Problems in MTV measurements in lymphoma

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with patient data from Michel Meignan

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Outline

- MTV measurement: current status
- How to go beyond the current limitations
  - make MTV calculation easier
  - use a cooperation approach
- Conclusion

Existing MTV delineation methods

- Many methods:

  - Using a fixed SUV threshold (eg, voxels with SUV>2.5 is tumor)

  - Using a relative SUV threshold (eg, voxels with SUV>41% SUV_{max} is tumor)

  - Using a threshold relative to the liver activity (eg, SUV > 1.25 SUV_{max_liver})

  - Using an adaptive threshold accounting for SUV_{max} and surrounding activity (eg, Nestle method[1])

  - Using a fitting method accounting for SUV_{max}, surrounding activity and spatial resolution of the imaging system (Tylski method[2])

  - Using a threshold adjusted iteratively as a function of the tumor-to-background activity, requiring a calibration curve (Daisne method[3])

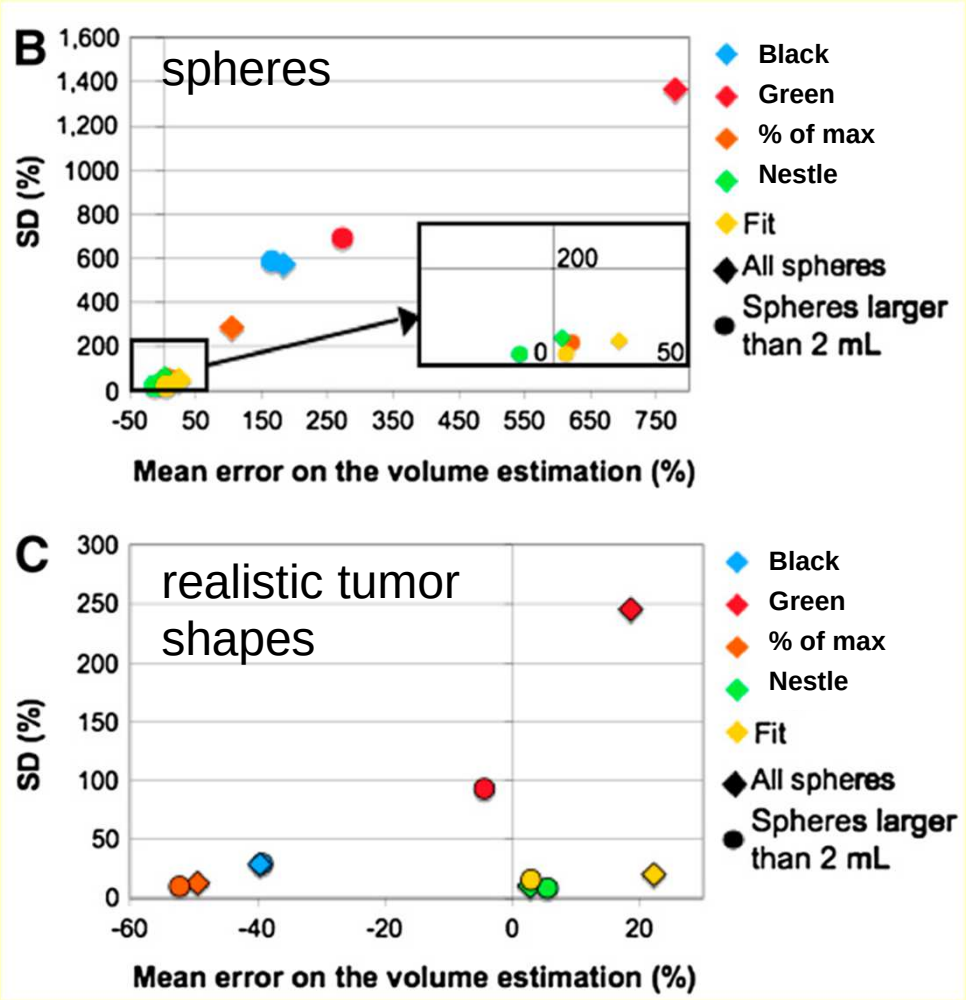
  - Using a threshold adjusted iteratively as a function of the mean SUV in the tumor region, requiring a calibration curve (Black method[4])

