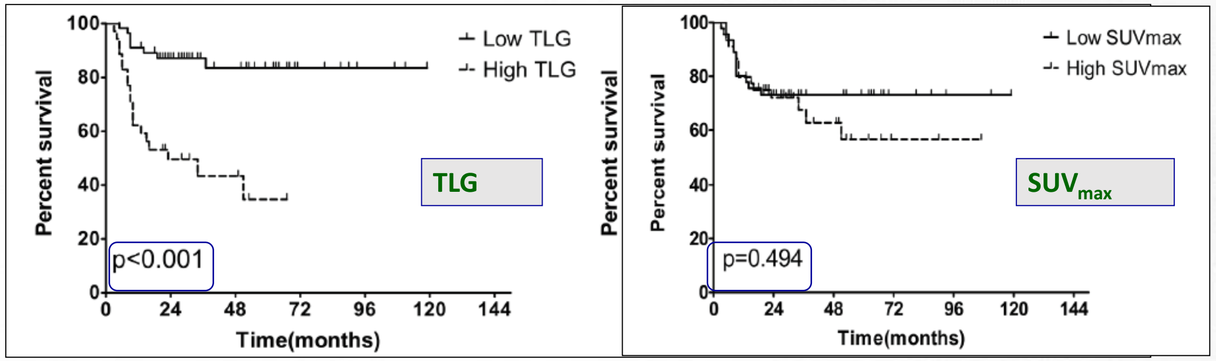
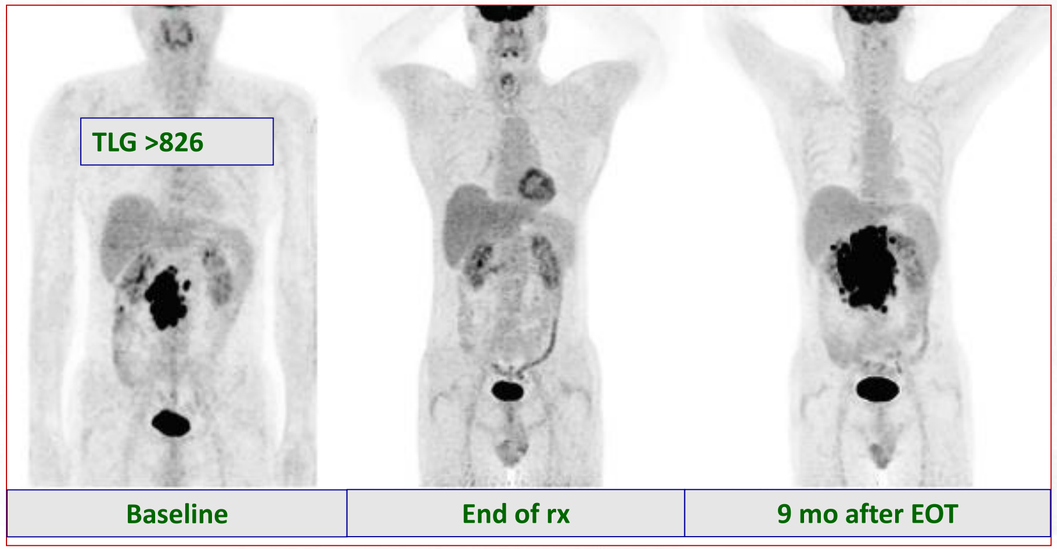
Prognostic value of TLG at baseline in DLBCL

N=91, retrospective, R-CHOP, med fu 30 mo





Segmentation threshold
Liver **SUV_{mean}+ 3 SD**

Zhou M, Oncotarget. 2016;7:83544

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Prognostic value of MTV at baseline in DLBCL

