Early interim PET (PET2) in diffuse large B-cell lymphoma (DLBCL) patients treated with R-CHOP

An International Validation Study (IVS)

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Deauville Criteria: Five points scale (5PS)

- 1. No uptake
- 2. Uptake ≤ mediastinum
- 3. Uptake > mediastinum but ≤ liver

- -

- 4. Uptake moderately increased above liver at any site
- 5. Markedly increased uptake at any site including new sites of disease

Purpose

- Predictive value of interim PET after 2 cycles of treatment, in a large prospective cohort of patients uniformly treated with R-CHOP **using Deauville Criteria?**

- **49 patients with newly diagnosed DLBCL**

- 4 centres (Rouen, Créteil, Cuneo, Dijon)

- May 2005 to July 2009

- Treatment: R-CHOP21 or R-CHOP14

Validation study: inclusion criteria

- DLBCL
- Therapy: R-CHOP (14 or 21) : 4 - 8 cycles
- Staging at baseline and after two courses of R-CHOP with PET-CT (PET-0 and PET-2)
- No treatment change depending on interim-PET results.
- Patients that have been treated with HDT followed by stem cell rescue for progressive /resistant lymphoma during R-CHOP chemotherapy are eligible only if HDT has been decided on evidence of persistent disease (clinical, histological or imaging data) **after at least 4 cycles** .
- PET scan performed with PET-CT technology
- PET-0 and PET-2 performed in the same PET center
- Agreement, by the nuclear team that have performed the scan to submit the studies to the central review panel and to upload the images on dicom format to the dedicated site for reviewing.

Patients characteristics

patients: n= 49	
Male	67%
Median age	58 y (23-76)
>60 y	18%
PS ≥ 2	22%
Ann Arbor III-IV	31%
LDH>1N	67%
>1 extranodal site	27%
IPI	
L (0-1F)	34%
L-I (2F)	24%
I-H (3F)	22%
H (4-5F)	20%

Treatments

IPI	R-CHOP14 n=23 (47%) n	R-CHOP21 n=26 (53%) n	Total
L (0-1 F)	4	12	16
L-I (2 F)	8	4	12
I-H (3 F)	6	5	11
H (4-5 F)	5	5	10

Treatment strategy

- **Induction: R-CHOP: 4 cycles**
- **PET after 2 cycles**
  - **R-CHOP14: median: 12 d (9-15)**
  - **R-CHOP21: median: 22 d (12-23)**
- **No impact of PET2 on therapeutic strategy**
- **Consolidation by age, aa-IPI, response at 4 cycles and local policies**

Consolidative treatment (after 4 cycles or more)

- **42 responding patients continued R-CHOP**
- **Four patients with bulky tumor received consolidative IF radiotherapy after 7-8 cycles**
- **Two patients progressed on the basis of IWC 99 criteria and were withdrawn from the study**
- **Five patients received high-dose chemotherapy followed by ASCT - after 3 cycles of RICE - on the basis of PET4 positive**

Analysis

- Median follow-up: 24 months

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

Methods

- 49 IVS patients from 4 PET centers
  (Créteil n=15; Dijon n=14; Cuneo n=11; Rouen n=9)
- PET/CT at baseline and 2 cycles
- Interpretation by 3 observers using the 5PS
- Transfers/readings on Positoscope workstations
- Inter-observer agreement (Kappa)
- Quantification with ΔSUV (66% cut-off)

5-point scale
weighted Kappa (Cohen)

Observer A	Créteil
Observer B	Dijon

Observer B	Observer A 1	2	3	4	5	
1	4	1	2	0	1	(16,3%)
2	3	4	0	0	0	(14,3%)
3	0	1	6	0	0	(14,3%)
4	0	1	1	7	2	(22,4%)
5	1	0	0	2	13	(32,7%)
	(16,3%)	(14,3%)	(18,4%)	(18,4%)	(32,7%)	

Weighted Kappa	0,744
Standard error (Kw'=0)	0,143
Standard error (Kw'#0)	

Observer A	Créteil
Observer B	Cuneo

Observer B	Observer A 1	2	3	4	5	
1	5	0	2	0	2	(18,4%)
2	3	5	2	1	2	(26,5%)
3	0	2	5	5	1	(26,5%)
4	0	0	0	3	7	(20,4%)
5	0	0	0	0	4	(8,2%)
	(16,3%)	(14,3%)	(18,4%)	(18,4%)	(32,7%)	

Weighted Kappa	0,568
Standard error (Kw'=0)	0,126
Standard error (Kw'#0)	

Observer A	Dijon
Observer B	Cuneo

Observer B	Observer A 1	2	3	4	5	
1	5	2	1	0	1	(18,4%)
2	2	4	3	1	3	(26,5%)
3	1	1	3	8	0	(26,5%)
4	0	0	0	2	8	(20,4%)
5	0	0	0	0	4	(8,2%)
	(16,3%)	(14,3%)	(14,3%)	(22,4%)	(32,7%)	

Weighted Kappa	0,604
Standard error (Kw'=0)	0,125
Standard error (Kw'#0)	0,099

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

Observer A	Créteil
Observer B	Dijon

Observer B	Observer A		
	0	1	
0	12	3	(30,6%)
1	3	31	(69,4%)
	(30,6%)	(69,4%)	

