instituut Verbeeten

RT in Hodgkin Lymphoma

Lesser is better?

Philip Poortmans, M.D. Ph.D.
Radiation oncologist
Tilburg, The Netherlands

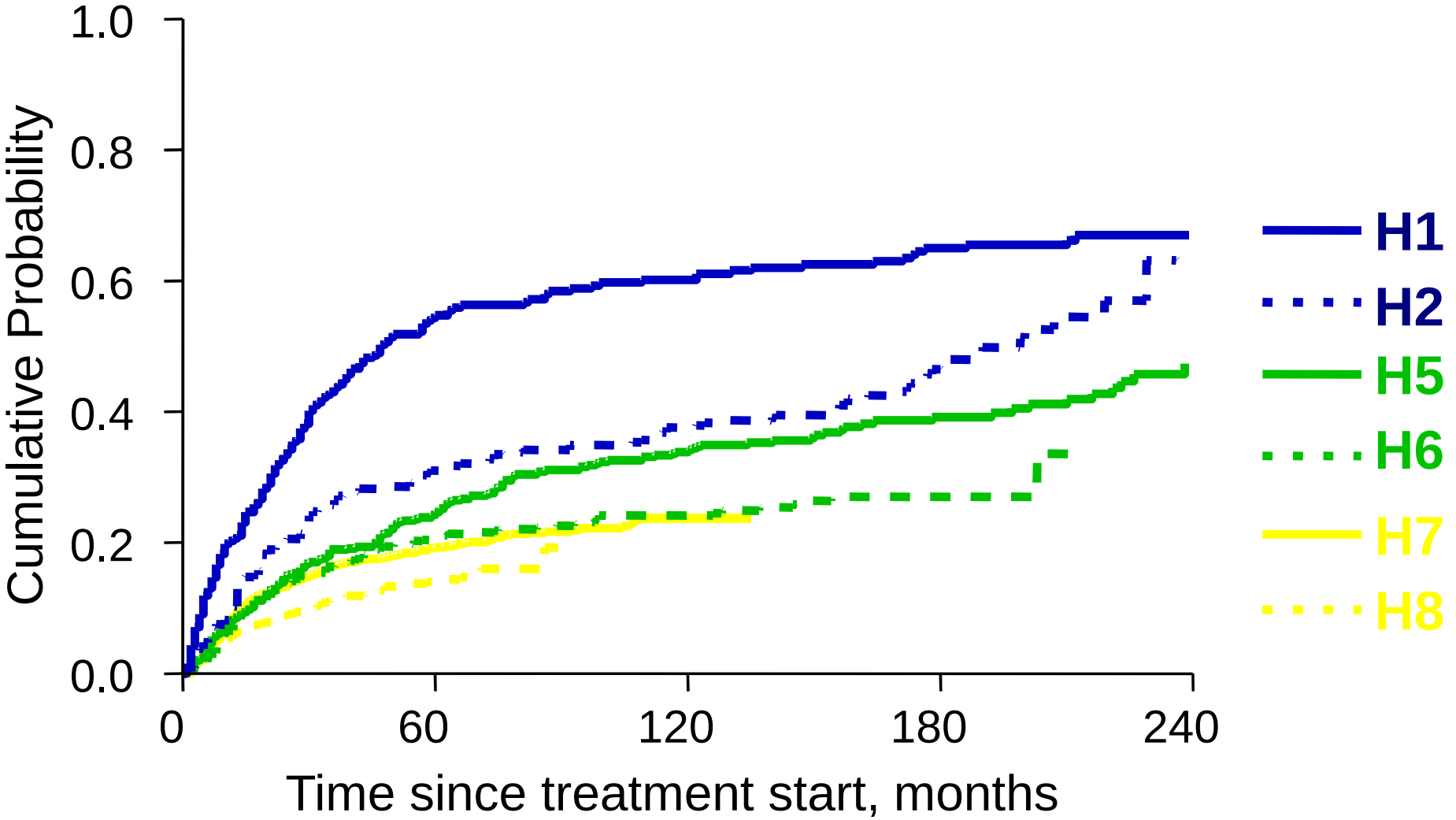
Radiation dose in Hodgkin Lymphoma

- Introduction
- Current evidence
- Guidelines

Early stage Hodgkin Lymphoma

The EORTC experience

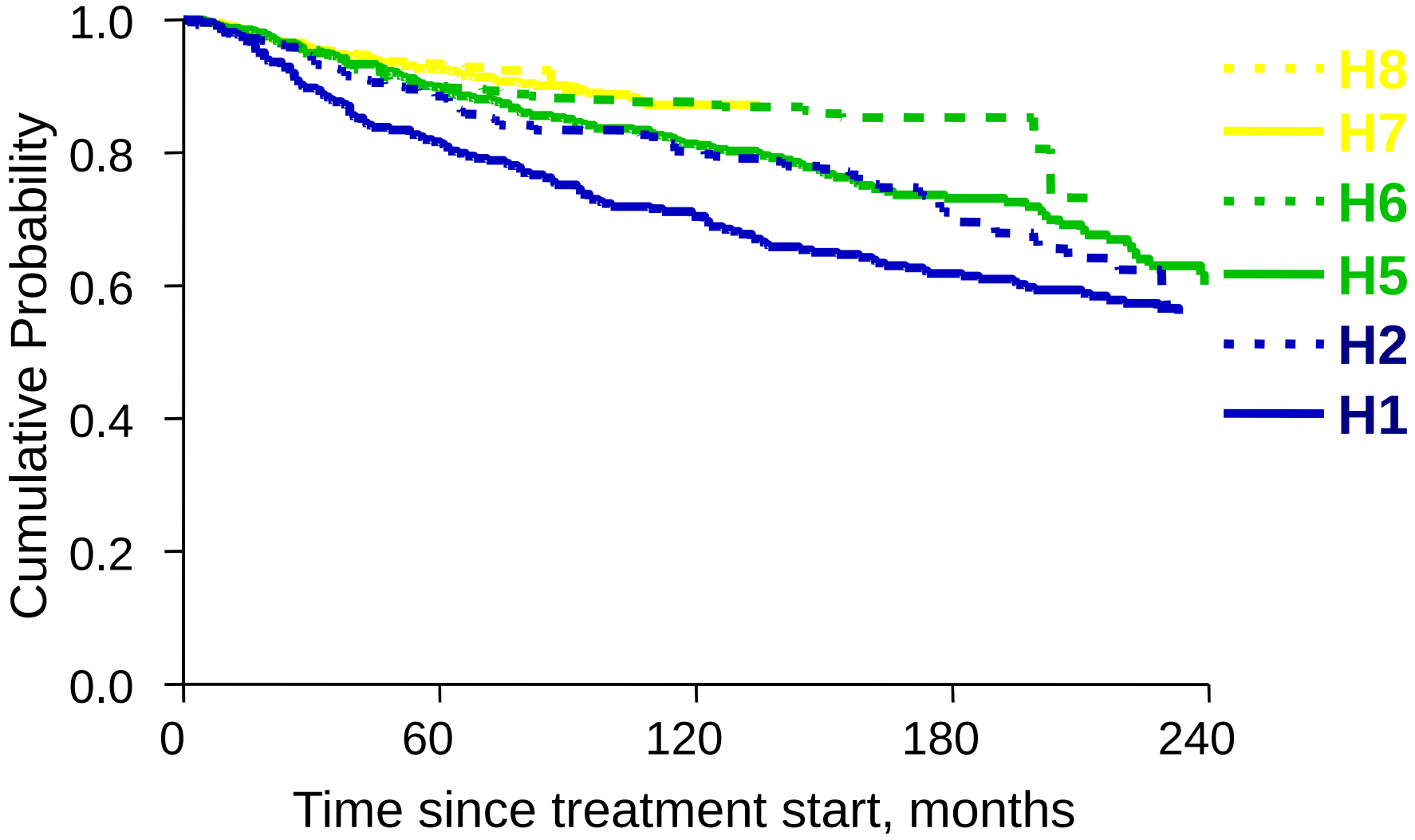
Treatment failure



