GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

TREATMENT OF LOCALLY ADVANCED NSCLC WITH CHEMO-RADIOTHERAPY

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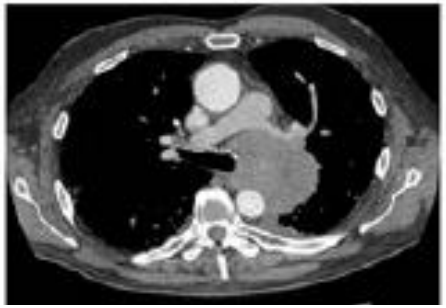
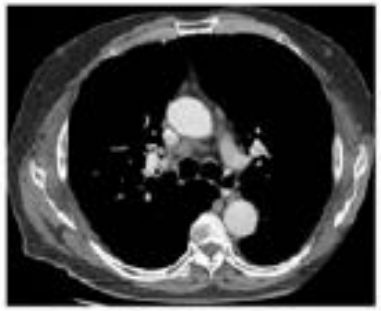
INTRODUCTION

- About 30% of non-small cell lung cancers are locally advanced, mainly unresectable
- This group of patients is very heterogeneous according to mediastinal lymph node burden
- The objectives of treatment are:
  - Local control of thoracic tumour and lymph nodes extension
  - Micro-metastatic disease control
- Despite progress in therapeutic strategies, prognosis remains poor with overall survival rate around 15%

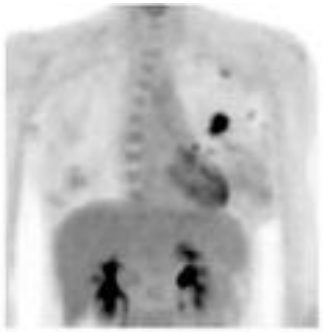
A VERY HETEROGENEOUS POPULATION OF PATIENTS



Mediastinal infiltration

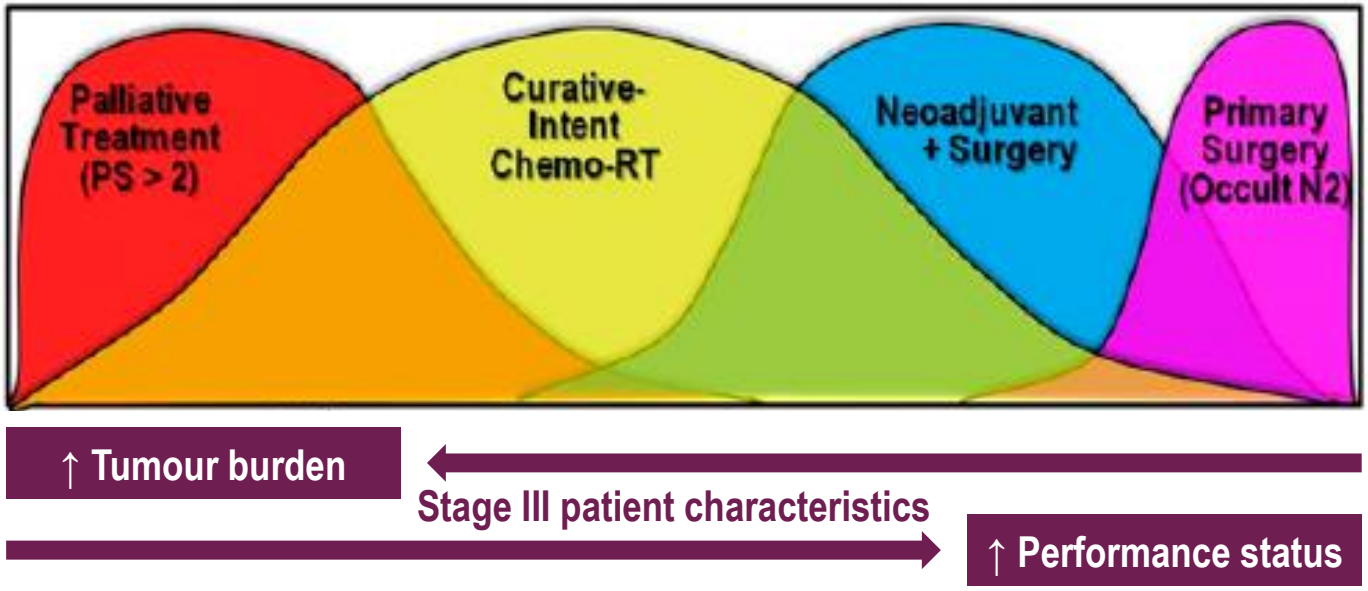


Discrete node enlargement



Clinically occult N2

Schematic of types of patients included in studies using different treatment approaches



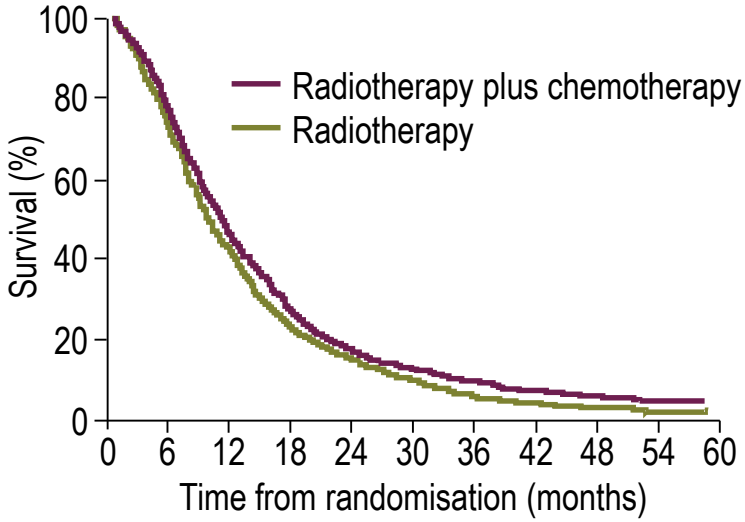
HISTORY

- In the 1960s, radiotherapy became standard therapy of patients with unresectable stage III NSCLC
- RTOG showed that local control was improved by increasing total dose to 60 grays delivered in 30 fractions over 6 weeks
- This radiotherapy schedule has been used until now in many countries
- In recent years, the aim of several studies has been to optimise radiotherapy administration in terms of total dose and to use new technologies

HISTORY

- A number of randomised phase III trials showed that chemo-radiotherapy association was better in terms of survival that radiotherapy alone
- These results were confirmed by a meta-analysis published in 1995

Survival in trials of radical radiotherapy vs radical radiotherapy plus chemotherapy (only trials using regimens based on cisplatin)



No at risk:

Radio plus chemo	887	666	406	244	157	119	90	70	59	49	43
Radiotherapy	893	626	367	210	141	92	60	44	36	29	25

The reduction of death-risk was 13% with the association

RR 0.87 (p = 0.005)

NSCLC Collaborative Group. BMJ 1995;311:899-909.

HOW TO ASSOCIATE CHEMOTHERAPY AND RADIOTHERAPY?

Sequential chemo-radiotherapy:

CT CT (CT) **RT**

Exclusive concomitant chemo-radiotherapy:

CT CT (CT)

RT

Induction chemotherapy before concomitant chemo-radiotherapy:

CT CT (CT) CT CT (CT)

RT

Consolidation chemotherapy after concomitant chemo-radiotherapy:

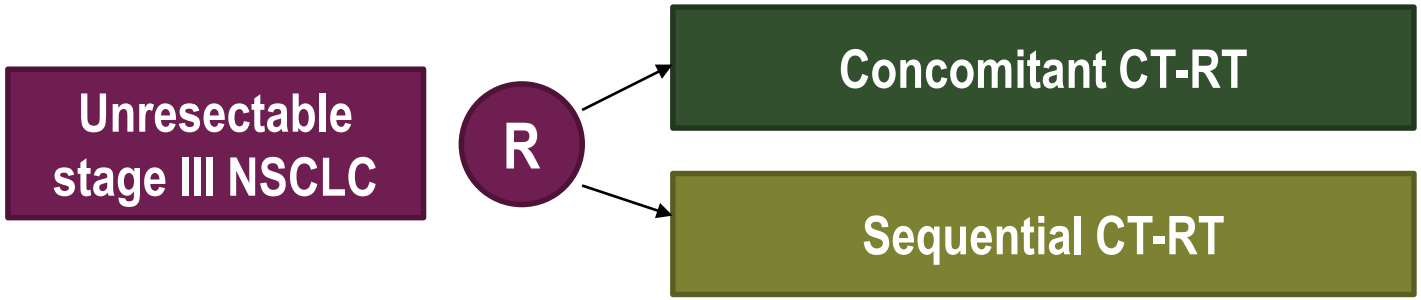
CT CT (CT) CT CT (CT)