Kappa	0,712
Standard error	0,110
95% CI	0,496 to 0,928

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

Observer A	Créteil
Observer B	Cuneo

Observer B	Observer A		
	0	1	
0	13	9	(44,9%)
1	2	25	(55,1%)
	(30,6%)	(69,4%)	

Kappa	0,533
Standard error	0,124
95% CI	0,289 to 0,776

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

Overall Kappa (Fleiss)
(3 obs.) $\kappa = 0.58$

Observer A	Dijon
Observer B	Cuneo

Observer B	Observer A		
	0	1	
0	13	9	(44,9%)
1	2	25	(55,1%)
	(30,6%)	(69,4%)	

Kappa	0,533
Standard error	0,124
95% CI	0,289 to 0,776

Observer A	Créteil
Observer B	Dijon

Observer B	Observer A		
	0	1	
0	21	1	(44,9%)
1	3	24	(55,1%)
	(49,0%)	(51,0%)	

Kappa	0,836
Standard error	0,078
95% CI	0,683 to 0,990

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

Observer A	Créteil
Observer B	Cuneo

Observer B	Observer A		
	0	1	
0	24	11	(71,4%)
1	0	14	(28,6%)
	(49,0%)	(51,0%)	

Kappa	0,555
Standard error	0,118
95% CI	0,323 to 0,787

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

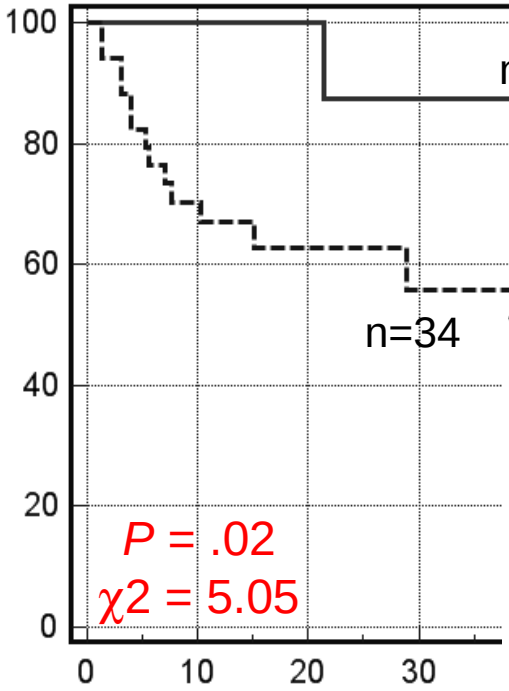
Overall Kappa (Fleiss)
(3 obs.) $\kappa = 0.61$

Observer A	Dijon
Observer B	Cuneo

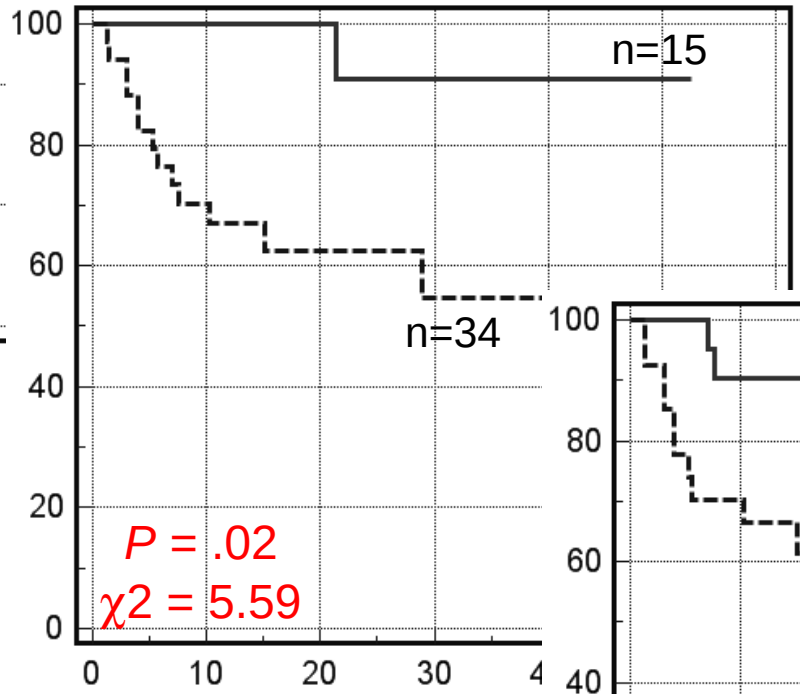
Observer B	Observer A		
	0	1	
0	22	13	(71,4%)
1	0	14	(28,6%)
	(44,9%)	(55,1%)	

