Gemelli
Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore
ART Advanced Radiation Therapy

MRO . ART

Art4ART

Modern Radiation Oncology.
Innovation in personalised oncology: back to the future

33° RESIDENTIAL COURSE

9 | 10 | 11 October 2023

BACK TO THE FUTURE: NSCLC CANCER

Fractionation: needs learned for modern treatments

Dr Cecile Le Pechoux

Department of Radiation Oncology

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

UNIVERSITÉ PARIS SUD
FACULTÉ DE MÉDECINE

ÉCOLE DES SCIENCES DU CANCER
GUSTAVE ROUSSY

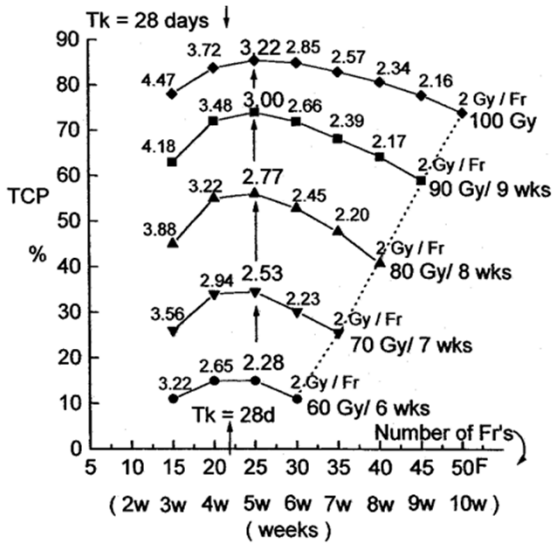
Centre International des CANCERS THORACIQUES
SOIGNER - INNOVER - GUÉRIR

Dr Cecile Le Pechoux Disclosures:

- No disclosure concerning topic of presentation
- Institutional honoraria for Participation to boards: Astra Zeneca, BMS, Roche, Varian
- Institutional honoraria for Participation to educational meetings: Astra Zeneca
- Support for Travel to meetings: Janssen, Roche, Ose Immunotherapeutics

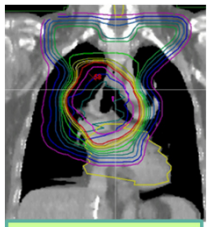
Rationale of accelerated and/or hyperfractionated RT

- A lot of interest in modified fractionation regimens in the past !
- Accelerated repopulation of tumour stem cells can occur 21-28 days after the start of radiation treatment → radiobiological rationale for accelerated treatments.
- Accelerated regimen may counteract repopulation, leading to reduced Overall Treatment Time , and possibly improved local control
- Hyperfractionated RT can reduce long-term normal-tissue morbidity



Tk = time when rapid repopulation of tumor cells begins)
TCP: Tumour control Probability
Based on Martel study (3DRT alone)

Withers et al, 1988; Maciejewski et al,1989; Fowler et al, 1991;Fowler 2001; Martel et al, 1999



Altered fractionation Trials with ENI

Standard Fractionation

60 Gy/30 fr
DD = 2 Gy
***ECOG 64 Gy**
CHARTWEL 66 Gy

5 days

Week-end

CHART=TD 54 Gy/36 fr
DD: 3X1,5 Gy with 6h interval

ECOG=TD 57,6 Gy/36 fr
DD : 1,5-1,8-1,5 Gy

CHARTWEL=60 Gy/40 fr
DD : 3X1,5 Gy

PMCI=60 Gy/30 fr
DD : 2X2 Gy

RTOG 8808/ECOG=69,6 Gy/58 fr
DD : 2X1,2 Gy

NCCTG=60 Gy/40 fr
DD : 2X1,5 Gy

Split course:2 wks

Several studies evaluating modified fractionation regimens in radiotherapy for both NSCLC and SCLC in the past century!

Types of altered fractionation schedules:

- Hyperfractionated
- Accelerated
- Hyperfractionated and accelerated (CHART…)
- Hypofractionated not really considered except in the UK

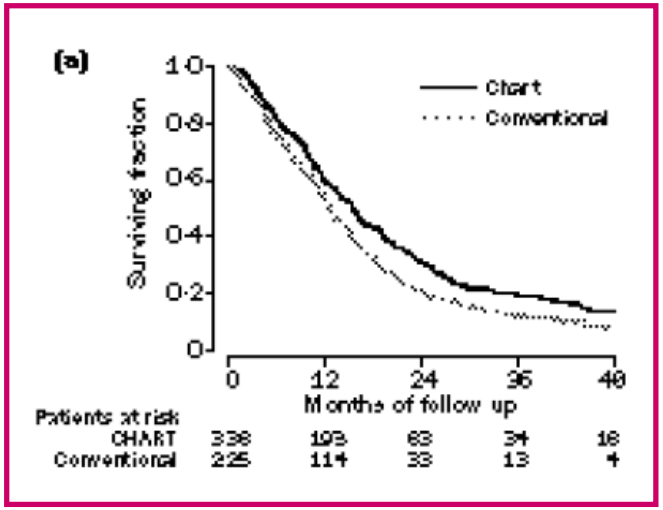
Promising results in prospective trials

Saunders et al, Lancet 1997; Baumann et al, R&O 2011; Belani et al, JCO 2005; Ball et al , R&O 1999; Sause et al, Chest 2000; Bonner et al, Cancer 1998; Schild et al,IJROBP 2002

Continuous hyperfractionated accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small-cell lung cancer: a randomised multicentre trial