RT

CONCOMITANT CHEMO-RADIOTHERAPY IS THE STANDARD OF CARE

CONCOMITANT *VS.* SEQUENTIAL CT-RT: A META-ANALYSIS

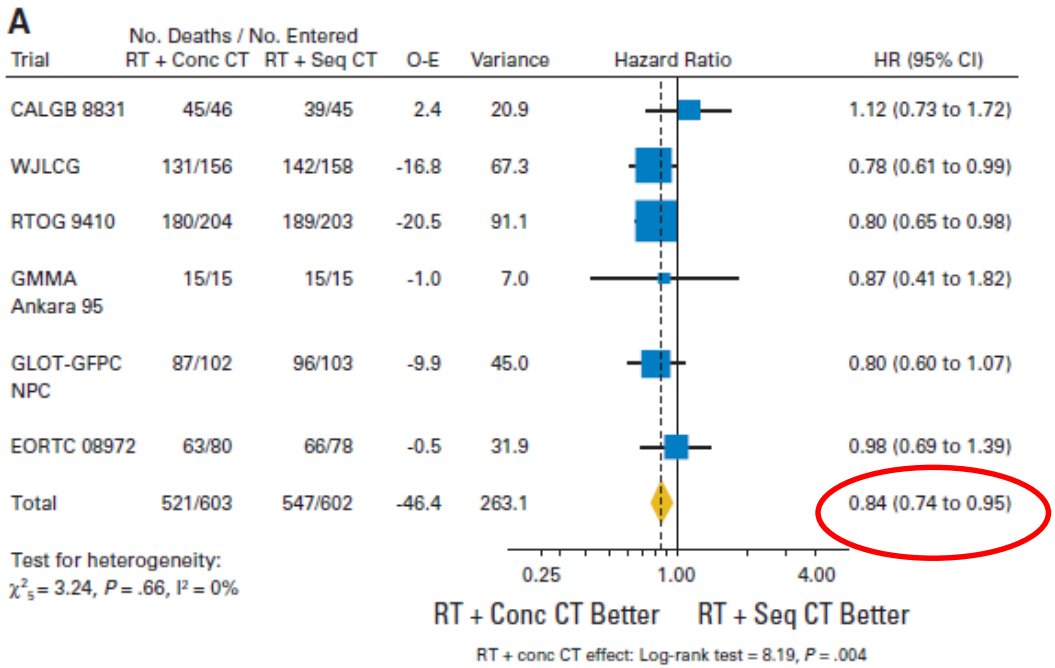
- Meta-analysis using up-dated data on individual patients:
  - 6 randomised available trials
  - 1 205 patients, NSCLC, PS = 0-1 : 97 %; stage IIIB : 61%

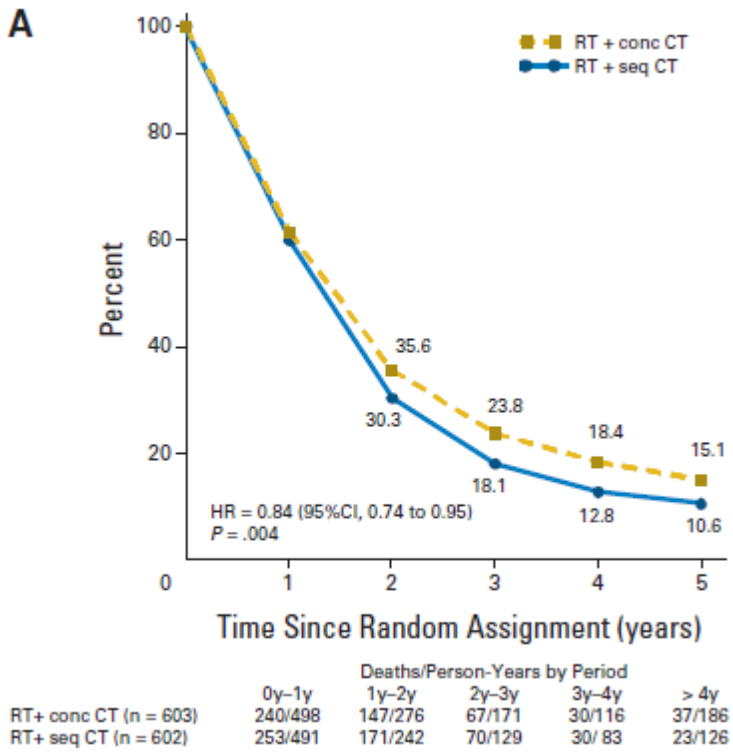


- Toxicities:
  - Concomitant CT-RT increased acute oesophageal toxicity (grade 3-4): from 4% to 18%; RR = 4.9 (95 % CI: 3.1 - 7.8) ; p < 0.0001
  - Non significant difference regarding acute pulmonary toxicity: RR = 0.69 (95 % CI: 0.42 - 1.12) ; p = 0.13

Aupérin A, *et al.*, J Clin Oncol 2010;28:2181–90.

CONCOMITANT *VS.* SEQUENTIAL CT-RT: A META-ANALYSIS





Overall survival: Absolute benefit		
2 years	**3 years**	**5 years**
5.3%	5.7%	4.5%

PROGNOSTIC FACTORS

- Less than 50% of patients are eligible to a concomitant chemo-radiotherapy[1]
  - 66% for patients ≤ 59 years *vs*. 0% for patients > 75 years
- Several factors are predictive of a poor outcome[1-4]:
  - Age > 75 years
  - GTV ≥ 100 cc (GTV = Gross Tumour Volume)
  - Alteration of pulmonary function tests:
    - FEV_1 ≤ 80%
    - Diffusion capacity (DLCO) ≤ 80%
  - Weight loss > 5% between start and third week of CT-RT5
    - Overall survival median = 23 months *vs*. 13 months

1. De Ruysscher D, *et al*., Ann Oncol 2009;20:98–102.
2. Oberije C, *et al.,* Int J Radiat Oncol Biol Phys 2015;94(3):612–20.
3. Kim HY, *et al*., Jpn J Clin Oncol 2016;46(2):144–51.
4. Warner A, *et al.,* Int J Radiat Oncol Biol Phys 2016;94(3):612–20.
5. Sanders KJC, *et al*., J Thorac Oncol 2016;11(6):873–9.

WHICH CHEMOTHERAPY TO ASSOCIATE WITH RADIOTHERAPY?

CHEMO-RADIOTHERAPY OR CHEMO-RADIOSENSITIZATION?

- In concurrent chemo-radiotherapy, chemotherapy is administered at full cytotoxic dose during radiotherapy. The objective is to have a synergistic effect on thoracic tumour and to control potential micrometastatic disease. The risk is to increase toxicities

- In chemo-radiosensitization, chemotherapy drugs are administered at low dose. The objective is to improve radiosensitivity of tumour cells. Several drugs are good radiosensitizers: cisplatin, carboplatin, taxane, gemcitabine, pemetrexed, etc…

CALGB 94-31 TRIAL

- CALGB trial is the first randomised phase II study which evaluates the contribution of a third generation drug with cisplatin in concomitant CT-RT

IIIAN2/B NSCLC	Gemcitabine (n = 62)	Paclitaxel (n=58)	Vinorebine (n=55)
Induction : **Cisplatin 80 mg/m² D1 & 22**	1250 mg/m² D1, 8, 22 & 29	225 mg/m² D1 & 22	25 mg/m² D1, 8, 22 & 29
Concomitant RT-CT: **RT = 66 Gy** **Cisplatin 80 mg/m²** **D43 & 64**	600 mg/m² D43, 50, 64 & 71	135 mg/m² D43 & 64	15 mg/m² D43, 50, 64 & 71
Grade 3 oesophagitis **Grade 4 oesophagitis**	35% 17%	35% 4%	13% 12%
Grade 3 pulmonary toxicity **Grade 4 pulmonary toxicity**	12% 2%	12% 8%	10% 10%*
Objective response rate at the end of treatment	74%	67%	73%
Median OS (months)	18.3	14.8	17.7
3-years survival	28%	19%	33%

*One patient died of acute pulmonary toxicity

- The best efficacy/tolerance ratio is obtained with cisplatin + vinorebine

ESMO

Vokes EE, *et al.,* J Clin Oncol 2002;20:4191–8.

MAIN CHEMOTHERAPIES USED IN CONCOMITANT CHEMO-RADIOTHERAPY

- Cisplatin-etoposide (SWOG):
  - Cisplatin 50 mg/m² D1, D8 + etoposide 50 mg/m² D1-D5
    - This old schedule is still very used in US
- Cisplatin-vinorelbine:
  - Cisplatin 80 mg/m² D1 + vinorelbine 15 mg/m² D1, D8
    - This schedule is mainly used in France and in other European countries
  - Cisplatin 80 mg/m² D1 + vinorelbine orally 20 mg D1, 3 and 5 or 40 mg/m² D1 et D8
    - This regimen is an option to avoid intravenous vinorelbine
- Carboplatin-paclitaxel:
  - Carboplatin AUC=2/week + paclitaxel 40 à 50 mg/m²/week
    - This schedule is commonly used in US and around the world
    - It is safe and easy to deliver in an outpatient setting
- Platinum-docetaxel:
  - Cisplatin 40 mg/m² + docetaxel 40 mg/m² D1, D8, D29, D36
  - Carboplatin AUC = 2/week + docetaxel 20 mg/m²/week
    - This protocol was mainly developed in Japan

SWOG: Southwest Oncology Group

CISPLATIN-ETOPOSIDE *VS.* CARBOPLATIN-PACLITAXEL?

