CONVENTIONAL AND ALTERED FRACTIONATION IN NSCLC

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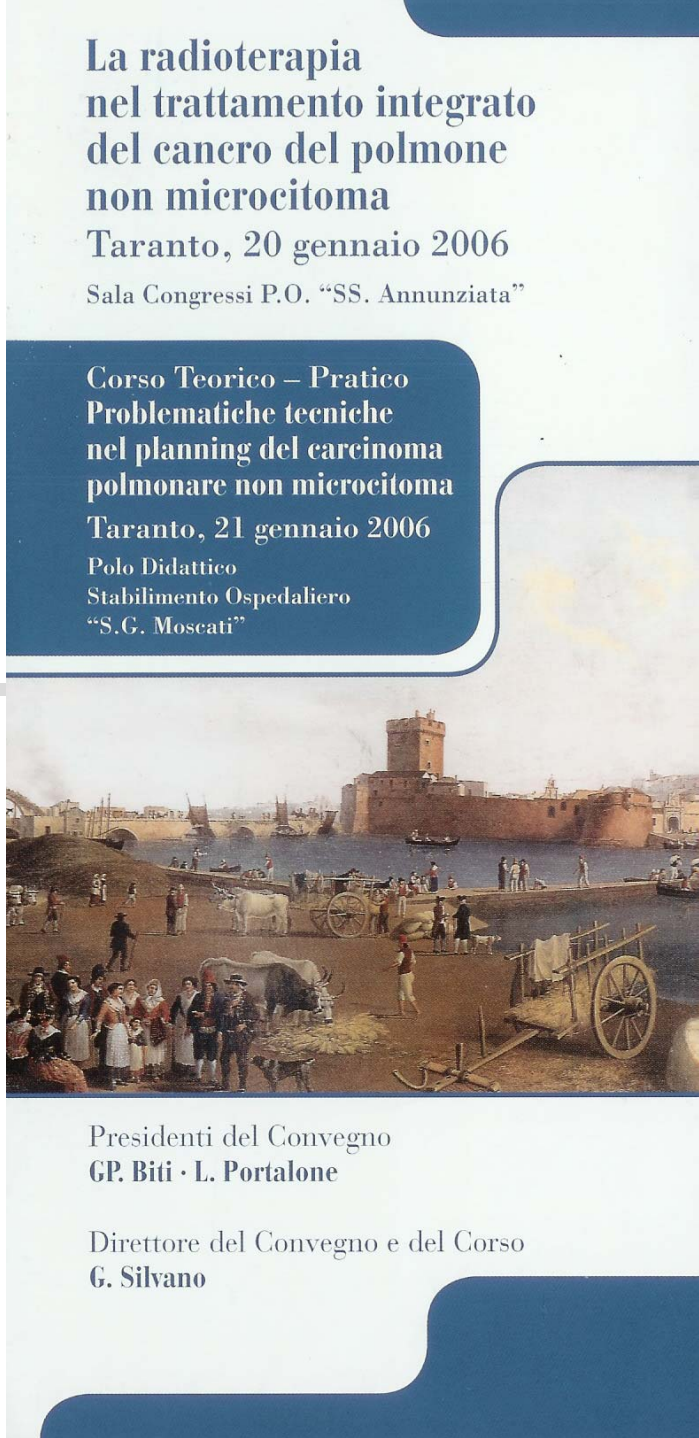


