State-the-art of the role of Radiotherapy in NSCLC

- Stereotactic RT for inoperable NSCLC
- Post-Operative Radiation Therapy (PORT) in resected N2 NSCLC
- Update on RT/CT for unresectable NSCLC

ESMO Preceptorship on NSCLC
Copenhagen July 7-8th 2015

Cécile Le Péchoux

Radiation Oncology Department

GUSTAVE ROUSSY
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IOT
Institut d'Oncologie Thoracique

NSCLC T1,T2N0 in XXth century

- **Conventional RT in inoperable patients**
  - Because of medical comorbidities related to smoke, about 25% of patients with early stage do not have standard surgical treatment
  - **Poor results CRT/surgery but different population +++ Palliative ttt**
  - OS at 2-yr and 5-yrs= 22–72%, 0–42%.
  - CSS at 2-yr and 5-yrs = 54–93%and 13–39%.
  - LRR= 6–70%. DRR= 25%
- **Major changes in outcome with Stereotactic RT**

Rowell systematic review Chest 2001

SRT: high dose in small volume Tumours:T1

Thus allowing for:

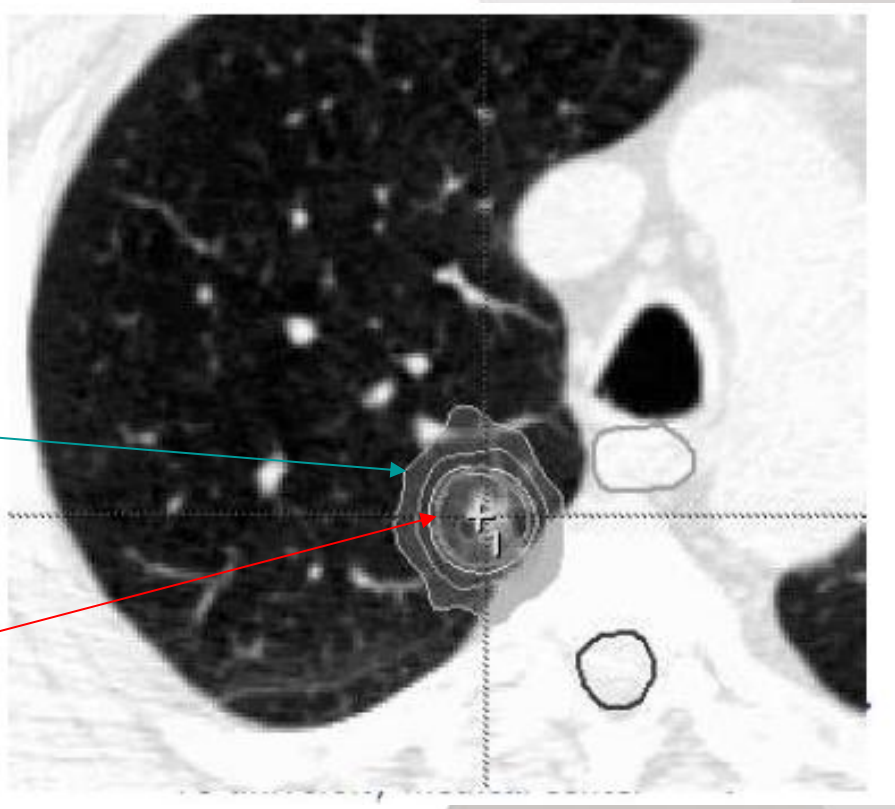
- Steep dose-gradients
- Hypofractionation (3-5x)
- High biological effective dose

40% isodose = BED 60 Gy

60% isodose = BED 112.5 Gy

80% isodose = BED 180 Gy

100% isodose = BED 262 Gy



Complex beam arrangements to conform high-dose regions to the tumor and create steep dose gradients around the target volume (RT or IMRT)

Kindly provided by Pr S. Senan

SRT in lung cancer: Results

Author	N pts	DT(Gy)D/jour	Reference point	LC (%)	OS
Timmerman 2010	59 44T1 at 15	54Gy	Edge of PTV	3Yr 90%	MS: 48 m
Baumann 200				3YrLC:92% LRel:7% RR:5% DM 16%	3y0S:60% 3yrCSS:88%
Baumann 200				LFail R:12% DM:25%	3yOS:52% 3yrCSS:66%
Lagerwaard				LFR:3% RFR:9%	34 m 2y0S:64%
Haasbeck 20				3yLC:89%	3yOS:45%

3 yr LC rate 90%

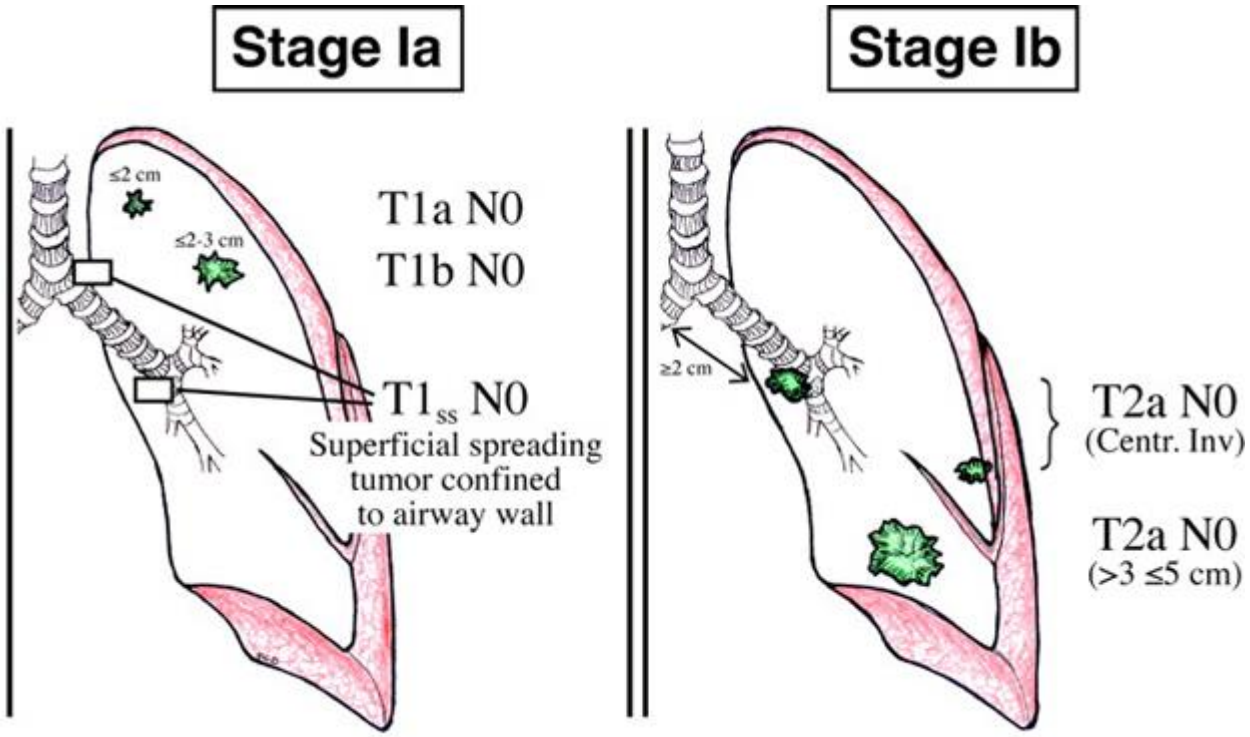
Mortality Rate in periph

Tumors: 0 %

Morbidity Rate: <10%

Timmerman JAMA 2010, Baumann JCO 09, Acta Onco 06; Lagerwaald IJROBP 08; Haasbeck Cancer 2010

Stage I



Stereotactic radiotherapy has become the new standard of care in inoperable patients due to co-morbidities and age

Vansteenkiste et al, ESMO lung guidelines 2014

Optimal dose?

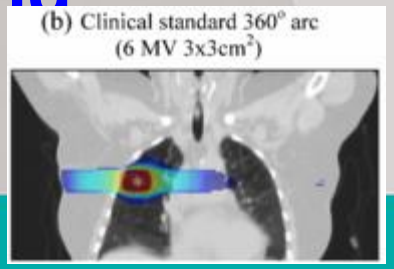
SRT for stage I NSCLC: a Japanese multi-institutional study (Onishi et al ASCO 06, Abstract 7045)

- 300 pts (193 T1N0, 107 T2N0; 190 inop et 110 operable) treated from 1993-2003
- Results: Median FU: 38 months

	BED≥100Gy	BED<100Gy	p
Local Control at 5 yrs	86%	67%	<0,001
5-yr-S^{al} Rate	65%	37%	
5-yr-S^{al} Rate Operable pts	74%	37%	<0,01
3-yr-Local progression-free-S^{al} Rate	St IA 81% St IB 67%		

ESMO lung cancer guidelines 2014

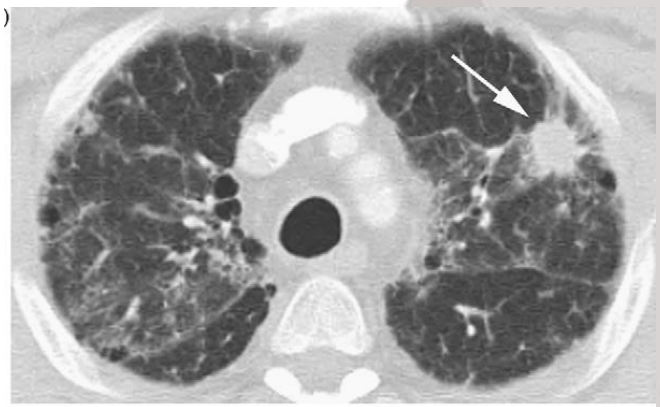
- **The non-surgical treatment of choice for stage I NSCLC is stereotactic ablative radiotherapy (SABR). The dose should be to a biologically equivalent tumour dose of ≥100 Gy, prescribed to the encompassing isodose [III, A].**
- **More and more centers are using Volumetric Modulated Arc Therapy (VMAT, RapidARC..) using complete or partial arcs allowing treatment to be delivered in <15 mn**



Vansteenkiste et al, Ann Onc 2014

ESMO lung cancer guidelines 2014

- **SABR for early-stage peripheral lung tumours is associated with low toxicity in patients with COPD and the elderly [III, A].**



Vansteenkiste et al, Ann Onc 2014

Palma et al, 2012; Henderson 2008;Stephans 2009; Magdeleinat 2005; Lau 2010; Stanic 2014
Widder IJROBP 2011, Haasbeck 2010

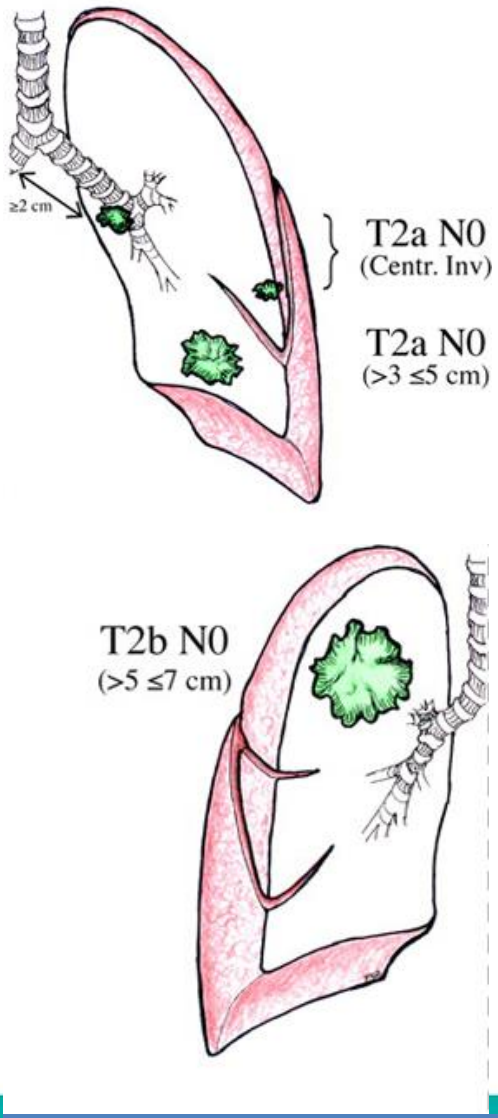
Challenges

- **Optimal dose fractionation**
- **Pathology**
- **Extension of indications to**
  - Larger Tumors
  - Central early lung cancer
- **Patterns of failure**
- **Difficulty of LC assessment**
- **Place of SRT/surgery**

Challenge 1: Optimal dose and fractionation?

- **No standard dose**
- **More common regimens**
  - > For stage I: 3X18-20 Gy, 3X15 Gy, 4X12 Gy
- **Risk adapted SRT needed according to size, location/OAR especially in mediastinum**
  - > For central tumors: 8X7,5 Gy, 8X7 Gy, 10X5 Gy
- **Better to use dose calculation algorythms type B**
- **Use of modulated beams possible (VMAT)**

Challenge2: extending SRT to larger T : Results according to Tumor size

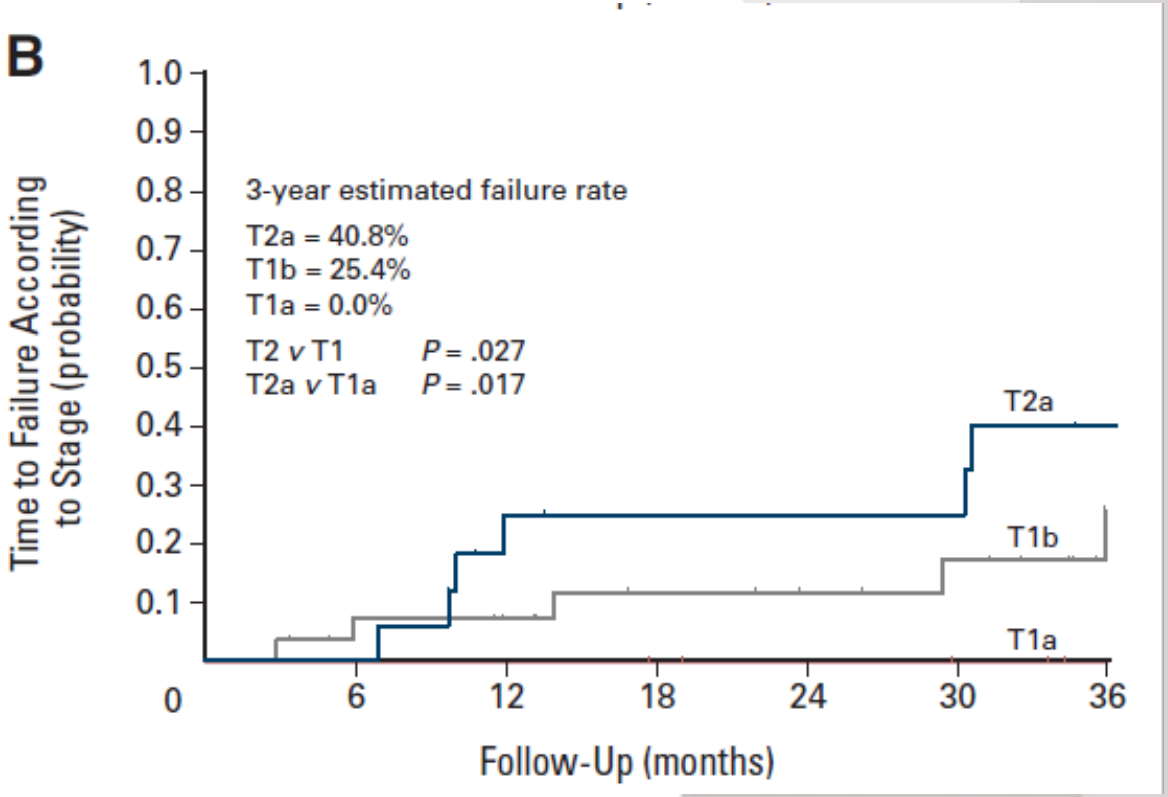


- Local control at 3 years: ~90%
- Increased local failure in larger Tumours frequently but not always
- Less evidence of SRT for T over 5 cm
- Some authors suggest higher doses for larger T (BED prescribed to encompassing isodose >100 Gy needed)
- Higher risk also of regional /distant recurrence

Timmerman JAMA 2010, Baumann JCO 09, Acta Onco 06; Chi systematic review 2010

SABR: Results according to Tumor size

- 57 pts with T1N0 (70%) or T2N0
- Dose=45 Gy (15 GyX3)
- BED periph:112
- Estimated risk of failures: 41% (T2) vs 18% (T1)



Baumann JCO 2009

The Impact of Tumor Size on Outcomes After Stereotactic Body Radiation Therapy for Medically Inoperable Early-Stage Non-Small Cell Lung Cancer

- **185 pts with 133 T1 and 52 T2**
- **82% biopsy proven NSCLC**
- Dose **T1: 48 Gy/4fr** **Larger T:54 to 60 Gy/3 fr**

  T adjacent to mediastinum: 60 Gy/8 fr or 50 Gy/10 fr
- **T size not related to local failure (LC of 94,5%) but Importance of BED for local control**
  - BED <100 Gy →LFR of 16.7%
  - If BED >100 Gy → LFR of 2.3%
- **GTV larger than 100 cm3 or T>5,7 cm are at higher risk of regional and distant failure**

Alibhai et al, MGH experience IJROBP 2013

Challenge 3: SABR for central tumours?

