Report of IVS analysis in DLBCL

E Itti, M Meignan, A Berriolo, A Biggi, A Cashen, P Vera,

H Tilly, B Siegel, A Gallamini, O Casasnovas, C Haioun

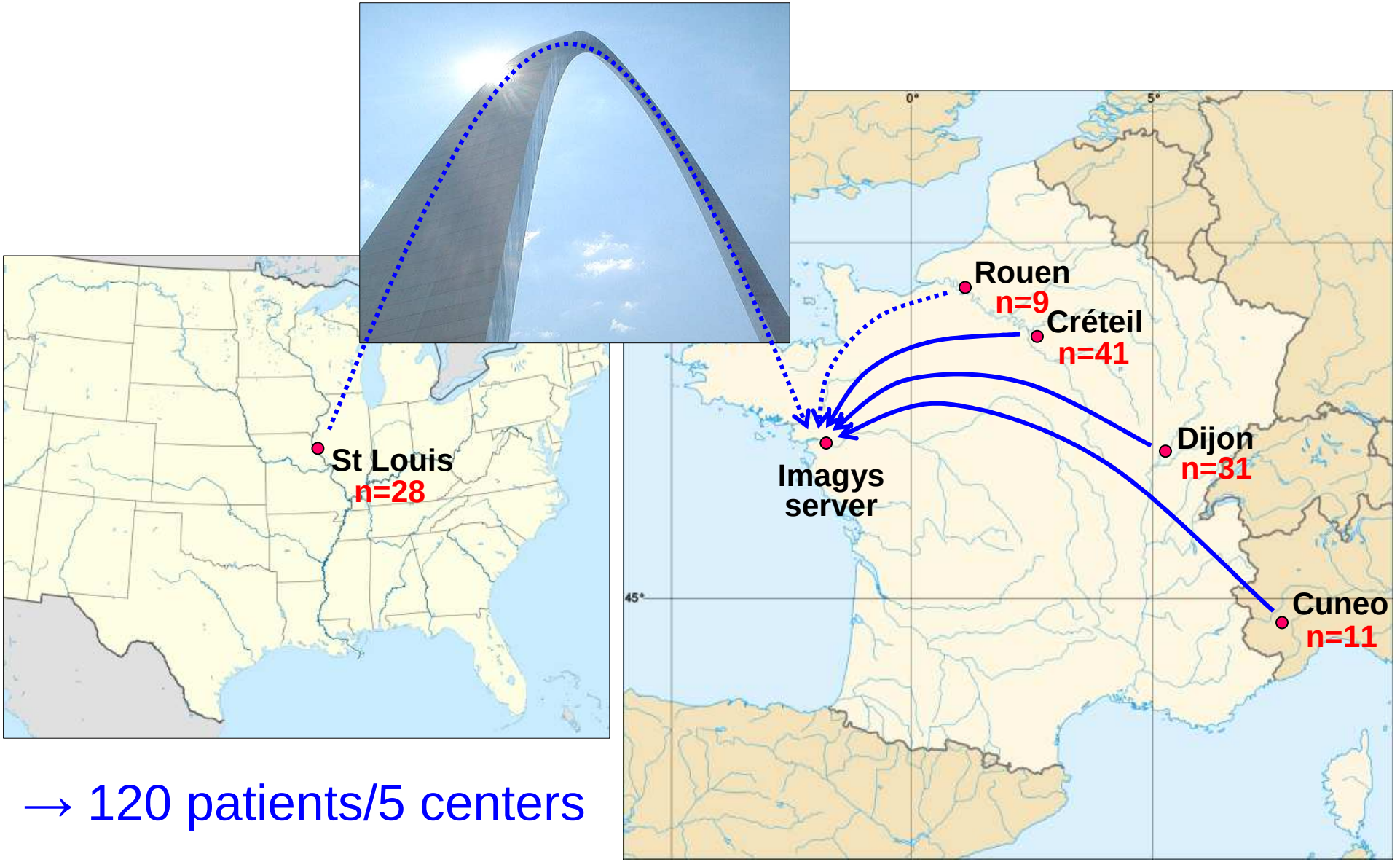
Créteil, Dijon, Cuneo, St. Louis (MI), Rouen

Menton September 26th, 2011

Conclusions of Menton 2010

- Need to recruit more patients/new centers
- Other immunochemotherapy regimens (DI/DD)
- Objective : to reach 100-200 pts (49 in 2010)
- Longer follow-up
- Continuous work instead of last-minute work!

Recruitment status



→ 120 patients/5 centers

Extension of inclusion criteria

- Newly-diagnosed DLBCL
- PET/CT at baseline and after 2 cycles, performed in the same center (6% PET only)
- No change of therapy based on interim PET
- R-CHOP (14 or 21) and R-ACVBP 14
- HDT+ASCT indicated in young (<60 y-o) higher-risk pts or as part of salvage treatment
- Central review

Patients characteristics

patients: n=120	
Male	60%
Median age	56 y (23-80)
>60 y	30%
PS ≥ 2	29%
Ann Arbor III-IV	82%
LDH>1N	68%
>1 extranodal site	31%
IPI	
L (0-1F)	30%
L-I (2F)	22%
I-H (3F)	16%
H (4-5F)	23%

Treatments

IPI	R-CHOP21 n=64 (53%)	R-CHOP14 R-ACVBP n=56 (47%)
L (0-1F)	19	17
L-I (2F)	14	12
I-H (3F)	16	15
H (4-5F)	15	12

Outcome assessment

- Study period : 03/2003 – 08/2011
- Median follow-up : 39.8 months

- EFS according to 5PS and ΔSUV
  - events being defined as modification of scheduled treatment, active disease (IWC+PET or PET only) or progression according to local criteria and death

5-point scale
weighted Kappa (Cohen)

Observer A	Créteil
Observer B	Dijon

Observer B	Observer A 1	2	3	4	5	
1	7	5	3	2	1	(15,0%)
2	8	8	4	1	0	(17,5%)
3	3	6	19	2	0	(25,0%)
4	0	1	5	18	8	(26,7%)
5	1	0	0	2	16	(15,8%)
	(15,8%)	(16,7%)	(25,8%)	(20,8%)	(20,8%)	

Weighted Kappa	0,608
Standard error (Kw'=0)	0,061
Standard error (Kw'#0)	

Observer A	Créteil
Observer B	Cuneo

Observer B	Observer A 1	2	3	4	5	
1	9	3	6	0	2	(16,7%)
2	7	9	4	3	2	(20,8%)
3	2	7	17	7	1	(28,3%)
4	1	1	4	15	13	(28,3%)
5	0	0	0	0	7	(5,8%)
	(15,8%)	(16,7%)	(25,8%)	(20,8%)	(20,8%)	

Weighted Kappa	0,492
Standard error (Kw'=0)	0,058
Standard error (Kw'#0)	

Observer A	Dijon
Observer B	Cuneo

Observer B	Observer A 1	2	3	4	5	
1	11	4	3	1	1	(16,7%)
2	2	9	7	4	3	(20,8%)
3	4	7	14	9	0	(28,3%)
4	1	1	6	17	9	(28,3%)
5	0	0	0	1	6	(5,8%)
	(15,0%)	(17,5%)	(25,0%)	(26,7%)	(15,8%)	

Weighted Kappa	0,475
Standard error (Kw'=0)	0,059
Standard error (Kw'#0)	0,058

Landis and Koch scale	
0.81 – 1.00	almost perfect
0.61 – 0.80	substantial
0.41 – 0.60	moderate
0.21 – 0.40	fair
0.00 – 0.20	slight
< 0	no agreement

5-point scale
binary (cut-off ≥3, MBP)
Kappa (Cohen)

Observer A	Créteil
Observer B	Dijon

Observer B	Observer A		
	0	1	
0	28	11	(32,5%)
1	11	70	(67,5%)
	(32,5%)	(67,5%)	

Kappa	0,582
Standard error	0,081
95% CI	0,424 to 0,740

Observer A	Créteil
Observer B	Cuneo

Observer B	Observer A		
	0	1	
0	28	17	(37,5%)
1	11	64	(62,5%)
	(32,5%)	(67,5%)	

Kappa	0,489
Standard error	0,085
95% CI	0,323 to 0,654

Landis and Koch scale	
0.81 – 1.00	almost perfect
0.61 – 0.80	substantial
0.41 – 0.60	moderate
0.21 – 0.40	fair
0.00 – 0.20	slight
< 0	no agreement

Overall Kappa (Fleiss)
(3 obs.) $\kappa = 0.49$

Observer A	Dijon
Observer B	Cuneo

Observer B	Observer A		
	0	1	
0	26	19	(37,5%)
1	13	62	(62,5%)
	(32,5%)	(67,5%)	

Kappa	0,416
Standard error	0,088
95% CI	0,242 to 0,589

5-point scale
binary (cut-off ≥4, liver)
Kappa (Cohen)

Observer A	Créteil
Observer B	Dijon

Observer B	Observer A		
	0	1	
0	63	6	(57,5%)
1	7	44	(42,5%)
	(58,3%)	(41,7%)	