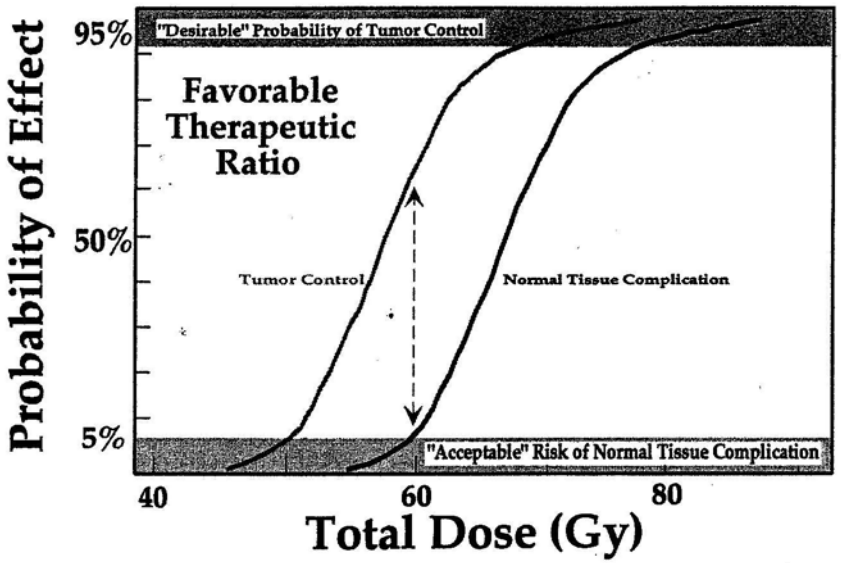
The gold standard

Michael Baumann

RTOG 73-10

400 pts

1. 40 Gy
2. 50 Gy
3. → 60 Gy
4. Split-course 40 Gy



Svv 5y: Stage I-II 20% Stage III: 5%

Recent data LC 10-20% and local failure the main cause of death!!

INTENSIFICATION OF LOCAL TREATMENT!!

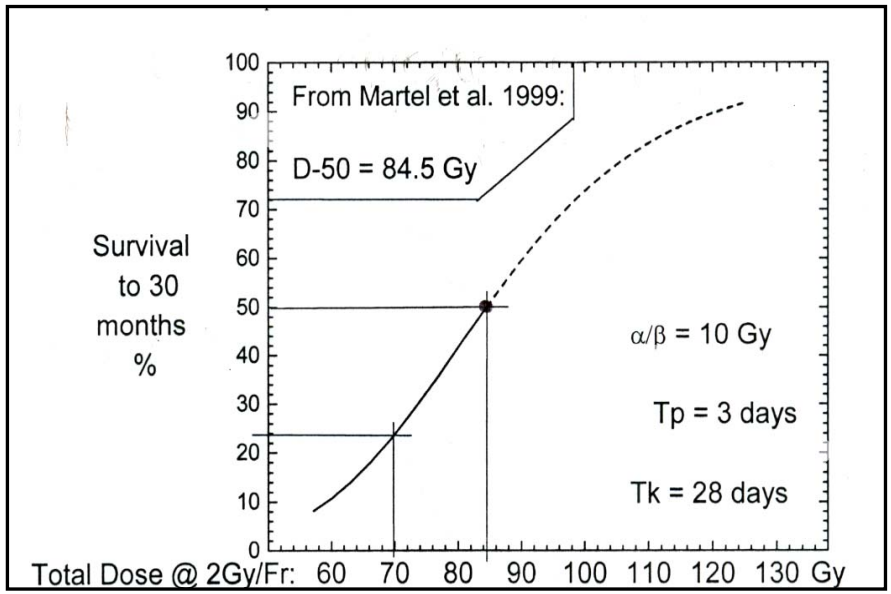
Perez '80 ,Dosorets '96, Morita '97, Dillmann'96, Le Chavalier '91, Saunders '97

INTENSIFICATION OF LOCAL TREATMENT

RADIOTHERAPIC PARAMETERS

- Total dose
- Time
- Fractionation

Total dose for NSCLC



Mehta, Int J Rad Onc Biol Phis '01:

1. NSCLC appears to be relatively radioresistant, so that conventional doses of 60-70 Gy have little change of locally controlling more than 15-25% of tumors …….
2. A much higher biologically effective dose (BED) must be given to NSCLC to have a reasonable change of TCP > 50%..... *60-70%:* ***90-100 Gy***

