

Improving Randomisation rates: Practical Steps

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Group - **COSS**
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Carrle 24.01.2008



EUROCORES Programme
European Collaborative Research

1. Key aspects of randomization
2. Randomization rates in EURAMOS-1
3. Missed randomizations-avoidable situations



Evaluation of diagnostic procedures and medical treatments



Uroscopy –
multipotent diagn.
procedure



Enema
universal medical treatment

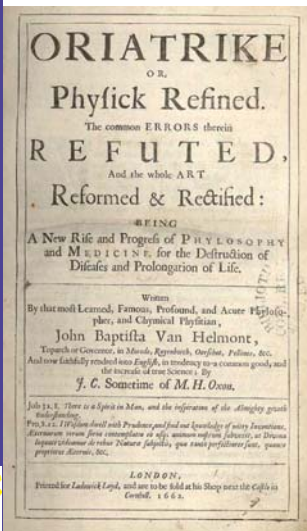


Bloodletting



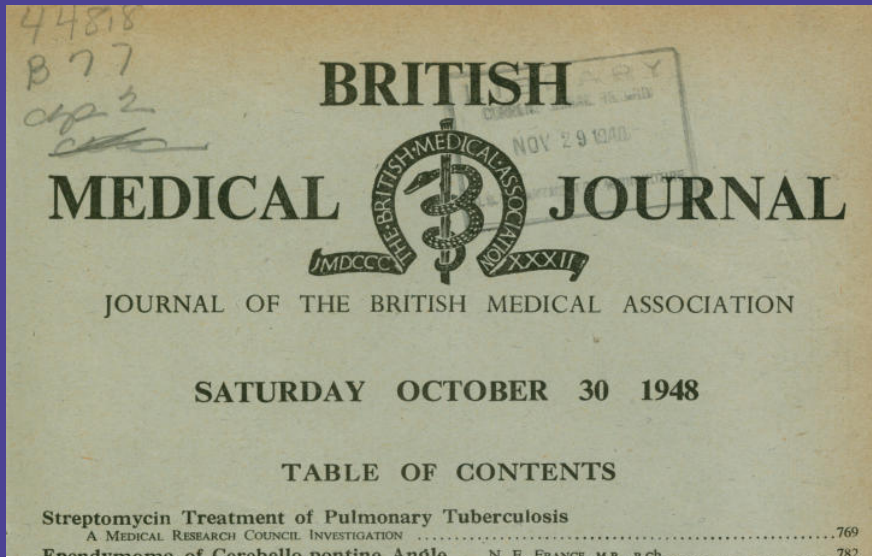
1st proposal for randomized trial 1662

For Medicine is not a naked word, a vain boasting, or vain talk, for it leaves a work behind it: Wherefore I despise reproaches, the boastings, and miserable vanities of ambition: Go to, return with me to the purpose: If ye speak truth, Oh ye Schooles, that ye can cure any kinde of Fevers without evacuation, but will not for fear of a worse relapse; come down to the contest ye Humorists: Let us take out of the Hospitals, out of the Camps, or from elsewhere, 200, or 500 poor People, that have Fevers, Pleurisies, &c. Let us divide them in halves, let us cast lots, that one halfe of them may fall to my share, and the other to yours; I will cure them without blood-letting and sensible evacuation; but do you do, as ye know (for neither do I tye you up to the boasting, or of Phlebotomy, or the abstinence from a solutive Medicine) we shall see how many Funerals both of us shall have: But let the reward of the contention or wager, be 300 Florens, deposited on both sides: Here your business is decided.



Carrie 24.01.2008

1940s



BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 30 1948

STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS

A MEDICAL RESEARCH COUNCIL INVESTIGATION

The following gives the short-term results of a controlled investigation into the effects of streptomycin on one type of pulmonary tuberculosis. The inquiry was planned and directed by the Streptomycin in Tuberculosis Trials Committee, composed of the following members: Dr. Geoffrey Marshall (chairman), Professor J. W. S. Blacklock, Professor C. Cameron, Professor N. B. Capon, Dr. R. Cruickshank, Professor J. H. Gaddum, Dr. F. R. G. Heaf, Professor A. Bradford Hill, Dr. L. E. Houghton, Dr. J. Clifford Hoyle, Professor H. Raistrick, Dr. J. G. Scadding, Professor W. H. Tytler, Professor G. S. Wilson, and Dr. P. D'Arcy Hart (secretary). The centres at which the work was carried out and the specialists in charge of patients and pathological work were as follows:

Brompton Hospital, London.—Clinician: Dr. J. W. Crofton, Streptomycin Registrar (working under the direction of the honorary staff of Brompton Hospital); Pathologists: Dr. J. W. Clegg, Dr. D. A. Mitchison.

Colindale Hospital (L.C.C.), London.—Clinicians: Dr. J. V. Hurford, Dr. B. J. Douglas Smith, Dr. W. E. Snell; Pathologists (Central Public Health Laboratory): Dr. G. B. Forbes, Dr. H. D. Holt.

Harefield Hospital (M.C.C.), Harefield, Middlesex.—Clinicians: Dr. R. H. Brent, Dr. L. E. Houghton; Pathologist: Dr. E. Nassau.

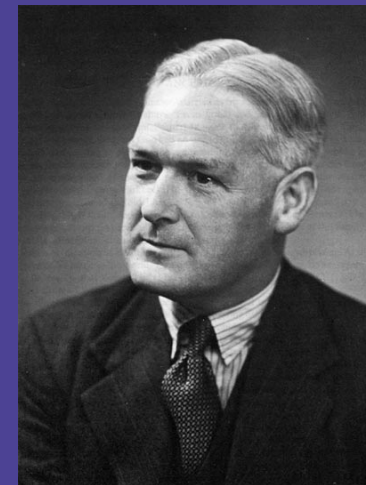
Bangour Hospital, Bangour, West Lothian.—Clinician: Dr. I. D. Ross; Pathologist: Dr. Isabella Purdie.

Killingbeck Hospital and Sanatorium, Leeds.—Clinicians: Dr. W. Santon Gilmour, Dr. A. M. Reeve; Pathologist: Professor J. W. McLeod.

Northern Hospital (L.C.C.), Winchmore Hill, London.—Clinicians: Dr. F. A. Nash, Dr. R. Shoulman; Pathologists: Dr. J. M. Alston, Dr. A. Mohun.

Sully Hospital, Sully, Glam.—Clinicians: Dr. D. M. E. Thomas, Dr. L. R. West; Pathologist: Professor W. H. Tytler.

The clinicians of the centres met periodically as a working subcommittee under the chairmanship of Dr. Geoffrey Marshall; so also did the pathologists under the chairmanship of Dr. R. Cruickshank. Dr. Marc Daniels, of the Council's scientific staff, was responsible for the clinical co-ordination of the trials, and he also prepared the report for the Committee, with assistance from Dr. D. A. Mitchison on the analysis of laboratory results. For the purpose of final analysis the radiological findings were assessed by a panel composed of Dr. L. G. Blair, Dr. Peter Kerley, and Dr. Geoffrey S. Todd.



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Comparison of therapeutic intervention

Similar groups

- similar at baseline (unknown risk factors)
- difference: interventions

→ different outcomes

= chance

or

= difference between interventions



Eliminating bias in allocation

Similar groups

Control unknown risk factors
(confounding factors)

that may influence outcome:

→ Randomisation



Reducing bias in analysis

Intention to treat analysis:

Essential prerequisite for valid result on effect of treatment in clinical trials

= analysis as randomized

(independent of adherence to assigned treatment)



Problem: Non-compliance with treatment

Concern: type 2 error (masking real effect)



Ethics: Uncertainty principle

Uncertainty What's Better

- no participation in clinical trial if believe, that one treatment superior
- no entry of patients if particular treatment is indicated

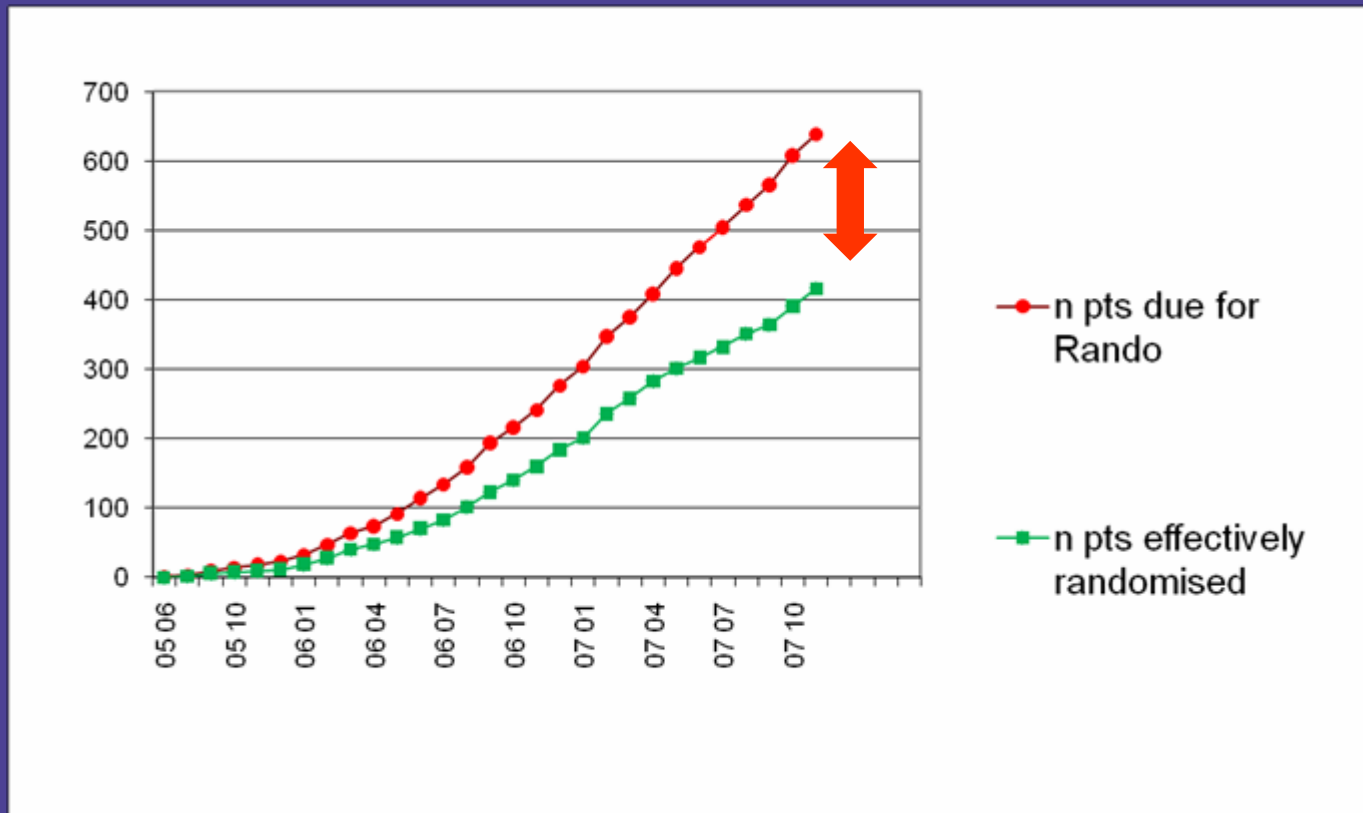


1. Key aspects of randomization
2. Randomization rates in EURAMOS-1
3. Missed randomizations-avoidable situations



Cumulative Randomization rate

Overall EURAMOS-1 30.11.07



Recruitment Non-upfront Rando

Experience EURAMOS-study-groups

COG	INT 0133	Up-front-rando	--
COSS	COSS 96 Standardriskgroup (2 similar Tx strategies)	Non-up-front rando	86%
EOI	3 randomised trials <ul style="list-style-type: none"> •Bramwell et al 1992 •Souhami et al 1997 •BO 06 trial/Lewis et al JNCI 2007 	Up-front-rando	--
SSG	Since 1979 three trials <ul style="list-style-type: none"> •SSG II •SSG VIII •SSG/SSG I (Italian-scand) 	Non-randomized	--



