What is the optimal radiotherapy combined with chemotherapy for stage III non-small cell lung cancer (NSCLC)?

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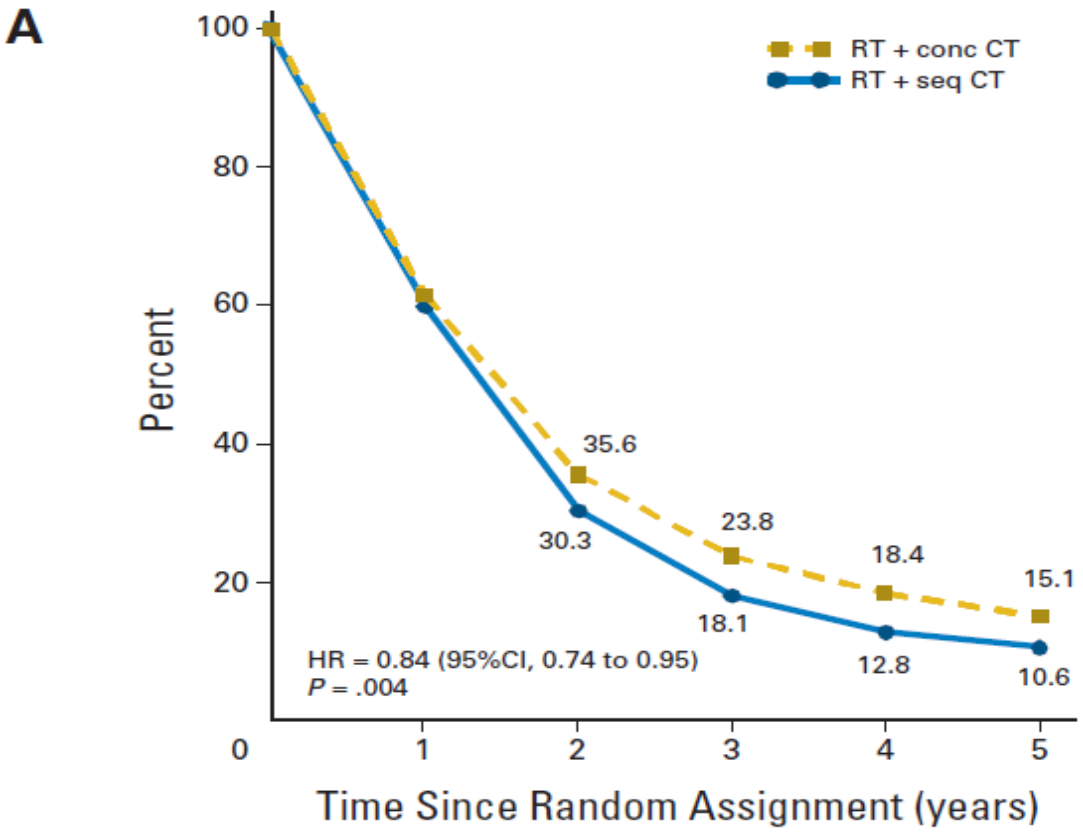
Definition of “optimal”

A condition, degree, amount or compromise that produces ***the best possible*** result

Phase III trials

- Concurrent chemo-radiotherapy is superior to sequential chemo-radiation
- No benefit for surgery after concurrent chemo-radiation over definitive concurrent chemo-radiation