4R: Repair, Reassortment, Repopulation, Reoxygenation

INTENSIFICATION OF LOCAL TREATMENT

RADIOTHERAPIC PARAMETERS

- Total dose
- Fractionation
- Time

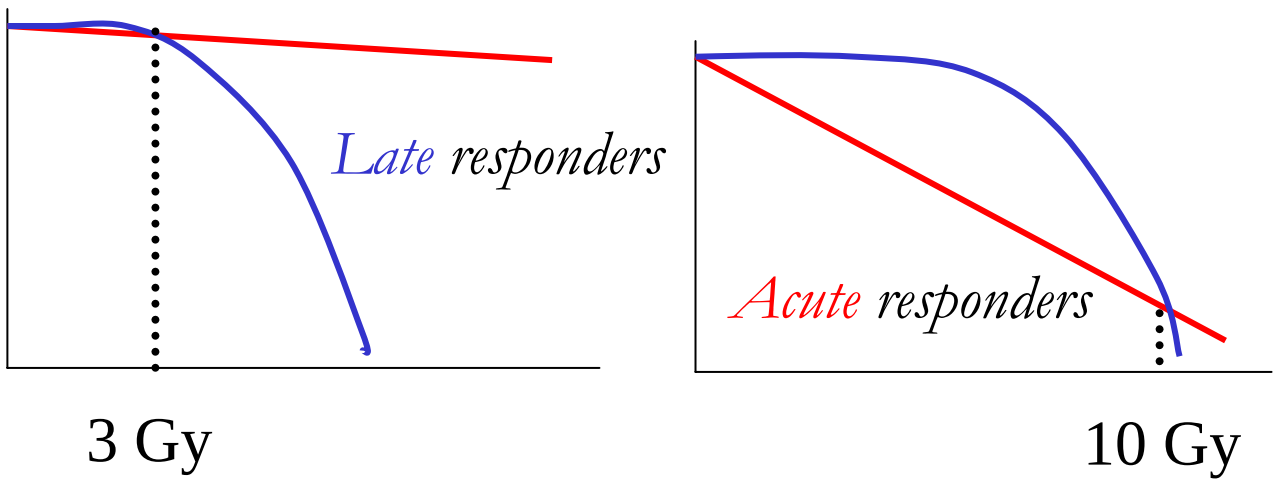
Linear-Quadratic Model

Alfa/Beta Ratio:

α linear component

β quadratic component

α/β



Altered Fractionations

Accelerated fractionation

Decrease overall treatment time

Hypofractionation

Increase size of dose per fraction (>2Gy/die)

Hyperfractionation

Decrease size of dose per fraction (<2Gy/die)

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ACCELERATED FRACTIONATION: RANDOMIZED TRIALS

CHART	N° pts	Stage	Schedule	Total dose (Gy)	Dose per fraction (Gy)
Saunders et al, 1999	225	I-IIIB	CF	60.0	2.0 in 30 fx
	338	I-IIIB	CHART	54	1,5 (t.i.d.) in 12 fx

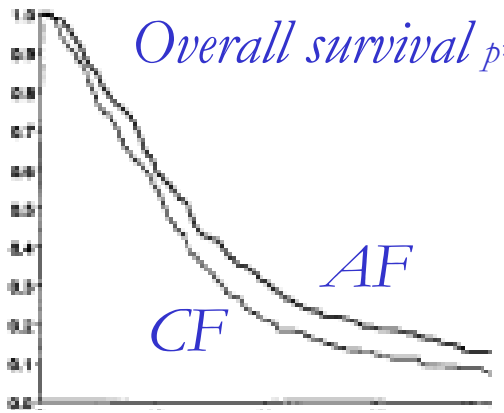
ACCELERATED FRACTIONATION:
RANDOMIZED TRIALS

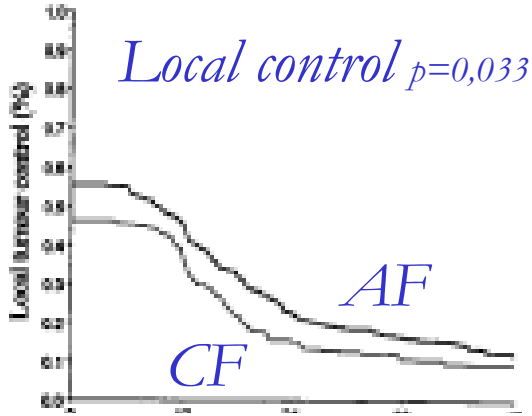
CHART

Saunders et al, 1999

Survival rate (%)