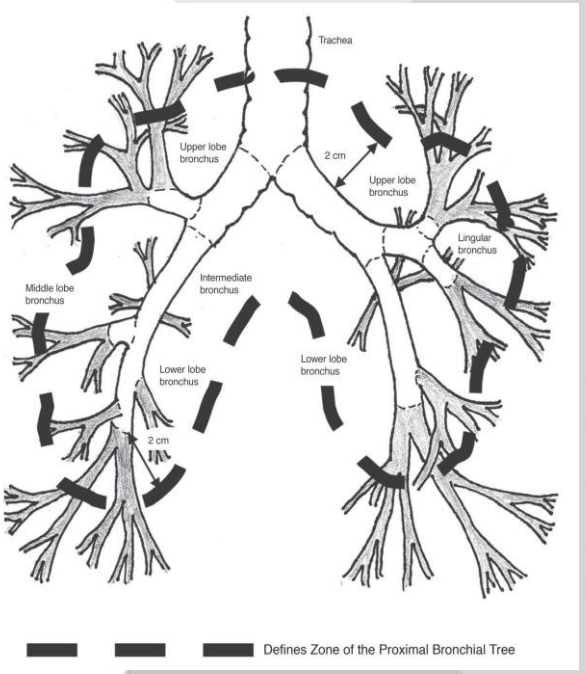
- Drawback in central lesions because of increased toxicity (Timmermann JCO 2006)
- 70 pts receiving 60-66 Gy/3fr
- 2-yr local control 95%
- Peripheral tumors

2-year free from severe toxicity : 83%

- Central tumors:

2-year freedom from severe toxicity: 5

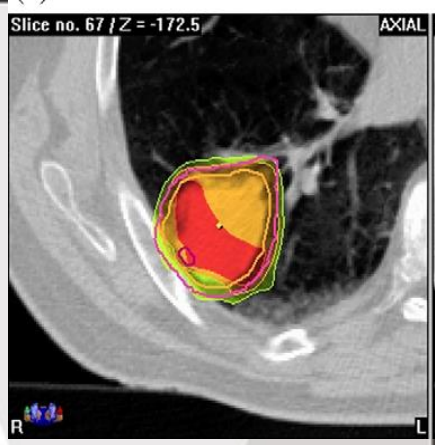
- Need for prolonged FU



Severe bronchial stenosis and fistula may occur ≥2 yrs when large bronchi have received >80 Gy

Timmerman JCO 2006, Miller 2005

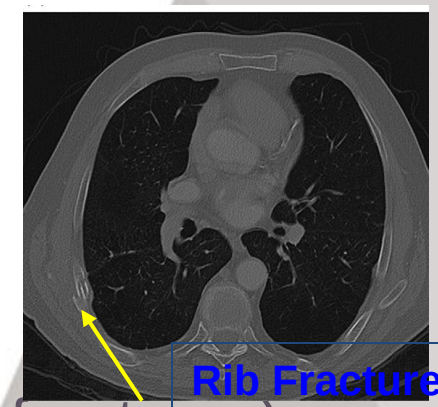
Concept of risk adapted SRT



Lageerwald et al, IJROBP 2008

- 206 pts T1T2N0M0
- Fractionation schemes used (T1:3 X 20 Gy, T1 with large contact to chest wall and T2: 5 X 12 Gy, and 8 X 7.5 Gy for central tumors) determined by
  - T stage
  - Risk of normal tissue toxicity
- Local failure : 7 patients (3%).
- Severe late toxicity : less than 3%

  of patients (6 pts with ≥Gr 3Pitis, 4 rib fractures)



Several articles published now on Constraints on chest wall
Andolino 2010,Bongers 2011,Petterson 2009, Nambu 2013, Spring Kong RTOG atlas

Systematic review

Outcomes of stereotactic ablative radiotherapy for central lung tumours: A systematic review

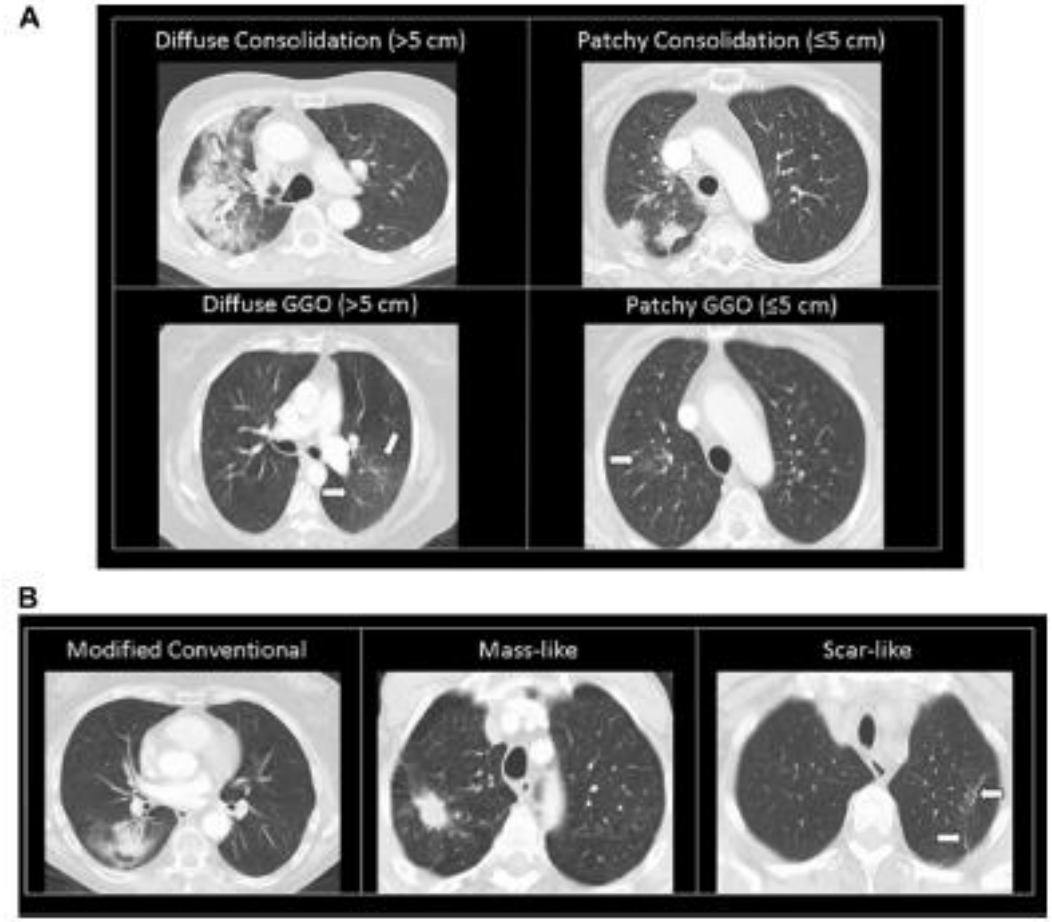
Sashendra Senthi *, Cornelis J.A. Haasbeek, Ben J. Slotman, Suresh Senan

- **315/563 patients with central T had early-stage NSCLC.**
- **Heterogeneity in the planning and dose prescription**
- **Local control rates = 85% if prescribed BED ≥100 Gy.**
- **Treatment-related mortality = 2.7%**
- **Grade 3 or 4 toxicities more frequent, but in less than 9% of patients.**
- **Conclusions: SABR achieves high local control with limited toxicity when appropriate fractionation schedules are used for central tumours**
- **EORTC trial has started : Lung TECH**

Senthi Rad & Onc 2013

Challenge: Is it local recurrence or radiation induced lung injury??

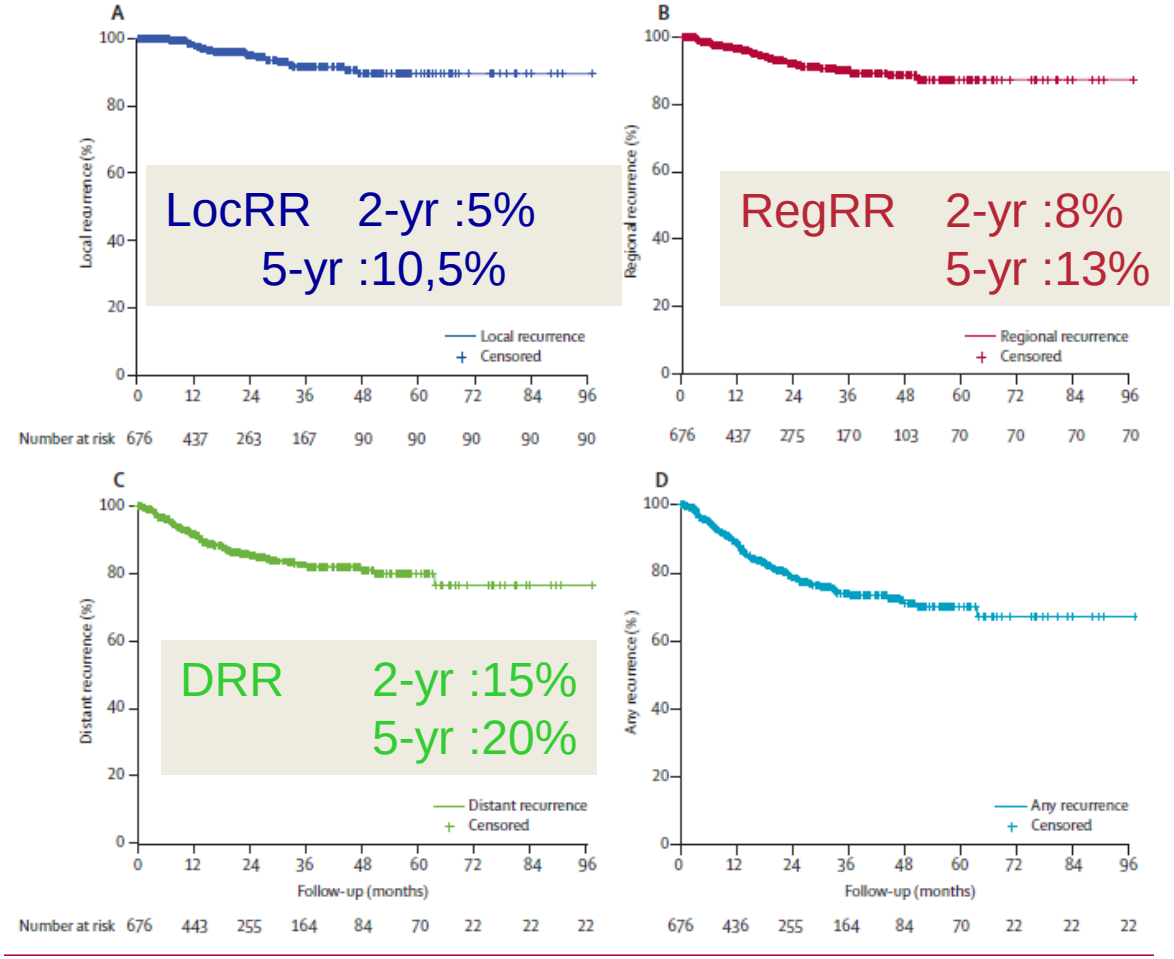
- On-going studies
- Importance of early detection so as to discuss salvage surgery (in operable pts)
- PET may help SUV max >5



Dahele 2011; Mattonen 2013

Patterns of recurrence after SABR: VU experience

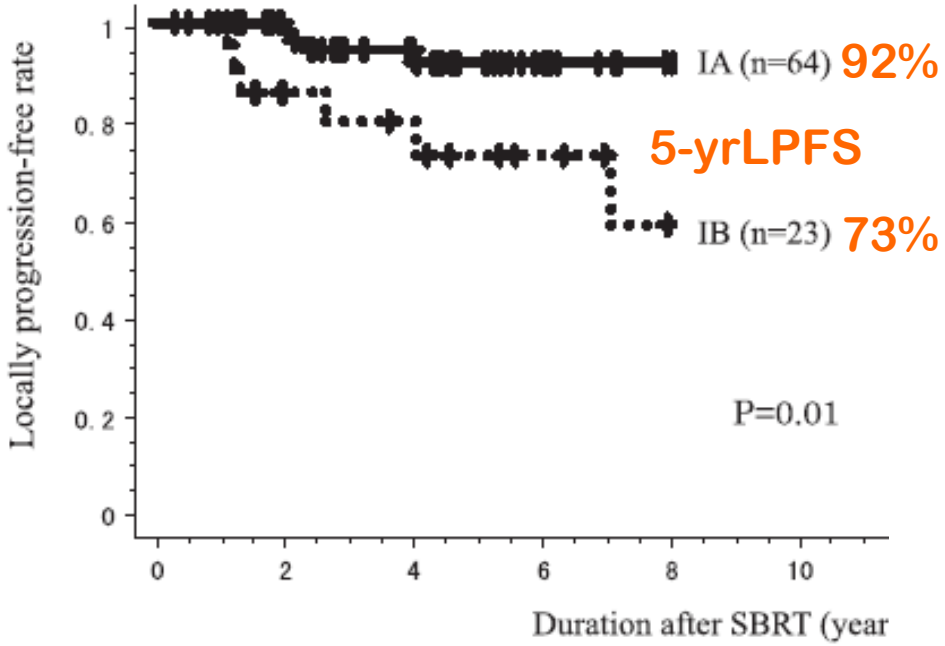
Actuarial rates at 2 and 5 years



- 676 pts 2003-2011
- Median FU:33 mo
- Median time to LR: 14·9 months
- Median time to RR : 13·1 months
- Median time to DR: 9·6 months
- 2nd primaries: 6%

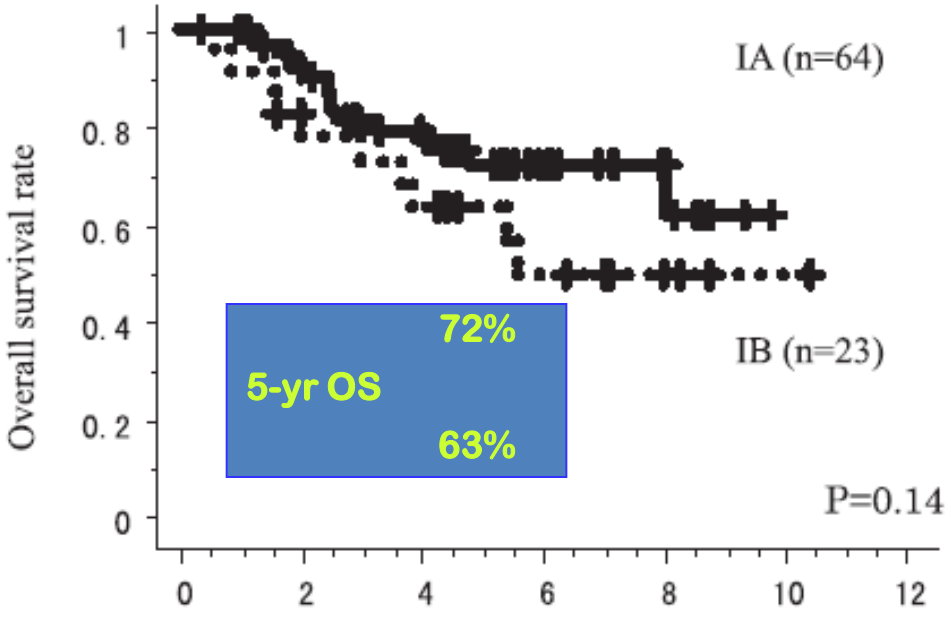
Senthi et al, Lancet Oncol 2012

Results in operable patients according to T size



Rate of

- Local recurrences 9%
- Nodal recurrences 15%
- Distant recurrences 22%



Onishi et al 2010

CLINICAL INVESTIGATION

STEREOTACTIC BODY RADIOTHERAPY (SBRT) FOR OPERABLE STAGE I NON–SMALL-CELL LUNG CANCER: CAN SBRT BE COMPARABLE TO SURGERY?