Better survival with concurrent chemo-radiotherapy vs. sequential

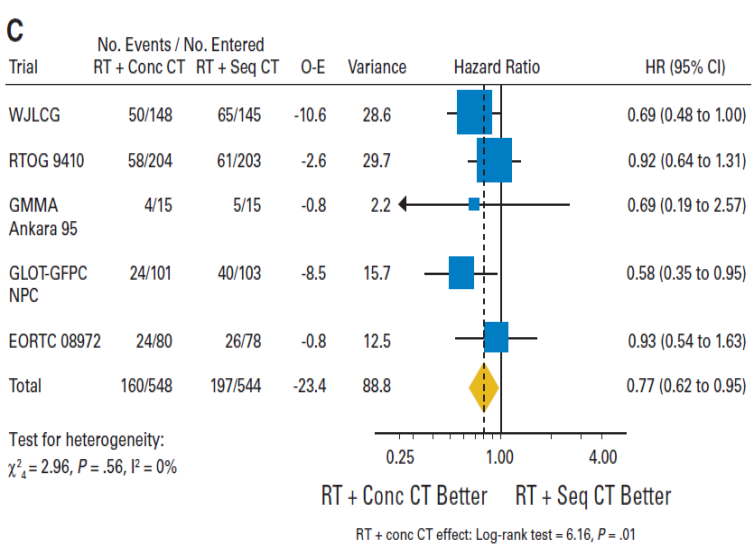


	Deaths/Person-Years by Period				
	0y–1y	1y–2y	2y–3y	3y–4y	> 4y
RT+ conc CT (n = 603)	240/498	147/276	67/171	30/116	37/186
RT+ seq CT (n = 602)	253/491	171/242	70/129	30/ 83	23/126

