Importance of individualisation of HD-MTX in osteosarcoma

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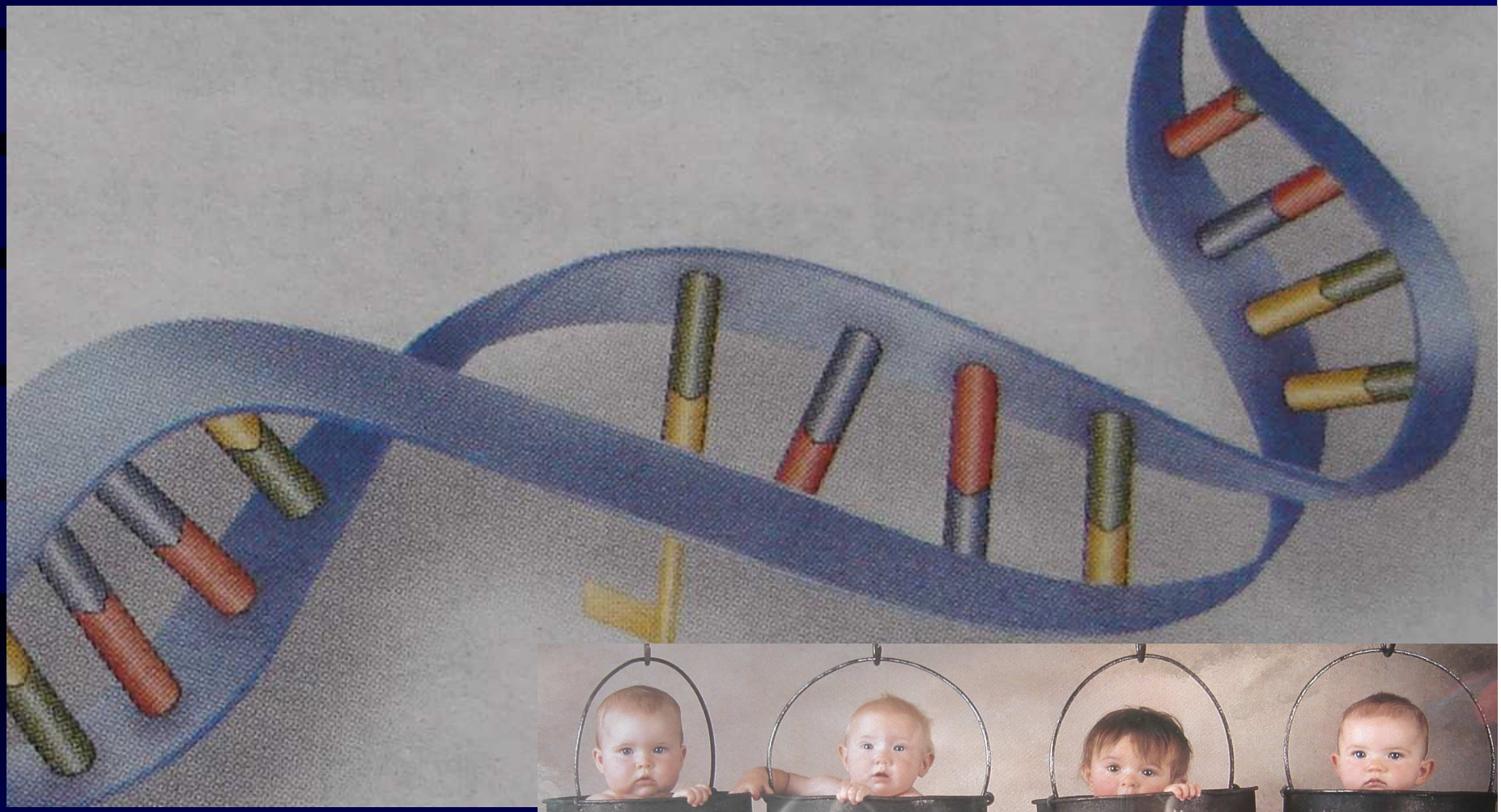
ALL DIFFERRENT, ALL UNIQUE

- **PROJET DE L'UNESCO ET DU PARLEMENT INTERNATIONAL DE LA JEUNESSE**
- **OXFAM COMMUNITY AID ABROAD**

Every human being is unique at birth.



We are all different : 3 main races

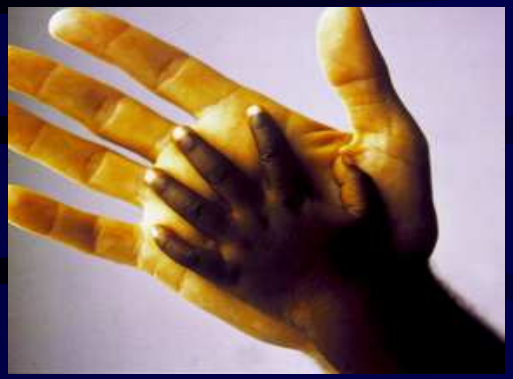
And so many others..

As we increase our experiences (food, illness, medications, environmental status) are unique

- and increase our differences

We are all different, all unique: Different weights

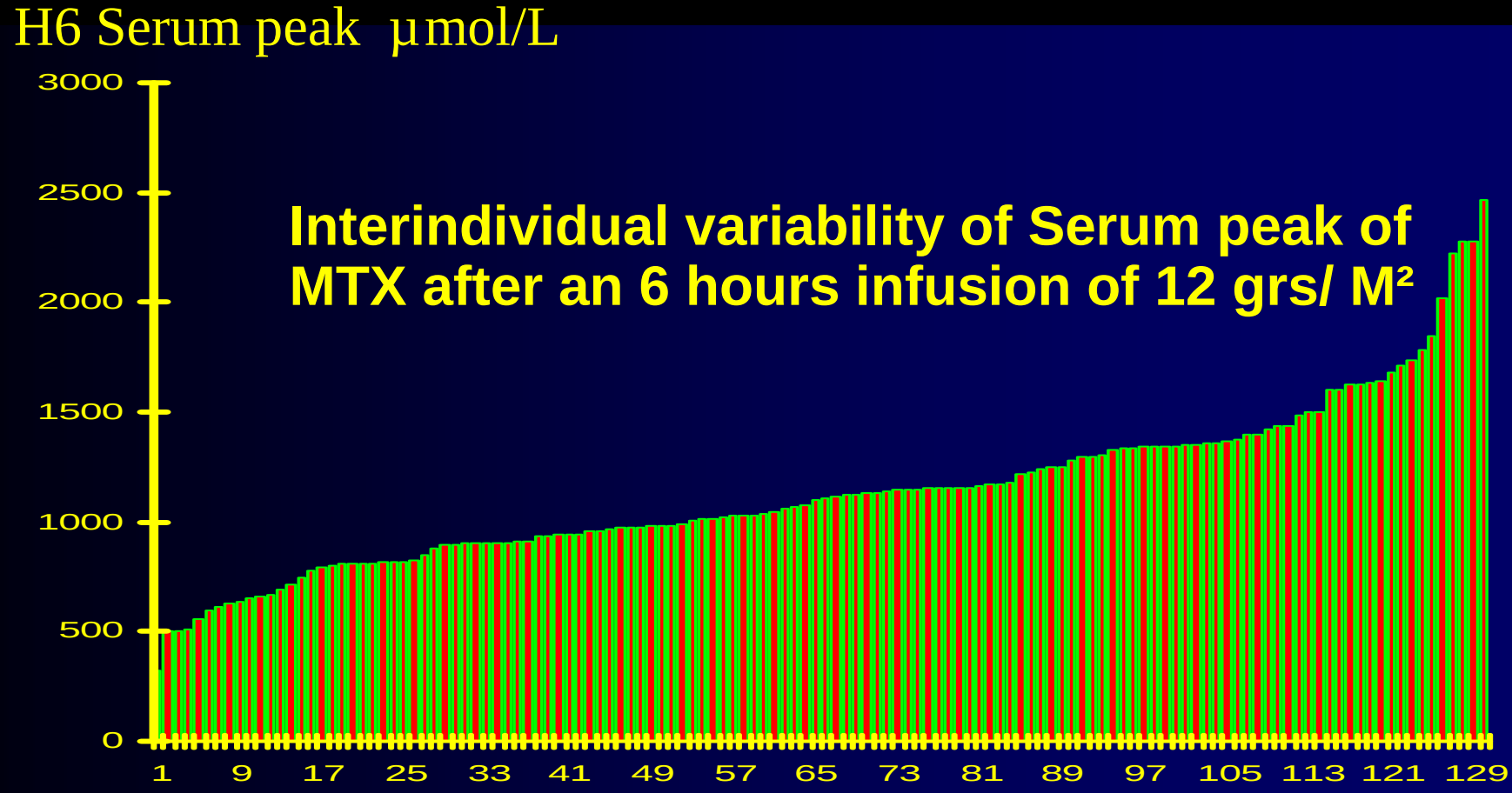
We are all unique, all different : sizes



These differences are not all well counterbalanced by the dosage in gr/m²

Husbands and wifes

Our pharmacokinetics of anticancer drugs are all unique, all different.



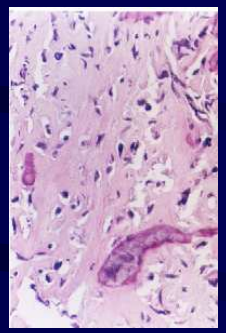
Pharmacockinetics of HD MTX. Conclusion about 622 courses performed in 4 years in children, teenager and adults. N. Delepine, G. Delepine, J.C. Desbois, H. Cornille, B. Brun, V. Subovici, S. Alkallaf, S. Nejmeh, C. Jasmin *Medical and Pediatric Oncology Vol 17 number 4 - page 304 ; 1989*

Tailoring the dose according individual PK

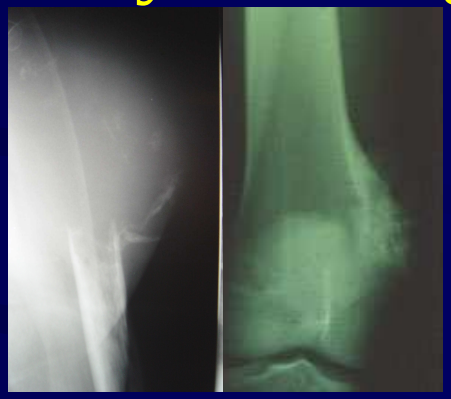
- If you infuse 12gr/sqm of MTX in 6 hours the peak of methotrexatemia can reach 2500 µmol /L or 350µmol/L resulting in increased risk of toxicity for some patients or ineffectiveness of treatment for others.
- Tailoring the dose according individual PK permits to overcome the inter individual variability for optimal therapeutic use.