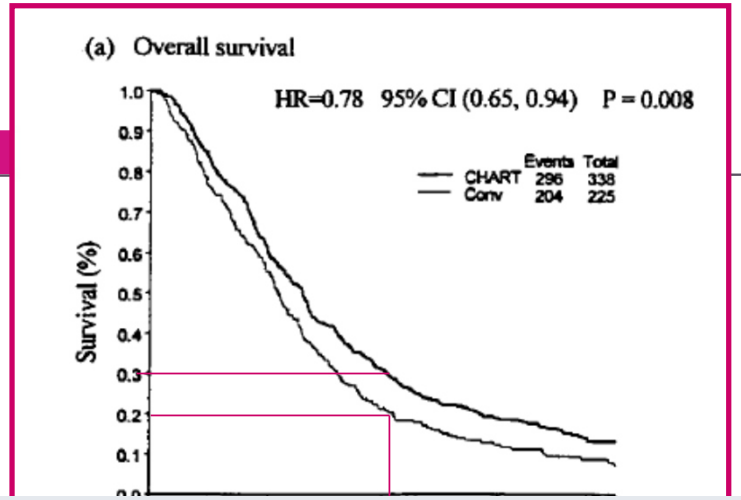
- Landmark study CHART
- Proof of concept: Efforts to improve local tumour control prolong survival.
- Rate of metastases reduced by more effective treatment to primary site.

563 pts	Conventional RT	CHART
Survival at 2/3 yrs	20%/13%	30%/20%
DF Interval at 2 yrs	9%	12%



Saunders et al, Lancet 1997

CHART : results at 3 years



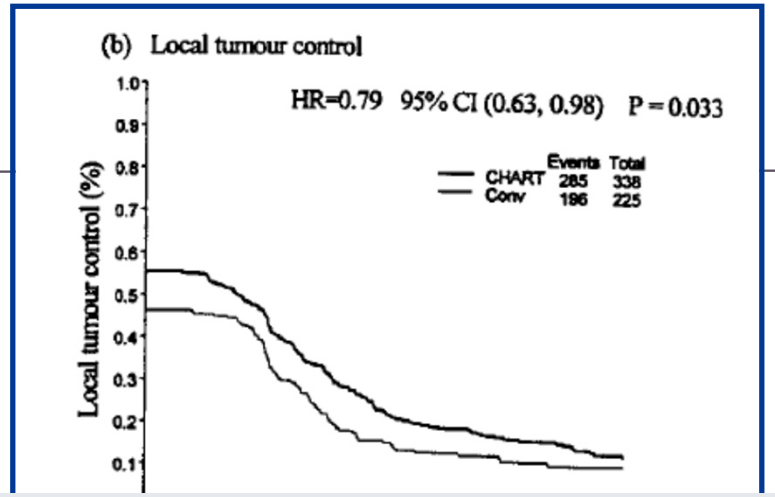
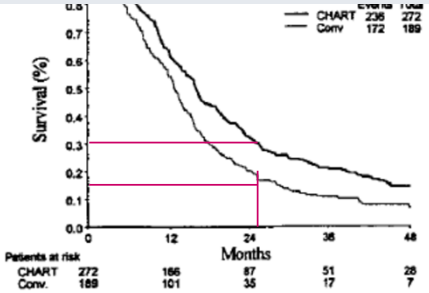
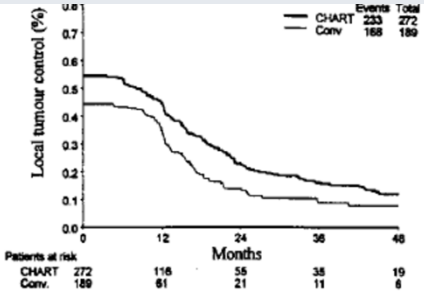


CHART: more efficacy but more toxicity
Especially esophageal toxicity
No compromise of compliance as toxicity occurs after RT





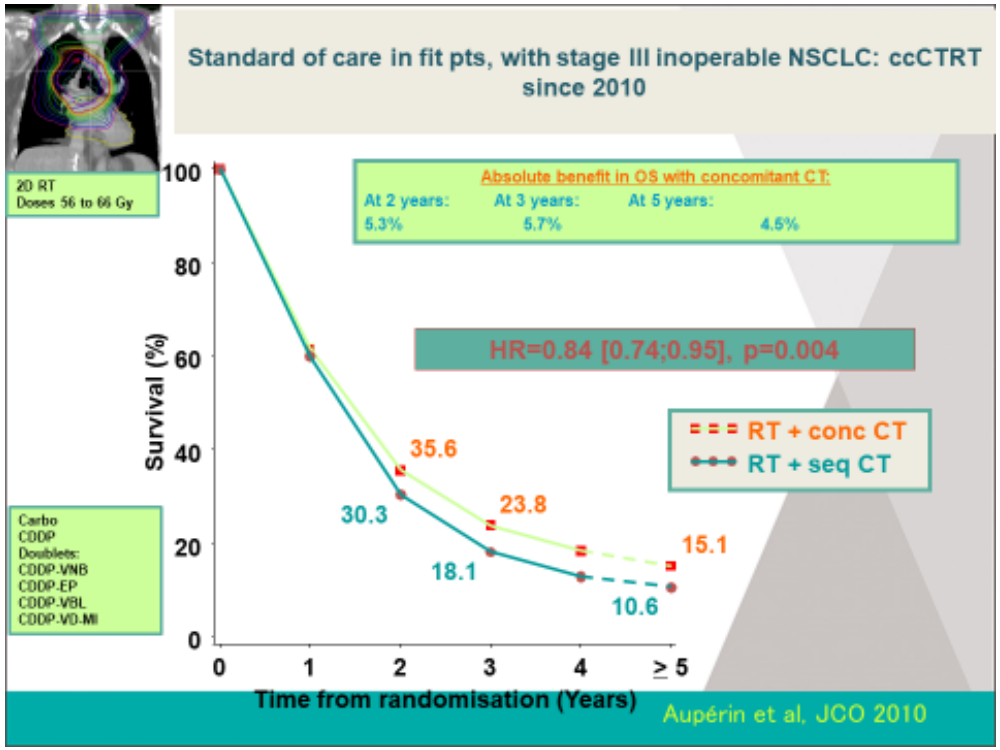
Saunders et al, Lancet 1997, Rad & Onc 1999