Early stage Hodgkin Lymphoma

The EORTC experience

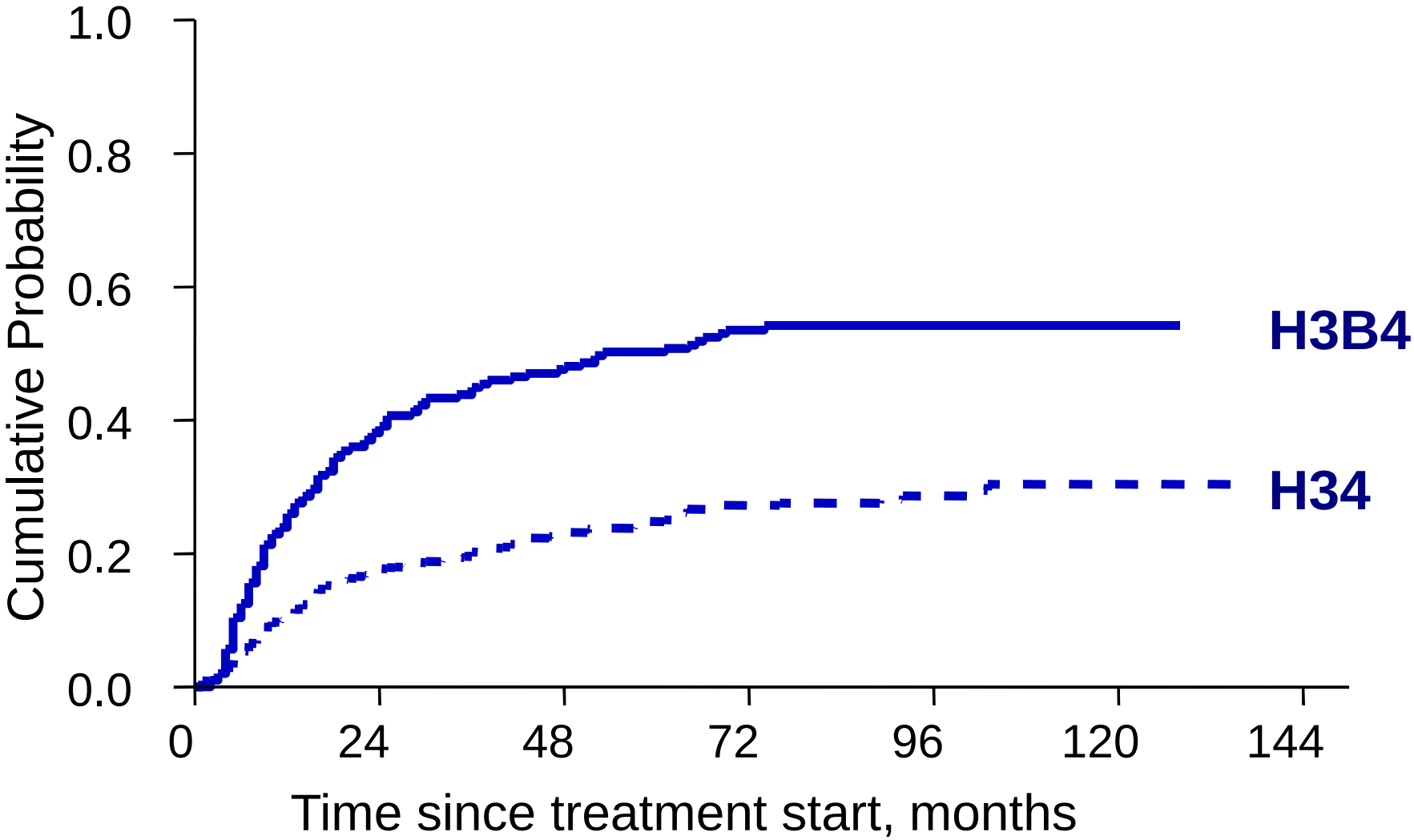
Overall survival



Advanced stage Hodgkin L

The EORTC experience

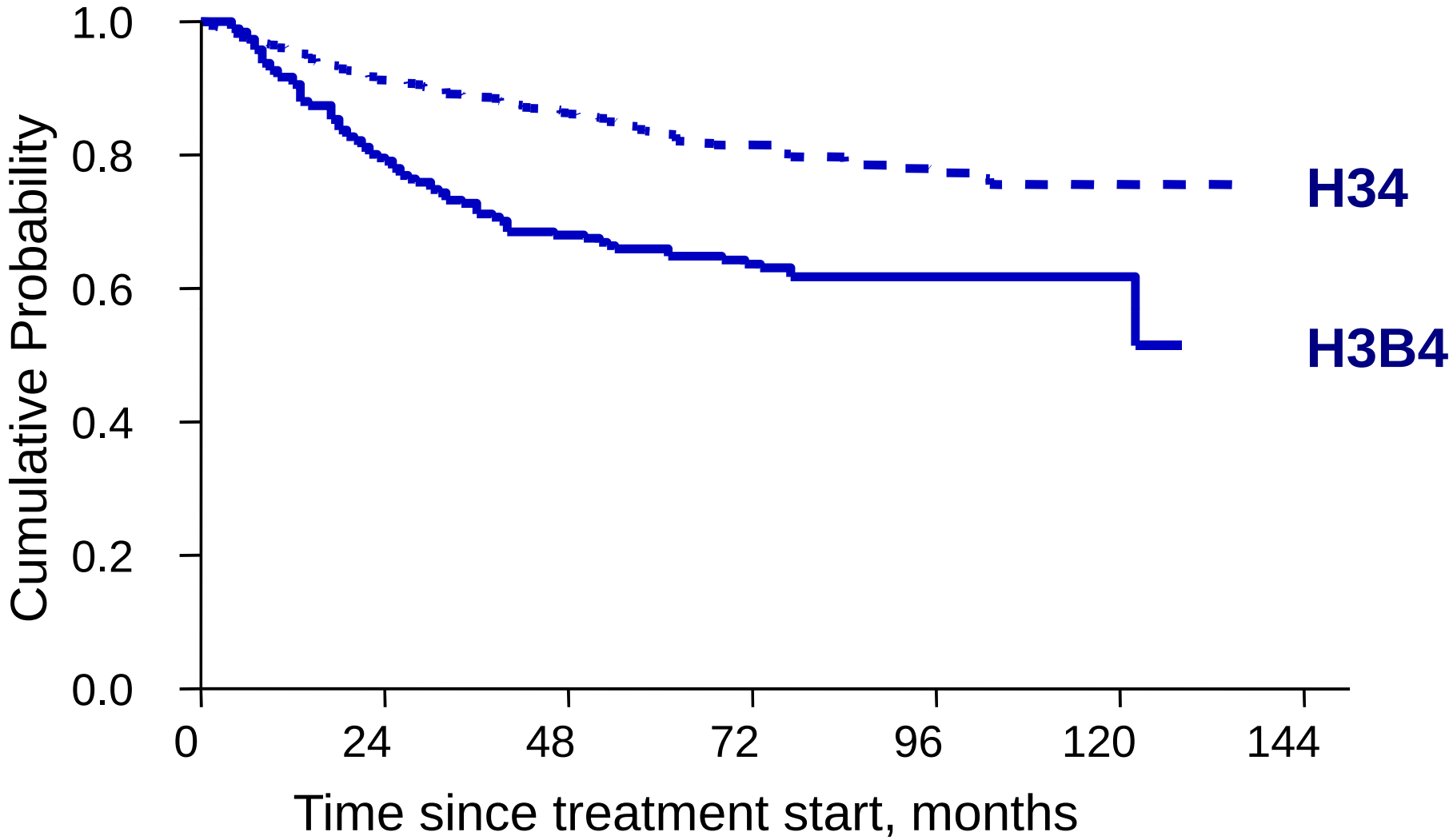
Treatment failure



Advanced stage Hodgkin L

The EORTC experience

Overall survival

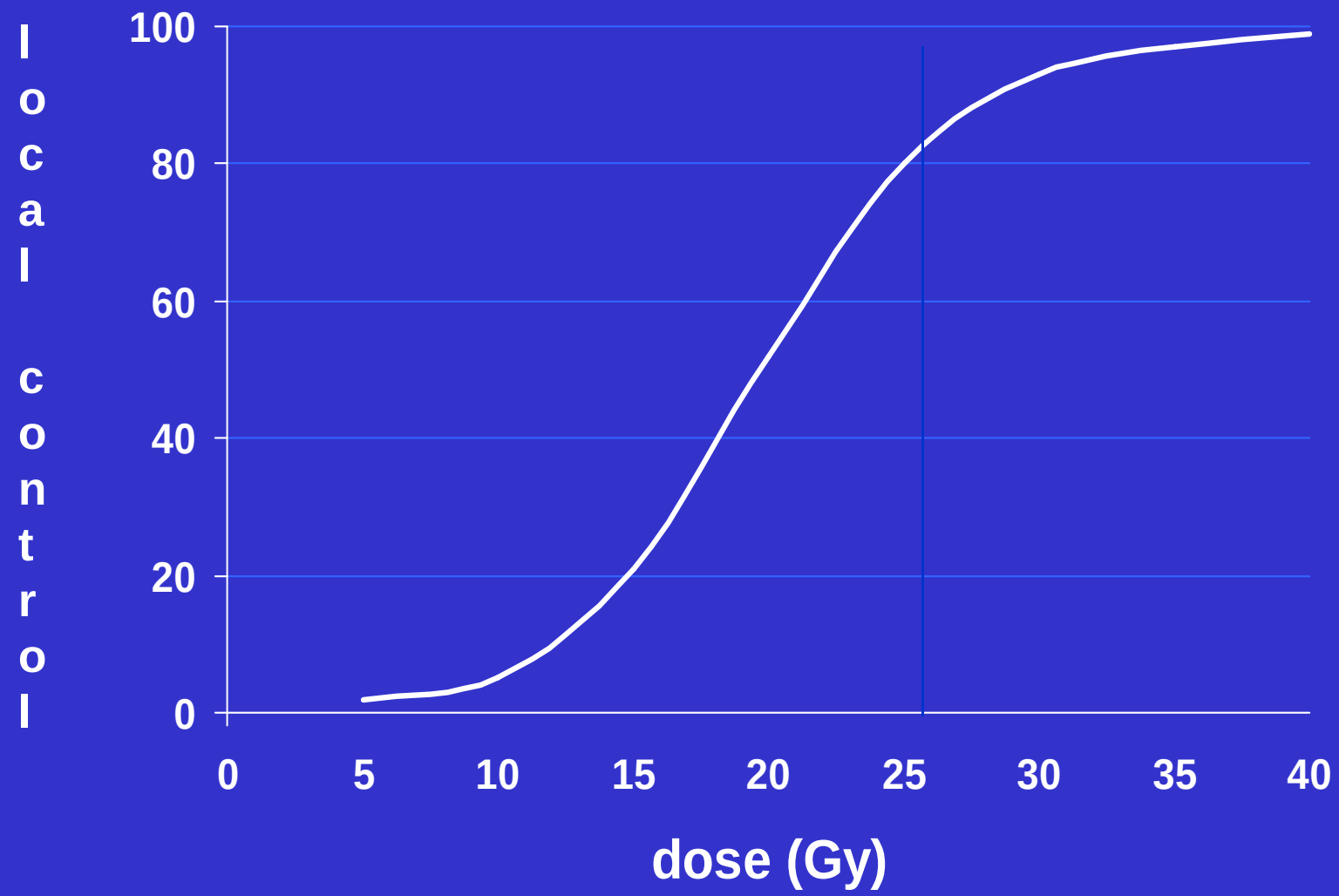


Radiation dose in Hodgkin Lymphoma

