

MULTICENTRIC RANDOMIZED TRIALS FOR HIGH GRADE OSTEOGENIC OSTEOSARCOMA. COST-EFFECTIVENESS ?

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Backgrounds

Randomization of treatment represents the best theoretical way to avoid bias when performing studies between two groups of patients.



Evidence based medicine ?

Unfortunately for many doctors, this rule of randomization leads to forget the other methodological and ethical aspects of clinical research on human beings and consists in an intellectual «terrorism».

Each non randomized trial is, a priori, doubtful.



- The publications, which relate the results of pilot studies are discriminated or refused in American reviews.
- It's the same for communications.



Question

**Are multicentric randomized trials
really efficient in clinical practice
for our patients ?
and the scientific progress ?
which are their cost for our
patients ?
and for social insurance systems ?**

Aim of the study

This study of the last 20 years tries to **compare the benefice /cost** of randomized trials in high grade osteosarcoma to those of monocentric studies **in term of disease free survival for patients and cost effectiveness for the community.**

Introduction

These last 20 years chemotherapy of patients with osteosarcoma has been dramatically improved. Nevertheless dilemmas and controversies have been continuously developed.



Main controversies

- 1°) Is chemotherapy useful for patients with high grade osteosarcoma?
- 2°) Is limb salvage dangerous for patients?
- 3°) Is methotrexate dose and/or pharmacokinetics a prognostic factor?



Search method

All published treatment studies about osteosarcoma have been detected.

- By a double computed search (Medline and Cancernet),
- By the analysis of literature of published data,
- Completed by the analysis of main orthopaedic and oncologic congresses abstracts.



Criteria for inclusion

After computed search of all published studies on treatment of osteosarcoma, we analyzed all studies including **more than 20 patients** in each treatment arm with **at least 5 years follow up and clear conclusions.**

Included studies

- Multicentric randomized trials
 - Randomized monocentric trials
 - Monocentric pilot studies
- when satisfying inclusion criteria



Nowaday established data

1. Chemotherapy is useful for high grade osteosarcoma
2. Conservative surgery is not dangerous when
3. Use of MTX gives better results



Evaluation

- Published conclusions were compared to actual state of the art.
- Useful trials (giving the right conclusions) were rated from +1 to +10 following their publication rank.
- Misleading conclusions of trials were rated - 1 to -10 following their potential consequences.



This scoring system has been applied :

- To the treatment conclusions with direct benefice to the patient
- To others conclusions useful to the knowledge of the illness.



RESULTS

The analysis of the literature demonstrates the following facts :



Observation 1

Multicentric trials never
reproduce completely
the good results of pilot
studies that led to them

!

Observation 2

No multicentric randomized trial has permitted to point out any factor able to improve the length or/and the quality of life of patients with osteosarcoma.

The first advocates of chemotherapy for osteosarcoma

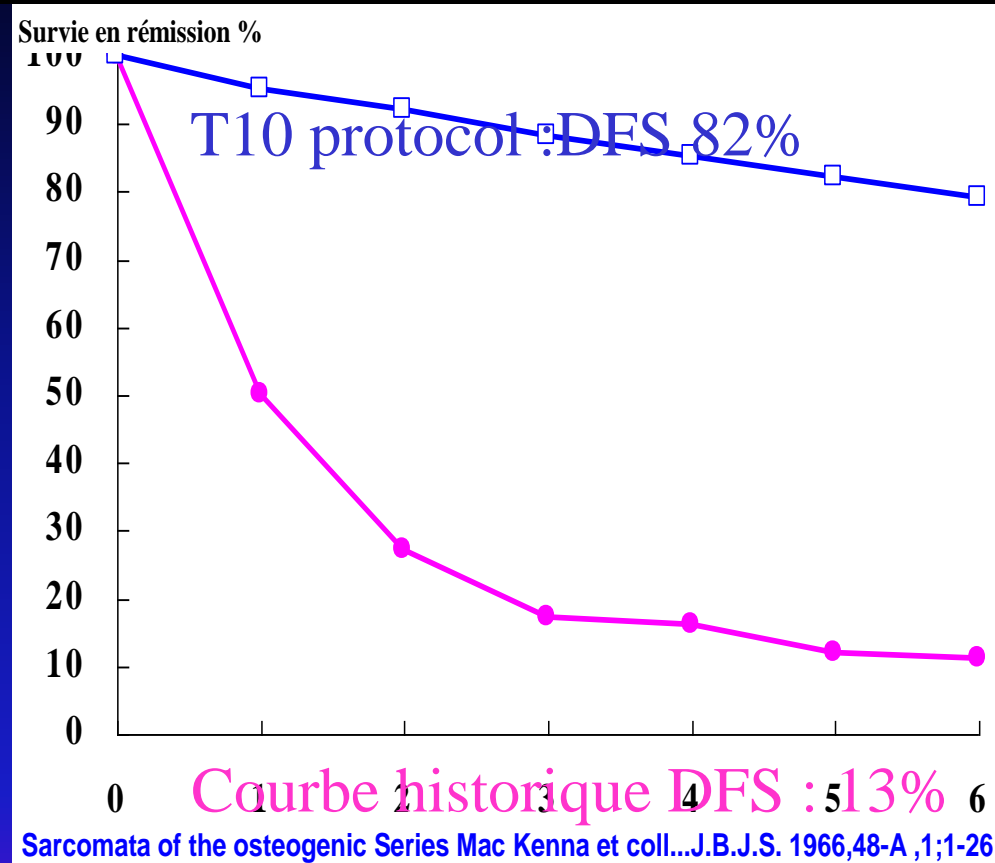
• <u>Cortes</u>	<i>N. Eng. J. Med.</i>	<i>1974</i>
• <u>Jaffe</u>	<i>N. Eng. J. Med.</i>	<i>1974</i>
• <u>Sutow</u>	<i>J. Bone Joint Surg.</i>	<i>1976</i>
• <u>Rosen</u>	<i>Cancer</i>	<i>1976</i>
• <u>Frei</u>	<i>J. Nat. Canc. Inst.</i>	<i>1978</i>
• <u>Bacci</u>	<i>J. Bone Joint Surg.</i>	<i>1980</i>
• <u>Bleyer</u>	<i>J. Bone Joint Surg.</i>	<i>1980</i>

All the studies (excepted study of Frei) were monocentric and non randomized...



In 1979 Jaffe and Rosen

Strongly advocated
adjuvant
chemotherapy .
Historical
comparaison was
demonstrative
enough



Any trial chemotherapy versus nothing would
be useless and unethical.

Controversy of 1980

- People who advocated randomized trials **among them the Mayo Clinic and the National Cancer Institute replied that a spontaneous amelioration of the illness and a stage migration could explain the difference.**
- They criticized the Rosen methodology and the use of historical comparison.



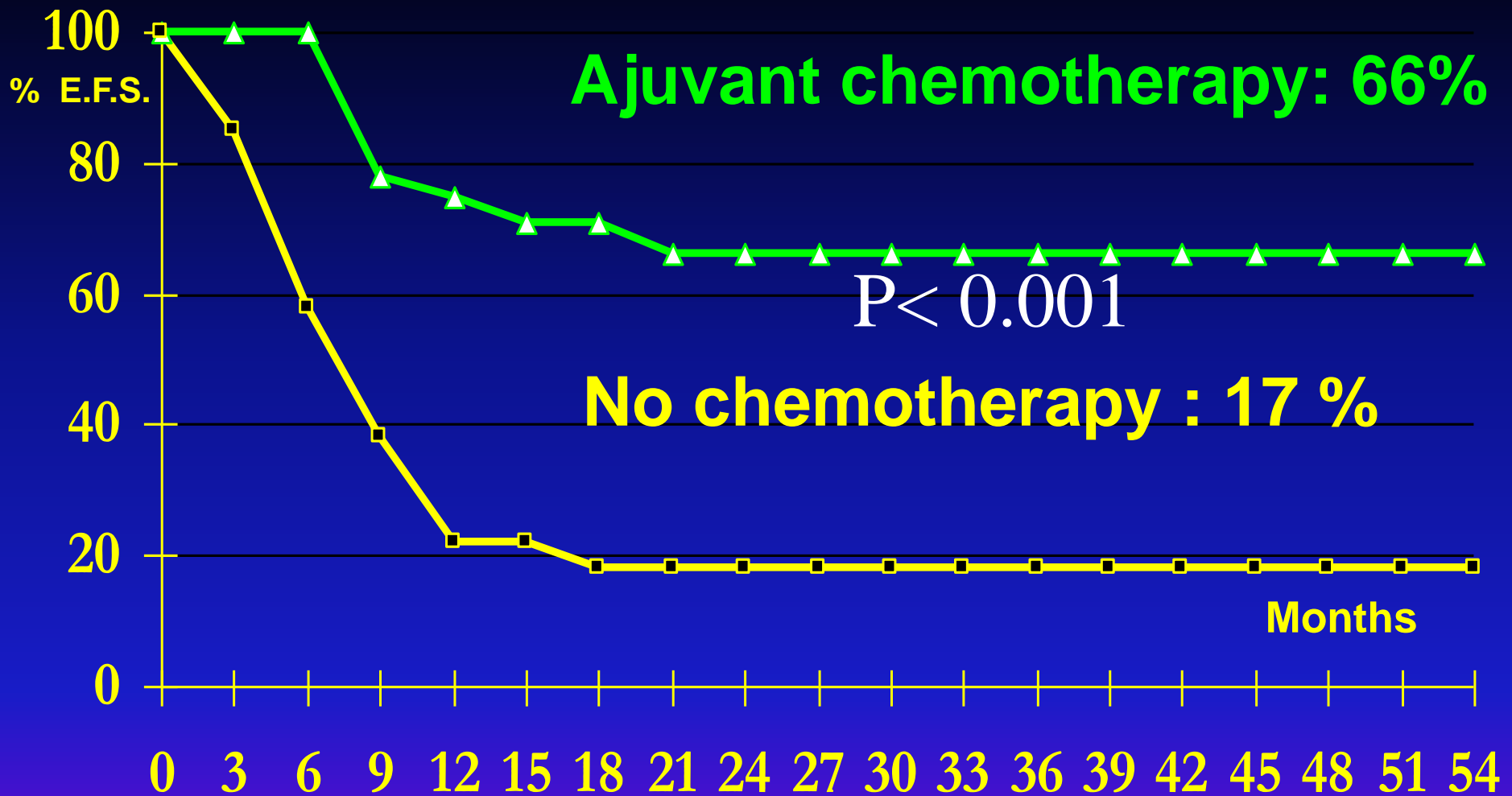
Detractors of chemotherapy in osteosarcoma