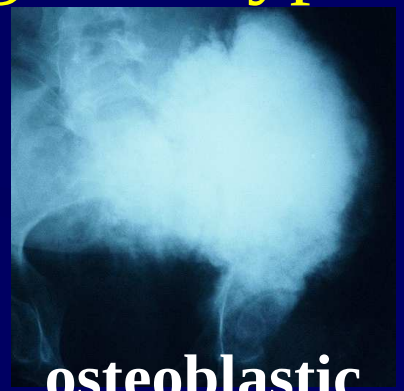
But Osteosarcomas are all different, all unique.

- Many histologic subtypes :
  - commun type
  - anaplasic
  - chondroblastic
  - telangectasic
  - fibroblastic...



- Many radiologic subtypes :





osteoblastic

- Many differents of cellular drug resistance.The presumed intrinsic MTX resistance has been ascribed to an impaired MTX polyglutamylation associated with both a decrease in FPGS activity and an increase in activity of FPGH.In addition, MTX uptake may be defective as observed whereas also high levels of (altered) DHFR have been reported

the genomic determinants of the antitumoral effects of MTX remain to be elucidated .

- The pharmacokinetics and pharmacodynamics of MTX in OS cells are well understood. Cellular uptake of MTX is mediated by the protein reduced folate carrier, whereas its efflux is mediated by ATP-binding cassette (ABC), subfamily C 1 (ABCC1) and ABCC4 .
- MTX is a tight-binding inhibitor of its primary target, enzyme dihydrofolate reductase (DHFR), which disrupts cellular folate metabolism. Within cells, MTX is metabolized into poly(γ-glutamate) forms (MTXPGs) by an adenosine triphosphate (ATP)-dependent reaction catalyzed by folylpolyglutamate synthetase.

such situation is comparable to treatment of severe septicemia.

- Bacteriologists use pharmacokinetics to adapt dose of antibiotics to individual PK
- and antibiogram to estimate the optimal serum concentration.

Which drug ?

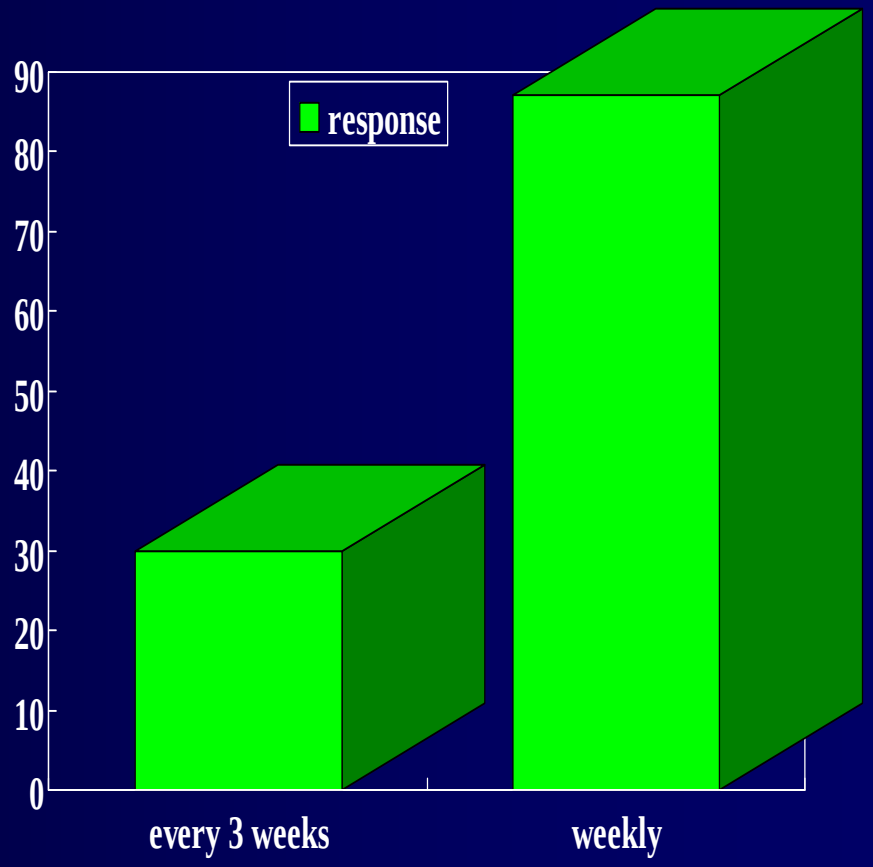
- Only two agents effective against osteosarcoma have a large therapeutic index permitting significant increase of dose : MTX and Ifosfamide .
- These two drugs demonstrated a dose/effect correlation on osteosarcoma.

Why do we prefer HDMTX ?

- MTX offers many advantages : It represents the only drug whose total dose and dose intensity are statistically correlated with 5 year disease free survival of patients
  - it can be infused with a weekly interval,
  - the pharmacokinetics can be easily studied,
  - the toxicity can be rescued by folinic acid,
  - and aplasia is usually not a problem when MTX is administrated in monotherapy.
  - For these reasons we use only MTX in preoperative CHT.

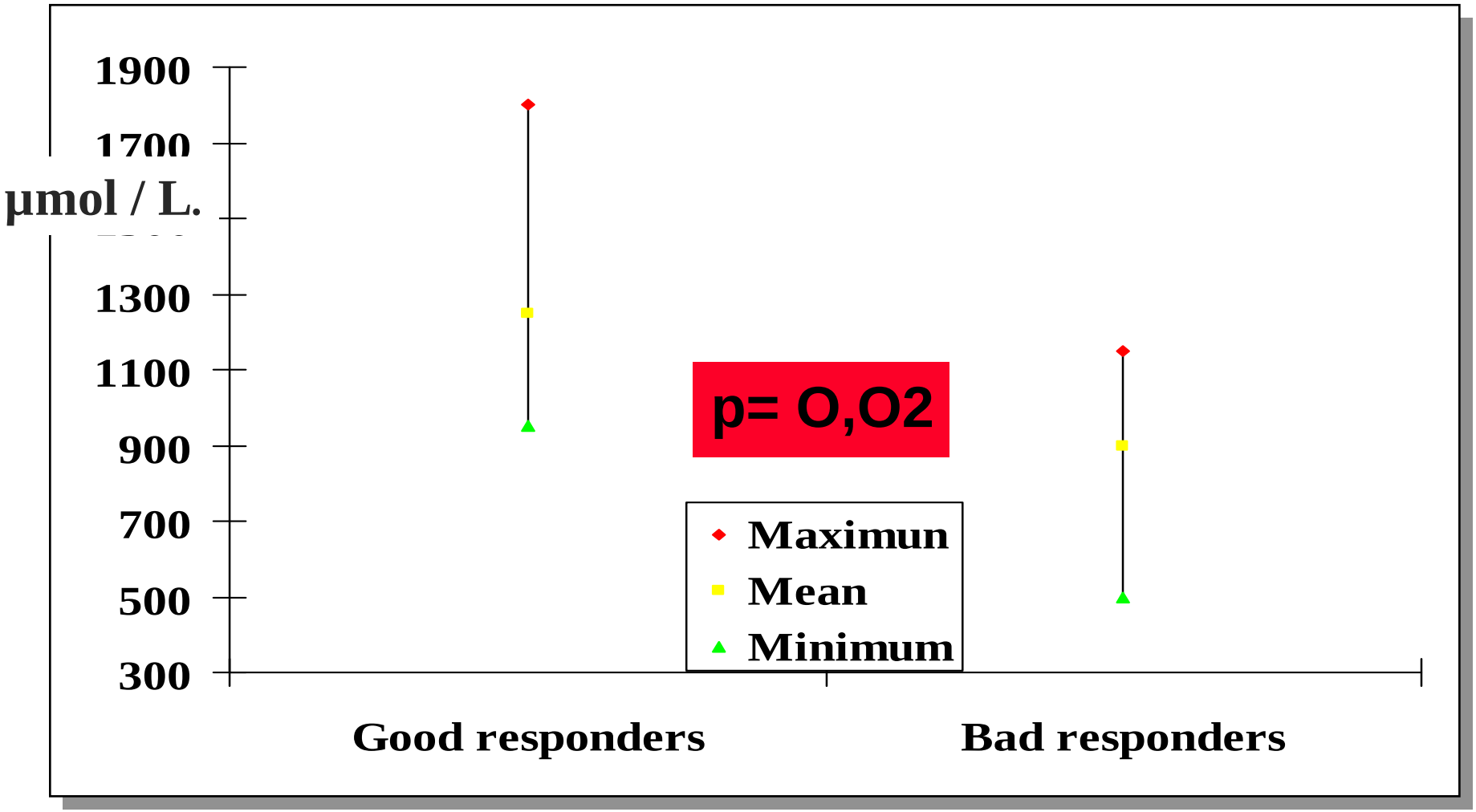
Jaffe demonstrated the correlation dose intensity of MTX/response of OS.

- High Dose Methotrexate (HDMTX) administered every 3 weeks obtain 30% response.
- but 87% when administered every week at higher dosage.