- Introduction
- Current knowledge & evidence
- Guidelines

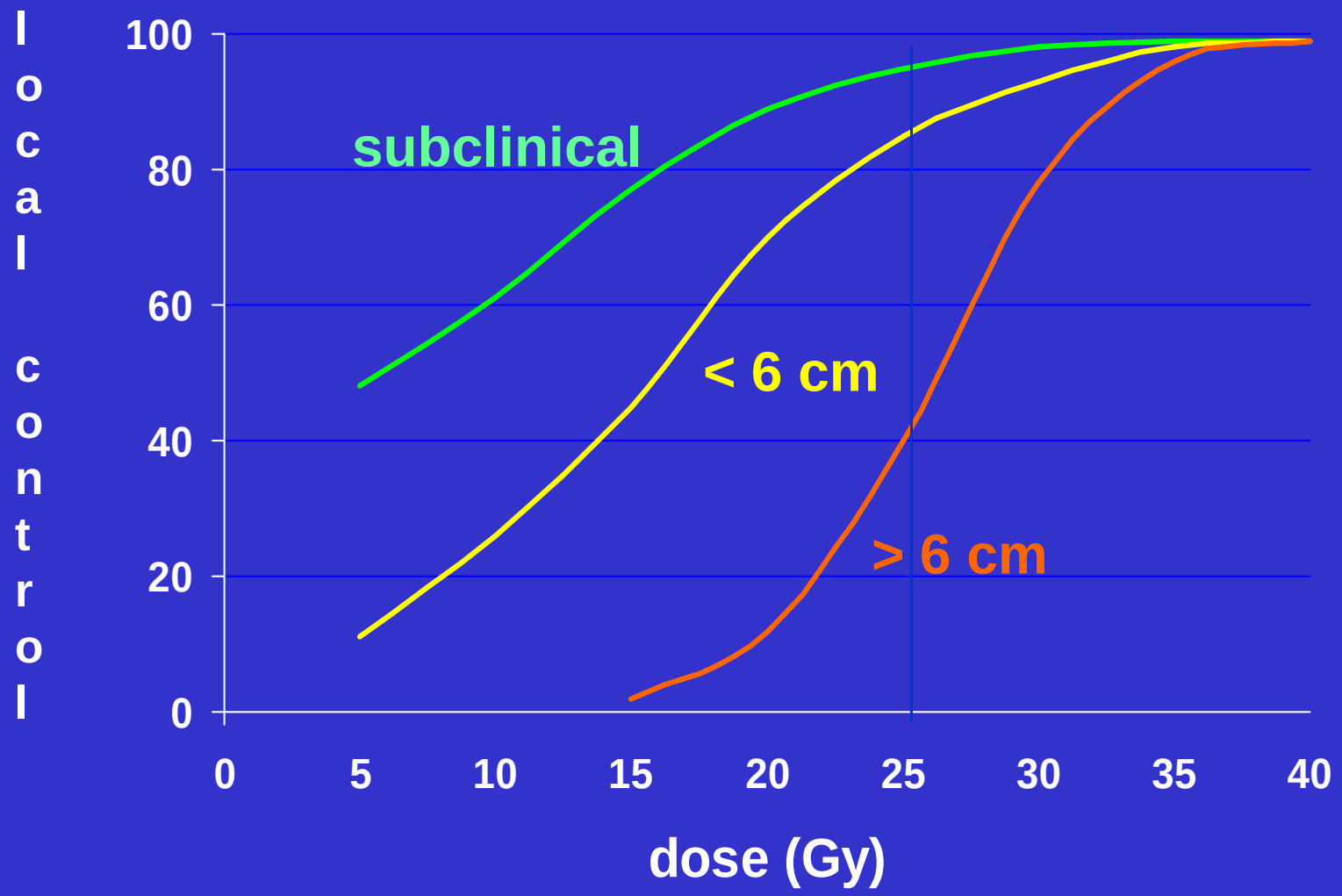
Dose-response curve Hodgkin's lymphoma

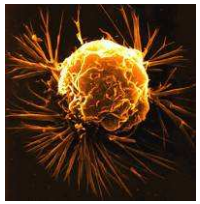
(Fletcher & Shukovsky 1975)

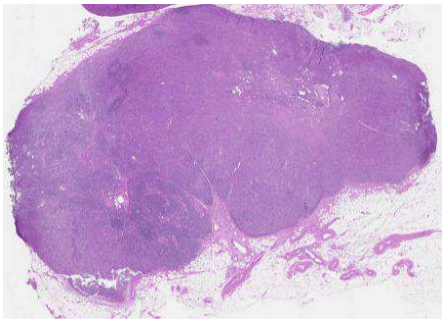


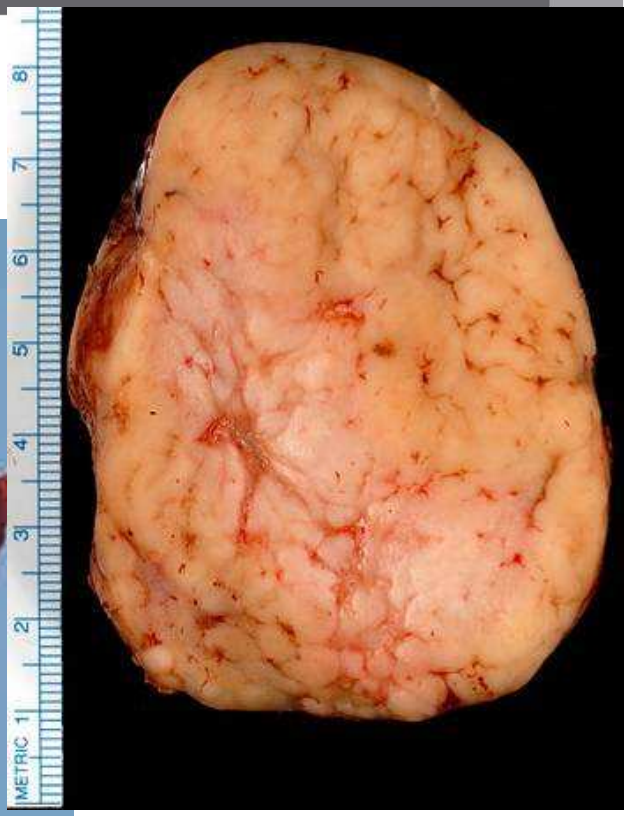
Dose-response curves Hodgkin's lymphoma

(Vijayakumar & Myrianthopoulos 1992)