N=147, retrospective, R-CHOP, fu 46 mo

Mikhaeel NG, EJNMMI 2016;43:1209

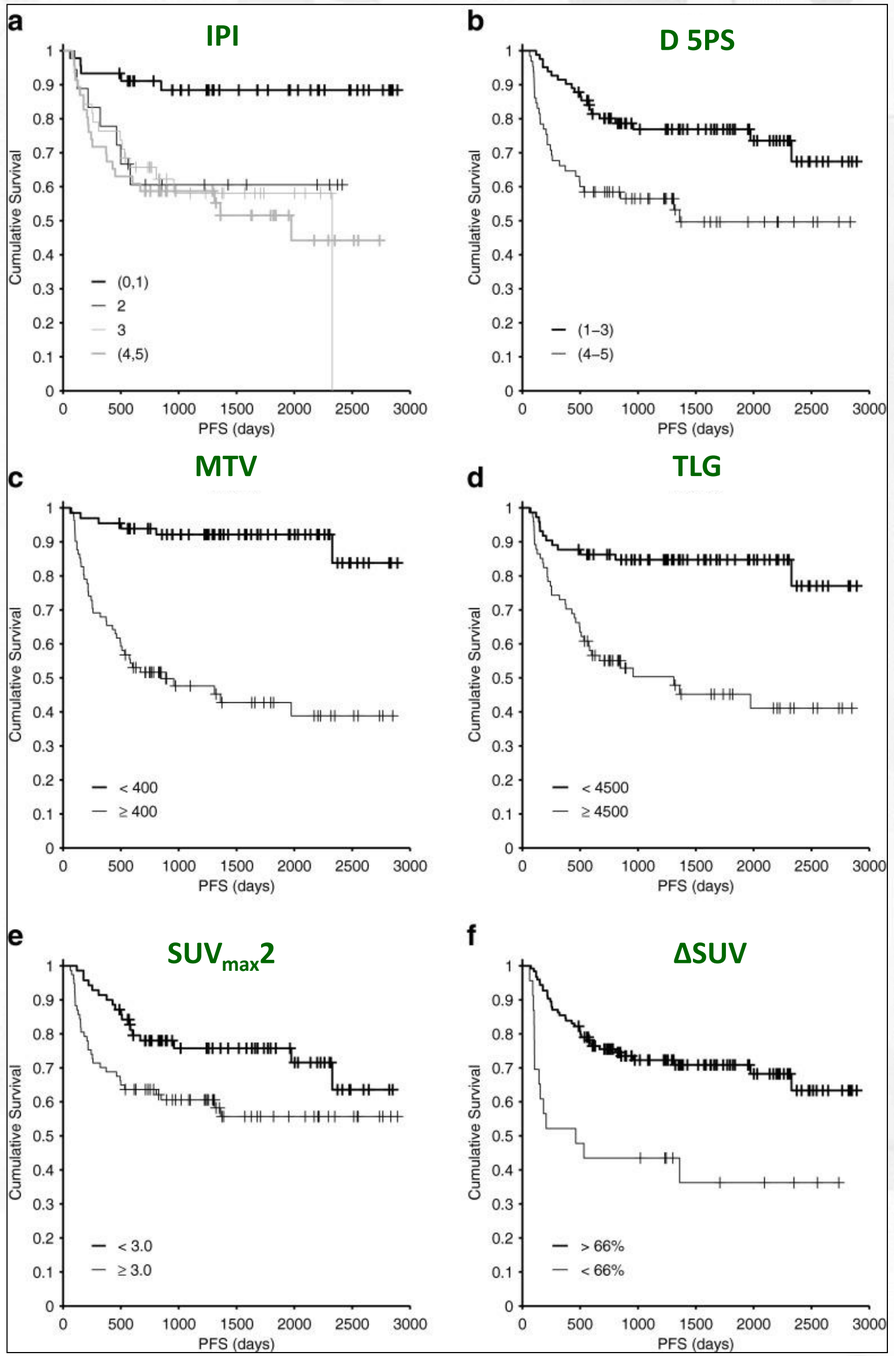
PET0 and PET2

MTV was found to be the only independent predictor of PFS (p=0.04)

ΔMTV and ΔSUV at PET2 less predictive

segmentation threshold
SUV_{max} > 2.5 cutoff

MTV-0 the only independent measure (p=0.04)
(TLG was not included in the MVA because MTV and TLG did equally in the univariate



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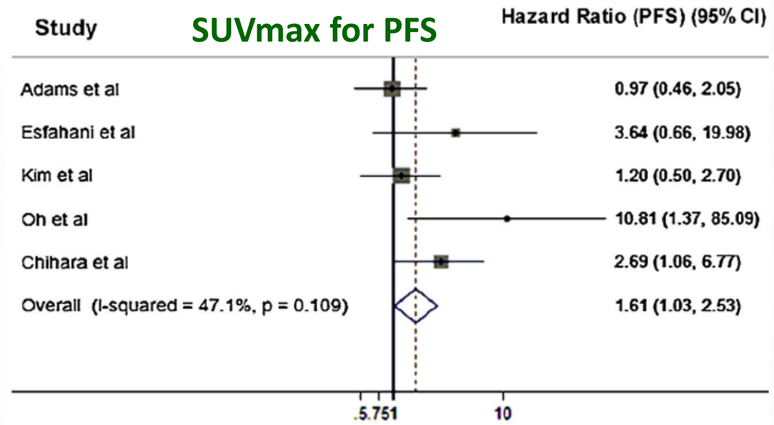
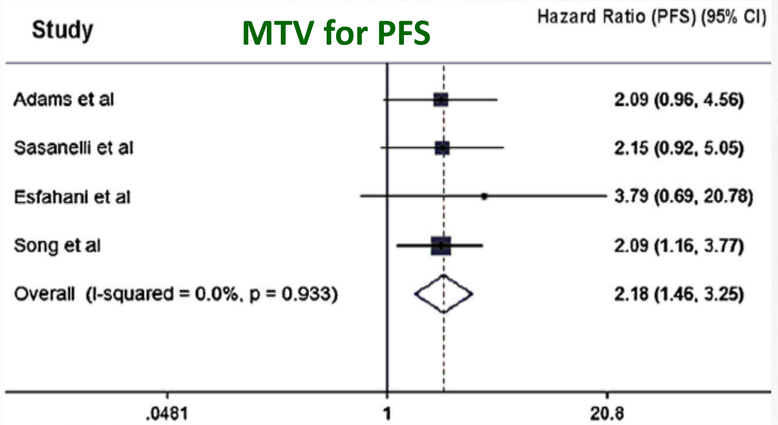
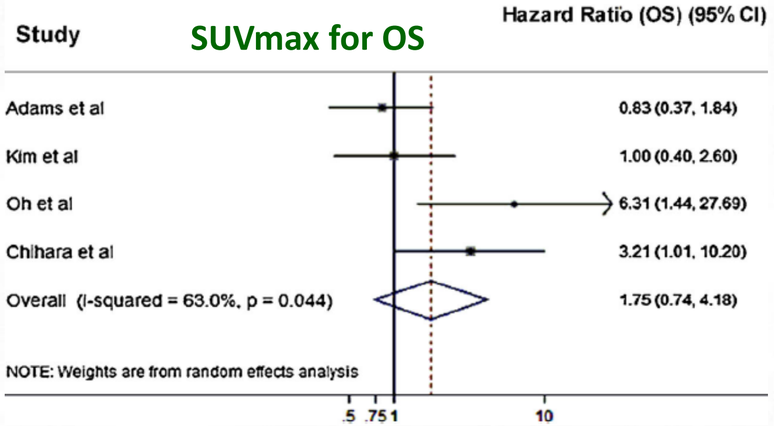
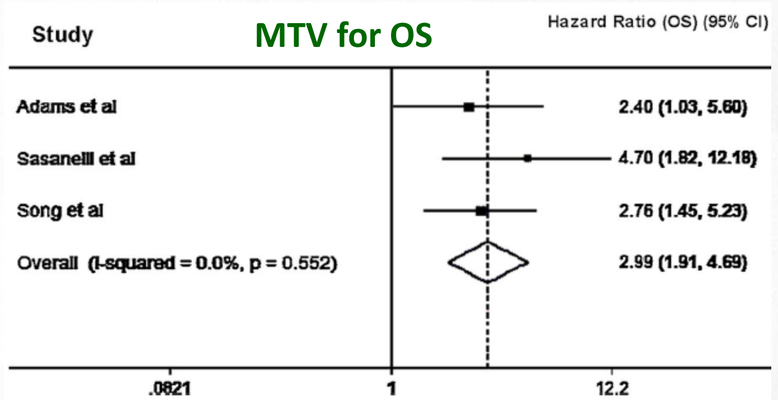
meta-analysis evaluating predictive value of MTV in DLBCL