Kappa	0,492
Standard error	0,121
95% CI	0,255 to 0,728

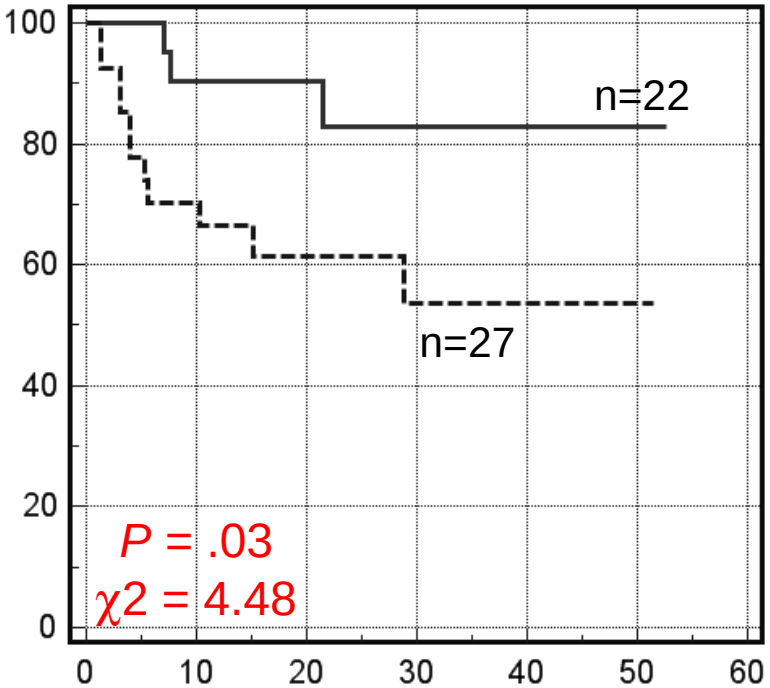
5-point scale (cut-off ≥3, MBP) Event-free survival