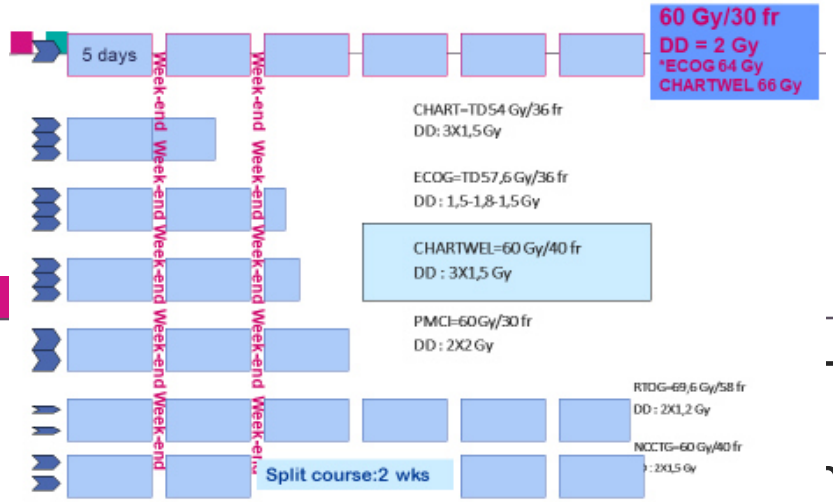
Change of standard of care in LANSCLC

CHEMOTHERAPY AND

ALTERED

FRACTIONATION ?





CHARTWEL

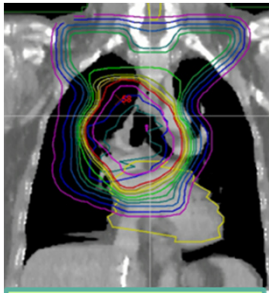
GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

but patients not treated during WE

ng for CHARTWEL revealed through dose escalation to 60 Gy

- expected improvement of the therapeutic ratio and increase of locoregional tumour control after 3 years by 7–14% (from 19% to 26–33%)/CHART

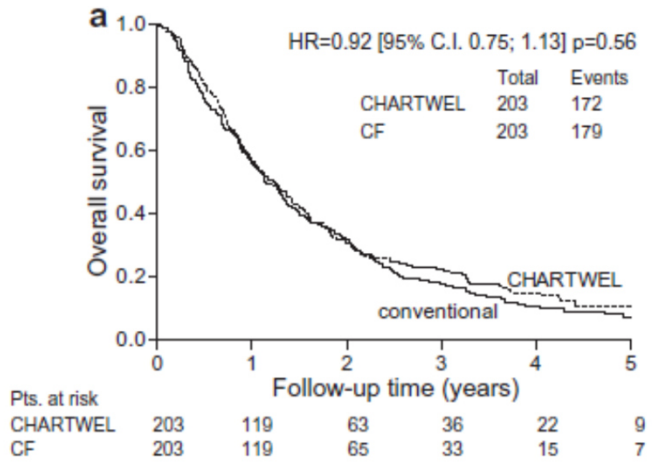
- 406 pts included 1997- 2005, from 1999 on induction CT allowed (75% no CT..), 3DRT but large volumes (PTV1: 50 Gy; PTV2:16 Gy and PTV1:39 Gy and PTV2:21 Gy)
- Control Arm 66 Gy/33 Fr