Kappa	0,778
Standard error	0,058
95% CI	0,664 to 0,892

Observer A	Créteil
Observer B	Cuneo

Observer B	Observer A		
	0	1	
0	64	15	(65,8%)
1	6	35	(34,2%)
	(58,3%)	(41,7%)	

Kappa	0,630
Standard error	0,073
95% CI	0,487 to 0,774

Landis and Koch scale	
0.81 – 1.00	almost perfect
0.61 – 0.80	substantial
0.41 – 0.60	moderate
0.21 – 0.40	fair
0.00 – 0.20	slight
< 0	no agreement

Overall Kappa (Fleiss)
(3 obs.) $\kappa = 0.65$

Observer A	Dijon
Observer B	Cuneo

Observer B	Observer A		
	0	1	
0	61	18	(65,8%)
1	8	33	(34,2%)
	(57,5%)	(42,5%)	

Kappa	0,545
Standard error	0,079
95% CI	0,390 to 0,700

5-point scale
binary (cut-off ≥5, >>liver)
Kappa (Cohen)

Observer A	Créteil
Observer B	Dijon

Observer B	Observer A 0	Observer A 1	
0	92	9	(84,2%)
1	3	16	(15,8%)
	(79,2%)	(20,8%)	

Kappa	0,667
Standard error	0,091
95% CI	0,489 to 0,846

Observer A	Créteil
Observer B	Cuneo

Observer B	Observer A 0	Observer A 1	
0	95	18	(94,2%)
1	0	7	(5,8%)
	(79,2%)	(20,8%)	

Kappa	0,381
Standard error	0,134
95% CI	0,117 to 0,645

Landis and Koch scale	
0.81 – 1.00	almost perfect
0.61 – 0.80	substantial
0.41 – 0.60	moderate
0.21 – 0.40	fair
0.00 – 0.20	slight
< 0	no agreement

Overall Kappa (Fleiss)
(3 obs.) $\kappa = 0.50$

Observer A	Dijon
Observer B	Cuneo

Observer B	Observer A 0	Observer A 1	
0	100	13	(94,2%)
1	1	6	(5,8%)
	(84,2%)	(15,8%)	

Kappa	0,411
Standard error	0,148
95% CI	0,122 to 0,701

Quantification
ΔSUV (cut-off >66%)
Kappa (Cohen)

Observer A	Créteil
Observer B	Dijon

Observer B	Observer A		
	0	1	
0	91	3	(78,3%)
1	2	24	(21,7%)
	(77,5%)	(22,5%)	

Kappa	0,879
Standard error	0,053
95% CI	0,775 to 0,983

Observer A	Créteil
Observer B	Cuneo

Observer B	Observer A		
	0	1	
0	89	5	(78,3%)
1	4	22	(21,7%)
	(77,5%)	(22,5%)	

Kappa	0,782
Standard error	0,070
95% CI	0,645 to 0,919

Landis and Koch scale	
0.81 – 1.00	almost perfect
0.61 – 0.80	substantial
0.41 – 0.60	moderate
0.21 – 0.40	fair
0.00 – 0.20	slight
< 0	no agreement

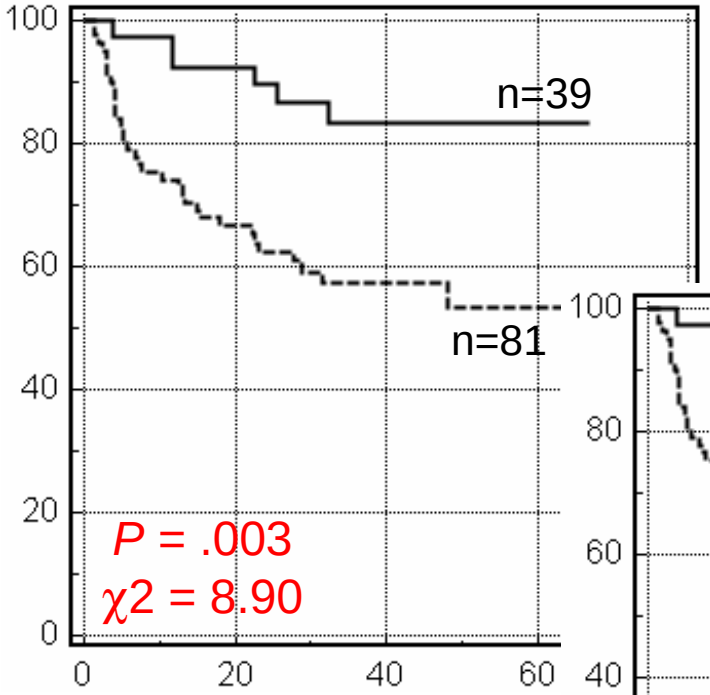
Overall Kappa (Fleiss)
(3 obs.) $\kappa = 0.81$

Observer A	Dijon
Observer B	Cuneo

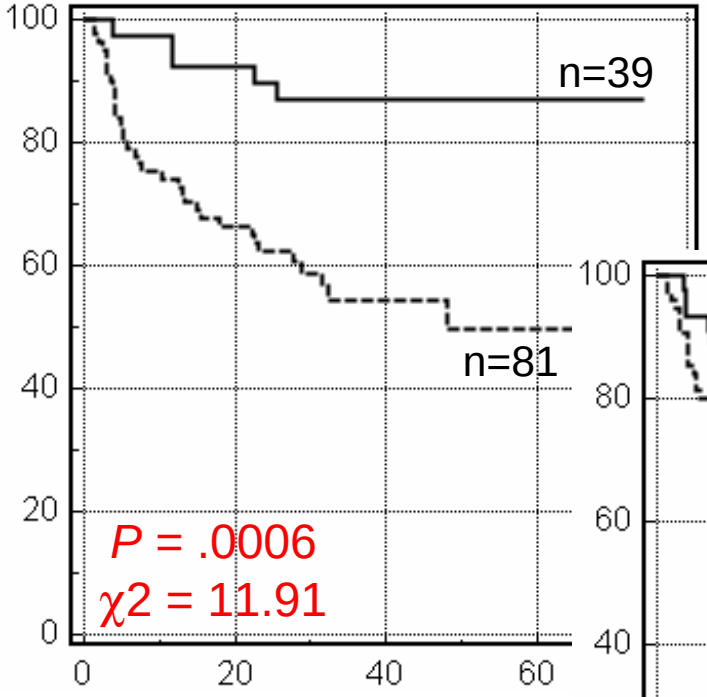
Observer B	Observer A		
	0	1	
0	89	5	(78,3%)
1	5	21	(21,7%)
	(78,3%)	(21,7%)	

Kappa	0,755
Standard error	0,074
95% CI	0,609 to 0,900

5-point scale (cut-off ≥3, MBP) Event-free survival

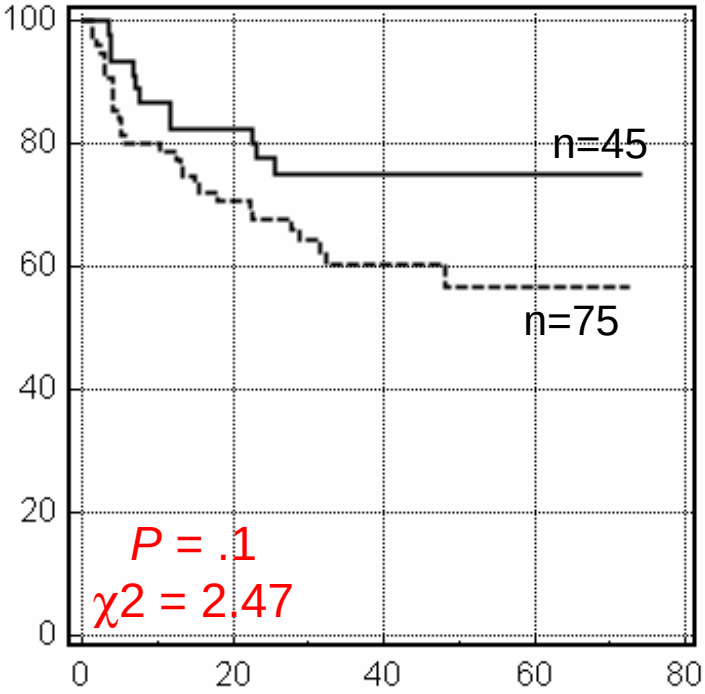


Créteil :
2-y EFS : 89.7% vs. 62.4%
HR : 0.291 (CI 0.198-0.715



Dijon :
2-y EFS : 89.7% vs. 62.2%
HR : 0.225 (CI 0.170-0.614

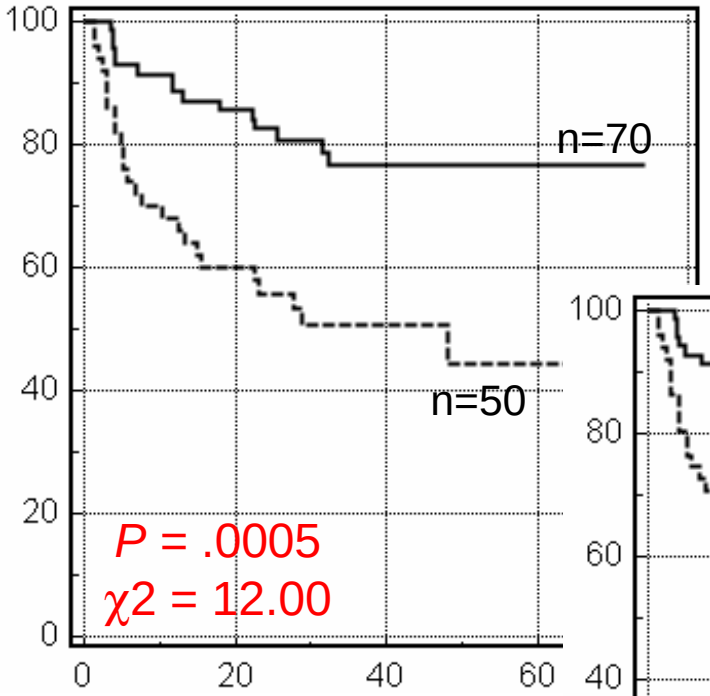
# of events = 40
Median f-u = 39.8 mo
(12.0-74.2 mo)