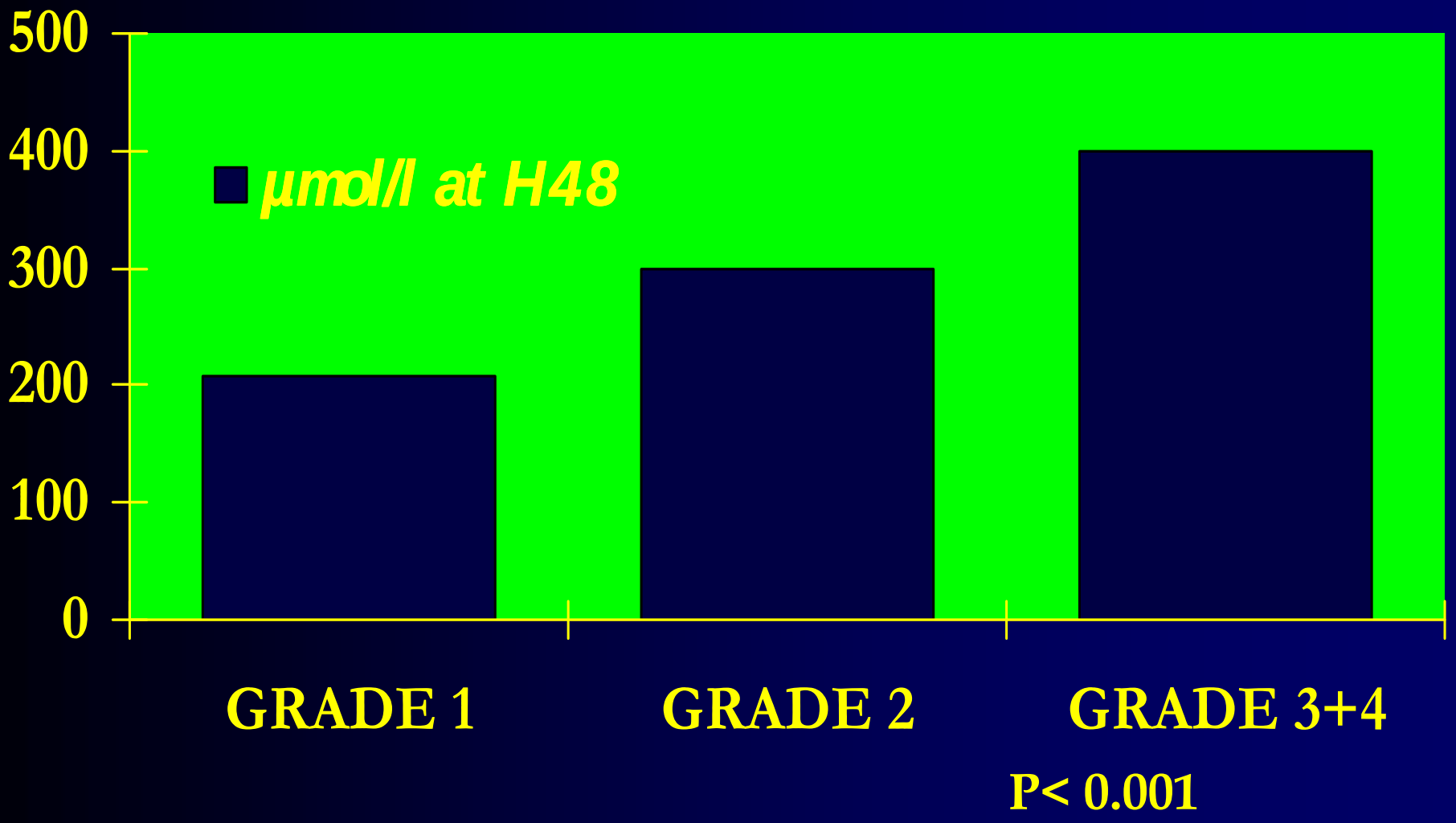
Récent advances in the chemotherapy of metastatic osteosarcoma **Cancer 1972,30: 1627**
"Weekly HDMTX and citrovum factor in osteogenic sarcoma **Cancer 1977, 39 : 45**

We have observed that mean methotrexatemia during preoperative phase is correlated with response.



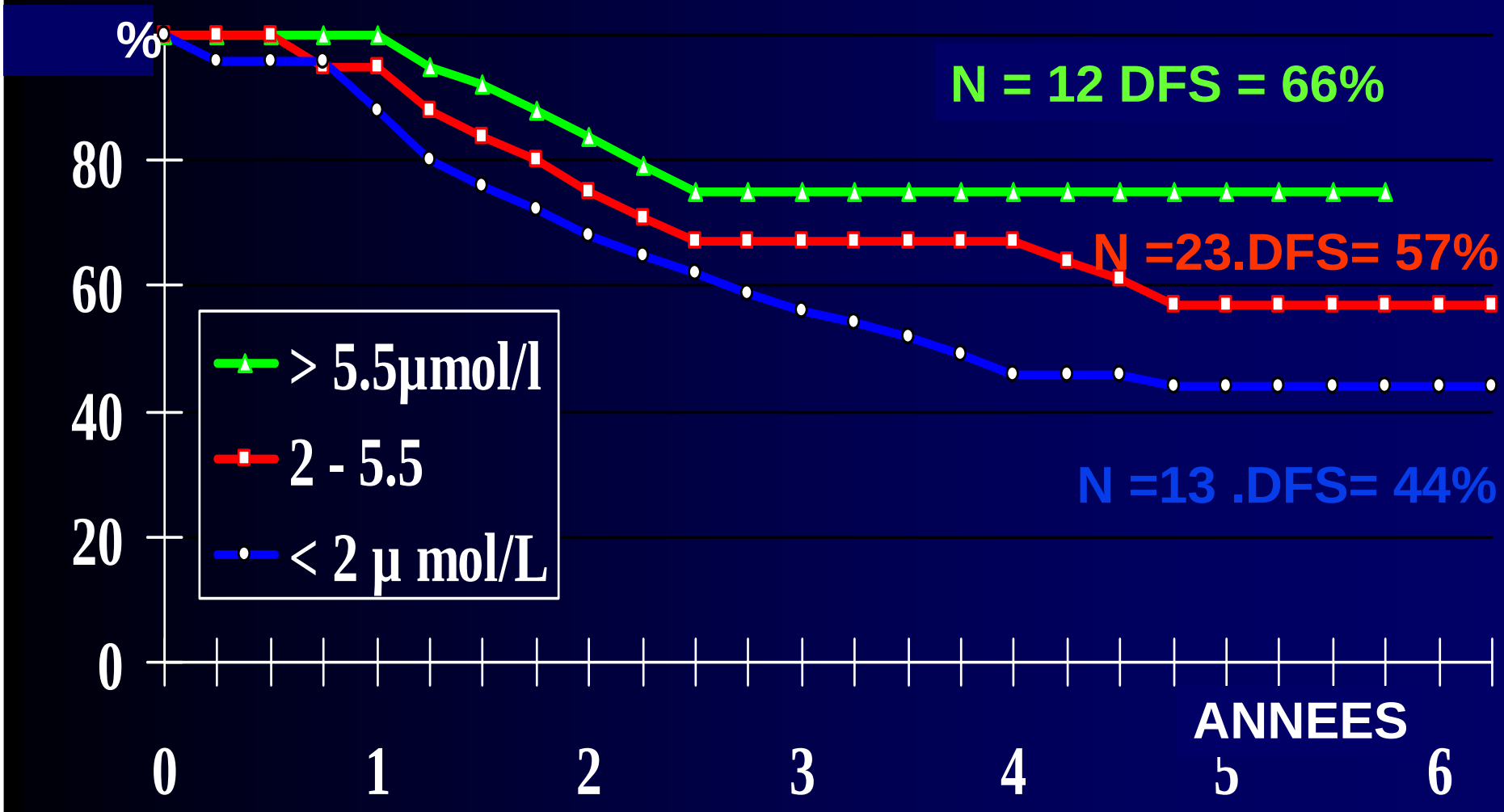
Correlation between seric methotrexate level and histologic response in osteogenic sarcoma. N. Delepine, G. Delepine, JC Desbois*Medical and paediatric oncology - Vol. 19 n° 5/1991*

ScandinavianT10.Correlation of H48 methotrexatemia and histologic response



SOLHEIM O . "THE TREATMENT OF OSTEOSARCOMA :PRESENT TRENDS. Annals of Oncology 3 (suppl..2) S 7 -S 11

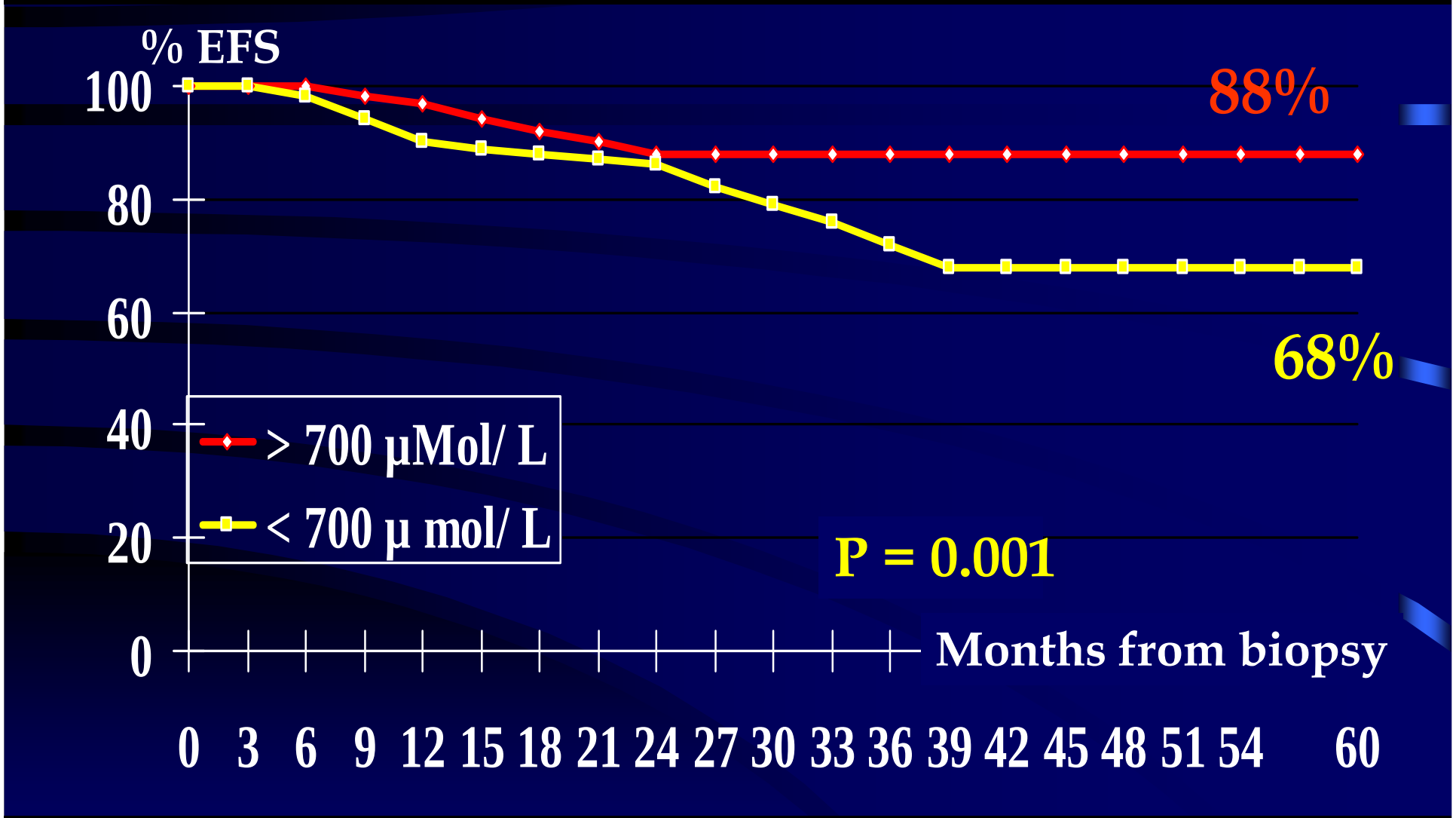
ScandinavianT10. Pronostic value of H48 methotrexatemia in grade 2 responders.