  - and many others …

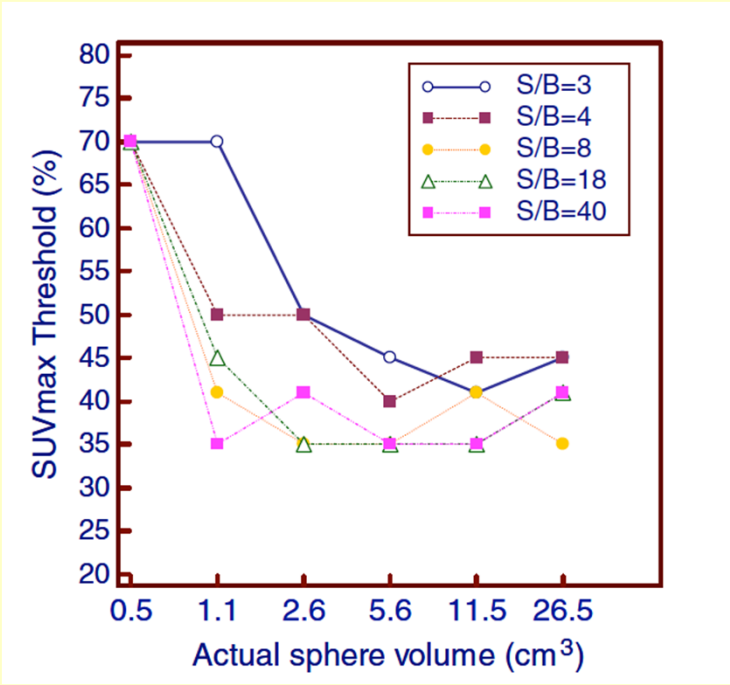
[1]Nestle et al J Nucl Med 2005
[2]Tylski et al J Nucl Med 2010
[3]Daisne et al Radiother Oncol 2003
[4]Black et al Int J Radiat Oncol Biol Phys 2004

Performance of these methods

- All have merits and weaknesses, eg:



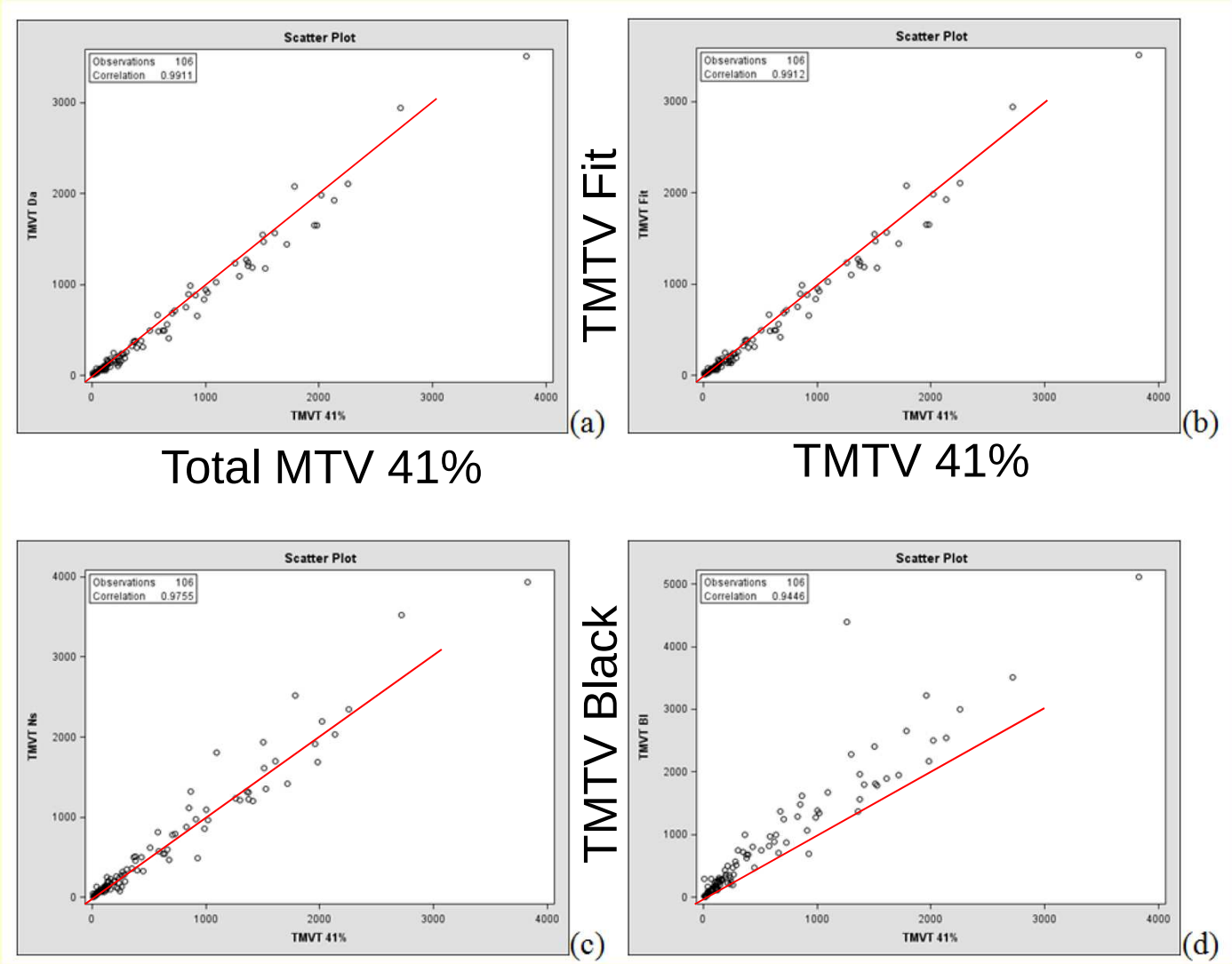
Tylski et al J Nucl Med 2010



Meignan et al EJNMMI 2014

Assessment of existing methods

- Fortunately, all of them provide correlated results

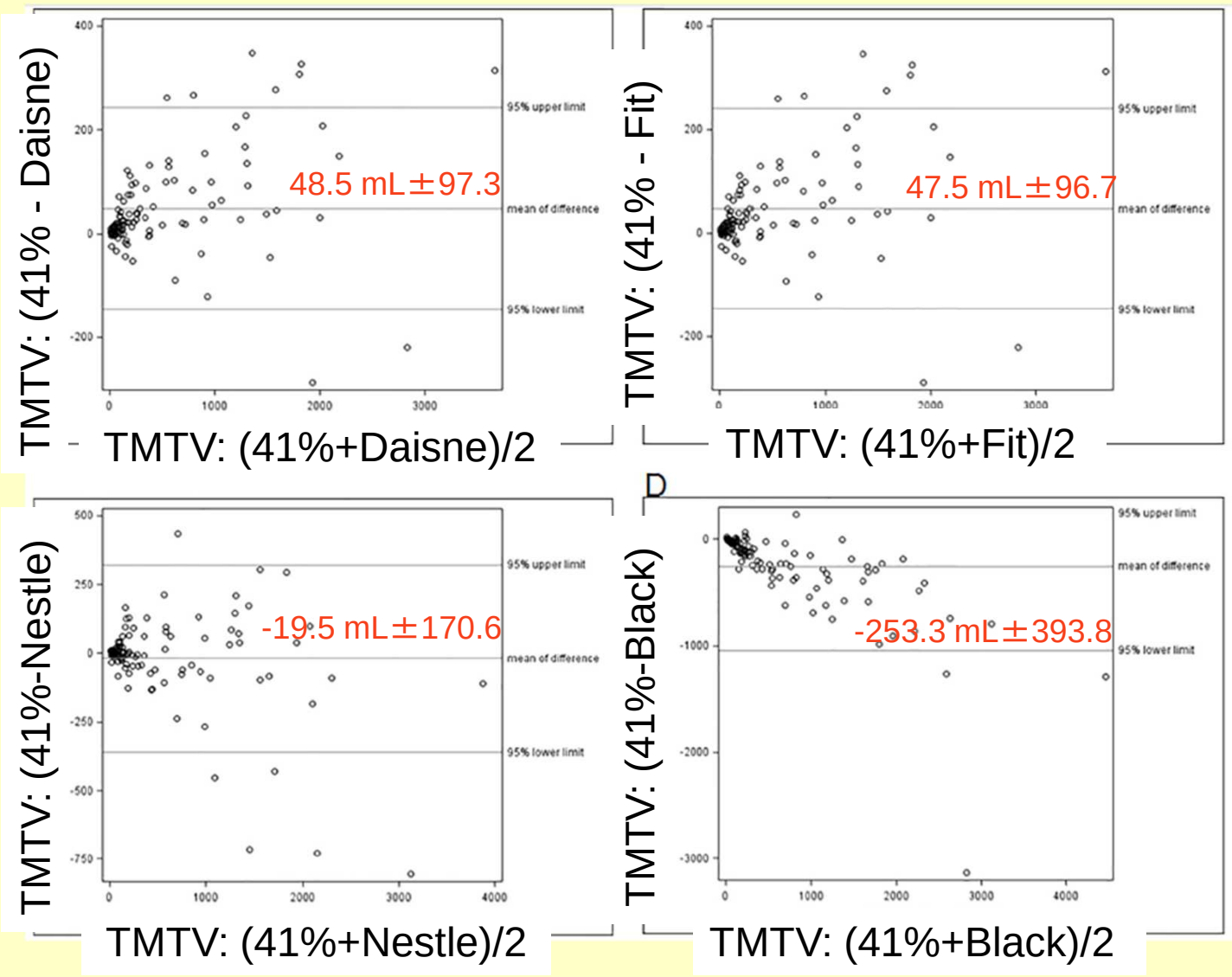


Peripheral T cell lymphoma

Cottereau et al
J Nucl Med 2016

Assessment of existing methods

… but with substantial differences : Bland Altman plots