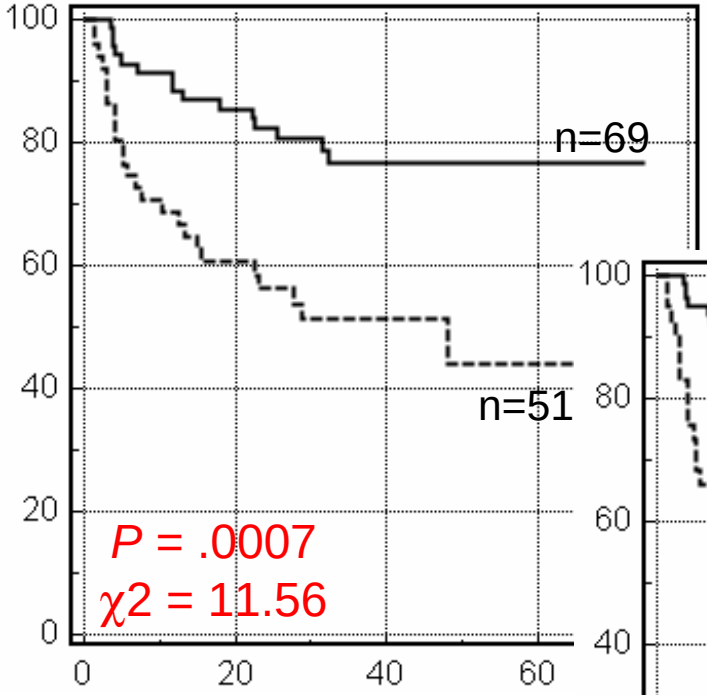
Cuneo :
2-y EFS : 77.5% vs. 67.7%
HR : 0.578 (CI 0.319-1.134)

→ Generates false-positives

5-point scale (cut-off ≥4, liver) Event-free survival

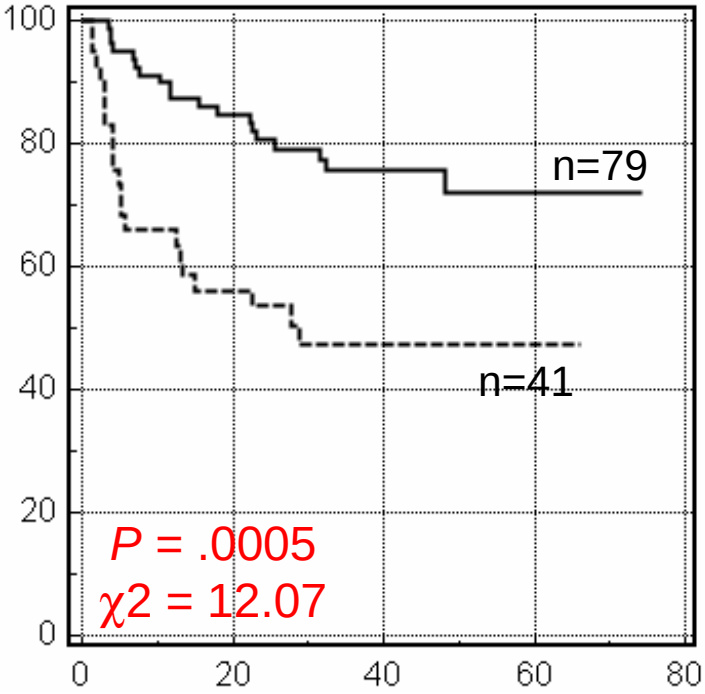


Créteil :
2-y EFS : 82.5% vs. 55.7%
HR : 0.341 (CI 0.167-0.609



Dijon :
2-y EFS : 82.3% vs. 56.4%
HR : 0.348 (CI 0.171-0.622

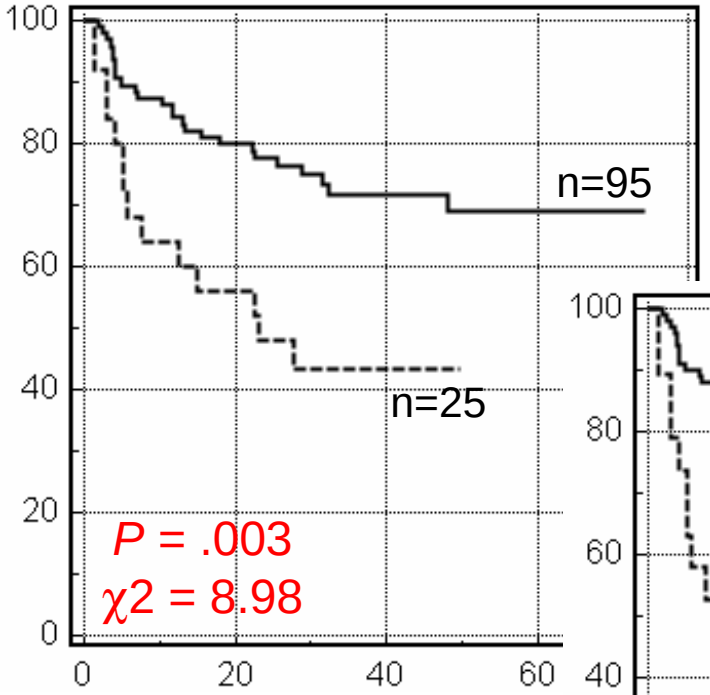
# of events = 40
Median f-u = 39.8 mo
(12.0-74.2 mo)



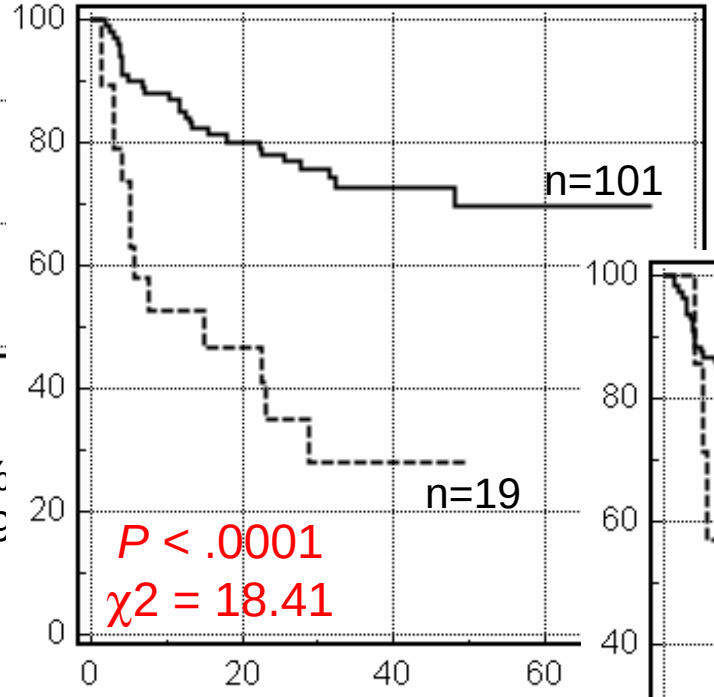
Cuneo :
2-y EFS : 80.6% vs. 53.5%
HR : 0.351 (CI 0.146-0.585)

→ Reduction of false-positives

5-point scale
(cut-off ≥5, >>liver)
Event-free survival

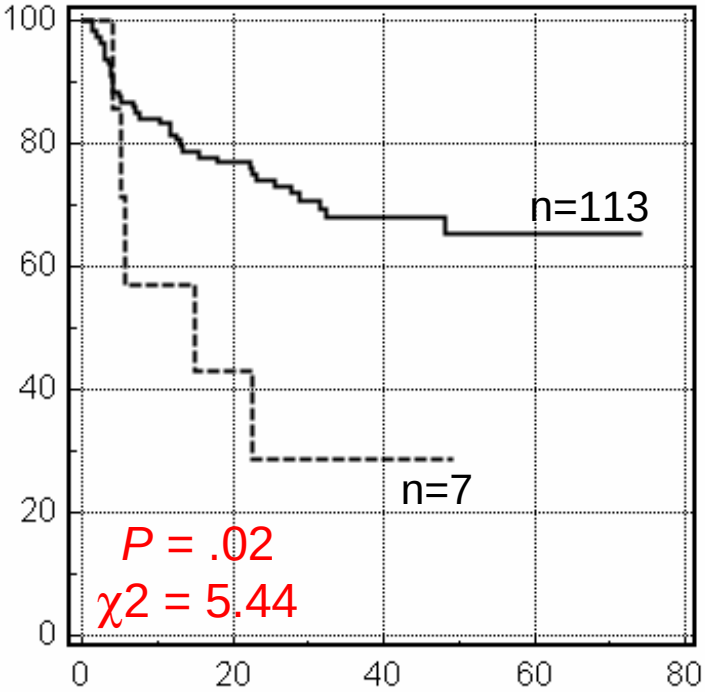


Créteil :
2-y EFS : 77.6% vs. 48.0%
HR : 0.453 (CI 0.157-0.849



Dijon :
2-y EFS : 78.0% vs. 35.1%
HR : 0.262 (CI 0.043-0.309)

