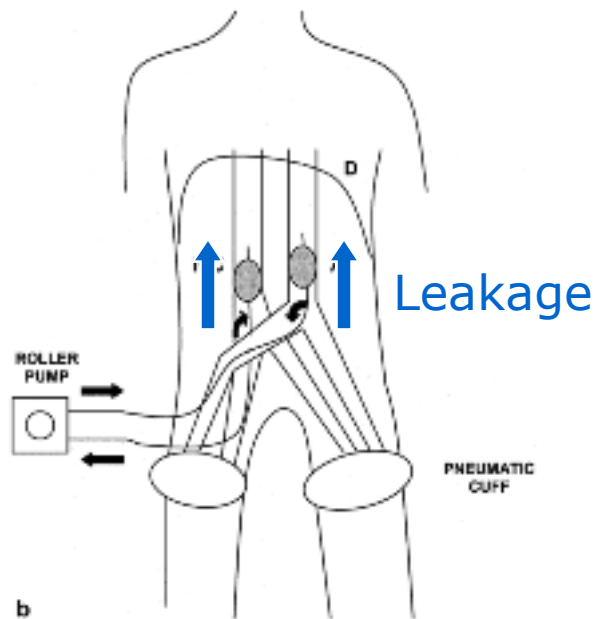




Isolated pelvis perfusion (IPP) with TNF α and melphalan for locally advanced pelvic cancers

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Surgery

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STOP FLOW

	Wanebo (Ann Surg Oncol. 2008) (n=26)	Pohlen (Anticancer Res. 2007) (n=59)	Strocchi (EJSO 2004) (n=10)
leakage	11% to 17% f(type of chemo)	13%	4% à 7% f(type of chemo)
Response	54% PR pelvis	37% PR abdominal	1 /10 CR 2 /10 PR pelvis

How to improve the results?

- To decrease the leakage?
- TNF α ?

G-suit combined with pelvic stop-flow: a pharmacokinetic study with cisplatin in calves

G suit pressure	40 mm Hg	125 mm Hg
pelvic/systemic exposure AUC ratios	5.92	14.93
% leakage (CDDP)	18%	7%



The G-suit increased the AUC ratio between pelvic and systemic compartments

Bonvalot Eur J Surg Oncol. 2007

Limb salvage with isolated perfusion for soft tissue sarcoma: could less TNF-alpha be better?

Group	0.5 mg (n=25)	1 mg (n=25)	2 mg (n=25)	3/4 mg (n=25)	Total (n=100)
CR (%)	32%	40%	32%	40%	36%

No dose effect in this range of dose p=0.71

Hyperthermic Isolated Limb Perfusion in Locally Advanced Soft Tissue Sarcoma and Progressive Desmoid-Type Fibromatosis with TNF 1 mg and Melphalan (T1-M HILP) Is Safe and Efficient

Response	MRI response (100 patients)	Pathological response (83 operated patients)
Complete response	30 (30%)	
Partial response	49 (49%)	
Stable	9 (9%)	
Progression	12 (12%)	
0% viable cells		16 (19%)
1-10		14 (17%)
11-50		18 (22%)
>50		35 (42%)

IPP Phase 2 on locally advanced pelvis cancers

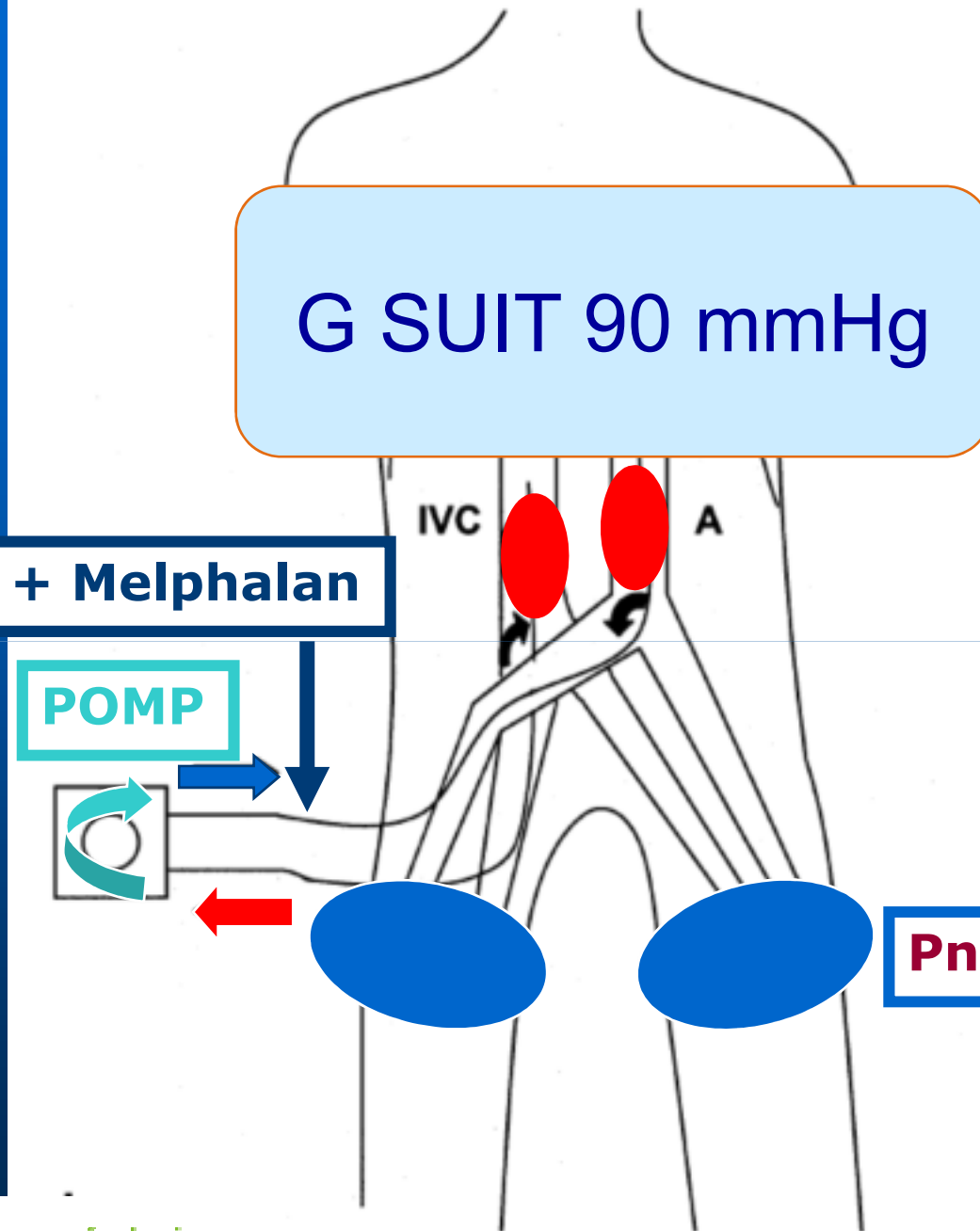
IPP Method

G SUIT 90 mmHg

TNF + Melphalan

POMP

Pneumatic cuff



G SUIT



Inflated 90 mmHg

IPP

- T 0 mn: TNF- α 0.3 mg
- T +5 mn : Melphalan 1.5mg/ kg
- T +30 mn : wash out

PK

- Pelvic and systemic blood samples were obtained to monitor melphalan and TNF
- Blood samples were stored at + 4°C
After centrifugation, samples were stored at -20°C until analysis