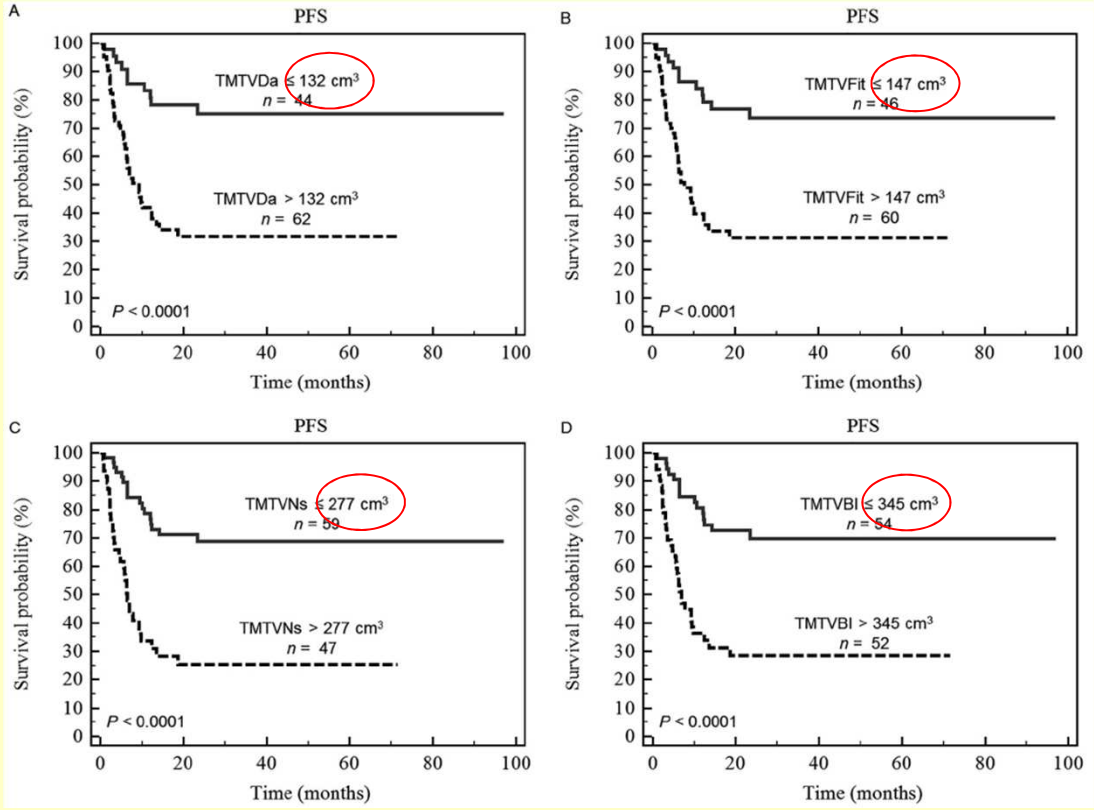
Peripheral T cell lymphoma

Cottereau et al
J Nucl Med 2016

Assessment of existing methods

- No method is always the most accurate: performance vary as a function of the activity distribution, noise, spatial resolution, contrast
- In a given setting, each method has some specific bias.
  A specific cut-off should ideally be used to distinguish between groups