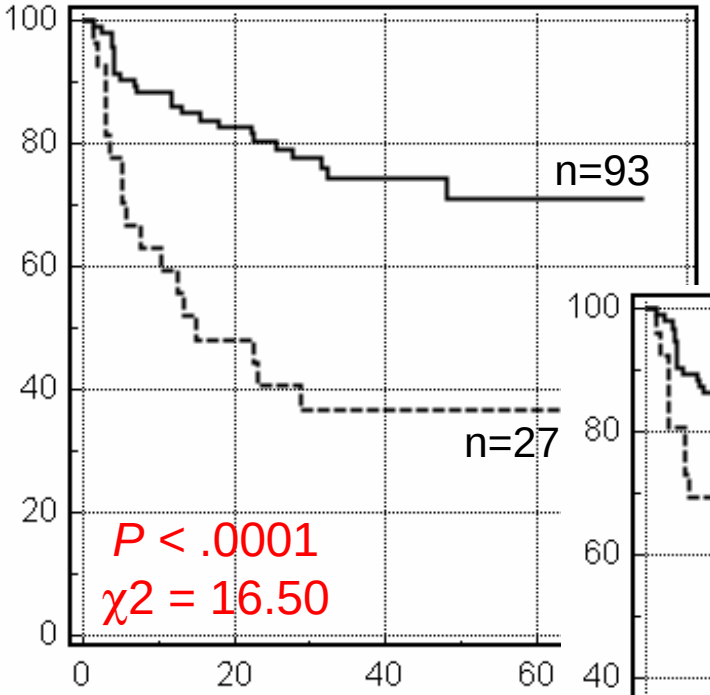
# of events = 40
Median f-u = 39.8 mo
(12.0-74.2 mo)



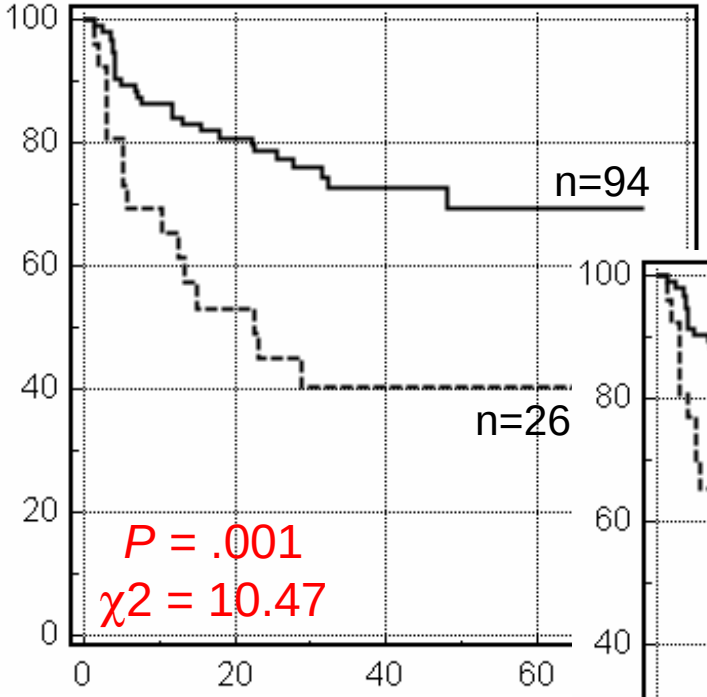
Cuneo :
2-y EFS : 74.0% vs. 28.6%
HR : 0.346 (CI 0.040-0.757)

→ Increase of false-negatives

Quantification
ΔSUV (cut-off >66%)
Event-free survival

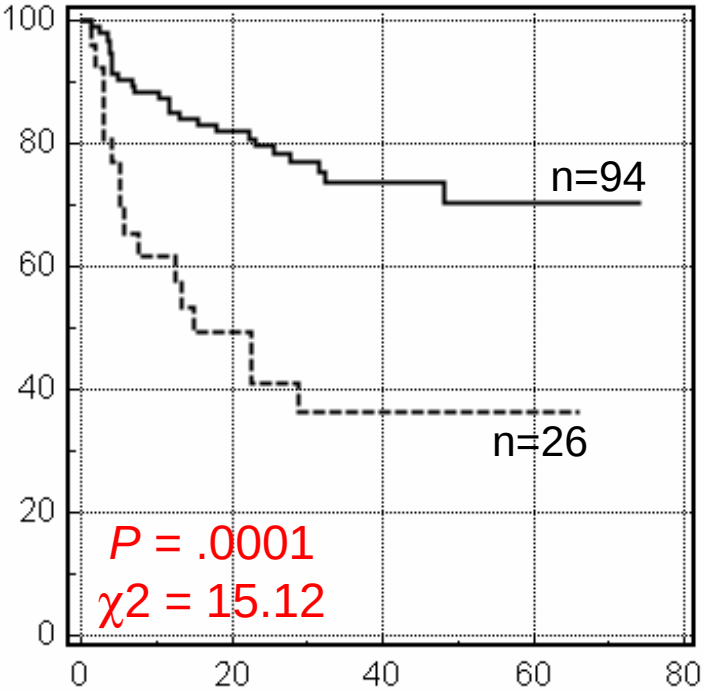


Créteil :
2-y EFS : 80.4% vs. 40.7%
HR : 0.296 (CI 0.083-0.419



Dijon :
2-y EFS : 78.5% vs. 45.0%
HR : 0.364 (CI 0.117-0.590

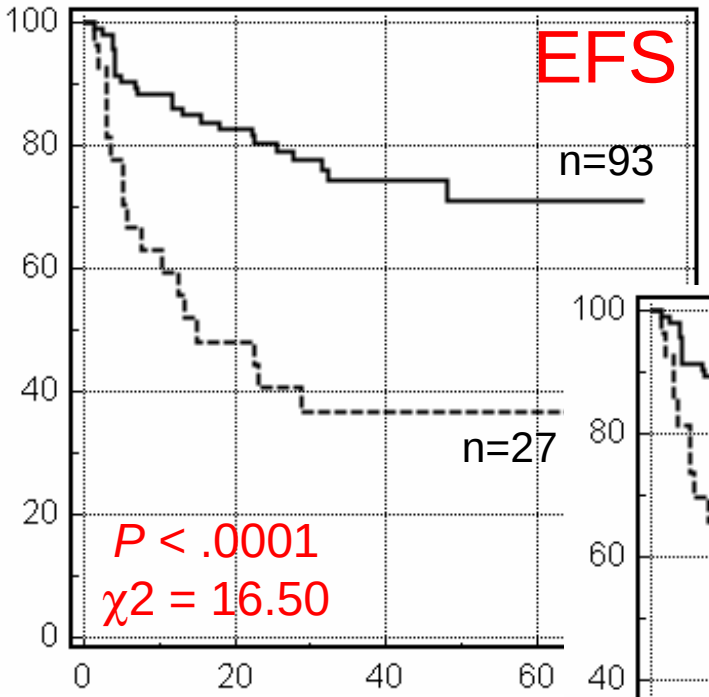
# of events = 40
Median f-u = 39.8 mo
(12.0-74.2 mo)



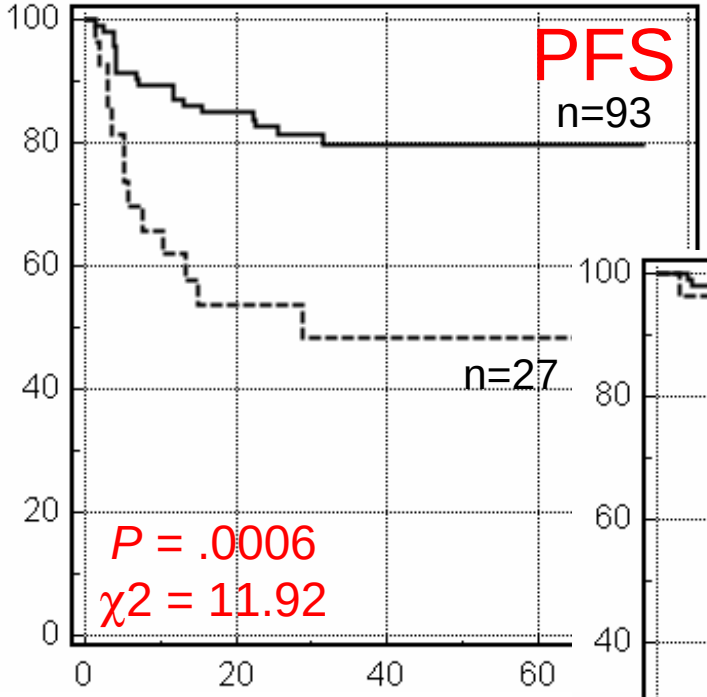
Cuneo :
2-y EFS : 79.6% vs. 41.0%
HR : 0.307 (CI 0.084-0.443)

