La radioterapia ipofrazionata in pazienti con NSCLC in stadio avanzato: esperienza di una singola Istituzione.

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Background

Hypofractionated RT

Higher dose per fraction

Reduced overall treatment time

Improve loco-regional control and survival

- Increased dose to the tumor volume
- Higher BED
- Reduce tumor cell repopulation*

** Van Braardwijk et al. Int J Radiat Oncol Biol Phys 2008*

Hypofractionated RT

Inoperable stage I-II NSCLC

Locally advanced NSCLC

Limits: higher toxicity rates

Modern techniques (3D-CRT, IGRT, IMRT, Tomotherapy, Hadrontherapy)

Systematic review

Dose escalation for non-small cell lung cancer: Analysis and modelling of published literature

Mike Partridge [a,*], Mónica Ramos [b], Angela Sardaro [b], Michael Brada [a]

[a] *The Institute of Cancer Research; and* [b] *The Royal Marsden NHS Foundation Trust, Sutton, UK*

Prescription dose was converted to BED corrected for repopulation.
Disease-free survival data were corrected for the stage profile of each cohort

In the normally fractionated schedules improved DFS was generally observed in the shorter schedules (max around 6 weeks). However, the best DFS were obtained for the hypofractionated schedules

No relationship beetween dose and lung or oesophageal toxicity

HypoRT (≤ 6 weeks) is predicted to be more beneficial than HyperRT or Conventional RT

Dose escalation can be conducted safety

Patridge et al. Radiother Oncol 2011.

Background: HypoRT for advanced NSCLC

Studies regarding HypoRT in advanced stage NSCLC 2008-2010

Study	*Year*	*N. Pts*	*Stage*	*Prior CHT**	*RT schedule*	*Concomitant CHT**	*Outcome*	*Grade 3-4 tox.*
Tsoutsou *et al.*	2008	14	IIIB IV	+ (9)/- (5)	*3D-CRT* 35Gy/10fr (3.5) split 17.5Gy/5fr	Vinorelbine +doxorubicin e Twice/w	2y OS 28% 2y LPFS 19%	No
Matsuura *et al.*	2009	10	IIIA IIIB	(-)	*3D-CRT* 65Gy/26fr (2.5) 70Gy/28fr (2.5)	CBDCA/PXT Once/w	2y OS 58% 2y LRFS 45%	No
Kepka *et al.*	2009	173	IIIA IIIB	+(118)/ - (55)	*3DCRT-SIB* 56.7Gy/21f (2.7) 60.9Gy/21f (2.9)	No	2y OS 32% 2y LPFS 40%	No G4 G3 11%
Pemberton *et.al*	2009	47 vs. 93	III (I-II)	+/-	*3D-CRT* HypoRT (55Gy/20fr) vs. CHART	No	2y OS 45% *vs.* 34% Median PFS 20 *vs.* 11.3 m	No G4 G2-3 25% *vs.* 30%
Bral *et al.*	2010	40	IIIA IIIB	+/-	*H. Tomotherapy* 70.5Gy/30fr (2.35)	No	2y OS 27% 2yLPFS 50% 1y MFS 43%	G3-4 30%

*CHT: Chemotherapy

Background: HypoRT for advanced NSCLC

Studies regarding HypoRT in advanced stage NSCLC 2011-2012

Study	***Year***	***N. pts***	***Stage***	***Prior CHT****	***RT schedule***	***Concomitant CHT****	***Outcome***	***Grade 3-4 tox.***
Zhu *et al.*	2011	34	III	+(31)/-(3)	*3D-CRT* 50Gy/20fr (2.5) 65-68Gy/22-23f	No	2y OS 38% 2y PFS 30% 2y LPFS 61%	No G4 Grade3 9%
Schwarzenbergen *et al.*	2011	36	IIIB IV	+/-	*3D-CRT (12w)* 60Gy/24fr (2.5Gyx2/d/w)	Oral Vinorelbine Once/w	Median OS 9.9 months SD 75% PD 25%	No
Amini *et al.*	2012	119 vs. 90 vs. 91	IIIA IIIB	+ (96)/- (23) vs. + (29)/- (61) + (64)/- (27)	*3D-CRT* 45Gy/15fr (3) vs. 60-63Gy (1.8-2) >63Gy (1.8-2)	No	Response/ OS/PFS (local and distant) NS*	ND*

*NS: Not Significant; CHT: Chemotherapy; ND: No Differences.

