Long-term results of comprehensive treatment for non-metastatic primary limb high-grade osteosarcoma (O.S.). Emphasis of escalating high dose methotrexate (HDMTX)

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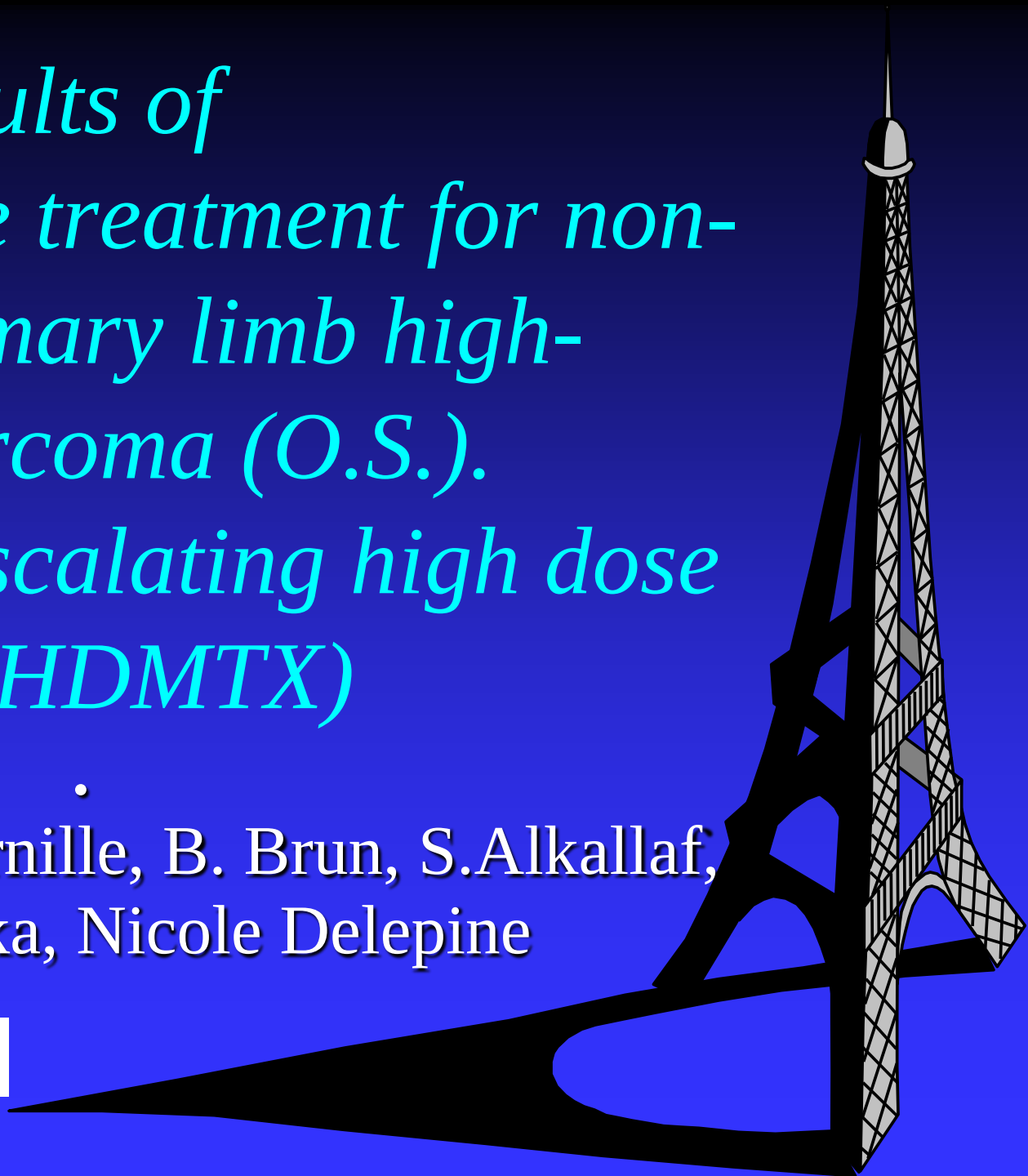
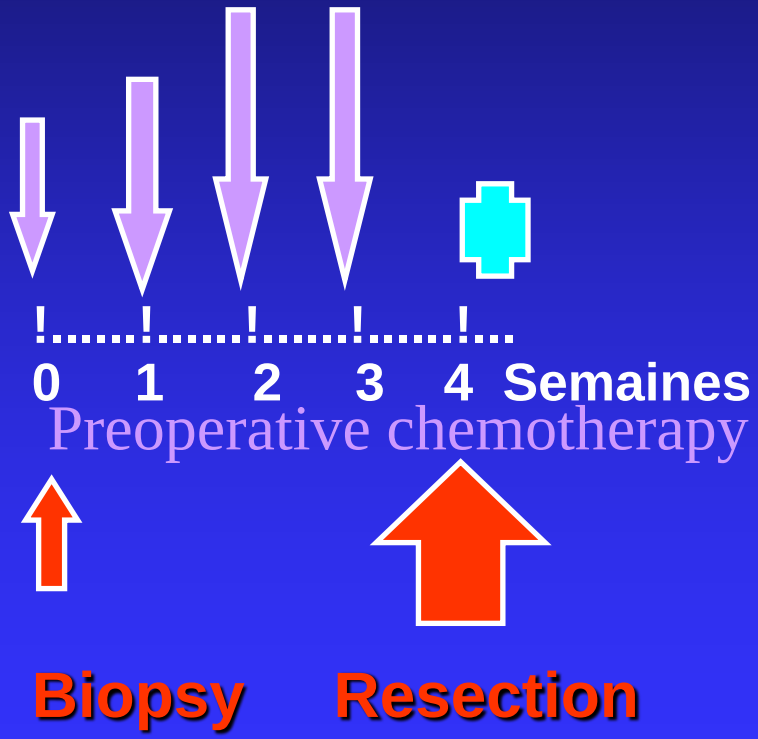
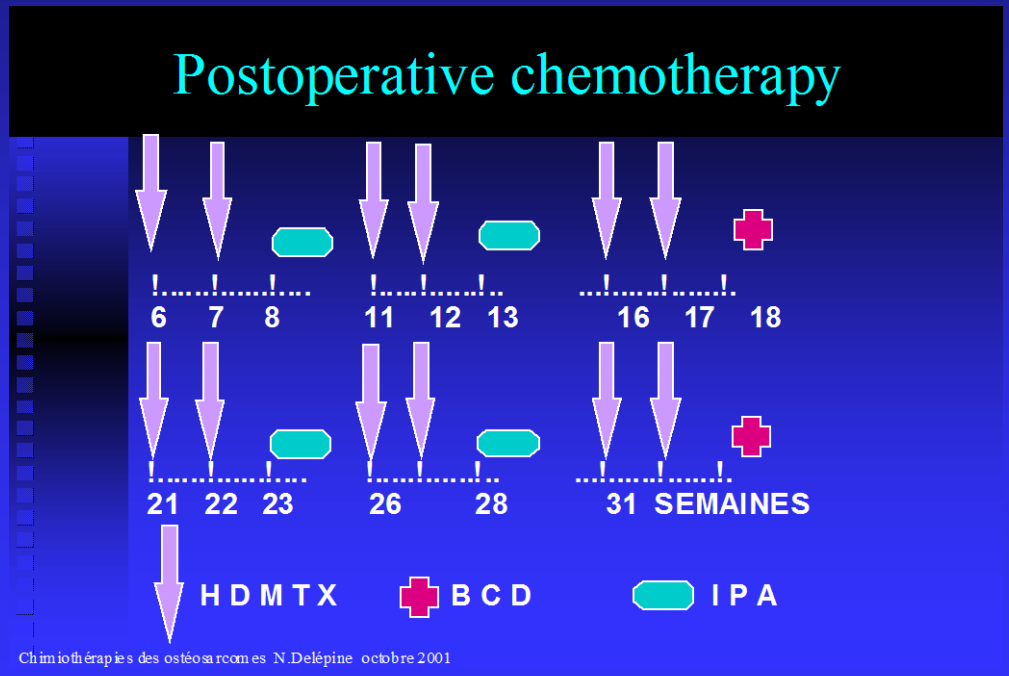