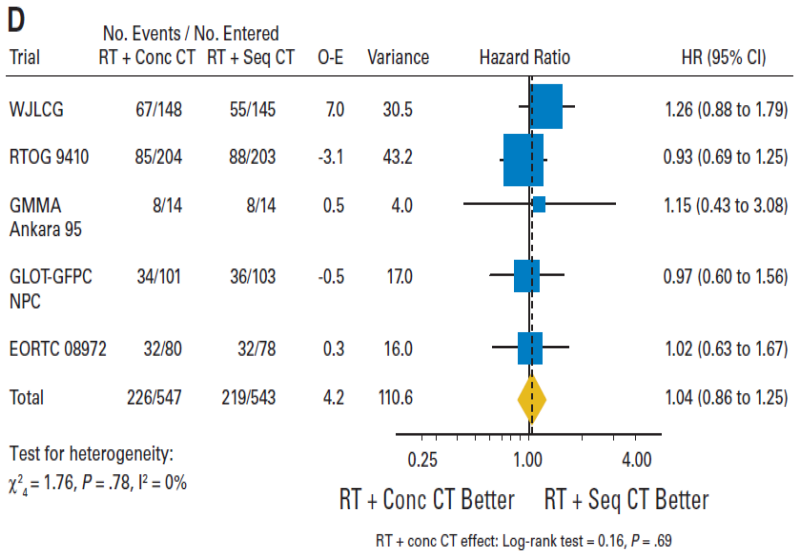
Aupérin et al. J Clin Oncol 2010

The overall survival benefit is associated with improved local control

Local tumour control better
still 30-40 % local progression



Same incidence of distant
metastases



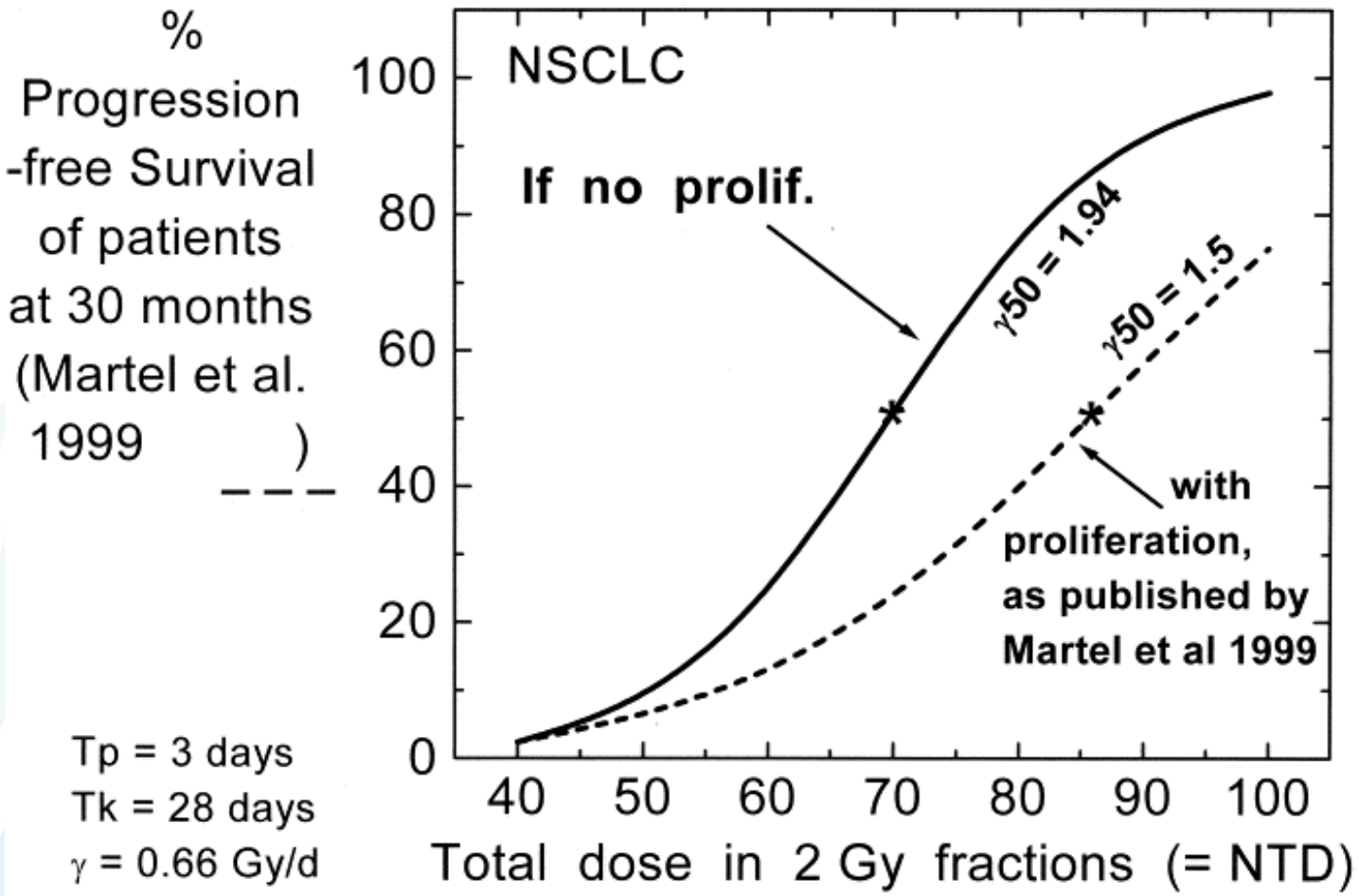
Aupérin et al. J Clin Oncol 2010

Most series used

- 60-66 Gy in 2 Gy/day fractions, 5 times per week
- Concurrently with
  - cisplatin-etoposide
  - cisplatin-vinorelbine
  - carboplatin-paclitaxel