→ Better agreement
between observers

Quantification
ΔSUV (cut-off >66%)
EFS, PFS, OS

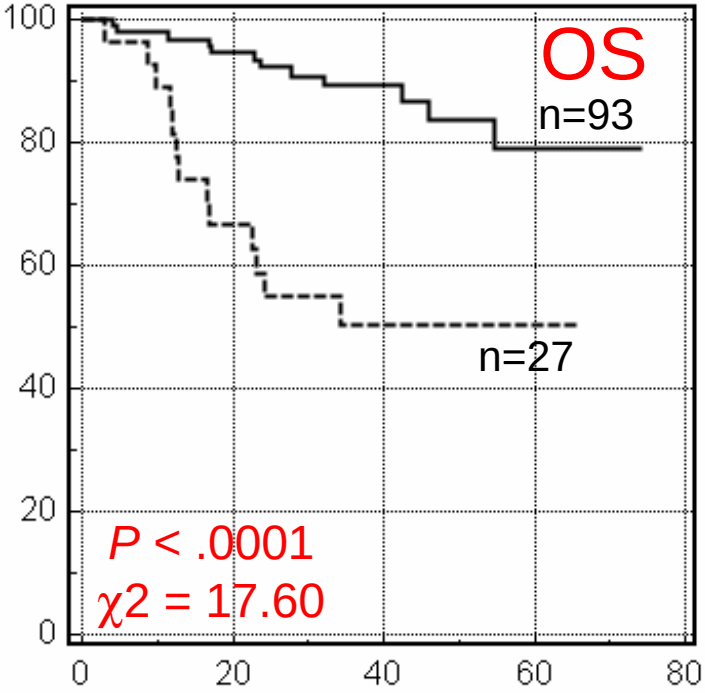


Créteil :
2-y EFS : 80.4% vs. 40.7%
HR : 0.296 (CI 0.083-0.419



Créteil :
2-y PFS : 82.5% vs. 53.7%
HR : 0.307 (CI 0.080-0.497

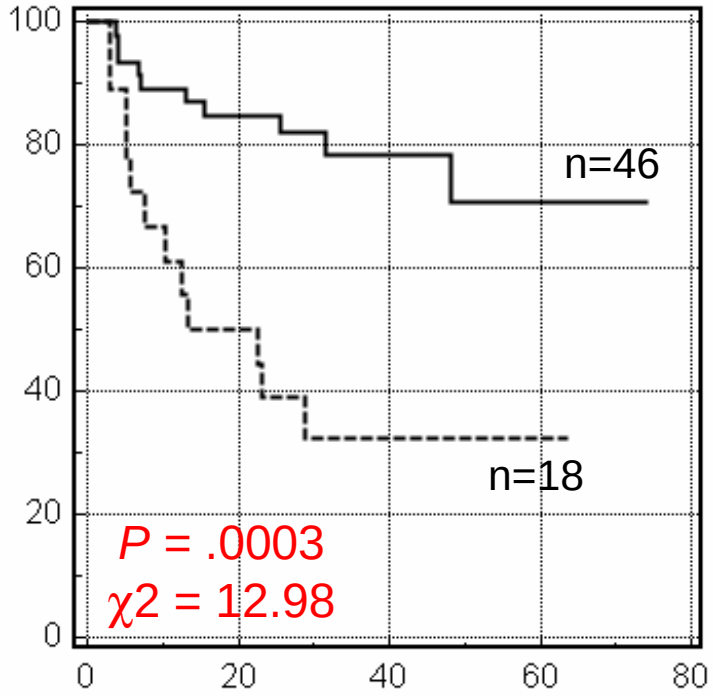
# of events = 40
Median f-u = 39.8 mo
(12.0-74.2 mo)



Créteil :
2-y OS : 92.2% vs. 54.9%
HR : 0.218 (CI 0.043-0.320)

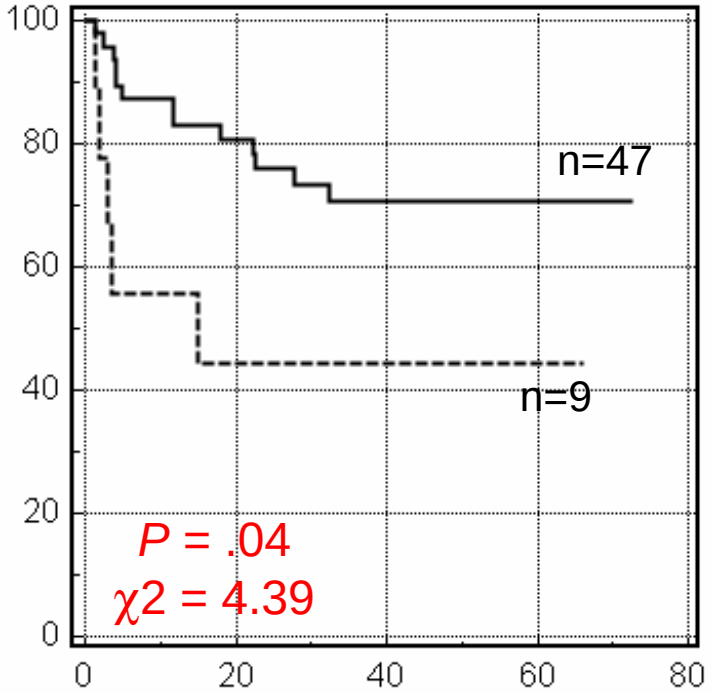
Quantification
ΔSUV (cut-off >66%)
R-CHOP21 vs DI/DD

R-CHOP21 (n=64)



Créteil :
2-y EFS : 84.7% vs. 38.9%
HR : 0.243 (CI 0.058-0.431)

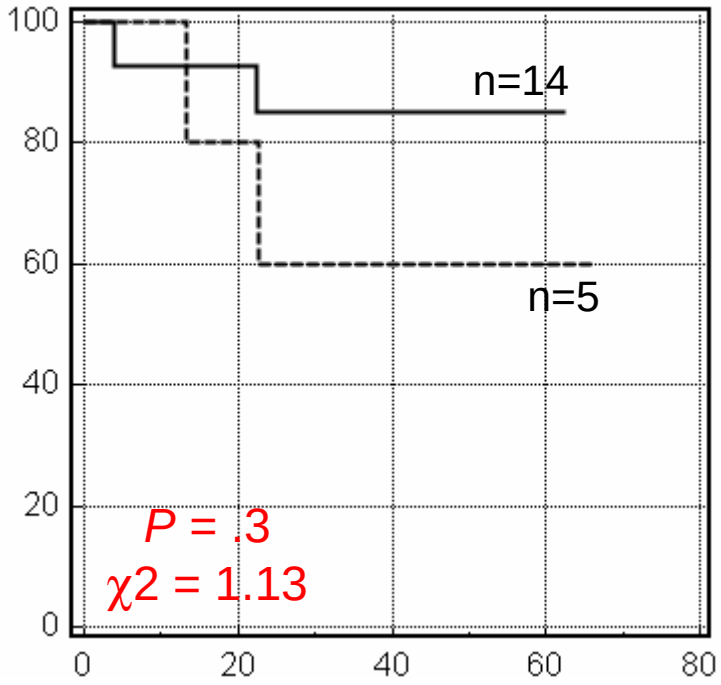
R-CHOP14/R-ACVBP (n=56)



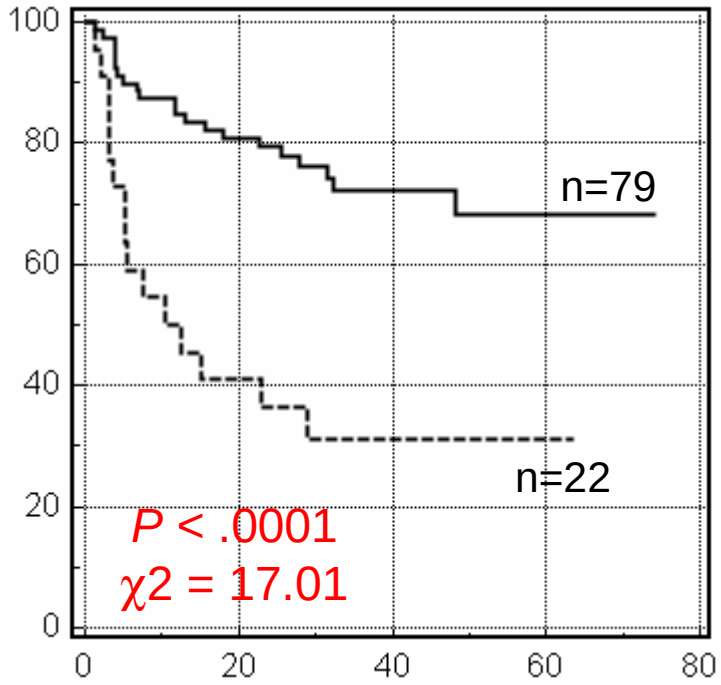
Créteil :
2-y EFS : 76.1% vs. 44.4%
HR : 0.350 (CI 0.052-0.906)