Response criteria

- Pelvis dynamic RMI
 - Before IPP
 - 2 months after
-
- RC: $> 90\%$ necrosis
 - PR: $\geq 50\%$ and $\leq 90\%$ necrosis
 - Stable: $< 50\%$ necrosis
 - Progression: size increase

STATISTIC

- IPP is efficient if $CR \geq 30\%$
- IPP is non efficient if $CR \leq 10\%$

- Procedure optimum of Simon
- At the end of the second step (25 evaluable patients):



6 (or more) CR: IPP is efficient

RESULTS

IPP Patients

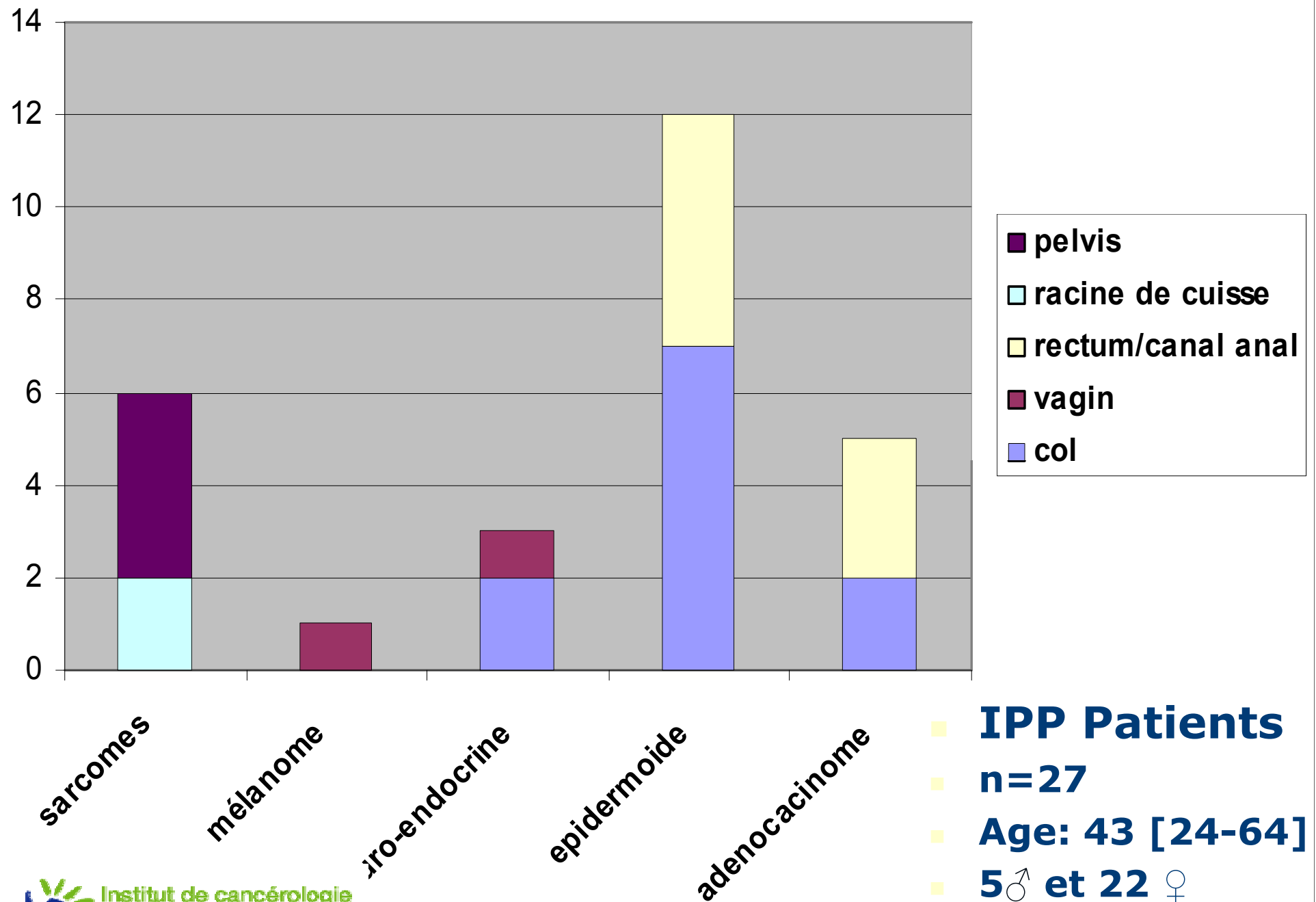
- **n=27**
- **Age: 43 [24-64]**
- **5♂ et 22 ♀**
- **Multifocality: 18 pts (67%)**
- **Size: 42 mm (6, 90)**
- **Metastasis: 4 pts (15%)**