- *Rosenberg C. Treatment Rep. 1979*
39 patients
- *Jasmin GETO-EORTC trial 1979*
8 centers 27 patients randomized
- *Edmonson J. Clin. Oncol. 1984*
*Mayo Clinic 38 patients randomized**
- *Taylor J. Nat. Canc. Inst. 1989*
9 centers 350 patients

**led to randomized trial MIOS 1984 (published by Link 1986).*

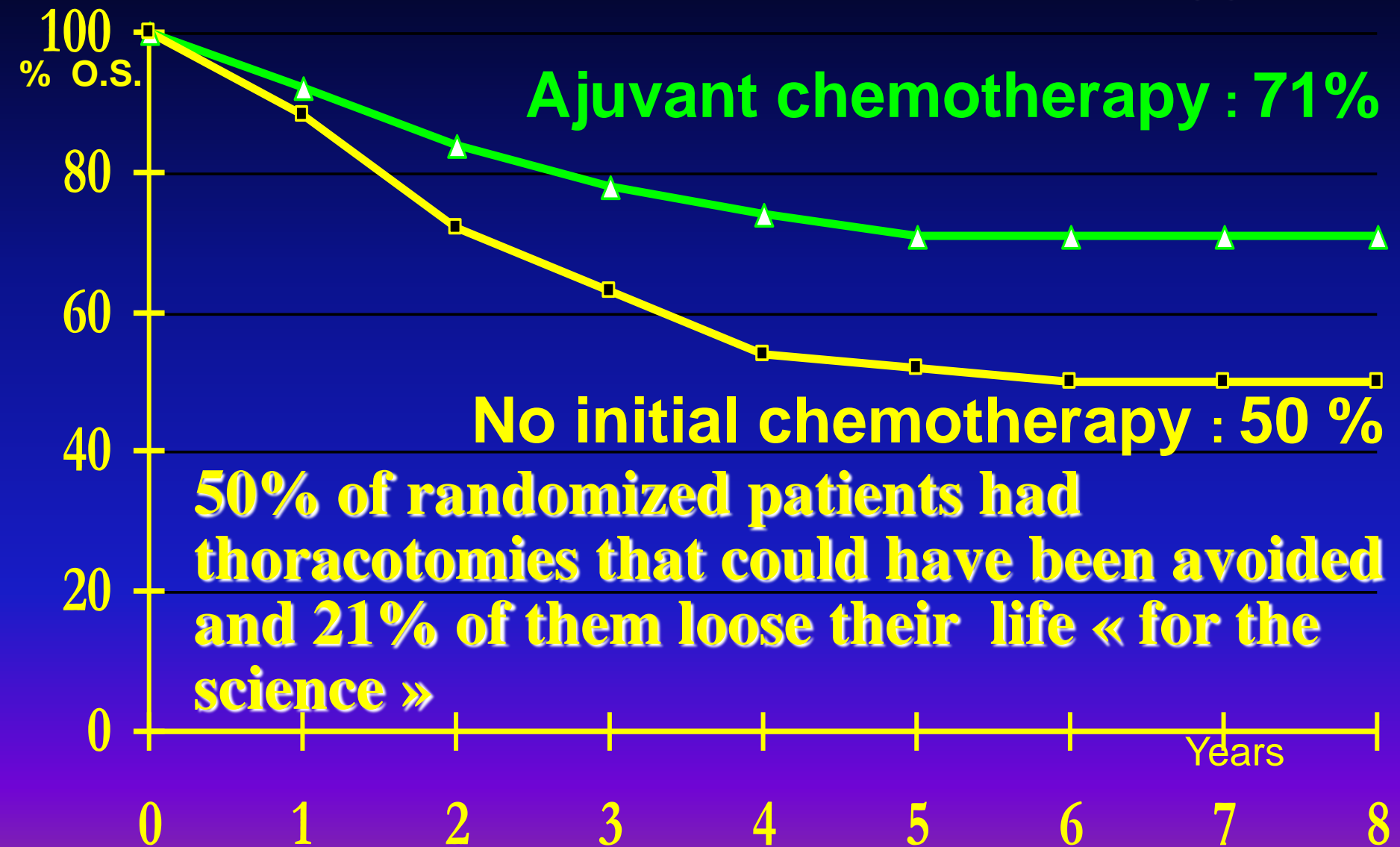


Results of MIOS trial



**Adjuvant chemotherapy increases by 4 times
the event free survival**

Consequences for patients to have been randomized in MIOS Trial(1)



- # **Critical Review of literature : Cost for U.S. patients of the randomized MIOS Trial**
- 1°) 50% of randomized patients had thoracotomies that could have been avoided and 21% of them loose their life « for the science »**
 - 2°)The randomized control of efficacy of chemotherapy delayed its application by 6 years 1979-1986 .**
 - 3°)resulting in secondary death from suboptimal therapy for about 4000 patients.**



Interest of the pre trial controversy

The open controversy which arose before the MIOS trial **permitted to patients to obtain a better information and to choose their treatment if they wanted.**

Among the 77 patients who refused to be randomized **(77%) choosed adjuvant chemotherapy arm**

demonstrating that **informed patients can be more Wise than doctors !**



First advocates of modern conservative surgery :

- | | | |
|---------------------------|-----------------|-------------|
| • <i>Marcove et Rosen</i> | <i>Cancer</i> | <i>1979</i> |
| • <i>Delepine</i> | <i>RCC</i> | <i>1985</i> |
| • <i>Goorin</i> | <i>JCO</i> | <i>1987</i> |
| • <i>Eilber</i> | <i>JCO</i> | <i>1987</i> |
| • <i>Sprinfeld</i> | <i>J.B.J.S.</i> | <i>1988</i> |

none of these works were neither randomized, nor multicentric.



Detractors of limb salvage

Coss 80 conclusion :

«Amputation and foot's reversal improve the survival in complete remission more than resection reconstruction with prosthesis».



WINKLER COSS 80 JCO 1986
MULTICENTRIC RANDOMIZED TRIAL
DESCRIBING DATA FROM 34 DIFFERENT
CENTERS.