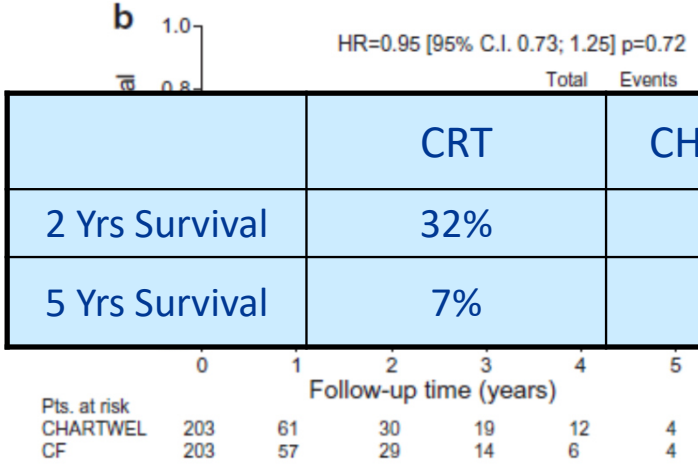


2D RT
Doses 56 to 66 Gy

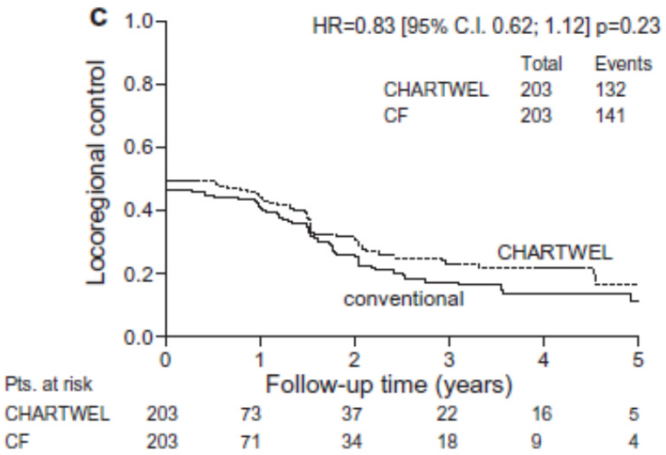
Baumann et al, Rad & Onc 2011

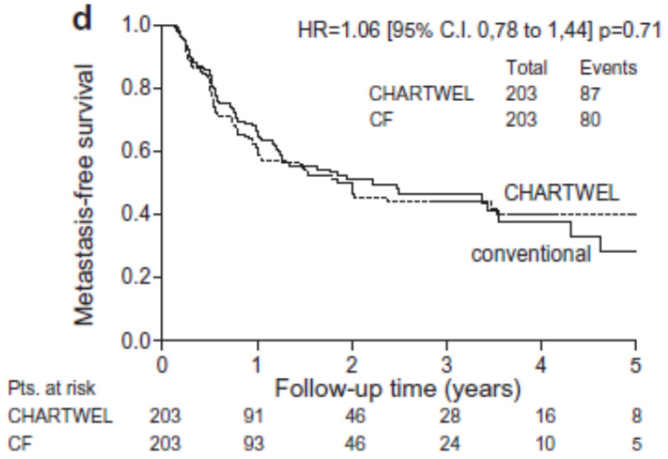
CHARTWELL





	CRT	CHARTWEL
2 Yrs Survival	32%	31%
5 Yrs Survival	7%	11%





Baumann et al, Rad & Onc 2011

CHARTWEL study

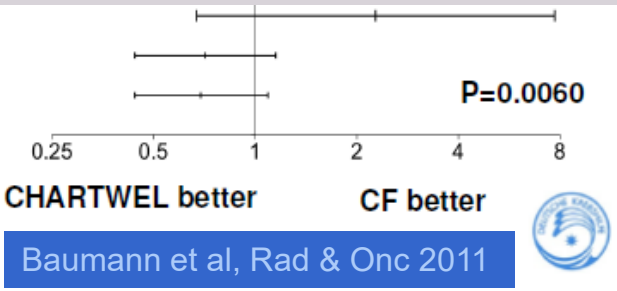
CHARTWEL-Bronchus (ARO 97-1)

Locoregional tumor control – exploratory analysis

	CF	CHARTWEL	HR	P	Cochrane/Armitage Trendtest
N-stage					
II	7/12	8/11	2.27 (0.67 ...7.72)	0.1875	
IIIA	57/76	47/78	0.71 (0.44 ... 1.15)	0.1673	
IIIB	68/93	64/93	0.69 (0.44 ... 1.09)	0.1135	

Lower TD in CHARTWEL arm compensated by shorter OTT, confirming a time factor for NSCLC

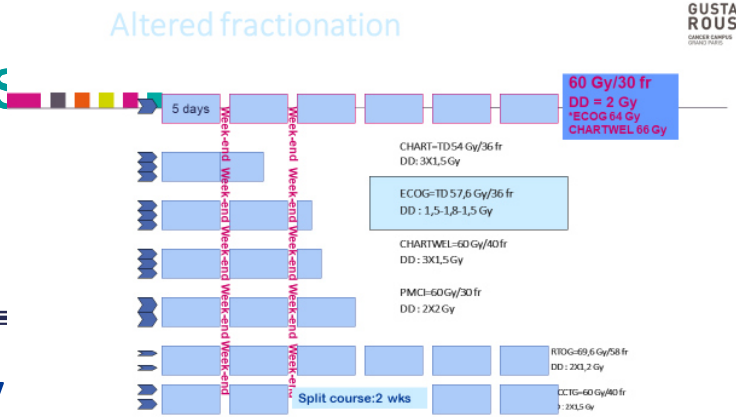
Significant trend for improved LC after CHARTWEL versus CRT with increasing stage (p = 0.006–0.025) and after neoadjuvant chemotherapy



Courtesy of M. Baumann

Baumann et al, Rad & Onc 2011

A phase III trial of Sequential CT-RT versus CT-HART in Stage III NSCLC (ECOG 2597)



R → 2 cycles CB^{AUC6}Pacl^{225} + Sq TRT 64 Gy

R → 2 cycles CB^{AUC6}Pacl^{225} + Sq HART 57.6 Gy **[55 pts]**

[3 fractions of 1.5 Gy, 4-H interval, on-cord fields spaced 8h apart]

Results	Sq CT-RT	Sq CT-HART	
Gr 3/4 Oesoph^{tis}	12%/3.5%	23%/2%	
MST	14.9 m	20.3 m	
2/3Year Survival	24/14%	44/34%	NS

Ccl: Study closed prematurely because of poor accrual, provocative efficacy HART after induction of carbo-Taxol