= *1 cell*

= *0,01 mm³*

= *10^6 cells*

= *1 mm³*

= *1 mg*

= *10^9 cells*

= *1 cm³*

= *1 g*

= *10^{12} cells*

= *1 dm³*

= *1 kg*

Radiotherapy & cell kill

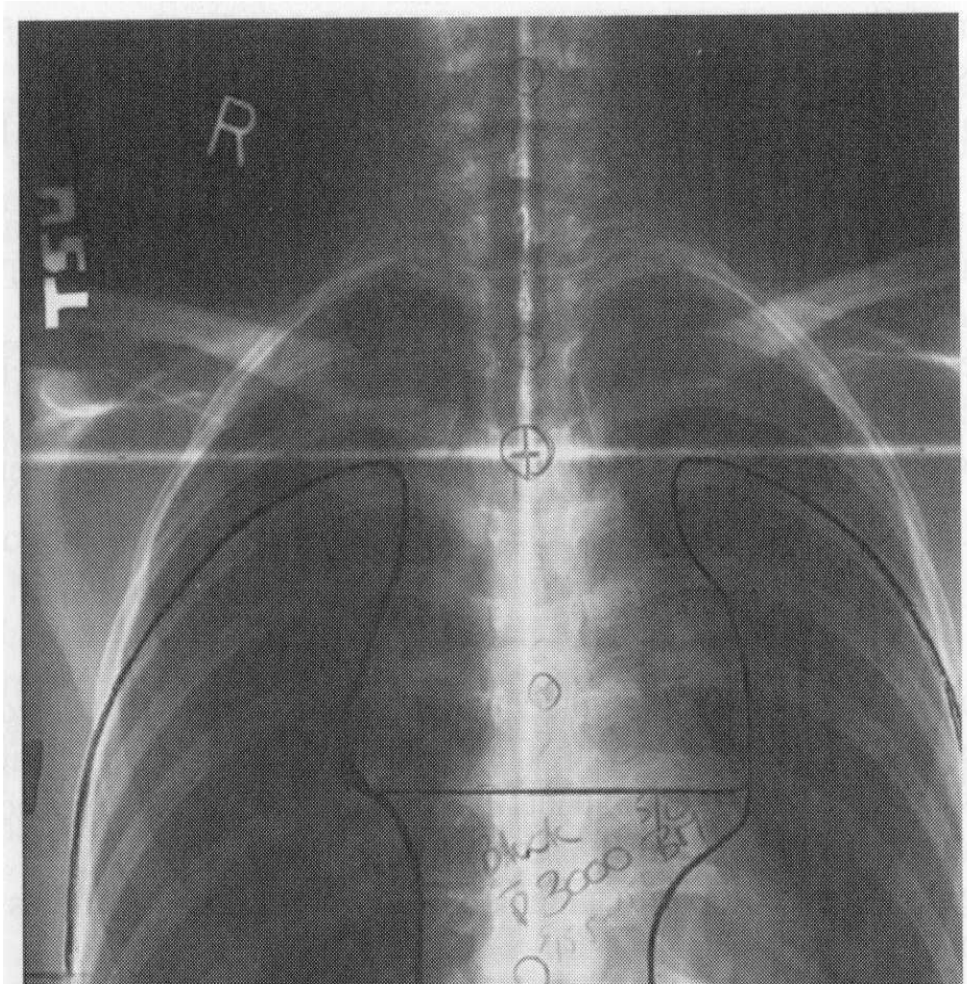
	nr cells	90% cure if
• Subclinical	$0 - 10^8$	20 Gy
• 1-5 cm	$10^9 - 10^{10}$	28 Gy
• 6-10 cm	$10^{11} - 10^{13}$	34 Gy

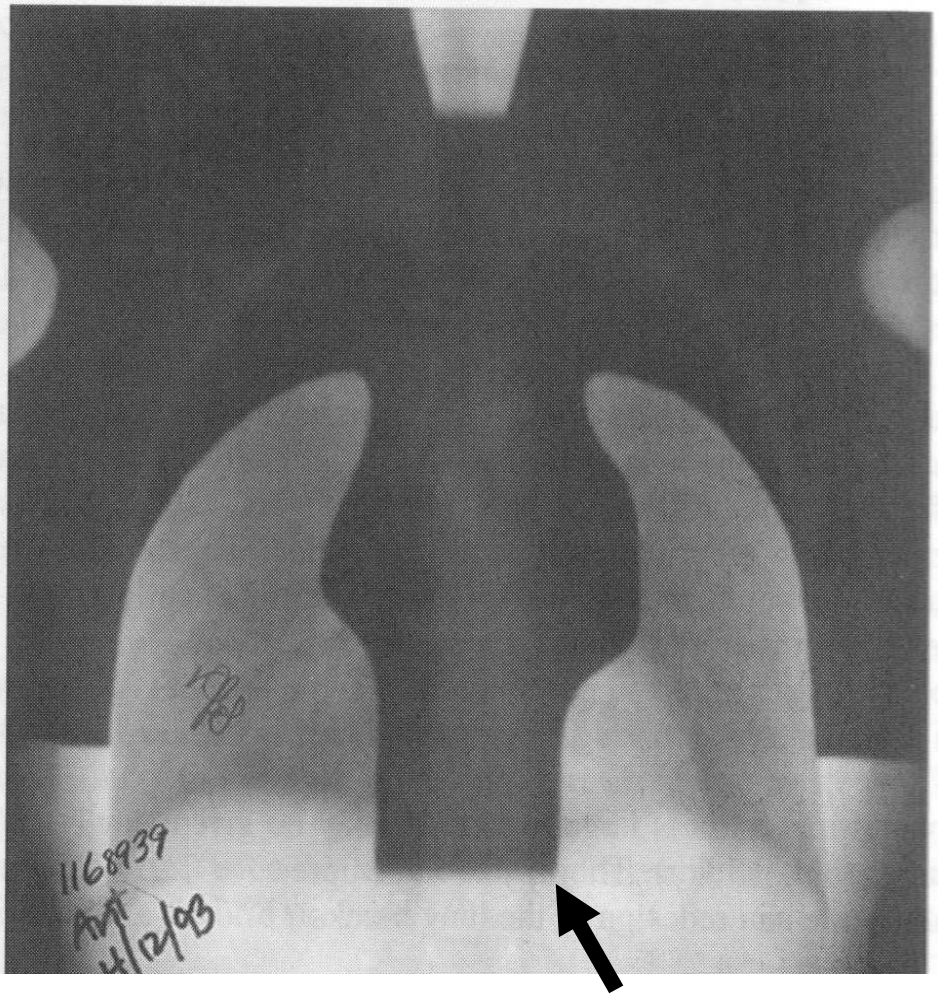
➔ *2 Gy kills about 80% of the cells*

Radiotherapy & cell kill

	90% cure if
• 2 Gy ➔ 20% residual cells	<1 cells
• 4 Gy ➔ 4% residual cells	2.5 cells
• 20 Gy ➔ 10^{-5} residual cells	10^{4} cells
• 30 Gy ➔ 3.10^{-9} log residual cells	3.10^{7} cells
• 36 Gy ➔ 3.10^{-11} log residual cells	3.10^{9} cells
• 40 Gy ➔ 10^{-12} log residual cells	10^{11} cells