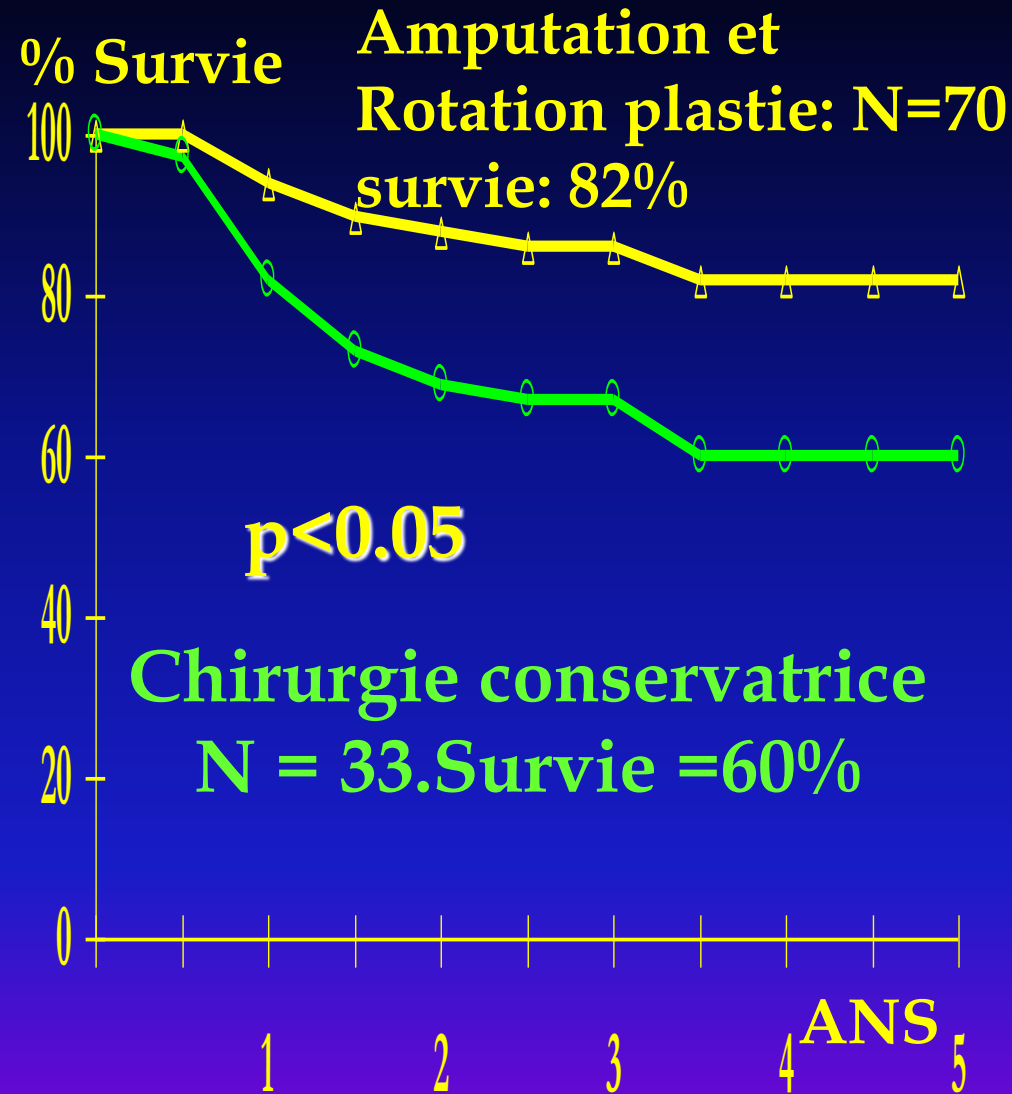


ECCO 1999
Vienna, Austria

MULTICENTRIC RANDOMIZED TRIALS FOR HIGH GRADE
OSTEOGENIC OSTEOSARCOMA. COST-EFFECTIVENESS ?



Résultat 1986 du protocole COSS 80



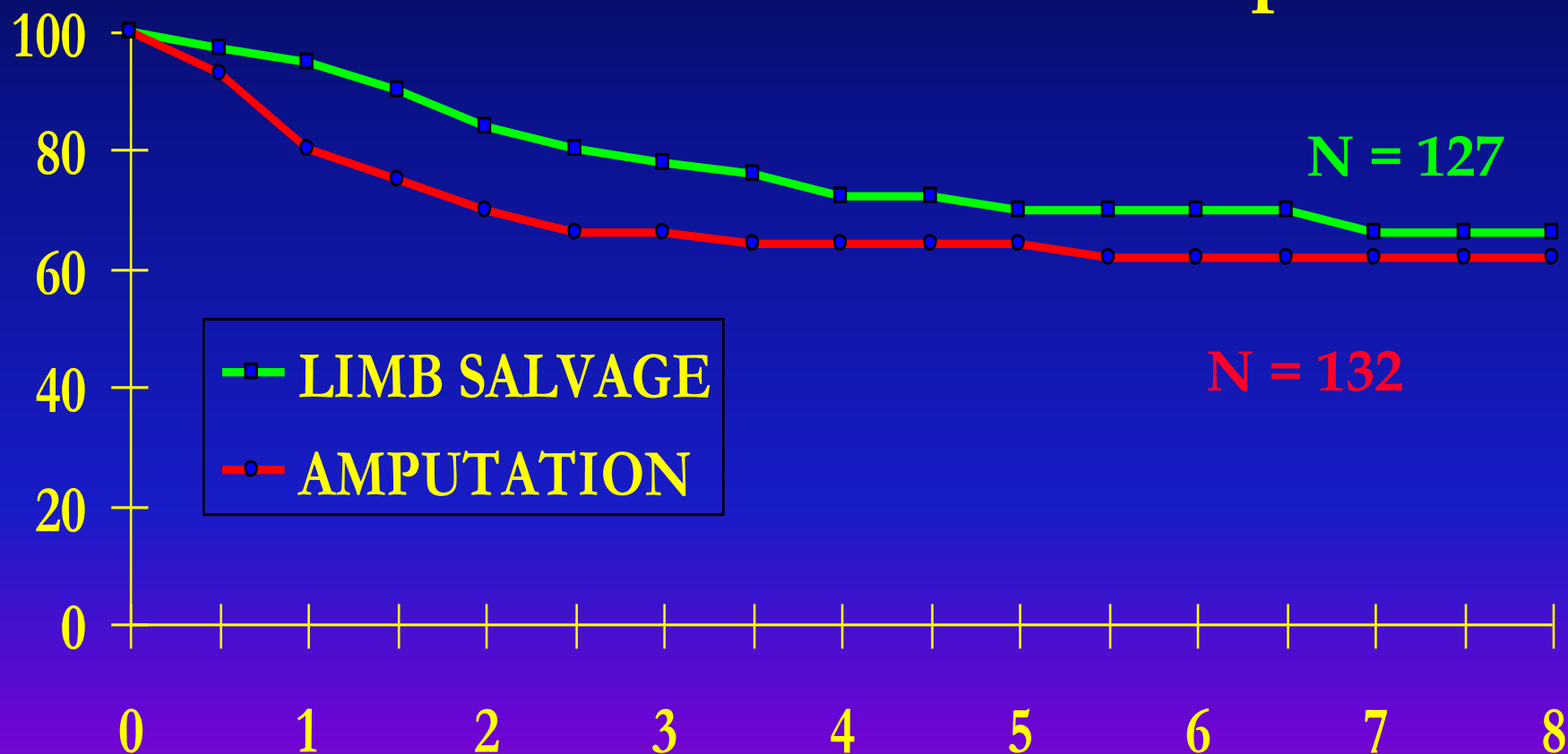
La publication en 1979 du protocole multicentrique du Cancer and Leukemia Group B * et en 1986 de l'essai multicentrique COSS 80 ** ont mis en évidence une diminution significative ($p<0.05$) de l'espérance de guérison chez les malades porteur de grosses tumeurs et traités par chirurgie conservatrice .

*Cortes Adjuvant therapy of operable osteosarcoma-Cancer and Leukemia Group B Experience Recent Results in Cancer Research 1979;68:16-24 **Winkler K. Einfluss des lokal chirurgischen Vorgehens auf die Inzidenz von Metastan nach neo-adjuvanter Chemotherapie bei Osteosarcomen Zeit schrift für Orthopädie und Grenzgebiete 1986