- The aim of this Veteran Health Administration retrospective study is to compare the outcome of patients treated with either etoposide-cisplatin (EP) or carboplatin-paclitaxel (CP)
  - 1842 patients were included
  - 762 patients were identified by a propensity score to receive either EP or CP

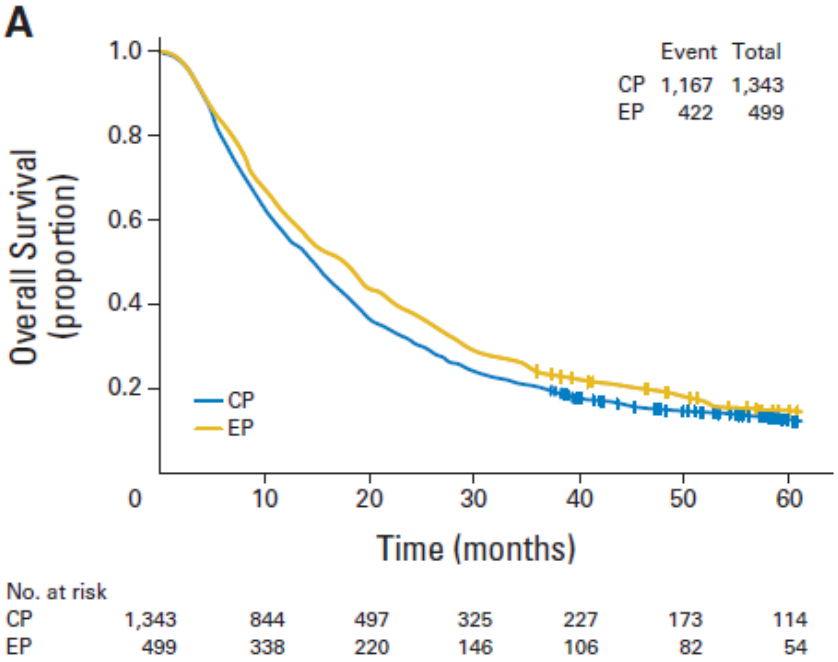
	Observational Data Set (n = 1,842)						Propensity Score–Matched Data Set (n = 762)					
	EP (n = 499)		CP (n = 1,343)				EP (n = 381)		CP (n = 381)			
Characteristic	No. of Patients	%	No. of Patients	%	Standard Difference	*P*	No. of Patients	%	No. of Patients	%	Standard Difference	*P*
Age, years					0.50	< .001					0.06	.3999
Mean	61.3		65.5				62.0		62.4			
SD	7.6		9				7.4		7.9			
Era of diagnosis					0.24	< .001					0	1
2001-2004	129	25.9	477	35.5			94	50	94	50		
2005-2007	194	38.9	393	29.3			152	50	152	50		
2008-2010	176	35.3	473	35.2			135	50	135	50		
Stage IIIB	281	56.3	759	56.5	< 0.01	.9379	189	49.6	204	53.5	0.8	.2769
Histology					0.11	.2112					0.07	.8158
Adenocarcinoma	110	22	252	18.8			82	21.5	85	22.3		
NOS	146	29.3	378	28.1			107	28.1	112	29.5		
Other	3	0.6	15	1.1			3	0.8	5	1.3		
Squamous cell	240	48.1	698	52			189	49.6	179	48.3		

CISPLATIN-ETOPOSIDE *VS.* CARBOPLATIN-PACLITAXEL?

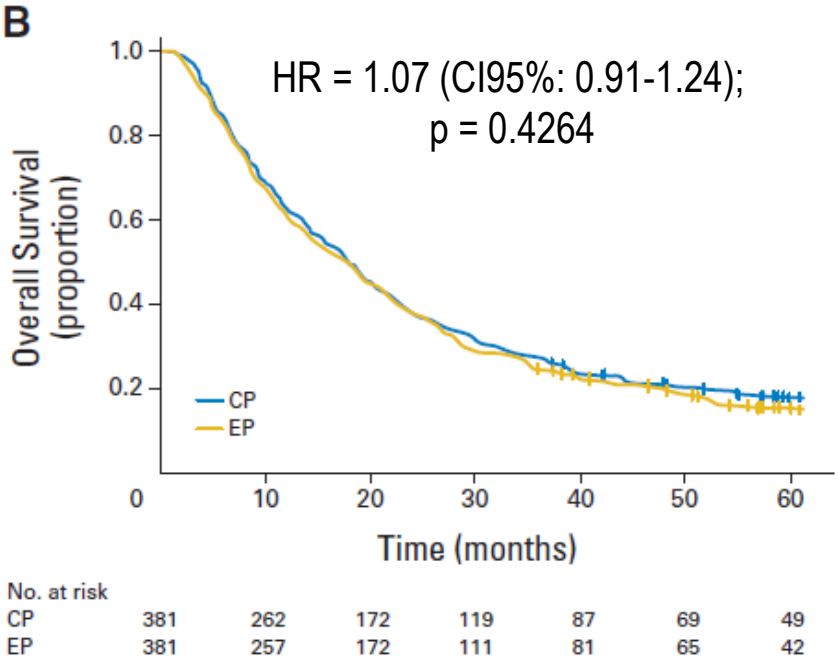
Overall survival

All patients

	EP	CP
Median OS (months)	17.3	14.6
HR = 0,88 (CI95%: 0.79-0.99); p = 0.0209		



Patients matched according to their propensity scores



- After accounting for prognostic variables, patients treated with EP *versus* CP had similar overall survival

CISPLATIN-ETOPOSIDE *VS.* CARBOPLATIN-PACLITAXEL?

- Systematic review of published trials to compare outcomes and toxic effects between cisplatin-etoposide and carboplatin-paclitaxel
- 79 screened trials from 1985 to 2015 (PubMed, Cochrane, EMBASE, abstracts from ASCO annual meetings and WCLC

Patients characteristics	Cisplatin-etoposide (EP) 31 trials (n = 3090)	Carboplatin-paclitaxel (CP) 48 trials (n = 3728)	p
Median age (years)	61	63	
Male (%)	65	65	
Median radiation dose (Gy)	63	64.6	
Induction therapy (%)	3	51	
Consolidation therapy (%)	46	39	
3-year survival (%)	30 (CI_{95} : 27–34)	25 (CI_{95} : 22–28)	0.5
Median OS (months)	19.6	18.4	0.40
Locoregional relapse (%)	38	37	0.63
Distant metastasis (%)	44	46	0.5

- Cisplatin-etoposide and carboplatin-paclitaxel regimens were associated with comparable efficacy when used with concurrent radiotherapy

ESMO

Steuer CE, *et al.*, JAMA Oncol 2017;3(8):1120–9.

CISPLATIN-ETOPOSIDE *VS.* CARBOPLATIN-PACLITAXEL?

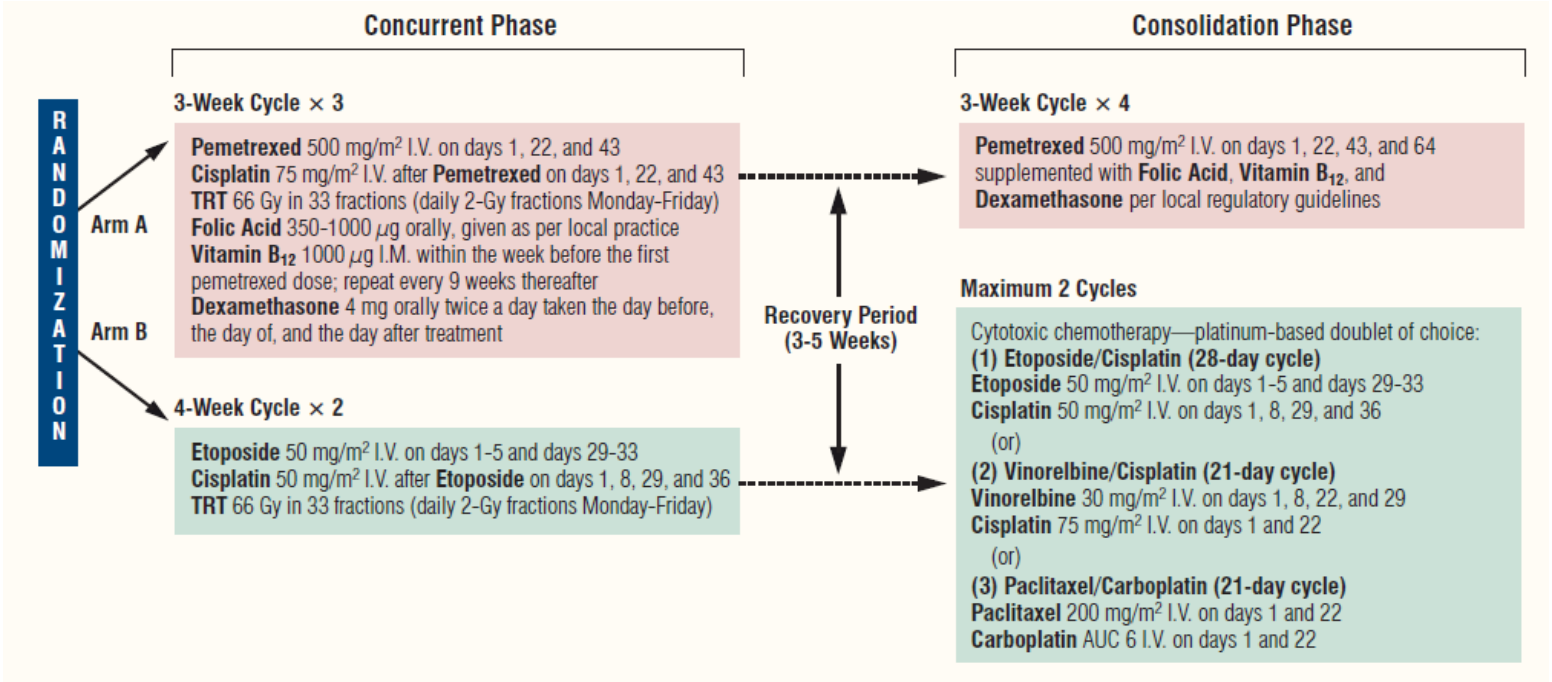
- Recently, a Chinese study compared head to head EP and CP in CT-RT for unresectable stage III NSCLC was published
- 200 patients were randomised:

Patients characteristics and results	Cisplatin-etoposide (EP) N = 95	Carboplatin-paclitaxel (CP) N = 96	p
Median age (years)	59	57	
Male (%)	84.2	88.5	
Radiation dose ≥ 60 Gy (%)	83.2	85.4	0.668
Chemotherapy (EP < 2 or CP < 5 weeks) (%)	13.7	35.5	< 0.001
Consolidation therapy (%)	50.5	35.4	0.035
3-year survival (%)	41,1 (CI_{95} : 31.1-50.7)	26 (CI_{95} : 17.8-35.1)	0.024
Median OS (months)	23.3	20.7	0.095

- In this trial, EP might be superior to CP
- However, deliverance of chemotherapy was inferior in CP arm

Liang J, *et al.,* Ann Oncol 2017;28:777–83.

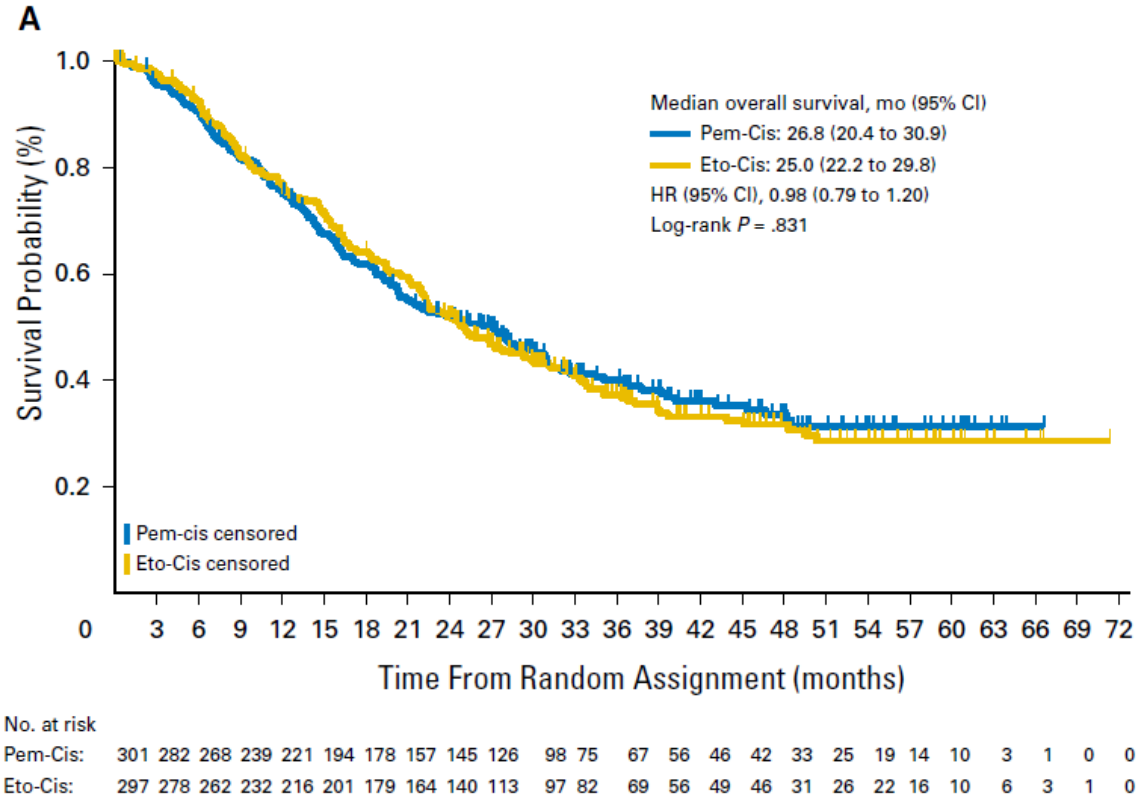
PHASE III PROCLAIM STUDY: CISPLATIN-PEMETREXED *VS.* CISPLATIN-ETOPOSIDE



- 600 patients were planned:
  - PS = 0 or 1, weight loss ≤ 5%
  - Stage IIIA /B unresectable non-squamous NSCLC
- Primary objective: OS improvement with cisplatin-pemetrexed + RT (HR = 0.74)

Reprinted from Clin Lung Cancer 10(3) Vokes EE, *et al.,* PROCLAIM: A Phase III Study of Pemetrexed, Cisplatin, and Radiation Therapy Followed by Consolidation Pemetrexed Versus Etoposide, Cisplatin, and Radiation Therapy Followed by Consolidation Cytotoxic Chemotherapy of Choice in Locally Advanced Stage III Non–Small-Cell Lung Cancer of Other than Predominantly Squamous Cell Histology:193-8, 2009, with permission from Elsevier

PHASE III PROCLAIM STUDY: OVERALL SURVIVAL



- Study was stopped early for futility
- 598 patients were included and 555 patients were treated
- Cisplatin-pemetrexed combined with concurrent RT and followed by pemetrexed was not superior to standard chemo-radiotherapy

Senan S, *et al.*, J Clin Oncol 34(9), 2016:953–62. Reprinted with permission © 2016 American Society of Clinical Oncology. All rights reserved.

INDUCTION OR CONSOLIDATION?

INDUCTION CHEMOTHERAPY *VS.* CONSOLIDATION CHEMOTHERAPY

	Advantages	Disadvantages
Induction or delayed RT-CT	◆ Tumour volume reduction before RT ◆ Full dose chemotherapy ◆ Time to organise RT ◆ Patients selection according to chemotherapy efficacy	◆ Delay to synergistic treatment administration ◆ Theoretical risk of cross resistance ◆ Chemotherapy doses reduction during RT ◆ Compromised administration of CT-RT by induction related toxicities
Consolidation or early RT-CT	◆ Early administration of synergistic association ◆ Theoretical decrease of cross-resistance ◆ Local control improvement	◆ Too large tumour volume ◆ Less eligible patients for concurrent CT-RT ◆ Delay to start CT-RT

INDUCTION CHEMOTHERAPY

CALGB 39801 trial

- Stage IIIA/B
- Unresectable NSCLC
- PS 0-1
- Without weight loss
- Criteria (WL)

R

Carboplatin AUC 2 + paclitaxel 50 mg/m²/week x 7 week + concurrent RT (66 Gy)

Carboplatin AUC 6 + paclitaxel 200 mg/m² every 3 weeks x 2 cycles (induction CT) then Carboplatin AUC 2 – paclitaxel 50 mg/m²/week x 7 week + concurrent RT (66 Gy)

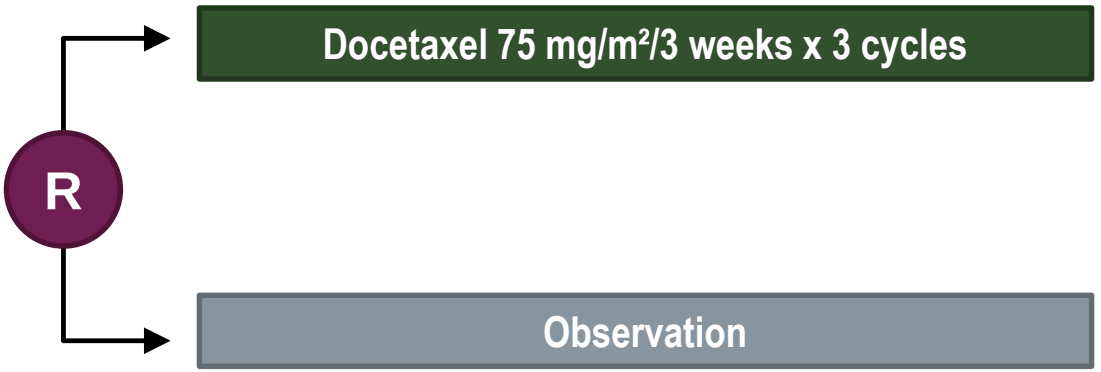
	CT/RT (n=161)	CT → CT/RT (n=170)	p
Stage IIIA/IIIB (%)	50/50	52/48	
WL < 5% / > 5% (%)	63/37	76/24	
Oesophagitis (gr 3-4)	32%	36%	NS
Pulmonary toxicity (gr 3-4)	4%	10%	NS
Median OS (months)	12	14	0,3
2-years survival	29%	31%	

ESMO

Vokes EE, *et al.*, J Clin Oncol 2007;25:1698–704

CONSOLIDATION CHEMOTHERAPY PHASE III RANDOMISED STUDY HOG LUN 01-24/USO-023

- Stage IIIAN2/B
- 203 pts
- Cisplatin 50 mg/m² D1, 8, 29, 36
- Etoposide 50 mg/m² D1–5 and D29–33
- RT = 59.4 Gy