Background: HypoRT for advanced NSCLC

Studies regarding HypoRT in advanced stage NSCLC 2013

Study	***Year***	***N. pts***	***Stage***	***Prior CHT***	***RT schedule***	***Concomitant CHT****	***Outcome***	***Grade 3-4 tox.***
Gomez *et al.*	2013	25	T1-4 N0-3	+/-	*phase I dose escalation study* *Proton Therapy* 45Gy 3Gy/fx 52.5Gy 3.5Gy/fx 60Gy 4Gy/fx	No	2y OS 38% 2y PFS 30% 2y LPFS 61%	2 pts grade ≥3
Liu *et al.*	2013	26	IIIB IV	+/-	*3D-CRT* *60-75 Gy 3Gy/fx*	vinorelbin carboplatin	Median OS 13 months CR 27% PR 54% SD 19%	15.4% G3 esophagitis 7.7% G3 Pneumonitis
Omar *et al.*	2013	609 IIIA 100pts IIIB117pts IV 4 pts	All stages	168/609	*3D-CRT* *50-55 Gy* *2.75Gy/fx*	No	2yOS IIIstage 42% median OS IIIstage 20.5 months	No Grade III-IV toxicities
Cannon *et al.*	2013	79 66 pts stage III-IV	All stages	Neo 17 Adj 33 Both 3	phase I dose escalation 57Gy 2.28Gy/fx 63.25Gy 2.53Gy/fx 69.25Gy 2.77Gy/fx 75Gy 3Gy/fx 80.5Gy 3.22/fx 85.5Gy 3.22/fx	No	Median OS 16 months 3yOS 29%	No ≥ G3 esophageal tox 6 pts G4 or G5 lung toxicities

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Clinical Investigation: Thoracic Cancer

Image Guided Hypofractionated 3-Dimensional Radiation Therapy in Patients With Inoperable Advanced Stage Non-Small Cell Lung Cancer

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Current study

End-points

- Survivals and local control
- Toxicity rates

Patients with advanced non-small cell lung cancer receiving hypofractionated 3DCRT (IGRT)

Materials and methods

Characteristics	*No.*	*%*
Age (years)		
Mean	70	
Range	44-87	
Gender		
Male	35	81.4
Female	8	18.6
T-stage		
T1	1	2.3
T2	12	27.9
T3	15	34.9
T4	15	34.9
N-stage		
N1	5	11.6
N2	23	53.5
N3	15	34.9
Stage (ajcc 2002)		
IIIA	14	32.6
IIIB	20	46.5
IV	9	20.9
M1-stage		
Lung	3	7
Liver	3	7
Bone	4	9.3
Histological type		
Adenocarcinoma	19	44.2
Squamous cell	17	39.5
NSCLC, other subtype	7	16.3

43 pts from 2008 to 2012 with advanced stage (III/IV) NSCLC

ECOG performance status ≤ 2

IV stage pts (≤ 2 metastases)

Treatment

Characteristics	*No.*	*%*
PTV (cc)		
Median	**276**	
Range	73-812	
Prior chemotherapy	**32**	**(74)**
Platinum-based chemotherapy	27	(84)
+ Docetaxel/Paclitaxel	13	(48)
+ Gemcitabine	10	(37)
+ Vinorelbine	4	(15)
Vinorelbine monotherapy	5	(16)
No Prior chemotherapy	**11**	**(26)**
Age	8	(19)
Comorbidities	3	(7)