N= 702 pts









Xie M-P, Med Oncol. 2015:32:446

- High MTV is associated with reduced survival in rCHOP treated DLBCL pts
- MTV tends to be superior to SUV_{max} in predicting survival
- Large-scale prospective studies needed to confirm prognostic value of qPET

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Author	stage	No. pts	Ret/ Pro	Multi ctr	Harmon scanner	Therapy	PET time	Segmentation method	MTV Cut-off	Med fu	PFS/OS
Esfahani SA 2013	All	20	RET	No	Yes	R-CHOP	PET0, PET2	1.5 liver SUV_{mean} + 2.5 SD	379 PET0 TLG=705 PET0 5.95 PET2 TLG=96.5 PET2	12	53% v 34% ns 56% v 29% p=0.02 50% v 35% ns 50% v 26% p=0.02
Kim P 2014	early	34	RET	No	Yes	R-CHOP	PET0	25% - 75% SUV_{max}	130cm^3	28	100% v 40%
Sasanelli 2014	82% adv	114	RET	Yes	No	R-CHOP21, RCHOP14+SCT	PET0	41% SUV_{max}	550 cm^3	39	3 y PFS 77% v 60% p=0.02 3 y OS 87% v 60% p=0.0003
Gallicchio 2014	Int IPI	52	RET	No	Yes	R-CHOP	PET0	42% SUV_{max}	16.1 cm^3 TLG 589	18	NS
Adams 2014	62% adv	73	RET	No	Yes	R-CHOP	PET0	40% SUV_{max}	272 cm^3 TLG 2955	33	NS
Malek 2015	58% early	140	RET	No	Yes	R-CHOP, R-DA-EPOCH	PET2-4	37% SUV_{max} &gradient	ΔMTV 52% in pts w ΔSUV_{max} 72%	37	78% v 68% p= 0.02
Mikhaeel 2016	69% adv	147	RET	No	Yes	R-CHOP	PET0, PET2	SUV_{max} 2.5 fixed	400 cm^3	114	5 y 90% v 29% - 58% (DS 4-5 v 1-3)
Cottereau 2016	80% adv	81	RET	No	Yes	R-CHOP	PET0	41% SUV_{max}	300 cm^3	64	5 y 76% vs 43% p=0.002
Ceriani 2015	PMBCL 94% early	103	PRO	Yes	No	R-CHOP, R-VACOBP+RT	PET0	25% SUV_{max}	703 cm^3 , TLG 5814	36	5 y 99% v 64% p<0.0001

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Baseline PET-derived MTV metrics predict progression-free and overall survival in DLBCL after first-line treatment: results from the Phase 3 GOYA study

(oral presentation at 2018 American Society of Hematology)

Lale Kostakoglu,[1] Maurizio Martelli,[2] Laurie H. Sehn,[3] David Belada,[4] Angelo-Michele Carella,[5] Neil Chua,[6] Eva Gonzalez-Barca,[7] Xiaonan Hong,[8] Antonio Pinto,[9] Yuankai Shi,[10] Yoichi Tatsumi,[11] Günter Fingerle-Rowson,[12] Gila Sellam,[12] Andrea Knapp,[12] Federico Mattiello,[12] Deniz Sahin,[12] Tina Nielsen,[12] Umberto Vitolo,[13] Marek Trněný[14]

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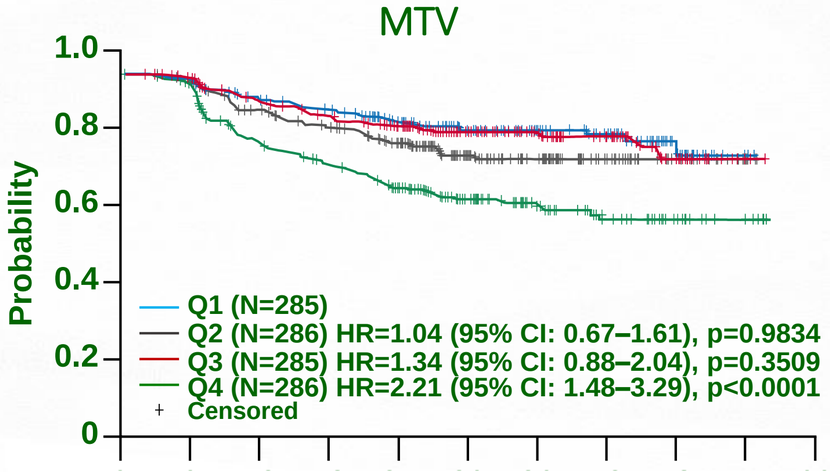
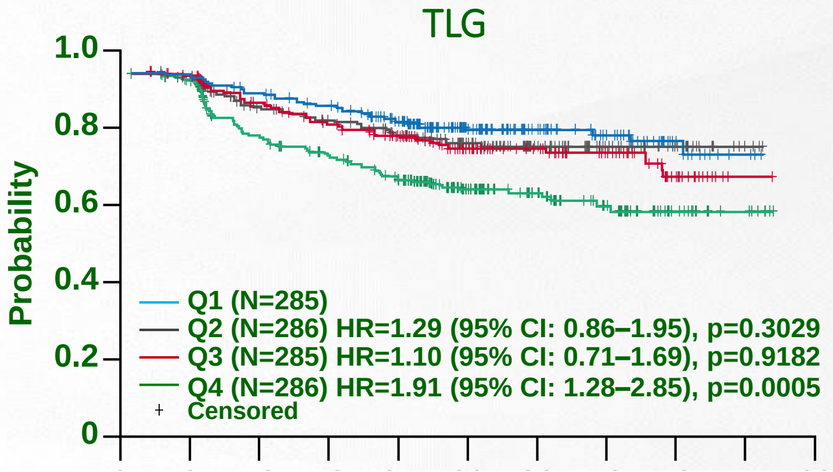
Prognostic value of baseline TMTV and TLG for PFS

1346 pts had baseline PET-CT





Time (months)

Q4	286	266	209	193	165	100	65	42	17	4

Q4	286	265	210	197	169	98	66	43	16	4

MTV	*3-yr PFS (95% CI)*
Q1	86% (81–89)
Q2	84% (78–88)
Q3	78% (72–83)
Q4	66% (59–71)

TLG	*3-yr PFS (95% CI)*
Q1	85% (80–89)
Q2	79% (73–84)
Q3	81% (75–85)
Q4	68% (61–74)