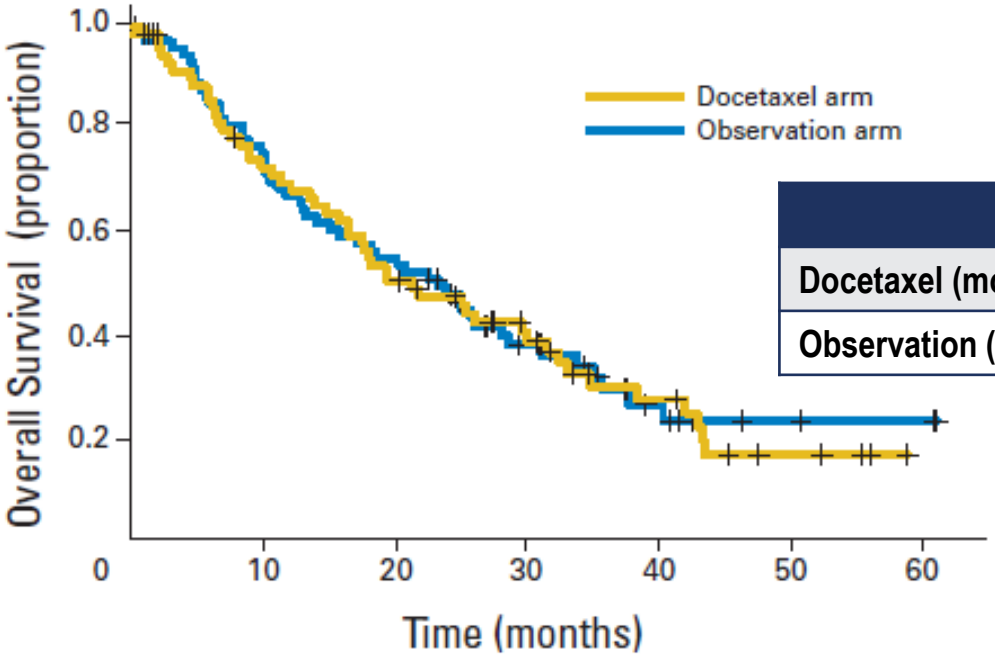
Grade 3-5 toxicities after RT-CT	Docetaxel (n=73)	Observation (n=74)	p
Infections	11%	0%	0.003
Pneumonitis	8.2%	1.4%	< 0.001
RT –related deaths	5.5%	0%	0.058
Hospitalisations	28.8%	8.1%	< 0.001

ESMO

Hanna N, *et al.*, J Clin Oncol 2008;26:5755–60

CONSOLIDATION CHEMOTHERAPY PHASE III RANDOMISED STUDY HOG LUN 01-24/USO-023

Overall survival: randomised patients (n = 147)

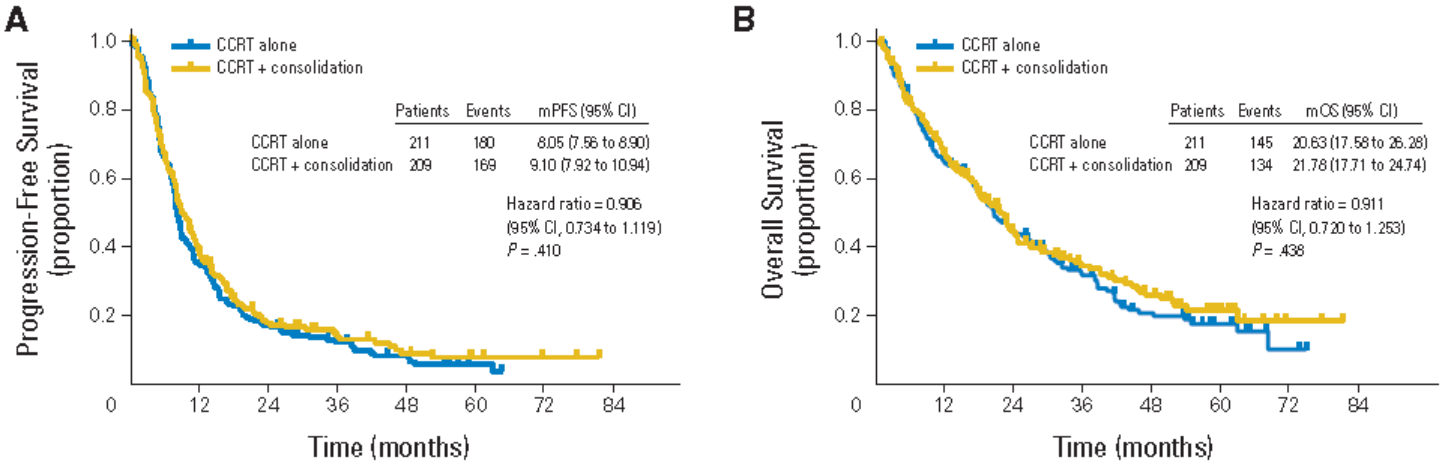


	Median	3-years survival
Docetaxel (months)	21.5	27.2%
Observation (months)	24	27.6%

- Consolidation docetaxel did not improve overall survival

KCSG-LU05-04 TRIAL CISPLATIN-DOCETAXEL CONSOLIDATION *VS.* OBSERVATION

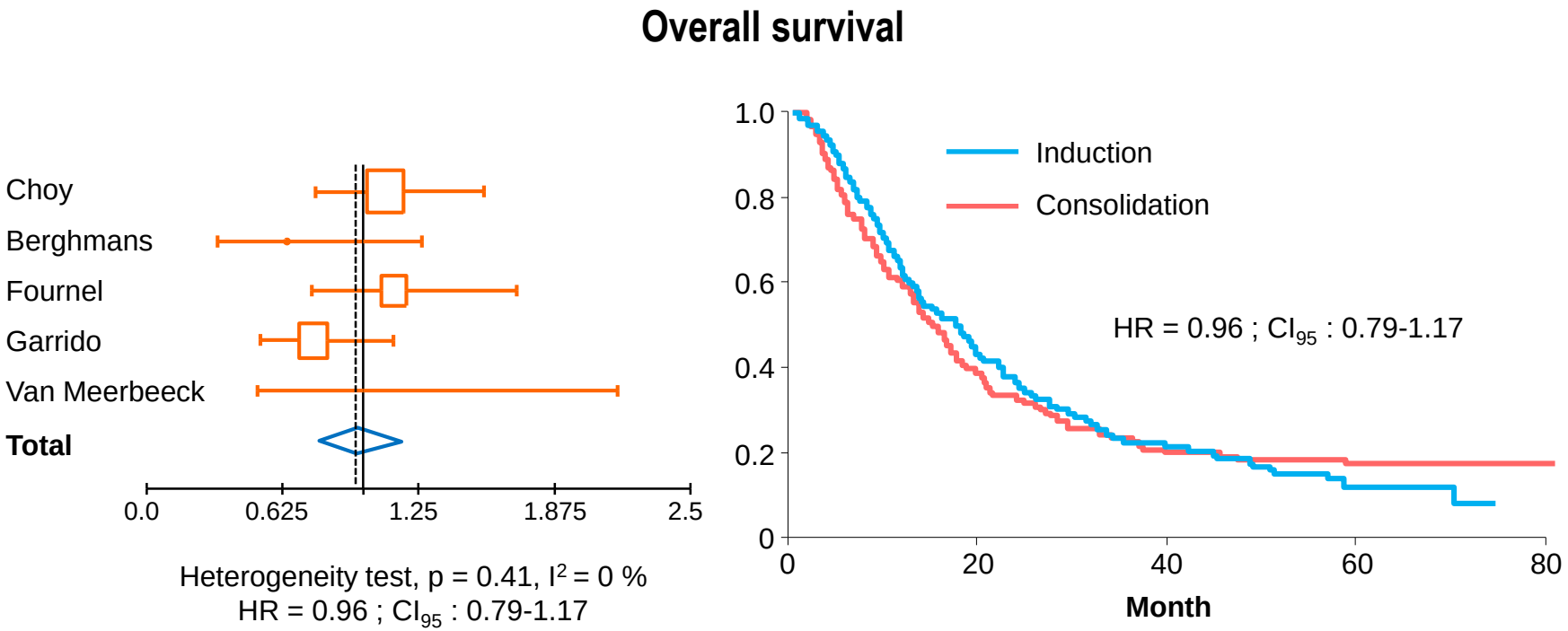
- CT-RT in first:
  - 420 patients
  - RT 66 Gy 33 fractions, 6 weeks
  - Concurrent chemotherapy: cisplatin 20 mg/m²/week + docetaxel 20 mg/m²/week
- Consolidation chemotherapy:
  - Cisplatin 35 mg/m² + docetaxel 35 mg/m² D1 and D8
  - 62% of patients received 3 cycles



- Progression-free survival and overall survival were not improved by consolidation chemotherapy

INDUCTION *VS.* CONSOLIDATION: A META-ANALYSIS

- The meta-analysis of 5 Phase 2 randomised trials shows similar results in terms of overall survival for induction or consolidation chemotherapy



Van Houtte P, *et al.*, WCLC® 2013. Abstr. P2.24-021.

WHICH RADIOTHERAPY IN 2017?