Radiation therapy

60 Gy in 20 fractions of 3Gy/each for 5 times per week

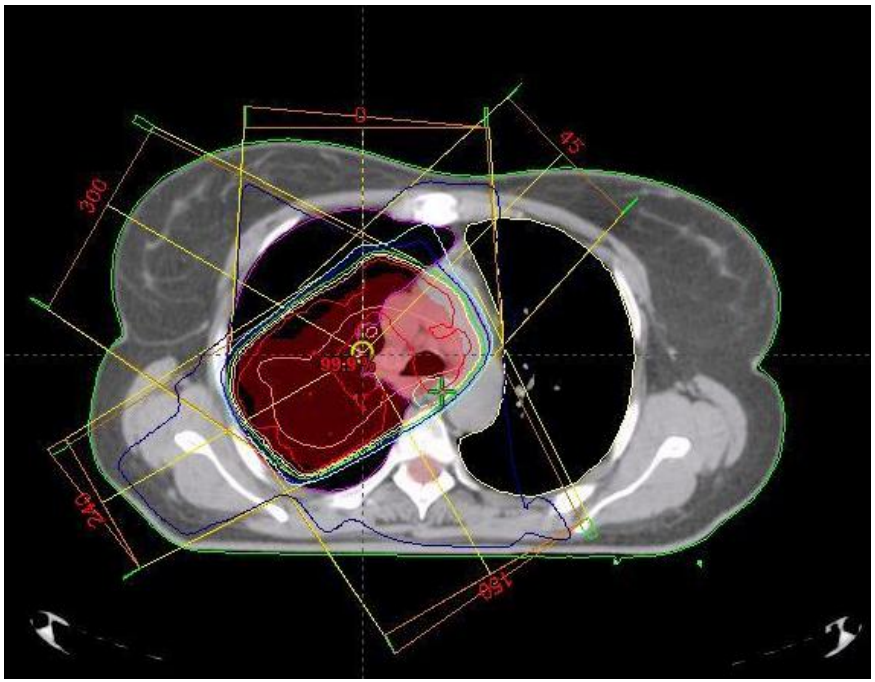
Overall treatment time 26 days

3-D CT planning, IGRT (daily cone-beam CT)

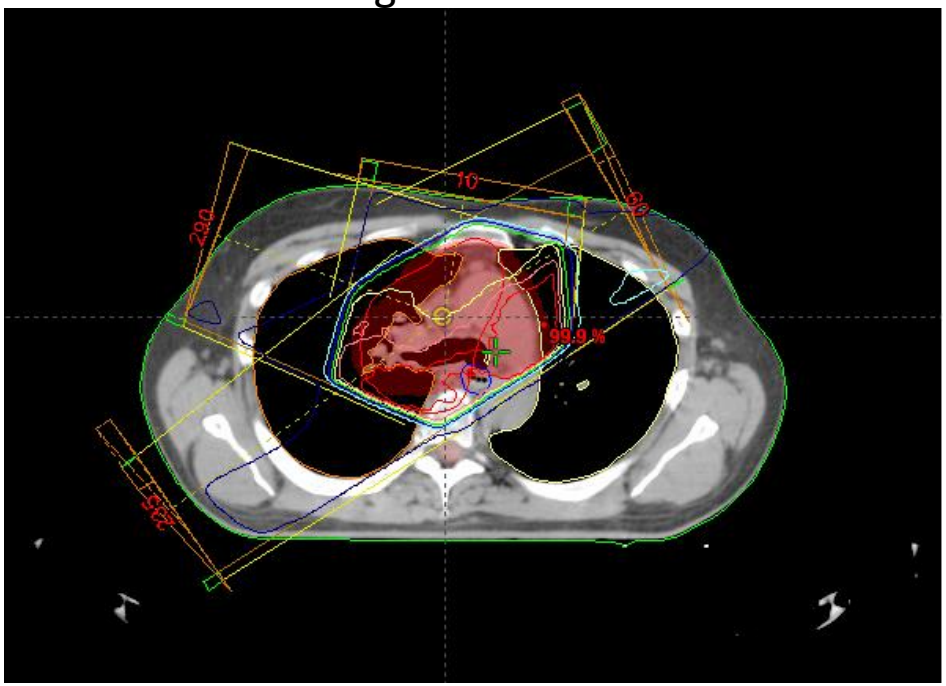
Radiation therapy

Planning

Patient with Stage IIIA NSCLC



Patient with Stage IIIB NSCLC



Radiation therapy

Constraints

- Lung : V16 < 25-30%
- MLD (Mean Lung Dose): ≤ 15 Gy
- Heart: V33 < 25%
- Esophagus: V42 < 32%
- Spinal cord: ≤ 36 Gy