Purpose of this study

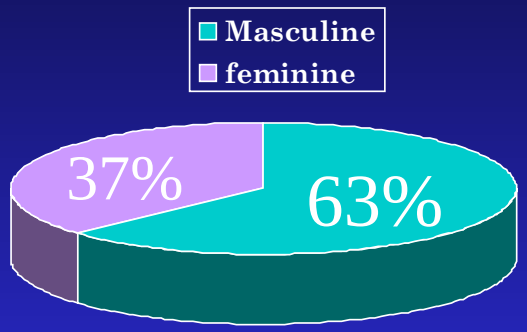
Evaluation of effects of escalating induction HDMTX on toxicity, response of tumours and survival of patients with osteosarcoma

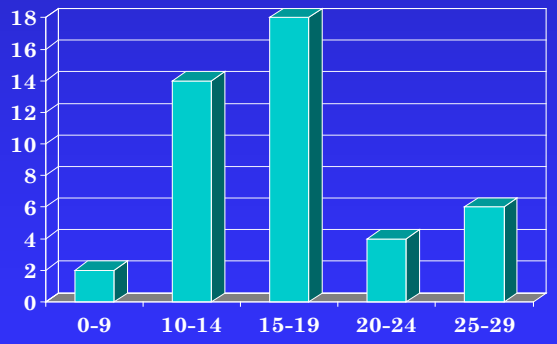


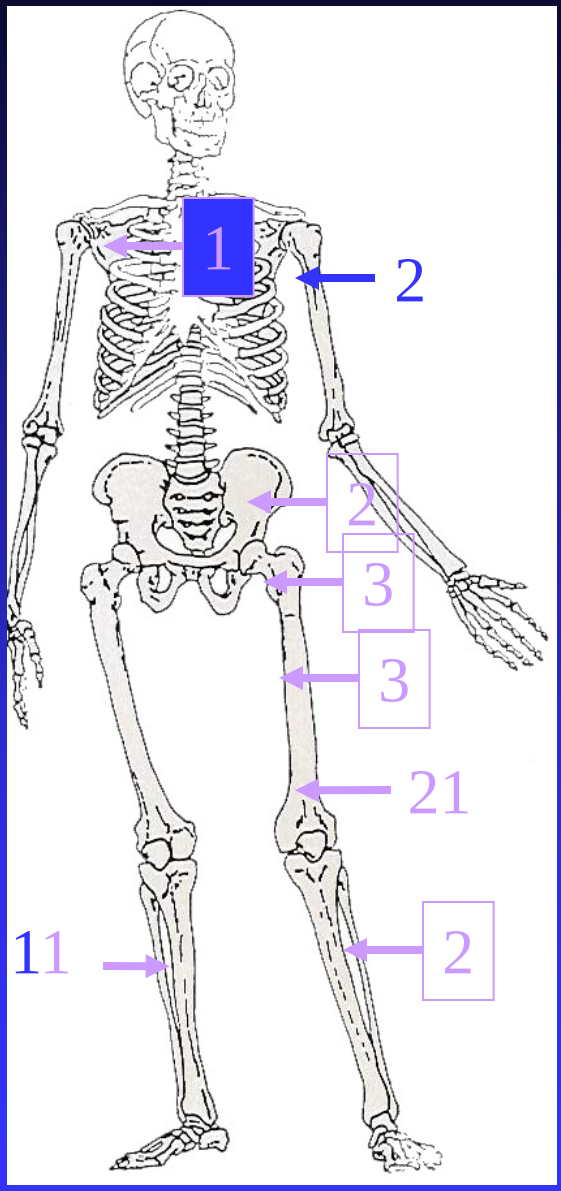


Patients

From 1/85 to 12/2000 :
46 patients with non metastatic limb osteosarcoma, previously untreated.
29 M, 17 F
(7 - 30 y, mean : 16.6)
were treated in one of AP-HP oncologic service

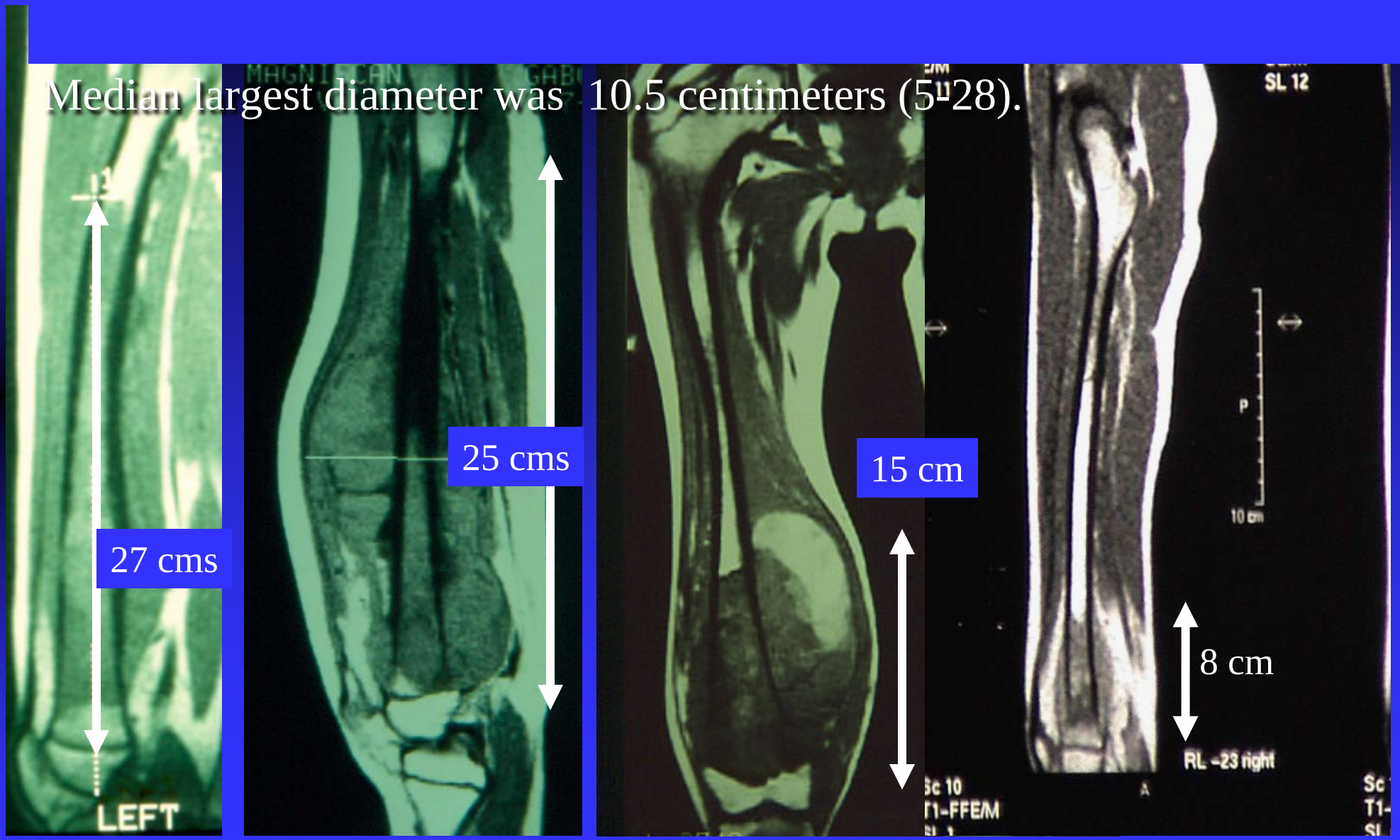






Size of the tumours

Median largest diameter was 10.5 centimeters (5-28).