1 year	*2 year*	*3 year*	
55	21	13	*p=0.004*
63	30	20	





- ↓ 30% RR of death
- ↓ 27% LP (p=0.012)
- ↓ 24% RRM+

Tox polm: = CF (9,2 vs 11%)

Tox esophagus > CHART
(G3-4: ***19% vs 3%)***

ACCELERATED FRACTIONATION: RANDOMIZED TRIALS

	N° pts	Stage	Schedule	Total dose (Gy)	Dose per fraction (Gy)	Survival rate (%) 1 year	2 year	3 year	5 year
Ball et al, 1999	42	III	CF	60.0	2.0	60	26		10
	36	III	AF	60.0	2.0 (b.i.d.)	61	28		13
Nestle et al 2000	41	III	CF + ChT	60.0	2.0	63	29		8
	41	III	AF + ChT	60.0	2.0 (b.i.d.)	59	20		5
	79	III-IV	CF	60.0	2.0	36	9		
	73	III-IV	AF	32.0	2.0 (b.i.d.)	38	9		
CHARTWEL Benzen et al, 2002	113	I-III	AF	60.0	1.5 (t.i.d.)		46		
HART, Belani JCO 2005	56	III	CF	64	2.0		24	14	
	56	III	AF	57.6	1.5 (t.i.d.)		44	34	

No significative differences in tox and svv!!!

Accelerated Fractionation

Radiobiological Rationale:

- > Local Control (in tumors with higher Tpot)
- > Acute Toxicity
- = Late Toxicity

Clinical Data confirm Radiobiological Rationale ??

Altered Fractionations

Accelerated fractionation

Decrease overall treatment time

Hypofractionation

Increasing size of dose per fraction

Hyperfractionation

Increase total dose

HYPOFRACTIONATION:
PALLIATIVE RADIOTHERAPY

"17 Gy in 2Fx is comparable to standard fractionation for sympton control and survival: Phase III Trial"

421 pts locally advanced

- Arm1: 17Gy, 8,5 Gy/fx
- Arm 2: 42 Gy, 2,8Gy/die
- Arm 3: 50Gy, 2 Gy/die

No significative differences in svv and symptom control

(EORTC-QLQ-C30, LC13)

Sundstrom S, JCO 2004

HYPOFRACTIONATION:

TRIALS

	N° pts	Stage	Schedule	Total dose (Gy)	Dose per fraction (Gy)
Gauden S, Chest 1995	347	I (T1-2N0)	HypoF	50	2.5
Noordijk Radiat Oncol 1988	50	I (T1-2N0)	HypoF	60	3 split
Slotman BJ, Radiother Oncol 1996	47	I (T1-2N0)	HypoF	32	6fx t.w.
Cheung et al 2002	33	I (T1-2N0)	HypoF	48	4

Acute Tox: 30% dermatitis

Late Tox: 25% subcutaneus fibrosis

Selected patients

HYPOFRACTIONATION:

STEREOTACTIC RADIOTHERAPY

"Preliminary data from Hypofractionated Stereotactic Radiotherapy suggest that very large fraction sizes (5-26 Gy) taken to moderate to high total doses (15-60Gy) result in *minimal pulmonary toxicity.* Local control appear to be superior to CF.