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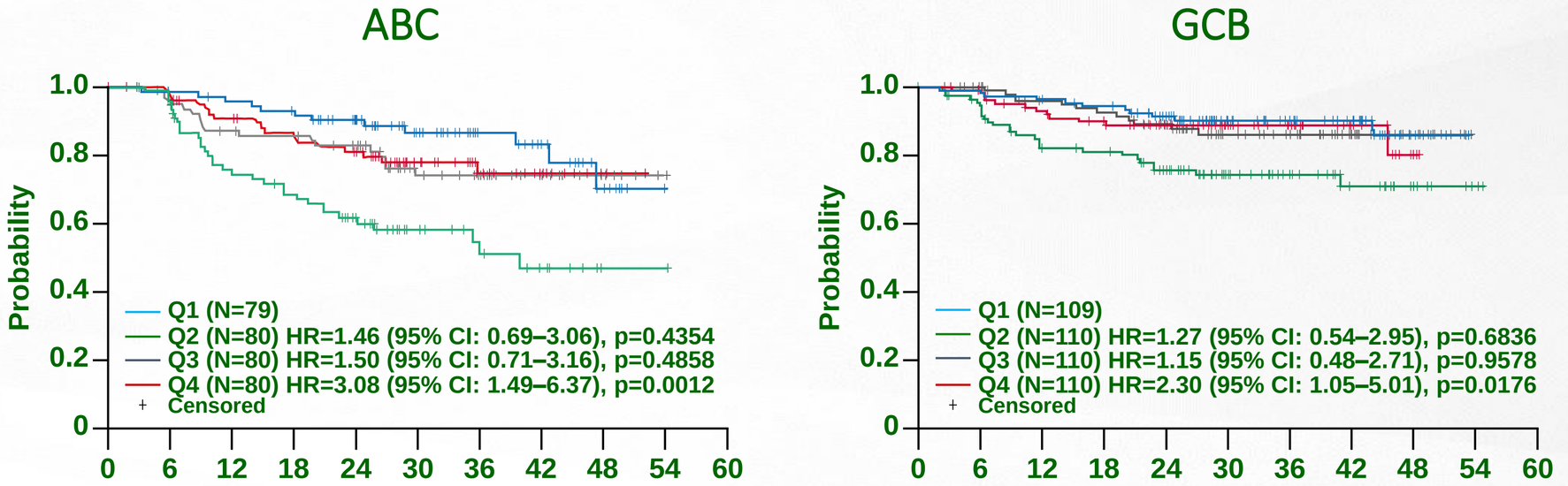
Prognostic value of baseline MTV for PFS by COO (immunophenotyping)



- COO was available in 880 patients with PET imaging; baseline characteristics were similar to the overall PET-ITT population
- High MTV at baseline predicts poorer outcome

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Multivariate Cox regression of factors associated with PFS

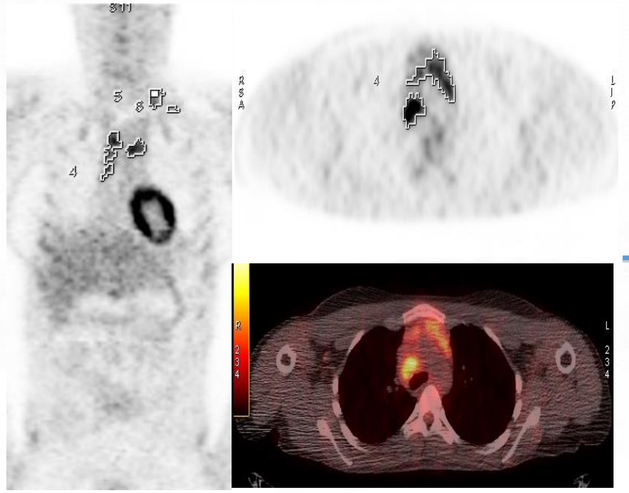
Factor*	HR	Wald 95% CI	P-value
MTV Q4 vs Q1	1.91	1.10–3.30	0.0211
COO ABC vs GCB	2.09	1.44–3.03	0.0001
IPI High vs low-intermediate	1.86	1.17–2.96	0.0088
Geographic region Western Europe vs Asia	0.61	0.41–0.92	0.0192
Time from initial diagnosis to randomization	0.66	0.46–0.95	0.0232

- MTV remained prognostic despite adjustment for other important covariates

n=754

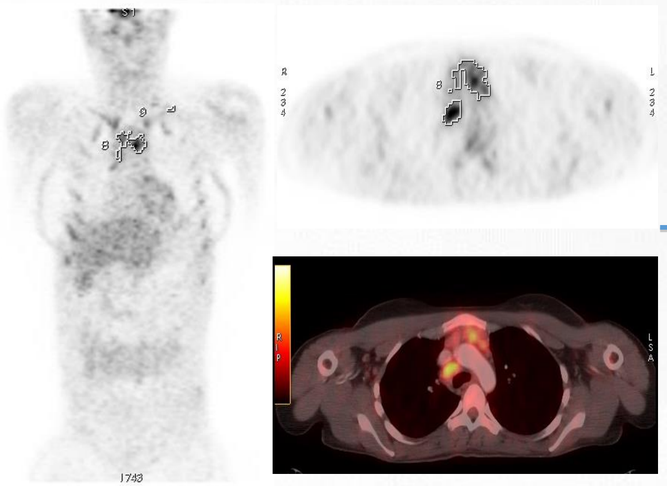
*Significant covariates shown. Total list of covariates tested included treatment group (G-CHOP vs R-CHOP); TMTV quartiles (Q2, Q3 and Q4 vs Q1), COO (ABC and unclassified vs GCB), IPI categories (high and high-intermediate vs low-intermediate), geographic region (Eastern Europe, North America, Western Europe, and other vs Asia), gender (female vs male), time from initial diagnosis to randomization, and sum of products of the 2 perpendicular dimensions of the target lesions at baseline. IRC, independent review committee

Baseline



- MTV 102.25 mL
- SUVmax 9.33 g/mL
- TLG 360.56 g/mL x cm^3

Int-PET



- ΔMTV 38.8% decrease
- Δ SUVmax 21% decrease (+)
- Δ TLG 51% decrease
- Deauville + FP

No disease progression at 36 mo

Relapsed at 20 mo

Baseline:

MTV 3063

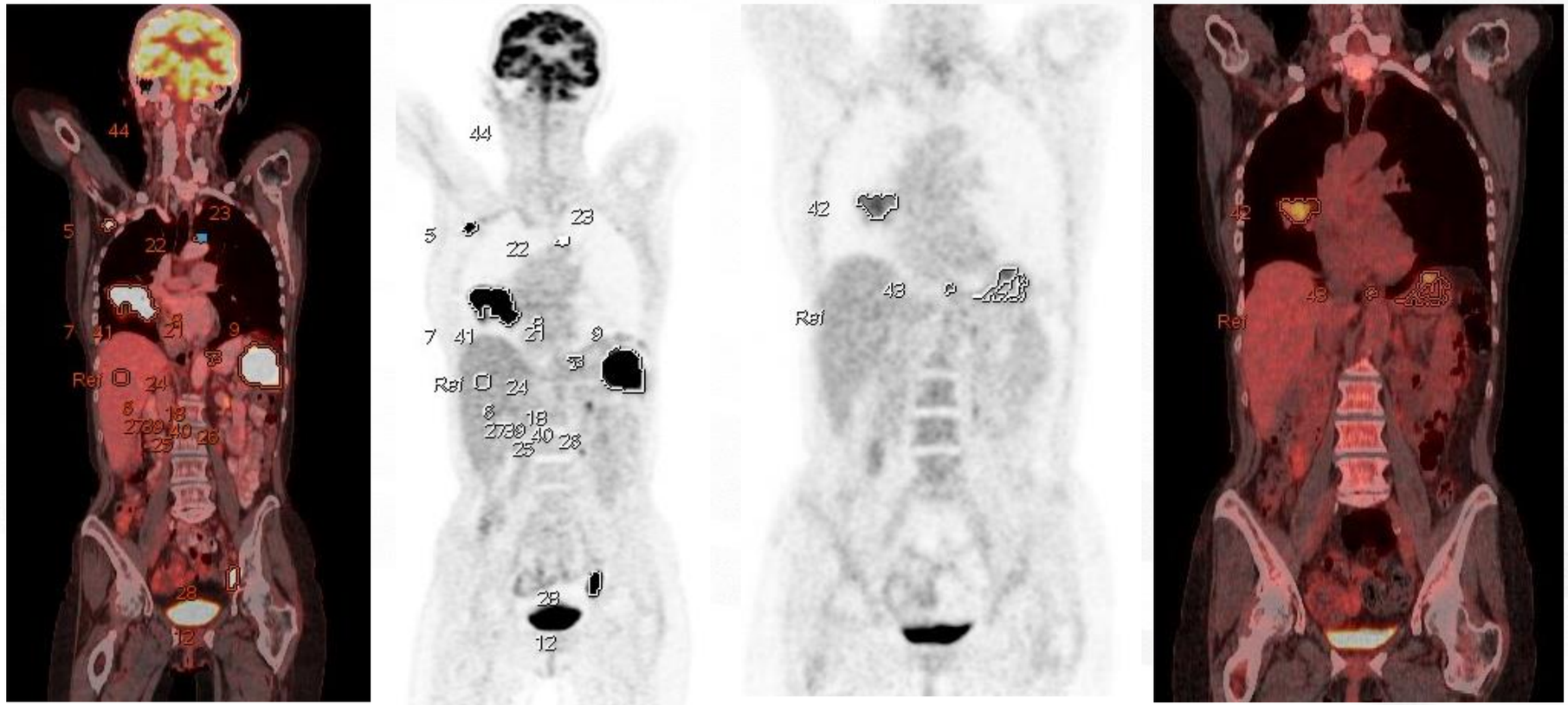
SUV_{max} 48 SUL_{peak} 32

at Interim:

SUV_{max} -82 SUL_{peak} -83

MTV -98 TLG -98

Deauville 4 - PMR



HL

Summary of studies in HL

Author	Dx	No. pts	Ret/ Pro	Multi-center	Harmon scanner	Therapy	PET time	Segmentation method	MTV Cut-off	Med F-U	PFS/OS
Casasnovas 2016	cHL IIB-IV	392	PRO	Yes	?	BEACOPPesc, ABVD PET-adap	PET0	41% SUV_{max}	350 cm^3	16.3	2 y 93% v 81% p=0.001
Kanoun S 2014	cHL, 67% adv	59	RET	No	No	anthra-based + IFRT	PET0, PET2	41% SUV_{max}	225 cm^3	50	4 y 85% v 42% p=0.001
Song M-K 2013	HL 100% early	127	RET	Yes	No	ABVD + RT	PET0	SUV_{max} 2.5 fixed	198 cm^3	46	96% v 66% p<0.001 97% v 71% p=0.001
Tseng D 2012	cHL 60% adv	30	RET	No	Yes	Stan V, ABVD, VAMP, BEACOPP+RT	PET0, PET2	region-growing algorithm	344 cm^3 PET0 44 cm^3 PET2 MTVΔ	50	NS NS P=0.01