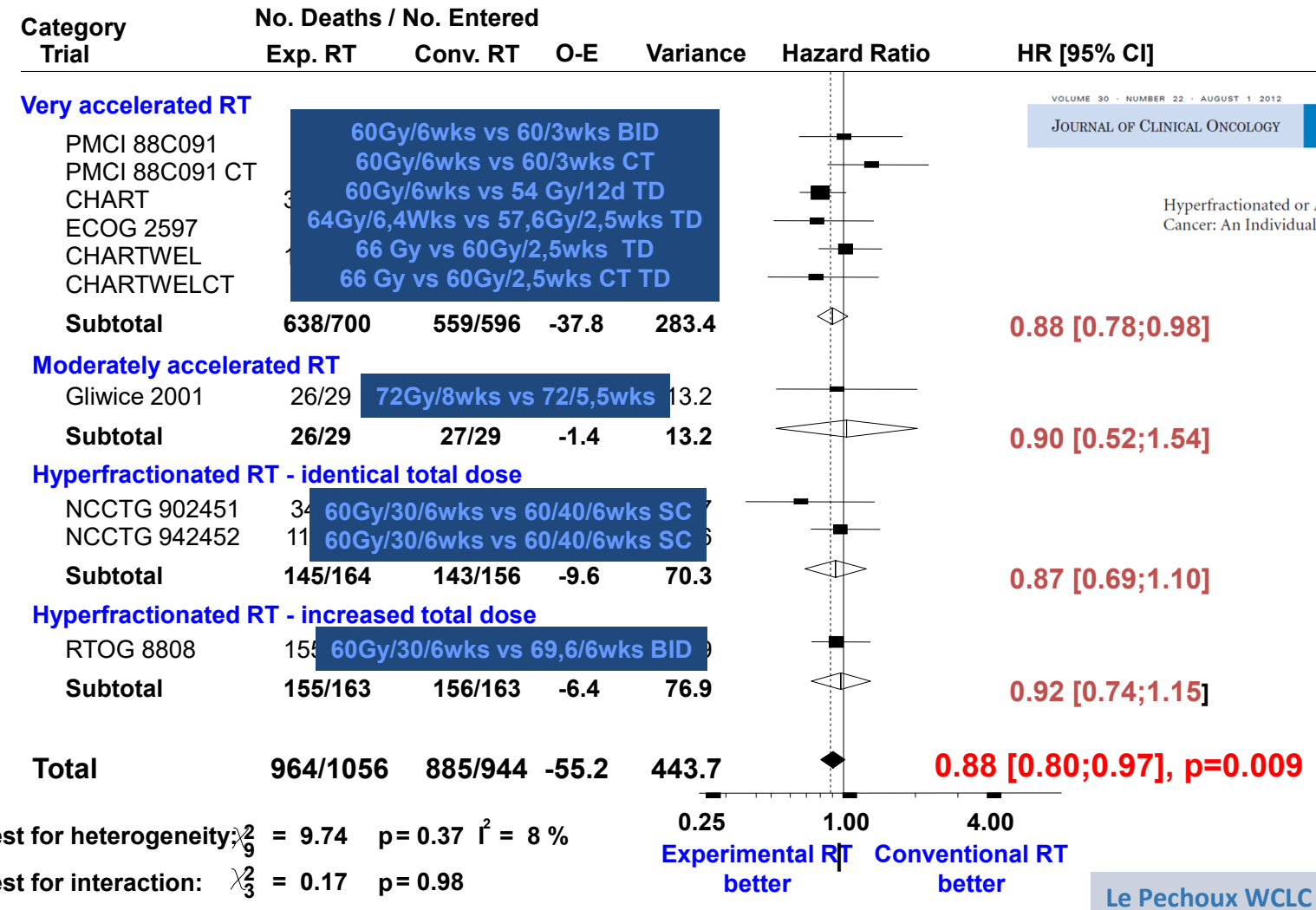
Belani et al, JCO 2005

Contrasting results of altered fractionation in randomised trials

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

- Over the years, several randomized trials evaluating ≠ altered fractionation schedules:
- Contrasting results
- Necessity of an individual patient data meta-analysis (IPD) to evaluate a potential benefit from modified fractionation radiotherapy schedules
  - Hyperfractionnated: higher number of fractions with smaller dose per fraction compared with conventional RT
  - Accelerated: reduced overall treatment time (OTT) compared with conventional fractionation and
  - Hyperfractionated and accelerated

Overall survival NSCLC (2000 pts)



VOLUME 30 · NUMBER 22 · AUGUST 1 2012

JOURNAL OF CLINICAL ONCOLOGY | REVIEW ARTICLE

Hyperfractionated or Accelerated Radiotherapy in Lung Cancer: An Individual Patient Data Meta-Analysis

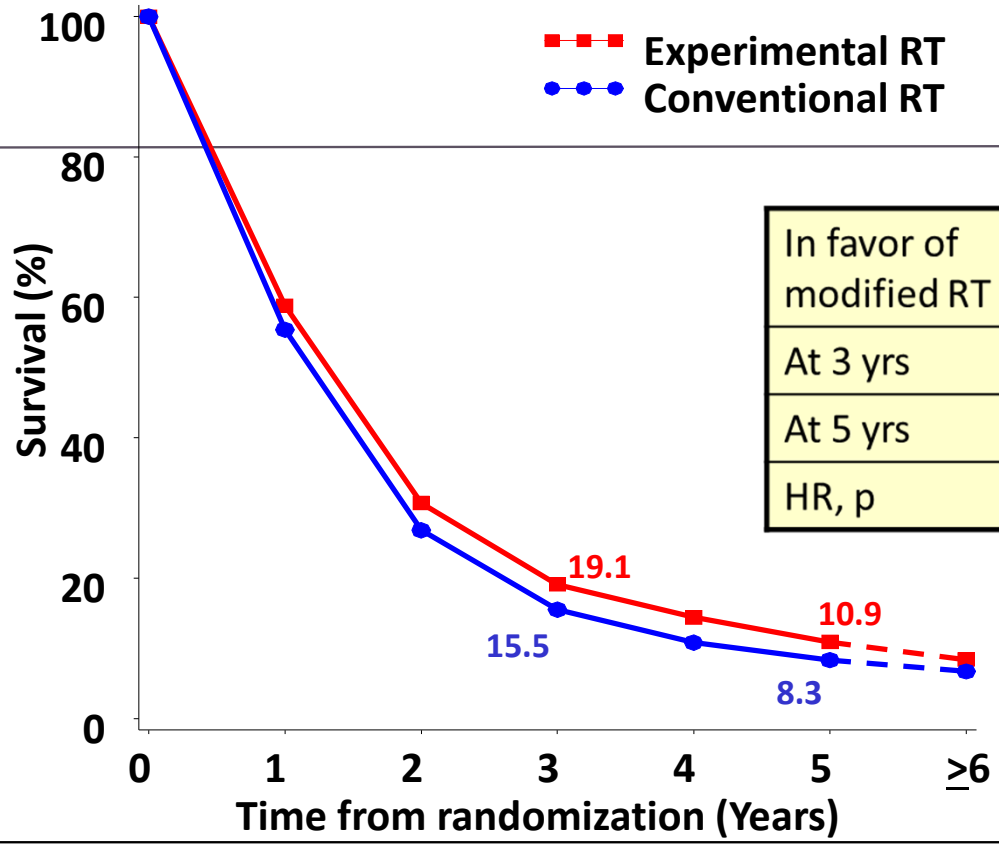
Test for heterogeneity: χ^2_9 = 9.74 p = 0.37 I^2 = 8 %