IPP Patients

Number of recurrences	1rst	2nd	3rd	4th
PTS (%)	11 48%	7 30%	4 17%	1 4%

Previous treatments	S	S+RT	S+RT+CT	CT	CT+RT
PTS (%)	1 4%	1 4%	16 59%	1 4%	8 30%

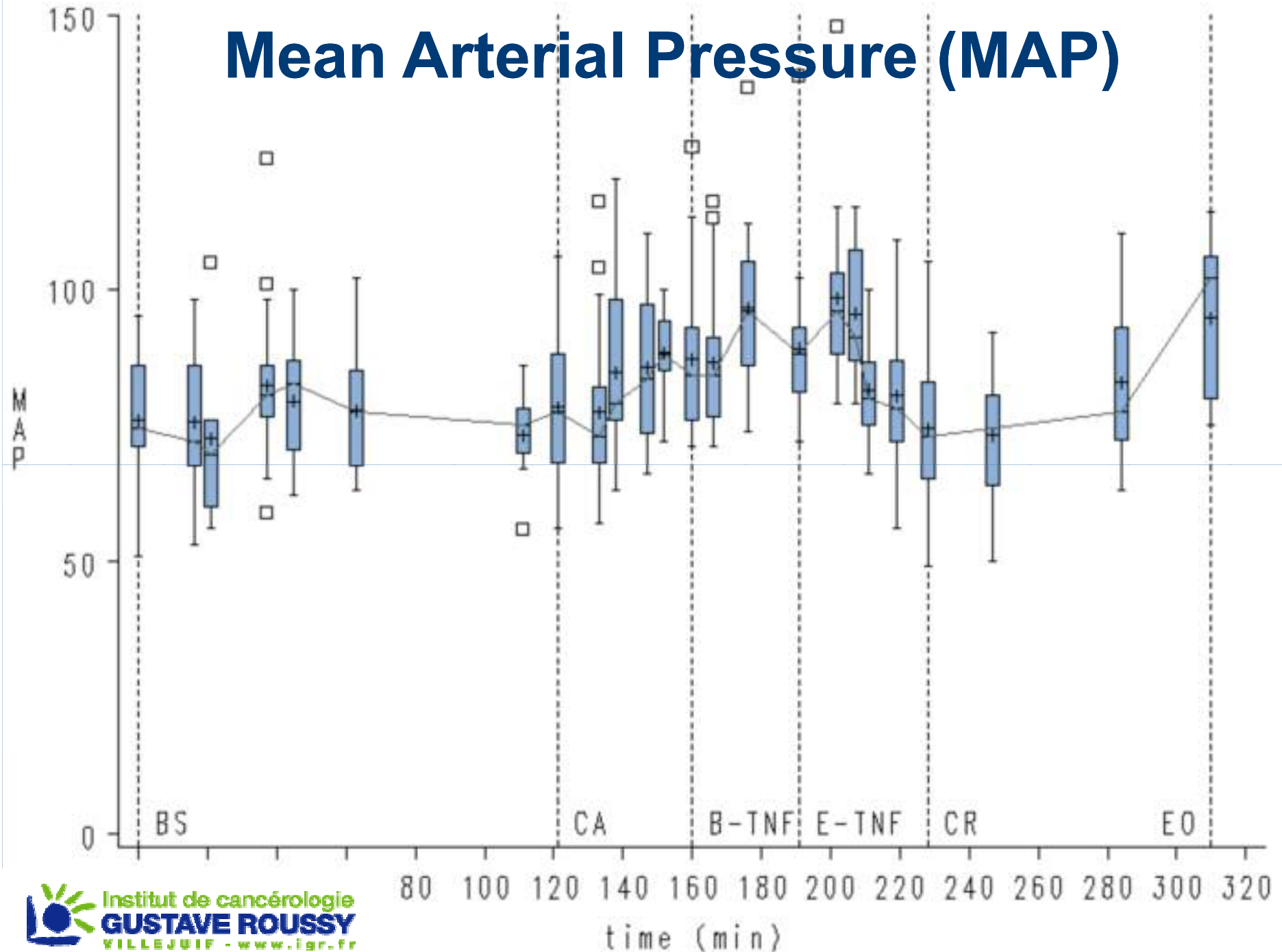
Time between primary treatment and IPP: 32 months (6, 239)



■ **IPP Patients**
■ **n=27**
■ **Age: 43 [24-64]**
■ **5♂ et 22♀**

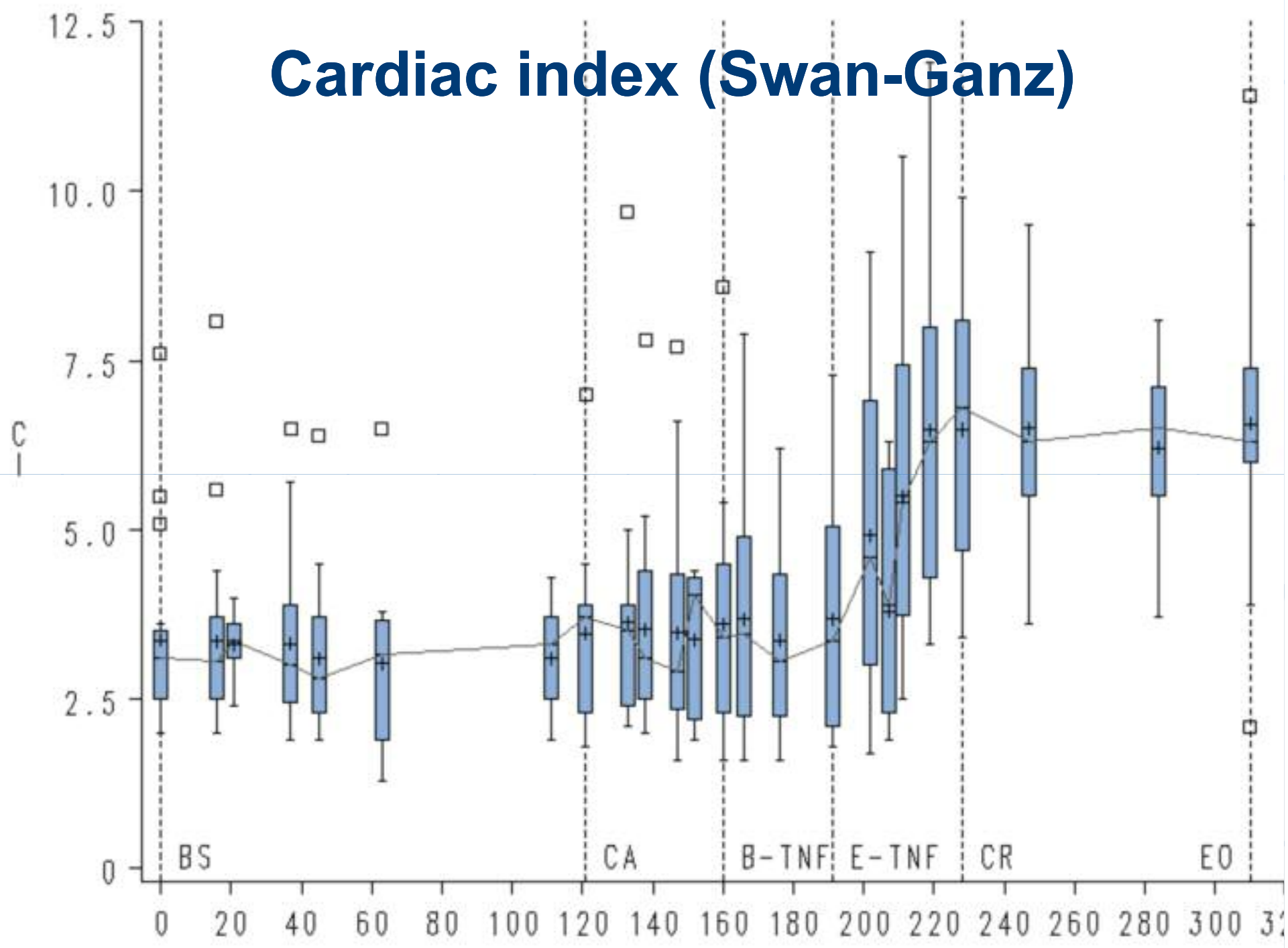
Per operative tolerance

Mean Arterial Pressure (MAP)