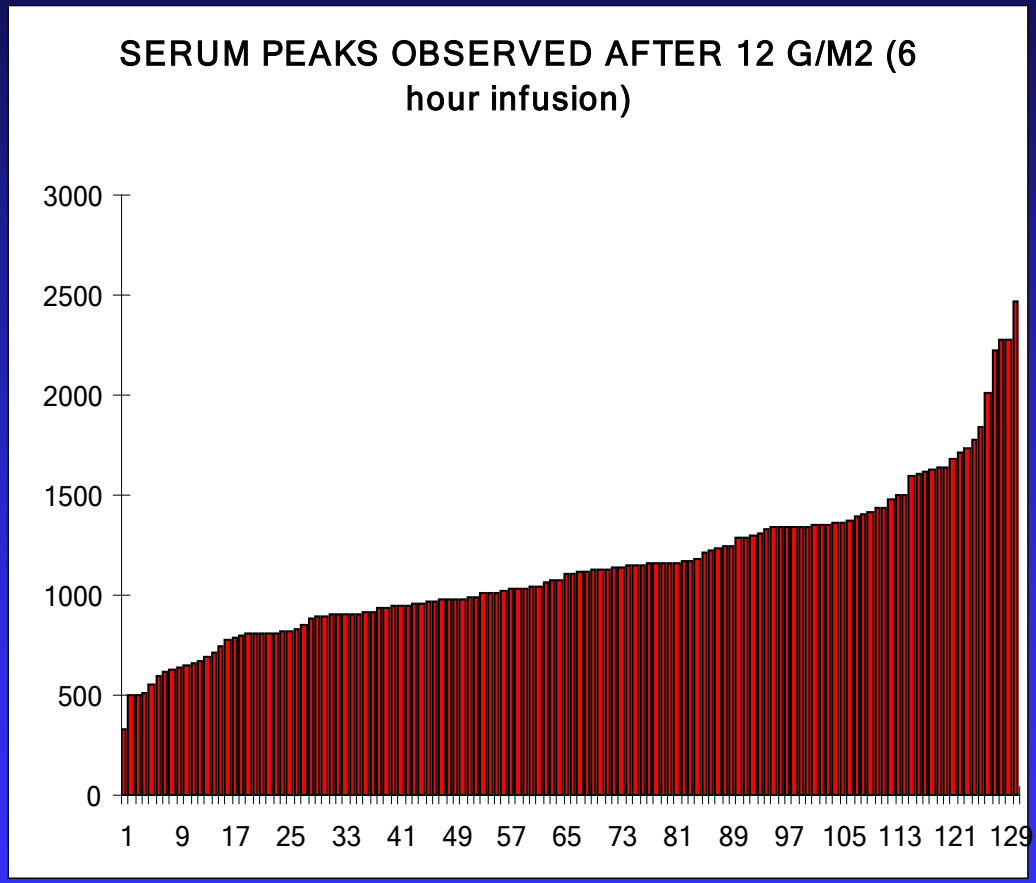


Escalating doses of MTX in OS. UICC 2002 OSLO delépine Alkhallaf

MTX dose of first course

was adapted to age
5-9 y : 18 g/m²,
10/15 y : 15 g/m²,
> 15 : 12 g/sqm .

For the same dose inter patient variability of serum peaks was high.