Test for interaction: χ^2_3 = 0.17 p = 0.98

Le Pechoux WCLC 2012; Mauguen JCO 2012

Overall survival

Use of Altered fractionation vs conventional NSCLC



In favor of modified RT	Absolute benefit OS	Absolute benefit PFS
At 3 yrs	3.8%	1.4%
At 5 yrs	2.5%	-0.2%
HR, p	0.88, p=0,009	0.94, p=0.19

No. events / PY	Years 0-2	Years 3-5	Years ≥6
Experimental RT	587 /1037	164 / 445	41 / 167
Conventional RT	550 / 851	130 / 293	26 / 111

Le Pechoux WCLC 2012; Mauguen JCO 2012

Altered fractionation and NSCLC

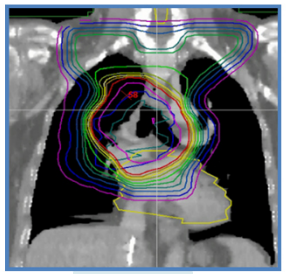
- Modified fractionation radiotherapy significantly improves overall survival in NSCLC
- In pts with delivered RT with BED ≥ 55 , decreased risk of death compared to pts with BED<55 Gy (HR=0.75 [0.65-0.85], p<10-4).

  ⟹ Absolute benefit of 5.1% at 3 years and 3.4% at 5 years
- Increased acute esophageal toxicity (OR=2.44, p=0,01) in experimental treatments
- Higher technology RT, better selection of patients : encouraging results in recent studies with better management of toxicity!
- In the mean time: 60-66 Gy with platin based ccCTRT still the standard in NSCLC

Le Pechoux WCLC 2012; Mauguen JCO 2012

But ccCTRT + Durvalumab has become SOC in stage III NSCLC with improved Outcome 5 year survival Rates from 1

Improvement of RT 3D, IMRT
More effective CT
Better toxicity management

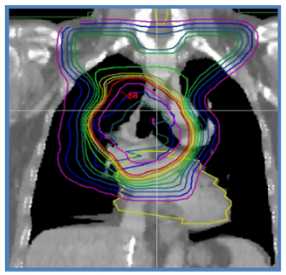


2D RT

6 %

1980's

Auperin et al , Ann Oncol 2006

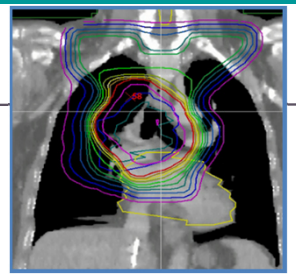


2D RT

8,3 %

CT-RTcc 2000's

Auperin Ann Oncol 2006

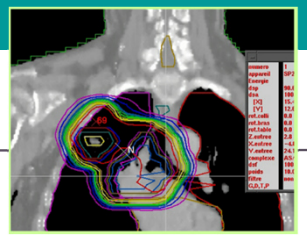


2D RT

ccCTRT/15,1 %
Vs
sqCTRT/10,6%

CT-RTcc 2010's

(Auperin JCO 2010)

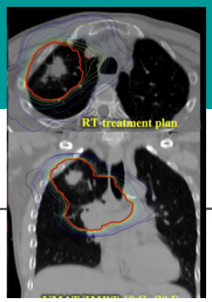


3D RT/IMRT

60 Gy/32,1%
Vs
74 Gy/18,3%

CT-RT 2017 IMRT

(Bradley RTOG 0617 JCO 2020)



3D RT/IMRT??

ccCTRT+IO 42,9 %
Vs
ccCTRT: 33,4%

CT-RTcc+Durva

(Antonia NEJM 2018)

Better selection of patients (Brain MRI, EBUS, PET Scan)

Adapted from N Girard slide

Hypofractionation

PAST

- Theoretically, no radiobiological benefit compared with standard fractionation
- Increased dose per fraction for late-responding normal tissues and shortened OTT for early responding tissues.
- To reduce risk of damage to late responding tissues, reduction in total dose potentially leading to a reduction in tumor control probability. Shorter OTT may compensate for this negative effect,

PRESENT AND FUTURE

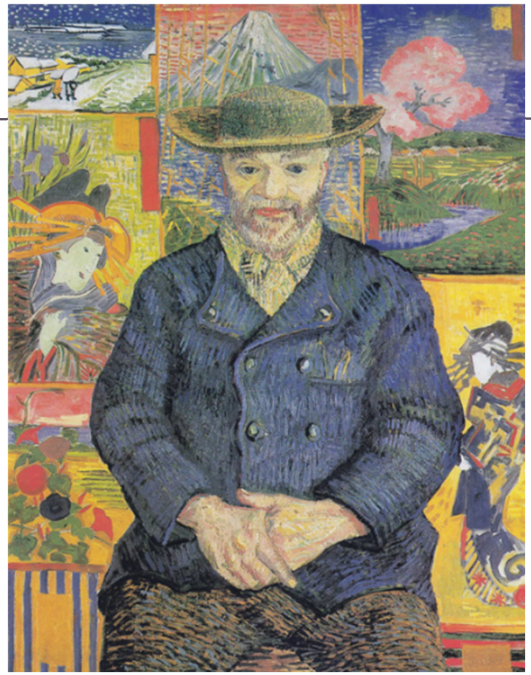
- We know now advances in target volume definition, image guidance and improved treatment planning (IMRT) reduce the risk of late complications..(Heart and Normal lung sparing, Lymphocyte sparing..)
- Trials comparing hypoRT with sq or ccChT: it can be done, no difference of outcome..
- Ongoing studies combining hypofractionation RT with ChT and IO but with