Hiroshi Onishi, M.D.,* Hiroki Shirato, M.D.,† Yasushi Nagata, M.D.,‡ Masahiro Hiraoka, M.D.,§ Masaharu Fujino, M.D.,†* Kotaro Gomi, M.D.,‖ Katsuyuki Karasawa, M.D.,¶ Kazushige Hayakawa, M.D.,# Yuzuru Niibe, M.D.,# Yoshihiro Takai, M.D.,** Tomoki Kimura, M.D.,†† Atsuya Takeda, M.D.,‡‡ Atsushi Ouchi, M.D.,§§ Masato Hareyama, M.D.,‖‖ Masaki Kokubo, M.D.,¶¶ Takuyo Kozuka, M.D.,## Takuro Arimoto, M.D.,*** Ryusuke Hara, M.D.,††† Jun Itami, M.D.,‡‡‡ and Tsutomu Araki, M.D.*

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Outcomes After Stereotactic Lung Radiotherapy or Wedge Resection for Stage I Non–Small-Cell Lung Cancer

Inga S. Grills, Victor S. Mangona, Robert Welsh, Gary Chmielewski, Erika McInerney, Shannon Martin, Jennifer Wloch, Hong Ye, and Larry L. Kestin

Onishi IJROBP 2010, Grills JCO 2010

Comparison SRT-Surgery

Systematic review

Stereotactic radiotherapy (SABR) for the treatment of primary non-small cell lung cancer; Systematic review and comparison with a surgical cohort

Francesca Soldà [a], Mark Lodge [b], Sue Ashley [c], Alastair Whitington [d], Peter Goldstraw [e], Michael Brada [f,*]

[a] Harley Street at University College Hospital, London, UK; [b] INCTR UK, Oxford, UK; [c] Keswick, Cumbria, UK; [d] SE London Cancer Network, Guy's Hospital, London, UK; [e] Academic Department of Thoracic Surgery, Royal Brompton Hospital, London, UK; [f] Leaders in Oncology Care, London, UK

- **3201 patients stage I NSCLC treated with SABR**
  - > 2-yr OS was 70% (95% CI: 67–72%)
  - > 2 yr local control = 91% (95% CI: 90–93%).
  - > No survival or local PFS difference with different RT technologies used for SABR
- **2038 stage I patients treated with surgery**
  - > 2yr-OS 68% (95% CI: 66–70)

Solda et al, Rad & Onc 2013

SABR in operable patients?

Attempts of randomized trials have failed (ROSEL, STARS, ACOSOG/RTOG)

Several projects planned to meet this challenge…

Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials

Joe Y Chang, Suresh Senan*, Marinus A Paul, Reza J Mehran, Alexander V Louie, Peter Balter, Harry J M Groen, Stephen E McRae, Joachim Widder, Lei Feng, Ben E E M van den Borne, Mark F Munsell, Coen Hurkmans, Donald A Berry, Erik van Werkhoven, John J Kresl, Anne-Marie Dingemans, Omar Dawood, Cornelis J A Haasbeek, Larry S Carpenter, Katrien De Jaeger, Ritsuko Komaki, Ben J Slotman, Egbert F Smit†, Jack A Roth†*

Chang et al, Lancet Oncol 2015

SABR vs lobectomy in pooled analysis of 2 ra

	Surgery 27 pts	SABR 31 pts
3 yr-OS	79%	95%
3 yr RFS	80% 1RR,2 DM	86% 1 LR,4 RR,2
Gr3/4 AE Gr 5 AE	44% 15% dyspnea 15% Chest pain 7% lung infect 1 death	10% (all gr3) 10% Chest pa 6% dyspnea, 3%rib fracture 0
Median FU	35,4	40,2

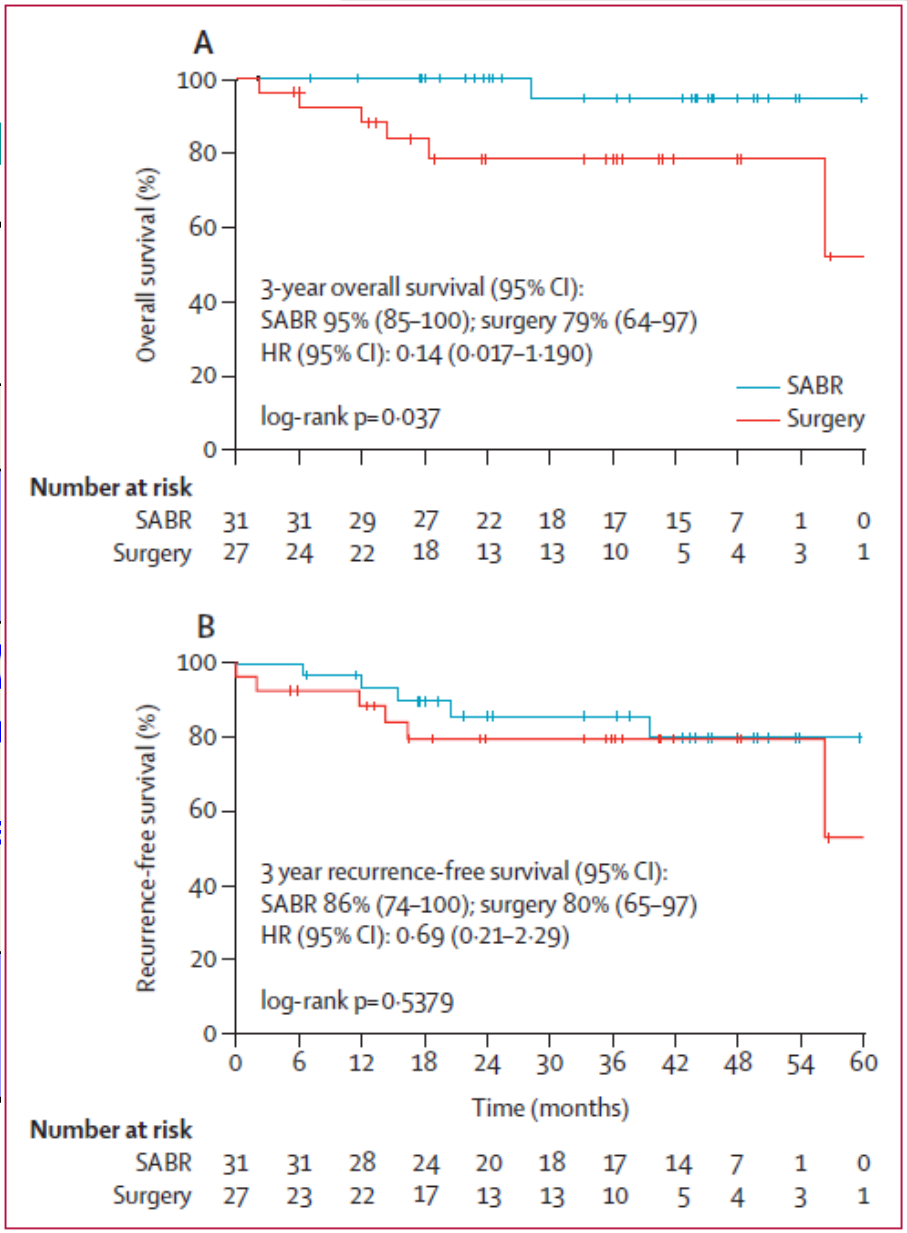


Figure 2: Overall survival (A) and recurrence-free survival (B)

Chang et al, Lancet Oncol 2015

Screening programs

- Prevalence of lung cancer= 1 to 2.8%
- % stage I = 54 to 85%
- 20.0% decreased mortality from LC in the low-dose CT group / Rx group.
- Screening for breast and prostate cancers may result in unnecessary treatment
- In Stage I tumors , ~ 40% of patients will die of lung cancer and benefit from radical treatment

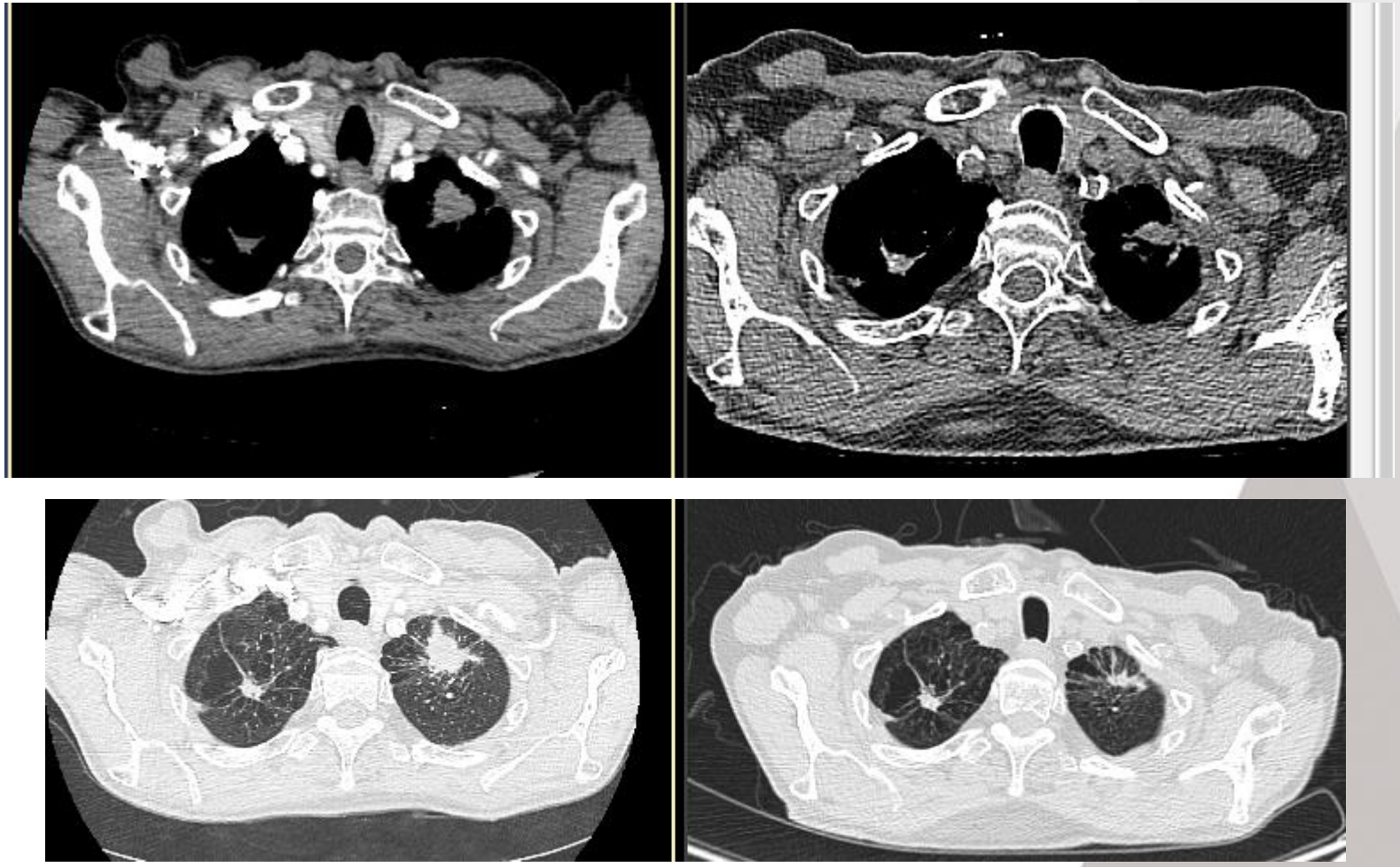
National Lung Screening Trial, NEJM 2011 2013;
Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial JAMA 2011,

Palma 2010; Varlotto 2014

Future for RT in early NSCLC

- **Need to pursue prospective studies**
- **Individualized RT treatment according to molecular profile and radiosensitivity profile**
- **As pts undergoing SRT may be more fit in the future:**
  - More extensive mediastinal and hilar work-up
  - Importance of long term follow-up
  - Role of adjuvant treatments in operable pts and combination of immunotherapy?

M F, severe BPCO, inoperable, with SCC of ULL T1b N0 M0. treated with SABR : 60 Gy (8 x 7,5 Gy) because of proximity to brachial plexus in June 2012.

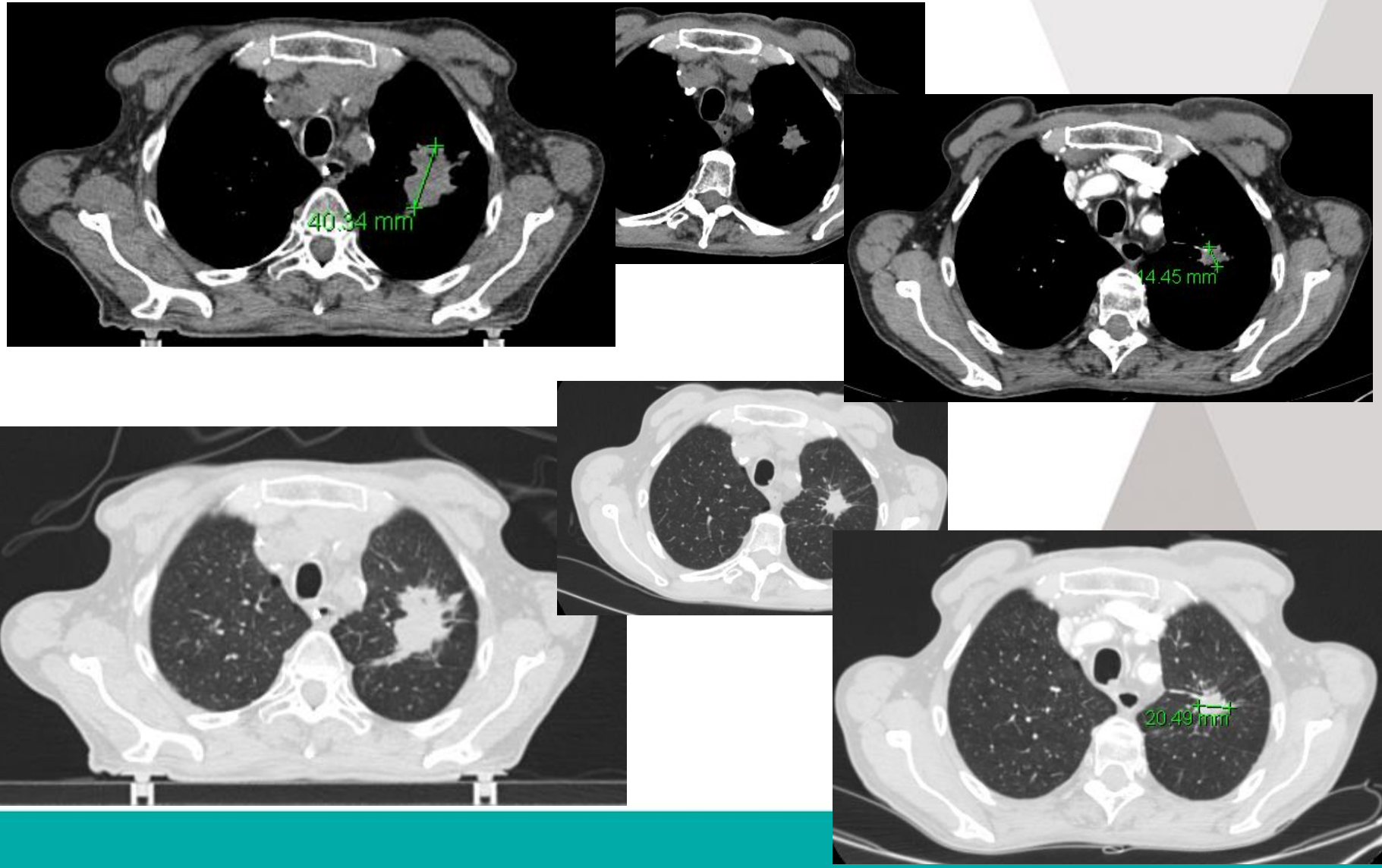


TDM Juin 2012

PET scan 08/2013: metabolic CR January 2015

M GM, SCC T2aN0M0 en July 2013 60 Gy en 5 fr of 12 Gy

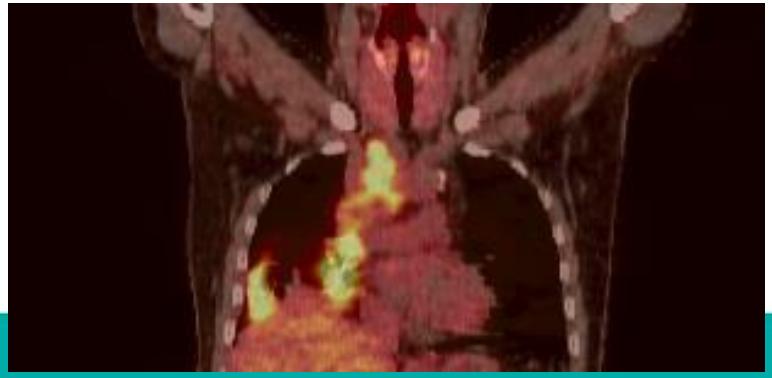
LC with mass-like residual image

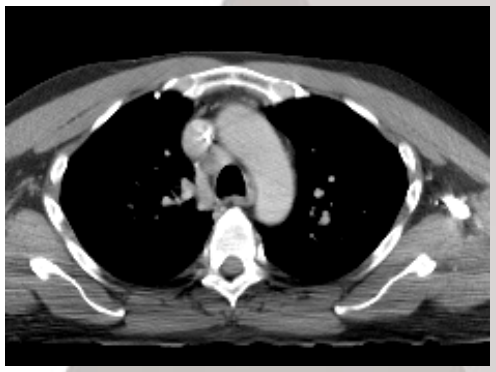


Stage III : importance of pluridisciplinary approach.