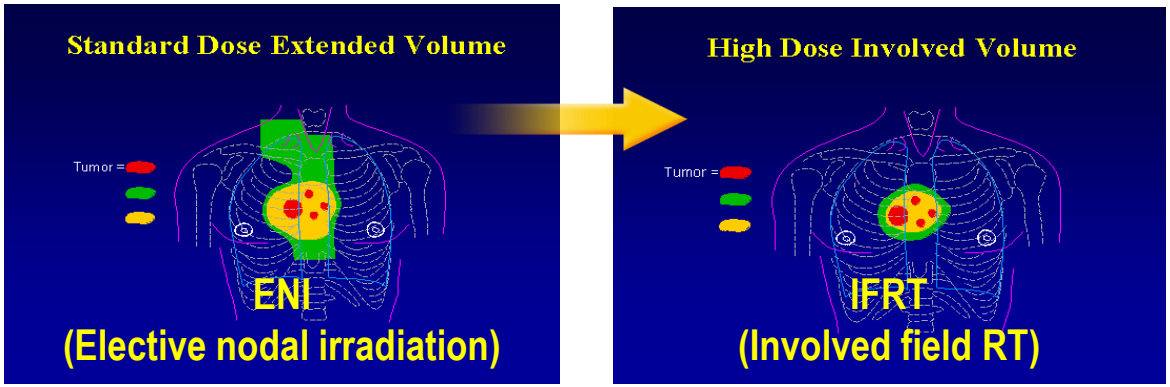
WHICH RADIOTHERAPY IN 2017?

- Conformational radiotherapy with 3D dosimetry should be systematically used in routine practice[1]
- Altered fractionation[2]:
  - Conventional daily 1.8 to 2.0-Gy fractionation is the standard in combination with radiotherapy
  - There is a little survival benefit in favour of accelerated or hyper fractionated radiotherapy but this modality is not easy to use in routine practice
- Intensity-modulated radiation therapy (IMRT)[3]:
  - Can reduce pulmonary and cardiac toxicities
  - Can optimise treatment of tumours close to organs at risk as spinal cord
  - Should be used to allow greater tailoring of the radiation dose distribution to patient anatomy

1. Van Meerbeeck JP, *et al.,* Oncologist 2008;13:700–8; 2. Mauguen A, *et al.,* J Clin Oncol 2012;30(22):2788–97
3. Chun SG, *et al.,* J Clin Oncol 2017;35(1):56–62

WHICH RADIOTHERAPY IN 2017?

- 4D techniques[1]:
  - 4D techniques and respiratory control (gating or tracking) during radiotherapy permit to exploit the full potential of IMRT
- Target definition[1,2]:
  - The impact of positron emission tomography scan (PET-SCAN) is essential to define target volume



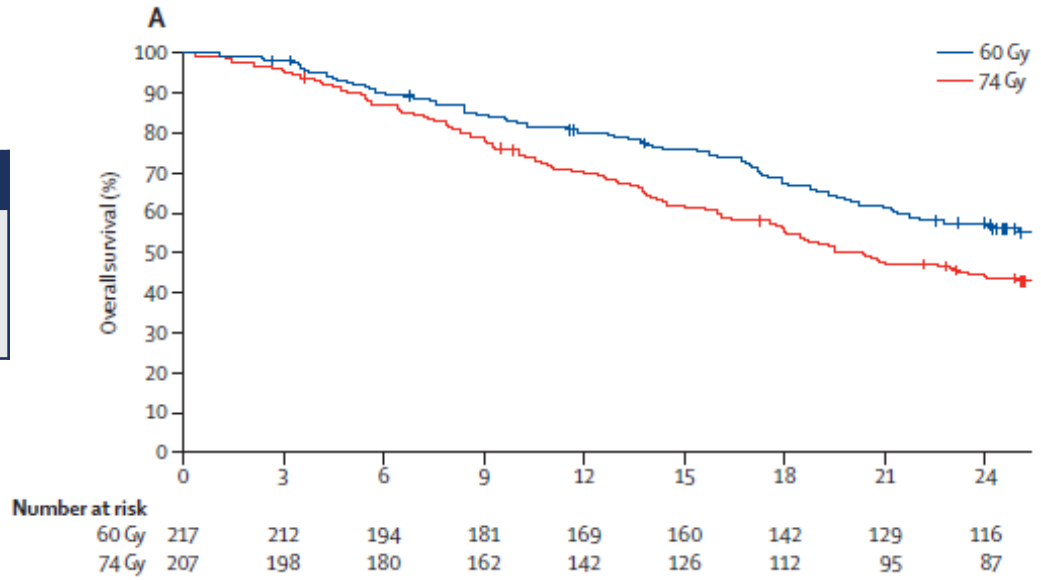
N=200 pts	2-years survival		5-years local control		Pneumonitis risk	
ENI (60 – 64 Gy)	25,6%	p=0.048	36%	p=0.032	29%	p=ns
IFRT (68 – 74 Gy)	39,4%		51%		17%	

1. Van Meerbeeck JP, *et al.,* Oncologist 2008;13:700–8; 2. Yuan S, *et al.,* Am J Clin Oncol 2007;30:239–44.

WHICH RADIOTHERAPY IN 2017?

- The total dose 60 to 66 Gy in 30 to 33 fractions should be used routinely[1]
- Dose escalation to 74 Gy is possible and safe in several phase II studies[1]
- Nevertheless, RTOG 06-17 trial showed that dose escalation to 74 Gy given in 2-Gy fractions with concurrent chemotherapy was deleterious compared with 60 Gy[2]

	Median OS	HR; p
74 Gy (months)	20.3	HR = 1.38 (CI95%: 1.09-1.76) p = 0.004
60 Gy (months)	28.7	



1. Stinchcombe TE, Bogart JA. The Oncologist 2012;17(5):682–93;
2. Reprinted from The Lancet Oncol 16(2), Bradley JD, *et al.,* Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or wihout cetuximab for patients with stage IIIA or IIIB non-small-cell lung lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study, 187–99, Copyright 2015, with permission from Elsevier.

TARGETED THERAPIES AND CHEMO-RADIOTHERAPY

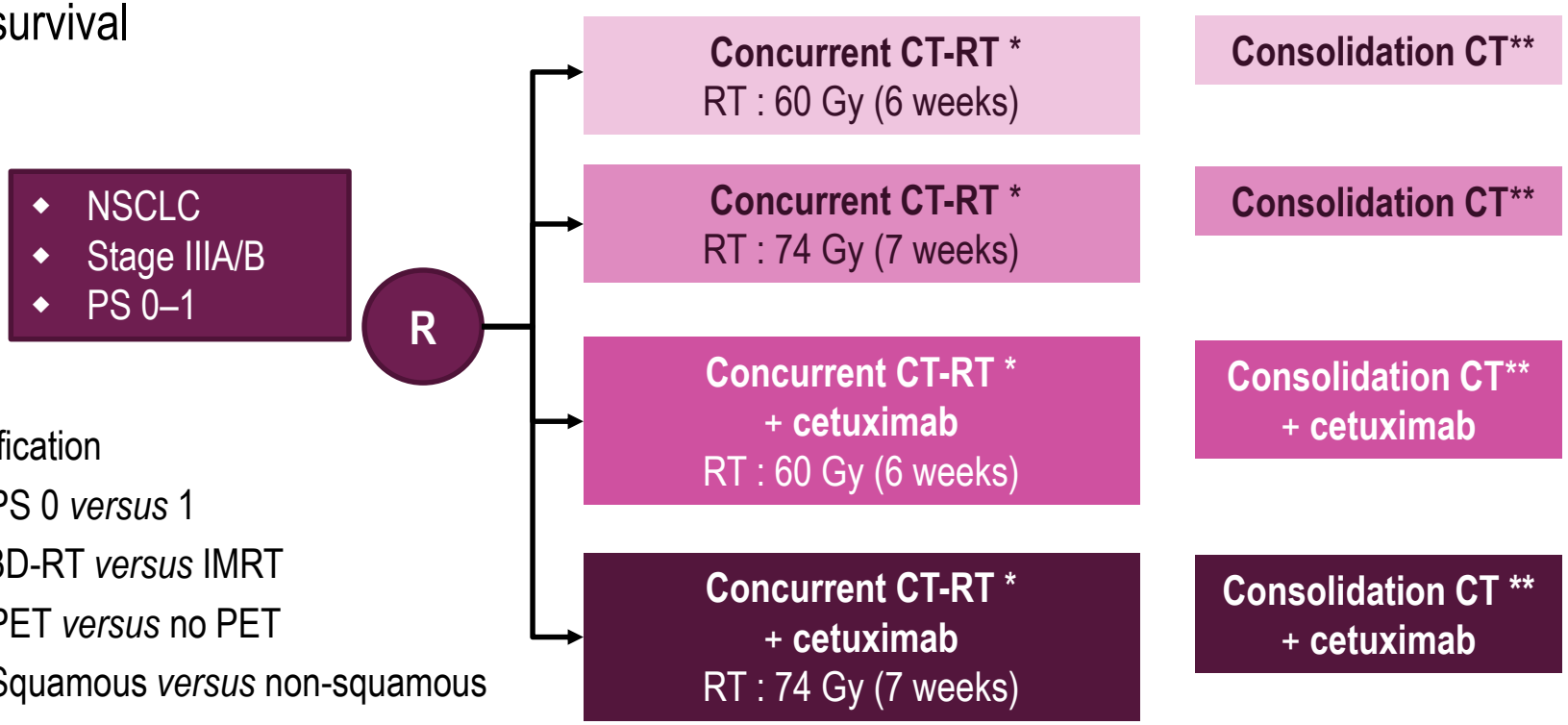
TARGETED THERAPIES AND CHEMO-RADIOTHERAPY