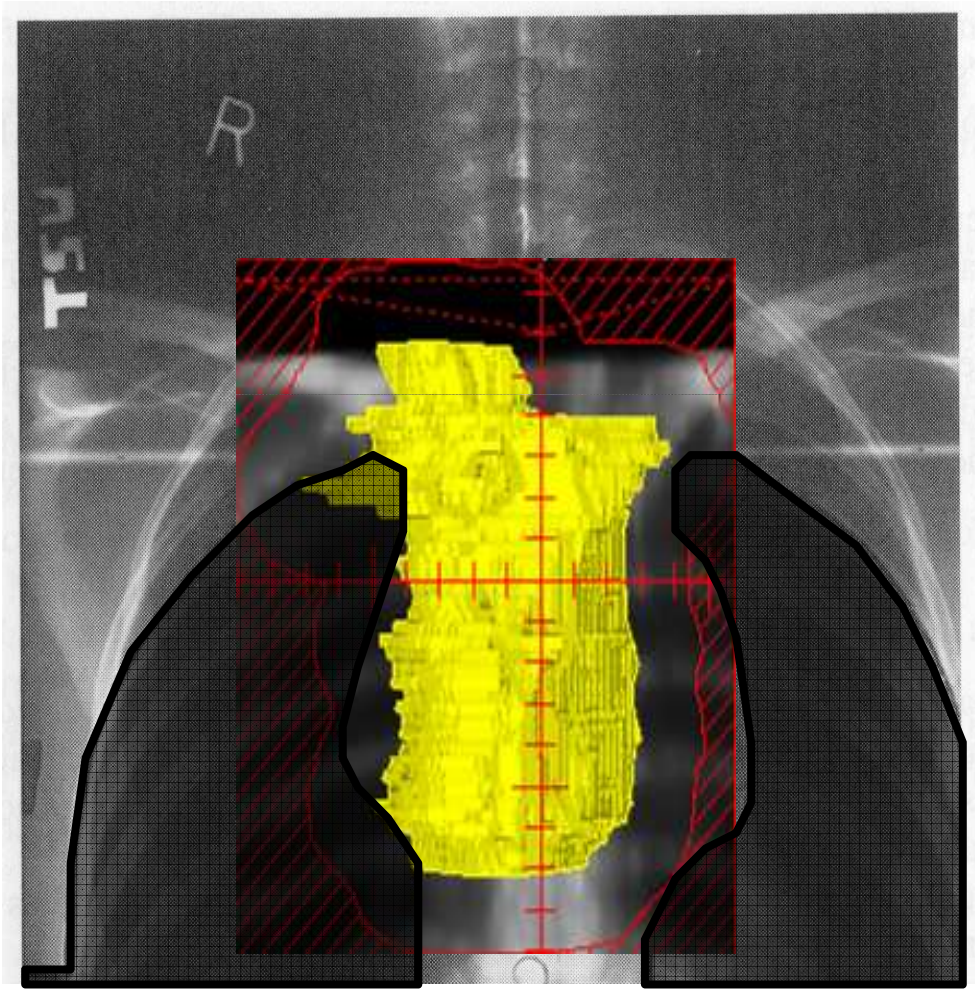
Radiotherapy & the target





Acceptable shift

Radiotherapy & the target



Radiotherapy & the target

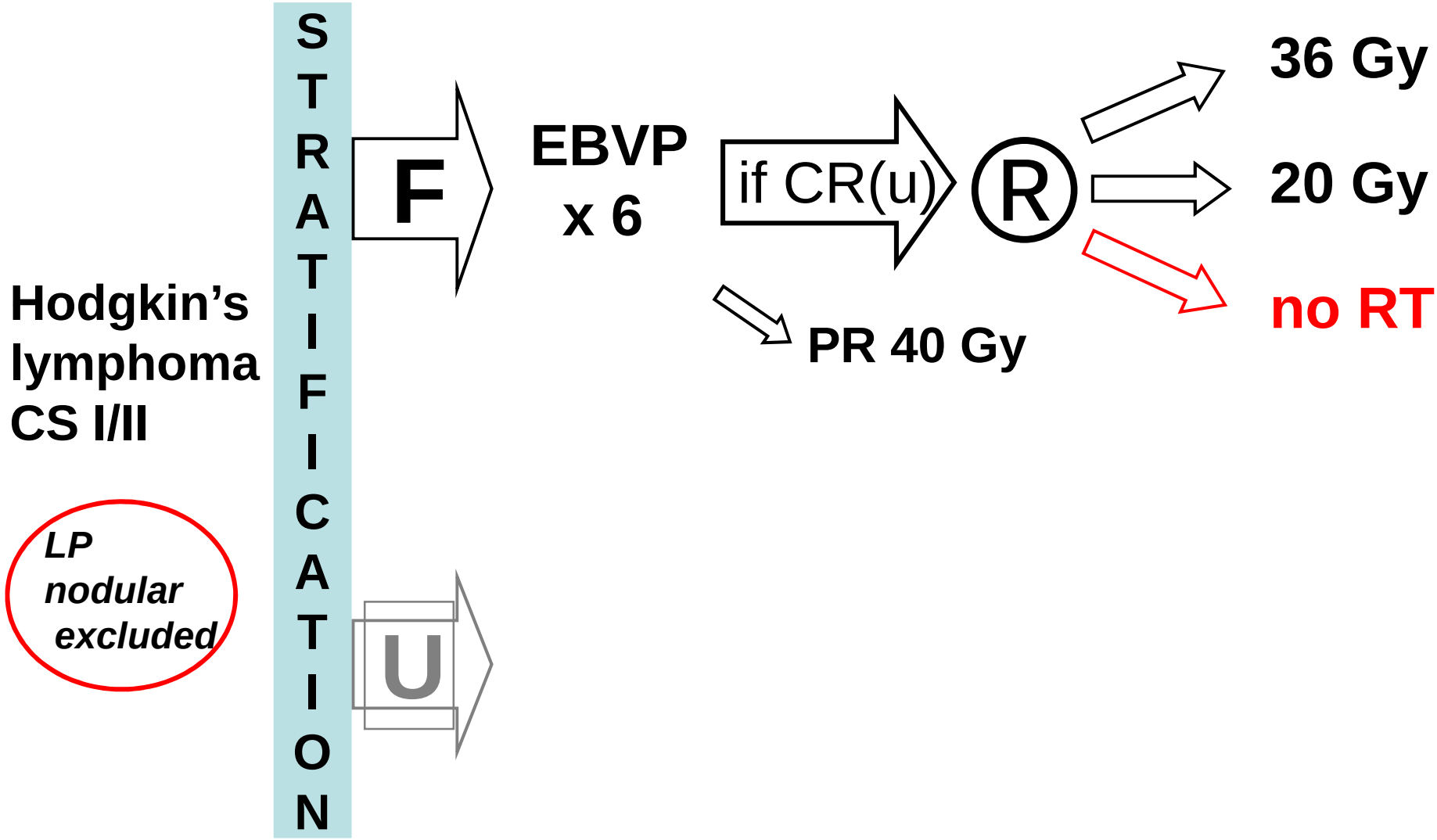
GTV → CTV → PTV ←→ standard fields

- GTV shrinks during treatment
- Patient set-up variation
- Movement internal structures