Saeter G. and all. " TREATMENT OF OSTEOSARCOMA. J.Clin.Oncol 9,10,1991:1766-1775

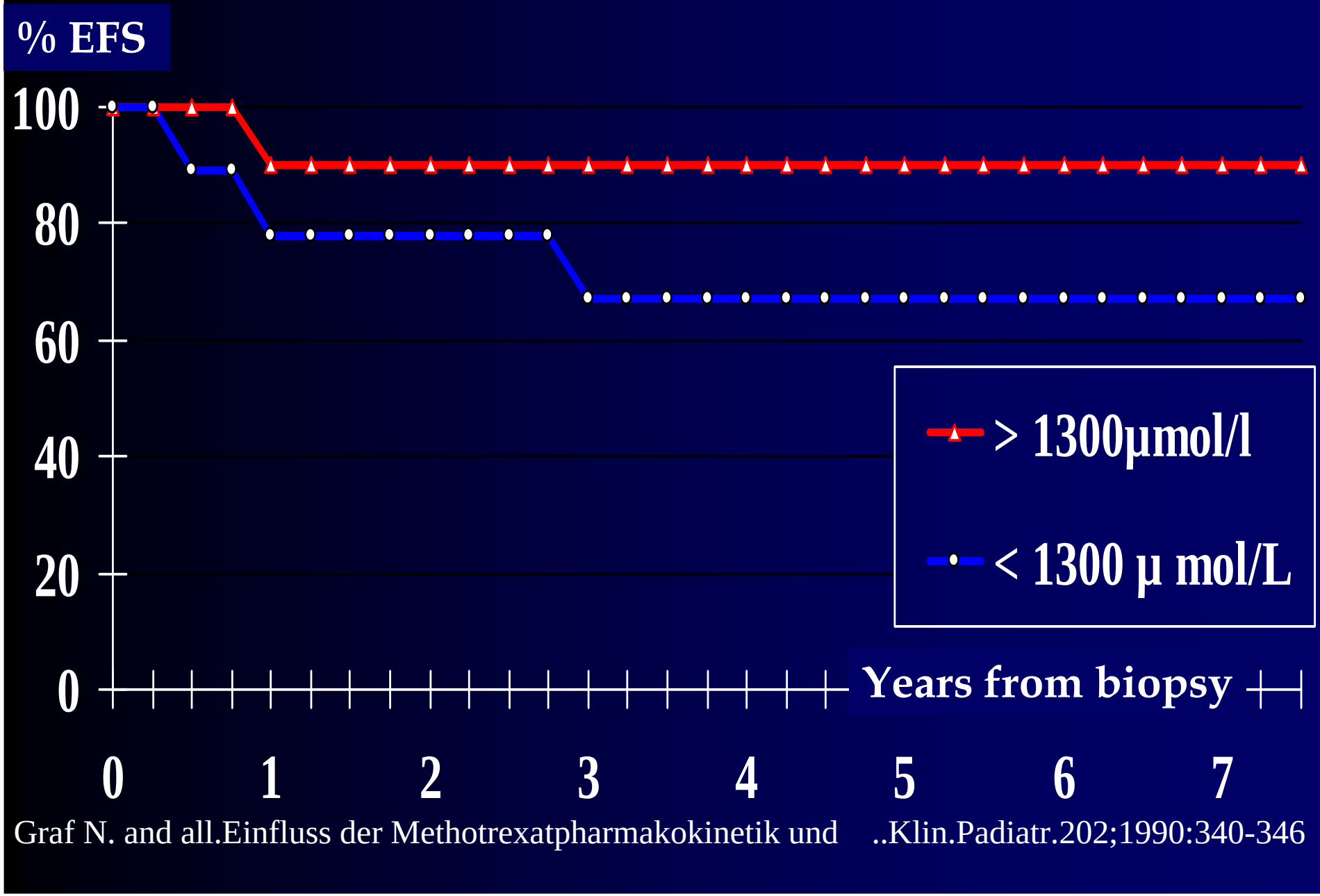
Pronostic value of H6 Methotrexatemia

PROTOCOLE RIZZOLI 2



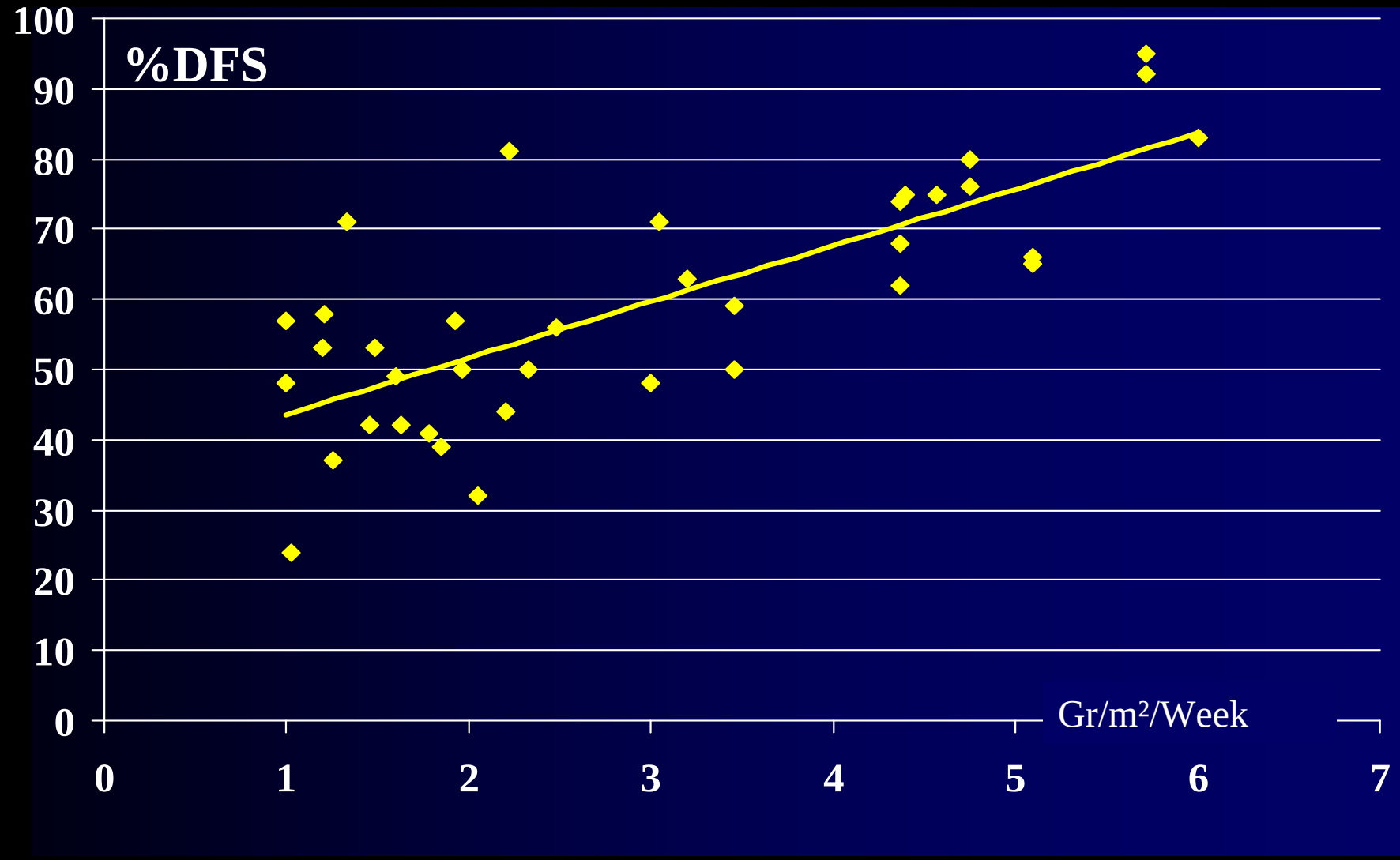
Bacci g.,Picci P. , Ruggieri P. et coll. "Primary chemotherapy and delayed surgery for osteosarcoma of the extremities." Cancer 65, 2539-2553 , 1990

GRAF N.Pronostic value of H4 methotrexatemia



Graf N. and all.Einfluss der Methotrexatpharmakokinetik und ..Klin.Padiatr.202;1990:340-346

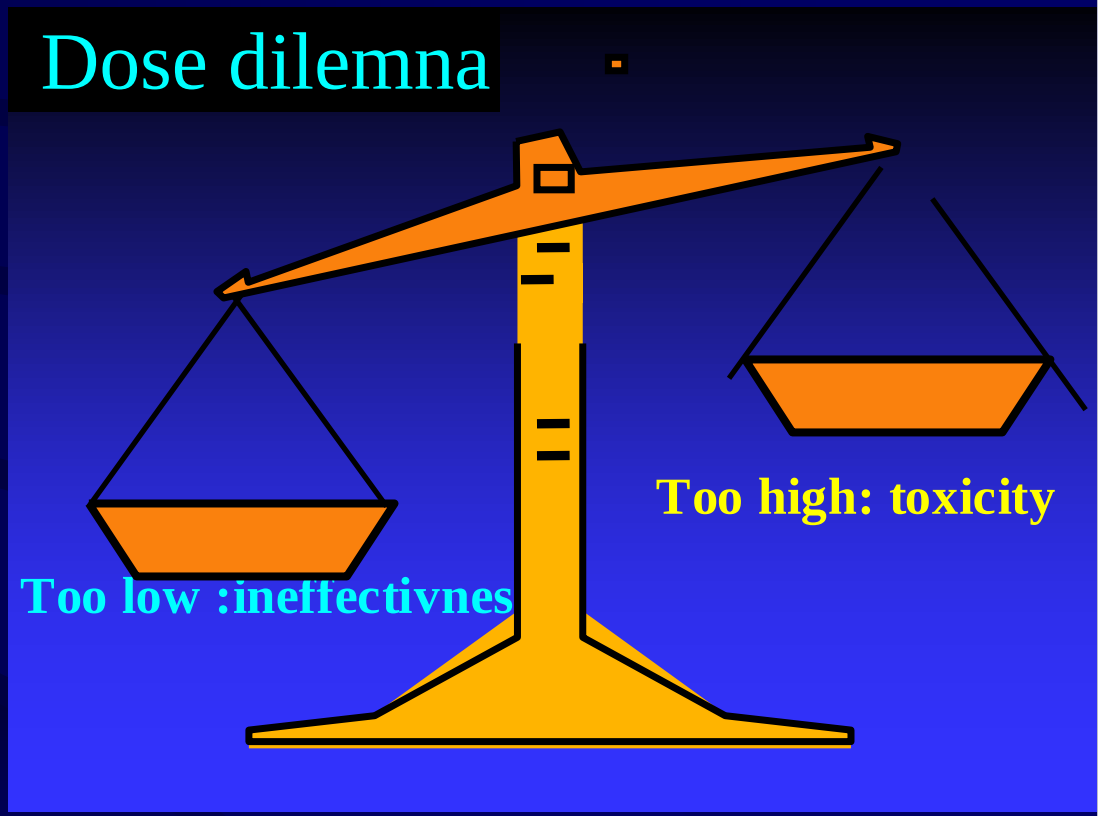
With MTX, more you give ,more you obtain : Correlation DFS/ dose intensity of MTX