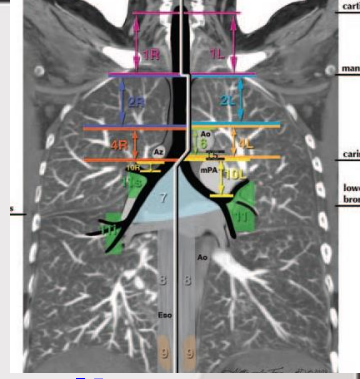
- **Very heterogenous population**
- **Several treatment available options in 2015**
  - TNM importance of nodal involvement
  - Age, PS and Co-morbidities

Importance of
PET-CT and brain imaging





Stage III A and selected III B



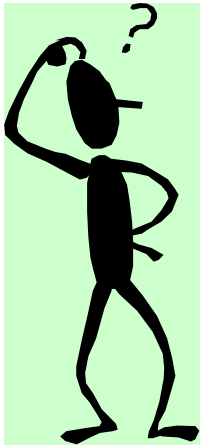
5-year survival : 20-25% [5-45%]

- **Treatment should be decided within a multidisplinary team UPFRONT**
  - > Surgery? RT? Both? Tri-modality or Bi-modality? timing of CT?)
- **High risk of recurrence (metastatic and local)**

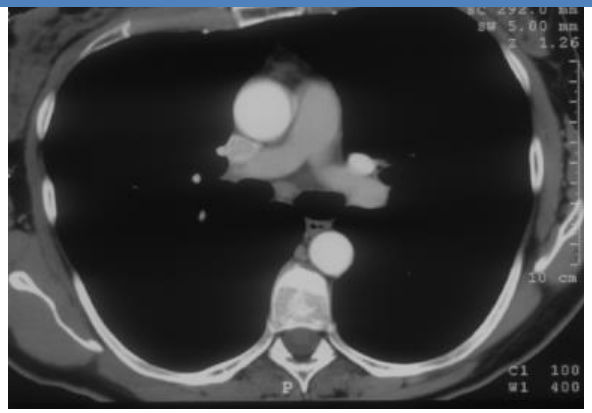
  Distant failure: 30 to 50% Brain 20 to 32%
- **Local Failure Rate at 3 years**
  - > In surgical series (15% to 60%)
  - > CTRT: Loco-regional progression rate<30%

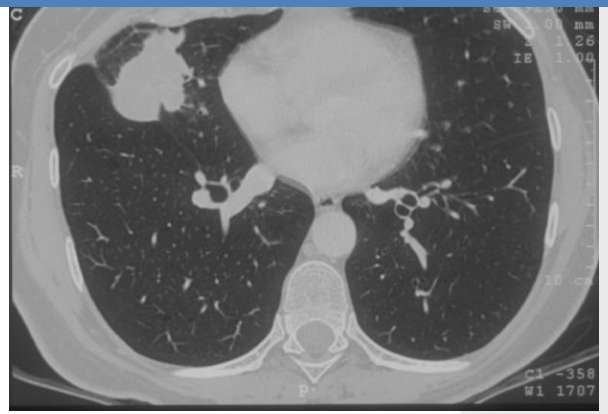
Douillard et al, 2006 and 2008; Andre 2001; Keller 2000; Machtay 2001; Rusch 2009 Betticher 2006; Scotti 2010; Moretti 2009; Matsugama 2011; Dai 2011; Taylor 2003; Le Pechoux Review on PORT 2013; Auperin 2010

Surgery the standard in early stage NSCLC!!

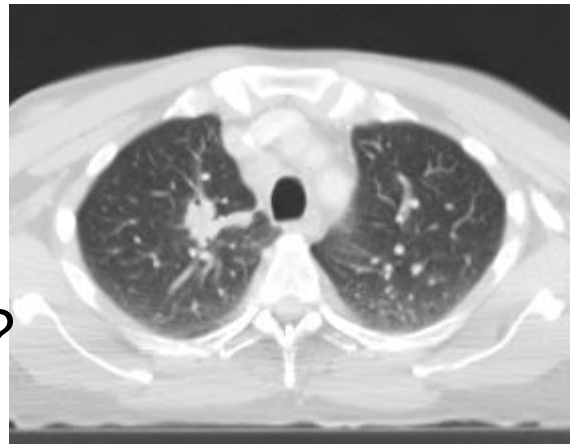


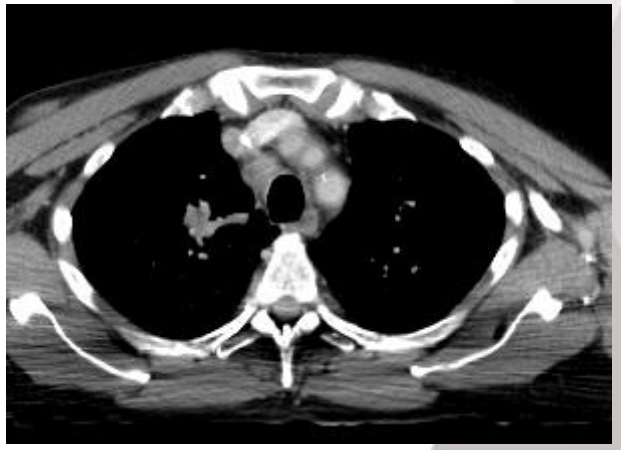
But for st III ?





Adenocarcinoma cT2N2 (médiastino+)

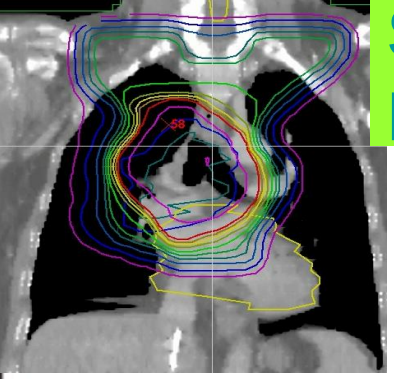




Large Cell Carcinoma cT2N2 (médiastino+)

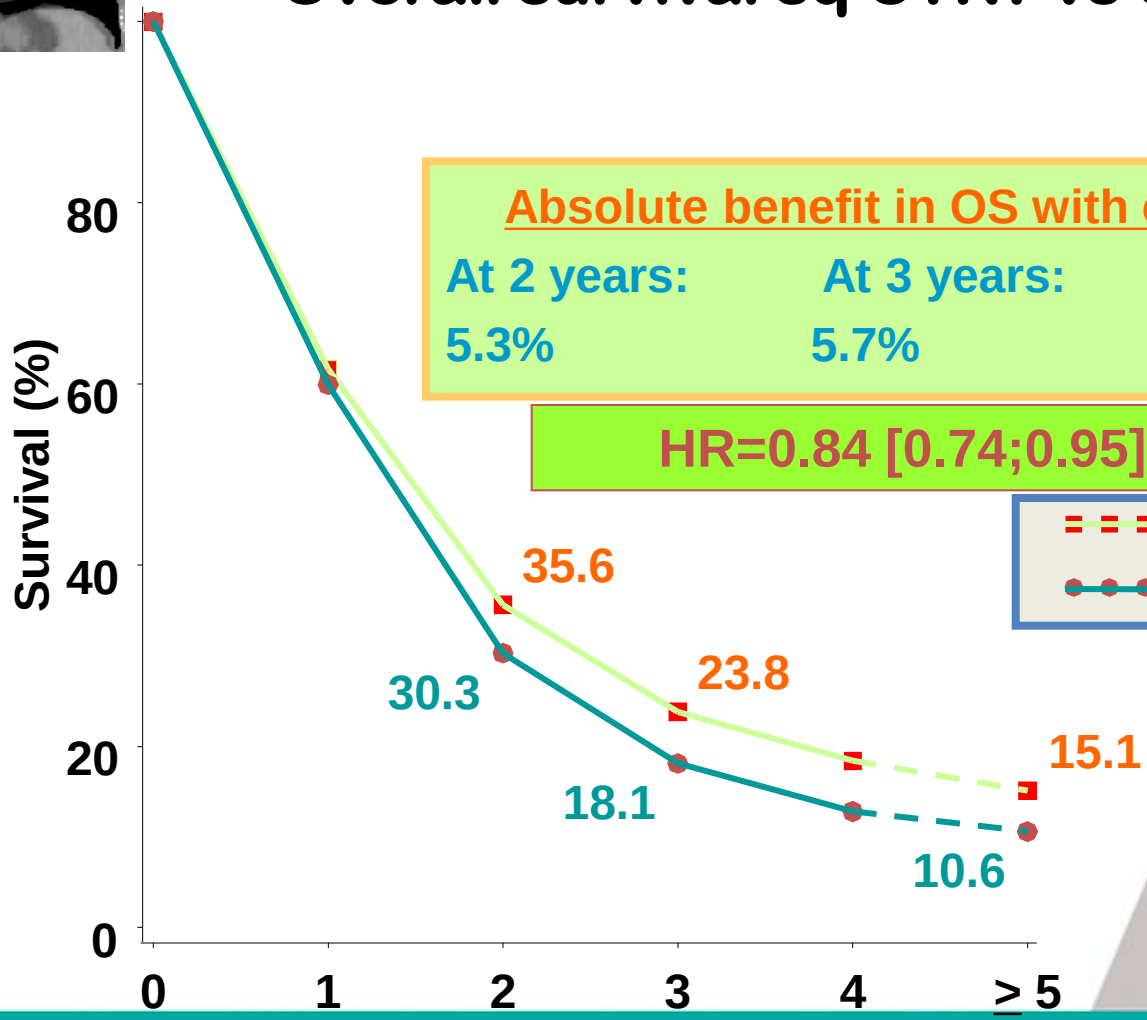
Local Treatment: Surgery or/and RT

CT Yes pre-op or post-op!



Standard of care in stage III inoperable NSCLC before 2010 : combined CTRT

Overall survival sq CTRT vs cc CTRT



Absolute benefit in OS with concomitant CT:

At 2 years:	At 3 years:	At 5 years:
5.3%	5.7%	4.5%

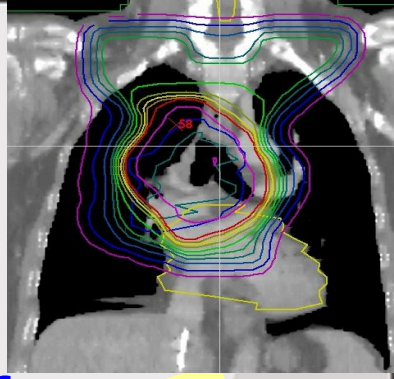
HR=0.84 [0.74;0.95], p=0.004

RT + conc CT

RT + seq CT

Aupérin et al, JCO 2010

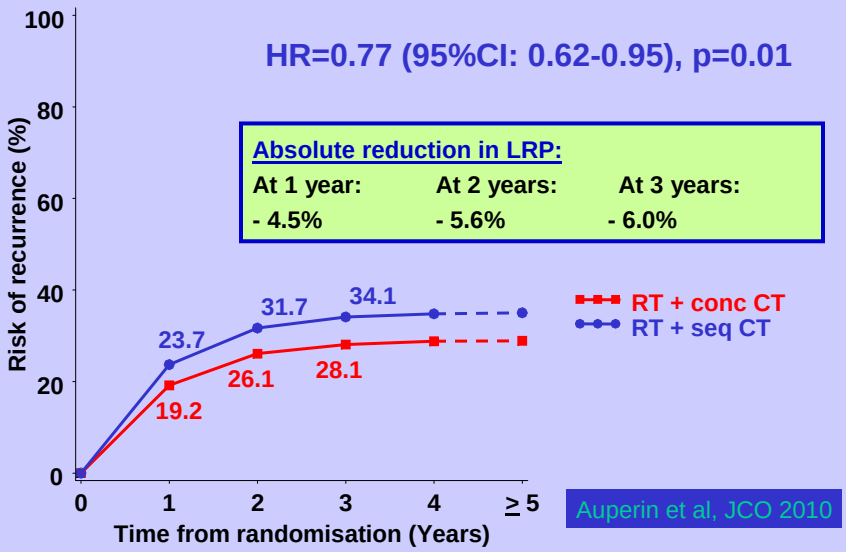
Standard of care in stage III inoperable NSCLC in 2013



- Concomitant chemoradiation : standard of ca
- Decreased loco-regional progressi
- Most studies 2D R
- Dose : 5
  2
- L cal Progression Free survival at 3 years 70%

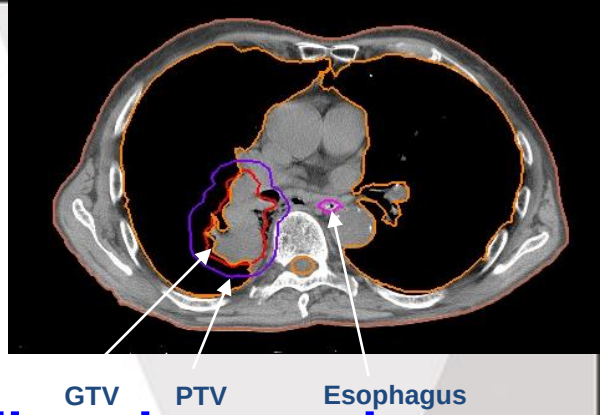
So place for improvement!!

umulative incidence of oco-regional progression (5 trials)