- Anti-angiogenic agents with chemo-radiotherapy[1,4]:
  - Do not improve results[2,3]
  - Are dangerous and must be prohibited[2,3]
- There is a rational to associate EGFR inhibitors with radiotherapy or chemo-radiotherapy in stage III NSCLC[4]:
  - EGFR is overexpressed in 80% of NSCLC
  - Preclinical models showed synergistic action between radiation and EGFR inhibitors (cetuximab or tyrosine-kinase inhibitors)
  - In locally advanced head and neck squamous-cell carcinoma, cetuximab plus radiotherapy improves local control and survival comparing to radiotherapy alone[5]

1. Hoang T, *et al.,* J Clin Oncol 2012;30:616–22
2. Spigel DR, *et al.,* J Clin Oncol 2009;28:43–48
3. Socinski MA, *et al.,* J Clin Oncol 2012:30:3953–9
4. Raben D, Bunn PA. J Clin Oncol 2012;30:3909–12
5. Bonner JA, *et al.,* Lancet Oncol 2010;11:21–8

RTOG 06-17 TRIAL

- On the basis of encouraging phase II trials, the second aim of this phase III study was to show if addition cetuximab to concurrent standard chemo-therapy improved survival



Stratification

- PS 0 *versus* 1
- 3D-RT *versus* IMRT
- PET *versus* no PET
- Squamous *versus* non-squamous

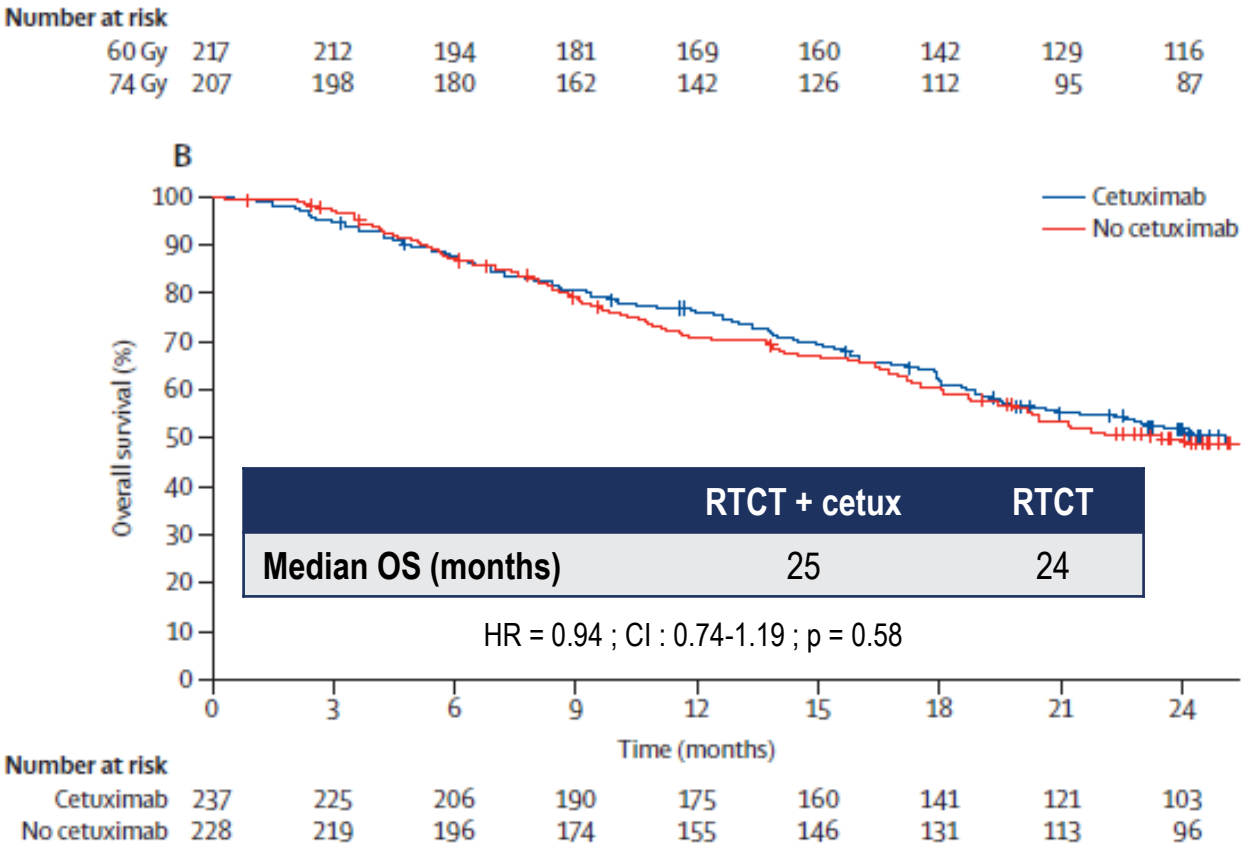
***CT-RT**
Carboplatin AUC=2 + paclitaxel 45 mg/m²/week. (6 à 7 weeks)
Cetuximab 400 mg/m² initial dose then 250 mg/m²/week.

****Consolidation CT**
Carboplatin AUC=6 + paclitaxel 200 mg/m² (2 cycles)
Cetuximab 250 mg/m²/week

Bradley JD, *et al*., Lancet Oncol 2015;16(2):187–99.

RTOG 06-17 TRIAL

Overall survival



- Addition of cetuximab to concurrent CT-RT and consolidation treatment provided no benefit survival in stage III unresectable NSCLC

Reprinted from The Lancet Oncol 16(2), Bradley JD, *et al.,* Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or wihout cetuximab for patients with stage IIIA or IIIB non-small-cell lung lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. 187-99, Copyright 2015, with permission from Elsevier.

PATIENTS WITH AN ONCOGENIC DRIVER

- Several trials showed efficacy of tyrosine-kinase inhibitors in first line in stage IV NSCLC with oncogenic drivers (EGFR mutations, ALK or ROS1 fusions)
- In stage III NSCLC with oncogenic drivers, there are 2 modalities using specific inhibitor:
  - Induction treatment with tyrosine-kinase inhibitor (TKI) to reduce tumour volume
  - Concurrent administration of TKI with radiotherapy or chemo-radiotherapy
- Several trials are ongoing in Asia

PATIENTS WITH AN ONCOGENIC DRIVER

- One small phase II study presented at 2017 ASCO meeting compared erlotinib plus concurrent radiotherapy (60 Gy) with standard concurrent chemo-radiotherapy (etoposide-cisplatin 2 cycles during radiotherapy) for stage III EGFR mutants NSCLC

	Erlo + RT (n=20)	CT-RT (n=21)	HR; p
PFS (months)	27.86	6.41	HR=0.0053; p<0.0001
ORR (%)	60	38.1	p=0.217

- In unresectable stage III EGFR mutant NSCLC patients, erlotinib/RT provides a statistically significant PFS improvement

Xing L, *et al.*, ASCO 2017: Abstract 8531

IMMUNOTHERAPY AND CHEMO-RADIOTHERAPY

DIFFERENT WAYS TO COMBINE IMMUNOTHERAPY AND RADIOTHERAPY

- Immunotherapy as adjuvant treatment after CT-RT:
  - Check-points inhibitors (anti PD-1 and anti PDL-1):
    - PACIFIC trial with durvalumab
  - Lung tumour vaccines:
    - Negative START study
    - START2 and INSPIRE trials
- Immunotherapy as induction treatment before surgery
- Immunotherapy during RT or CT-RT:
  - Locally advanced stage IIII NSCLC:
    - One trial with pembrolizumab during CT-RT
  - Stage IV disease:
    - SABR on one site + immunotherapy
    - Abscopal effect?
    - Case reports

Daly ME, *et al.,* J Thorac Oncol 2015:10;1685–93; Clinical.trial.gov

START STUDY (TECEMOTIDE OR L-BLP25)

- Stage III NSCLC
- Unresectable
- Non-progressive after CT-RT
- Platin-based CT
- RT > 50 Gy
- Sequential or concurrent CT-RT