41% threshold:
230 cm^3 cut-off



Peripheral T cell lymphoma

Cottereau et al J Nucl Med 2016

Assessment of existing methods

Table 1. Studies on the Prognostic Value of MTV in Lymphoma

Study	Type of Lymphoma	Patients (No.)	Tumor Volume Parameters: Median SUV	Threshold (%)	Median MTV (cm^3)	Range (cm^3)*	Predictors of PFS	Determination of MTV Cutoff
Kanoun et al[15]	HL	59	NR	41	117	4-1,611	MTV 225 cm^3 yields 4-year PFS 85% *v* 42%	ROC analysis†, no validation sample
Sasanelli et al[17]	DLBCL	114	NR	41	313	4-2,650	MTV 550 cm^3 yields 3-year PFS 77% *v* 60%	ROC analysis, no validation sample
Adams et al[11]	DLBCL	73	22.0	40	272	6-2,454	Neither MTV nor TLG predicted outcome	N/A
Mikhaeel et al[16]	DLBCL	147	27.2	41	595	2-7,360	MTV 396 cm^3 yields 5-year PFS 92% *v* 42% Best predictive model combines MTV with i-PET Deauville score	ROC analysis, no validation sample
Cottereau et al[26]	DLBCL	81	18	41	320	IQR: 106-668	MTV 300 cm^3 yields 5-year PFS 75% *v* 42%	ROC analysis, no validation sample
Schöder et al[18]	DLBCL	65	23.4	Various‡	226	9-3,453	MTV did not predict outcome	N/A
Ceriani et al[12]	PMBL	103	18.8	25	406	NR	MTV 703 cm^3 yields 5-year PFS 97% *v* 60% TLG 5,814 yields 5-year PFS 99% *v* 64%	ROC analysis, no validation sample
Cottereau et al[13]	PTCL	108	14	41	224	3-3,824	MTV 230 cm^3 yields 2-year PFS 71% *v* 26%	ROC analysis, no validation sample
Meignan et al[19]	FL 1-3a	185	10.0	41	297	IQR: 135-567	MTV 510 cm^3 yields 2-year PFS 87% *v* 58%	X-tile analysis

Schöder et al JCO 2016

Assessment of existing methods

- These results regarding MTV are consistent with previously reported results regarding SUV to assess tumor response

Metastatic colorectal cancer
Interim PET @ day 14 of treatment
Targeting a 95% sensitivity for detecting responding lesions

Index	Cut-off	Sensitivity	Specificity
ΔSUV_{max}	-14%	95%	53%
$\Delta SUV_{mean40\%}$	-22%	95%	64%
ΔSUV_{max}	-15%	80%	53%
$\Delta SUV_{40\%}$	-15%	95%	53%

Buvat et al EJNMMI 2012

Current limitations in MTV measurements in lymphomas

- There is no such thing as THE accurate method for MTV estimate
- TMTV measurement is tedious: tumors should first be roughly delineated
- Choice of the “optimal” threshold unclear for prospective studies
- Results are good but far from perfect, eg:

  AUC ~ 0.68 to 0.71 for PFS prediction in peripheral T cell lymphomas[1]
  AUC ~ 0.60 to 0.62 for OS prediction in peripheral T cell lymphomas[1]
  AUC ~ 0.62 for PFS prediction in follicular lymphomas[2]

- Standardization of PET image quality is on-going and useful but:
  - scanners are evolving faster than standardization
  - what about “old” cohorts?

Is MTV calculation worth the effort? How can we move forward?

[1] Cottereau et al J Nucl Med 2016
[2] Meignan et al JCO 2016

How can we go beyond? First track

Make the TMTV calculation **easy**, traceable, reproducible, so that a large number of centres can gain experience with this metrics and more results can be obtained

This involves:

1) Simplifying the initial delineation of regions

2) Having several MTV delineation methods available

3) Allowing for user interaction as no method is perfect and medical expertise is required

4) Making a software widely available

5) Providing user assistance

Texture analysis: is it worth it and where are we?

- In lymphoma, still to be investigated closely[1], but worth dedicated studies see posters

- Textural metrics calculated from PET images start being understood:
  - How they correlate to conventional metrics[2,3]
  - How robust they are[2,4]
  - How they should be calculated[5,6]
  - How they relate to visual assessment of activity distribution heterogeneity[7]
  - How they relate to the spatial organisation of cells as seen on pathological slides[8]

[1]Lartizien et al IEEE J Biomed. Health Inform 2014
[2]Orlhac et al J Nucl Med 2014
[3]Hatt et al J Nucl Med 2015
[4]Yan et al J Nucl Med 2015
[5]Orlhac et al Plos One 2015
[6]Leijenaar et al Sci Rep 2015
[7]Orlhac et al J Nucl Med 2016b (in press)
[8]Orlhac et al J Nucl Med 2016a