Fowler 2001; Belderbos et al Randomized phase III study EORTC 08972-22973 EJC 2007; Maguire et al SOCCAR Randomized phase II study EJC 2014

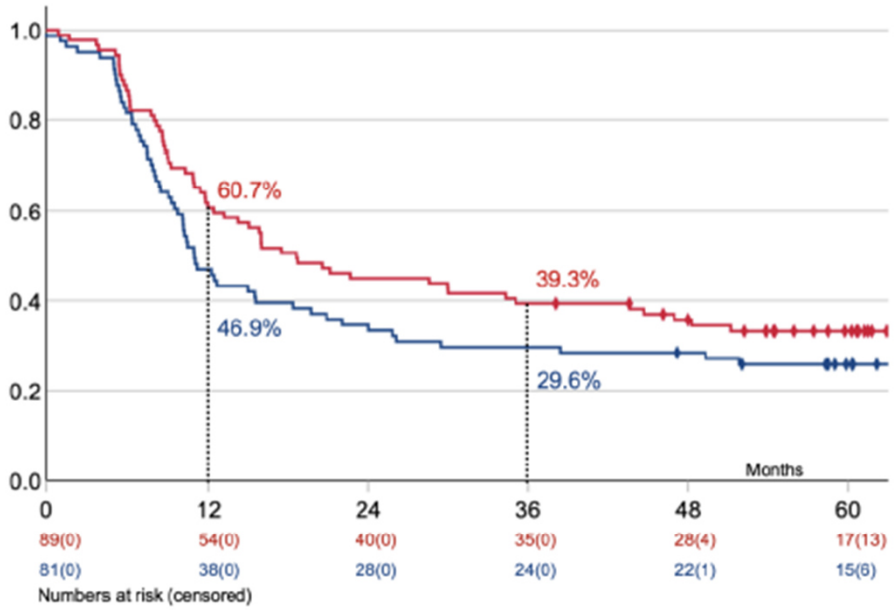
GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

BACK TO THE FUTURE

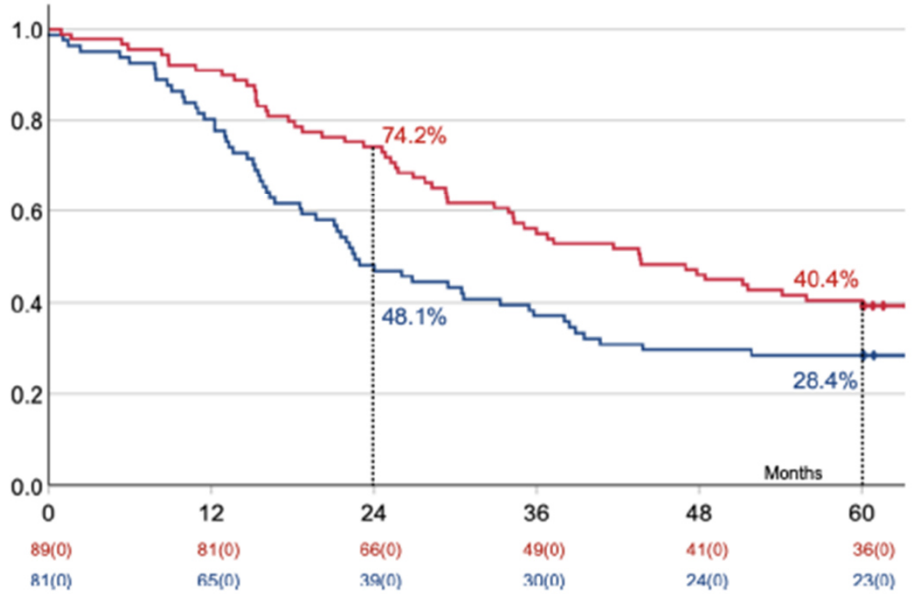
More data in SCLC



Hyperfractionated accelerated high-dose TRT



	Median PFS	1-year PFS
BID 60 Gy	18.6 months	60.7%
BID 45 Gy	10.9 months	46.9%

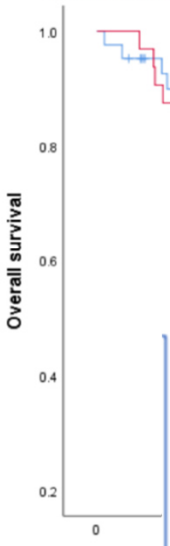


	Median OS	5-year OS
BID 60 Gy	43.6 months	40.4%
BID 45 Gy	22.6 months	28.4%

Gronberg et al. Final survival data from a randomized phase II trial comparing high-dose with standard-dose twice-daily (BID) thoracic radiotherapy (TRT) in limited stage small-cell lung cancer (LS-SCLC). J Clin Oncol 41, 2023 (suppl 16; abstr 8512)

Gronberg et al, ASCO and WCLC 2023

Overall survival in patients with HypoTRT or HyperTRT



1=HypoTRT group
2=HyperTRT group

OS	HypoTRT group N=42	HyperTRT group N=32	p

randomly assigned

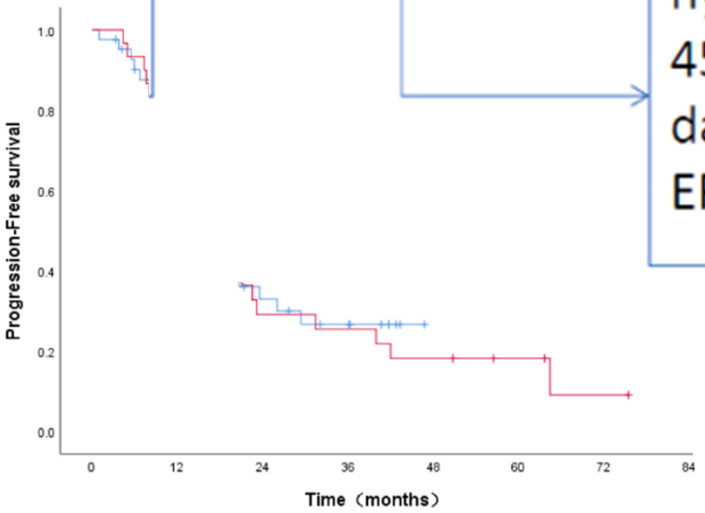
hypofractionated group: 45Gy in 15 fractions once a day concurrently with the 2nd EP/EC