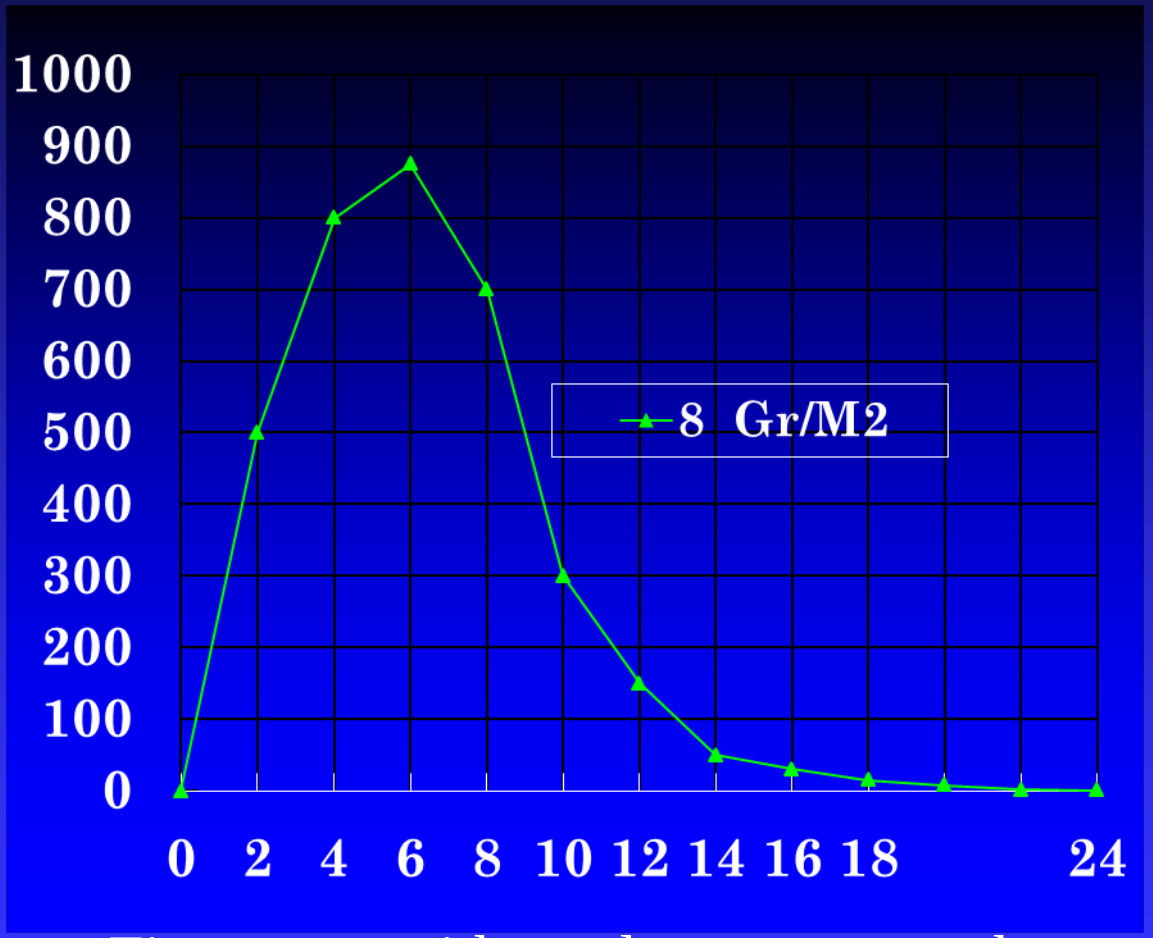


inter patient variability of serum peaks with 12g/sqm

Dose escalation schedule

MTX was escalated from 2 to 4 gr/sqm if

- the serum peak H6 < 1000 µmol/l
- or in case of clinical ineffectiveness.

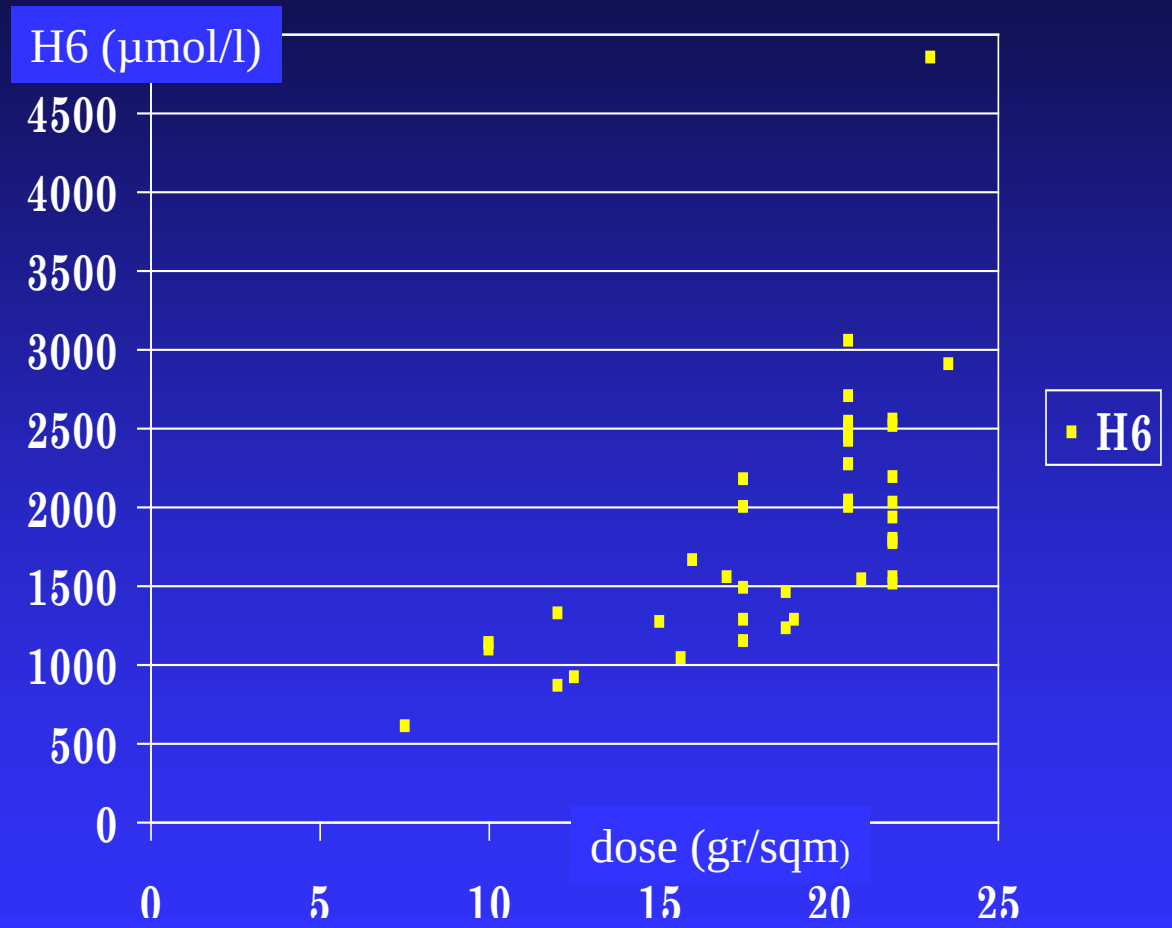


First curse with too low serum peak

Correlation between H6 and dose

In each patient Correlation between H6 (µmol/l) and dose (gr/sqm)

was linear.