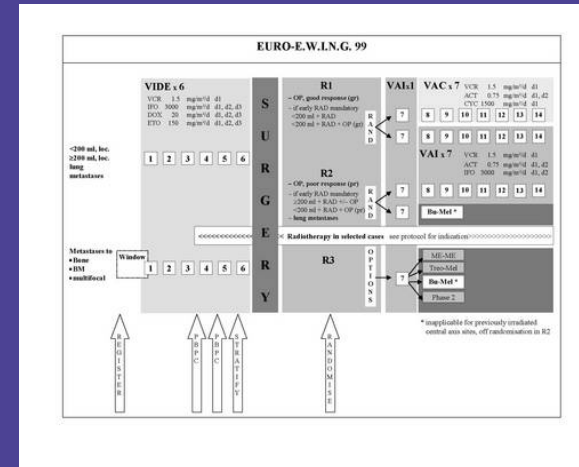
Recruitment Non-upfront Rando

Experience other study groups

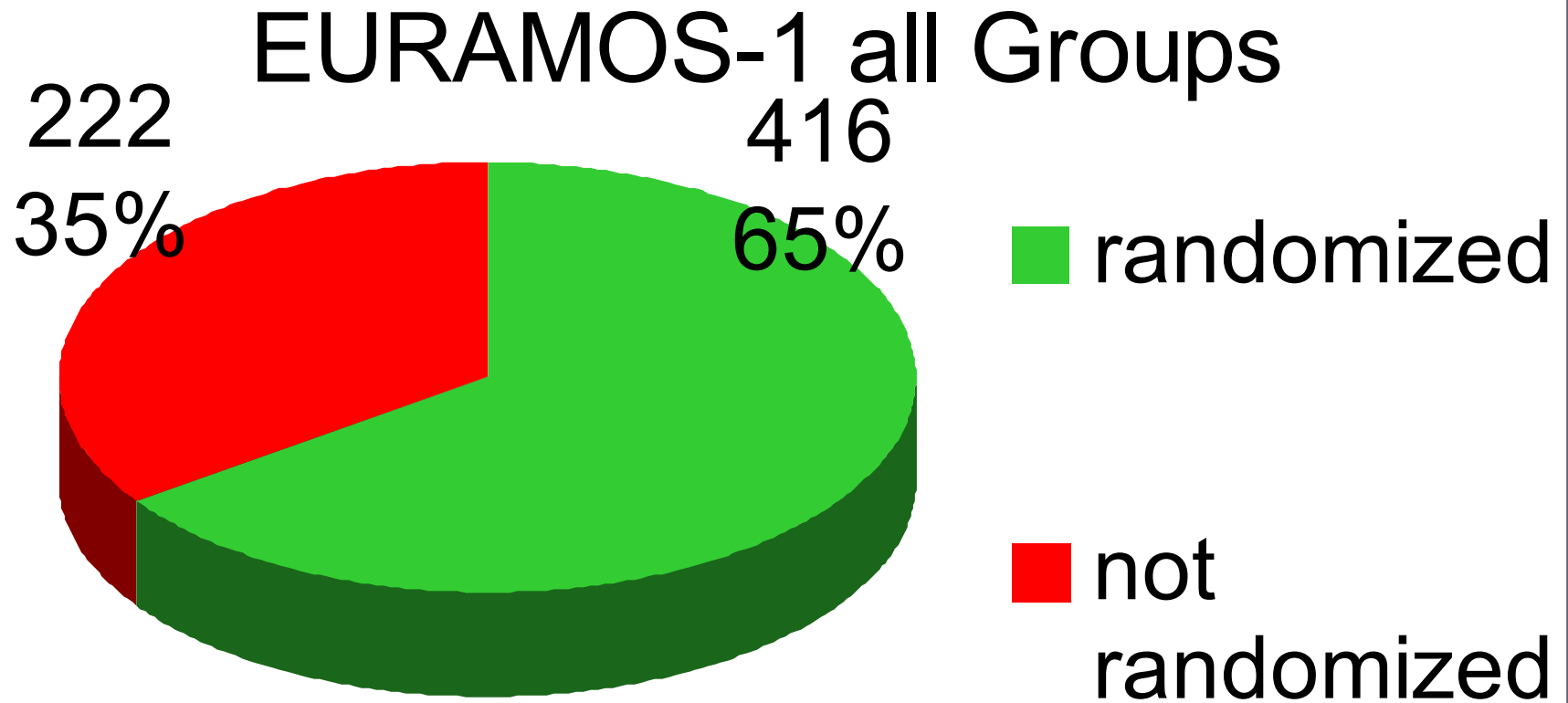
- EURO-E.w.i.n.g.99
- N=1014 Pat randomized

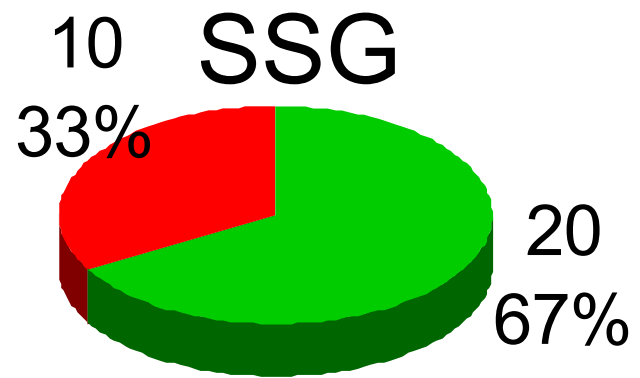
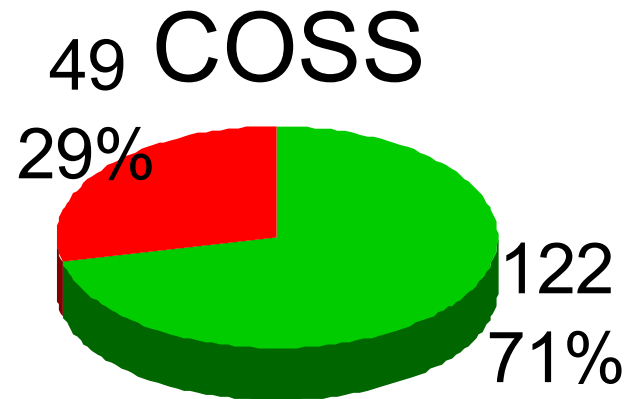
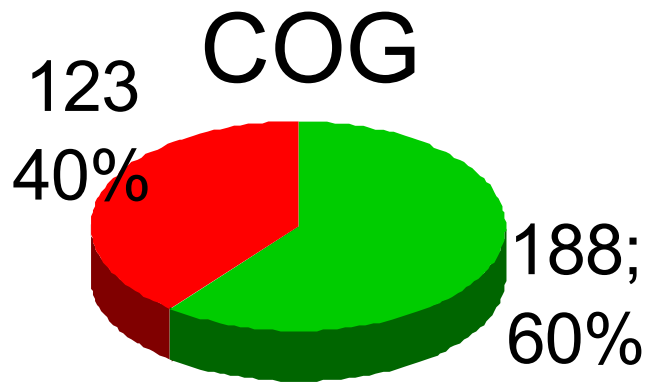
Randorates:

- Standardtx: 80%
- HD-Chemotx vs Standardtx: 60%

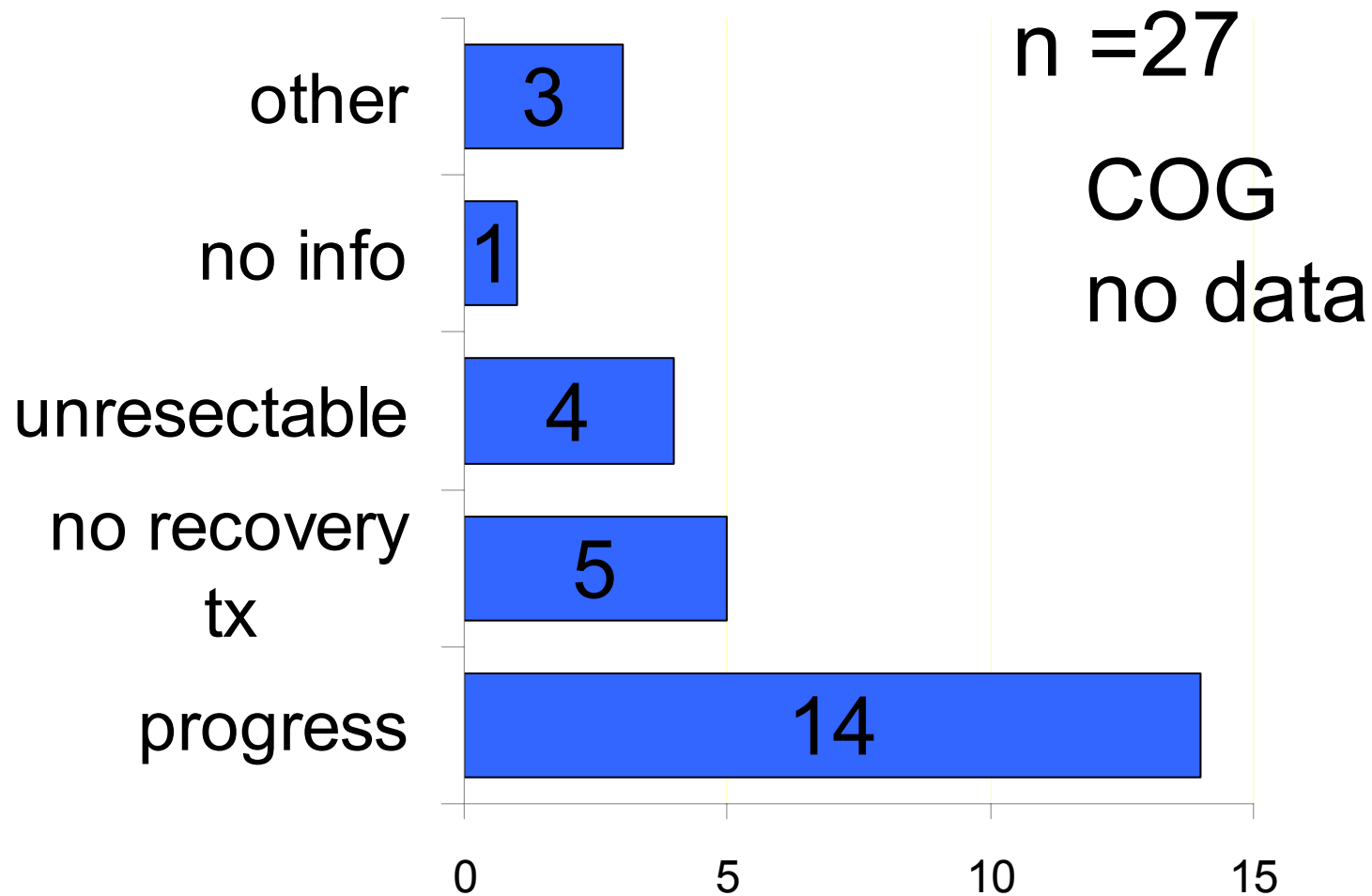


Missed randomizations

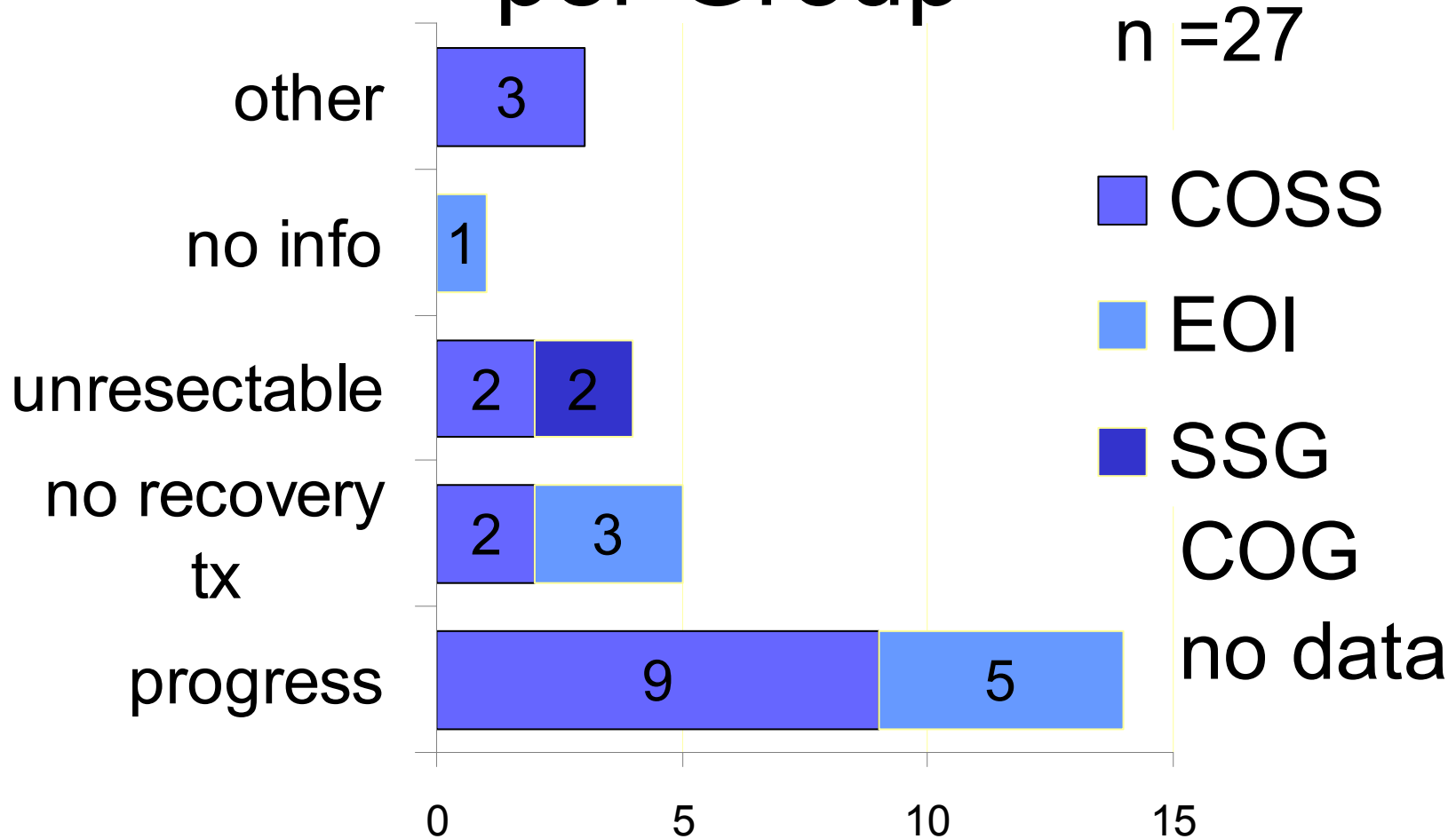




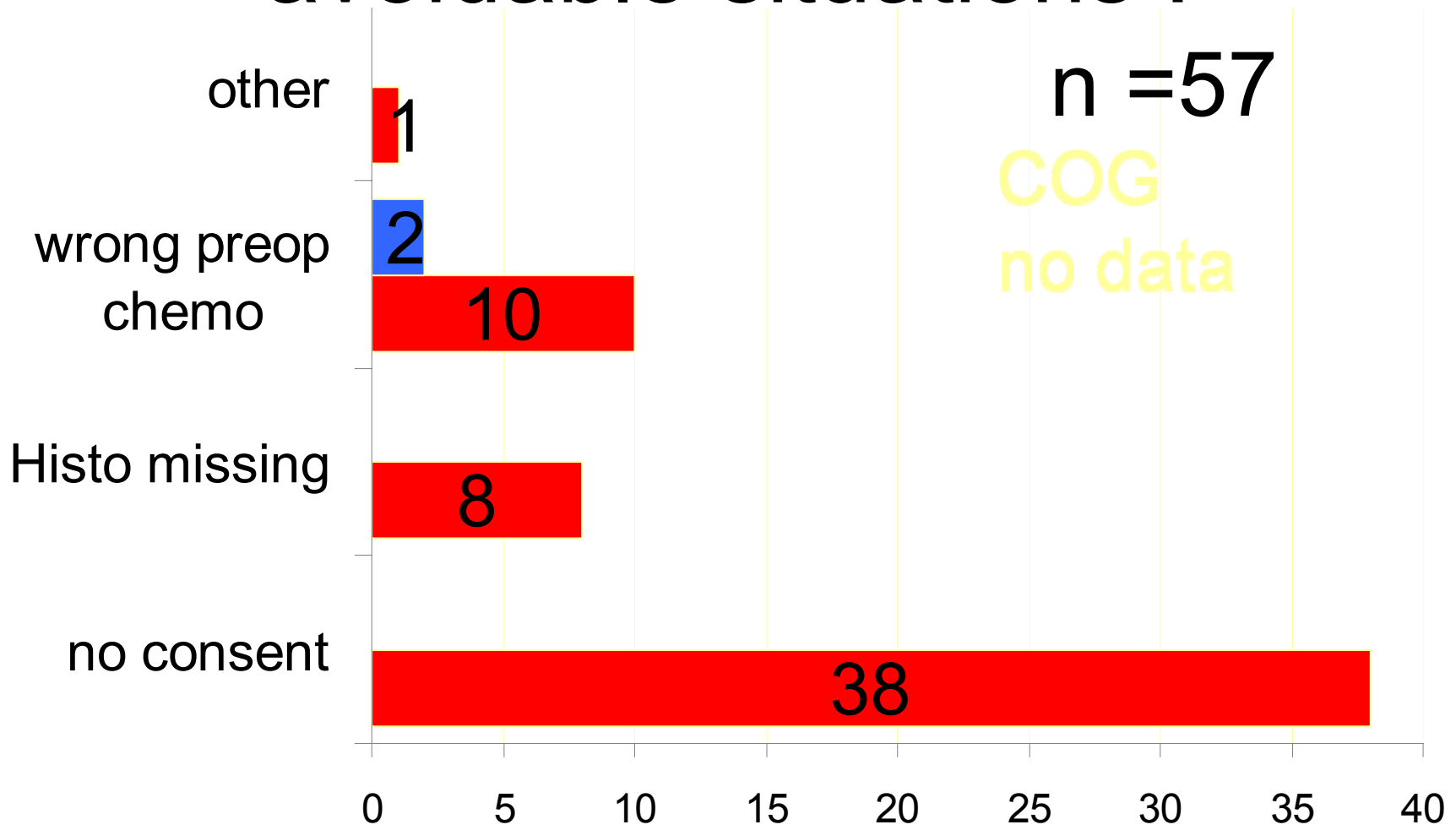
Missed rando: unavoidable



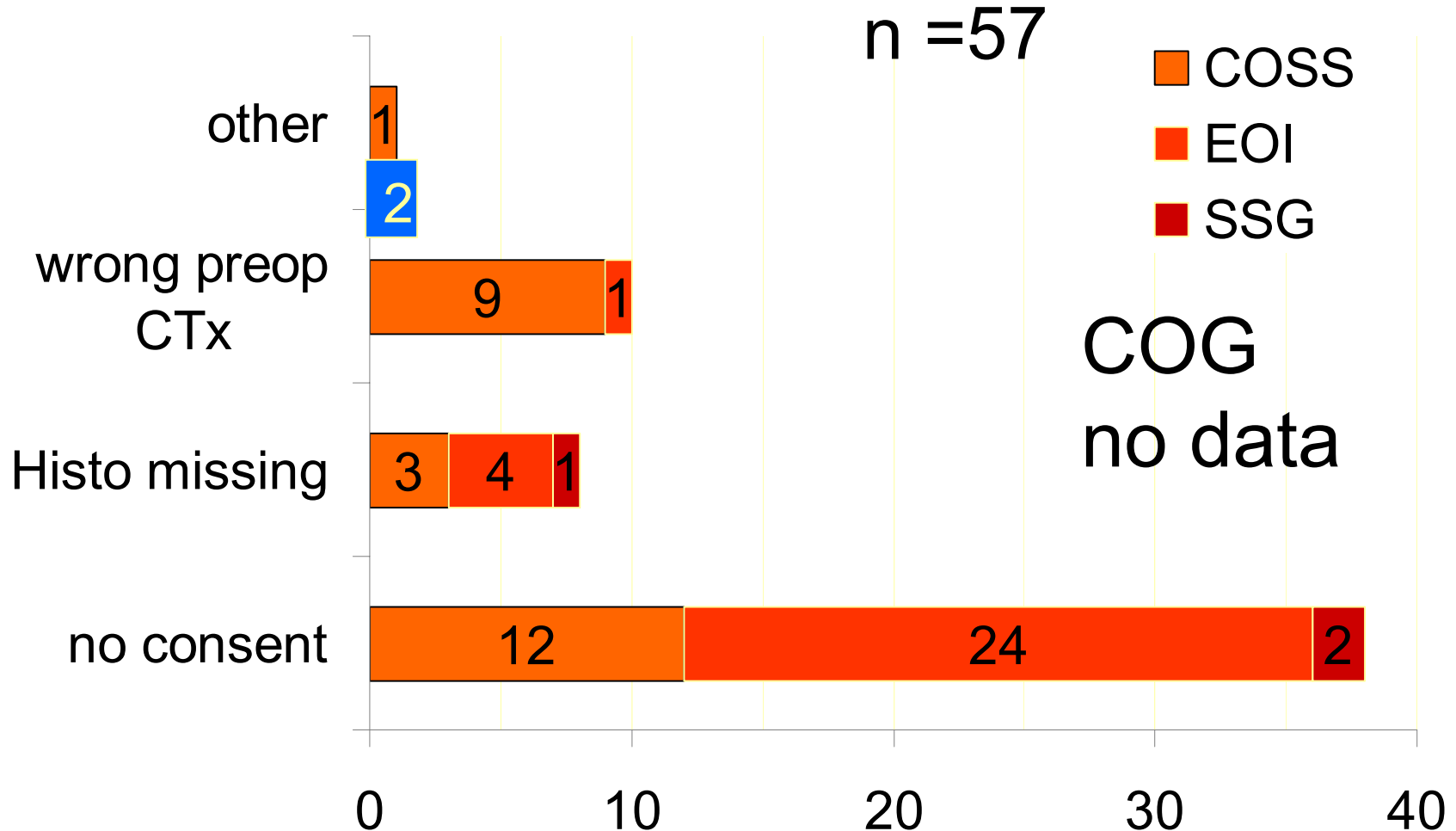
Missed random: unavoidable per Group