Créteil :
2-y EFS : 88% vs. 63%



Dijon :
2-y EFS : 91% vs. 63%

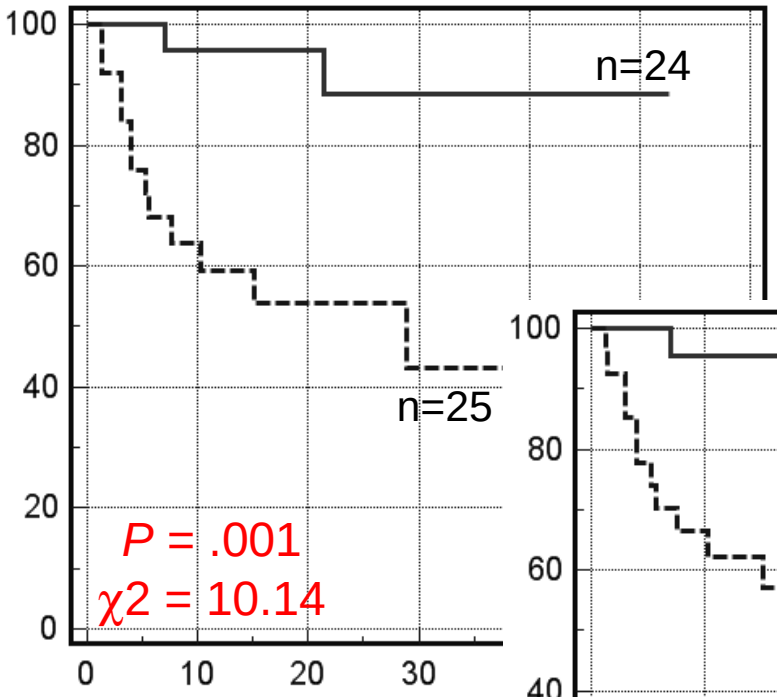


Cuneo :
2-y EFS : 83% vs. 61%

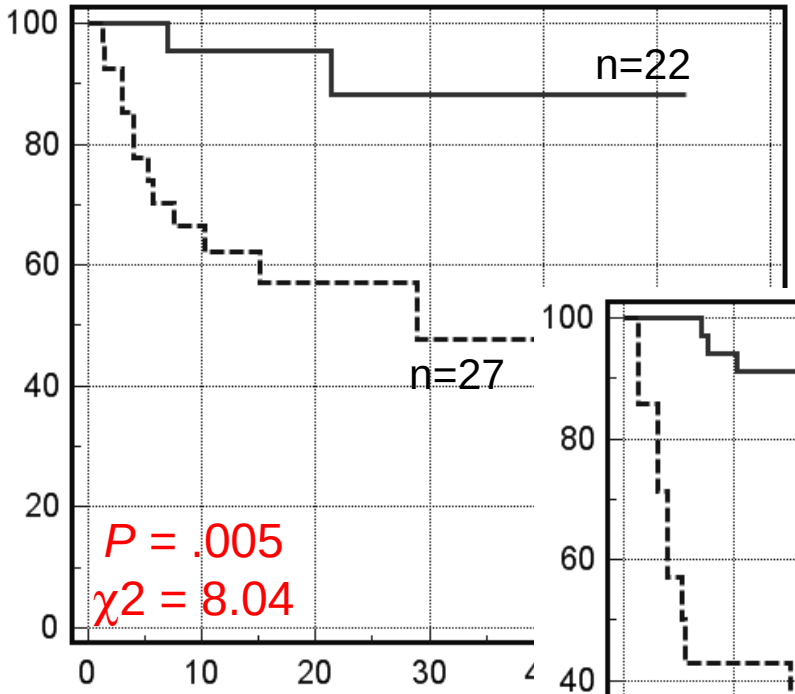
# of events = 14
Median f-u = 25 mo

→ Generates false-positives

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

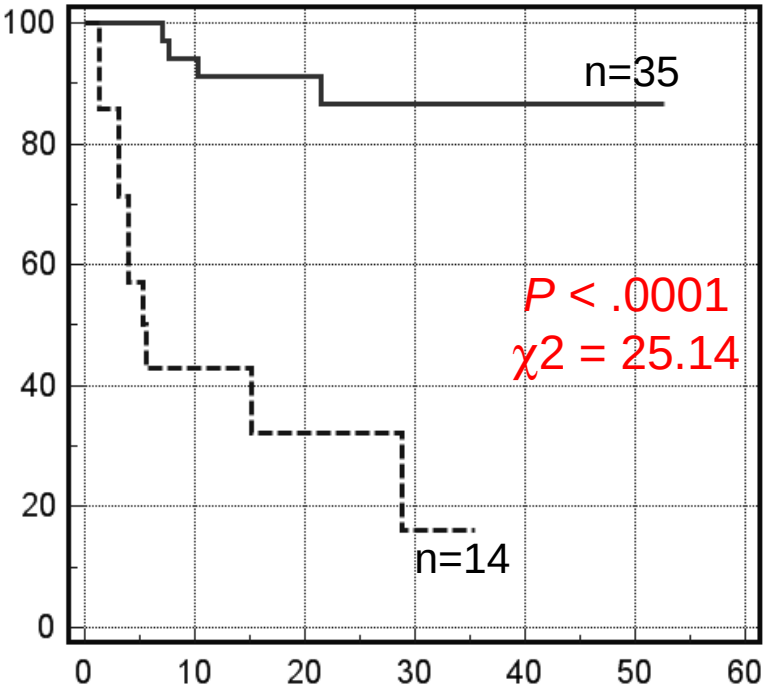


Créteil :
2-y EFS : 89% vs. 54%



Dijon :
2-y EFS : 88% vs. 57%