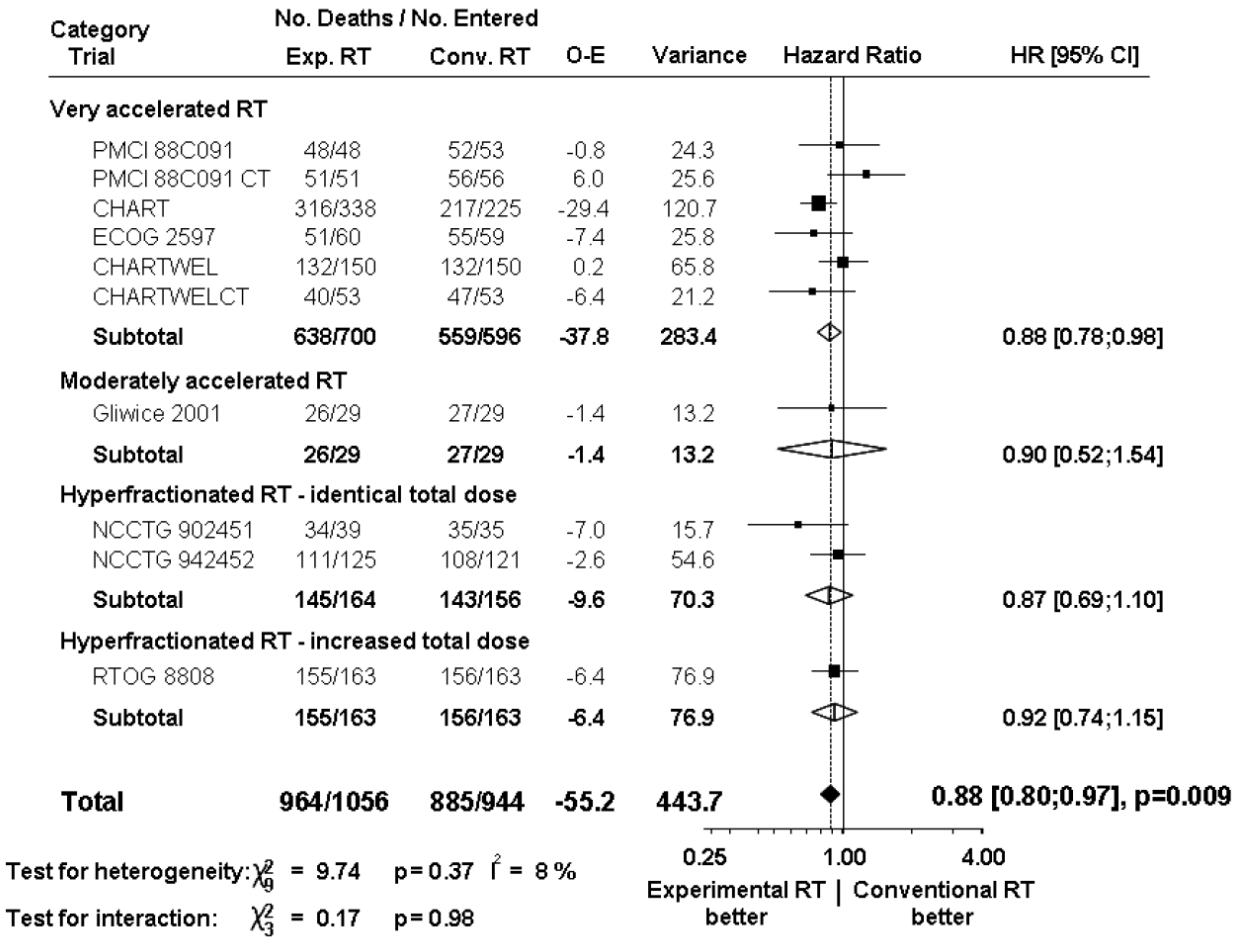
➔ Much improvement is needed for systemic *and* local control

“Radioresistance does not exist”