Sloan Kettering Cancer Center

Experience New York

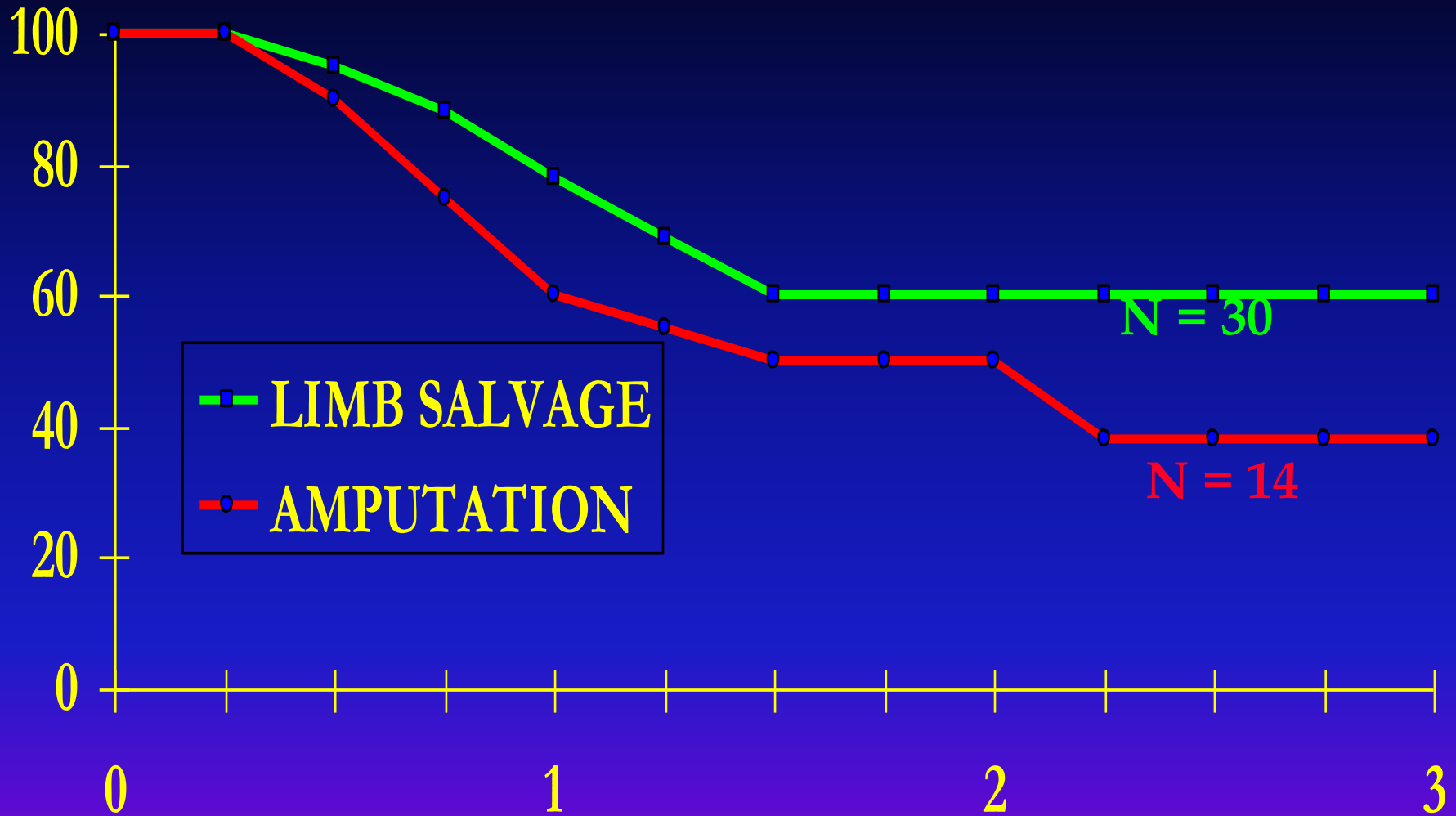
Mutilating surgery does not improve
disease free survival of patients



MEYER and all."CHEMOTHERAPY FOR NON METASTATIC OSTEOGENIC
OSTEOSARCOMA: THE MEMORIAL S.K.C.C.EXPERIENCE " J.Clin.Oncol.10,1,5-15 , 1992

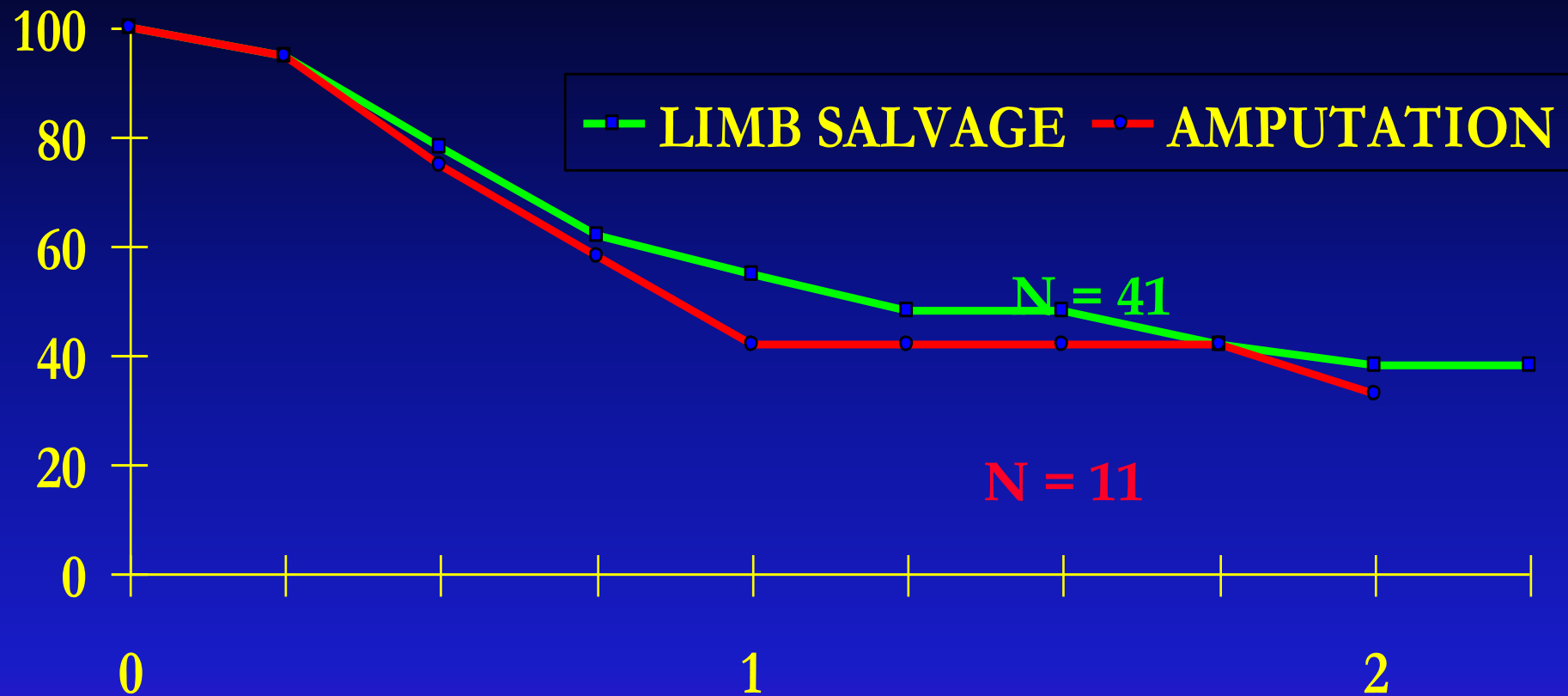
Florida University Experience

Mutilating surgery does not improve disease free survival of patients



Graham Pole J. and all. "Neoadjuvant chemotherapy for patients with osteosarcoma :University of Florida studies" in B.Humphrey ed.1993 Kluwer Ac.Publis.