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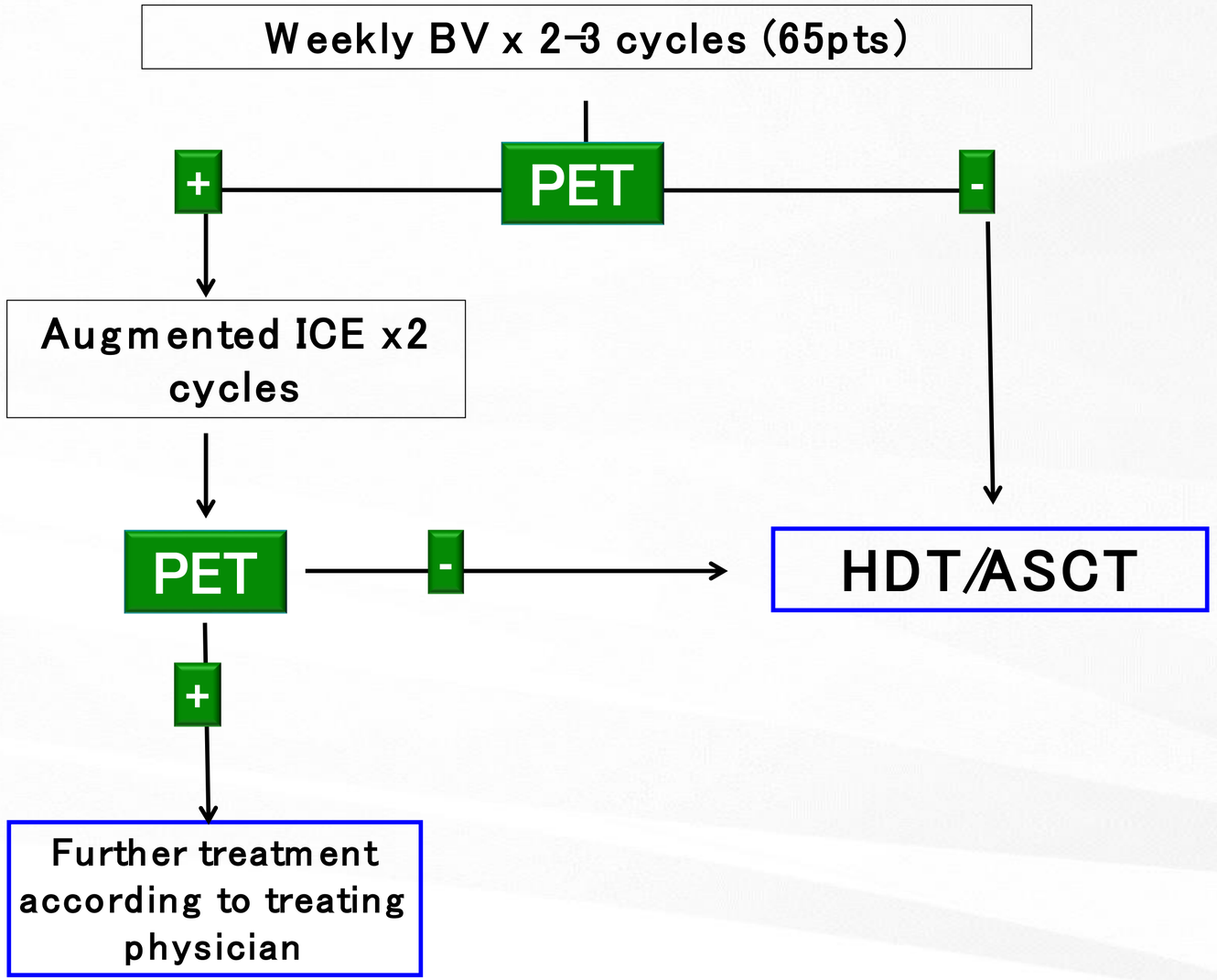
BV as initial 2L therapy for R/R HL



Moskowitz AJ et al Lancet Oncol 2015 16:284-92

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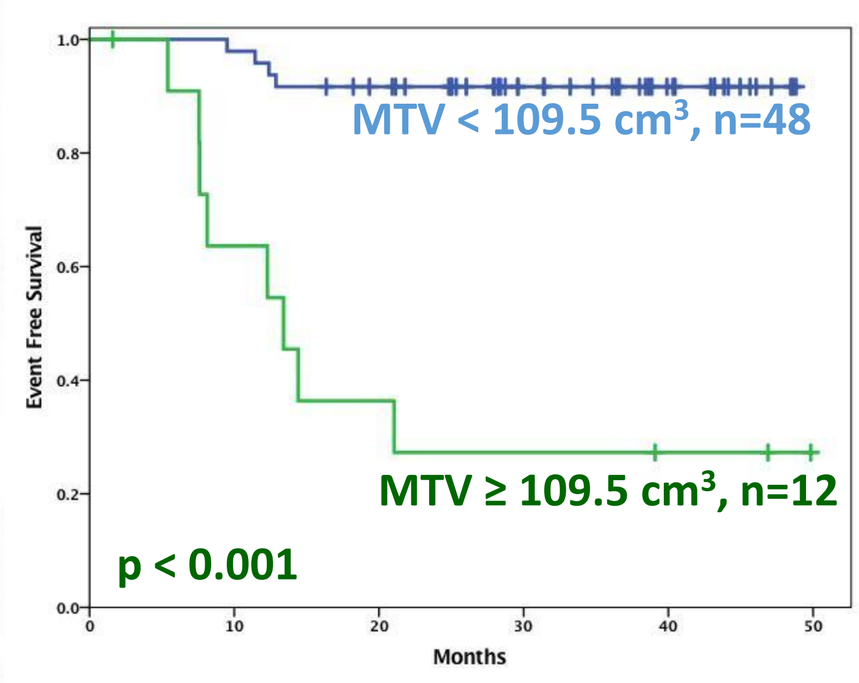
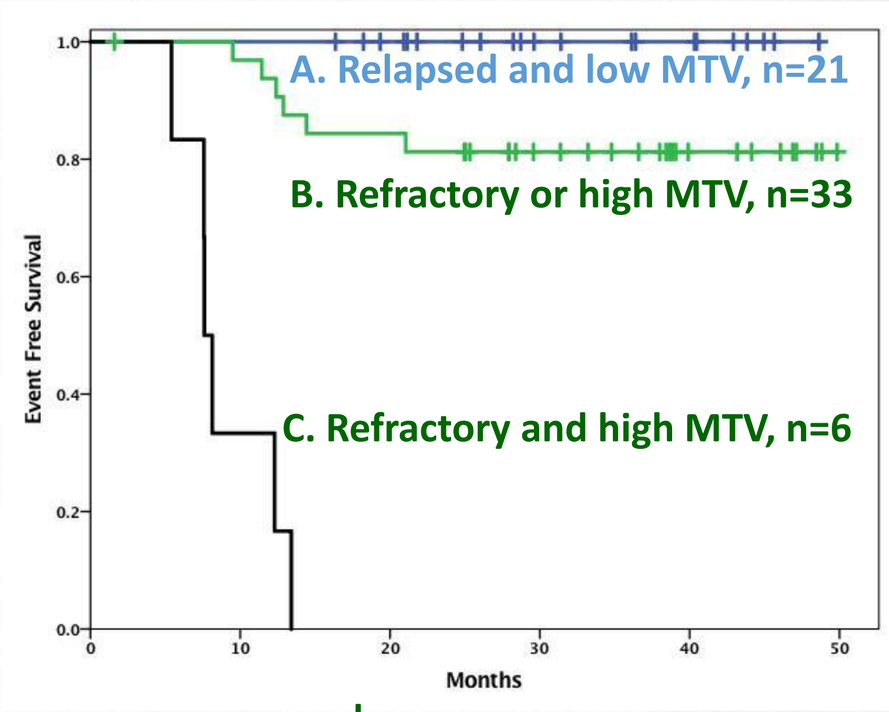
Metabolic tumor volume and refractory disease impact on EFS