Randomized phase II study comparing 2 ccCTRT regimen Hypofractionated RT in 3 wks vs Hyperfractionated accelerated RT in 3 wks

hyperfractionated group: 45Gy in 30 fractions twice a day concurrently with the 2nd EP/EC chemotherapy

Patients with CR or PR receive PCI at 25Gy in 10 fractions once a day

Progres



Sun et al, IASLC WCLC 2023

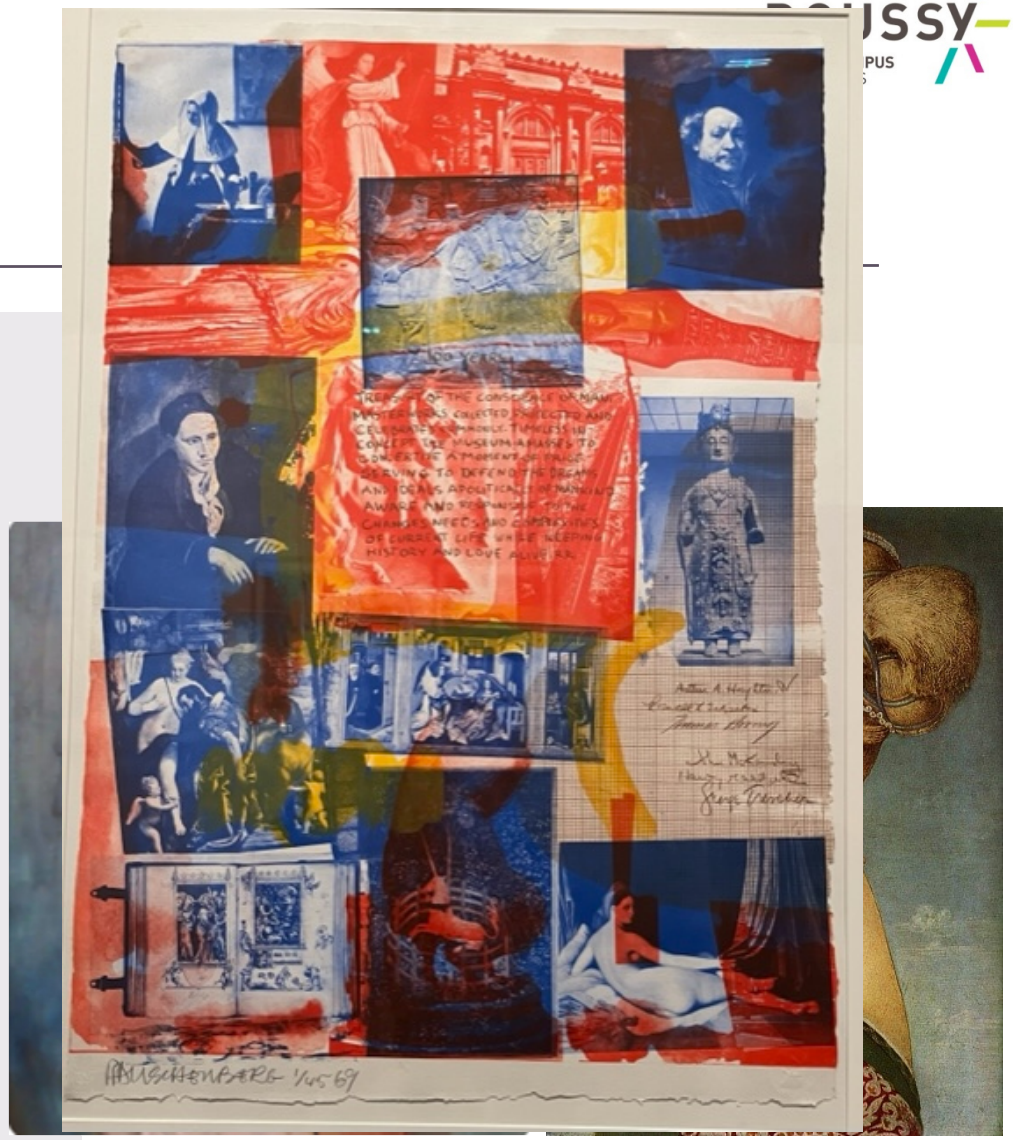
Take Home message

- After several randomized studies evaluating altered fractionation in NSCLC in the 80,90s (when CTRT was not a standard) with conflicting results (poorer results in LANSCLC, combined with ChT) and poor implementation rates of HAFRT in most centers
- We are back to conventional fractionation considering that ccCTRT and consolidation IO in fit pts has become SOC in LANSCLC since 2017
- SBRT has become one of the success stories in NSCLC in st I NSCLC and OMD (extreme hypofractionation but in small size tumours or mets)
- More interest now in hypofractionation combined with systemic treatments in more advanced NSCLC -High precision RT
- On going studies, but we need to better select pts who could benefit from such strategies (PET CT, Genomics..). One size does not fill all!
- More active research regarding fractionation in SCLC..

Acknowledgements to Pr Gambacorta, Pr Valentini, Pr Indovina and all the Gemelli Team

Journey in the past to go forward

Thank you, Grazie for your attention! Any questions??



ESTRO 2024

ANNUAL ESTRO CONGRESS

3-7 May 2024
Glasgow, UK

Abstract submission deadline:
25 October 2023

Radiation Oncology: Bridging the Care Gap

WWW.ESTRO.ORG

#ESTRO24