Delepine, Rosen ,Bacci and coll Influence of methotrexate dose intensity on outcome of patients with high grade osteogenic osteosarcoma. A litterature analysis, about 1909 cases. Cancer, 1996, 78 : 2127-35.

But no gold standard for dose of MTX !

- **Pharmacokinetics of patients are individual.**
- Resulting for a fixed dose, in increased risk of toxicity for some patients and ineffectiveness of treatment for many others.



The resistance of OS to MTX cannot be accurately measured by in vitro methods such as the MTT assay

- For this reason, we used the in vivo response of newly diagnosed patients to initial single-agent MTX treatment, measured as an initial decrease in tumoral vascularization, to quantitate the antiosteosarcoma effects of MTX

Rationale of preoperative chemotherapy

Rosen G. and all. Primary Ostogenic Sarcoma .The rationale for preoperative Chemotherapy and Deayed Surgery. Cancer 43:2163-2177,1979

- Rosen thought that the follow up of the tumor during chemotherapy could permit to realize an antimitogram in vivo
- He gave preoperative chemotherapy to optimize the dose for an unique patient.

30 years ago G Rosen underlined that preoperative chemotherapy is an investigative method , Not a recipe

Chemotherapy for Osteogenic Sarcoma: An Investigative Method, Not a Recipe[1]

Gerald Rosen* and Anita Nirenberg[2]

The controversy over the role of chemotherapy for the treatment of osteogenic sarcoma arises because osteogenic sarcoma has been in the past and always will be a difficult and resistant tumor to treat with chemotherapy. In the majority of instances, the various pro-

with evaluable primary tumors. Experience in the direct observation of patients with evaluable disease who received this treatment has allowed us to determine the optimal dose of high-dose methotrexate for each patient. In addition, extensive pharmacokinetic

Allowed us to determine the optimal dose of HDMTX for each patient

[1]Received Mar 22, 1982; accepted Apr 8, 1982.

[2]Departments of Pediatrics (*G. Rosen* and *A. Nirenberg*) and Medicine (*G. Rosen*), Memorial Sloan-Kettering Cancer Center, New York, NY.

**Reprint requests to:* Gerald Rosen, MD, Department of Pediatrics, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10021.

Preoperative chemotherapy permits to find "the optimal dosage" for individual patient.

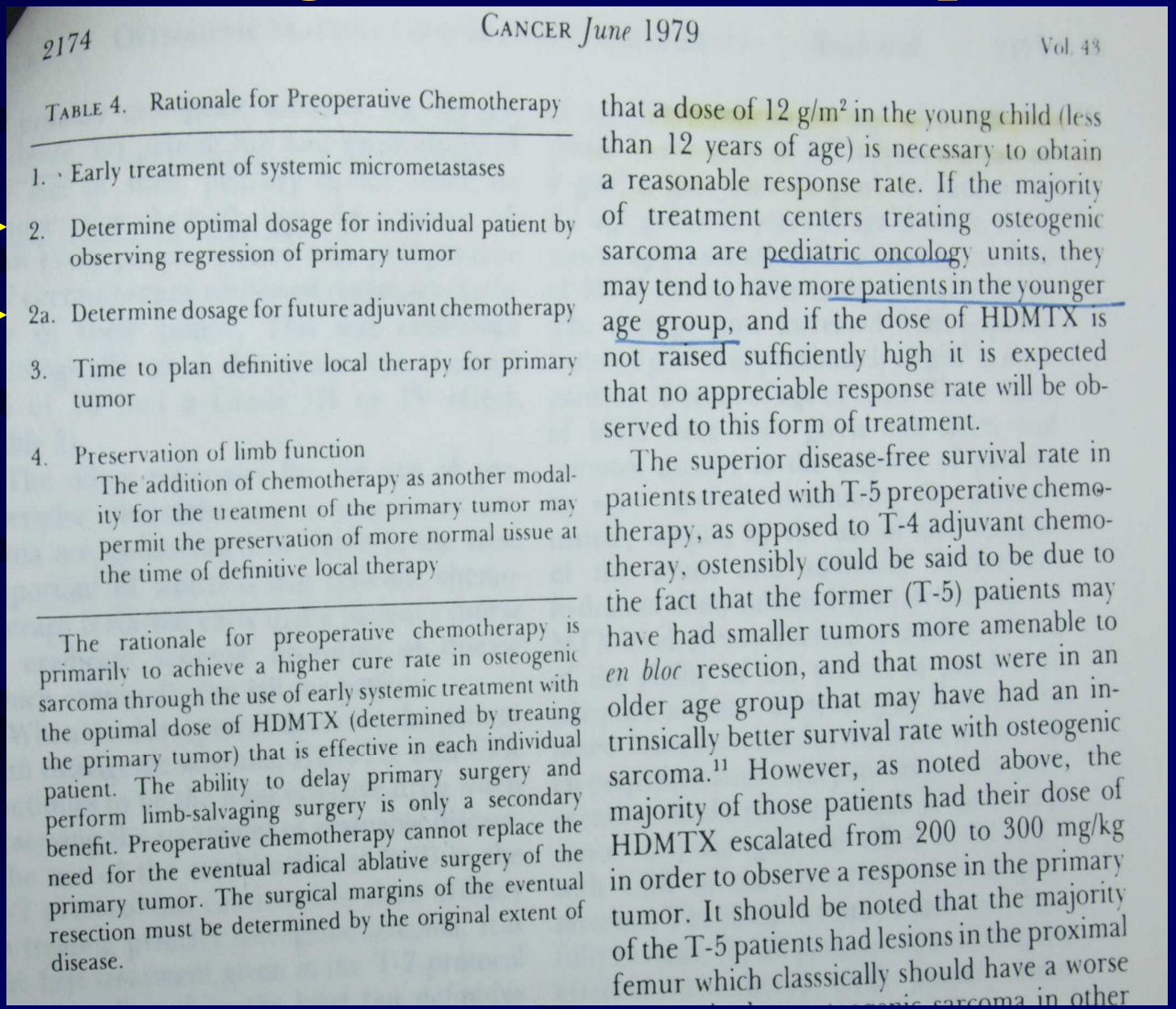


TABLE 4. Rationale for Preoperative Chemotherapy

1. Early treatment of systemic micrometastases
2. Determine optimal dosage for individual patient by observing regression of primary tumor
2a. Determine dosage for future adjuvant chemotherapy
3. Time to plan definitive local therapy for primary tumor
4. Preservation of limb function
   The addition of chemotherapy as another modality for the treatment of the primary tumor may permit the preservation of more normal tissue at the time of definitive local therapy

The rationale for preoperative chemotherapy is primarily to achieve a higher cure rate in osteogenic sarcoma through the use of early systemic treatment with the optimal dose of HDMTX (determined by treating the primary tumor) that is effective in each individual patient. The ability to delay primary surgery and perform limb-salvaging surgery is only a secondary benefit. Preoperative chemotherapy cannot replace the need for the eventual radical ablative surgery of the primary tumor. The surgical margins of the eventual resection must be determined by the original extent of disease.