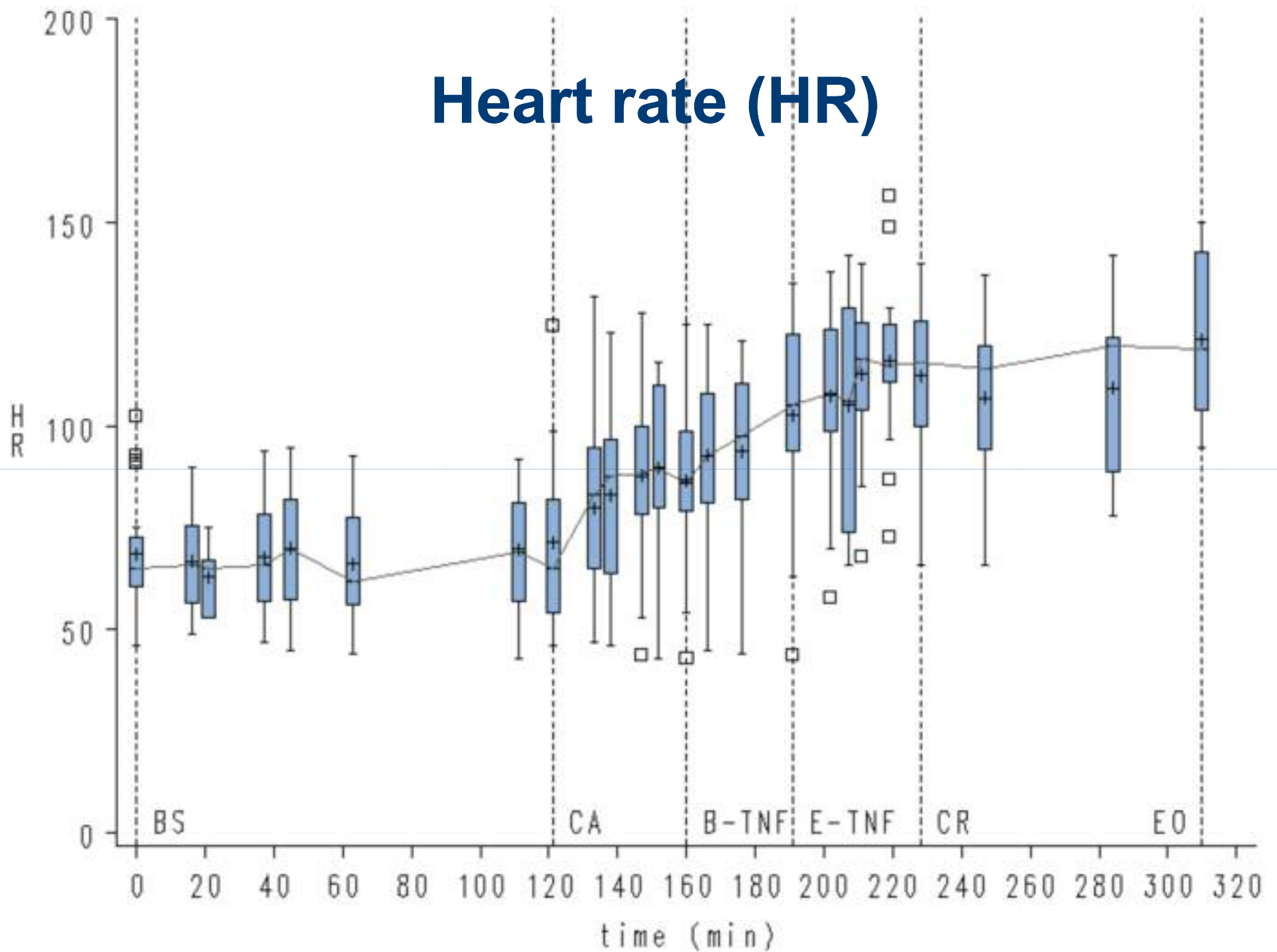


Cardiac index (Swan-Ganz)