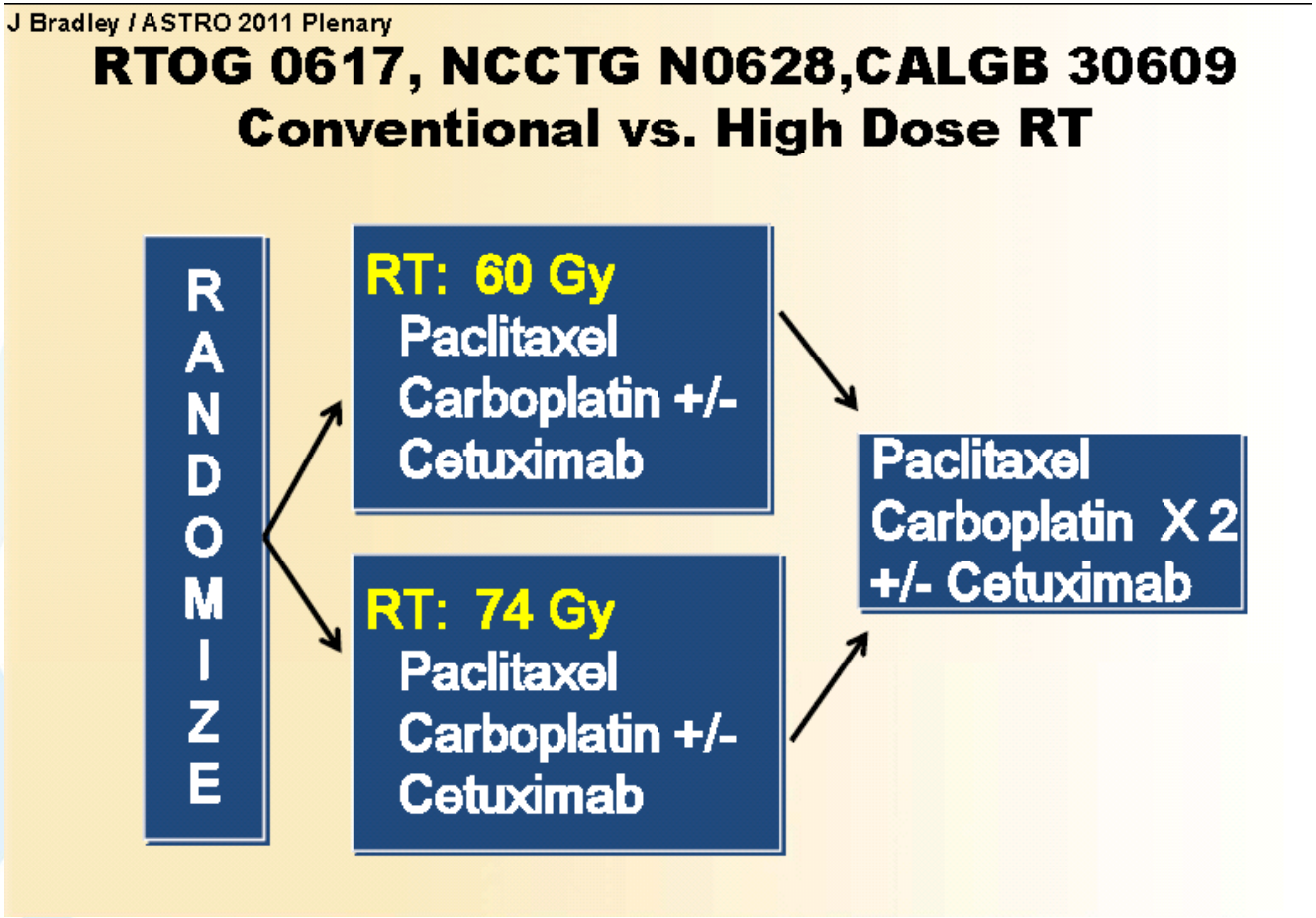
Fowler et al. Int J Radiat Oncol Biol Phys 2004

Influence of overall treatment time of radiotherapy on survival in stage I-III NSCLC *without* concurrent chemo-radiotherapy