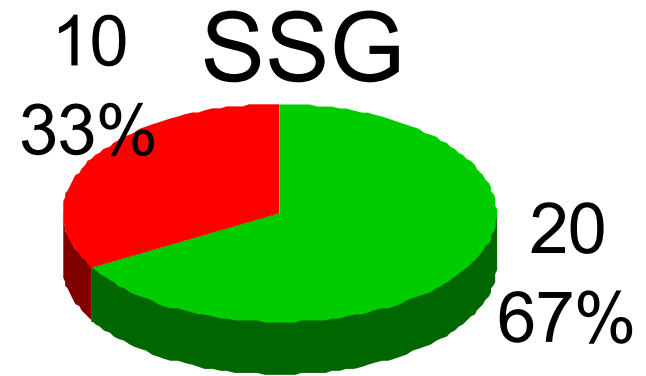
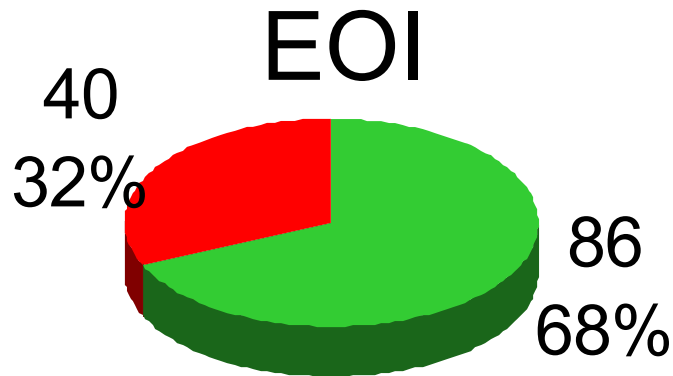
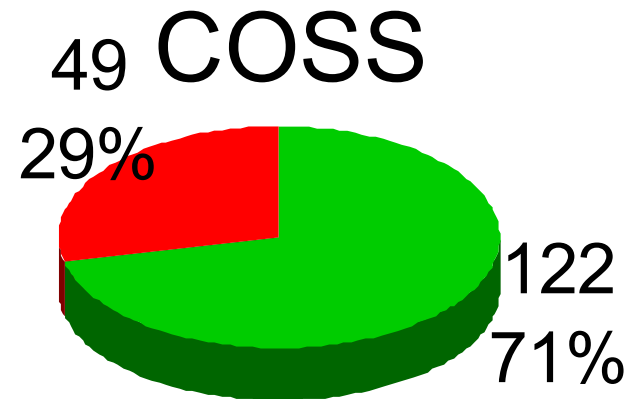
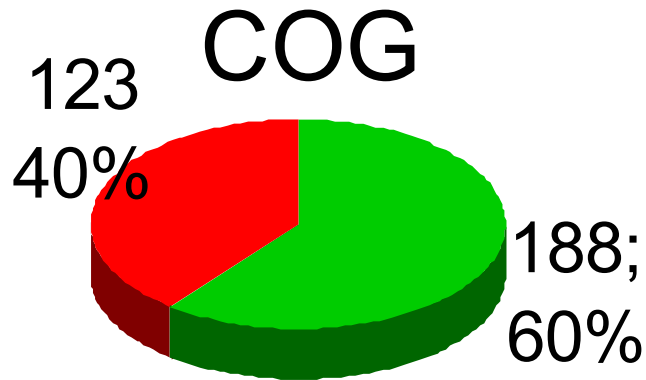


missed randomisations - avoidable situations !



Missed randomisations per Group - avoidable situations !