α/β of late responding tissue = 3

α/β of lung cancer = 10
n - number of fractions
d - dose per fraction
T - overall treatment time
T_k - proliferation time starting at 28 days

$$BED = nd\,[1 + d/(\alpha/\beta)] - \ln_2 (T - T_k)$$

$$BED_{\text{(current study)}} = 79\ Gy$$

Results

Response

All patients completed RT treatment

Patterns of response after ≤ 6 months from HypoRT completion:

- CR (Complete Response): **4 pts** (10%)
- PR (Partial Response): **29 pts** (67%)
- NR (Non Response): **10 pts** (23%)

Results

Follow up
Median 13 months
Range: 4-58 months

At the time of analysis

19 pts (44%) alive with median follow up of 12 months (range: 2-41 months)

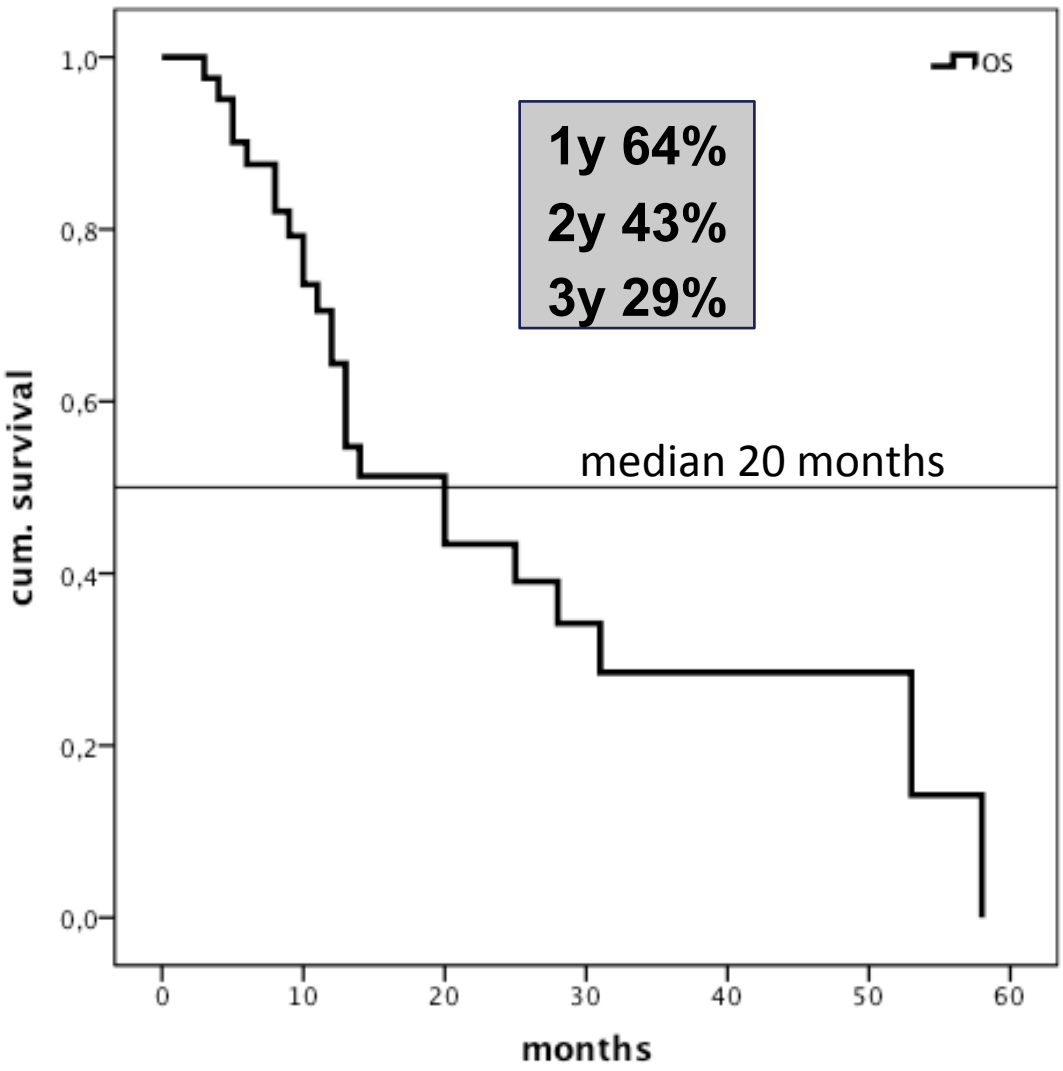
Distant and local SD: **12 pts**

Distant and/or local PD: **7 pts**

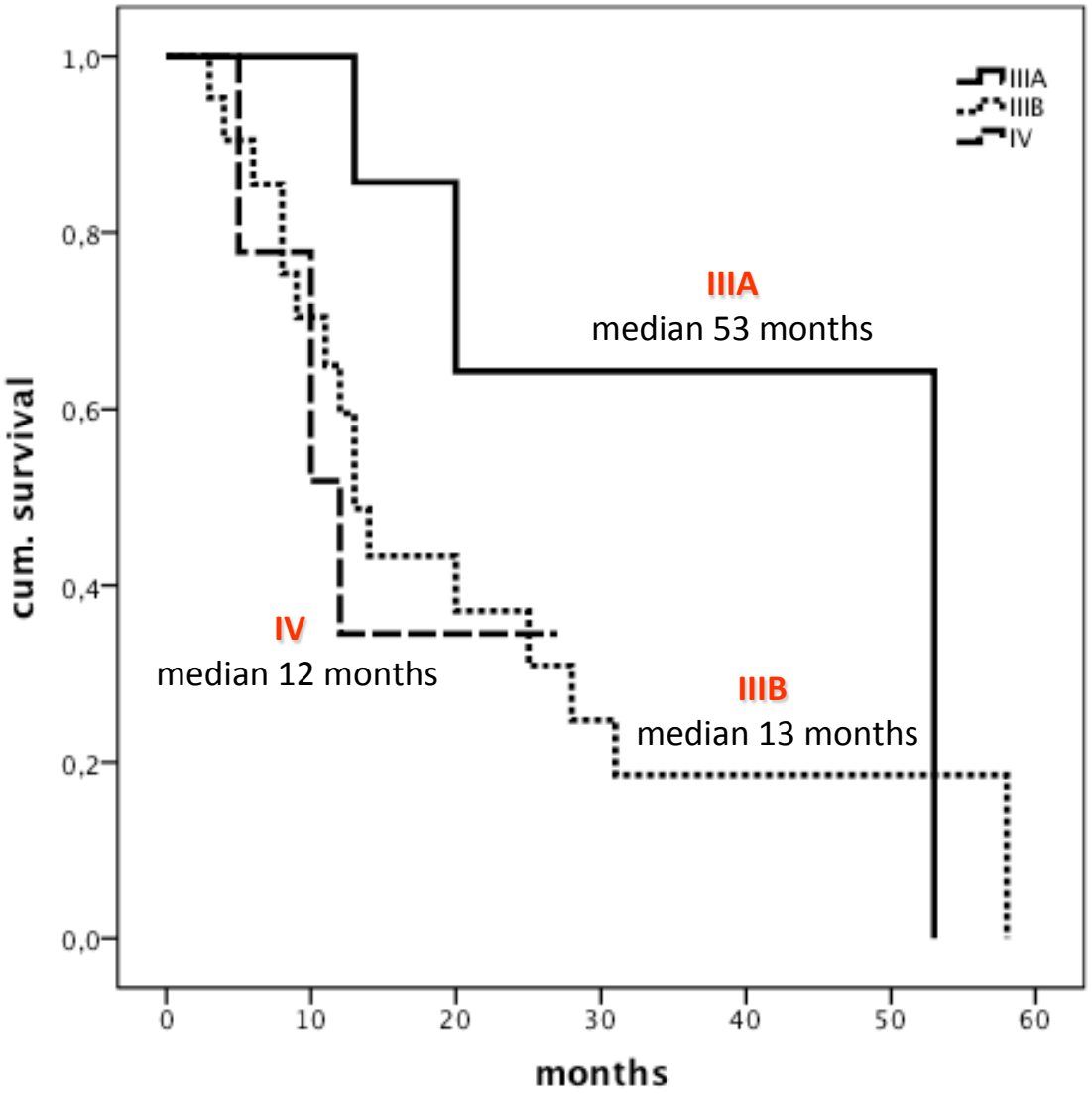
24 deaths (56%) for: PD local and/or distant: 20 pts (47%)