Quantification
ΔSUV (cut-off >66%)
ASCT vs noASCT

ASCT (n=19)

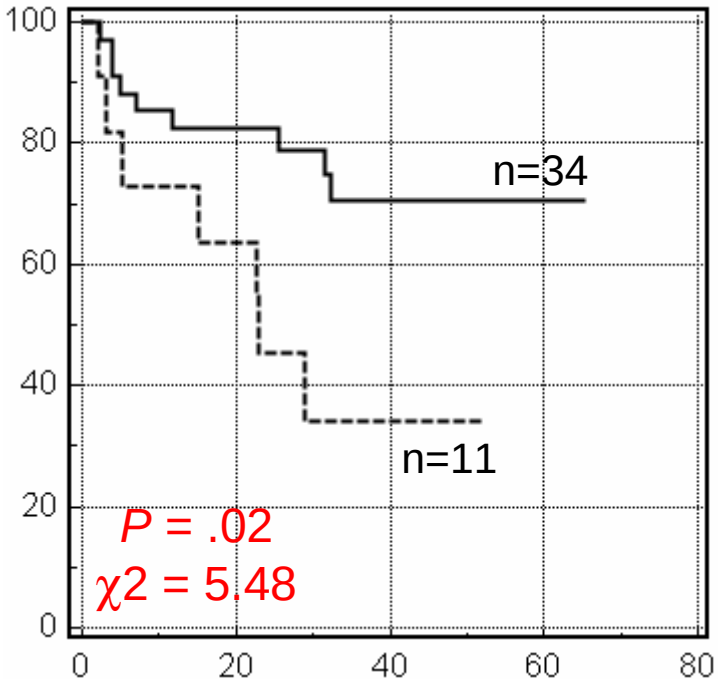


noASCT (n=101)

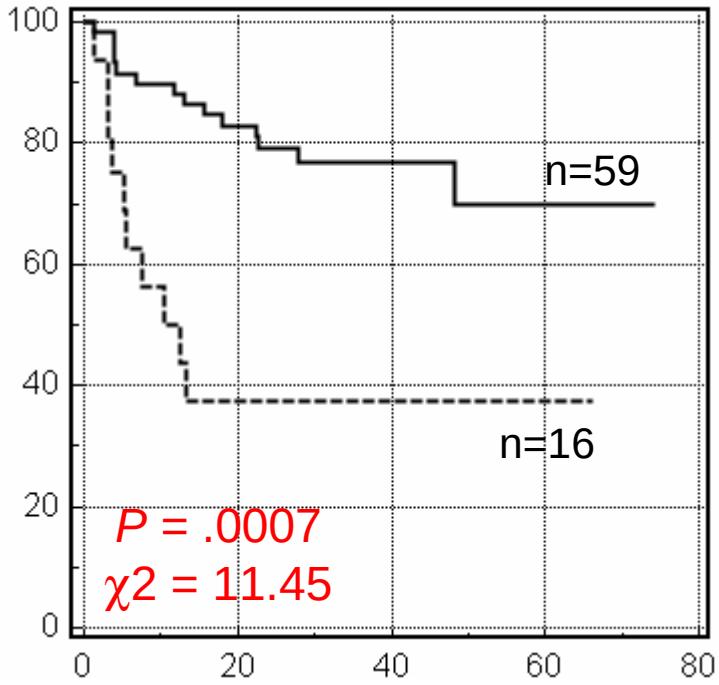


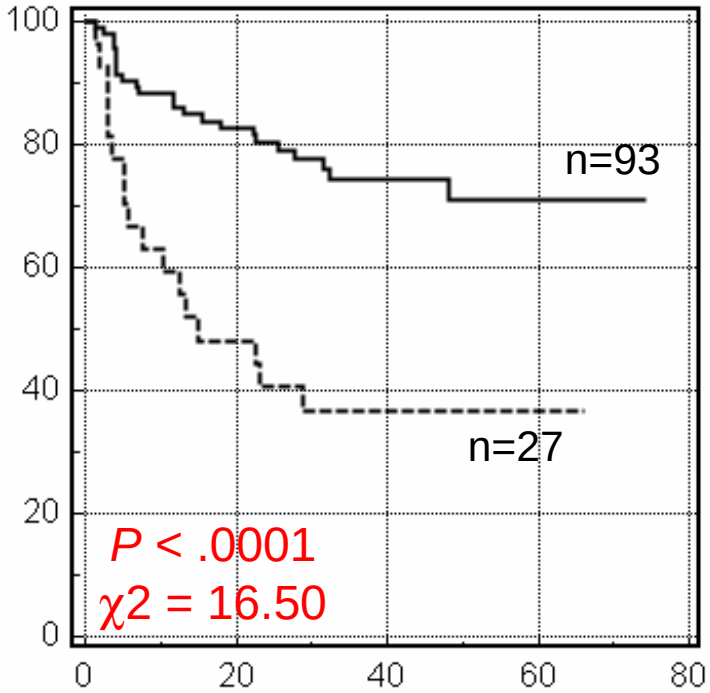
Quantification
ΔSUV (cut-off >66%)
aaIPI 0-1 vs 2-3

aaIPI 0-1 (n=45)

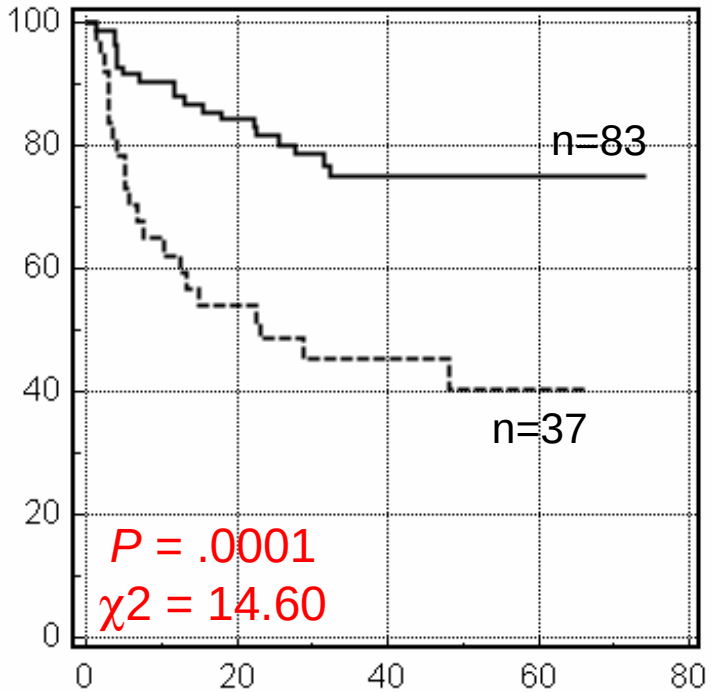


aaIPI 2-3 (n=75)



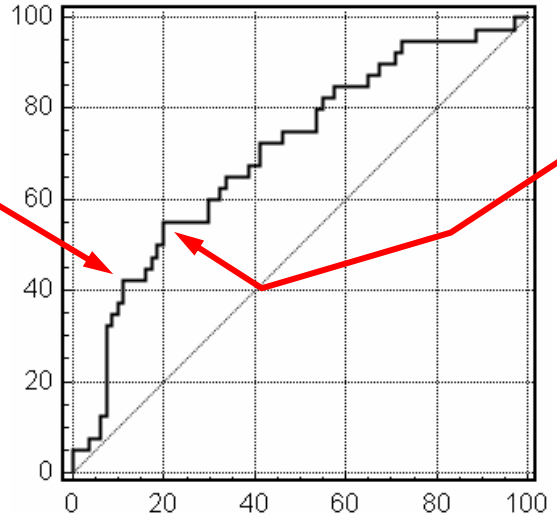


Créteil :
2-y EFS : 80.4% vs. 40.7%
HR : 0.296 (CI 0.083-0.419)