Auperin et al, JCO 2010

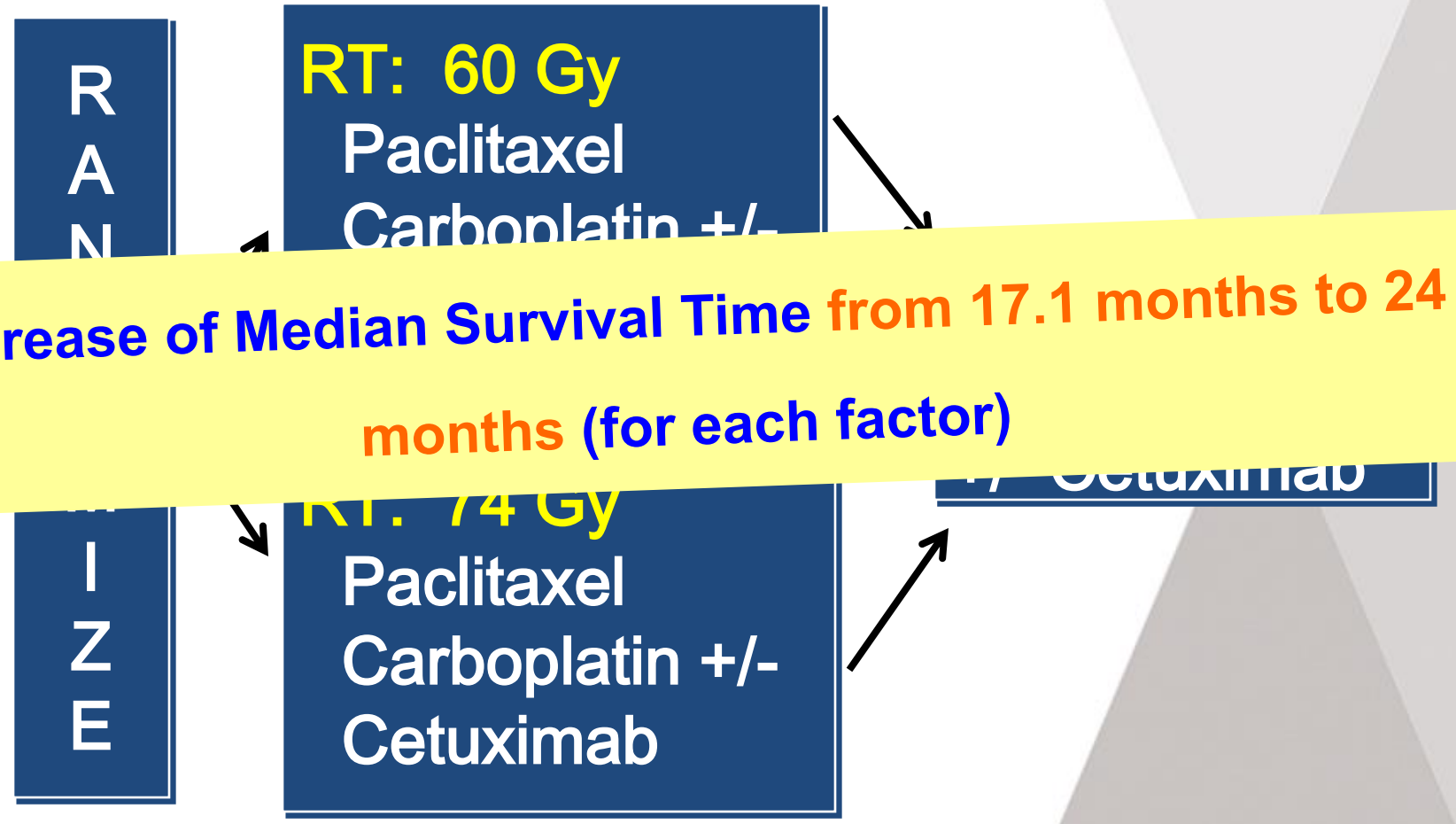
Conformal RT and Stage III NSCLC



- Local control is a challenge in locally advanced NSCLC
- How to improve results?
  - Dose escalation, Altered fractionation
  - More precise RT (optimized treatment planning: PET-CT based, 4D CT planning, IGRT)
  - Combination of targeted agents to CTRT ?
  - New CT regimen combined with RT
  - Surgery after neoadjuvant CTRT

Dose escalatation, altered fractionation

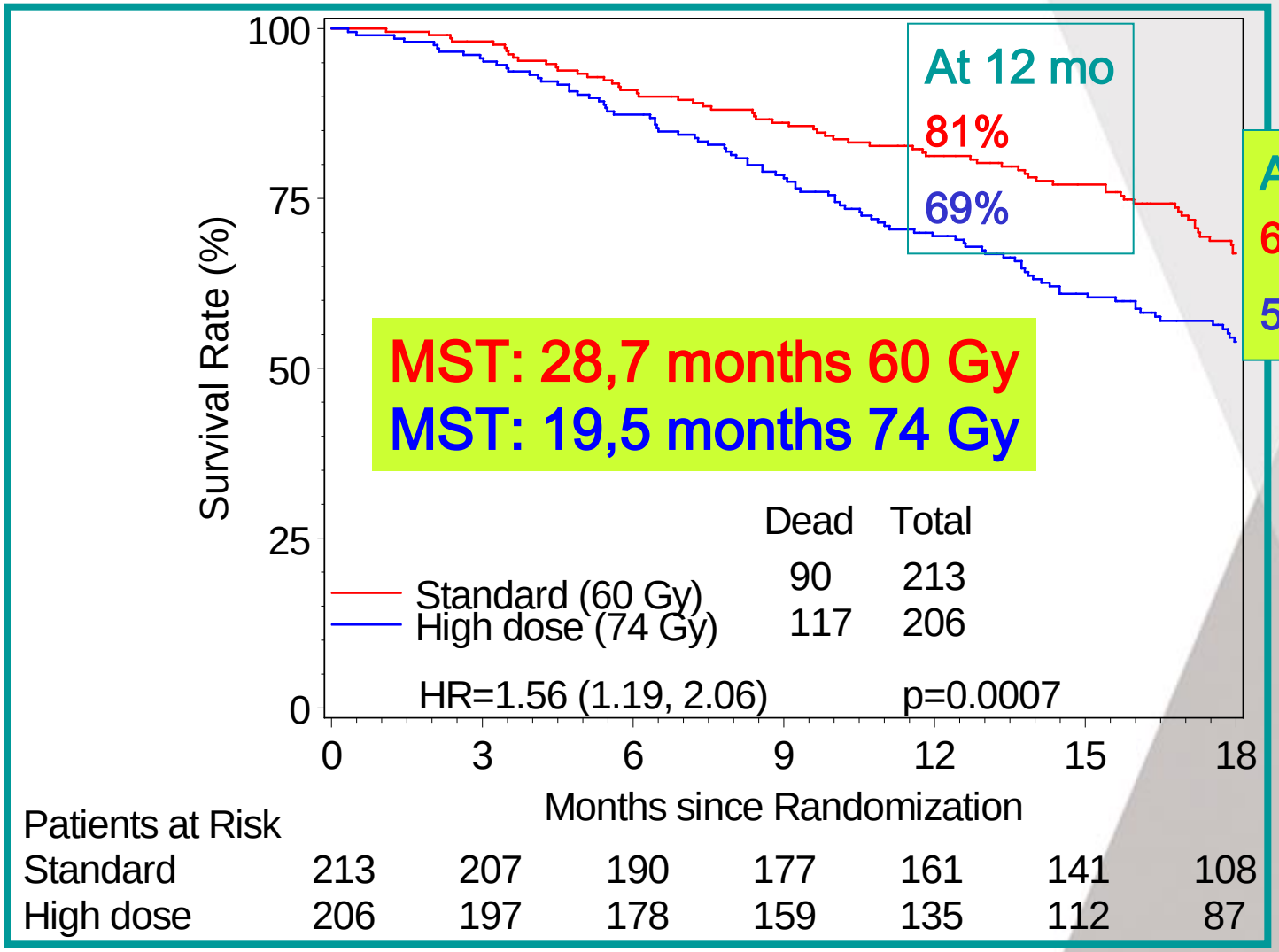
RTOG 0617, NCCTG N0628,CALGB 30609
Conventional vs. High Dose RT



Increase of Median Survival Time from 17.1 months to 24 months (for each factor)

- **Primary objective: To compare the overall survival of patients treated with high-dose versus standard-dose conformal RT with concurrent CT.**

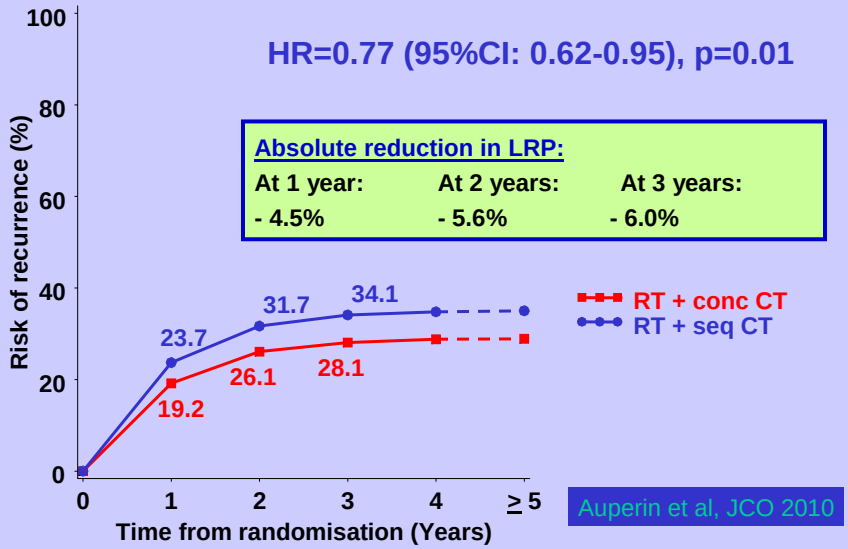
RTOG 0617: Overall Survival



RTOG 9410 CON-QD 1yr survival = 62.1%, MST = 17.0 months

Bradley, ASCO 2013, Lancet Oncol 2015

Cumulative incidence of loco-regional progression (5 trials)



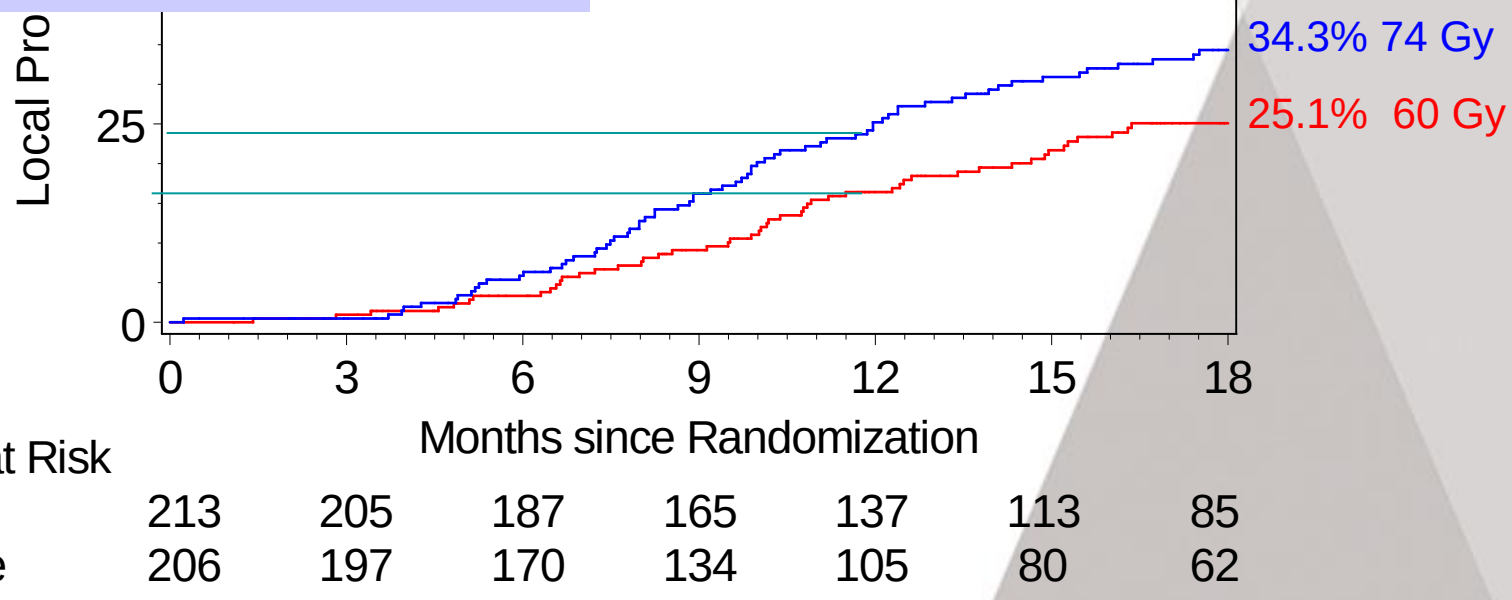
Auperin et al, JCO 2010

0617

	Fail	Total
	65	213
y)	81	206

1.89) p=0.0319

18-Month Local Progression Rate



Patients at Risk							
Standard	213	205	187	165	137	113	85
High dose	206	197	170	134	105	80	62

Bradley, ASCO 2013, Lancet Oncol 2015

Conclusions RTOG 0617

- **The high dose arm experienced higher local failure rates.**
- **Several possible explanations for the poorer survival on the high dose arms.**
  - more treatment-related deaths in the high-dose chemoradiotherapy and cetuximab groups (74 Gy vs 60 Gy: 8 vs 3 pts; cetuximab comparison: 10 vs 5 pts)
  - Confoundicg factors: Cetuximab
  - increased heart dose
  - extended therapy duration
  - combination of these factors

OS and patterns of failure RTOG 0617

	60 Gy (n=217)*	74 Gy (n=207)	Cetuximab (n=237)*	No cetuximab (n=228)
Local failure				
Fail	77	86	95	77
1 year	16·3% (11·4–21·3)	24·8% (18·9–30·7)	22·2% (16·8–27·5)	17·6% (12·6–22·7)
2 year	30·7% (24·5–36·9)	38·6% (31·9–45·3)	38·2% (31·9–44·5)	30·7% (24·6–36·9)
HR	1·26 (0·93–1·71)	..	0·82 (0·61–1·11)	..
p value (Gray, two-sided)	0·13	..	0·20	..
Distant metastasis				
Fail	106	107	124	98
1 year	32·2% (25·9–38·5)	35·1% (28·5–41·6)	35·0% (28·9–41·2)	29·8% (23·8–35·9)
2 year	46·6% (39·9–53·4)	51·0% (44·1–57·9)	52·6% (46·0–59·1)	42·0% (35·4–48·6)
HR	1·10 (0·84–1·43)	..	0·80 (0·61–1·04)	..
p value (Gray, two-sided)	0·48	..	0·09	..

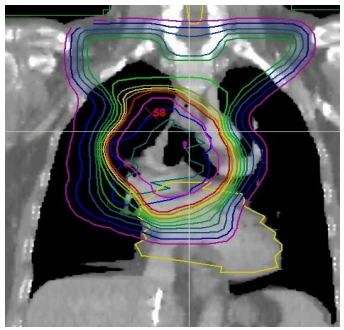
Jeff Bradley-Lancet Oncology 2015

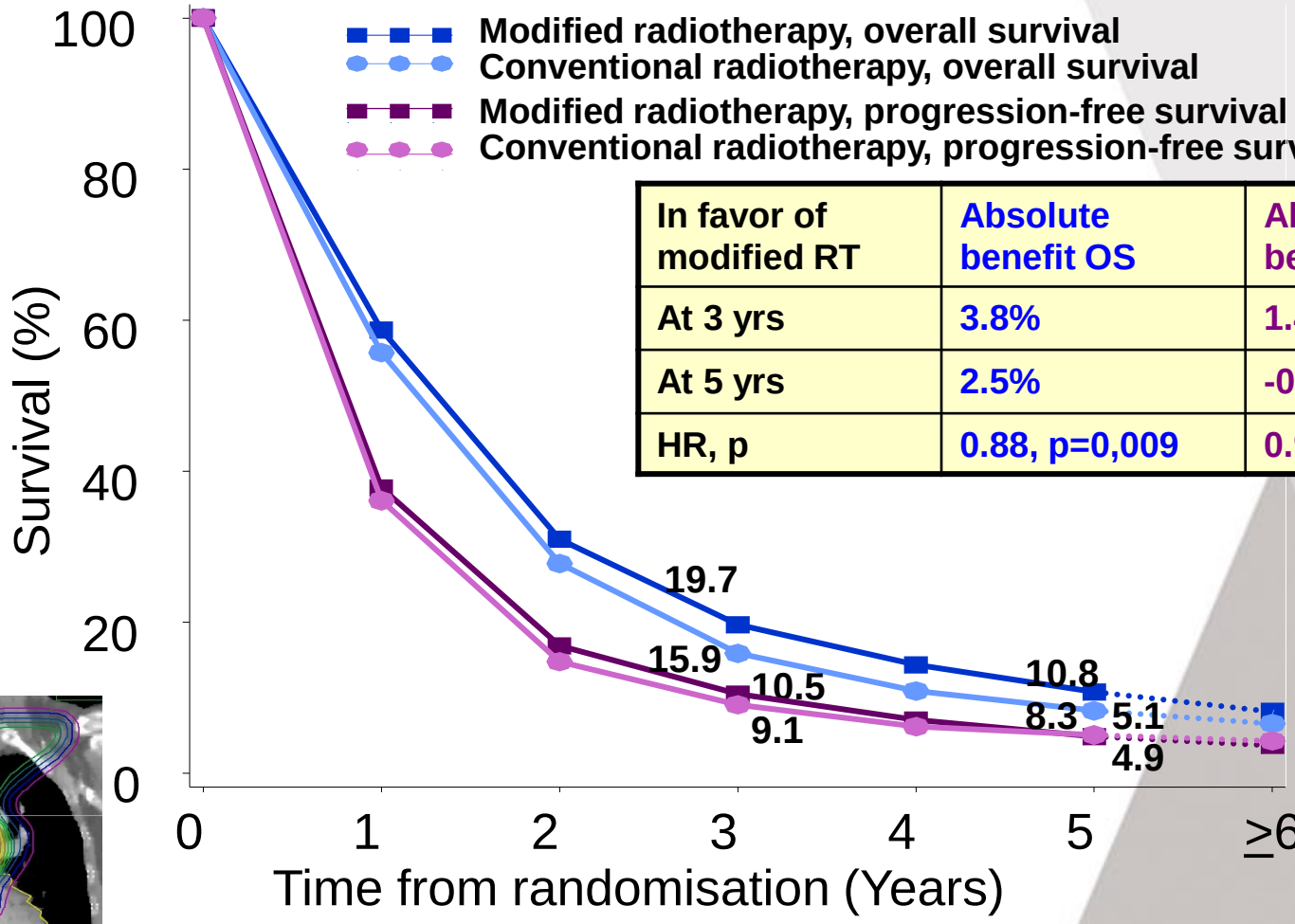
Dose intensification: accelerated and/or hyperfractionated RT

- Accelerated repopulation of tumour stem cells,21-28 days after the start of radiation treatment → radiobiological rationale for accelerated treatments
- Acceleration of RT leading to reduced Overall Treatment Time (<2 wks-5 wks) compared to 6 wks could lead to improved local control ???
- Hyperfractionated RT can reduce long-term normal-tissue morbidity

Withers et al, 1988; Maciejewski et al,1989; Fowler et al, 1991;Saunders 1997; Baumann et al, 2008

Overall and Progression-Free Survival 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

Mauguen et al, JCO 2011

Have we reached the limit with altered fractionation

- Modified fractionation radiotherapy significantly improves overall survival in NSCLC
- If BED ≥ 55 , $\Rightarrow$ Absolute benefit of 5.1% at 3 yrs //3.4% at 5 yrs
- 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!