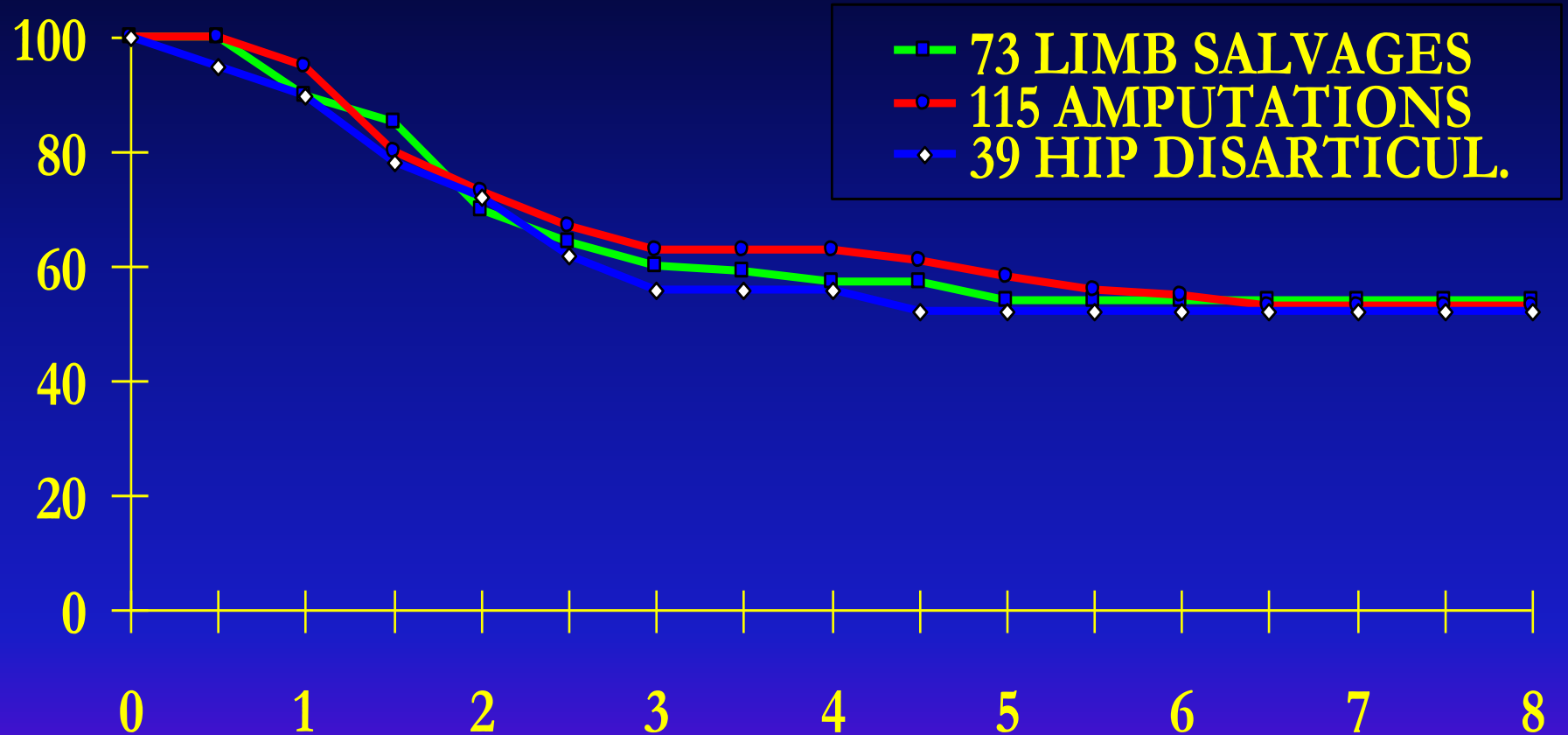
UCLA Experience



Mutilating surgery does not improve disease free survival of patients

ECKARDT J. J. and all "Management of stage I I B osteogenic sarcoma : Experience at the university of california , Los Angeles" Cancer Treat.Symp 3 :117-130 ,1985 .

American multicentric study .



Mutilating surgery does not

improve disease free survival of patients

SIMON M.A. and all "Limb salvage treatment versus amputation for osteosarcoma of the distal end of the femur" J. Bone Joint Surg. 68A,9:1331-1338, 1986

Rosen Rules for osteosarcoma.

- 1°) Preoperative chemotherapy is an investigational method not a recipe
- 2°) Give at least **240 grammes / m² de MTX**
- 3°) **Do not give too much liquid after MTX**
- 4°) **Never delay the MTX courses**
- 5°) Increase the doses if response is uncertain.
- 6°) Increase the doses if si serum peak is insufficient ($H_4 > 1500 \mu\text{mol/L}$)* * Rule added since 1995.

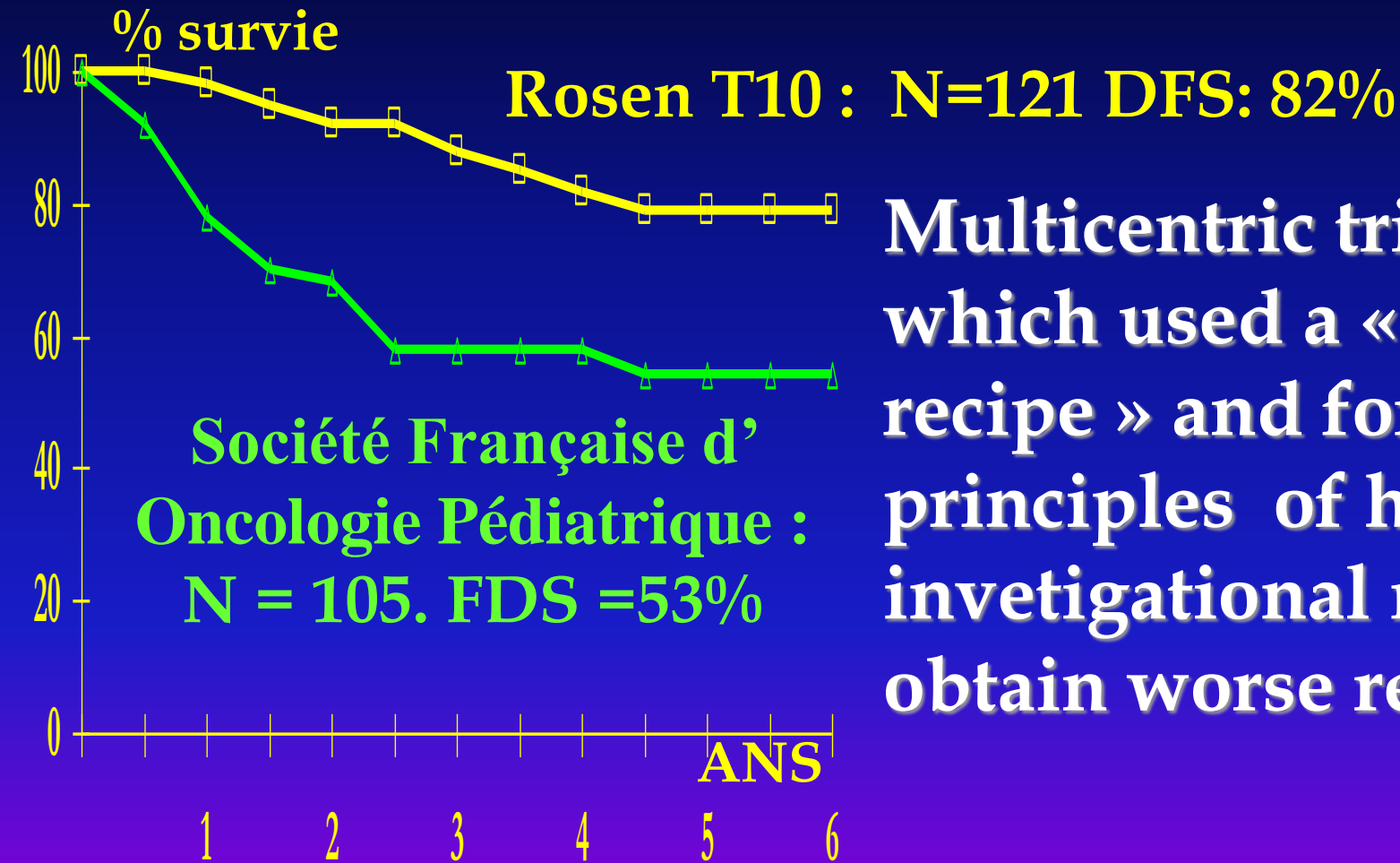


Critical Review of literature : State of the art in 2001.

Nevertheless multicentric groups still discuss the efficacy of Rosen scheme and pretend to obtain « non statistically different results with easier protocols ».



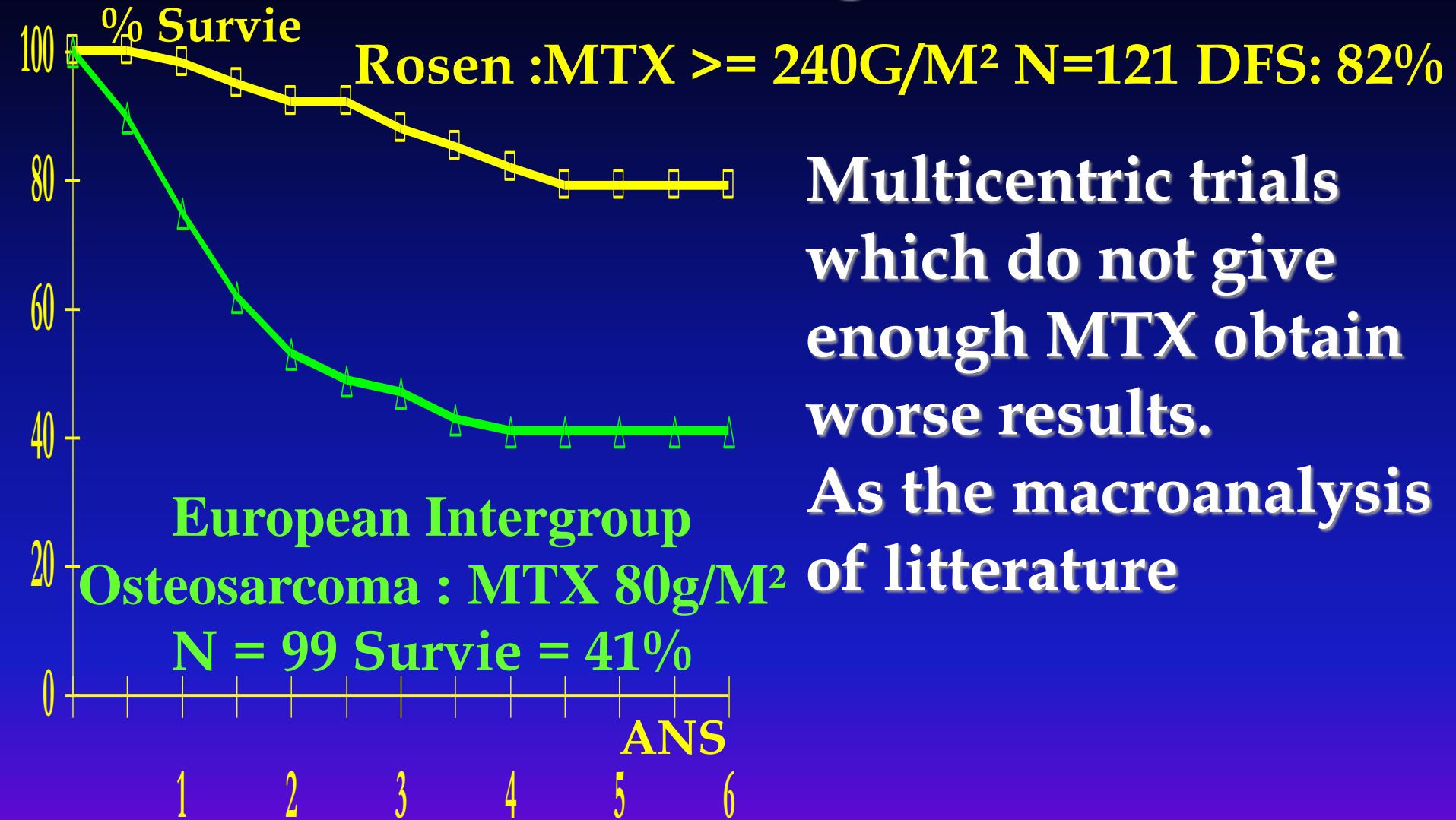
Preoperative chemotherapy : an investigational method not a recipe