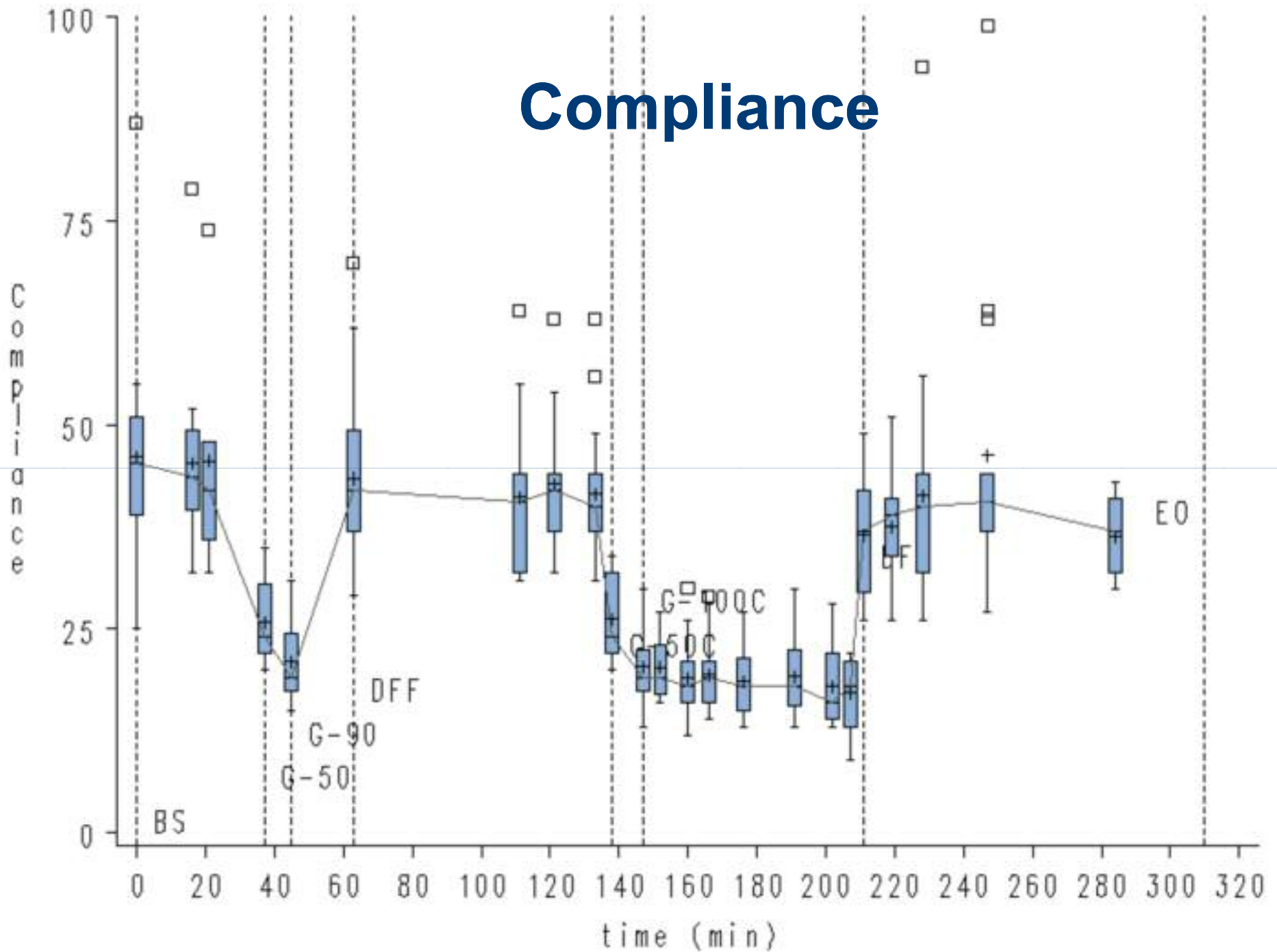
C



Heart rate (HR)