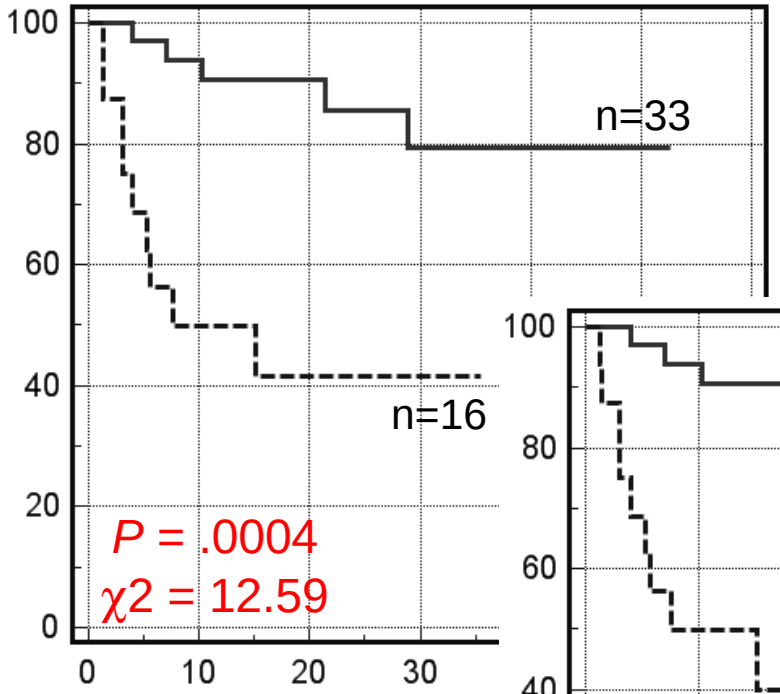
# of events = 14
Median f-u = 25 mo



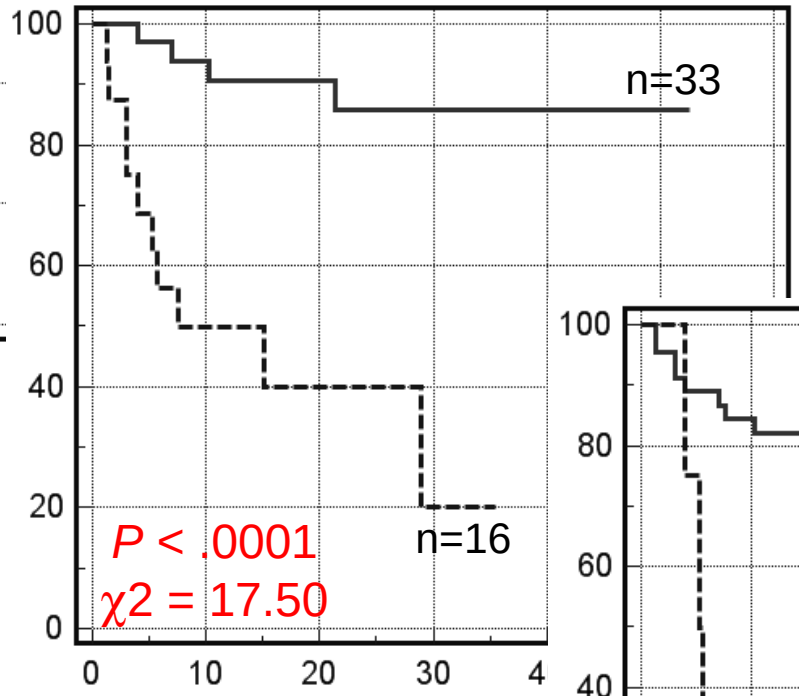
Cuneo :
2-y EFS : 87% vs. 32%

→ Reduction of false-positives
→ Cuneo's interpretation ++

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

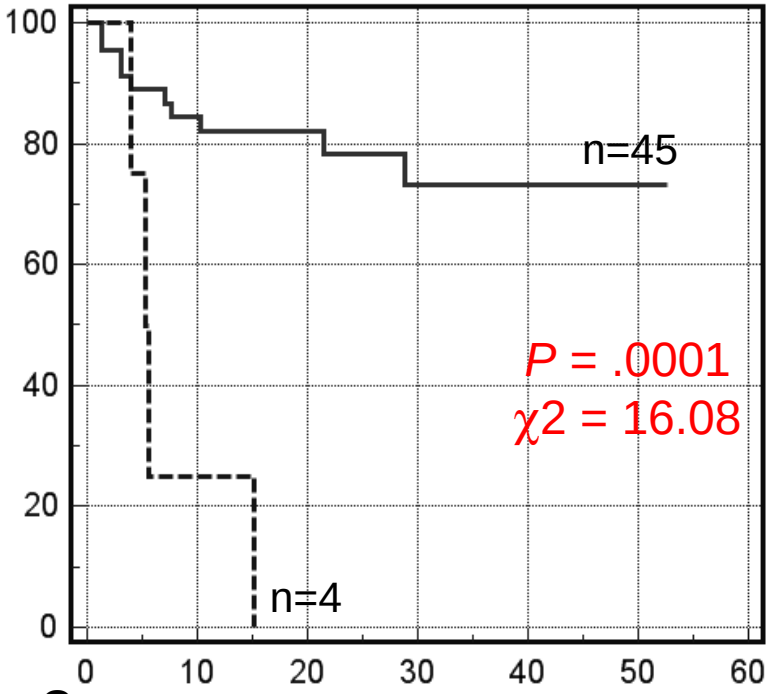


Créteil :
2-y EFS : 86% vs. 42%



Dijon :
2-y EFS : 86% vs. 40%

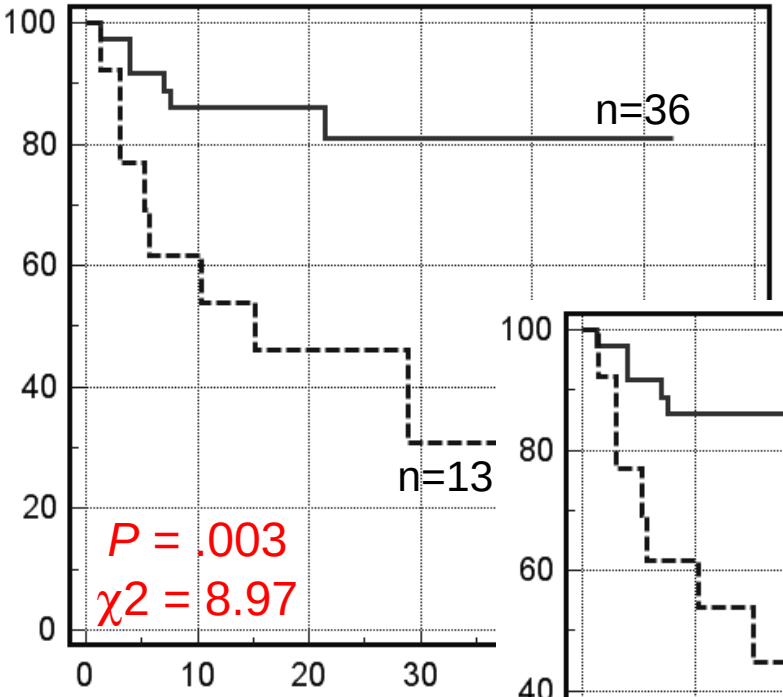
# of events = 14
Median f-u = 25 mo