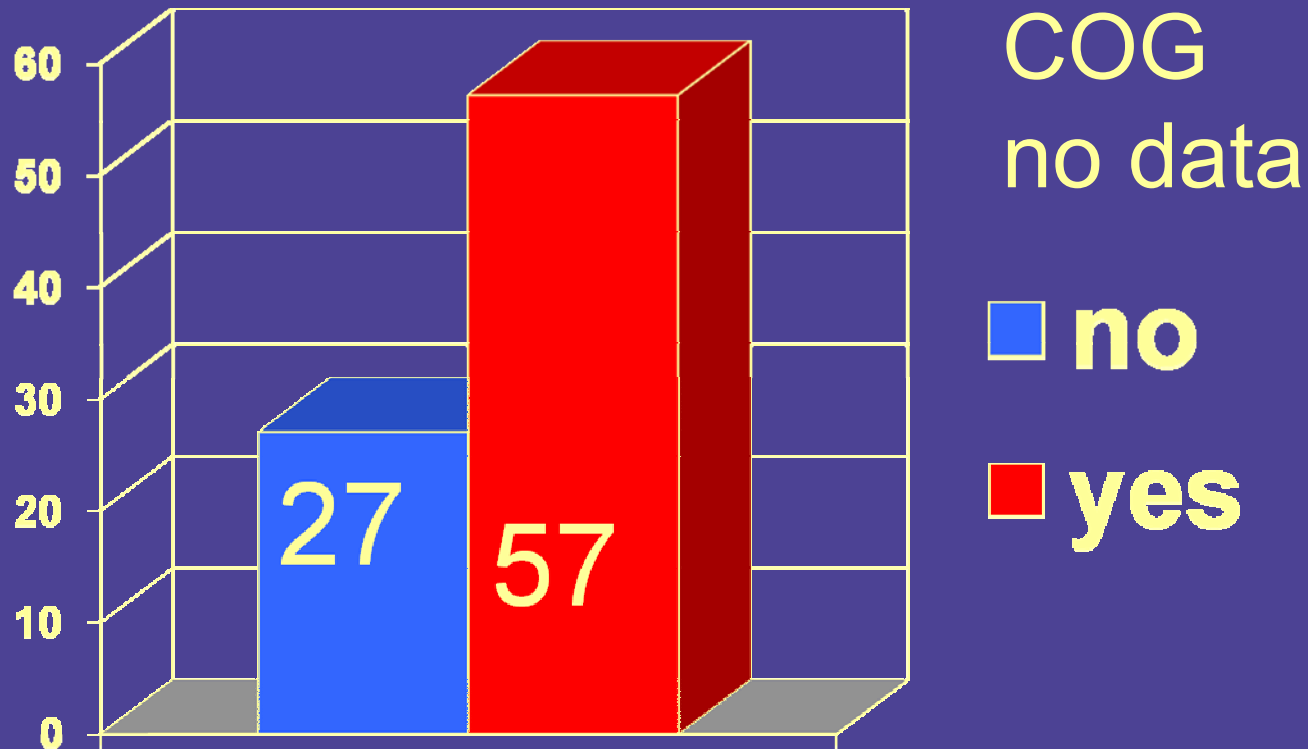


Randomization criteria

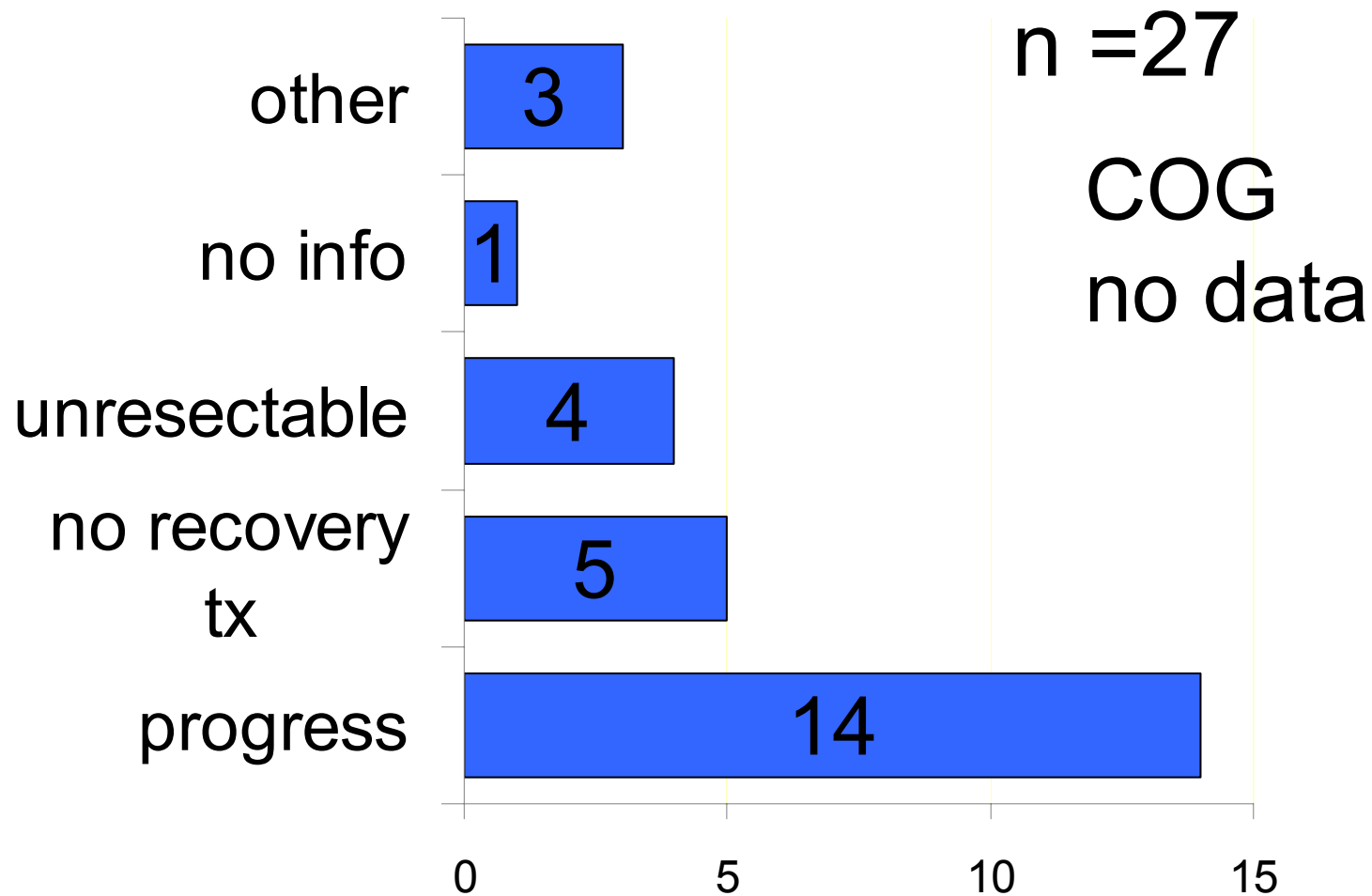
- Histol. response \leq 35 day Sx (\pm Reference pathology)
- Preoperative Chemoth
 - 2 x AP
 - (2) – 4 – (6) x MTX
- Continuation of protocol tx
- Surgery primary tumor: macroscopically complete
- Metastases: complete removal
- no progress of disease (primtumor/met; A6)
- Good response: age $>$ 5 yrs
- Written consent
- Documentation



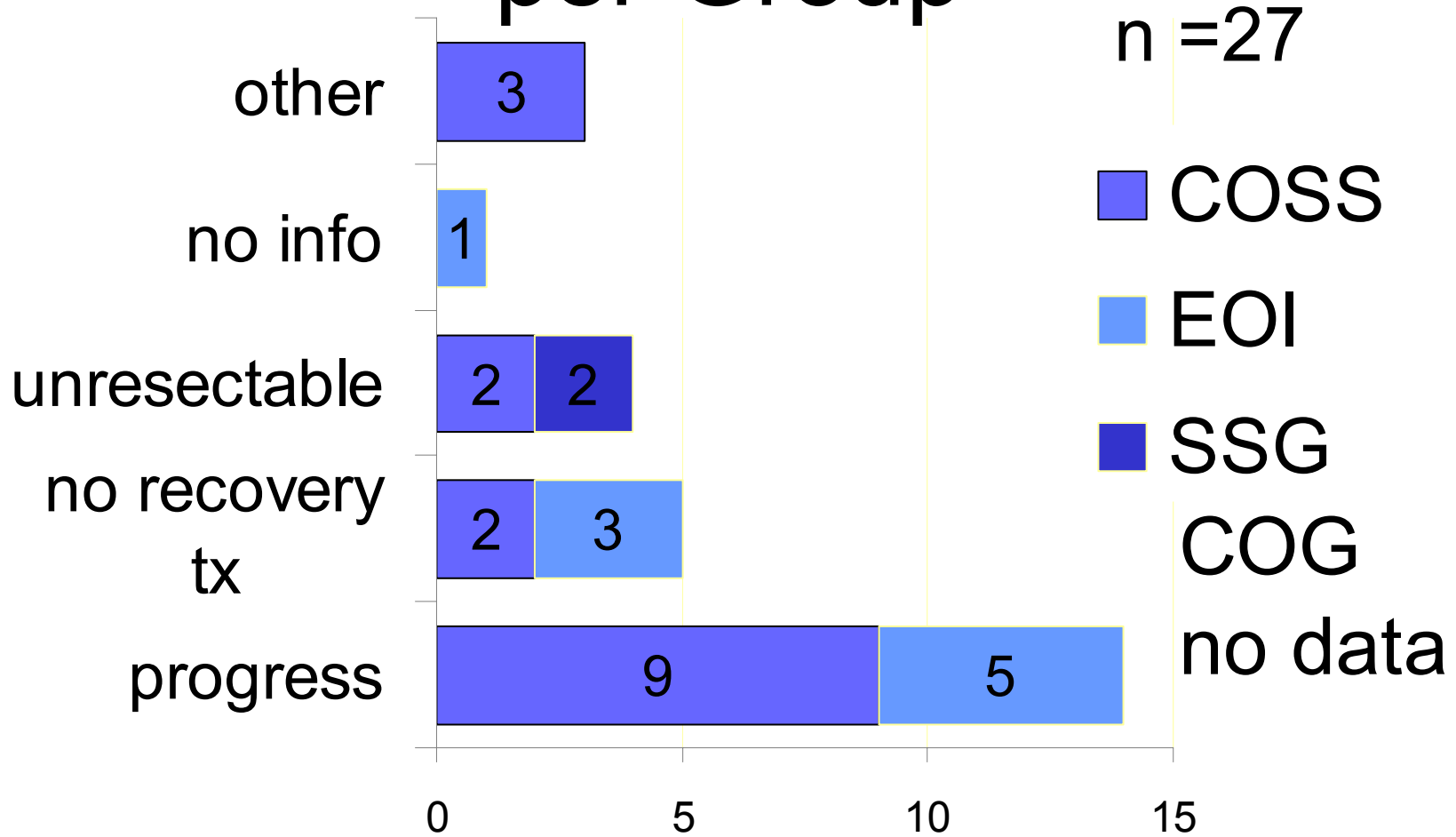
Missed randomizations - avoidable situations?