Multicentric trials which used a « Rosen recipe » and forgot the principles of his invetigational method obtain worse results

Rosen G, Marcove Nirenberg Chemotherapy for Osteogenic Sarcoma: An Investigative Method not a Recipe Cancer Treat.Resp.1982;9;1687-1697 . **M.BRUNAT-MENTIGNY** "La reproduction du protocole de ROSEN pour les ostéosarcomes. Bull.Cancer 1988.75:201-206.

« At least 240 grammes / m² »

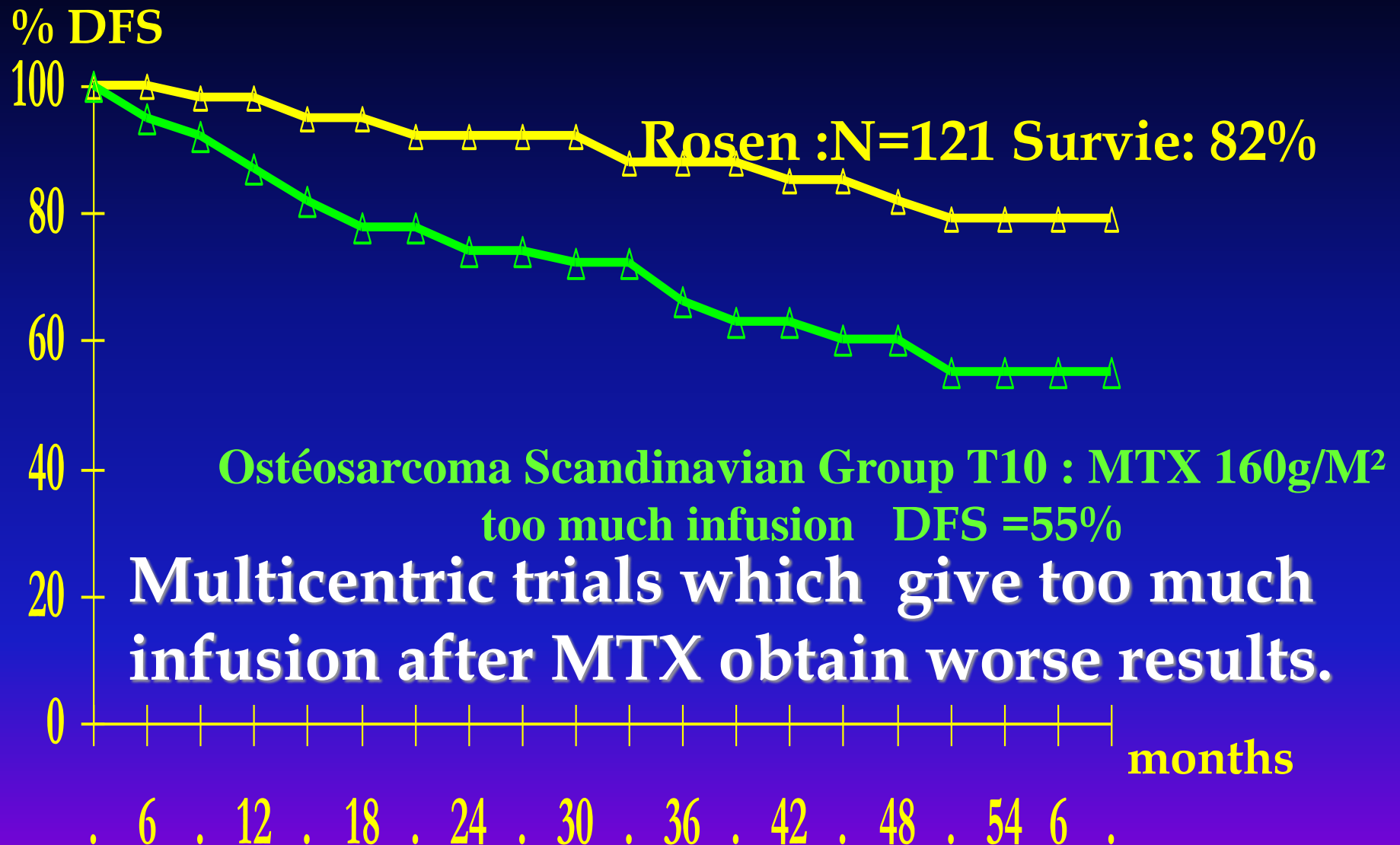


Multicentric trials
which do not give
enough MTX obtain
worse results.

As the macroanalysis
of literature

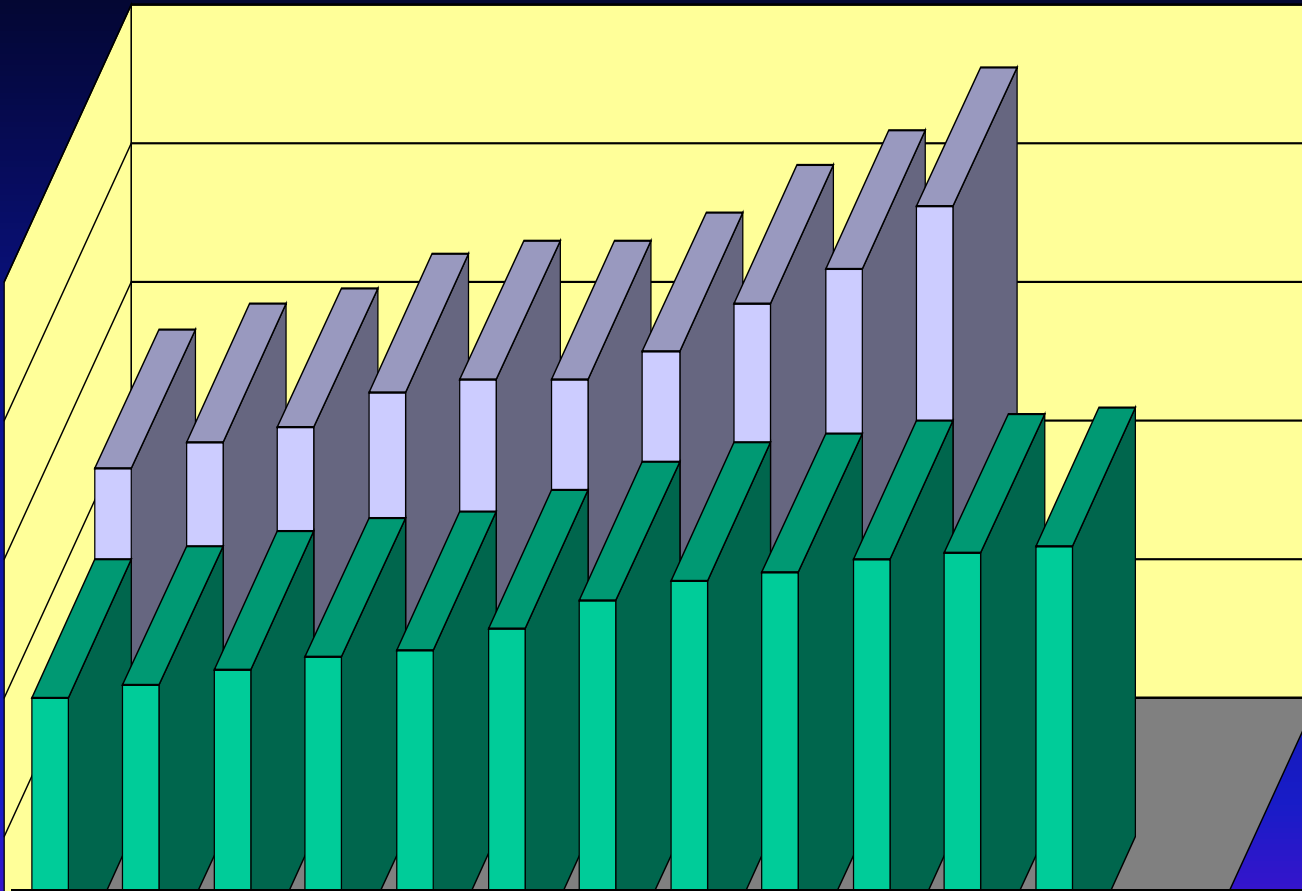
Rosen G, Marcove RC, Caparros B et al. Primary osteogenic sarcoma. The rationale for preoperative chemotherapy and delayed surgery. Cancer, 1979 ; 43 : 2163-77. Bramwellet all A Comparaison of two short Chemotherapy Regimen in operable Osteosarcoma of Limbs in Children and Young Adults: The first Study of the European Osteosarcoma Intergroup J.Clin.Oncol.1992 10:1579-1591