} *this & high dose com-pensates missing GTV*

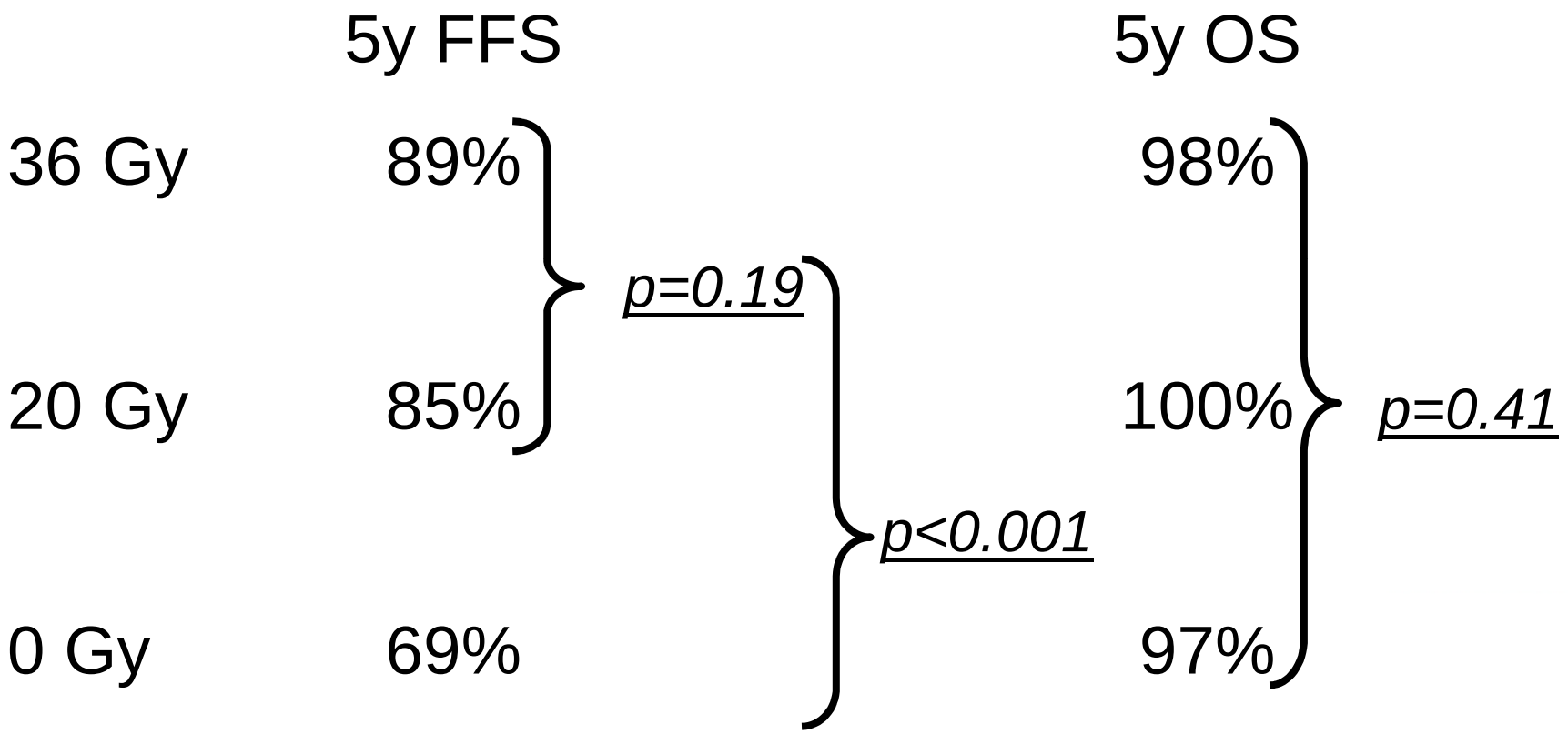
EORTC H9F trial

early stage "Favourable" Hodgkin's lymphoma



EORTC H9F trial

early stage "Favourable" Hodgkin's lymphoma



➔ *0 Gy treatment arm preliminary closed*

EORTC H3 - 4 trial

stages III / IV Hodgkin's lymphoma

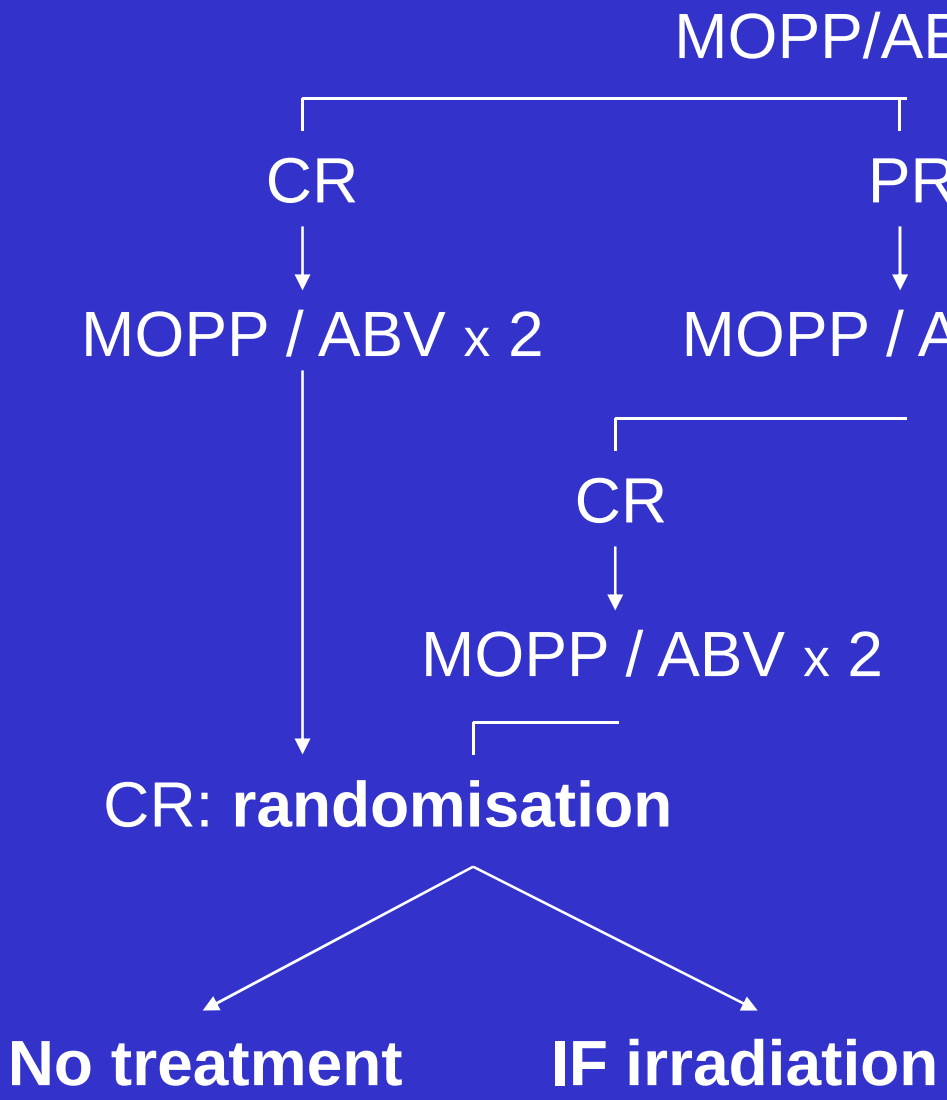
➔ The role of IF-RT

➔ in stage III and IV HD

➔ after MOPP/ABV chemotherapy

EORTC H3 - 4 trial 1989 - 2000

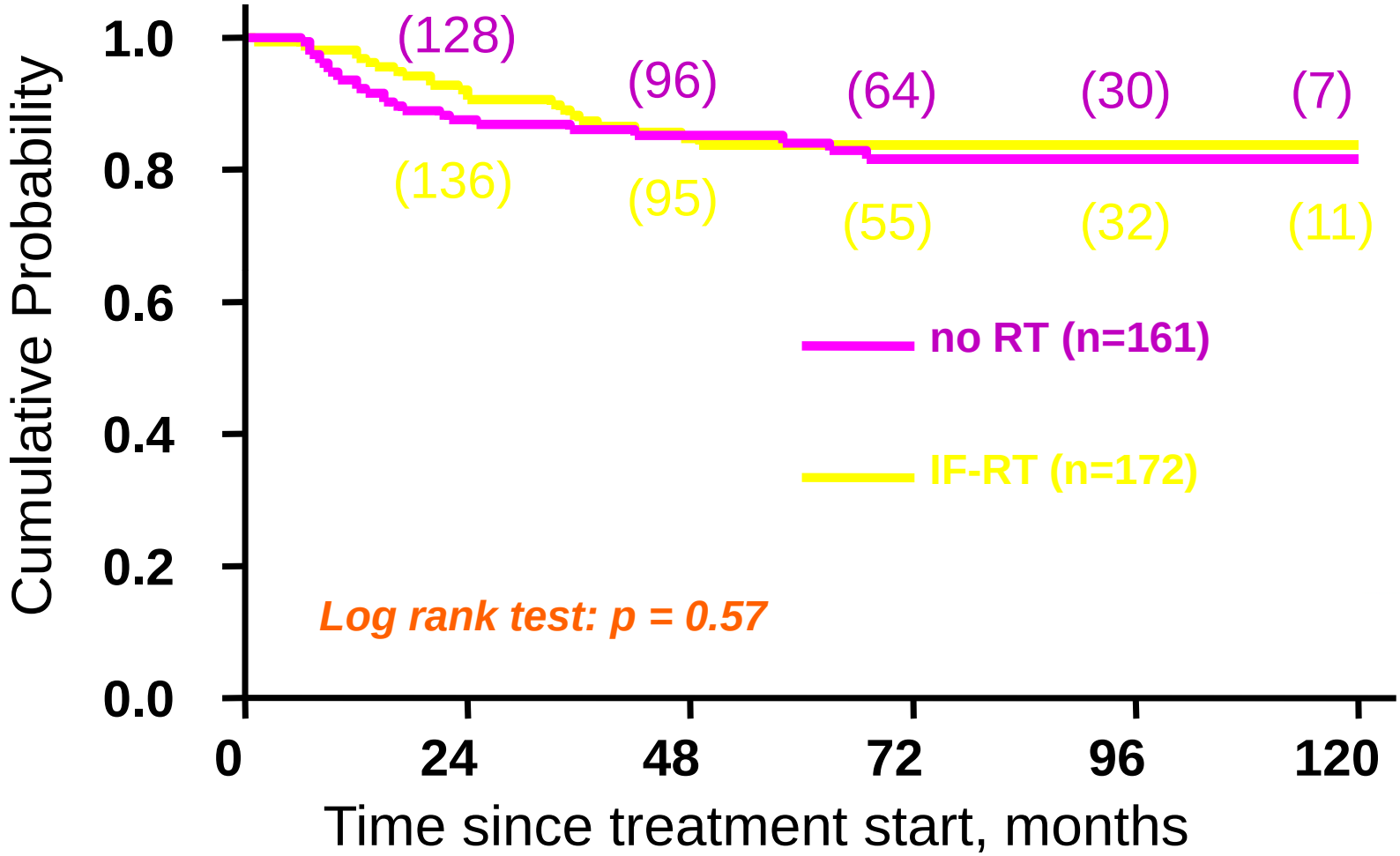
EORTC H3 - 4 trial 1989 - 2000



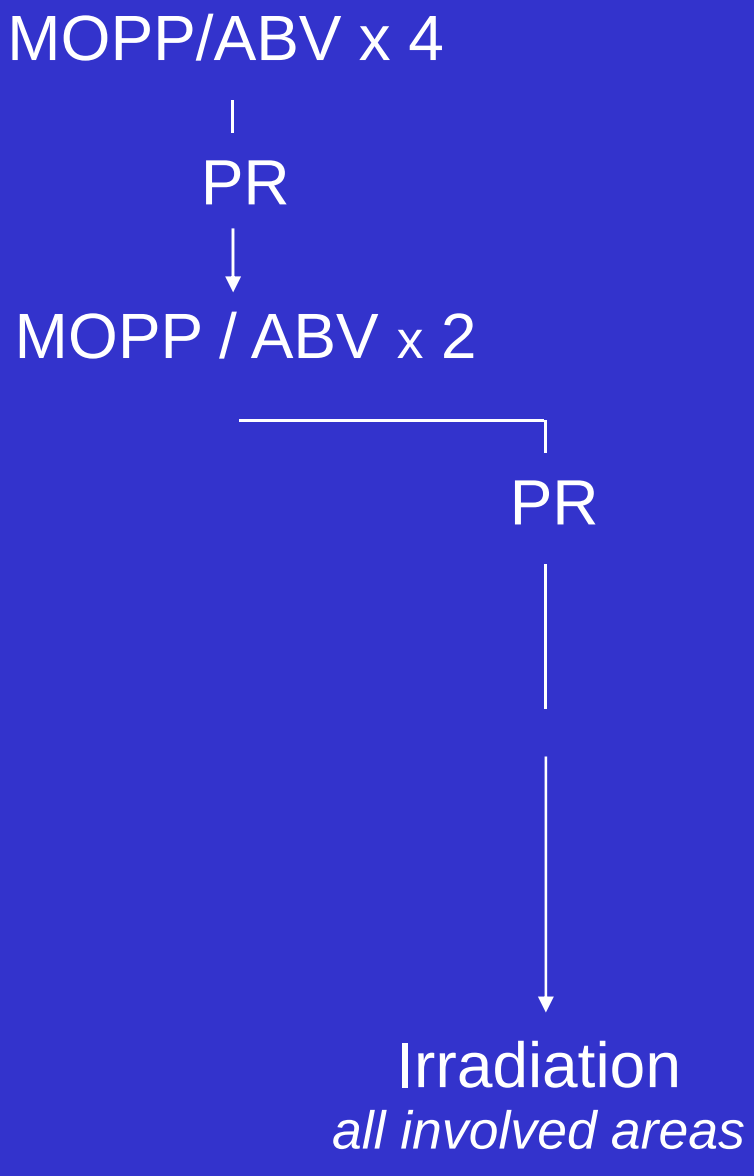
Advanced stage Hodgkin L

H34 trial: randomised pts (n=333)

Relapse free survival



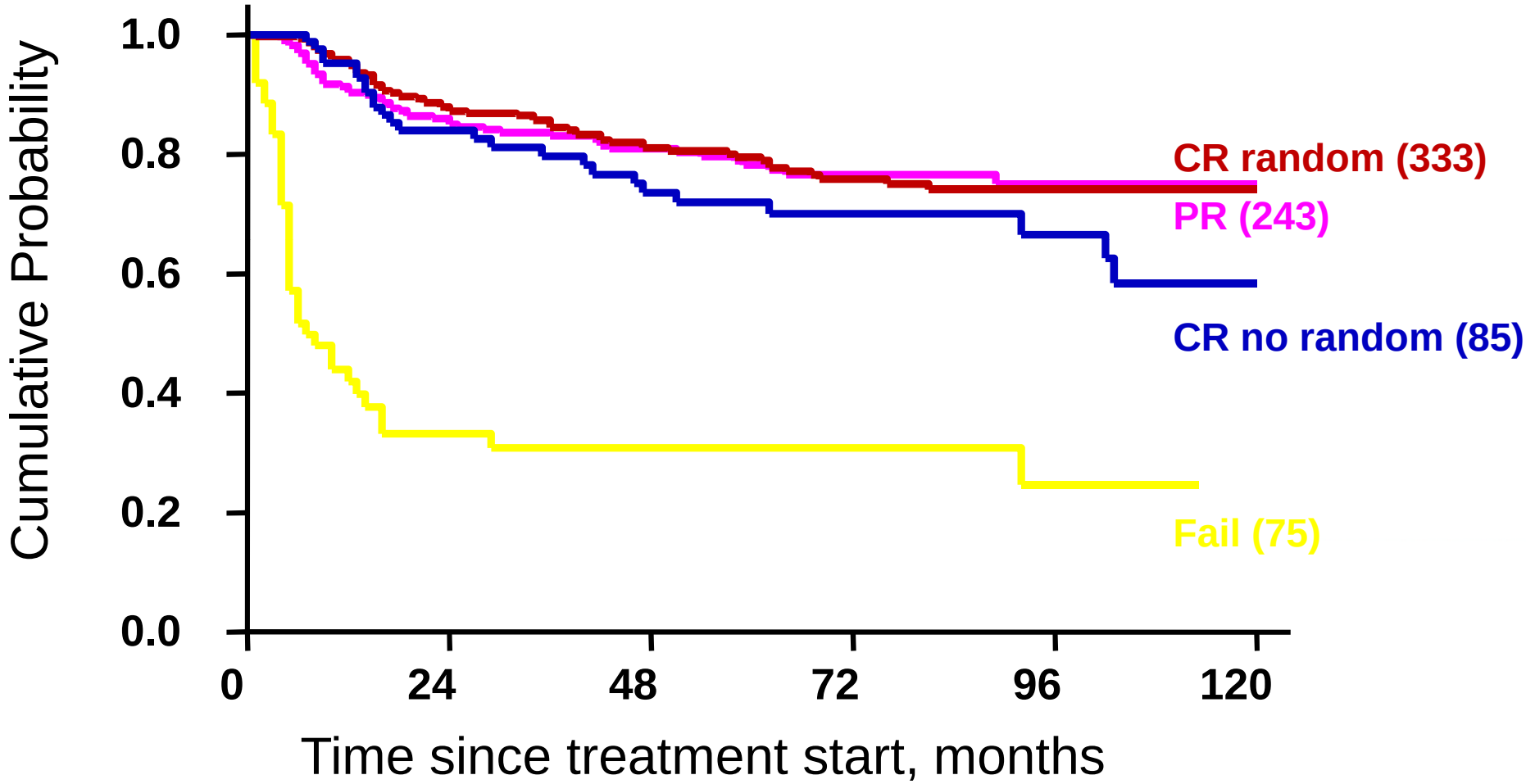
EORTC H3 - 4 trial 1989 - 2000



Advanced stage Hodgkin L

H34 trial: all pts (n=736)

Event free survival



Advanced stage Hodgkin L

H34 trial

Conclusions

After CR:

➔ IF-RT (24 Gy) does not improve outcome after 6-8 cycles MOPP/ABV