Other causes: 4 pts (9%)

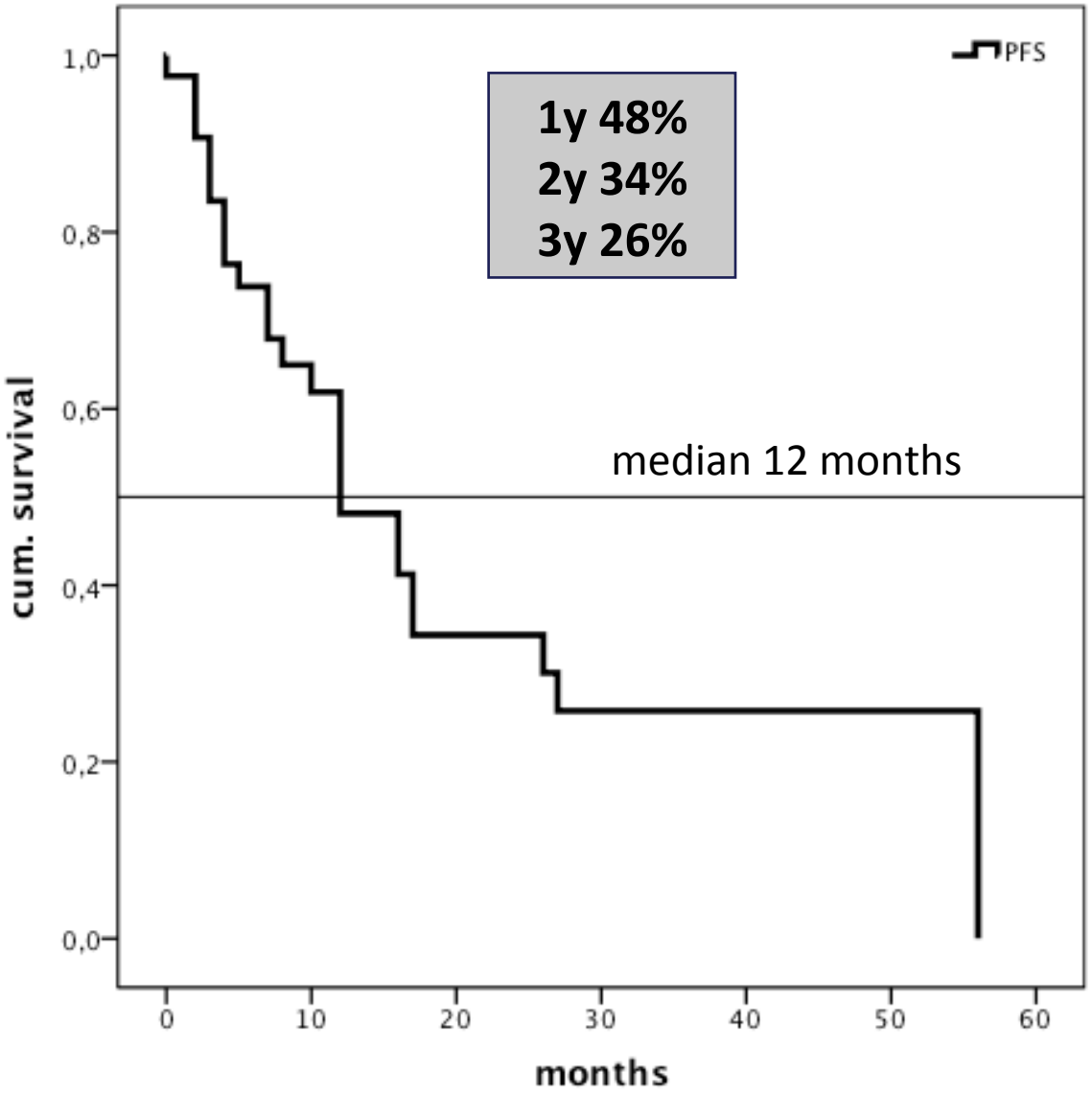
Overall Survival



Overall Survival

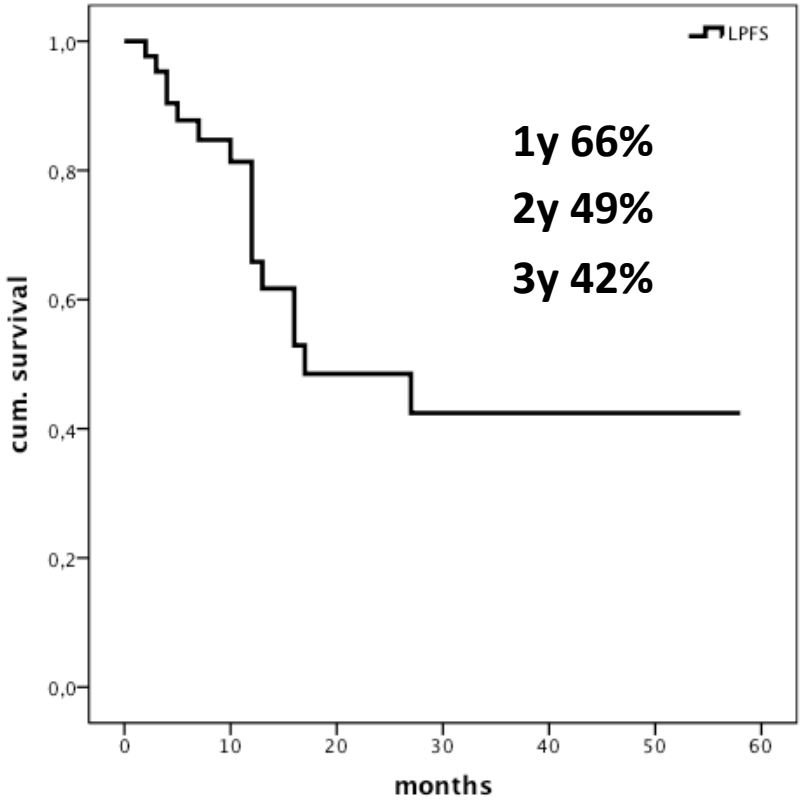


Progression-Free Survival

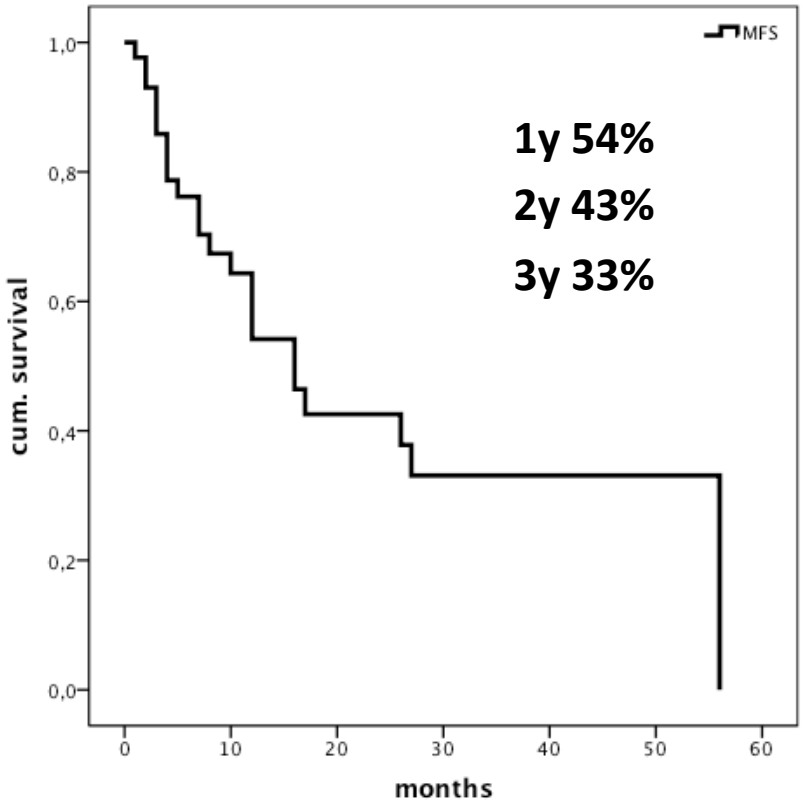


Local and distant progression

LPFS



MFS



Toxicity rates

Treatment-related toxicities based on RTOG (Radiation toxicity grading) acute and late morbidity scale.

Toxicity	*Grade 1*		*Grade 2*		*Grade 3*		*Grade 4*		*Total*	
	N.	%	N.	%	N.	%	N.	%	N.	%
Acute										
Erythema	4	(9)	0	(0)	0	(0)	0	(0)	4	(9)
Esophagitis	6	(14)	10	(23)	1	(2)	0	(0)	17	(40)
Cough	4	(9)	3	(7)	0	(0)	0	(0)	7	(16)
Odynophagia	2	(5)	2	(5)	0	(0)	0	(0)	4	(9)
Pneumonitis	3	(7)	5	(12)	3	(7)	0	(0)	11	(26)
Hematological	6	(14)	2	(5)	1	(2)	0	(0)	9	(21)
Late										
Esophagitis	0	(0)	1	(2)	1	(2)	0	(0)	2	(5)