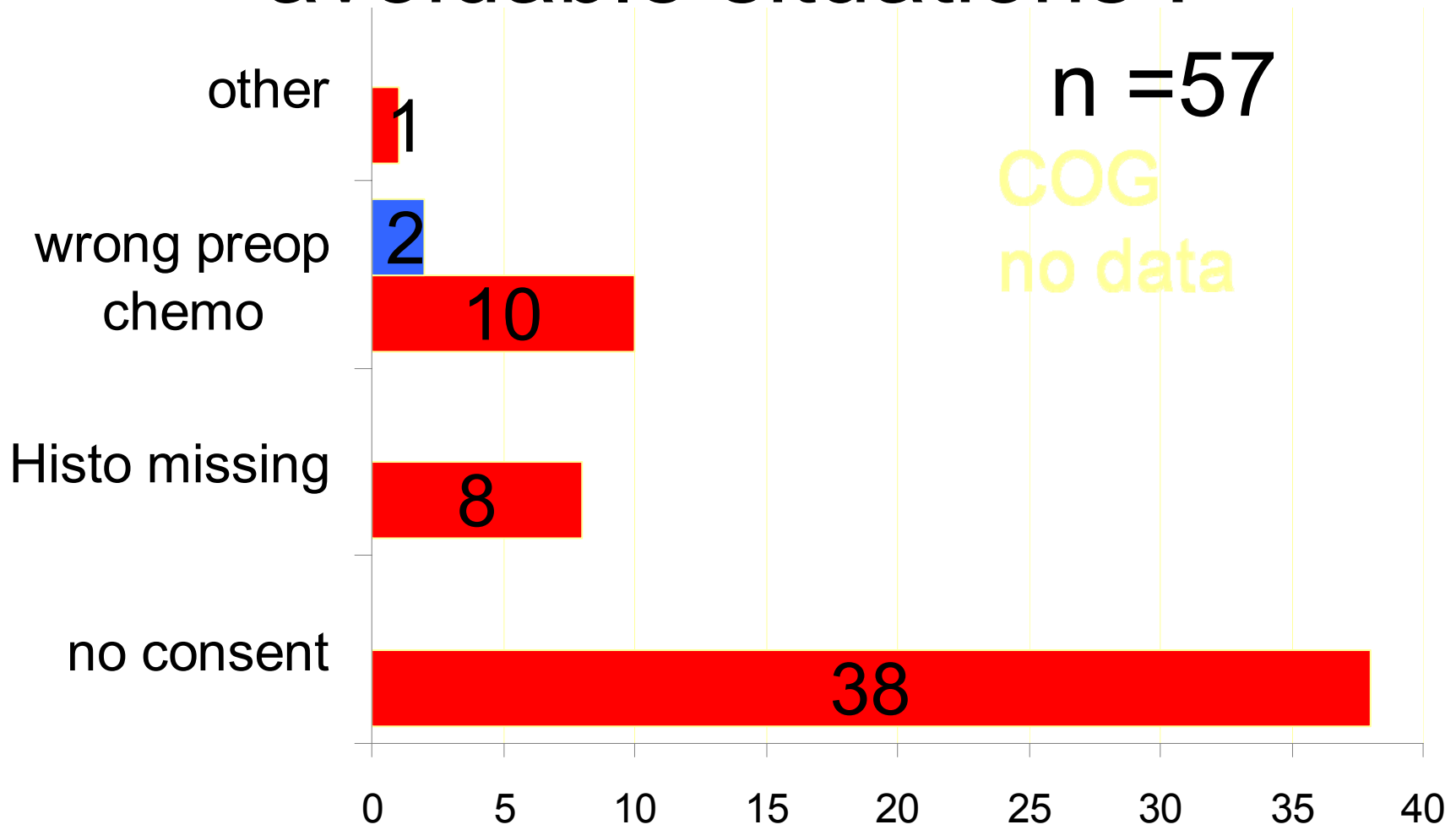
Missed rando: unavoidable



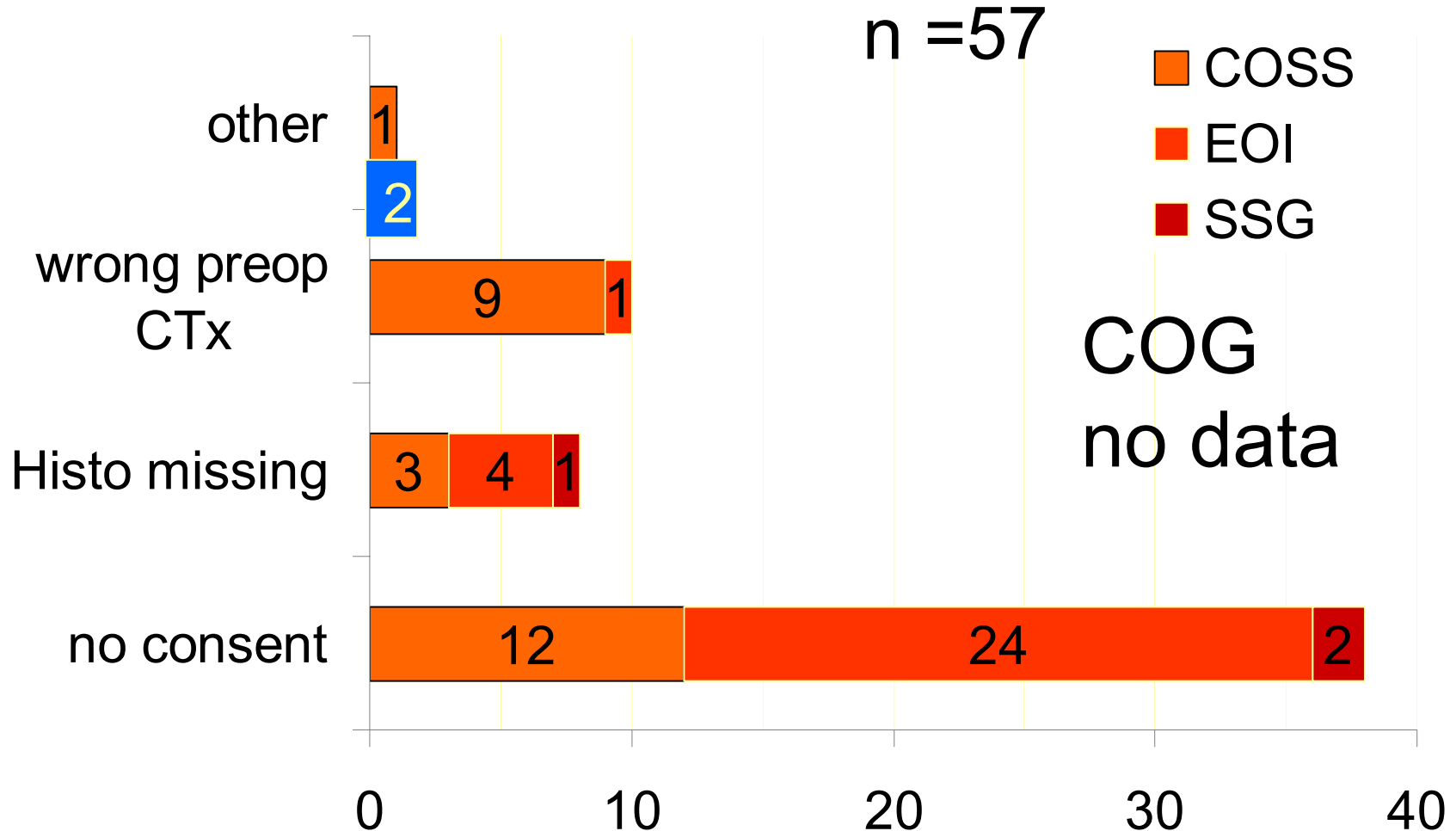
Missed random: unavoidable per Group



missed randomisations - avoidable situations !



Missed randomisations per Group - avoidable situations !



1. Key aspects of randomization
2. Randomization rates in EURAMOS-1
3. Missed randomizations - focus on avoidable situations



Missed rando: unavoidable

Progress

COSS 9

EOI 5

1. 29 y ♂, OS femur + bone met vertebrae
progredient bone spine
2. 29 y ♂, OS calcaneus
new lung met within 6 weeks from diagnosis,
further on bone met spine
3. 13 y ♂, OS tibia + multiple meta (lung + skip)
new bone met spine
4. 24 y ♀, OS Tibia + multiple meta (pulm + oss + skip)
lokal progress + bone Meta (dose reduction MTX)



Protocol criteria for local progress (Appendix 6)

Radiology

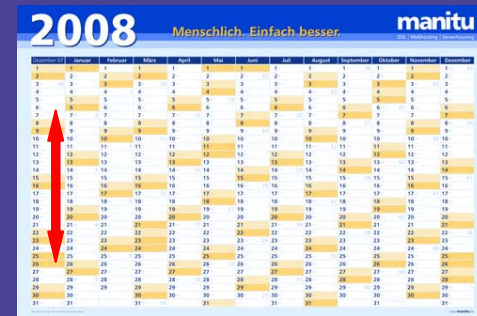
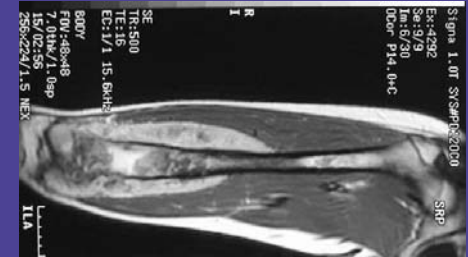
Increase $\geq 20\%$ in any dimension

+ Clinical Symptoms of Progression

of progression like increased pain, inflammatory signs, rising Alk Phosphatase

+ Repeated assessment

in ≥ 3 weeks



(un?)avoidable: no Consent

COSS 12

EOI 24

S2

COSS (Sept 06)

Good n=5

Postop Chemoth/Info n=3

Compliance problems with Tx in
general (Sx refused/delayed)

Psychiatrist involved

PEG-Intron

MAP

Poor n=4

Postop Chemoth/Info n=3

MAP

High-risk Arm

MAPIE



(un?)avoidable: no Consent

COSS 12

EOI 24

S2

EOI

Good n=13

Info on Postop Chem
n=6 MAP n=1 DOXO

reason given n=2

(UK) Compliance problems

(UK) did not wish to prolong Tx

Poor n=11

Info on Postop Chem
n=10 MAP n=1 MAPIE

reason given n=9

(UK) pt refused further Tx

(NL) preferred MAPIE

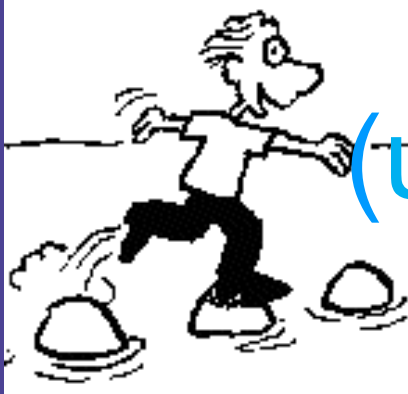
N= 7 (NL=4 UK=3)

- Intensive arm too heavy+too long
- shorter Chemo (career planing)
- fears toxicity





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(un?)avoidable: no Consent

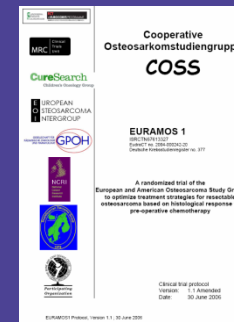
COSS 12

EOI 24

S2

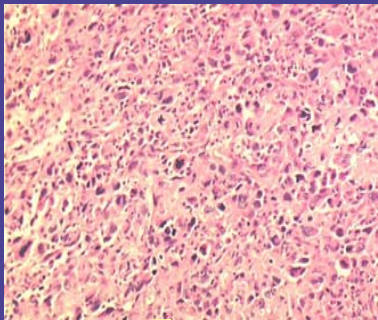
Information:

- Study objectives /rationale



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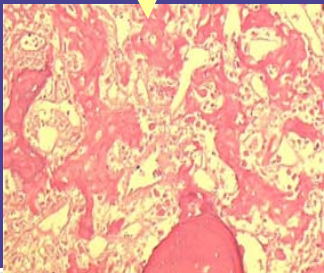
Histolog. Response + Prognosis



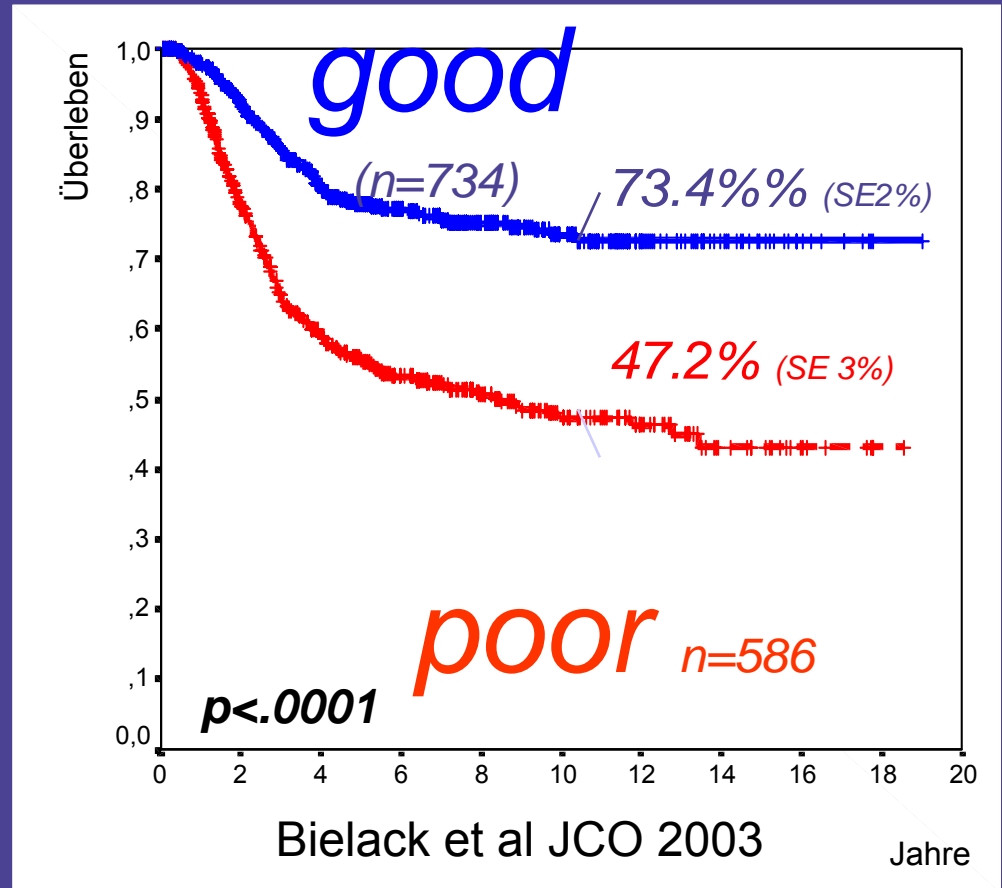
Bx



Preop
Chemo



Resected
specimen



Salvage Chemotherapy for poor responders

Preoperative Chemotherapy for Osteogenic Sarcoma: Selection of Postoperative Adjuvant Chemotherapy Based on the Response of the Primary Tumor to Preoperative Chemotherapy