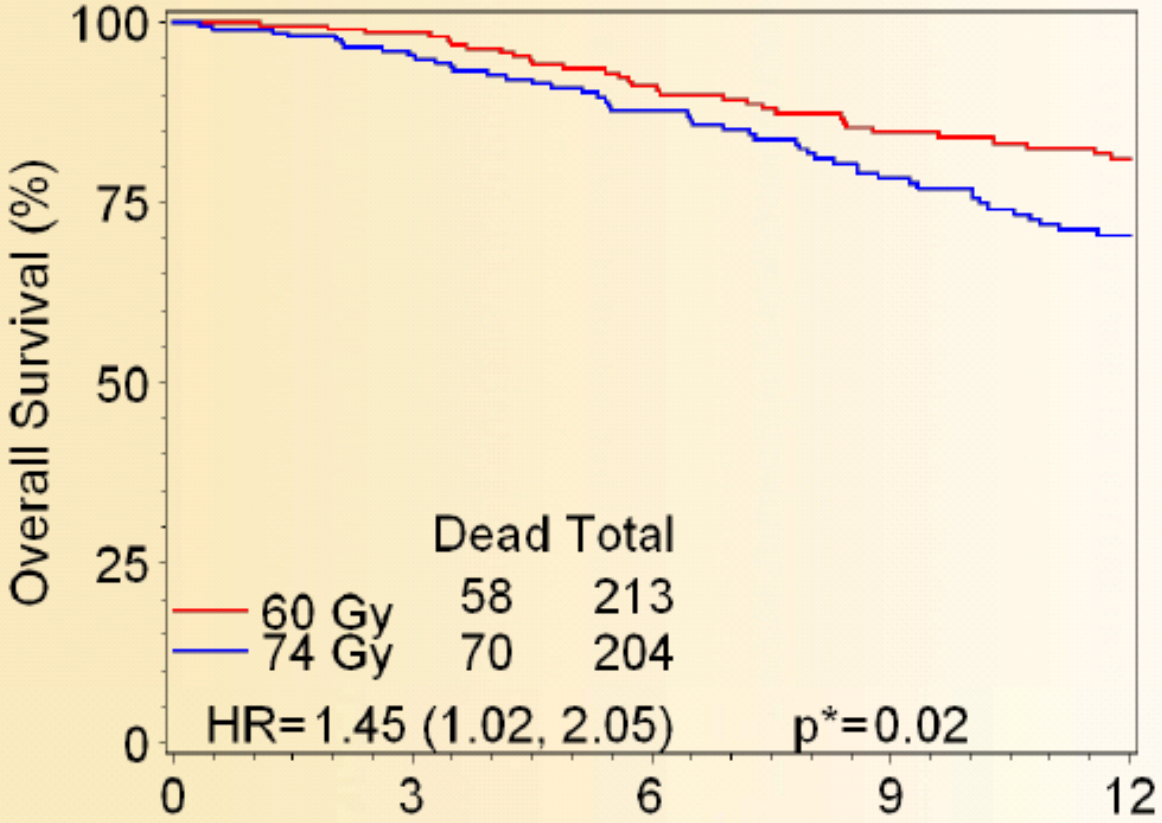


Mauguen et al. J Clin Oncol 2012

Radiation dose escalation with concurrent chemotherapy *and* prolongation of the overall treatment time



Overall Survival



Patients at Risk					
60 Gy	213	190	149	124	104
74 Gy	204	175	137	116	93

*One-sided p-value, left tail

Overall Survival – RT Comparison

	Standard Dose: 60 Gy		High Dose: 74 Gy	
Months	% Alive	# at Risk	% Alive	# at Risk
0	100.%	213	100.0	204
3	98.5%	190	95.4%	175
6	91.2%	149	87.7%	137
9	84.7%	124	78.4%	116
12	**81.0%**	**104**	**70.4%**	**93**
Dead/Total	58/213		70/204	
Median Sv	**21.7 mos**		**20.7 mos**	

p = 0.02 (one-sided p-value, left tail)

(RTOG 9410 CON-QD one-year survival = 62.1%, MST = 17.0 months)

Why did RTOG0617 “fail”?

- Unknown
  - Preliminary results
  - No subgroup analysis yet of cetuximab subgroup
  - Interaction between 74 Gy and cetuximab?
  - Added toxicity of adjuvant chemotherapy and 74 Gy radiotherapy?
  - Technical factors (e.g. inhomogeneity 120 %, no delineation of mediastinal OARs …)
  - …

Many ongoing dose-intensification trials

- *Biological* dose escalation → dose intensification
  - Standard total doses, shorter overall time
- Individualisation
  - *Physical*
  - *Biological, including molecular imaging*

Examples

- IDEAL-RT
- I-START
- Isotoxic IMRT
- CHART-ED
- BIG Lung Trial (consisting of the CARSoN and ASCaN trials) in the UK.
- European PET-boost trial: Radiation dose redistribution within the tumour using an INDAR schedule: max Gy/ 24 fractions/ 5 weeks
- PET-plan trial in Germany randomises dose escalation based on the omission of elective nodal irradiation on FDG-PET scan. No acceleration component.
- ESPATÜ: 65 Gy/ 5.5 weeks
- RTOG 1106/ ACRIN 6697 is a randomised study looking at individualised dose escalation based on FDG-PET response with in the experimental arm a dose up to 85.5 Gy given in 30 daily fractions in 6 weeks.

But,… RTOG0617 shows

- That the OS with “current 60 Gy” is better than in the past (patient selection, staging, imaging integration in radiotherapy planning, planning and delivery …)
- … which leads to “reasonable” median survival rates of 21 months

➔ Dummy run shows that many centres could improve their results by emphasising the quality of the *whole* treatment chain!

Conclusions

- Radiotherapy to a dose of 60-66 Gy in 2 Gy per day, 5 days per weeks remains the standard when delivered concurrently with chemotherapy *(arguments in favour of high-dose, accelerated radiotherapy in non-concurrent schedules)*
- Individualised (accelerated, isotoxic) radiotherapy schedules are being investigated in many clinical trials and are still of much importance
- Improvement the quality of the *whole* diagnostic and treatment chain most probably improves overall survival