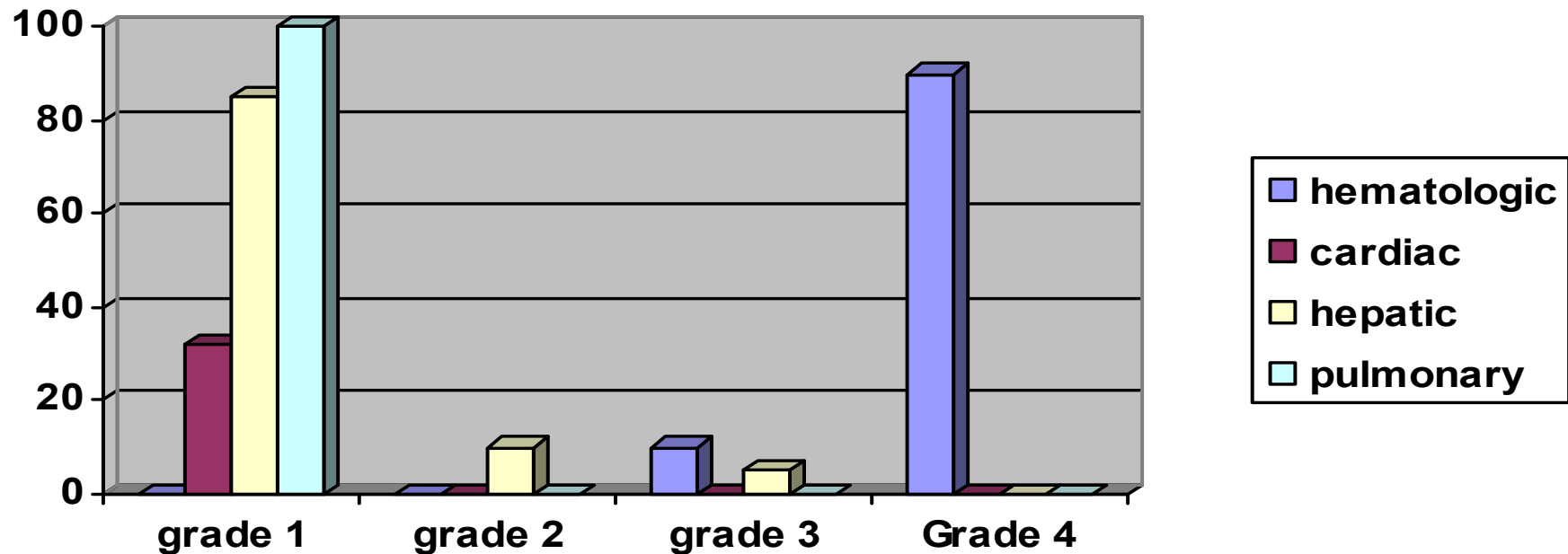


Compliance



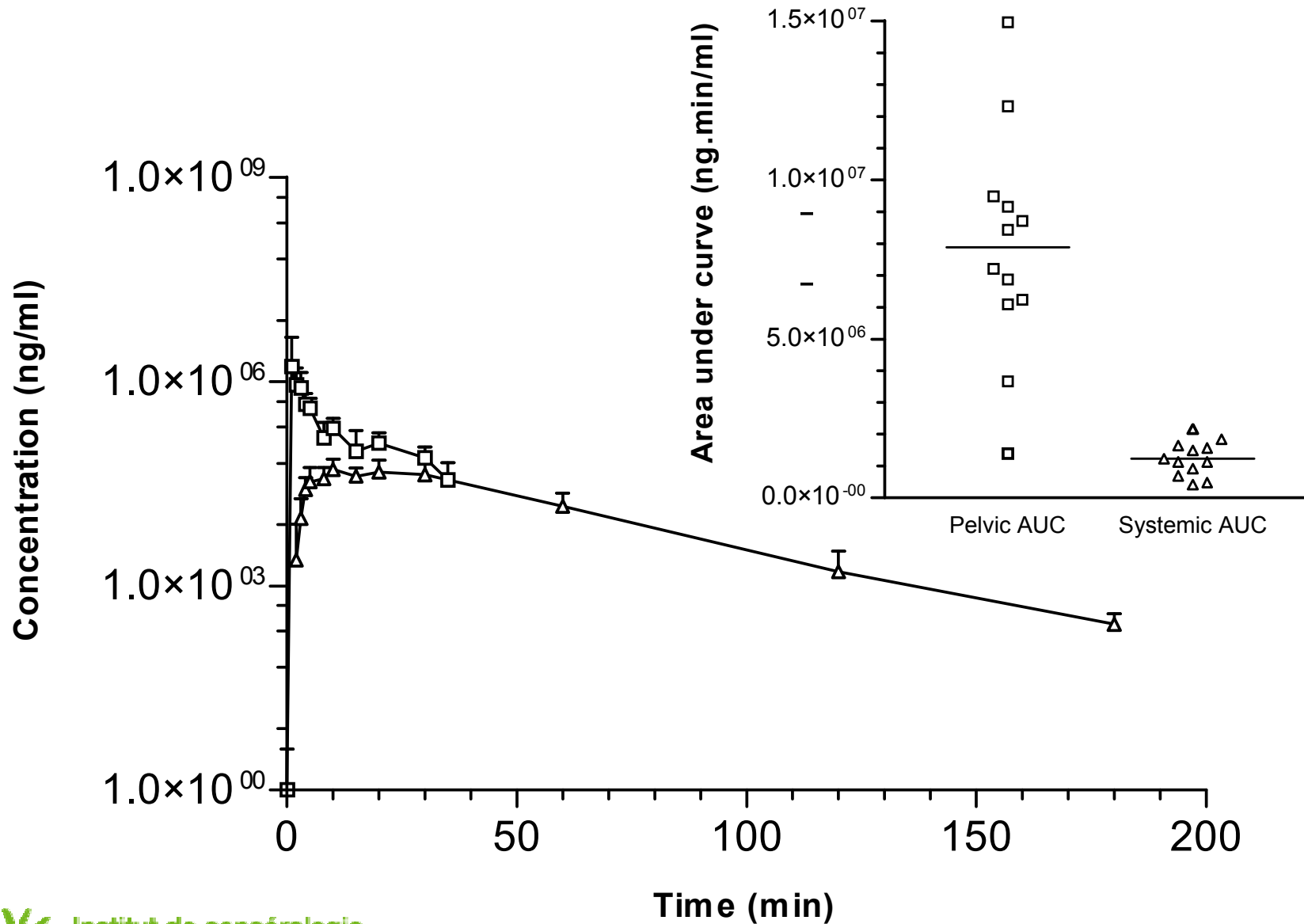
Toxicity

- No toxic death and no surgical morbidity
- 47% pts had alopecia.
- 1 pt had a fracture and was operated
- 5 pts had a fistula due to the clinical response



PK TNF

Pelvic and systemic exposures through area under curves of TNFa



PK TNF α

Concentrations (ng/ml)

AUCs (ng.min/ml)

C_{max}

Mean \pm SD

Mean \pm SD

Pelvic

1.66 10^6

409,239 \pm 142,244

7.87 $10^6 \pm 3.59 10^6$

Systemic

50,610

19,630 \pm 5,246

1.23 $10^6 \pm 0.54 10^6$

P/S ratio

ND

ND

7.0 \pm 3.6

Leakage (%)

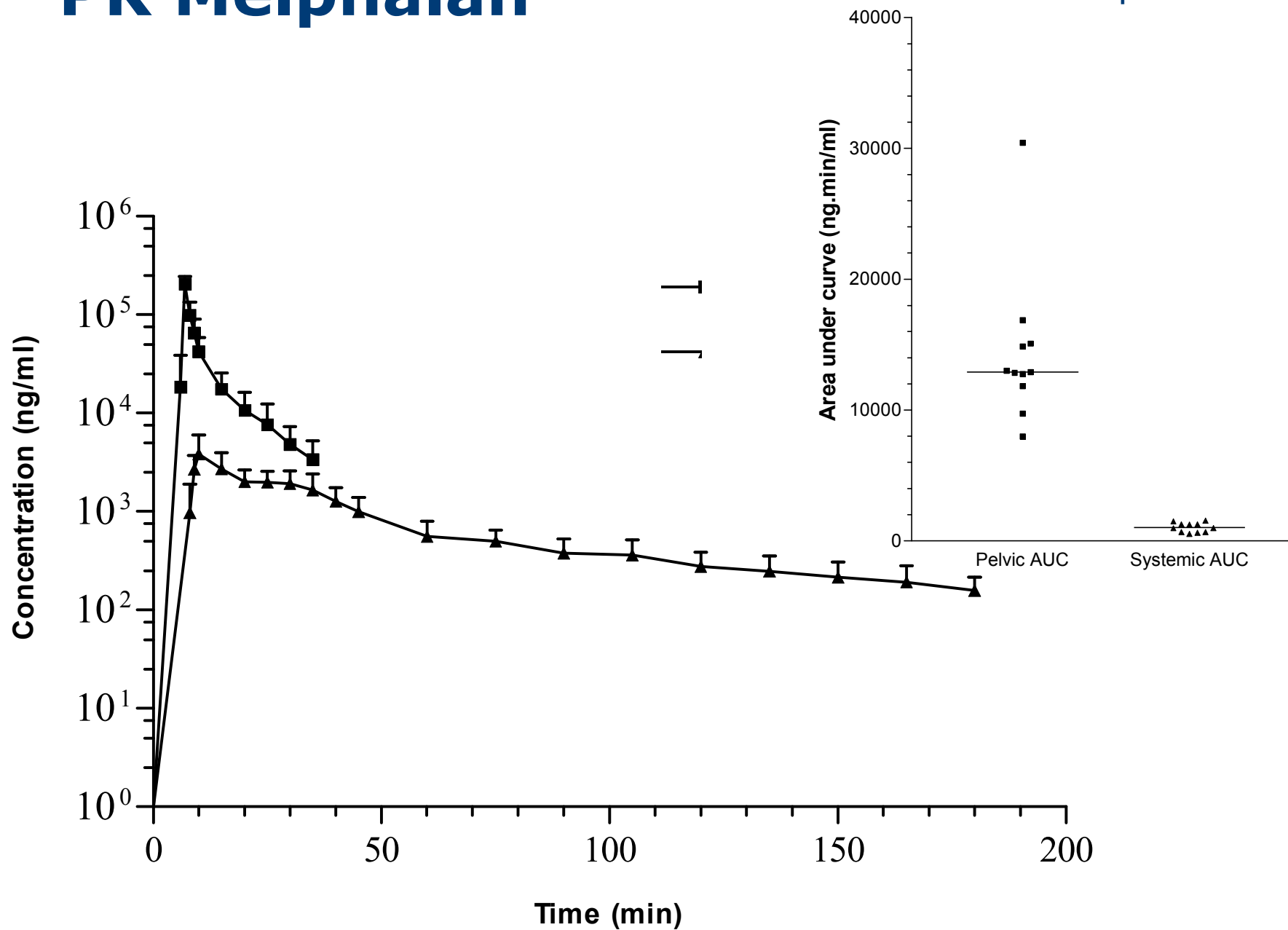
ND

ND

17.8 \pm 7.0

PK Melphalan

Pelvic and systemic exposures through area under curves of Melphalan



PK Melphalan

Concentrations (ng/ml)