GERALD ROSEN, MD, RENDIA CAPARRIOS, MD,* ANDREW G. HUVOS, MD,† LITHA KOSLOFF, MS,§ ANITA NIRENBERG, RN, C,‡ DORIS CACAVIO, RN,† RALPH C. MARCOVITZ, MD,† JOSEPH M. LANE, MD,† SURESH K. MEHTA, PhD,‡ AND CHRISTIAN URBAN, MD,†

Since June 1978, 57 patients with primary osteogenic sarcoma of the extremity were treated with high-dose methotrexate (HDMTX) and cyclophosphamide and bleomycin (BCD) for 4-16 weeks prior to definitive surgery. Histologic examination of the resected primary tumor determined the effect of preoperative chemotherapy with many primary tumors showing greater than 90% tumor necrosis attributable to preoperative chemotherapy. All patients having a favorable effect of chemotherapy on the primary tumor were continued on the same chemotherapy regimen postoperatively (regimen B). However, in those patients not having a good effect of chemotherapy on the primary tumor, HDMTX with cyclophosphamide and bleomycin (BCD) was given postoperatively (regimen A). The 57 patients were divided into two groups: 22 patients who had a good histologic response and 35 patients who had a poor response to preoperative chemotherapy. The 22 patients who had a good histologic response and were treated with regimen B postoperatively did not demonstrate a good effect of chemotherapy on the primary tumor and were assigned to regimen A postoperatively. Of these 35 patients, 32 (91%) had a good histologic response to postoperative chemotherapy. The 22 patients who had a good histologic response and were treated with regimen B postoperatively, there has been only one relapse in a patient who had a local recurrence in the area of an inadequately resected primary tumor 18 months after the cessation of chemotherapy. Thus, 51 of 57 patients (89%) are considered to have no evidence of recurrent or metastatic disease from 35 months to 20 months from the start of treatment. This study demonstrates that a good histologic response to preoperative chemotherapy in responding patients and a poor histologic response in nonresponding patients substantially increased the effectiveness of alternative postoperative adjuvant chemotherapy. Failure to have a good response to preoperative chemotherapy. This individualized chemotherapy strategy has yielded the highest disease-free survival rate reported to date for osteogenic sarcoma.

Cancer 49:1221-1230, 1982.

Adjuvant Chemotherapy of Osteosarcoma: Results of a Randomized Operative Trial (COSS-82) With Salvage Chemotherapy Based on Histological Tumor Response

Winkler, G. Beron, G. Dellinger, U. Heise, H. Kobisch, C. Pufürst, J. Berger, J. Ritter, H. Jüngerlein, N. Graf, W. Russe, E.R. Gruenewald, W. Franks, R. Koltz, P. Preusser, G. Prindull, W. Brauer, G. Lindbeck

Observation of the predictive value of the extent of tumor cell destruction after preoperative chemotherapy for metastasis-free survival in osteosarcoma, a randomized study was undertaken with the aim of (1) sparing some patients unpleasant side-effects of highly toxic drugs like doxorubicin (DOX) and cyclophosphamide (CPD) by administering these drugs postoperatively only in patients with a major preoperative response, and (2) giving the prognosis of patients responding poorly the initial treatment by use of salvage chemotherapy postoperatively. The available patients were divided into two groups. Those in the study arm receiving preoperative chemotherapy consisting of high-dose methotrexate (HDMTX) and the combination of bleomycin, cyclophosphamide, and doxorubicin (BCD) versus those in the control arm receiving HDMTX and BCD alternatively with CPD postoperatively. The 57 patients were divided into two groups: 22 patients who had a good histologic response and 35 patients who had a poor response to preoperative chemotherapy. The 22 patients who had a good histologic response and were treated with regimen B postoperatively did not demonstrate a good effect of chemotherapy on the primary tumor and were assigned to regimen A postoperatively. Of these 35 patients, 32 (91%) had a good histologic response to postoperative chemotherapy. The 22 patients who had a good histologic response and were treated with regimen B postoperatively, there has been only one relapse in a patient who had a local recurrence in the area of an inadequately resected primary tumor 18 months after the cessation of chemotherapy. Thus, 51 of 57 patients (89%) are considered to have no evidence of recurrent or metastatic disease from 35 months to 20 months from the start of treatment. This study demonstrates that a good histologic response to preoperative chemotherapy in responding patients and a poor histologic response in nonresponding patients substantially increased the effectiveness of alternative postoperative adjuvant chemotherapy. Failure to have a good response to preoperative chemotherapy. This individualized chemotherapy strategy has yielded the highest disease-free survival rate reported to date for osteogenic sarcoma.

J Clin Oncol 6:329-337. © 1988 by American Society of Clinical Oncology.

Chemotherapy for Nonmetastatic Osteogenic Sarcoma: The Memorial Sloan-Kettering Experience

By Paul A. Meyers, Glenn Heller, John Healey, Andrew H. Hsu, Joseph Lane, Ralph Marcove, Anne Applewhite, Vaia Vlamis, and Gerald Rosen

Purpose: Adjuvant chemotherapy improves disease-free survival (DFS) for patients with osteogenic sarcoma (OS). We reviewed our experience with OS to determine prognostic factors, the role of preoperative chemotherapy and subsequent histologic response to the salvage chemotherapy after poor initial response.

Methods: From 1975 to 1984 we saw 22 patients with previously untreated OS without metastasis. All patients received intensive chemotherapy and underwent surgical resection of primary tumor. Chemotherapy included high-dose methotrexate; Adriamycin (doxorubicin; Adria Laboratories, Columbus, OH); and bleomycin, cyclophosphamide, and dactinomycin (BCD). Selected patients also received cisplatin.

Results: DFS was not affected by use of preoperative chemotherapy versus immediate surgery, by use of limb-sparing surgery versus amputation, by age, sex, or dose intensity of chemotherapy. DFS did correlate with serum lactate dehydrogenase (LDH), alkaline phosphatase, pri-

mary tumor site, race, and histologic response to preoperative chemotherapy. There was no difference in DFS for patients with a poor histologic response who did or did not receive cisplatin, although patients who did receive cisplatin had a longer median survival. The 5-year DFS was 66% for patients aged ≤ 21 years who had extremity primary tumors and were treated with the T10 protocol. Conclusions: Intensive chemotherapy can achieve DFS in a high proportion of patients with OS. Although it is a powerful predictor of DFS, histologic response to preoperative chemotherapy cannot be assessed at diagnosis. We have not shown an ability to salvage patients with an unfavorable response. We need to increase the proportion of patients with a favorable response, identify the patients who have an unfavorable response, and develop novel treatments to salvage poor responders.

J Clin Oncol 10:1515-1521. © 1992 by American Society of Clinical Oncology.

Winkler et al.: JCO1988

Rosen et al.: Cancer 1982

Meyers et al.: JCO1992

We have not shown an ability to salvage patients with an unfavorable response"



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Salvage Chemotherapy for poor responders

~~Preoperative Chemotherapy for Osteogenic Sarcoma: Selection of Postoperative Adjuvant Chemotherapy Based on the Response of the Primary Tumor to Preoperative Chemotherapy~~
~~Adjuvant Chemotherapy of Osteosarcoma: Results of a Randomized Operative Trial (COSS-82) With Salvage Chemotherapy Based on Histological Tumor Response~~
~~Chemotherapy for Nonmetastatic Osteogenic Sarcoma: The Memorial Sloan-Kettering Experience~~

No proof

by controlled trial with positive results

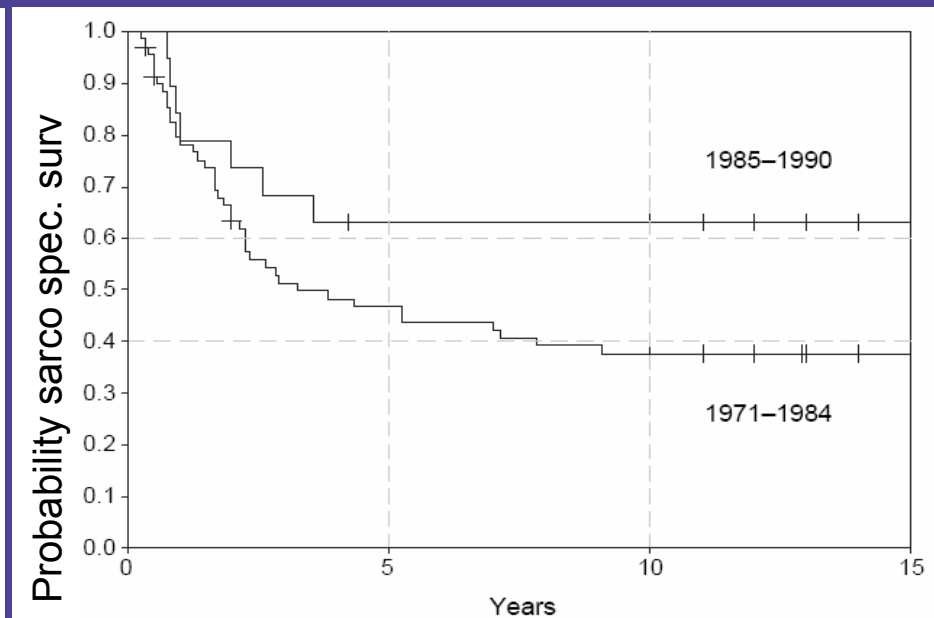
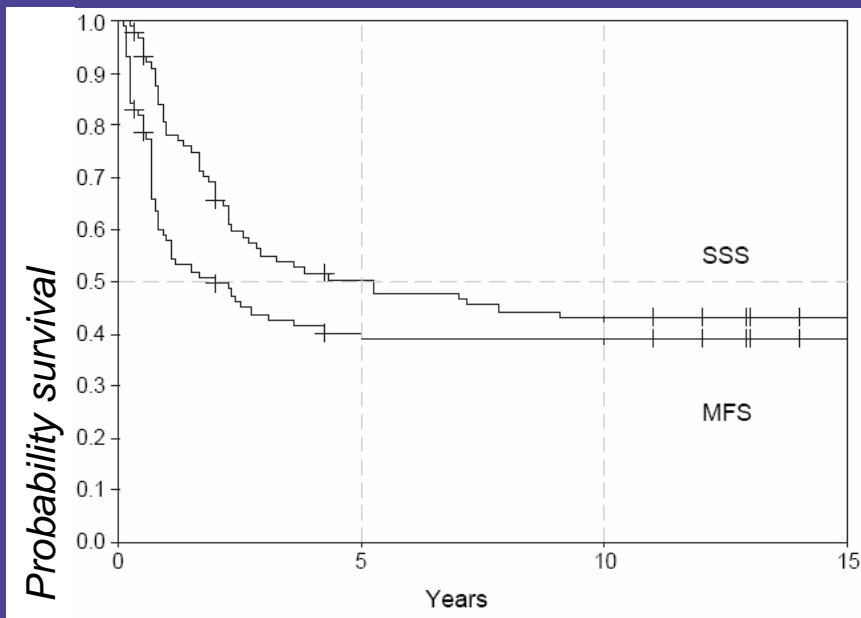
→ Larger number

→ EURAMOS-1

1400 patients/700 poor responders



Maintenancetherapie for good Responder Interferon



Müller et al; Acta Onc 2005



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No Consent

Choosing treatment arm instead of consenting to Rando?