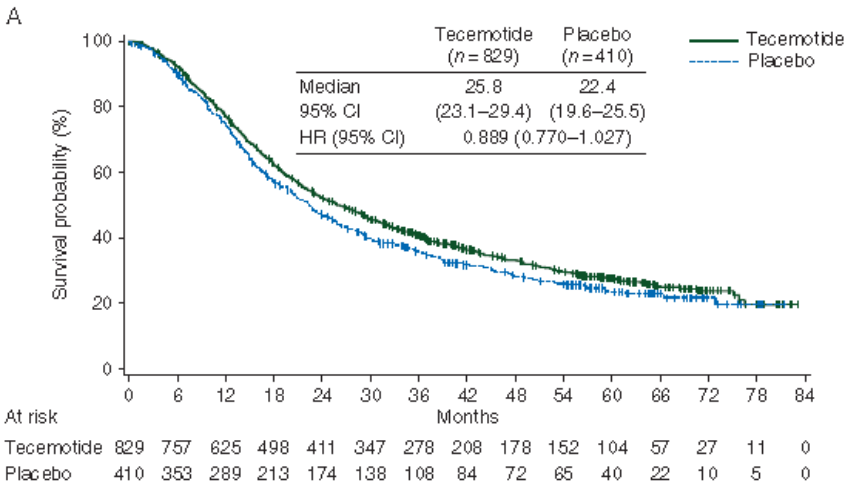
n = 1513

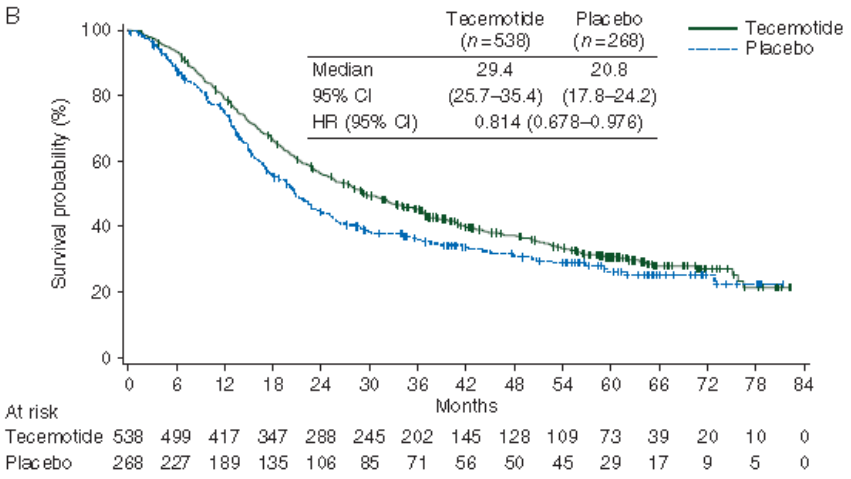
R

2:1

CTRT followed by L-BLP25
Until disease progression

CTRT followed by placebo
Until disease progression





- No difference in terms of OS,
- Significant benefit in terms of OS for patients treated by concurrent CT-RT:
  - 29.4 months *vs*. 20.8 months
  - HR = 0,81 (CI95%: 0.68-0.98); p=0.026
- Development has been discontinued

Butts C, *et al.*, Lancet Oncol 2014;15:59–68; Mitchell P, *et al.*, Ann Oncol 2015;1134–42, by permission of Oxford University Press on behalf of the European Society for Medical Oncology

PACIFIC TRIAL: DURVALUMAB AFTER CTRT

- Stage III NSCLC
- Unresectable
- Non-progressive after at least 2 cycles of chemotherapy and radiotherapy
- Platin-based CT

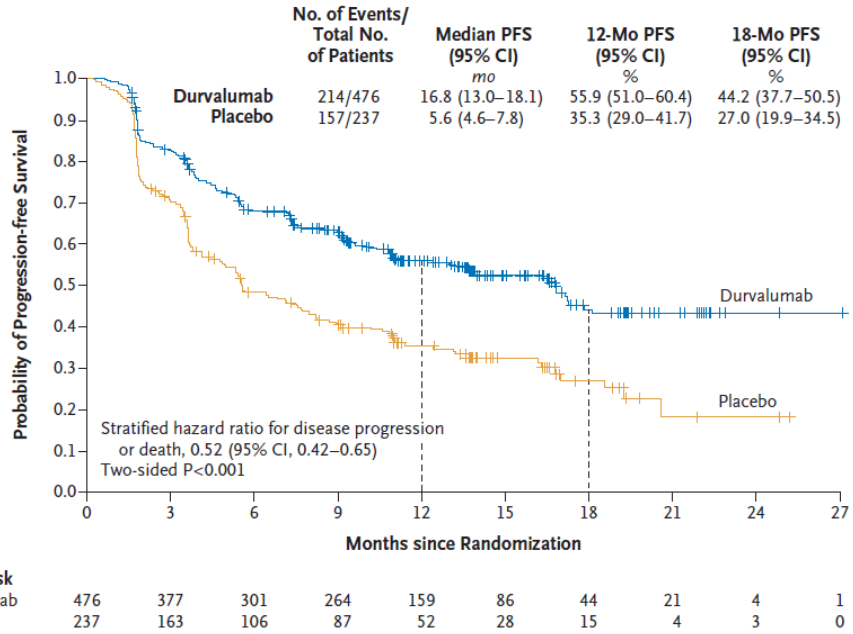
1-42 days after cCRT

R 2:1

Durvalumab
10 mg/kg/2 weeks until 12 months
(N = 476)

Placebo
10 mg/kg/2 weeks until 12 months
(N = 237)

- Primary objective:
  - PFS
- Secondary objectives:
  - Overall survival
  - Response rate
  - Safety



- Progression-free survival was significantly longer with durvalumab than with placebo. The secondary end points also favoured durvalumab, and safety was similar between the groups
- There was a small increase in the frequency of radiation pneumonitis and immune-related adverse events as expected in the durvalumab arm

FOR CLINICAL PRACTICE IN 2017

- Concurrent chemo-radiotherapy is the standard treatment for patients with unresectable stage III NSCLC:
  - Fit patients with PS = 0 or 1, age <70 or 75 years, weight loss <5%, without important co-morbidities
  - Conformational 3D-RT, 60 to 66 Gy, 1.8 to 2 Gy daily, to begin early,
  - PET-SCAN to define target volume to treat
  - Platinum-based chemotherapy at cytotoxic dose , 3 to 4 cycles or carboplatin-paclitaxel weekly
  - No consolidation, no maintenance chemotherapy
  - Induction chemotherapy 1 to 2 cycles if delay needed to begin radiotherapy or to reduce tumour volume
- Only 40% of patients with unresectable stage III NSCLC are eligible for concurrent chemo-radiotherapy
- For the other patients, sequential chemo-radiotherapy or chemotherapy or radiotherapy alone are preferable
- 2nd ESMO Consensus Conference on Lung Cancer

De Ruysscher D, *et al.,* Ann Oncol 2009:20:98–102
Eberhardt WEE, *et al.,* Ann Oncol 2015;26:1573–88

FOR CLINICAL PRACTICE IN 2017

CT CT CT

RT 60 – 66 Gy

or

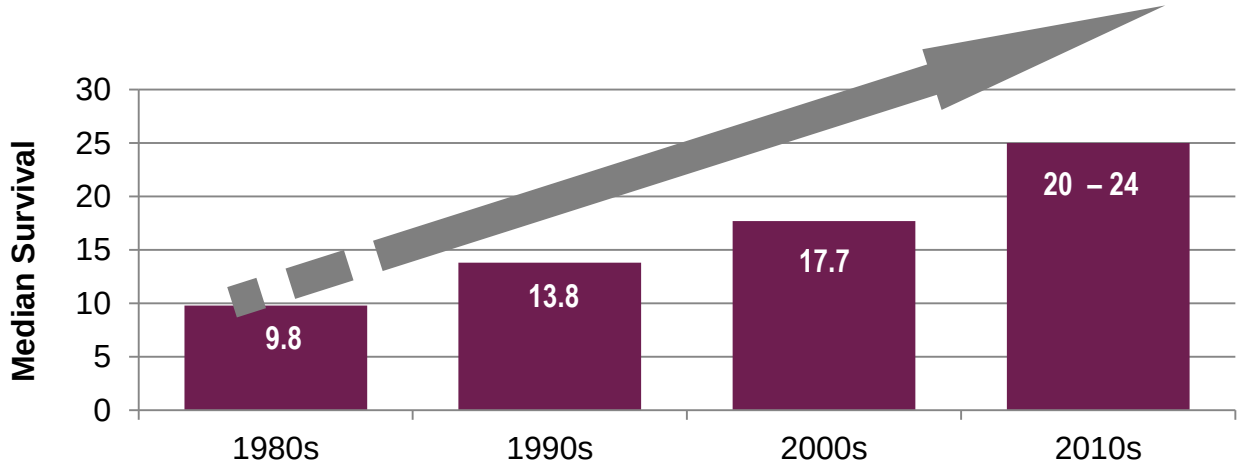
CT CT CT CT

RT 60 – 66 Gy

or

CT CT CT

RT 60 – 66 Gy



IS PROGRESS DUE TO BETTER TREATMENT OR BETTER PATIENTS SELECTION?

	CT	RT	Median OS (months)
K. Furuse (1999)	MVP	56 Gy (split)	16
Y. Segawa (2010)	MVP	60 Gy	23.7
N. Yamamoto (2010)	MVP	60 Gy	20.5

- In these 3 trials, chemotherapy is the same, only radiotherapy changes
- In 10 years, the overall survival improvement can be due to:
  - A better selection of patients with stage migration:
    - PET-SCAN, brain CT or MRI systematically at initial diagnosis
  - The impact of new technologies in radiotherapy: conformational 3D-RT, IMRT, better definition of target volume, related-RT toxicities decrease
  - A better management of chemo-radiotherapy and treatment-related toxicities

ESMO

Furuse K, *et al.,* J Clin Oncol 1999:17:2692–9; Segawa Y, *et al.,* J Clin Oncol 2010;28:3299–306; Yamamoto N, *et al.*, J Clin Oncol 2010;28:3739–45.

THANK YOU!