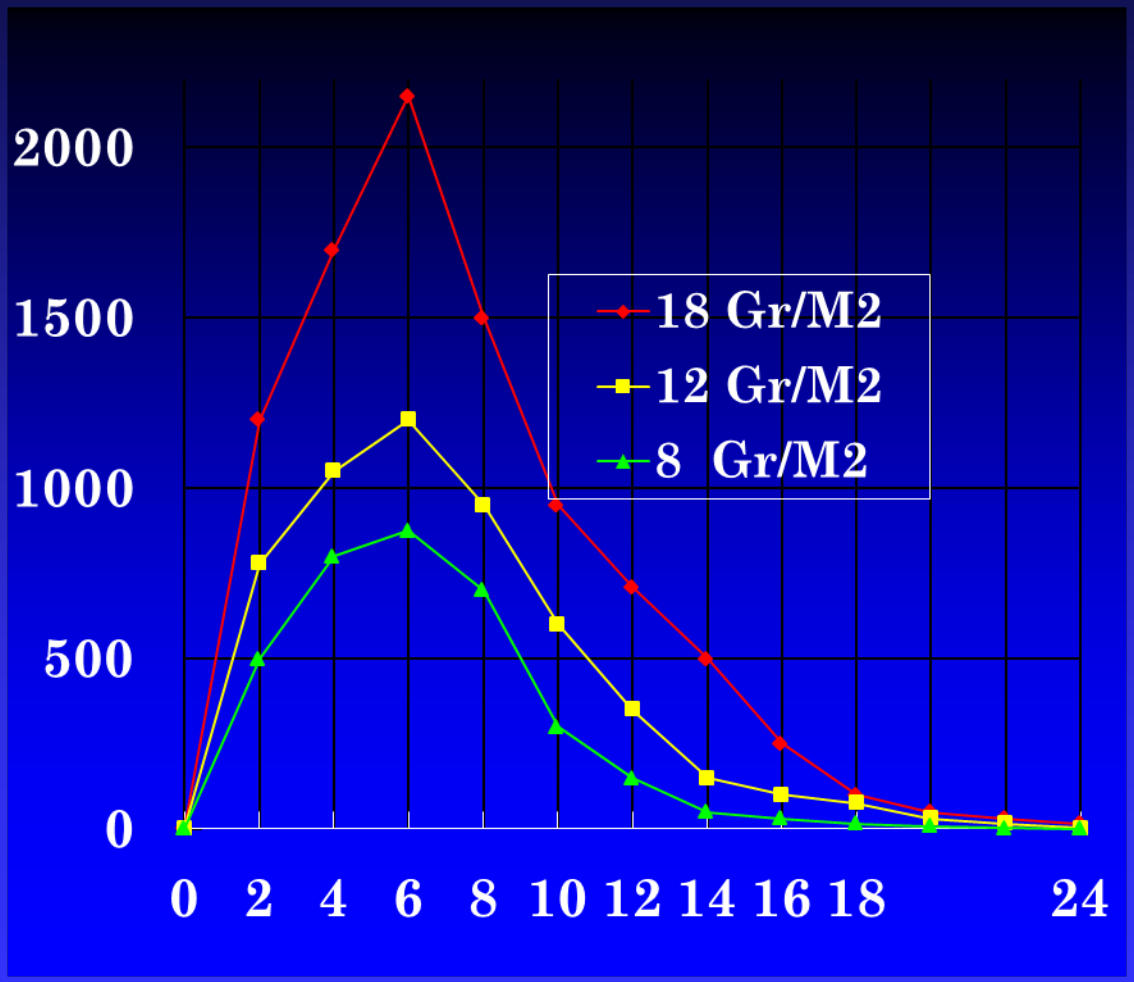


Pharmacokinetics : In our cases, the pharmacokinetics of MTX were bicompartmental in 95 % of cases. The maximum serum peak (H6) is highly correlated with thearea under the curve and represents a good evidence of he therapeutic intensity.

Frequency of dose escalation

Escalation was necessary in 80 % of patients (37/46) due to

- low H6 (13),
- lack of clinical response (9)
- or both (15).



Preoperative dose escalation

Average increase of dose was 40 %

p. received a mean preoperative dose : 14.3 gr/m²/course (8-24 g/m²),

mean H6 : 1248 µmol/l (570-3600).

Observed toxicity

- Induction therapy was well tolerated.
- The most frequent postoperative toxicity was

hematologic grade 4 :