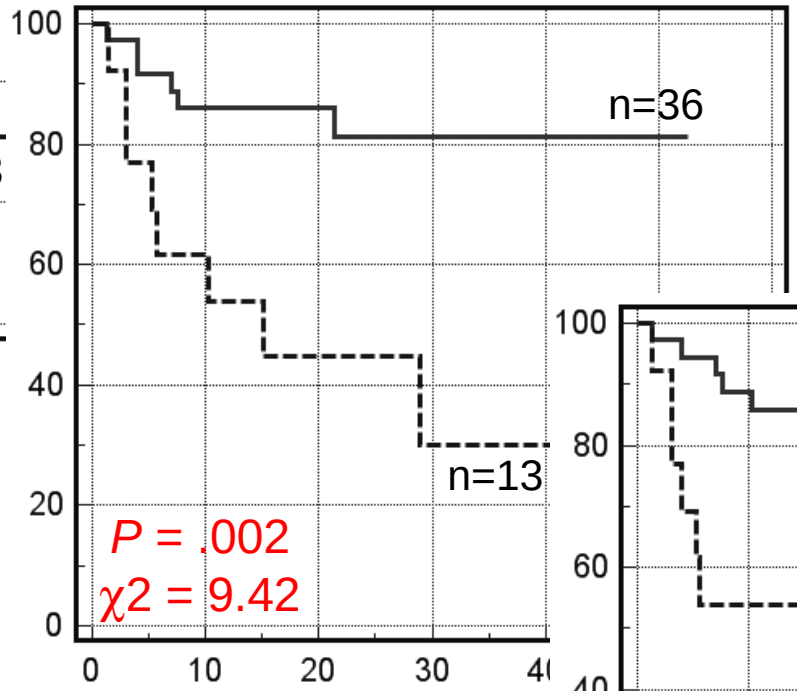
Cuneo :
2-y EFS : 78% vs. 0%

→ Créteil-Dijon's interpretations ++
→ Cuneo : generates false-negatives

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

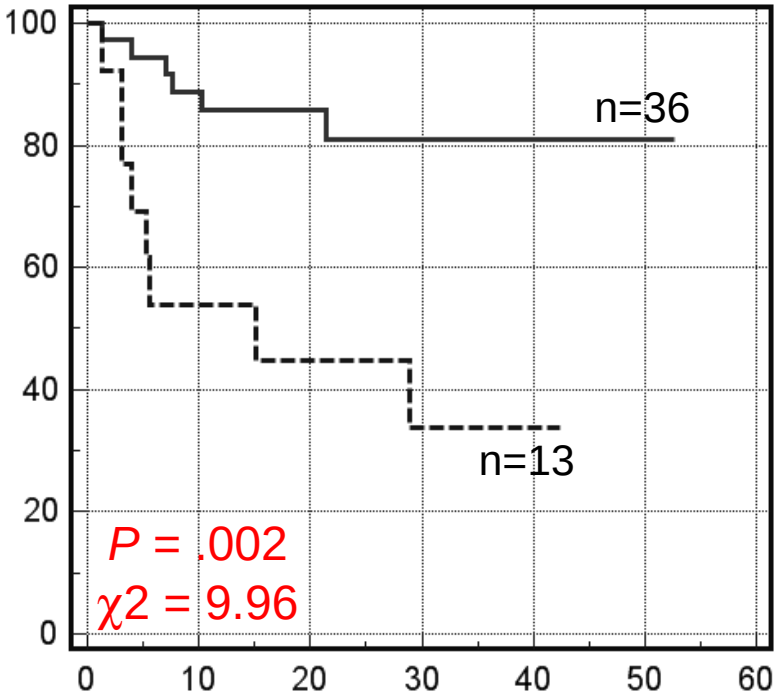


Créteil :
2-y EFS : 81% vs. 46%



Dijon :
2-y EFS : 81% vs. 45%

# of events = 14
Median f-u = 25 mo

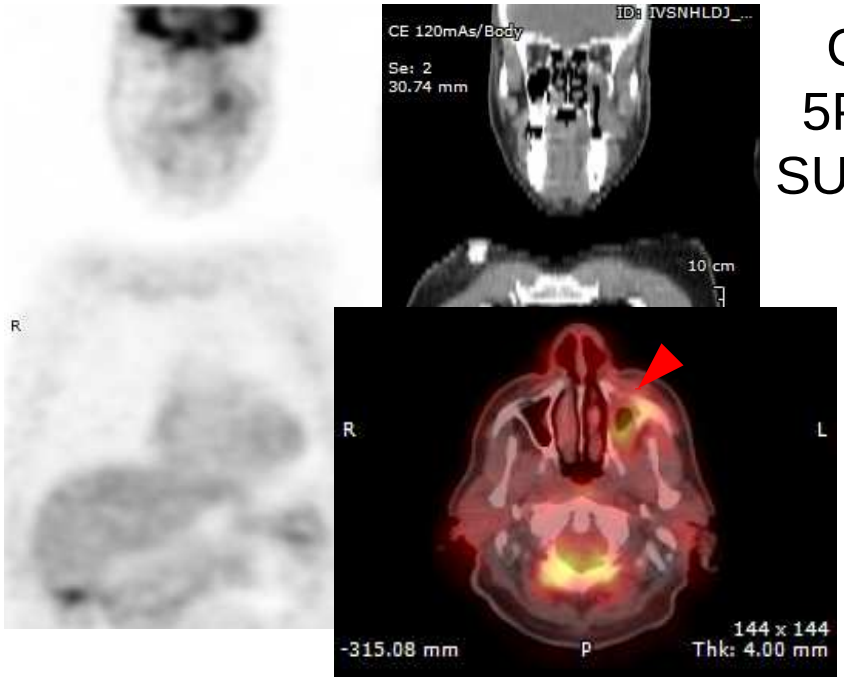


Cuneo :
2-y EFS : 81% vs. 45%