Moskowitz et al BLOOD, 16 NOVEMBER 2017 x VOLUME 130, NUMBER 20





p values

A-> B: p=0.042

A->C: p<0.001

B->C: p<0.001

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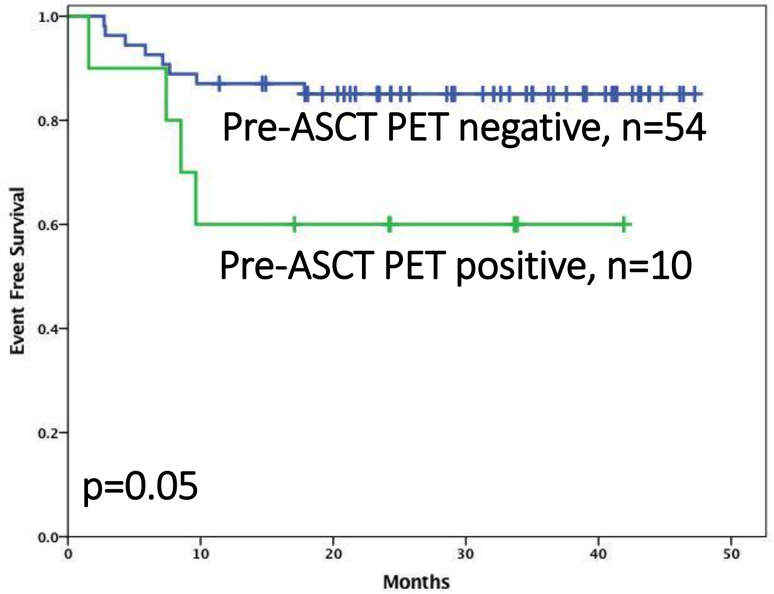
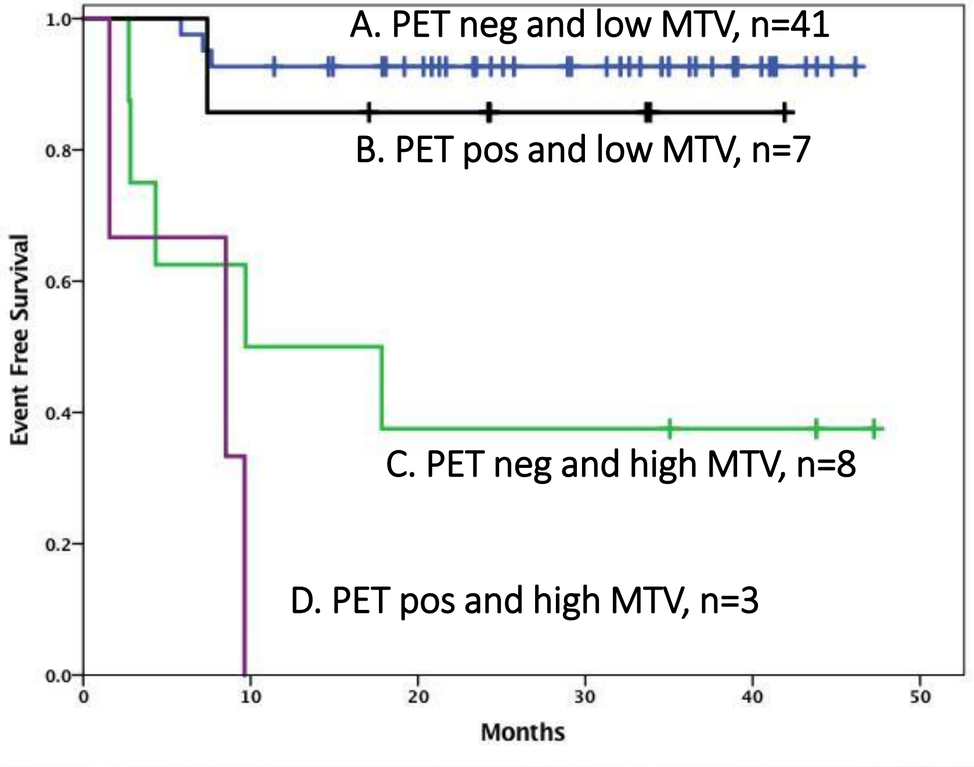
Baseline Metabolic Tumor Volume and pre-ASCT PET