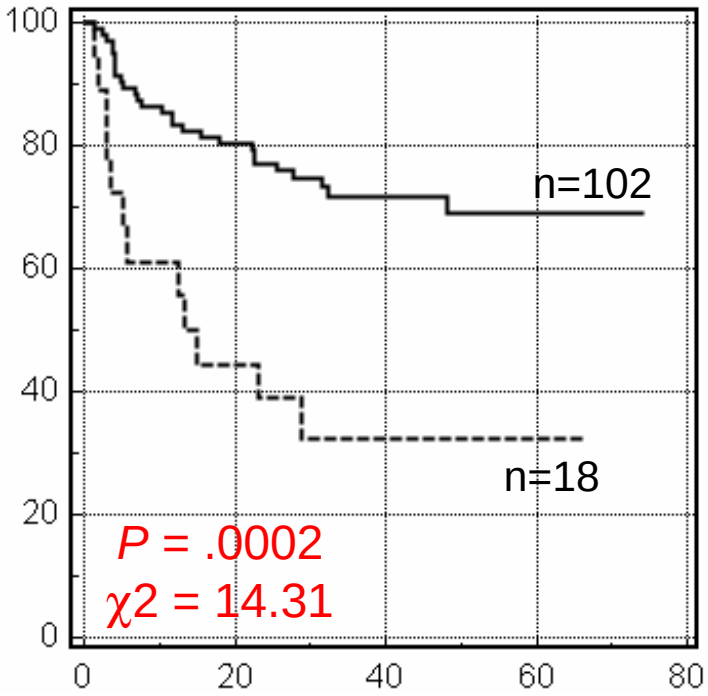
Créteil :
2-y EFS : 81.6% vs. 48.6%
HR : 0.319 (CI 0.124-0.510)

66% cutoff

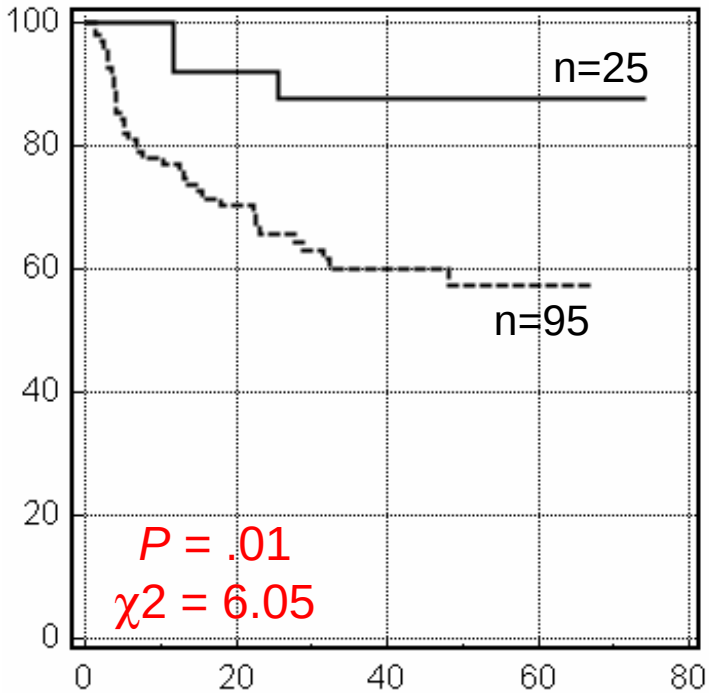


ROC-optimized cutoff : 73.7

→ no better cutoff

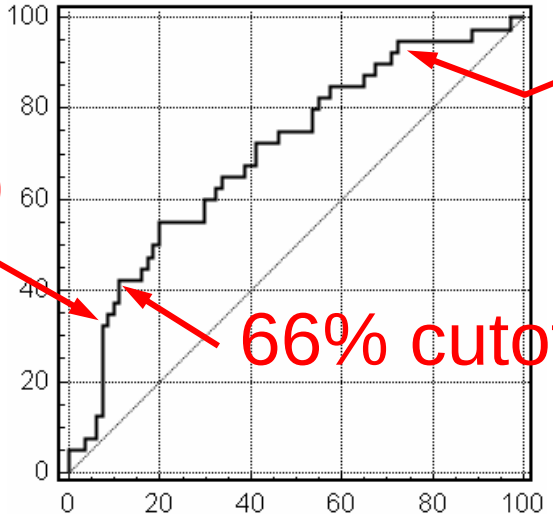


Créteil :
2-y EFS : 77.1% vs. 38.9%
HR : 0.294 (CI 0.056-0.400)



Créteil :
2-y EFS : 92.0% vs. 65.8%
HR : 0.256 (CI 0.194-0.831)

Best specificity
61% cutoff
(Se 33%, Sp 93%)



Best sensitivity
90% cutoff
(Se 95%, Sp 28%)

→ escalation vs
de-escalation

Quantification
125% SUV liver
Kappa (Cohen)

88pts

Observer A	Créteil
Observer B	Dijon

Observer B	Observer A 0	1	
0	63	6	(57,5%)
1	7	44	(42,5%)
	(58,3%)	(41,7%)	

Kappa	0,778
Standard error	0,058
95% CI	0,664 to 0,892

Observer A	Créteil
Observer B	Cuneo

Observer B	Observer A 0	1	
0	64	15	(65,8%)
1	6	35	(34,2%)
	(58,3%)	(41,7%)	

Kappa	0,630
Standard error	0,073
95% CI	0,487 to 0,774

Observer A	Dijon
Observer B	Cuneo

Observer B	Observer A 0	1	
0	61	18	(65,8%)
1	8	33	(34,2%)
	(57,5%)	(42,5%)	

Kappa	0,545
Standard error	0,079
95% CI	0,390 to 0,700

Landis and Koch scale	
0.81 – 1.00	almost perfect
0.61 – 0.80	substantial
0.41 – 0.60	moderate
0.21 – 0.40	fair
0.00 – 0.20	slight
< 0	no agreement

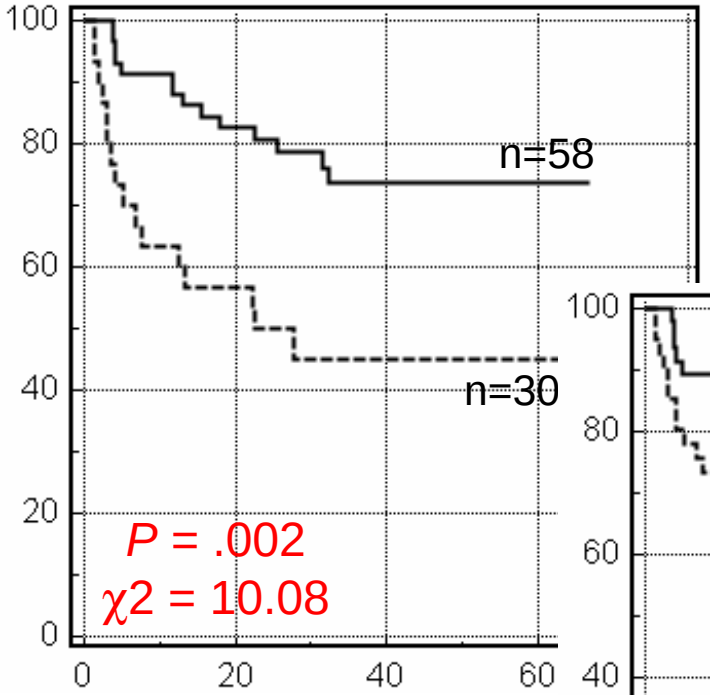
Overall Kappa (Fleiss)