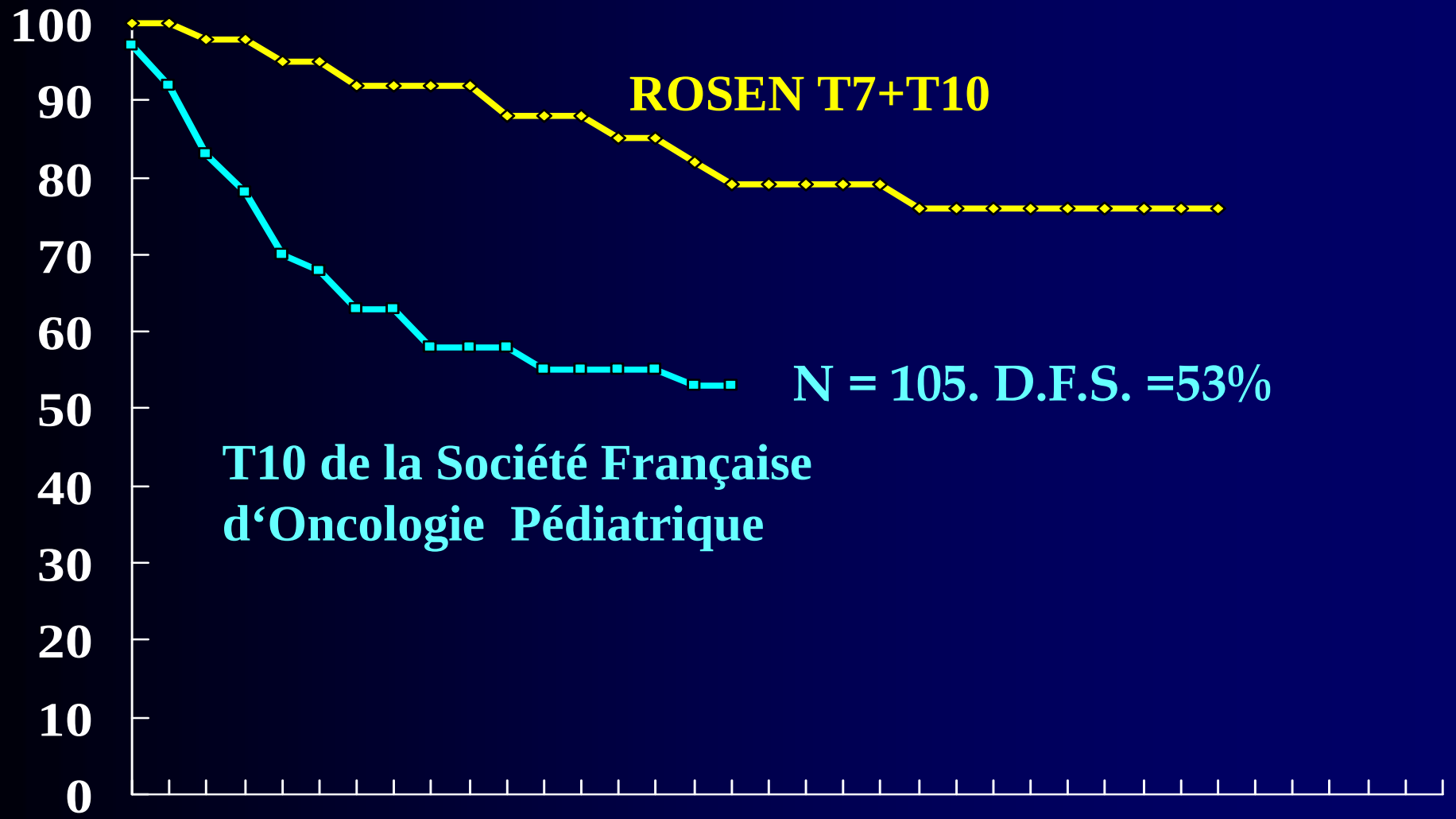
that a dose of 12 g/m² in the young child (less than 12 years of age) is necessary to obtain a reasonable response rate. If the majority of treatment centers treating osteogenic sarcoma are pediatric oncology units, they may tend to have more patients in the younger age group, and if the dose of HDMTX is not raised sufficiently high it is expected that no appreciable response rate will be observed to this form of treatment.

The superior disease-free survival rate in patients treated with T-5 preoperative chemotherapy, as opposed to T-4 adjuvant chemotheray, ostensibly could be said to be due to the fact that the former (T-5) patients may have had smaller tumors more amenable to *en bloc* resection, and that most were in an older age group that may have had an intrinsically better survival rate with osteogenic sarcoma.[11] However, as noted above, the majority of those patients had their dose of HDMTX escalated from 200 to 300 mg/kg in order to observe a response in the primary tumor. It should be noted that the majority of the T-5 patients had lesions in the proximal femur which classsically should have a worse

But all multicentric protocols derivated from Rosen forgot the rationale

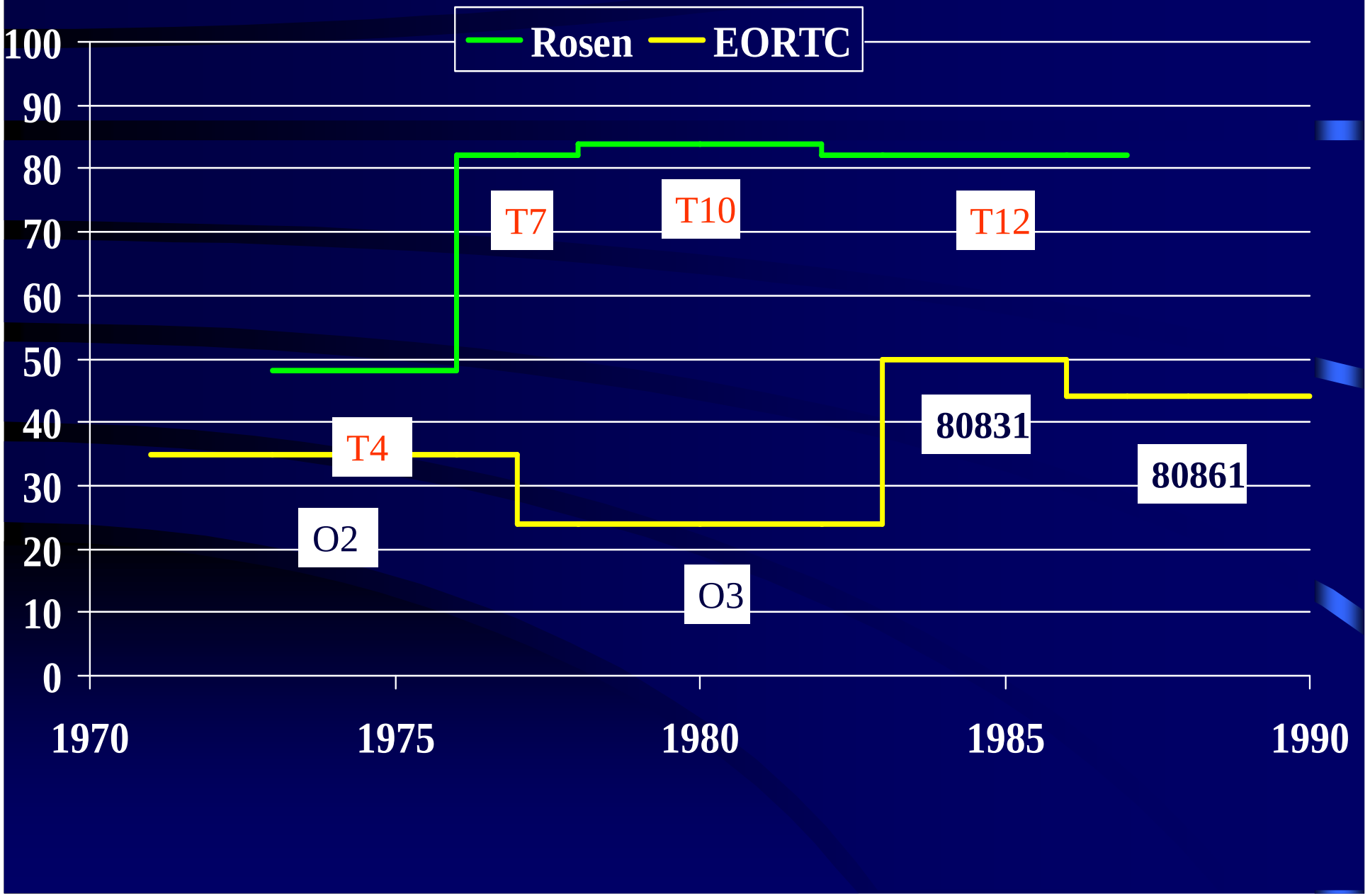
- They used the same dose for all patients.
- Resulting in too much toxicity in some patients
- And suboptimal dosage of MTX in others
- They did not reproduce the method
- they did not reproduce the results

Results of SFOP " T10 "1979-1986

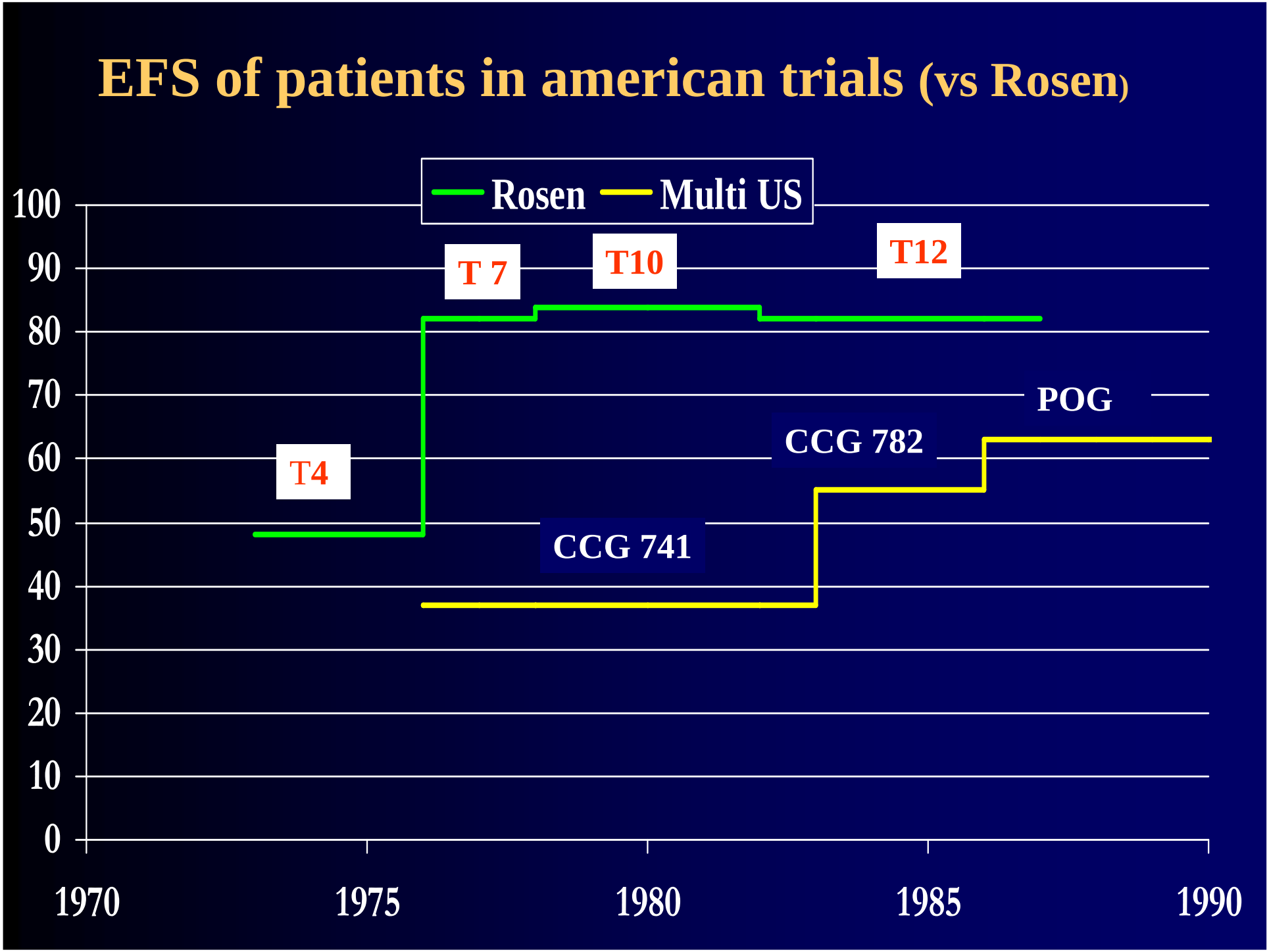


M.BRUNAT-MENTIGNY 1988 "La reproduction du protocole de ROSEN pour les osteosarcomes. Bull.Cancer 1988,75:201-206.