Irradiating Stage I NSCLC ***"Hard and Fast"***

Cheung

Uematsu, IJRBOP 2001; Nagata IJRBOP 2002, Hara IJRBOP 2002, Lee Lung cancer 2003, Onishi Lung cancer 2004

Hypofractionation

- ✓Feasible in palliative treatment
- ✓Useful in periferical and small tumors
- ✓Clinical results in StereoRT

RADIOBIOLOGICAL CHARACTERISTICS AND THERAPEUTIC CHALLENGES

Accelerated fractionation

Decrease overall treatment time

Hypofractionation

Increasing size of dose per fraction

Hyperfractionation

Increase total dose

HYPERFRACTIONATION:
RANDOMIZED TRIALS

	N° pts	Stage	Schedule	Total dose (Gy)	Dose per fraction (Gy)	Survival rate (%) 1 year	2 year	3 year	4 year
RTOG/ ECOG ***Sause 1995*** ***Komaki 1997***	152	II-IIIB	CF	60.0	2.0	46	20		4
	154	II-IIIB	HFX	69.6	1,2 (b.i.d.)	51	24		9
Fu et al, 1994	51	I-IIIB	CF	63.9	1,8-2.0	32	9		
	54	I-IIIB	HFX	69.6	1,15-1,25 (b.i.d.)	53	13		
Kagami et al, 1992	18	III	HypoF	65	2,5		31	0	
	18	III	HFX	71,5	1,375		50	22	

No significative differences in tox and svv!!!

HYPERFRACTIONATION:
RANDOMIZED TRIALS

Sause, CHEST 2000

	N°	Stage	Total dose	Dose/fx	Median svv	Early tox	Late tox
RT-CF	163	II-IIIA-B	60Gy	2.0	11,4	1	3
RT-HF	164	II-IIIA-B	69.6	1.2 bid	12	4	5
CT → RTCF	163	II-IIIA-B	60	2.0	13.2	77	5

This study failed to confirm a benefit of HF-RT

HYPERFRACTIONATION:
RANDOMIZED TRIALS

Baumann 2001:

Based on radiobiological data, dose escalated HF may improve svv however, **no strong evidence** from randomized trial support this approach; additional information from RTOG 94-10

RADIO-CHEMOTHERAPY AND ALTERED FRACTIONATION

***RTOG 94-10**, Curran ASCO 2003:*

1. *ChT → RT CF 63Gy*
2. *ChT + RT CF 63Gy*
3. *ChT + RT HF 69,6Gy*

Grade 3-5	CT → Standard RT	CT + Standard RT	**CT + HF RT**
Acute Pneumonitis	7%	4%	**3%**
Acute Esophagitis	4%	25%	**47%**
Late Pneumonitis	13%	11%	**13%**
Late Esophagitis	1%	2%	**3%**

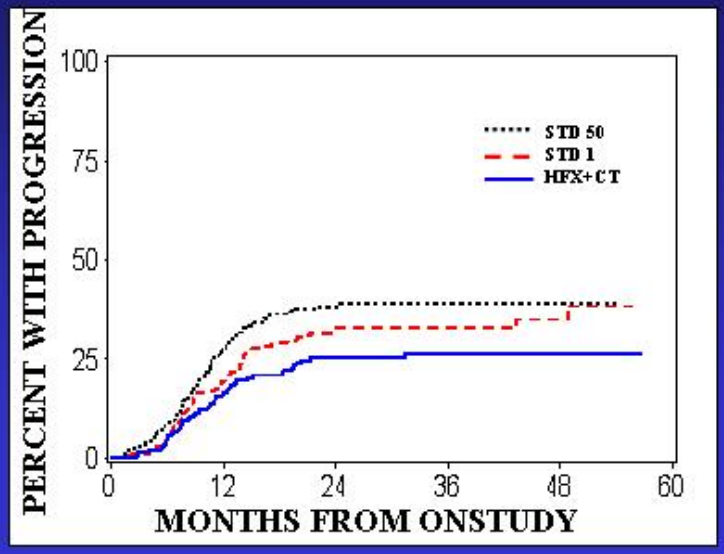
RADIO-CHEMOTHERAPY AND ALTERED FRACTIONATION