Visual : $\kappa = 0.65$

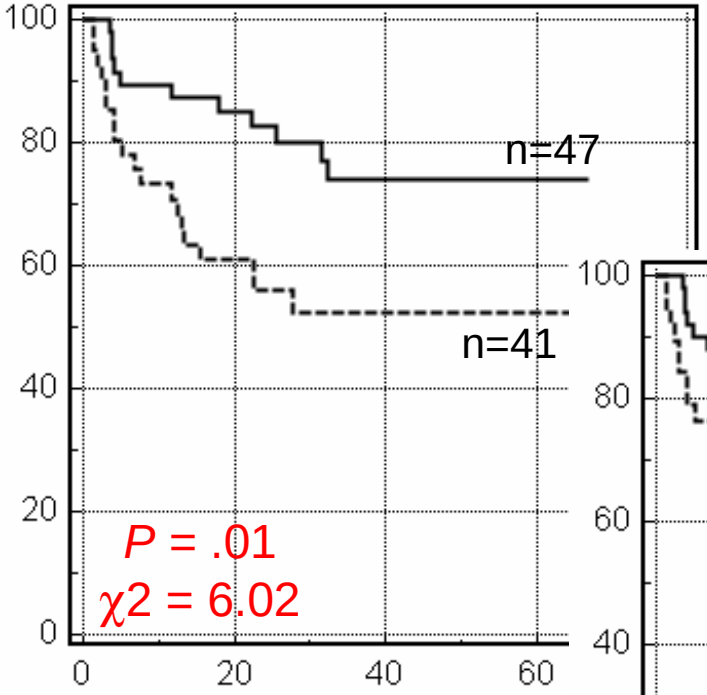
Quantit : $\kappa = 0.68$

Quantification
125% SUV liver
Event-free survival

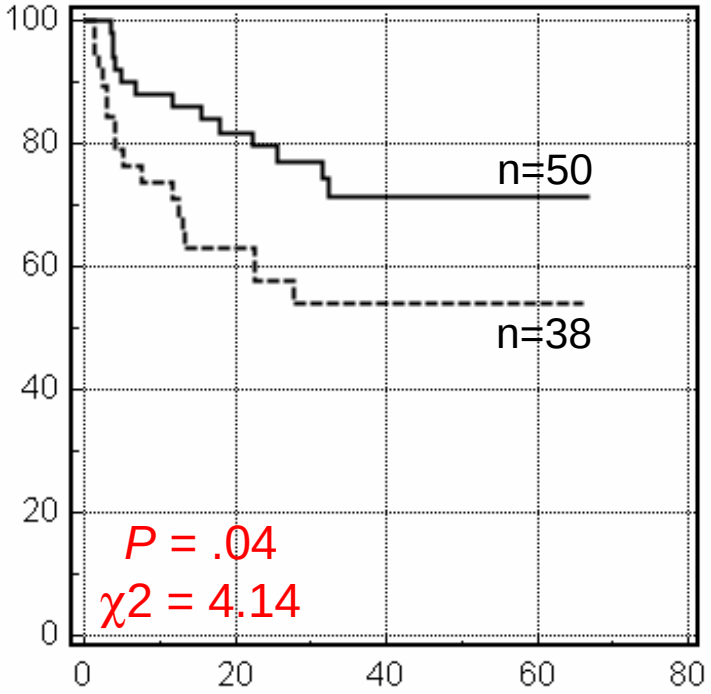
88pts



Créteil :
2-y EFS : 80.7% vs. 50.0%
HR : 0.333 (CI 0.121-0.607



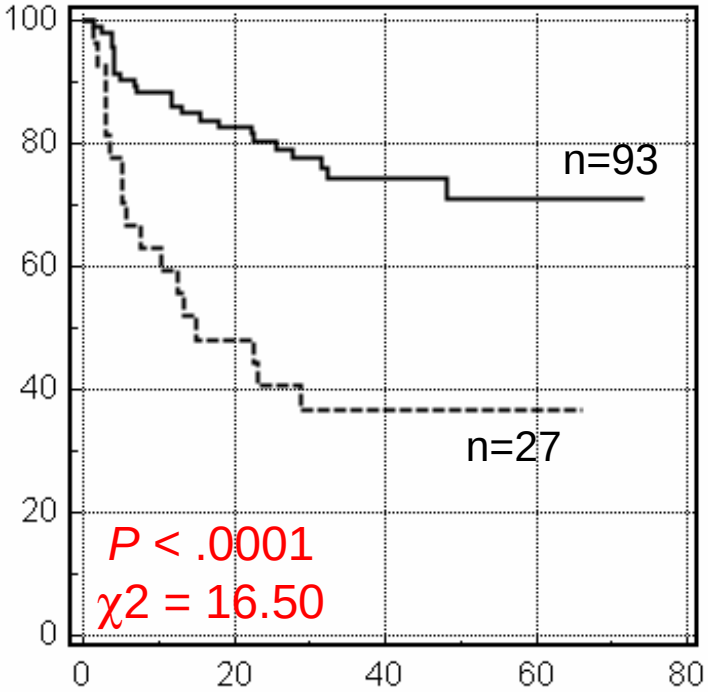
Dijon :
2-y EFS : 82.6% vs. 55.9%
HR : 0.409 (CI 0.194-0.832



Cuneo :
2-y EFS : 79.6% vs. 57.7%
HR : 0.481 (CI 0.223-0.972)

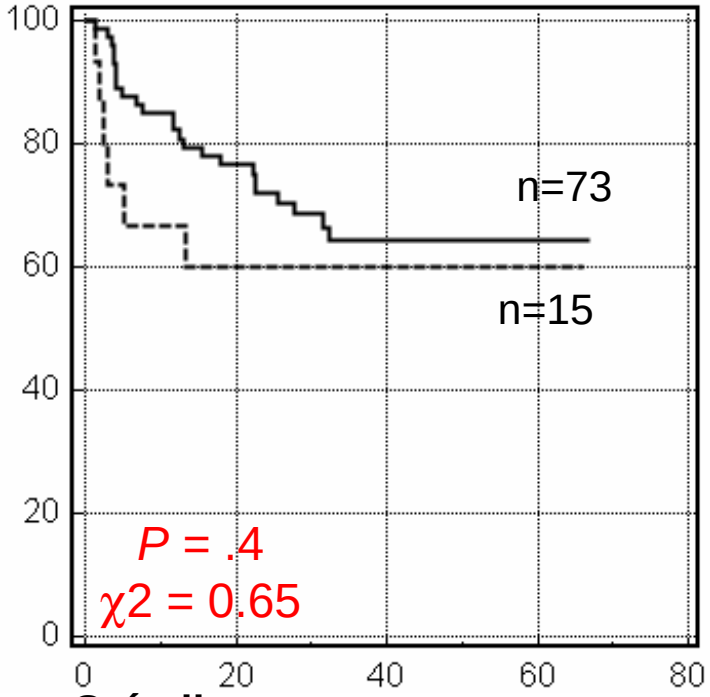
Normalization to MBP activity

Raw ΔSUV
(cutoff 66%)



Créteil :
2-y EFS : 80.4% vs. 40.7%
HR : 0.296 (CI 0.083-0.419)

ΔSUV / MBP
(cutoff 66%)



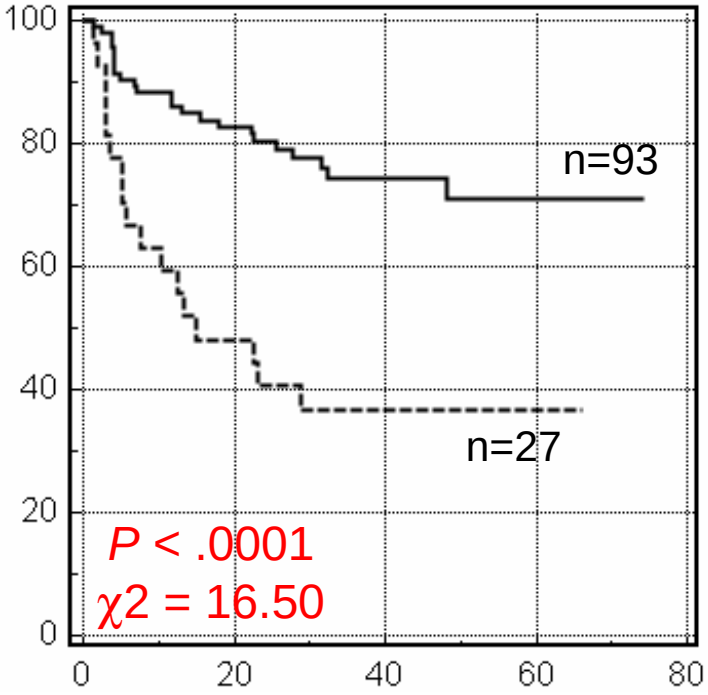
Créteil :
2-y EFS : 72.1% vs. 60.0%
HR : 0.695 (CI 0.241-1.814)

$$\Delta SUV = 100 \times \frac{SUV_{T1}/SUV_{M1} - SUV_{T2}/SUV_{M2}}{SUV_{T1}/SUV_{M1}}$$

88pts

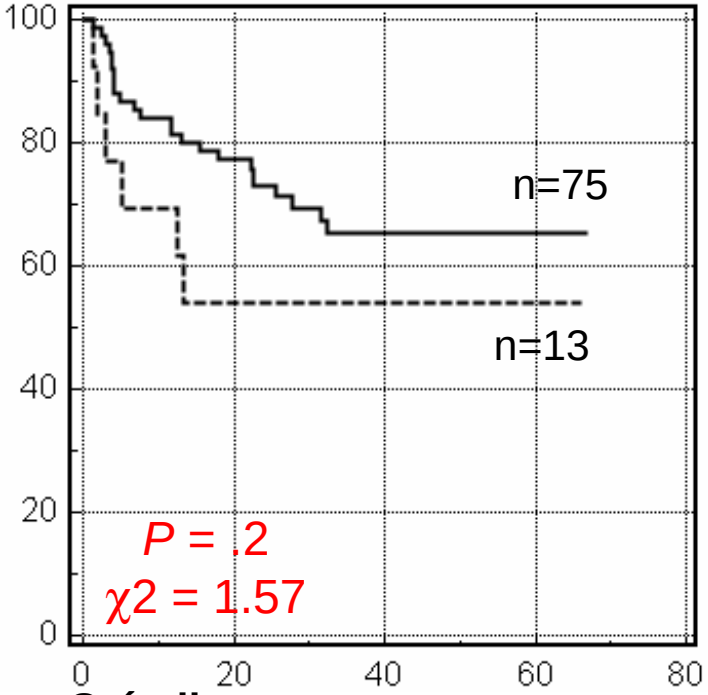
Normalization to liver activity

Raw ΔSUV
(cutoff 66%)



Créteil :
2-y EFS : 80.4% vs. 40.7%
HR : 0.296 (CI 0.083-0.419)

ΔSUV / liver
(cutoff 66%)



Créteil :
2-y EFS : 72.9% vs. 53.8%
HR : 0.570 (CI 0.169-1.480)

$$\Delta SUV = 100 \times \frac{SUV_{T1}/SUV_{L1} - SUV_{T2}/SUV_{L2}}{SUV_{T1}/SUV_{L1}}$$

88pts

Conclusions

- 120 patients/5 centers → stop, difficulty to recruit
- visual analysis (5PS) → moderate to substantial
  → best reference = liver
- quantitative (ΔSUV) → substantial to almost perfect
  → better prediction of EFS
- other types of NHL, other time points