« Do not give too much liquid after MTX »



Rosen G, Marcove RC, Caparros B et al. Primary osteogenic sarcoma. The rationale for preoperative chemotherapy and delayed surgery. Cancer, 1979 ; 43 : 2163-77.
Saeter G. Treatment of osteosarcoma of the extremities with emphasis of the effects of preoperative Chemotherapy .J.Clin.Oncol.1991;9;1766-1775

Litterature : Résultats of neoadjuvant protocols

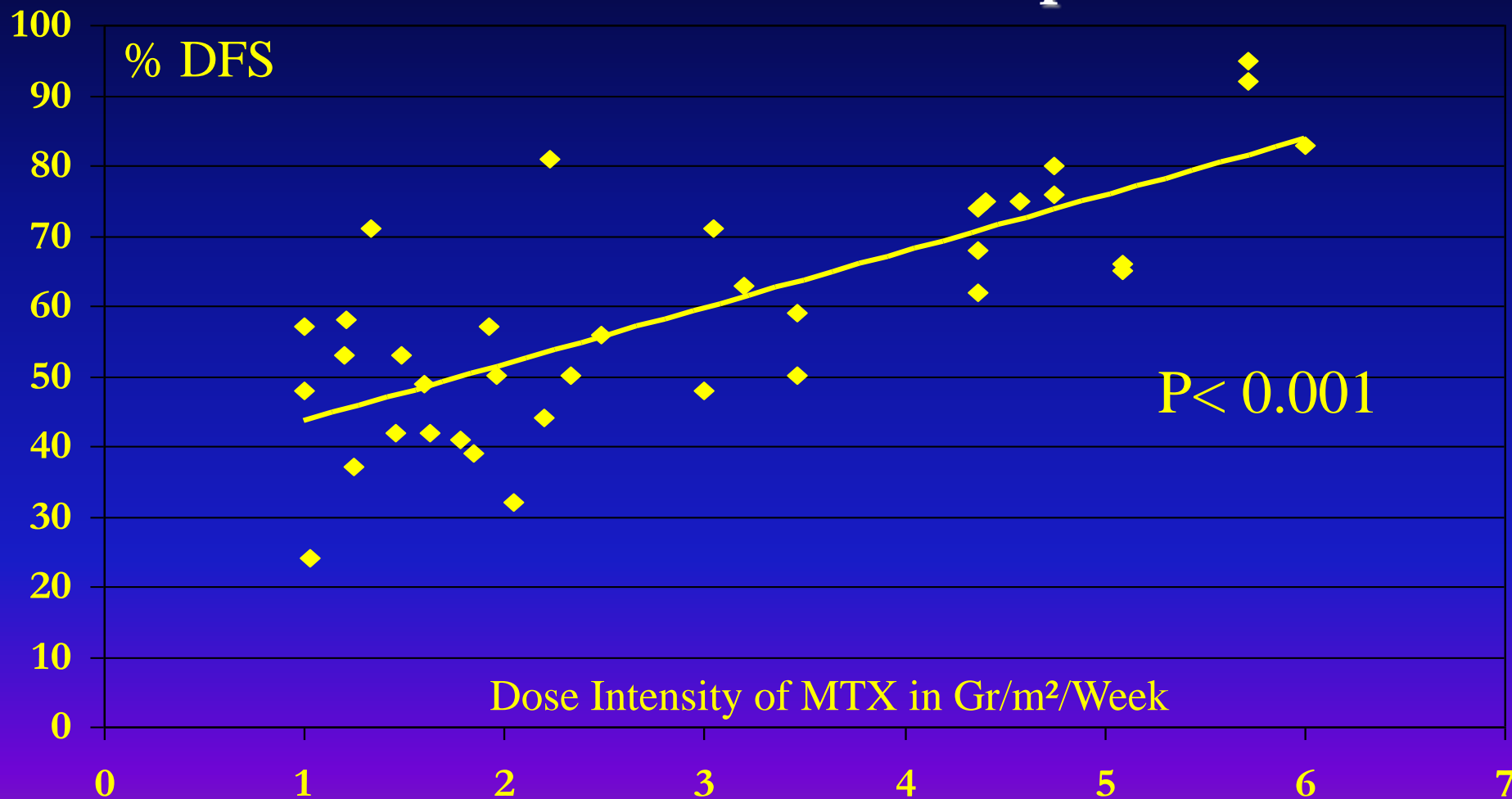


5 year DFS :70% for HDMTX protocols
49% for protocols without HDMTX

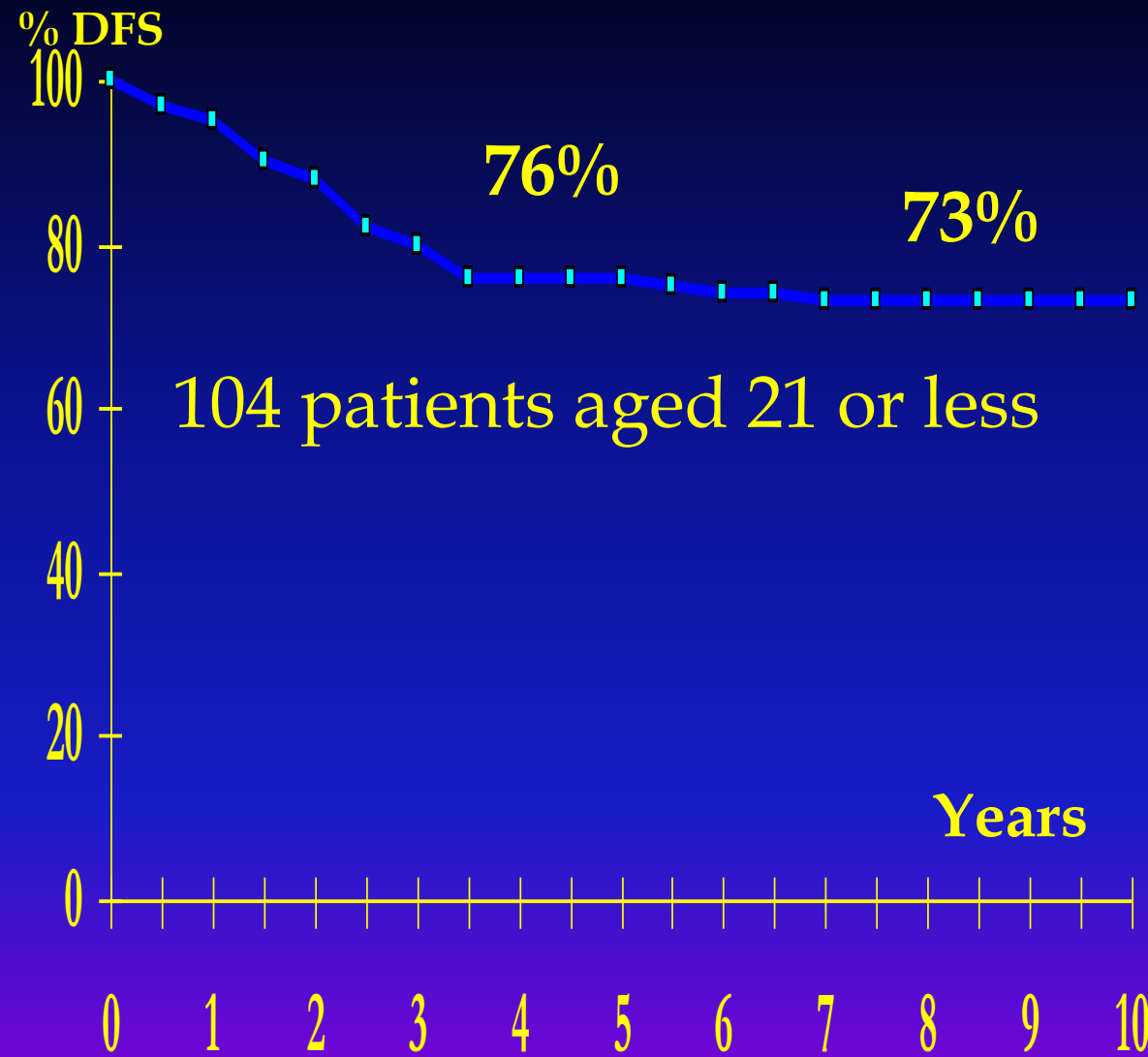
Protocols which do not give HDMTX decrease the disease free survival of patients by 20%.