Phase III study

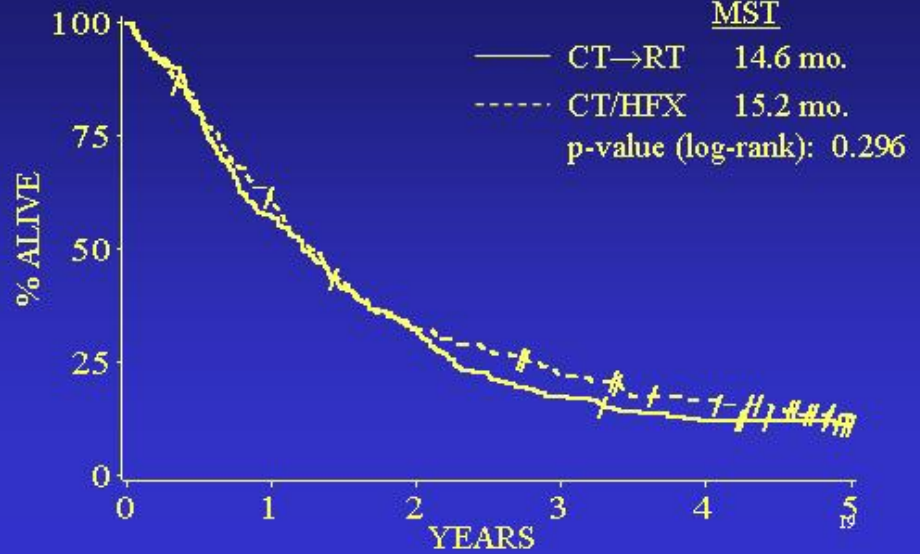
RTOG 94-10, *Curran ASCO 2003:*

1. *ChT → RT CF 63Gy*
2. *ChT + RT CF 63Gy*
3. *ChT + RT HF 69,6Gy*

RTOG 9410: All Patients
Time to Infield Progression



9410 : SURVIVAL
CT/HFX vs CT→RT



Hyperfractionation

Radiobiological Rationale:

- < Late Toxicity
- ↑ Dose : > Local Control
- > Acute Toxicity

Clinical Data do not confirm any survival benefit

DOSE FRACTIONATION IN NSCLC

Conventional or Hyperfractionated Radiotherapy concurrent with chemotherapy in the neoadjuvant treatment of NSCLC:

a phase II randomized trial

Trodella 2005

AIM OF THE STUDY

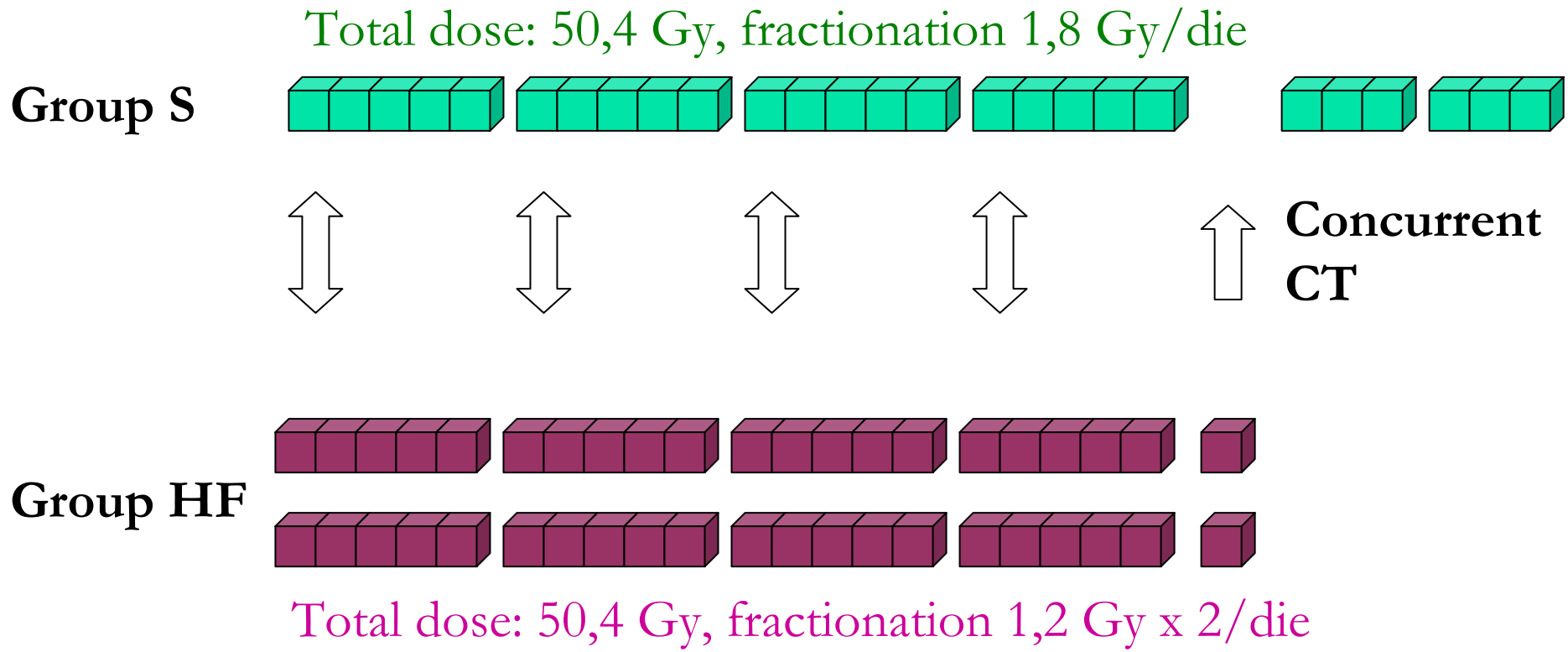
To assess the role of fractionation on

toxicity and pathological downstaging (primary objectives)

clinical response and resectability (secondary objectives)

in patients affected by locally advanced NSCLC and treated with neoadjuvant concurrent radiochemotherapy

STUDY DESIGN



STATISTICS

- Randomization: by 1:1 methods
- Stratification by stage (IIIAN2 vs. IIIBT4)
- Expected difference: 20% in pathological downstaging
- Planned accrual: 50 patients for each group are required.
- A preliminary analysis have been planned when 60% of accrued patients have been reached.

CHARACTERISTICS OF PATIENTS

	Standard	Hyperfrx
N° of patients	34	34
Age: mean (range)	67 (50-82)	64 (47-78)
Stage		
IIIAN2	27 (79.4%)	27 (79.4%)
IIIBT4	7 (20.6%)	7 (20.6%)
Histology		
Squamous	19 (55.8%)	17 (50.0%)
Adenoca	12 (35.3%)	13 (38.2%)
Other	3 (8.9%)	4 (11.8%)

NON-HAEMATOLOGICAL TOX

Acute	Standard	Hyperfrx
Esophagitis		
Grade 1-2	10 (29.4%)	13 (38.2%)
Grade 3-4	1 (2.9%)	1 (2.9%)
Pneumonitis		
Grade 1-2	1 (2.9%)	0
Grade 3-4	2 (5.8%)	2 (5.8%)
Late pneumonitis	1 (2.9%)	3 (8.8%)

RESPONSE AND SURGICAL RESECTION

	Standard	Hyperfrx
Partial response	27 (79.5%)	31 (91.3%)
No change disease	5 (14.7%)	2 (5.8%)
Progressive disease	2 (5.8%)	1 (2.9%)

Radically resected	20 (58.8%)	24 (70.5%)

PATHOLOGICAL DOWNSTAGING

	Standard	Hyperfrx
pStage 0	9 (45%)	5 (20.8%)
pStage I	6 (30%)	12 (50%)
pStage II	1 (5%)	3 (12.5%)
pStage III	4 (20%)	4 (16.7%)

Lymphnode clereance	15 (75%)	17 (71%)

CONCLUSION

These results do not confirm any role of fractionation on:

- Acute and late pulmonary and esophageal toxicity
- Pathological downstaging

So this trial has been concluded after the preliminary analysis