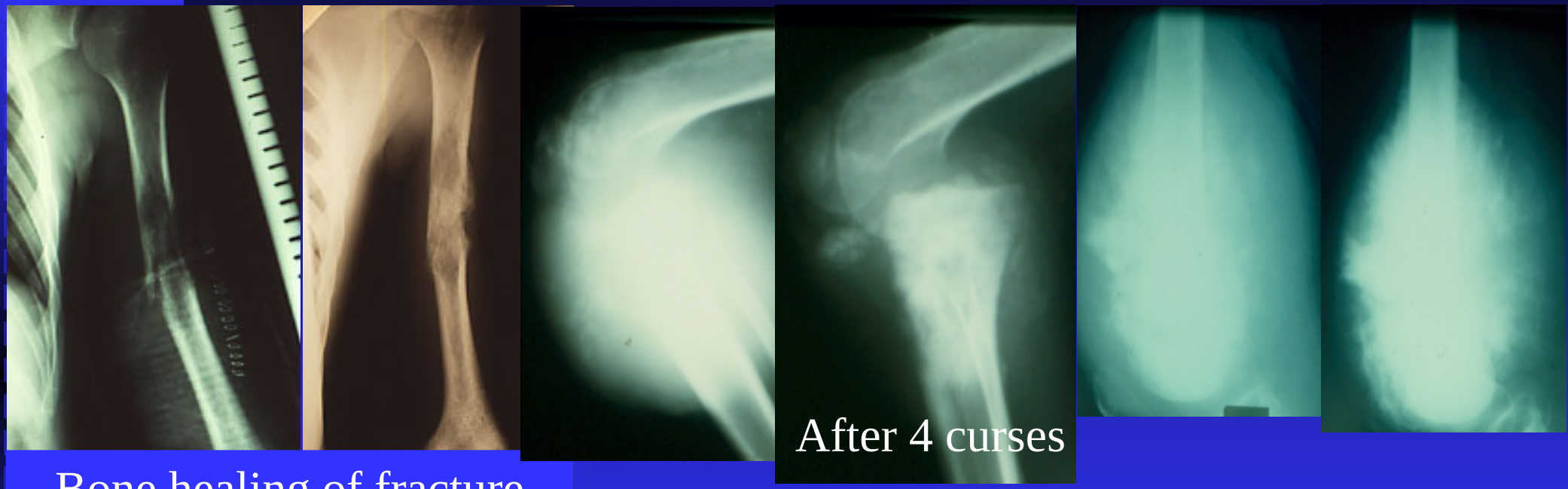
90 % of IPA (IFO,CDDP,ADR).

Limiting factor of dose escalation

Hepatic toxicity was the main limiting factor of postoperative MTX.

Observed in 60 courses of MTX (7 %) it resulted in early stopping of MTX in 4 patients.

radiological responses



Bone healing of fracture

- Good in 30
- Stable disease : l2
- Inevaluable :4.

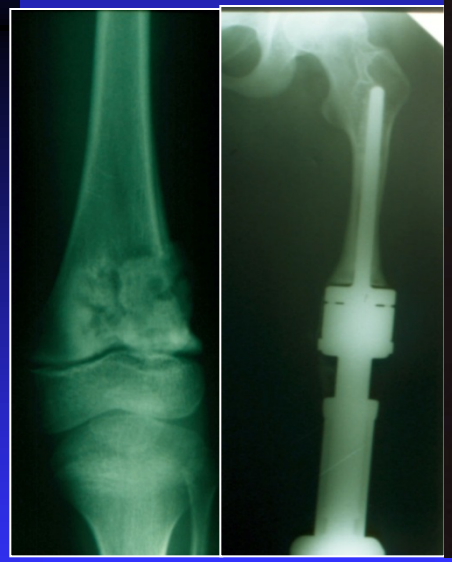
Local treatment

All patients were primarly treated by limb salvage even in case of :

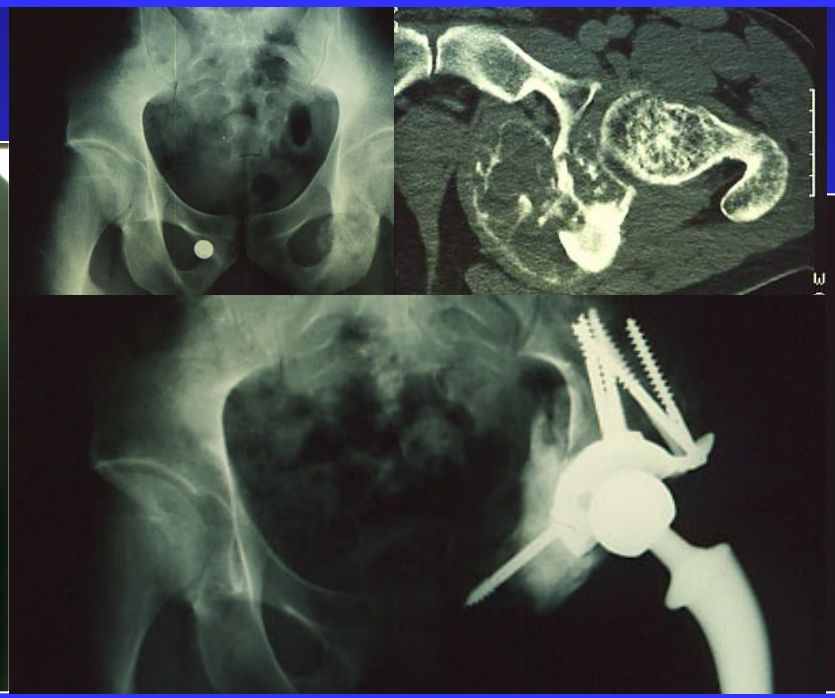
Huge tumor

Young child

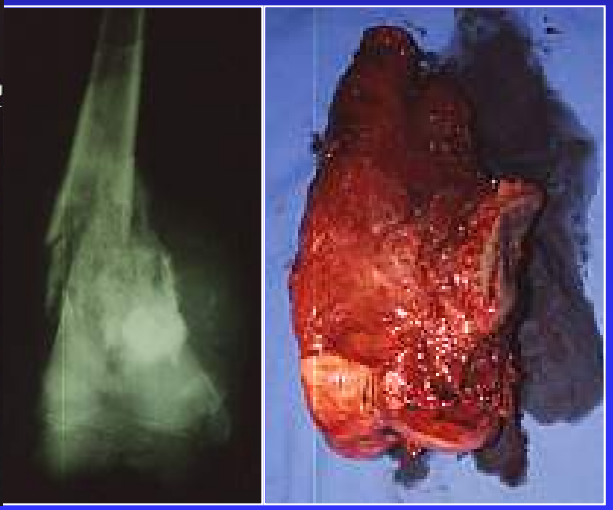
Fracture..