Mauguen et al, JCO 2011

Better Conformal Radiotherapy

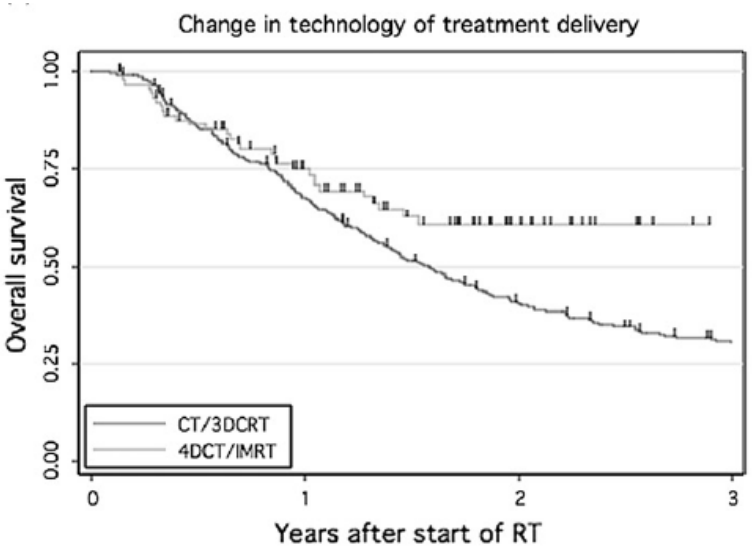
- **Technical refinements such as intensity modulated radiotherapy (IMRT) may further decrease**
  - incidence and severity of side effects
  - allow increased individualised radiotherapy doses

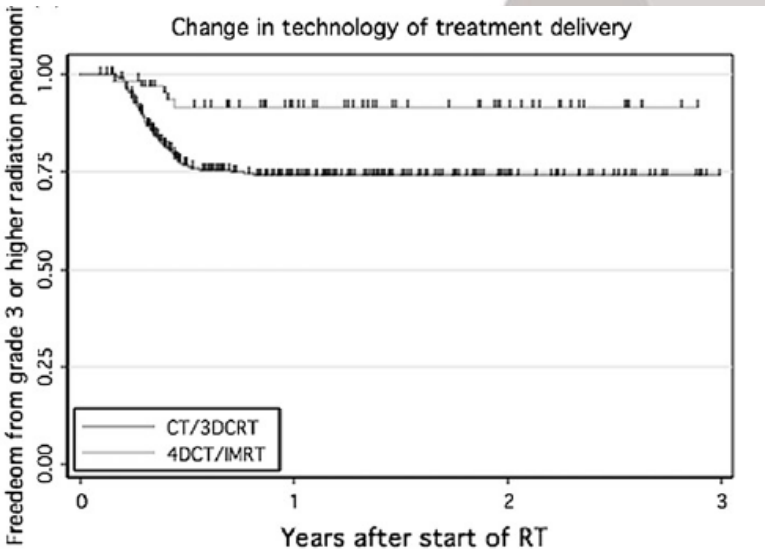
INFLUENCE OF TECHNOLOGIC ADVANCES ON OUTCOMES IN PATIENTS WITH UNRESECTABLE, LOCALLY ADVANCED NON–SMALL-CELL LUNG CANCER RECEIVING CONCOMITANT CHEMORADIOTHERAPY

IJROBP 2010

ZHONGXING X. LIAO, M.D.,* RITSUKO R. KOMAKI, M.D.,* HOWARD D. THAMES, JR., PH.D.,§ HELEN H. LIU, PH.D.,† SUSAN L. TUCKER, PH.D.,‡ RADHE MOHAN, PH.D.,† MARY K. MARTEL, PH.D.,† XIONG WEI, M.D.,* KUNYU YANG, M.D.,* EDWARD S. KIM, M.D.,‖ GEORGE BLUMENSCHEIN, M.D.,‖ WAUN KI HONG, M.D.,‖ AND JAMES D. COX, M.D.*

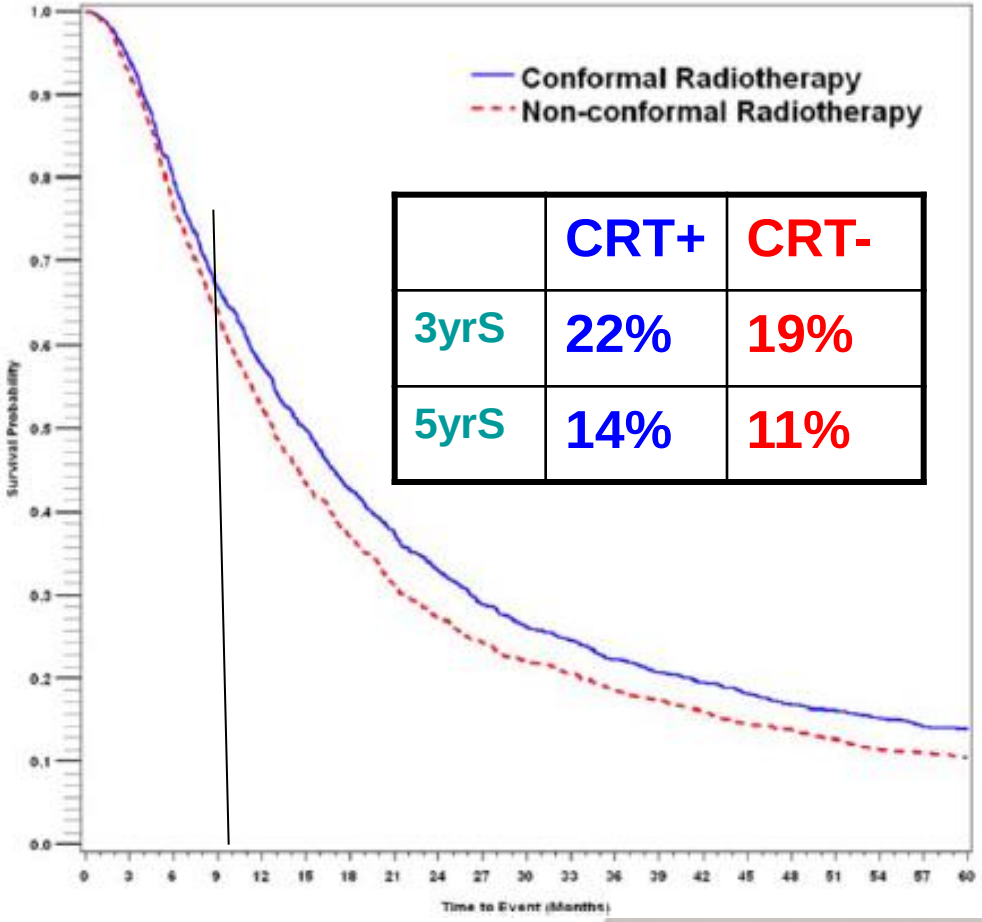
- **Historical comparison:318 pts treated with 3DRTC (49% had PET) vs 91 pts 4DCT planning and IMRT (82% had PET)**
- **Similar TD, similar CT regimen but difference of FU**





SEER data Base study: 3D RT or IMRT vs 2D RT (13292 pts treated 2003-2005)

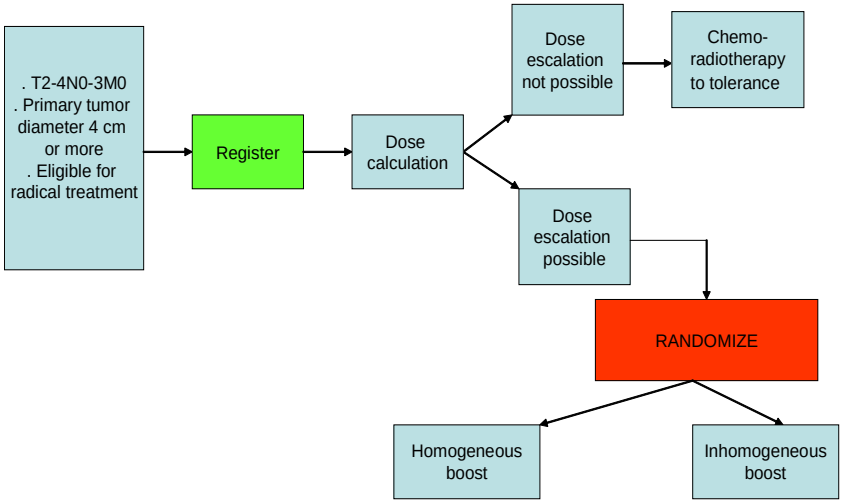
- Importance of loco-regional control in pts with stage III
- This encourages use of high tech RT in stage III LC

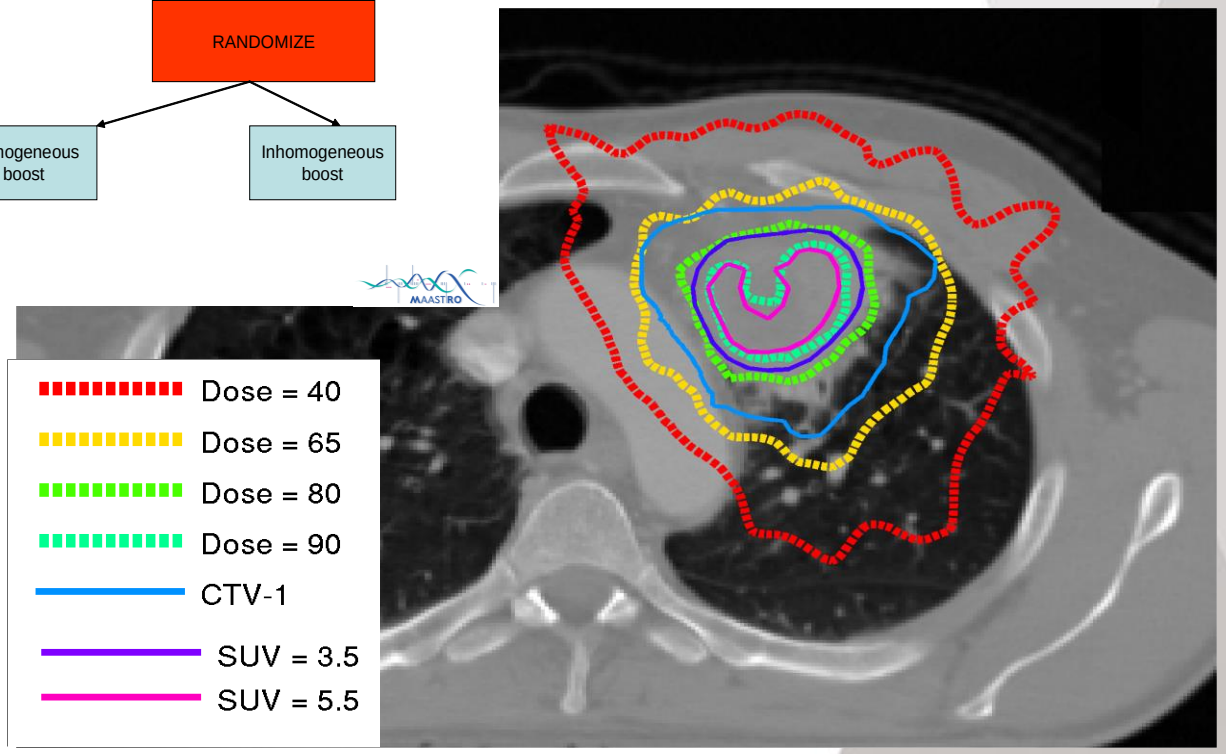


	CRT+	CRT-
3yrS	22%	19%
5yrS	14%	11%

Sher et al, Cancer 2014

Trial investigating the concept of individual radiation dose redistribution within the tumour based on FDG-PET uptake





Courtesy from JJ Sonke, D De Ruysscher et al

Platinum based CT (CDDP-VNB, CDDP-VP16, Carbo-Taxol) 2-4 cycles is the standard in combined CTRT

- **Why not add Targeted agents to CTRT?**

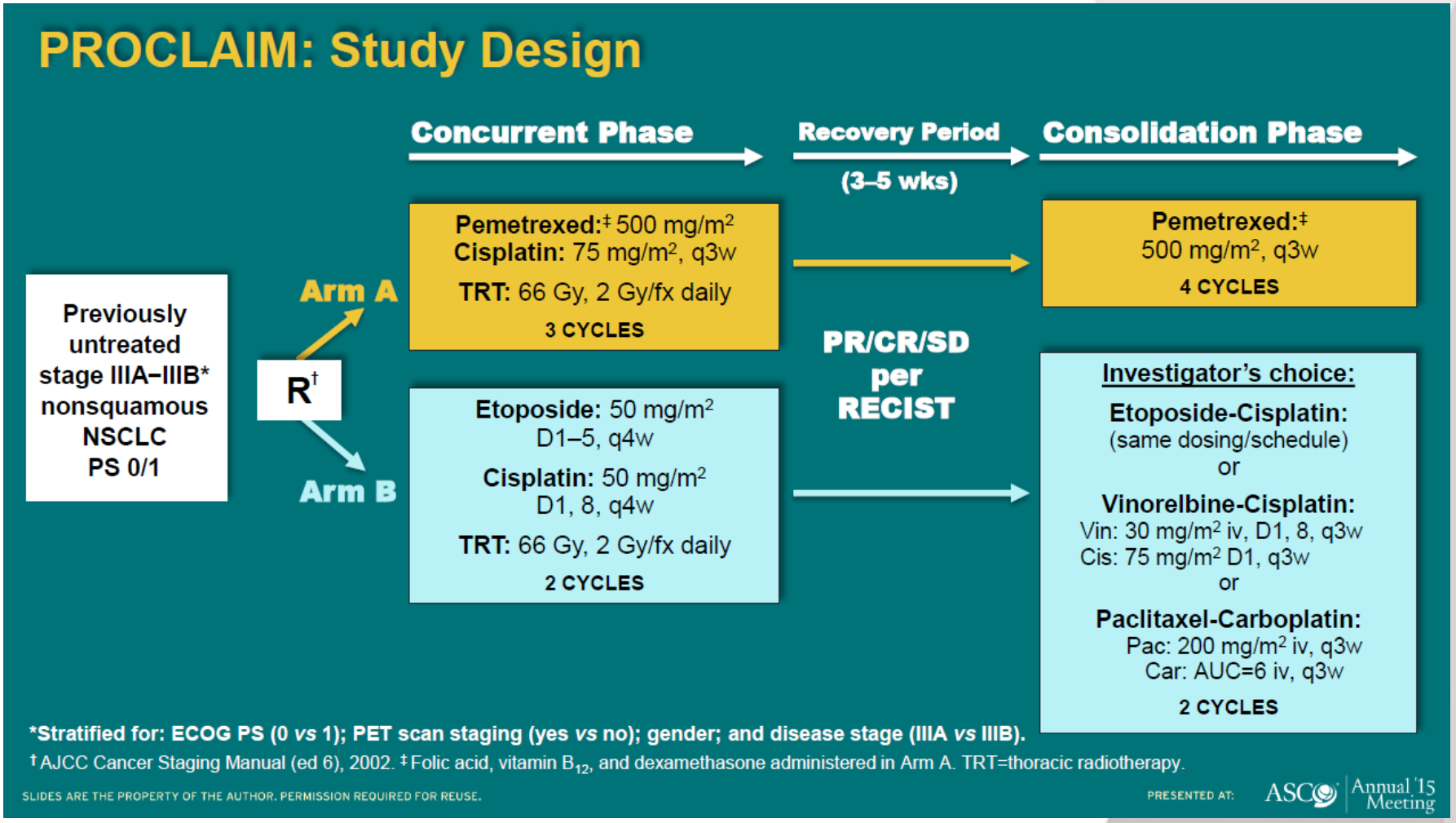
  No benefit in a non selected population (Kelly JCO 2008)