After PR:

➔ IF-RT (36 Gy) results in the same excellent RFS, EFS and OS as in CR patients

HD10: Investigating reduction of CMT intensity in early favorable HL. Interim analysis of a randomized GHSG trial.

JCO, 2005 ASCO Annual Meeting 2005: abstract 6506

® 4 cycles vs. 2 cycles of ABVD

® 30 Gy IF vs. 20 Gy IF

Endpoint = freedom from treatment failure (FFTF).

After 2 years FFTF = 96.6% with no statistical differences.

Conclusions: *Further analysis will show if these promising interim results will allow to reduce further therapy intensity.*

HD11: Intensification of chemotherapy and reduction of radiation dose in early unfavorable HL. Interim analysis of a randomized GHSG trial.

Blood ASH Annual Meeting 2005: abstract 816

® 4 of ABVD vs BEACOPP

® 30 Gy IF vs. 20 Gy IF

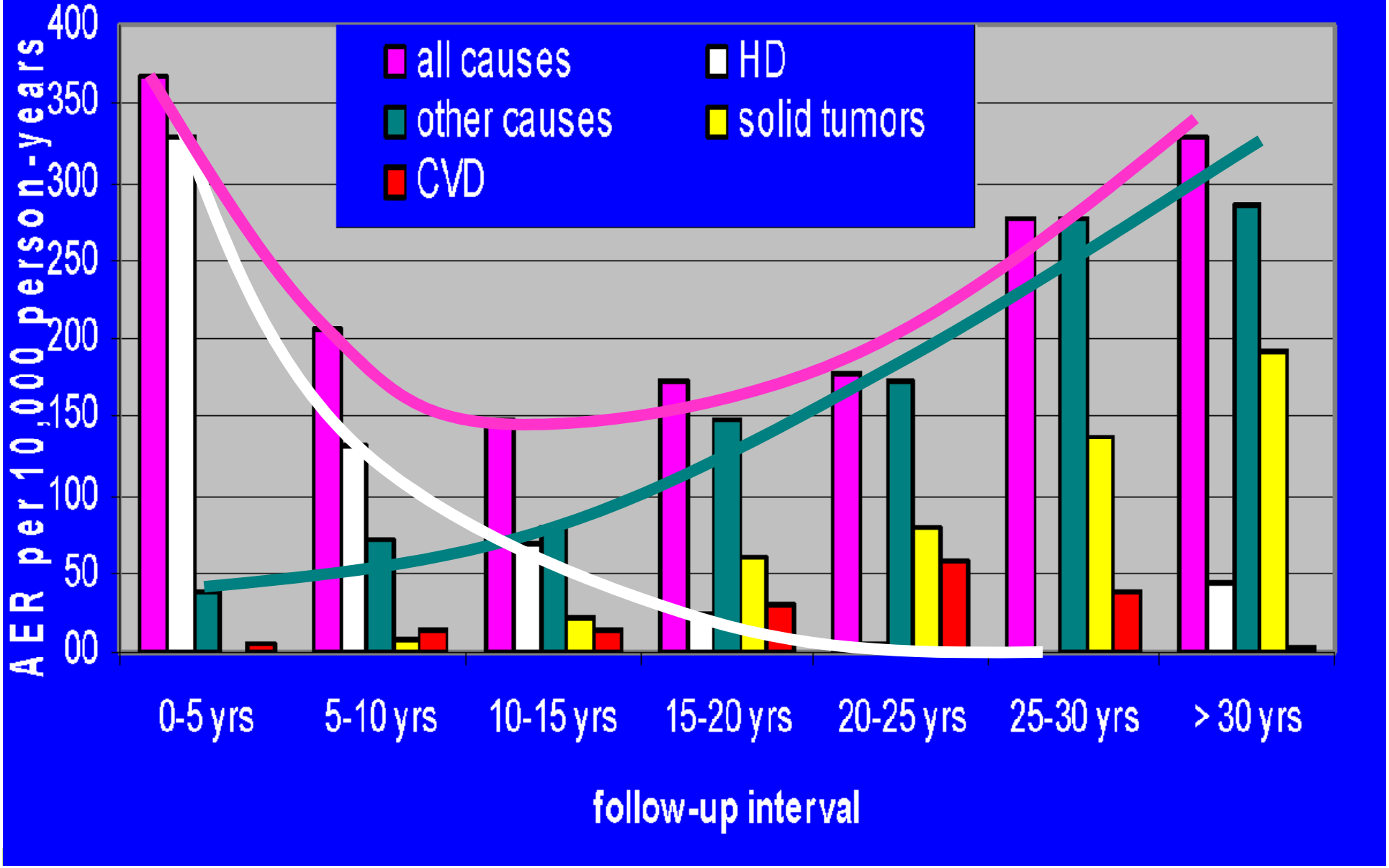
Endpoint = freedom from treatment failure (FFTF).