Young child



Periacetabular resection+prosthesis



Fractured sarcoma

Histological Response

Graded according Huvos and Rosen criteria was:

- good : in 25,
- bad : 21.

Total doses of MTX therapy

- given dose of MTX Averaged
  250 g/sqm in 41 wks.
- Mean MTX intensity 6.3 g/m²/week,
- Mean value H6 : 1380 µmol/l.

Oncologic results

- Relapses : out of 46 patients, we observed one local and 7 distant relapses

  4 lung, 3 bone.

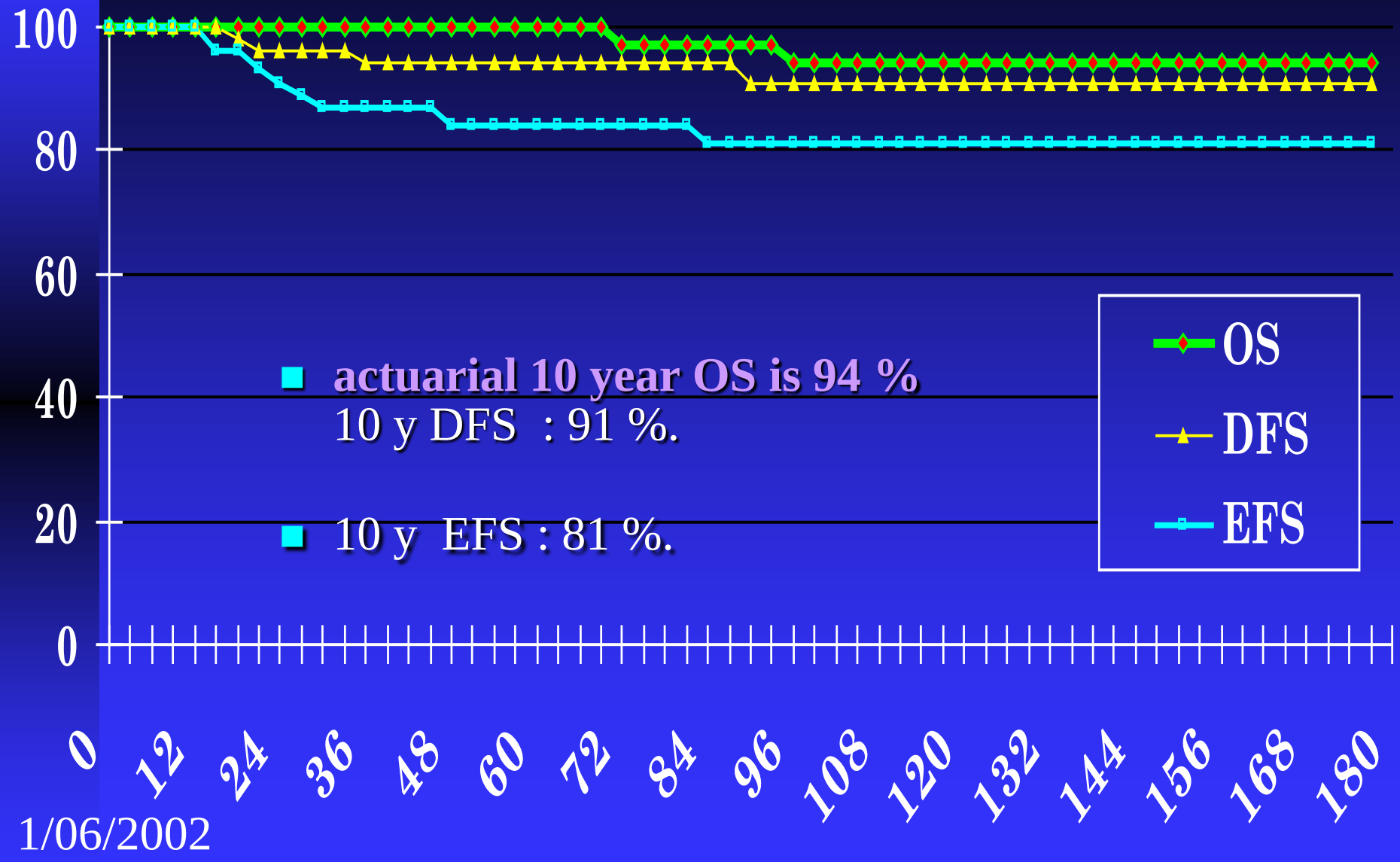
  Average time to relapse was 25 m. (8-75).

- Final outcome :

  2 p. died, 2 p. are living with evolutive disease

  42 others are in CR

Oncologic results



- **actuarial 10 year OS is 94 %**
  10 y DFS : 91 %.
- 10 y EFS : 81 %.

1/06/2002

Conclusion 1

- In our patients escalating doses following Rosen's rules and pharmacokinetics monitoring permits :
- 1.The given dose of methotrexate, the dose intensity and the serum concentration X time, to be increased by 40 % in patients who needed it.
- 2.To increase the event free, the disease free and the overall survival rate of patients .
- 3.Without severe increase of toxicity

Conclusion 2

- Protocols for OS should require not only a good total (> 240 g/sqm) dose MTX but a serum peak over 1000 µmol/l at after 6 hours infusion or 1450 µmol/l after 4 hours infusion.