AUCs (ng.min/ml)

Cmax

Mean \pm SD

Mean \pm SD

Pelvic

206,400

43,170 \pm 18,760

14,390 \pm 5852

Systemic

3,811

1,039 \pm 229

1,015 \pm 359

P/S ratio

ND

ND

14.2 \pm 5.2

Leakage (%)

ND

ND

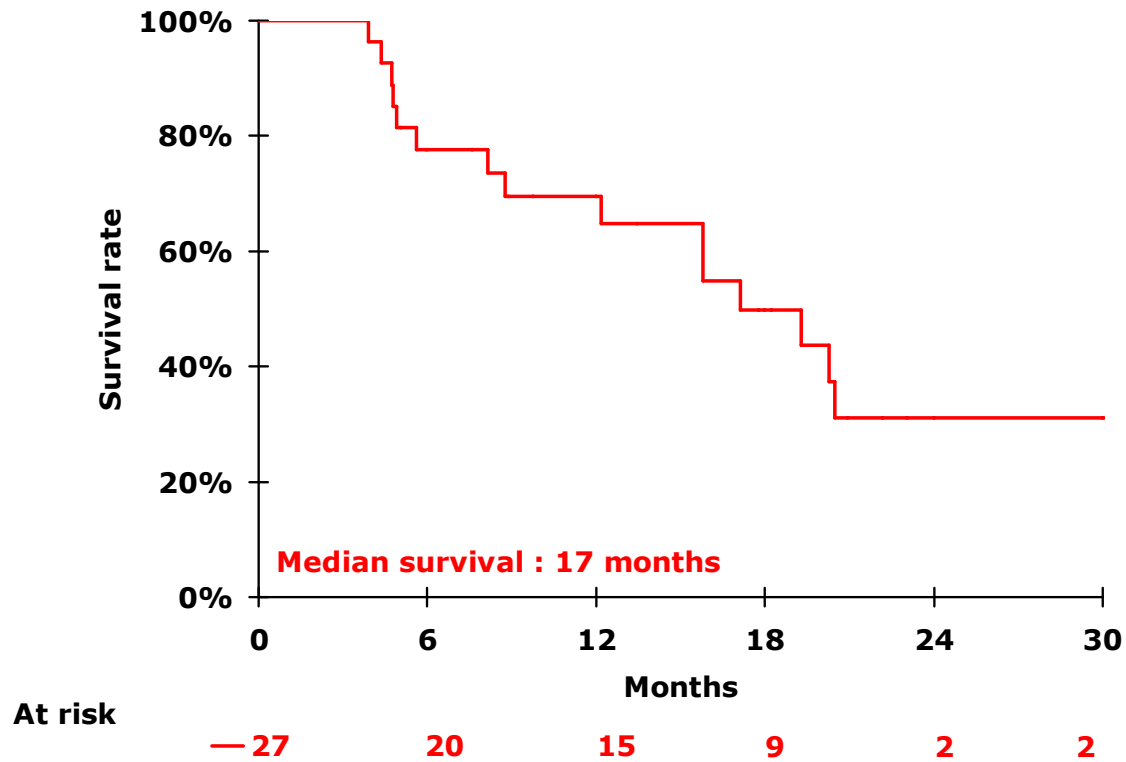
7.1 \pm 2.6

MRI Response

- 27 patients
- Not perfused = 2 (7%)
- CR= 8 (30%) IC 95%: (12%, 47%)
- PR= 8 (30 %)
- Stable = 5 (19%)
- Progression: 4 (15%)

- % necrosis: 70 (0, 100)