After 3 years FFTF = 87% with no statistical differences.

Conclusions: *Further analysis needed but more relapses in 20 Gy RT arms.*

Absolute excess mortality for various causes of death over time

Aleman et al., JCO 2003; 21(18):3431



Radiotherapy & the target

Strong advices

- *Avoid other risk factors!!!*
  - Smoking
  - Obesity
  - Hypertension
  - …
- *Do not overtreat your patients*
  - *Dose*
  - *Volume*

Quality assurance

GHSG = > 500 participating centers; > 11,000 patients

Central RT reference center from 1978 on for QA programs

1. Central prospective RT review;
2. Retrospective analysis of the RT;
3. Multidisciplinary HD12 panel;
4. Initiation and integration of a teleradiotherapy network.

Results:

- Major deviations of RT portals and dose = unfavorable prognostic factors.
- Corrections of fields in 49% for early stages and 67% for intermediate stages.
- Significant impact on correctness of stage definition, allocation to treatment groups and on the extension of the IF treatment volume.

Müller RP et al (GHSG), S&O 2005;181:557-666

Quality assurance

Current procedures:

- Central prospective review of all diagnostic imaging by expert radiation oncologists ➔ control disease extension & define the IF treatment volume.
- Participants are trained on the definition of IF-RT during workshops (GHSG & DEGRO meetings).
- Advanced stages: multidisciplinary panel evaluates treatment response to chemotherapy ➔ patients with poor response receive additional RT based on panel's recommendation.
- Teleradiotherapy improves dialogue between central RT reference center and study participants.

Müller RP et al (GHSG), S&O 2005;181:557-666

Quality assurance

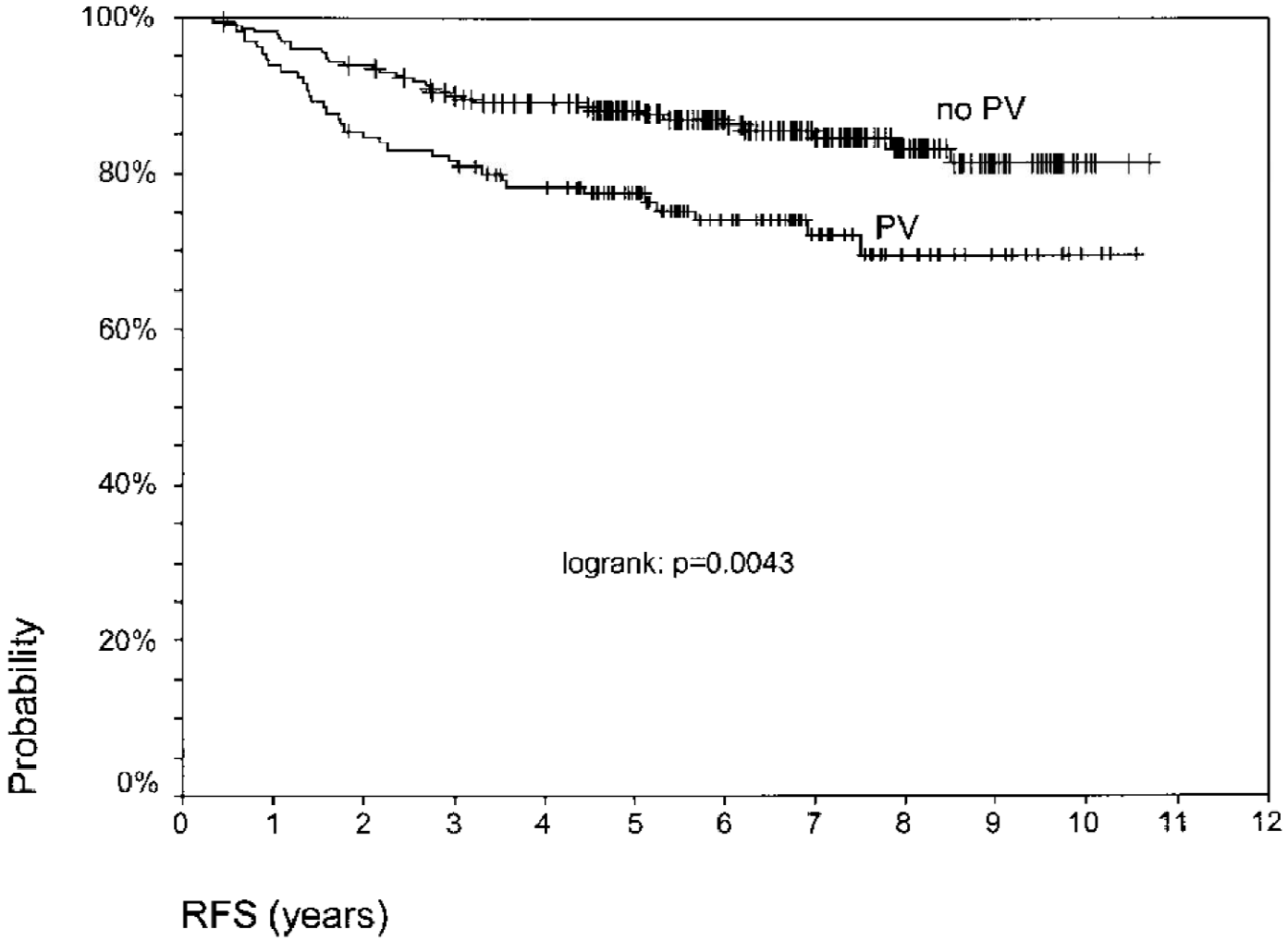
- Favourable early stage
- EF alone
- ® 40 vs 30 Gy to non-involved regions ➔ no difference

Table 6. PVs as Prospectively Assessed by the Radiotherapy Review Center

	Arm A, % (n = 190)	Arm B, % (n = 186)
Technical (T)	2	6
Volume too large (V+)	2	1
Volume too small (V−)	29	28
Dose too large (D+)	—	2
Dose too small (D−)	6	5
Dosage too slow (Ds)	5	6
Any protocol violation **(= PV)**	38	37

Dühmke et al (GHSG), JCO 2001;19:2905-2914

Quality assurance



Dühmke et al (GHSG), JCO 2001;19:2905-2914

Radiation dose in Hodgkin Lymphoma

- Introduction
- Current evidence
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Guidelines

Combinations

- Subclinical disease

  ➔ chemotherapy

- Clinical disease

  ➔ chemotherapy + IN RT

- Extensive disease

  ➔ extensive chemotherapy

  ➔ consolidating RT if residual disease

Guidelines

Radiation dose

- after limited chemotherapy: IN principle
  - CR(u) 30 Gy, probably lower ~ 20 Gy
  - PR 30 ± 6 Gy
- after extensive chemoth.: IN & iceberg principle
  - CR(u) 0 Gy
  - PR 30 ± 6 Gy

Guidelines

Quality assurance

- Target volume delineation
  - IN principle
  - Image co registration: planning CT before chemotherapy
- Treatment delivery
  - Appropriate margins ~ immobilisation

Conclusions

Further optimization of combination chemotherapy + RT:

“Less of both might be better than much of one of them!”

Conclusions

Further optimization of RT:

- ✓ lower doses
- ✓ smaller fields
- ✓ further individualisation

Role of the radiation oncologist!!!

Many thanks to:

- The radiotherapy subcommittee of the EORTC Lymphoma Group:

  Berthe Aleman, Ed Noordijk, Paul Meijnders, Rick Haas, Théo Girinsky, Yolande Lievens, Richard van der Maazen, Lena Specht, et al.
- John Raemaekers
- Floor van Leeuwen
- and many others