- **Role of consolidation or induction CT?**

  No role (Vokes JCO 2007, Hanna 2008)

- **New CDDP based regimen combined to RT such as Pemetrexed-CDDP**

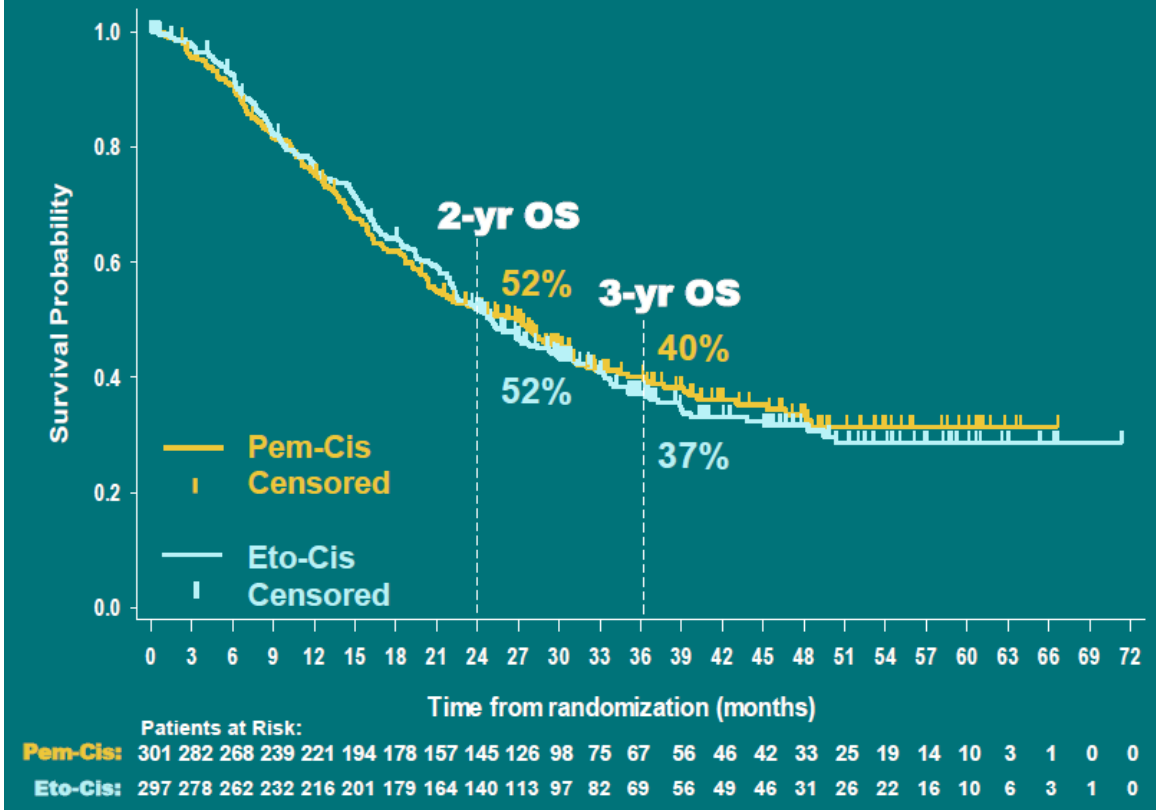
Better CT combined to 3DRT?



Courtesy of Pr Senan ASCO 2015

Randomized study PemCis based CTRT vs EP CTRT

PROCLAIM: Primary Endpoint, OS



HR (95% CI): 0.98 (0.79, 1.20)
Log-rank p=0.831
Median OS (95% CI), mos
Pem-Cis: 26.8 (20.4, 30.9)
Eto-Cis: 25.0 (22.2, 29.8)

Median follow-up times (mos [range])
- All patients: Pem-Cis, 22.2 (0.1–66.6)
  Eto-Cis, 22.6 (0.0–71.4)
- Patients alive: Pem-Cis, 32.9 (0.1–66.6)
  Eto-Cis, 35.7 (0.0–71.4)

Total events: 357
- Pem-Cis: 177 events/301 patients
- Eto-Cis: 180 events/297 patients

PRESENTED AT: ASCO Annual '15 Meeting

Courtesy of Pr Senan ASCO 2015

Randomized study PemCis based CTRT vs EP CTRT

PROCLAIM: Conclusions

- **The trial did not demonstrate superiority in OS, in keeping with early stopping of enrollment for futility:**
  - HR (95% CI) = 0.98 (0.79, 1.20); p=0.831
    Median 26.8 months (Pem-Cis) *vs* 25.0 months (Eto-Cis)
- **PFS trended in favor of Pem-Cis, although it did not reach statistical significance:**
  - HR (95% CI) = 0.86 (0.71, 1.04); p=0.130
    Median 11.4 months (Pem-Cis) *vs* 9.8 months (Eto-Cis)
- **The Pem-Cis arm had a significantly lower incidence of drug-related grade 3–4 AEs (all events combined), including neutropenia, during the overall treatment period.**
- **Pem-Cis combined with radiotherapy followed by consolidation Pem showed an acceptable safety profile.**

- **CDDP-Pemetrexed may be an option in non-squamous NSCLC**

Courtesy of Pr Senan ASCO 2015

Need for additional systemic treatment

- **Targeted agents combined with CTRT? On-going studies in EGFR, ALK selected pop**
- **Other targeted agent difficult to associate!!**

More is not always better !

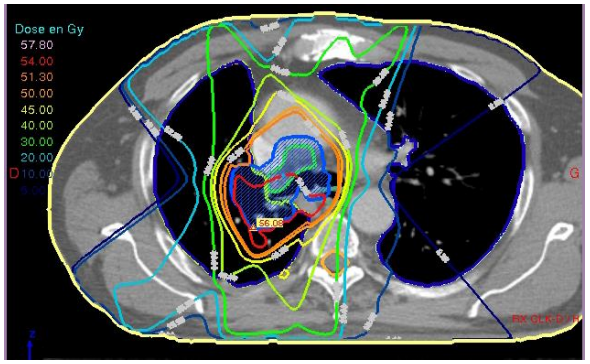
VOLUME 28 · NUMBER 1 · JANUARY 1 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Tracheoesophageal Fistula Formation in Patients With Lung Cancer Treated With Chemoradiation and Bevacizumab

David R. Spigel, John D. Hainsworth, Denise A. Yardley, Eric Raefsky, Jeffrey Patton, Nancy Peacock, Cindy Farley, Howard A. Burris III, and F. Anthony Greco



And what about approaches integrating surgery in stage III NSCLC ??

Adjuvant Radiotherapy in the post-operative setting

No recent phase III Trials evaluating PORT published

Randomized evidence regarding post-operative radiotherapy in 2015 ?

- *Post-Operative RadioTherapy Overview*
- **2232 pts in 10 randomized (added Trodella study including stage I pts)**

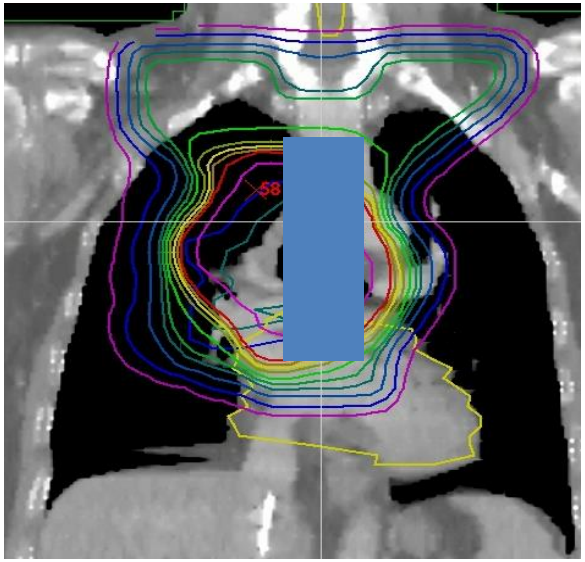
Surgery alone (1125 pts)

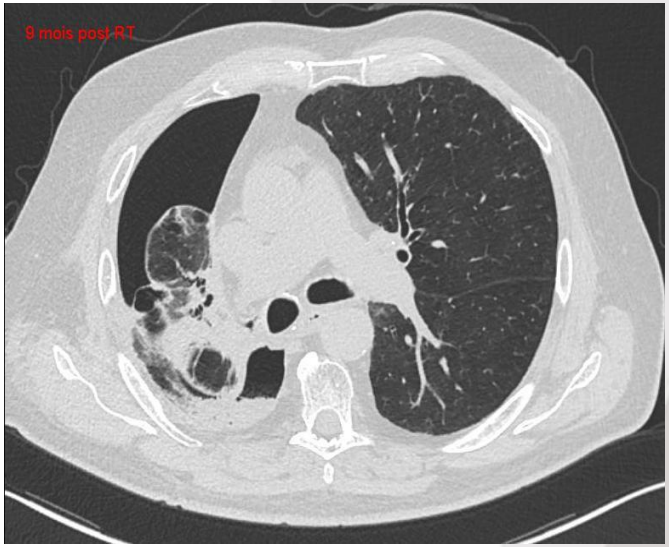
Surgery + PORT (1107 pts)

2-year Survival: 58%

2-year Survival: 52%

Burdett et al, Lung Cancer 2005, Cochrane Review





Any place for RT after complete resection?

NO according to MA and studies of MA

in pN0,N1(lower risk pts)

Overadded toxicity and/or poor LC:

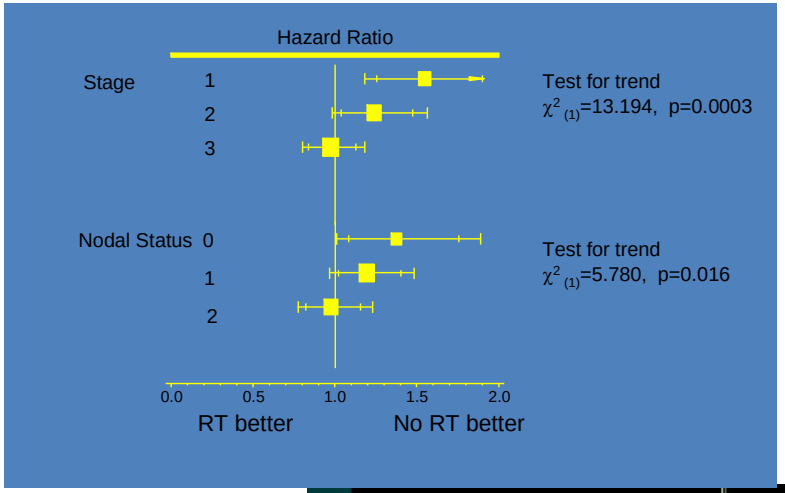
Dose > 54 Gy, Daily fraction >2 Gy

Large volume RT, no CT-based treatment planning

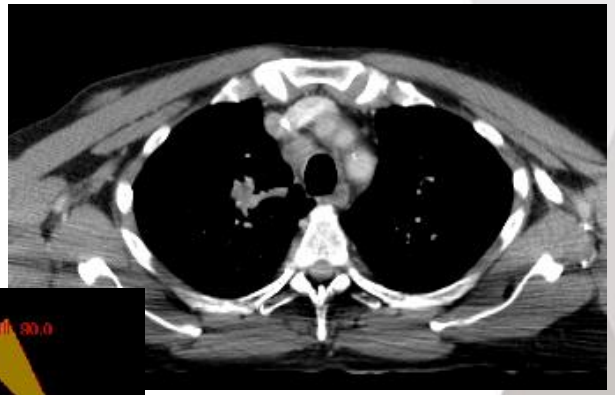
Old technique (Cobalt, spinal cord block)

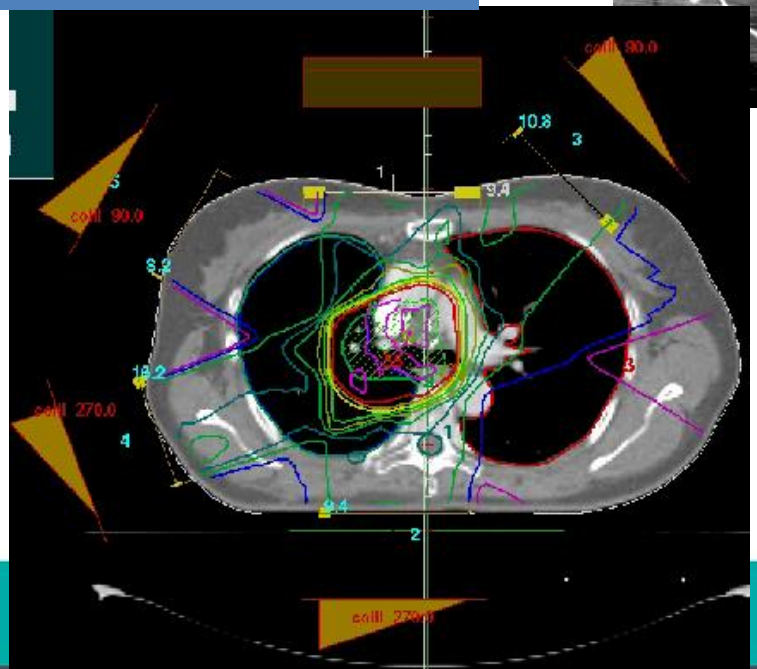
Contributing to OVERMORTALITY

Lessons learned from PORT Meta-analysis more personalised treatment



- **PORT in selected cases : N2**





More conformal RT

Post-operative adjuvant treatment after complete resection of NSCLC (St II or III)

R

RT (50.4 Gy / 28 fr +/- 10.8 Gy)

488 pts from 121 hosp

4 cycles CDDP -VP16 + RT cc (50.4 Gy)

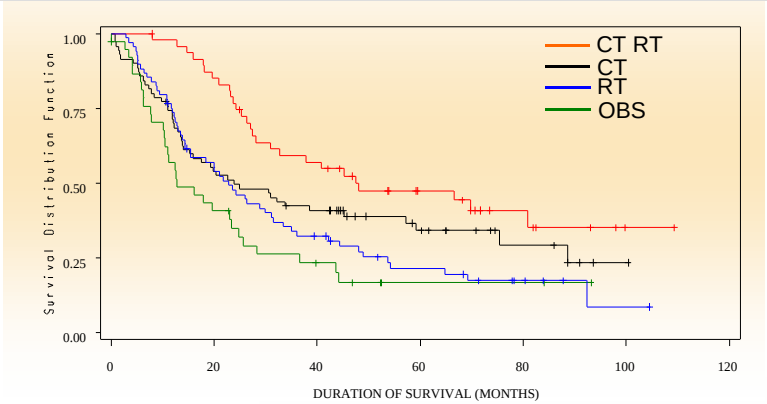
Results (median Follow-up 44 m)

	RT	
Intra-thoraX LR	**21%**	**24 % (Med TTLP 28m)**
[illegible]	**52 %**	**50 %**
[illegible]	**9 %**	**3 %**
[illegible]	**9 %**	**38 m**
In-Field LR	**13%**	**12%**

NOT in favour of adjuvant cc CTRT

Keller et al, NEJM 2000,343:1217

ANITA trial: Phase III Adjuvant Vinorelbine and Cisplatin versus Observation



- Subgroup analysis according to RT in favour of sequential CT and PORT
- One should always be cautious with such analyses