EFS of patients in EORTC- EIO trials (vs Rosen)

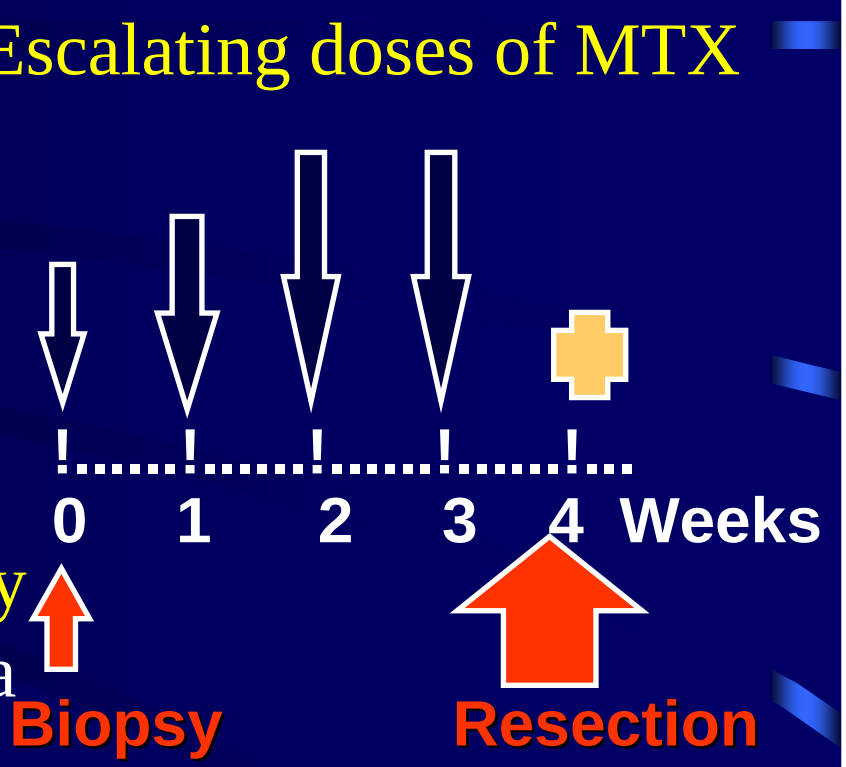


EFS of patients in american trials (vs Rosen)



We tried to apply Rosen ’s rationale

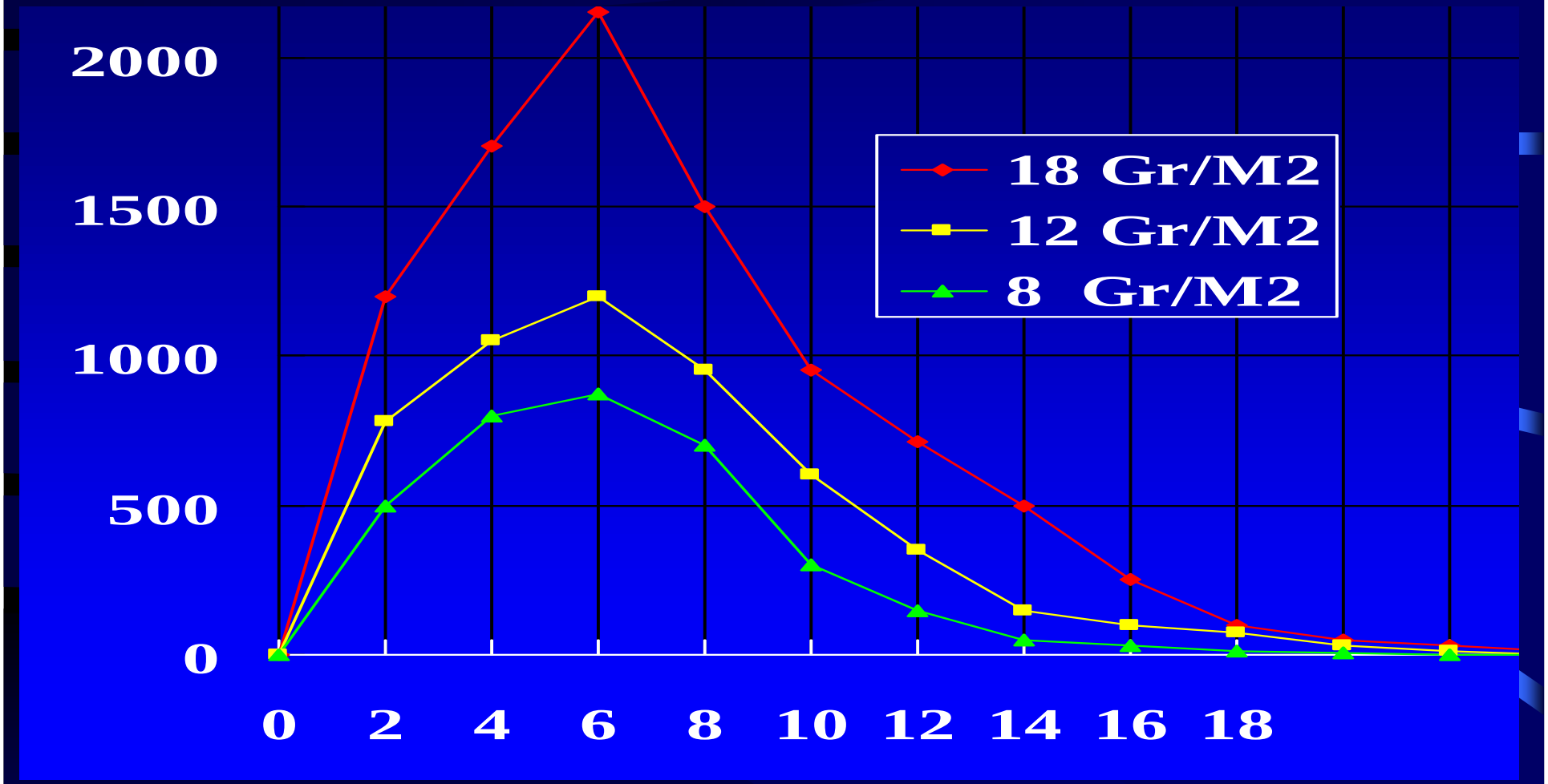
- As soon after biopsy we start with HDMTX (8 to 15 G/Sqm according to age) with complete PK study.
- On D7 the second curse is administered with a tailored dose to obtain :
- a clinical response of the primary (decreasing of local hyperthermia and vascularisation).
- And a serum peak of 1000µmole/L



During preoperative chemotherapy the surgeon must evaluate the tumor every week

- we increase the dose
- If the serum peak is too low
- less than **1000µmol/l if infusion of 6 hours**
- Rosen propose **1450µmol/l for an infusion of 4 hours**
- if pain or local hyperthermia remains

OS.DD protocols …Preoperative chemotherapy

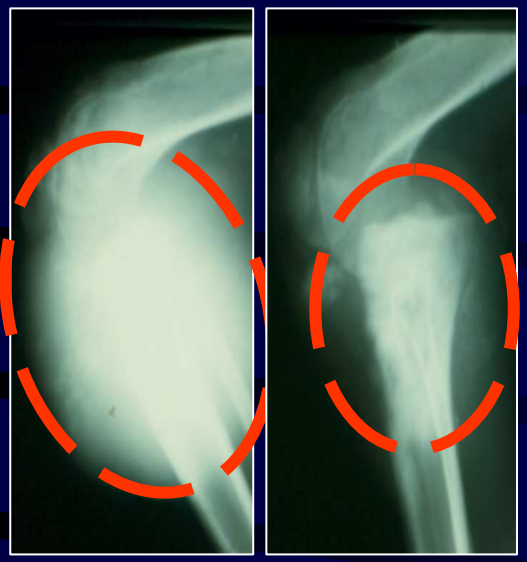


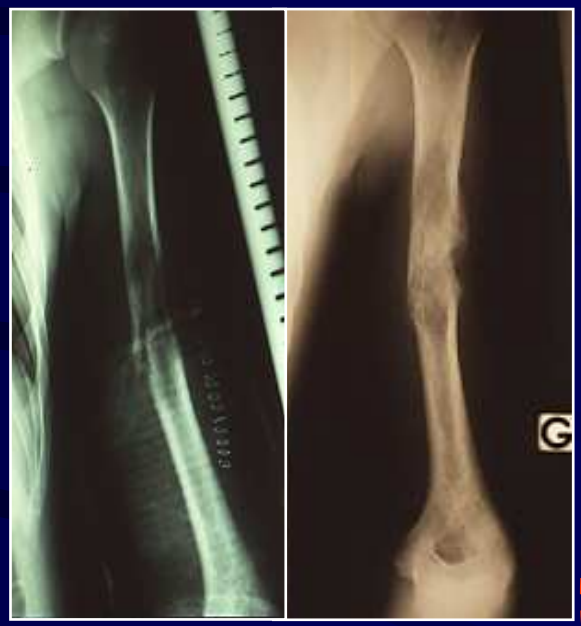
MTX doses are increased if the serum peak is too low of if tumor does not respond enough

60% of our patients received escalating doses

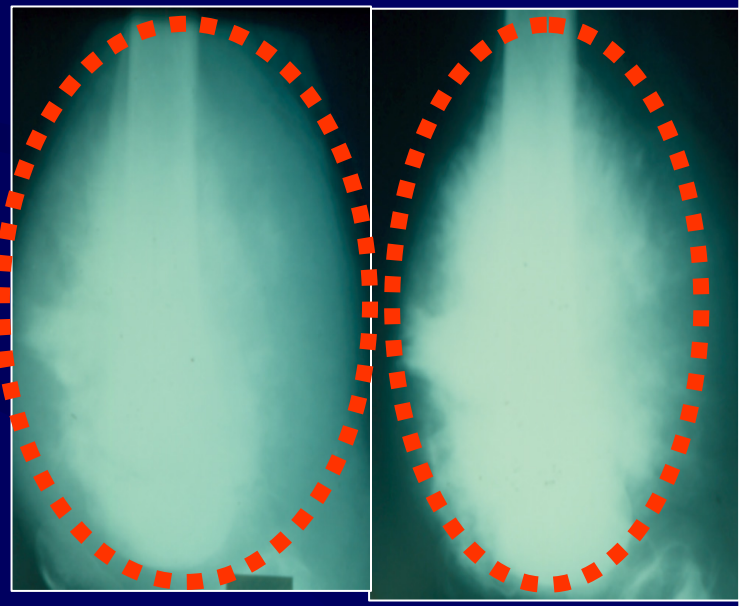
- The mean increase of dose is 40%; We had sometimes to increase the dose up to 22 G/Sqm per curse.
- With such a method we always obtain clinical response of primary OS and never more observe progression of disease during preop chemotherapy.
- With a reinforced rescue they do not suffer of increased toxicity