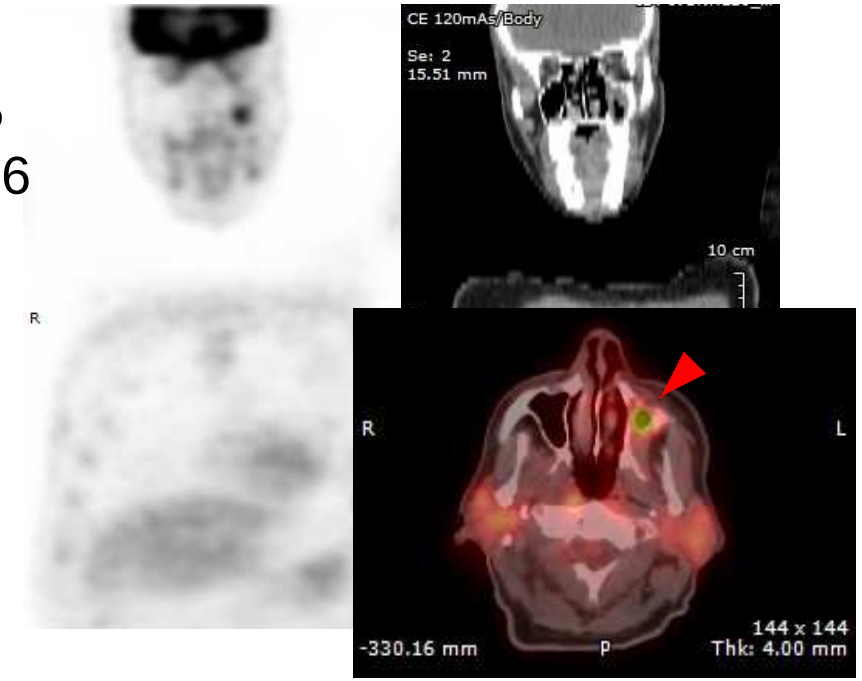
→ Better agreement between observers

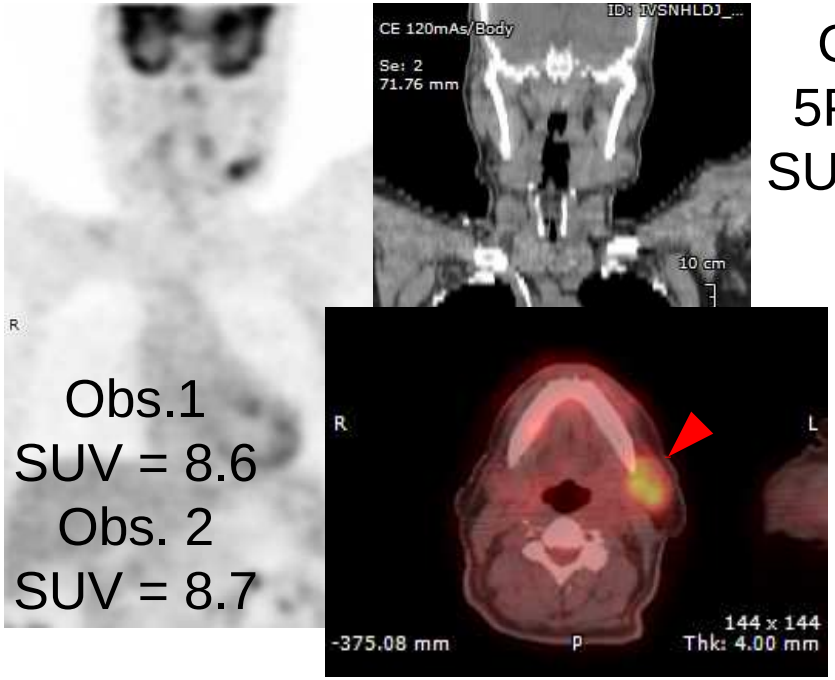
IVS problems : Clinical

- Inclusion criteria not fully observed
  - therapy modification guided by PET
  - short follow-up (inclusions after April 2009)
- Small number of patients (49)
- Small number of centers (4)
- Identification of the target pre/post-therapy
- Variability 5PS/SUV computation