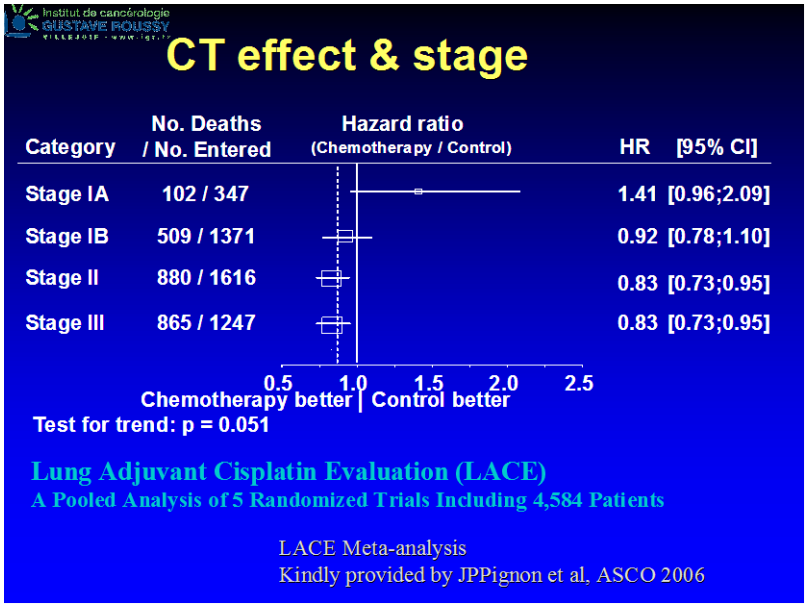
PORT in N2 Patients

N2	RADIOTHERAPY		NO RADIOTHERAPY	
N=224	No CT	IV VRL+CDDP	No CT	IV VRL+CDDP
Number of patients	68	48	38	70
MS, mos	22.7	47.4	12.7	23.8
1 year survival	73.5 %	97.9 %	56.8 %	71.2 %
2 year survival	47.6%	76.6%	34.8%	49.4 %
5 year survival	21.3%	47.4%	16.6%	34.0 %
% deaths	54 (79%)	28 (58 %)	30 (79%)	46 (66%)

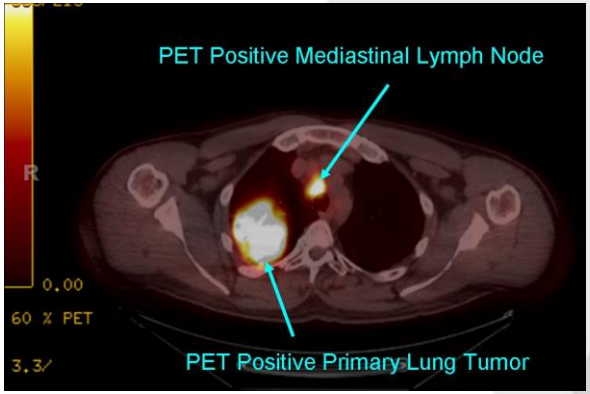
Douillard JY, ASTRO 06 plenary Sesssion, Lancet Oncol 2006

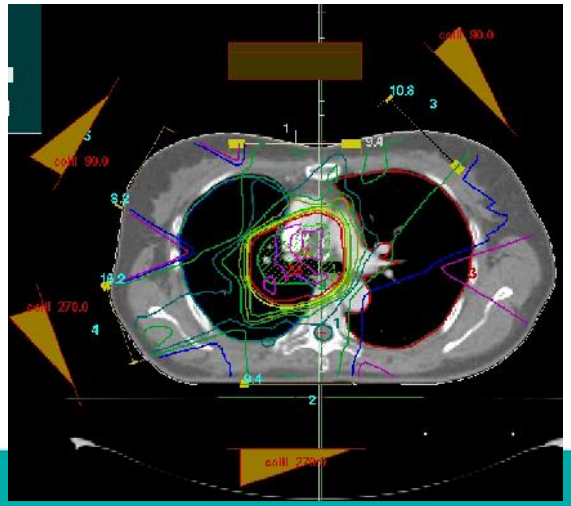
Population-based cohort, Lally et al, JCO 2006

Many changes since publication of PORT Meta-analysis: selection and treatment of pts



LACE Meta-analysis
Kindly provided by JPPignon et al, ASCO 2006





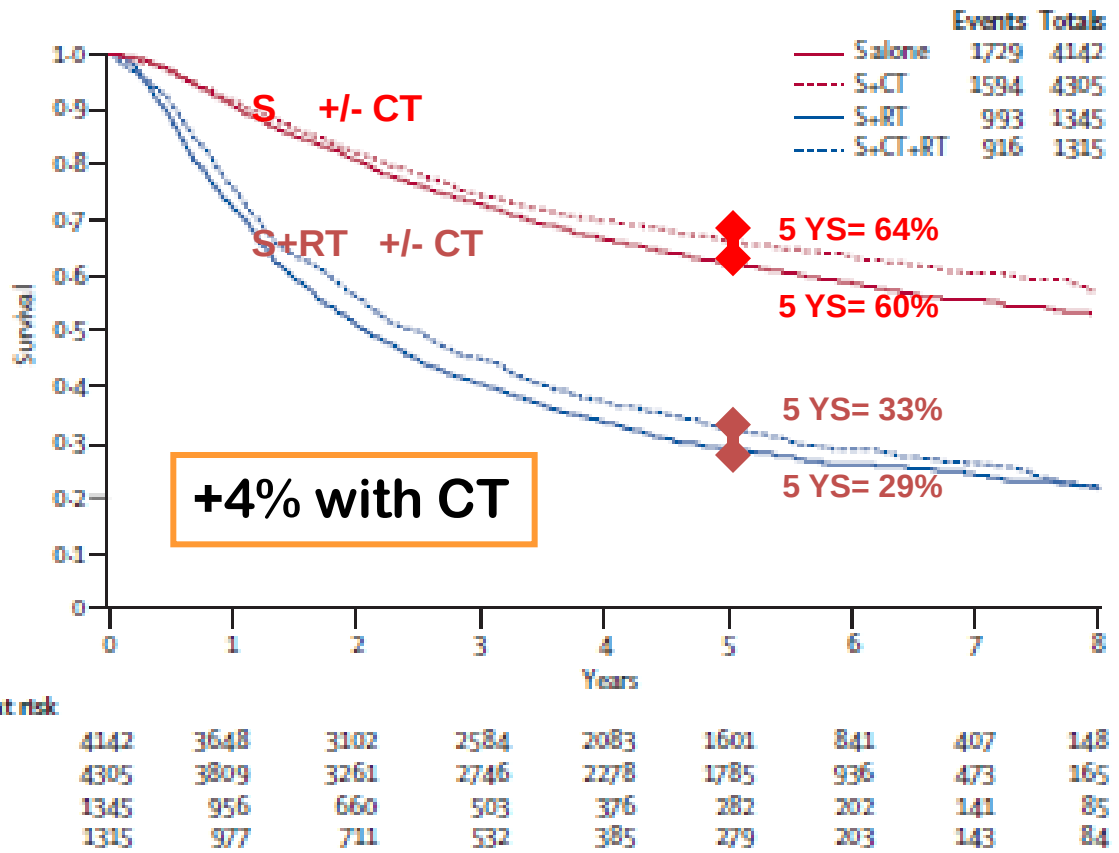
- **Better selection (PET, Brain imaging)**
- **Better Quality of surgery**
- **(Neo-) adjuvant CT**

  has now become a standard of care in stage II and III pts
- **Better radiotherapy**

Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data

NSCLC Meta-analyses Collaborative Group*

Lancet 2010



Preoperative chemotherapy for non-small cell lung cancer:

Trials between 1979 and 2003

RT for pts at higher risk (N+) or incomplete resection

86% of all pts: St I,II
14% of all pts: St III

63% of all pts: St III
35% of all pts: St II
1% of all pts: St I

Pre-operative CT: Absolute 5-yr survival improvement of 5% from 40% to 45%. NSCLC MA group Lancet 2014

VOLUME 33 · NUMBER 8 · MARCH 10 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

OS at 5 yrs in pN2 pts: 39,8% (CT + PORT) vs 34,7 % (adj CT).

Postoperative Radiotherapy for Pathologic N2 Non–Small-Cell Lung Cancer Treated With Adjuvant Chemotherapy: A Review of the National Cancer Data Base

Cliff G. Robinson, Aalok P. Patel, Jeffrey D. Bradley, Todd DeWees, Saiama N. Waqar, Daniel Morgensztern, Maria Q. Baggstrom, Ramaswamy Govindan, Jennifer M. Bell, Tracey J. Guthrie, Graham A. Colditz, Traves D. Crabtree, Daniel Kreisel, Alexander S. Krupnick, G. Alexander Patterson, Bryan F. Meyers, and Varun Puri

In conclusion, in an analysis of the NCDB for patients with pathologic N2 NSCLC, all of whom received adjuvant chemotherapy, PORT seemed to confer an additional improvement in OS. Investigators are strongly encouraged to enroll patients on randomized trials such as LungART.

Postoperative Radiotherapy is Associated with Better Survival in Non–Small Cell Lung Cancer with Involved N2 Lymph Nodes

Results of an Analysis of the National Cancer Data Base

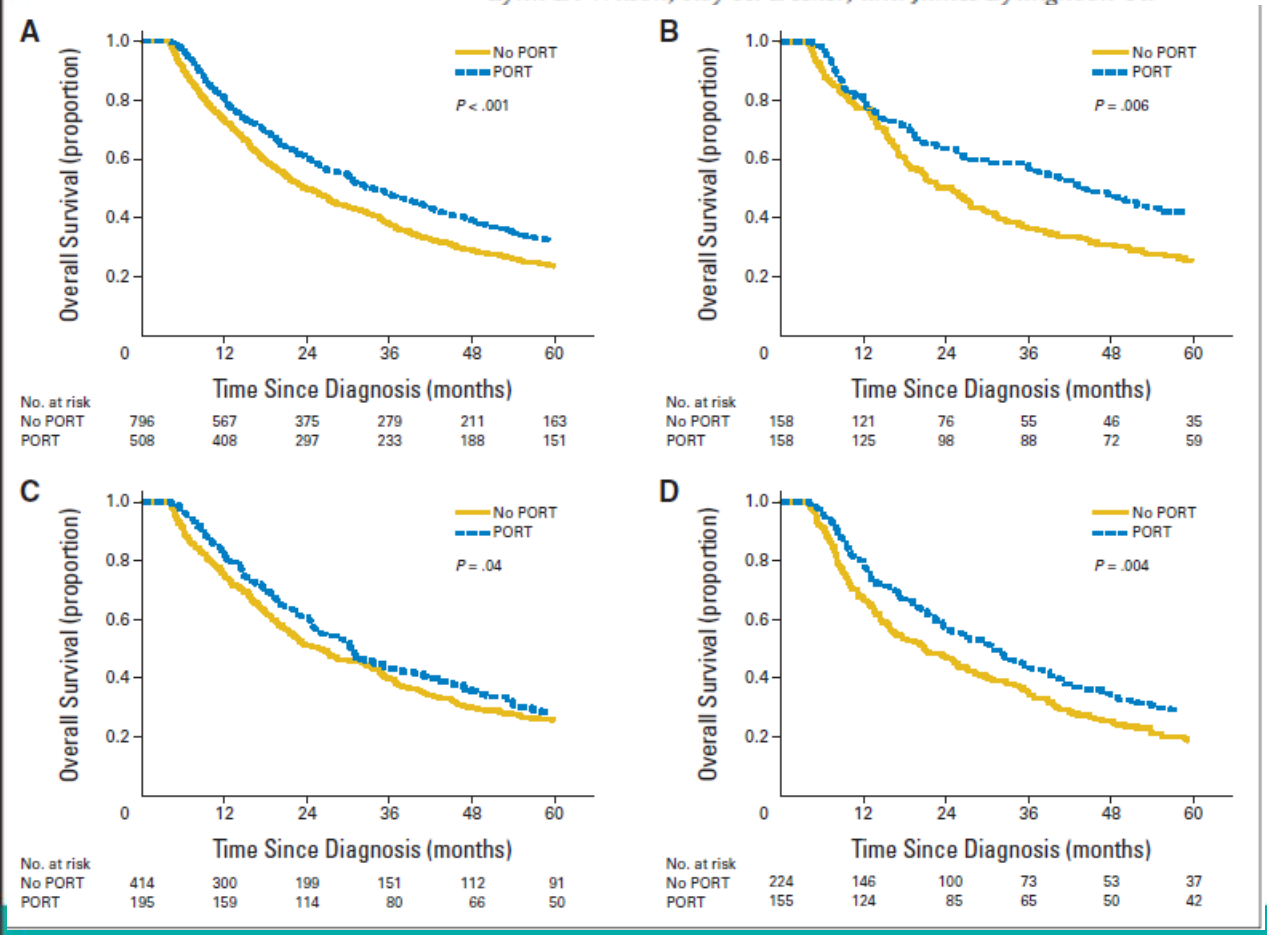
John L. Mikell, MD,¶ Theresa W. Gillespie, PhD,†‡¶ William A. Hall, MD,*¶ Dana C. Nickleach, MA,§¶ Yuan Liu, PhD,§¶ Joseph Lipscomb, PhD,‖¶ Suresh S. Ramalingam, MD,†¶ Raj S. Rajpara, MD,*¶ Seth D. Force, MD,‡¶ Felix G. Fernandez, MD,‡¶ Taofeek K. Owonikoko, MD, PhD,†¶ Rathi N. Pillai, MD,†¶ Fadlo R. Khuri, MD,†¶ Walter J. Curran, MD,*¶ and Kristin A. Higgins, MD*¶*

involved LN. Though caution should be taken when interpreting studies based on retrospective cohorts, evidence of the value of PORT in the adjuvant treatment paradigm in patients with pN2 NSCLC continues to build. The results of the pending LungART randomized trial should provide a more definitive answer to this persistent clinical question.

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Postoperative Radiation Therapy Is Associated With Improved Overall Survival in Incompletely Resected Stage II and III Non–Small-Cell Lung Cancer

Elyn H. Wang, Christopher D. Corso, Charles E. Rutter, Henry S. Park, Aileen B. Chen, Anthony W. Kim, Lynn D. Wilson, Roy H. Decker, and James Byunghoon Yu



- Salvage RT can be improve outcome of pts with incompletely
- Resected NSCLC However, better quality of surgery is warranted!

Is RT necessary in completely resected patients with mediastinal involvement ??

Maybe….

Technical advances of radiotherapy may enhance the ability of RT to improve local relapse free survival, DFS and possibly overall survival

BUT this has to be proven….

Several options in the pre-operative setting

More mature results are necessary. Lung ART is also exploring PORT in pts having pre-op CT

LUNG ART phase III Trial

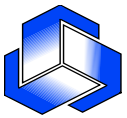
(IFCT O5O3-UK group-EORTC 22055-08053)

Trial registry: NCT00410683

Completely resected NSCLC with mediastinal histo or cytologically proven nodal involvement

IFCT

Lung ART UK



Possibility of adjuvant CT

R

Pre-op and/or Post-op CT

Control

Conformal PORT (54 Gy)

Main end-point : DFS, 700 pts needed to show a 10% difference in DFS (from 30% to 40%)

INSTITUT NATIONAL DU CANCER

With the support of INCa (French National Cancer Institute)

Resected stage IIIA patients
Local Recurrence Rate

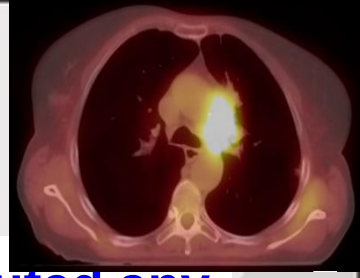
At 3 years

- **Without radiotherapy (according to nodal exploration): around 30%**
  - 22% - 40%
- **With « more modern » RT pre-op or post-op: around 15%**
  - 11% (Machtay et al JCO 2001)
  - 13% (Etude ECOG, Keller et al, NEJM 2000)
  - 14.7% (PORT) vs 28.9%(No PORT) (ANITA trial, Douillard IJROBP 2008)
  - SAKK trial comparing pre-operative sequential CTRT versus CT: Local relapse 15% vs 30%

What about Long Term results…

Machtay 2001; Keller 2000; Douillard 2008; Le Pechoux, 2011; Pless 2014

Conclusion



- **In the pre-PET era, high rate of distant metastases diluted any real effect of local control on overall outcome**
- **Population of stage III patients has changed**
  - Better staging (PET CT, brain MRI)
- **Operable pts**
  - Better surgery (lung sparing techniques, pre-op and post-op care …) and better RT
  - Adjuvant or Neo-Adjuvant chemotherapy: a standard
  - Different options available integrating chemotherapy, surgery and radiotherapy (40% at 5 years in recent trials)
  - Need of multidisplinary experienced team especially for tri modality approaches
- **Inoperable pts**

Have we reached the limit ?

- Concept of « one size fits all » has reached its limit!
- Progress in high Tech RT allows better combinations with CT or surgery
- More biologically driven dose escalation ongoing
- Ongoing studies in selected populations as trials were negative in non selected populations
- Stage III: challenging group of pts with high risk of local and distant failure

Collaborations and prospective studies needed!!!

Thank you for your attention

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