Response after individualized preoperative MTX





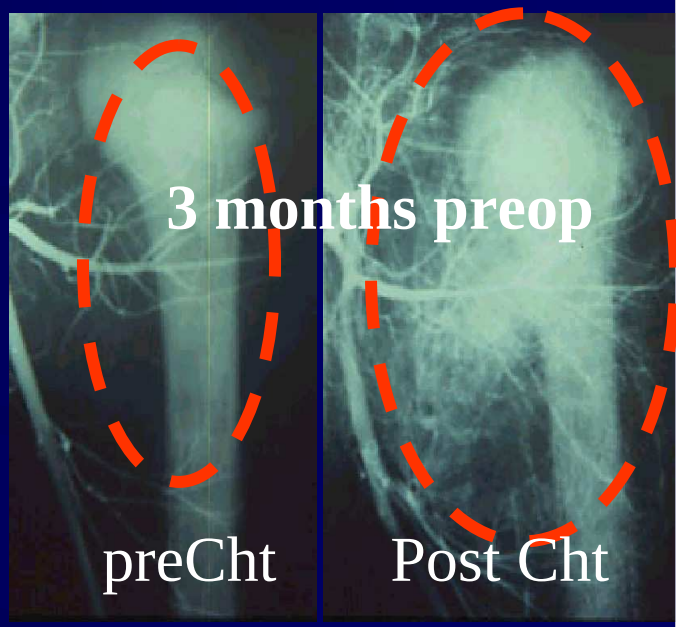
ONE MONTH Preop

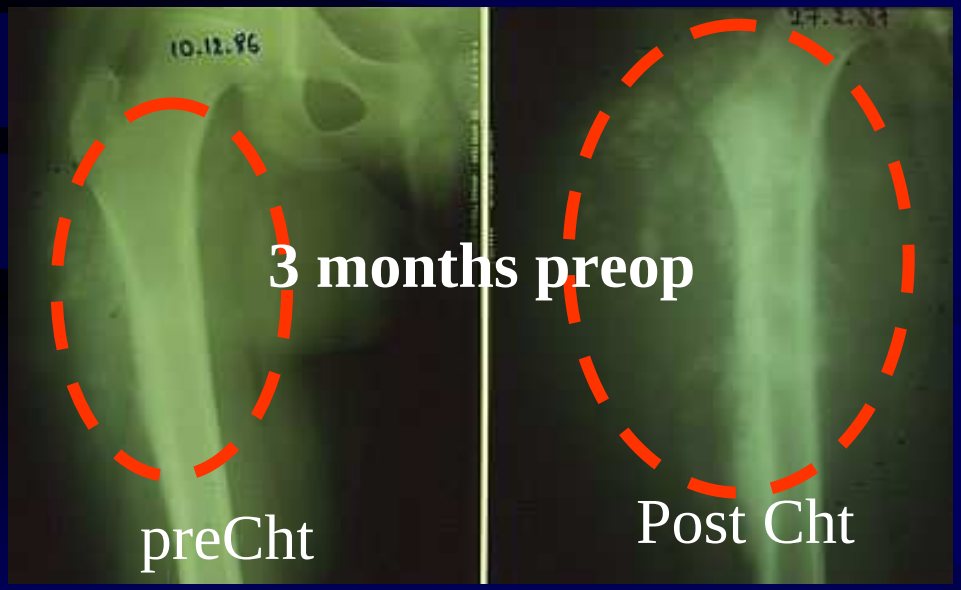


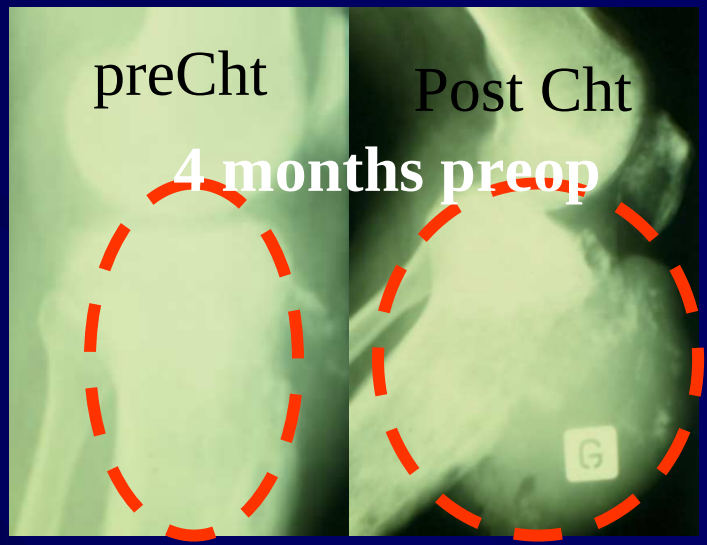
- 4 to 5 courses of individualized doses of MTX are enough for surgeon even in case of fracture

Preoperative chemotherapy can be dangerous

Too long preoperative chemotherapy may be dangerous if chemotherapy is not effective enough and may increase the risk of induction of chemoresistance and of metastases.







All these patients died

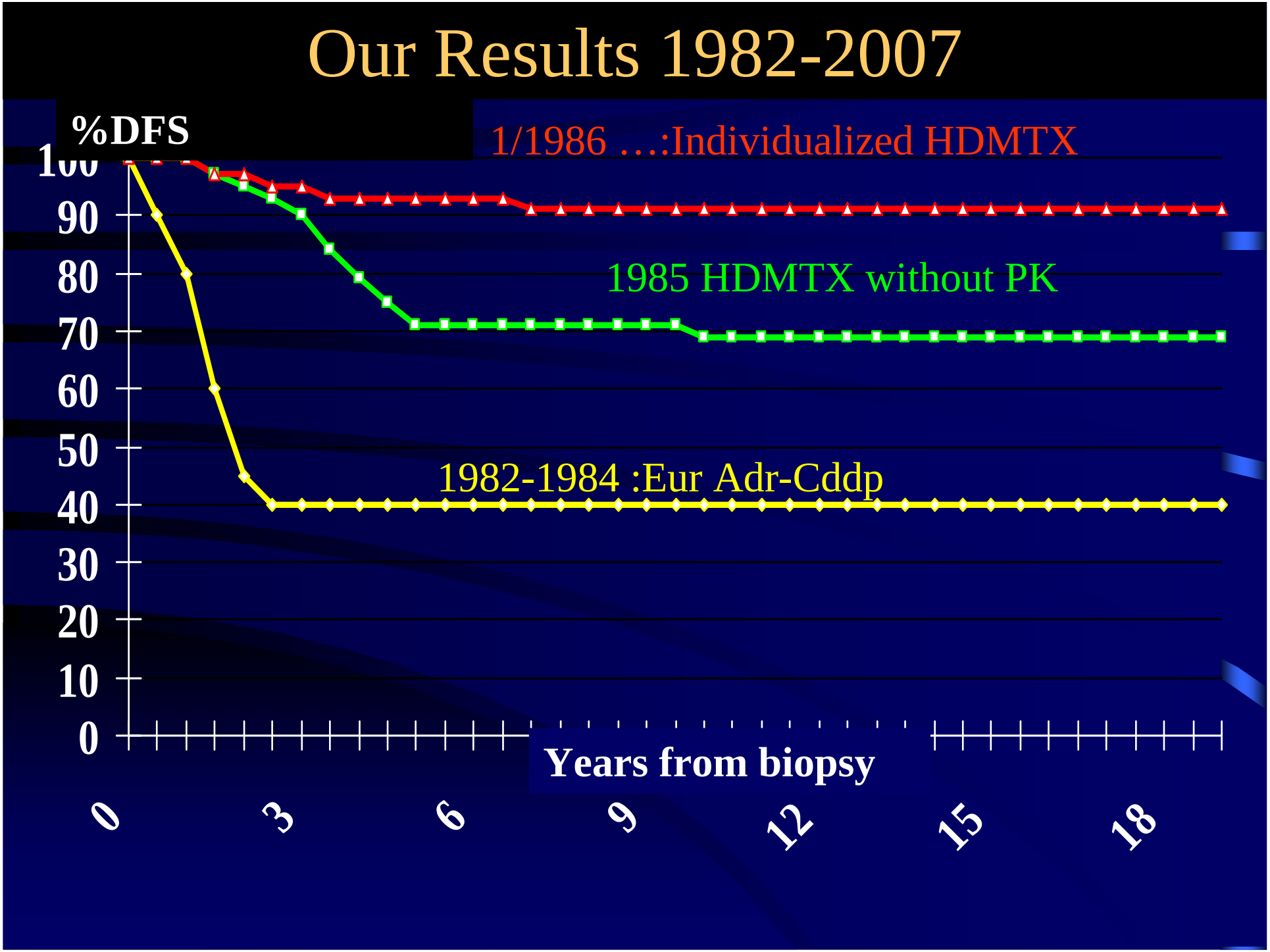
Timing of surgery

- After usually 4 courses we resect the tumor. In our practice we never need to primary amputate patients seen before biopsy.
- Peri operative chemotherapy is administered immediately following surgery (day 2 to day 4) using Ifosfamide alone.

Postoperative chemotherapy

- uses HDMTX (12 additional courses at the effective dose), IFO (3 courses with 12 G/m² or more), Theprubicin and CDDP (3 courses).
- We use the same drugs in good and bad responders
- Bad responders received two cycles more.

Our Results 1982-2007



Conclusions

- We are all unique , all different.
- Osteosarcomas are all different.
- We all know that tailored suit fit us better than standardized suit.
- We treat severe infection with individualized antibio therapy accorded to pharmacokinetics and antibiogram.
- We should treat patients with individualized doses of HDMTX