Moskowitz et al BLOOD, 16 NOVEMBER 2017 x VOLUME 130, NUMBER 20





p-values

A->C, p<0.001 B->D, p=0.012

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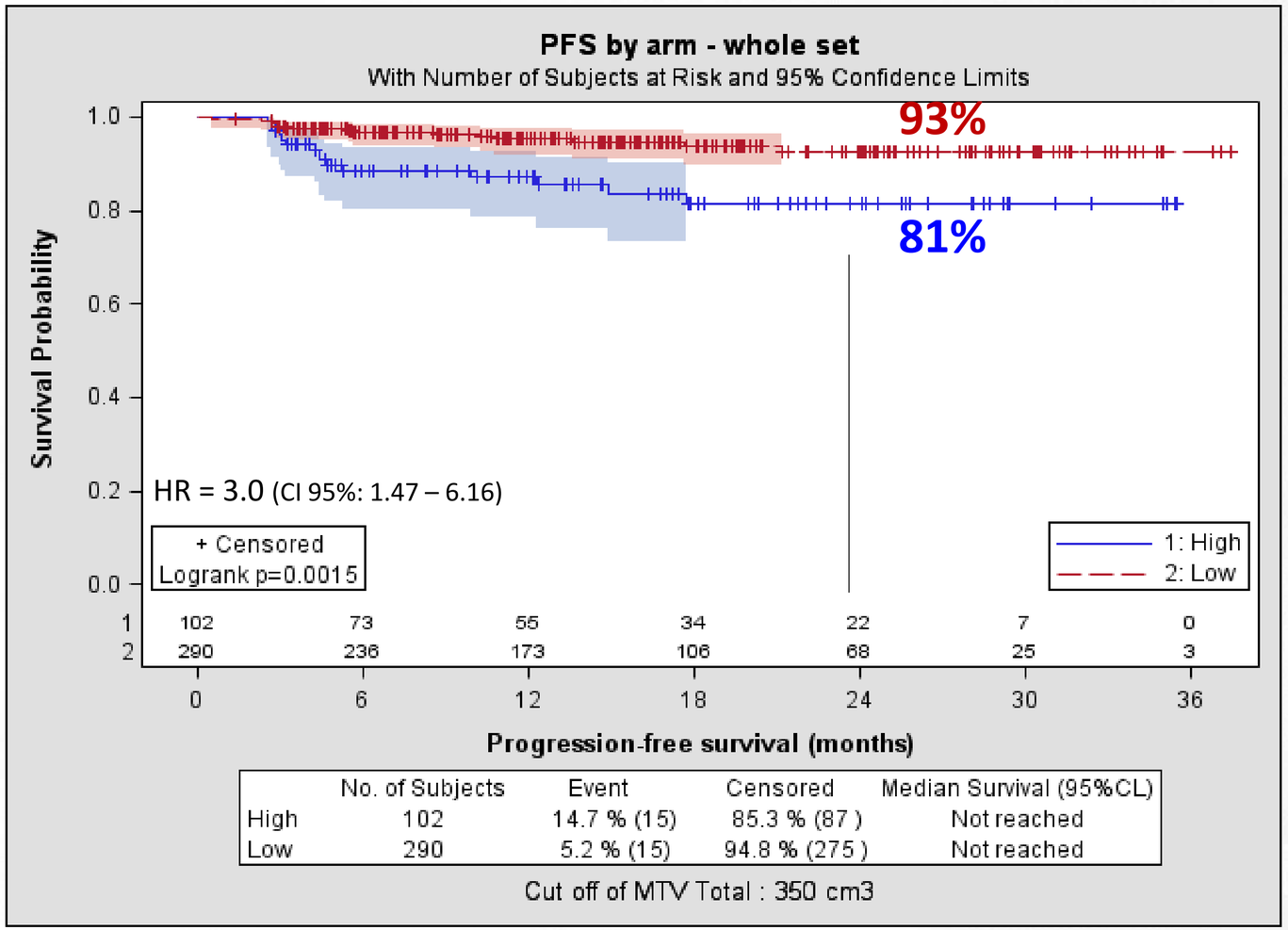
MTV and PET2

Pre-TX and on TX nuclear medicine assessment, ASHL

AHL2011: PFS according to the TMTV

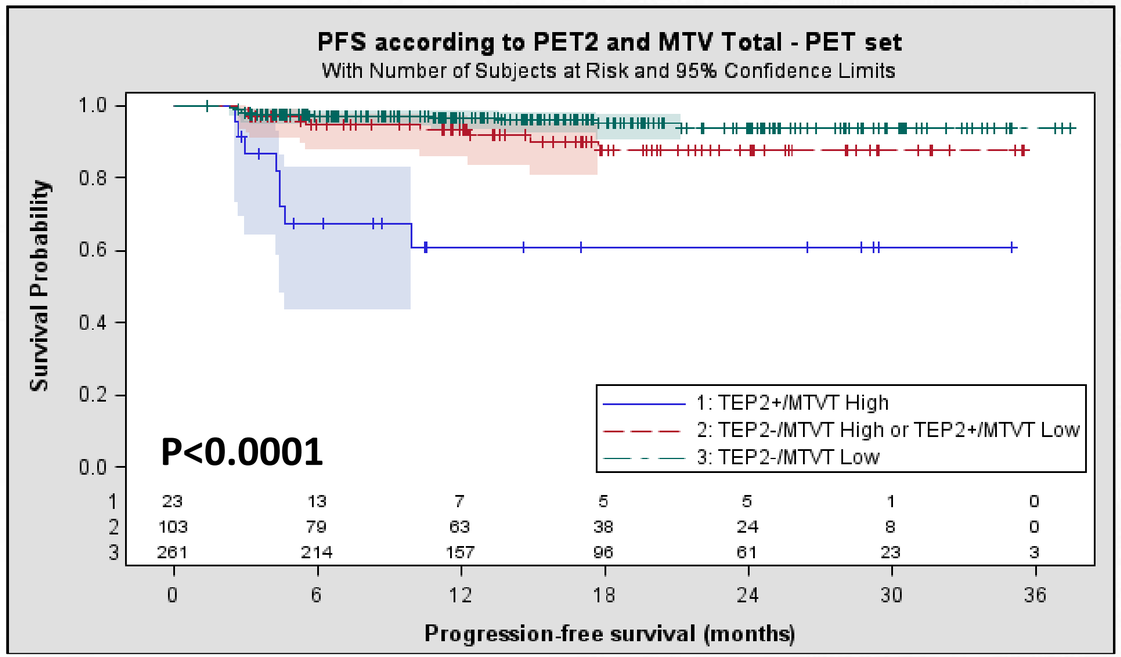


26% High TMTV

CI, confidence interval; CL, confidence limit; HR, hazard ratio; PFS, progression-free survival; TMTV, total metabolic tumour volume

Casasnovas R-O, et al. J Clin Oncol 2016;34(Suppl):abstract 7509.

AHL2011: PFS according to TMTV and PET2 results



	2y-PFS, %	HR
TMTV ≤ 350 ml and negative PET2 (n = 261; 67%)	93.8	1
TMTV > 350 ml or positive PET2 (n = 103; 26%)	87.9	2.08 (95%CI: 0.86 – 5.03)
TMTV > 350 ml and positive PET2 (n = 23; 6%)	60.7	10.9 (95%CI: 4.38 – 27.32)

HR, hazard ratio; PET2, positron emission tomography after 2 cycles of chemotherapy; MTV, metabolic tumour volume; PFS, progression-free survival; TMTV, total metabolic tumour volume

Casasnovas R-O, et al. J Clin Oncol 2016;34(Suppl):abstract 7509.

Lysa

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Summary

- Studies are retrospective
- Patient populations are not uniform
- Treatment is not uniform
- Methods used to determine MTV are not uniform
- Imaging times are not uniform
- Cutoffs are not uniform

- **Results are interesting, likely prognostic, and additive to preexisting risk assessment models**

- **Ready for primetime clinical use off of a clinical trial: Not yet**