Correlation DFS/ Dose Intensity of MTX

The crucial importance of Doses of MTX is obvious when we analyzed the results of all published trials.



T 10 RESULT FOR NON METASTATIC OSTEOSARCOMA OF THE EXTREMITIES



With 15 years follow up the Rosen 's protocols reviewed by independant investigators remain the gold standart

MEYER and all."CHEMOTHERAPY FOR NON METASTATIC OSTEOGENIC OSTEOSARCOMA: THE MEMORIAL S.K.C.C.EXPERIENCE " J.Clin.Oncol.10,1,5-15 , 1992

Promoters of chemotherapies intensification

- Rosen 1976 Cancer
- Jaffe 1977 Cancer
(weekly Methotrexate)
- Cortes 1978 R.R.C.R.
(full dose of Adriamycin)

Promoters of chemotherapy's intensification

- Rosen 1979 Cancer
(achieved by neoadjuvant chemotherapy and individualisation)
- Bacci 1980 J.B.J.C.
(**HDMTX > MTX**)
- Rosen 1982 Cancer



These who doubted of the importance of methotrexate's dose

- *Kraila CCG741 1987 Med. Ped. Onc.*
«Dose of Methotrexate of 690 mg by course led to the same results !»
- *Burgers EI080831 1992 JCO*
« ADR-CDDP lead to better results than ADR-CDDP-MTX »
- *Craft EI080861 1996 « ADR-CDDP lead to the same result than a more complex protocol including methotrexate. »*



these trials didn't respect the most important backgrounds of Rosen's protocol:

- delay between 2 courses of methotrexate,
- individualization of methotrexate dose upon evaluation of clinical efficacy,
- too large hydration of patients receiving methotrexate too long preoperative phase,
- too low numbers of methotrexate courses,
- etc.).



Furthermore, independent evaluation of T7 and T10 demonstrates, 15 years later, that these protocols remain the most effective in osteosarcoma disease free survival at 10 years.



W.H. Meyer, M.D. Link, J.C.O. 1992

- **The impressive incremental success since the 1970's has been accomplished by empirical, often flawed clinical trials using chemotherapy agents that singly range in effectiveness from fair to mediocre. This speaks well for the perserverance and inventiveness of the clinical investigators who are responsible for this remarkable success.**



Preoperative chemotherapy

- In his pilot study preoperative chemotherapy has been used by G. Rosen, as the best way to test cytotoxics and effective dosages on the primitive tumor.
- This technique has optimized the treatment of occult metastases by individualization.



Preoperative chemotherapy

Multicentric trials, that tried to «reproduce» Rosen's protocol, have forgotten the analytic thought of this phase and have only retained «the receipt».



Main causes of the low efficacy of multicentric studies

- Minimal goals in order to permit inclusion of patients from small centers.
- Controlled studies but ignoring main prognostic factors as surgery !, as MTX hydration...
- Heavy administration leading to late publications of already known results !



1) The multicentric trials to verify the effectiveness of chemotherapy in osteosarcoma delayed the systematic use of chemotherapy for 3 or 4 years.

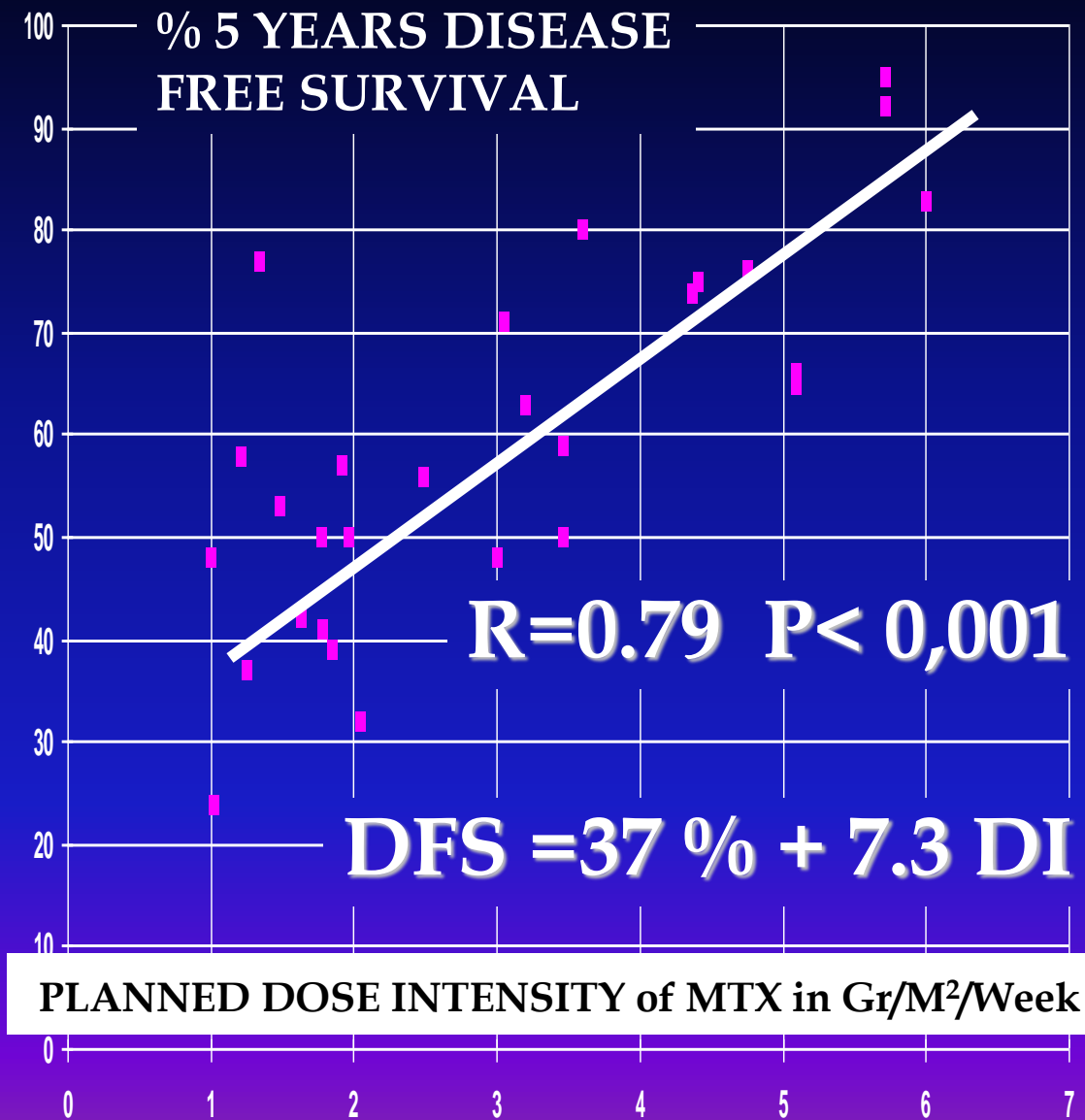
2) Preliminary results of COSS 77-82 which falsely concluded that amputated patients had more chances of disease free survival than others, delayed the conservative surgery for 5 years. The definitive conclusions of these trials invalidated their preliminary reports.



3°) The superiority of Rosen's protocols has been continuously challenged for 15 years, by randomized studies.

Correlation between DFS and MTX D I

The fundamental value of high dose methotrexate became evident by macro-analysis of all published trials on this subject



Macroanalysis of osteosarcoma trials.. N. Delépine and all. Cancer, 08/1996.

Conclusion 1

In osteosarcoma multicentric randomized trials led always to worse results than pilot studies performed by experimented teams.

Multicentric randomized trials of the last 25 years have not been effective for patients with osteosarcoma.

Even they have been harmful to them !



Conclusion 2

- Multicentric randomized trials have rarely been helpful to the knowledge of the illness.
- Their high costs (linked to the heavy organisation) are not justified by their direct results.



Conclusion 3

Multicentric randomized trials served only to convince reticent medical community of the necessity of chemotherapy in osteosarcoma.

In the same time, many patients let their limb or/and their life because of these bad trials.

Side utilities of randomized studies

- Regular meetings between doctors from different countries and specialities
- Revision of pathologic slides
- International registers.



Conclusion 4 Future ,

Isn't possible to obtain these marginal effects with a lower cost ?

- Grant-aided meetings
- Central register
- etc...

Conclusion of the COSS trials

- It is necessary to increase the dosage of MTX
- Adriamycin is a main drug
- CDDP IV = CDDP IA

Results of the E.O.I.

- ADR CDDP > HD MTX
Combination (60 % versus 40 %)
- ADR-CDDP = HDMTX
(40 % versus 40 %)
- These results are the same of all
protocols that don't use HDMTX