Standard-Tx

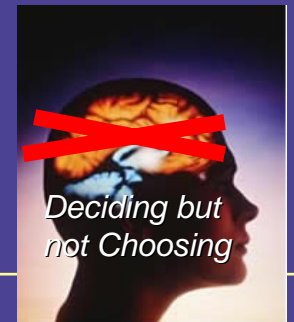
yes

Experimental Tx

no

Good n=5
Postop Chemoth
Compliance problems with Tx in general (5x refused/delayed) Psychiatrist involved
NA
NA
MAP
MAP

Poor n=4
Postop Chemoth
NA
MAP
High-risk „according to protocol.“
MAP





(un?)avoidable: no Consent

COSS 12

EOI 24

S2

Information:

- Study objectives /rationale



Communication skills → previous talk



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Avoidable: missing Histo/Deadline

C3 E4 S1

- Histo missing/deadline
 ≤ 35 d post-Sx (\pm Referenzpathologie)





Avoidable: missing Histo/Deadline

C3 E4 S1

- Histo missing/deadline
 ≤ 35 d post-Sx (\pm Referenzpathologie)



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Avoidable: Wrong preop Chemoth

C2

COSS 9 1 EOI

Randocriteria for preop Chemoth:

2 x AP

(2) - 4 - (6) x MTX



Missed rando: unavoidable Wrong preop Chemoth

C2

COSS 9 1 EOI

33 y ♂ OS humerus:

No of preop chemocycles

After 1st AP-Block „premature“

amputation b/o massive arterial bleeding
from tumor vessel



Avoidable: Wrong preop Chemoth

C2

COSS 9 1 EOI

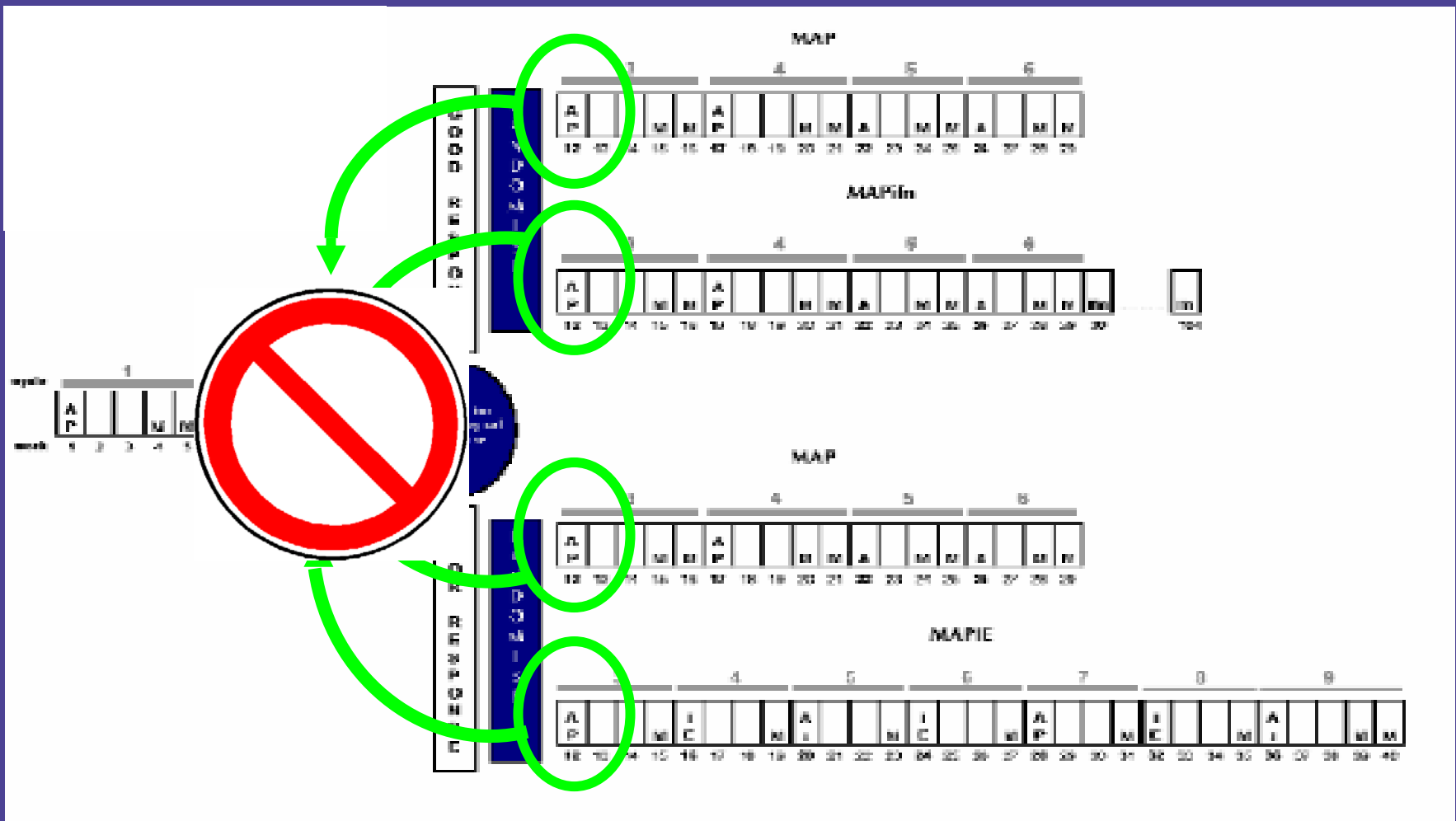
3rd. AP: n= 5

Reason: delay of surgery (n=3)



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Avoidable: Wrong preop Chemoth





Avoidable:

Wrong preop Chemo th

C2

COSS 9 1 EOI 1

3rd. AP: n= 5

Reason: delay of surgery (n=3)

- Early planning/liaison with surgeon
- Bridging possible

Randocriteria: 2 x AP



(2) – 4 – (6) x MTX



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Choosing treatment arm after Rando

- Happens from time to time
- No systematic data
- Anecdotal cases from enquiries to COSS-office



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Choosing treatment arm after Rando

- Patient randomized for MAP-Poor Response
 - Parents now disappointed with random allocation
 - have hoped for MAPIE (more is better?)
 - consider to „choose MAPIE“
- Patient was randomized to MAP-(GR) arm and is going to complete it shortly
 - „Can he have additionally PEG-Intron?“



Choosing treatment arm ??

Standard-Tx

yes

Experimental TX

no

Good n=5	Poor n=4
Postop Chemoth	Postop Chemoth
Compliance problems with Tx in general (5x refused/delayed)	NA
Psychiatrist involved	MAP
NA	High-risk, according to protocol.
NA	NAPE
EG-Intron	
MA	



Withdrawal of protocol treatment
at personal wish of patient
theoretically **always** possible





Choosing treatment arm after Rando

But withdrawal
after rando
may reduce
power of study

Intention to treat analysis

Essential prerequisite for valid result on effect of treatment in clinical trials

= analysis as randomized
(independent of adherence to assigned therapy)

Concern: type 2 error
(masking real effect)



Choosing treatment arm after Rando

- Pat had marginal resection and poor Response. She was randomised to MAP.
„We think she should have **MAPIE** instead.“



Choosing treatment arm after Rando

Patient refuses MAP-ifn after Rando:

„Our patients always refuse MAP-Ifn because we, their clinicians are **not** convinced it works!!!“

But since there is always a 50% possibility that they get MAP you will have a 50% chance that the Good-Responder remain on study“



Ethics + Results:

Uncertainty principle

Uncertainty what's better

- **no participation** in clinical trial if **believe**, that **one** treatment superior
- **no entry** of patients if **particular** treatment is **indicated**



Intention to treat analysis

Essential prerequisite for valid result on effect of treatment in clinical trials

= **analysis as randomized** (independent of adherence to assigned therapy)

Concern: type 2 error (masking real effect)



Choosing treatment arm after Rando

Teenager randomised for MAP-GR

Pat+Parents want a shortened chemotx schedule instead

(tumor totally necrotic – thinks less Chemo would be appropriate)



Choosing treatment arm after Rando



Withdrawal at
personal wish
theoretically
always possible
But after rando
may **reduce**
power of study



Intention to treat analysis

Essential prerequisite for valid
result on effect of treatment in
clinical trials

= analysis as randomized
(independent of adherence
to assigned therapy)


Concern: type 2 error
(masking real effect)

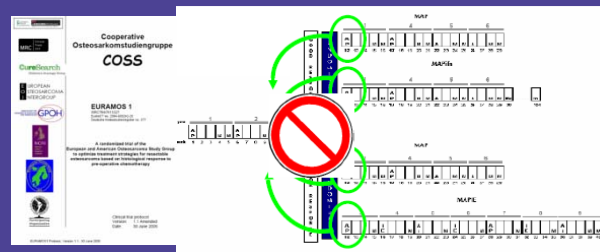




Summary

Areas for further improvement:

- **Deadline**  Pathology report/Rando
- **Preoperative Chemo**
2x AP + 2-6 x MTX
- **Consent:** communicate information



Improving Randomisation Rates: Practical Steps to take (at) home



ESF-Trainingscourse London 24.01.2008



Carrle 24.01.2008