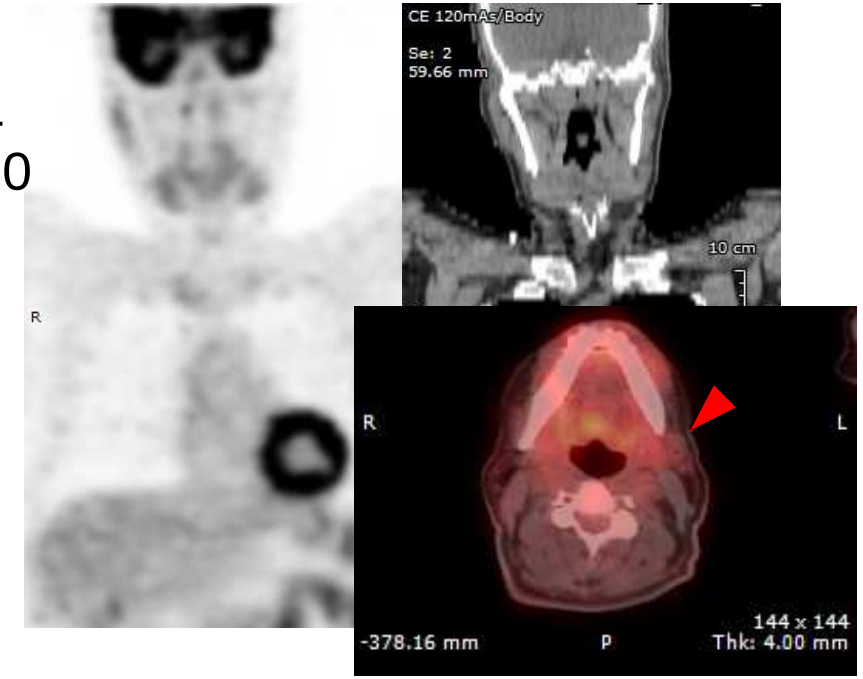
Obs.1
5PS = 5
SUV = 5.6





Obs.1
SUV = 8.6
Obs. 2
SUV = 8.7

Obs.2
5PS = 1
SUV = 1.0

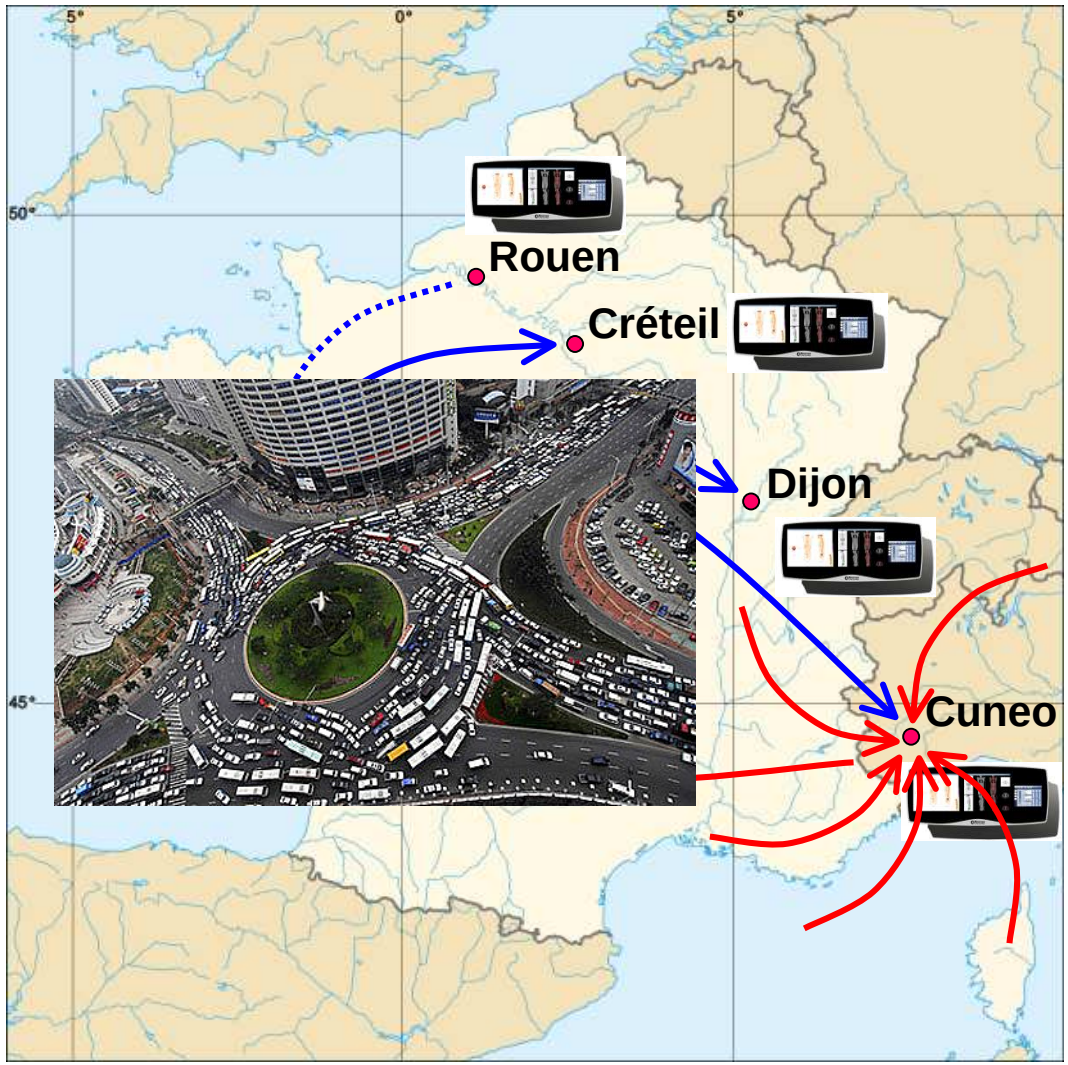


IVS problems : Technical

- Acquisition parameters not available
  - glucose level, SUV calibration factor
  - delay between inj. and scanning (to be computed)
- Corrupted files (need to re-transfer)
- Non attenuation-corrected scans missing
- Absence of organization of the data transferred
  - NAC, CT-AC, CT, CECT, CECT-AC

Network traffic

NHL: 49 patients; HL: 108 patients



2 IVS at the same time :

- **98 PET/CTs for NHL**
  over a 1-month period
  (≈ 15 GB)
- **216 PET/CTs for HL**
  over a 2-day period
  (≈ 32 GB)

Conclusion

- Need to recruit new patients, new centers
- Other immunochemotherapy regimens (DI)
- Objective : to reach 100-200 pts
- Better control of inclusion/exclusion criteria
- Continuous work instead of last-minute work