Overall survival

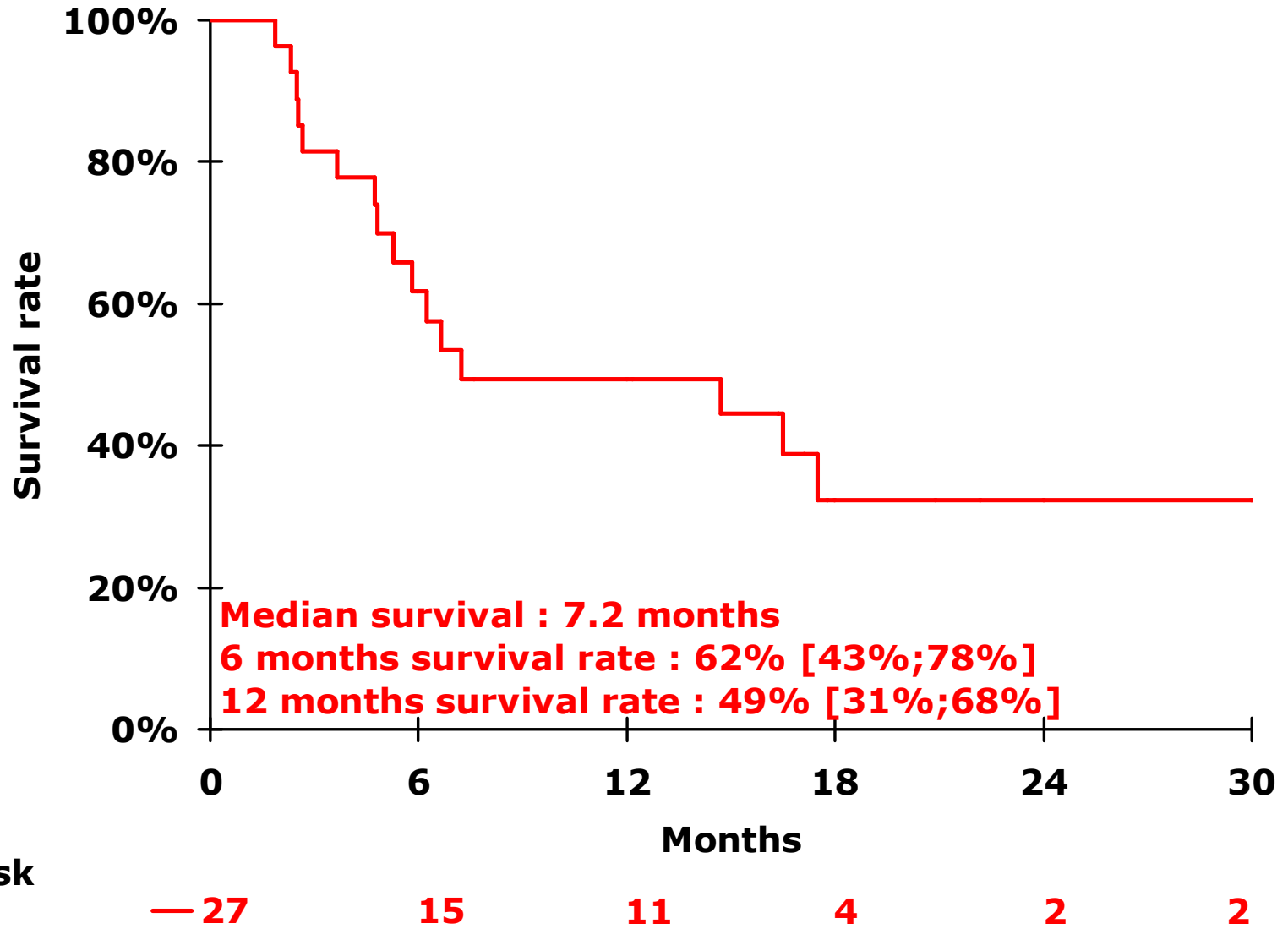


- Median follow up: 21 months
- Median OS: 17 months

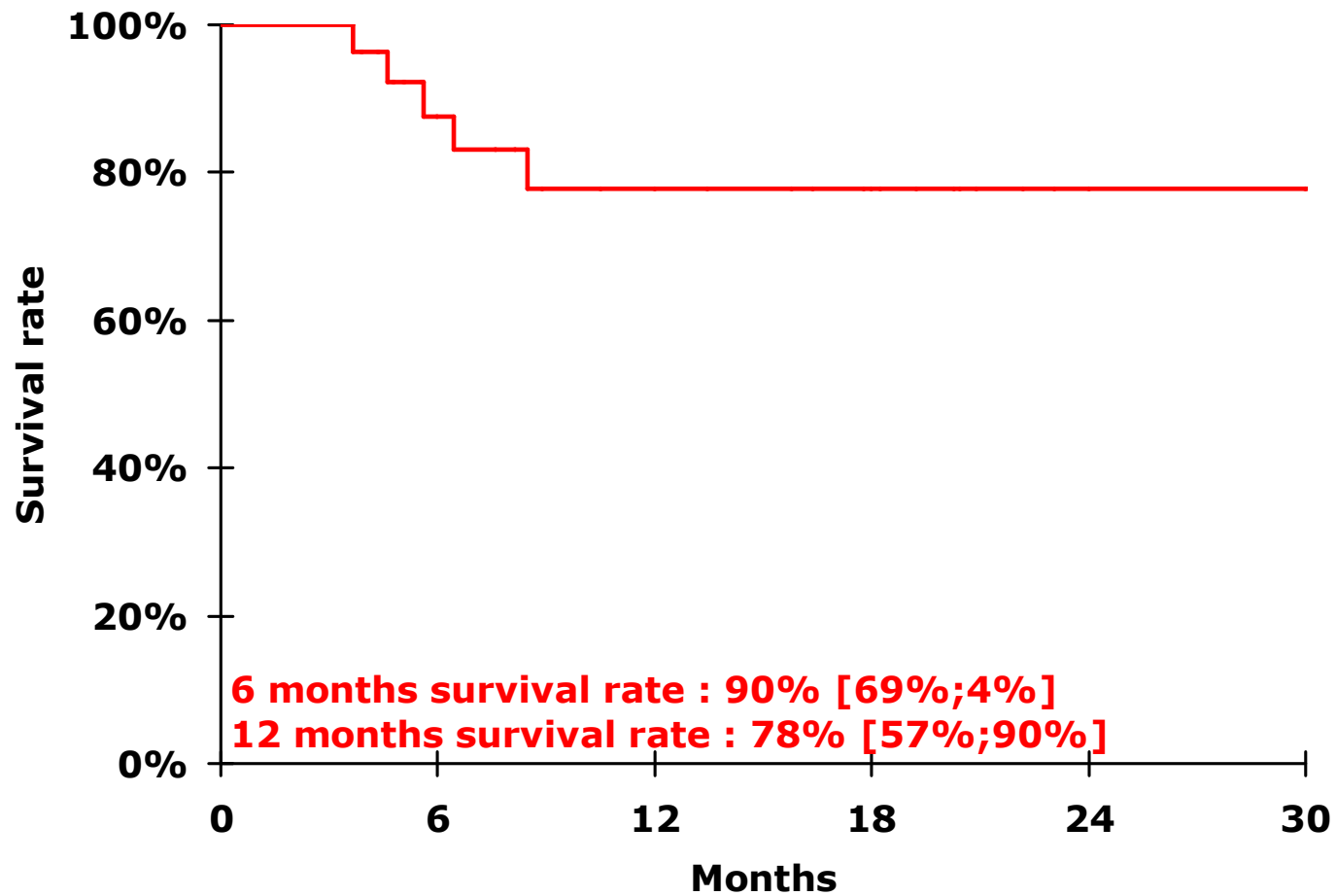
Pelvic exenterations

- Berek JS, et al. Pelvic exenteration for recurrent **gynaecologic malignancy**: survival and morbidity analysis of the 45-year experience at UCLA Gynecol Oncol 2005
R1: 1 year OS: 25%
- **Rectum**: Pelvic exenteration 5 years OS (R0 + R1): 10 à 20%
(Hahnolser 2003, Shoup 2002, Lopez-Kostner 2001, Garcia-Aguilar 2001, Hashiguchi 1999, Willet 1991, Salo 1999, Suzuki1996)
- Mortality: 0 to 16%
- Morbidity: 20 to 40% (Huguier 1998, Elias 1991, Salo 1999, Holm 1995)

Local DFS



Metastatic DFS



At risk

17 19 13 9 2 2

Conclusions

- The addition of 0.3 mg TNF α allowed a better response rate than that already published with an acceptable toxicity
- G suit and stop flow allowed a greater pelvic exposure than the systemic compartment's one
- Survival compares favorably with the results of R1 pelvic exenterations
- We started a phase 3 (TNF-IPP/ pelvic exenterations) (35 pts included/122 expected)



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