Pneumonitis	4	(9)	6	(14)	3	(7)	0	(0)	13	(30)

Acute toxicities:
Esophagitis Grade 1-2: 16 pts (37%), **Grade 3: 1 pts** (2%)
Pneumonitis Grade 1-2: 8 pts (19%), **Grade 3: 3pts** (7%)
Hematological Grade 1-2: 8 pts (19%), Grade 3: 1pt (2%)

Late toxicities:
overall Grade 1-2 toxicities (33%);
Grade 3 toxicities: esophagitis 1pts and pneumonitis 3pts

Prognostic factors

Variables		Univariate analysis				Multivariate analysis			
	N. pts	OS	PFS	LPFS	MFS	OS	PFS	LPFS	MFS
Gender									
- Male	34	0,894	0,947	0,685	0,778	0.986	0,904	0,622	0,761
- Female	8								
T size									
- ≥ 5cm	20	0,095	**0,032**	0,697	0,097	0.223	0,274	0,741	0,171
- < 5cm	23								
Stage									
- IIIA	13	0,128	0,653	0,667	0,412	**0.019**	0,084	0,225	0,116
- IIIB	21								
- IV	9								
Prior chemotherapy									
- Yes	31	0,938	0,161	0,657	0,361	0.527	**0,022**	0,205	0,436
- No	12								
PTV									
- ≥ 250 cc	26	0,436	0,939	0,600	0,861	0.843	0,906	0,994	0,833
- < 250 cc	17								
Histology									
- SCC	17	0,068	0,134	0,388	0,820	0.087	0,079	0,254	0,757
- Non SCC	26								
Age									
- ≥ 75	30	0,427	0,838	0,491	0,778	0.678	0,108	0,211	0,883
- < 75	13								
Response									
- CR	4	0,295	0,195	0,825	0,075	0.108	0,266	0,713	0,151
- PR	29								
- NR	10								

Conclusions

Hypofractionated radiation therapy offers good disease control for advanced inoperable NSCLC patients

PROSPECTIVE STUDIES

Acceptable toxicity rates – 3DRT/IGRT

RT patterns **RANDOMIZED TRIALS**
HypoRT *vs.* Standard RT - CHT ***ns to be defined***

REGIONE LAZIO

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Grazie