

# Smoking Cessation as Part of Cancer Therapy: Does It Really Impact Outcomes?

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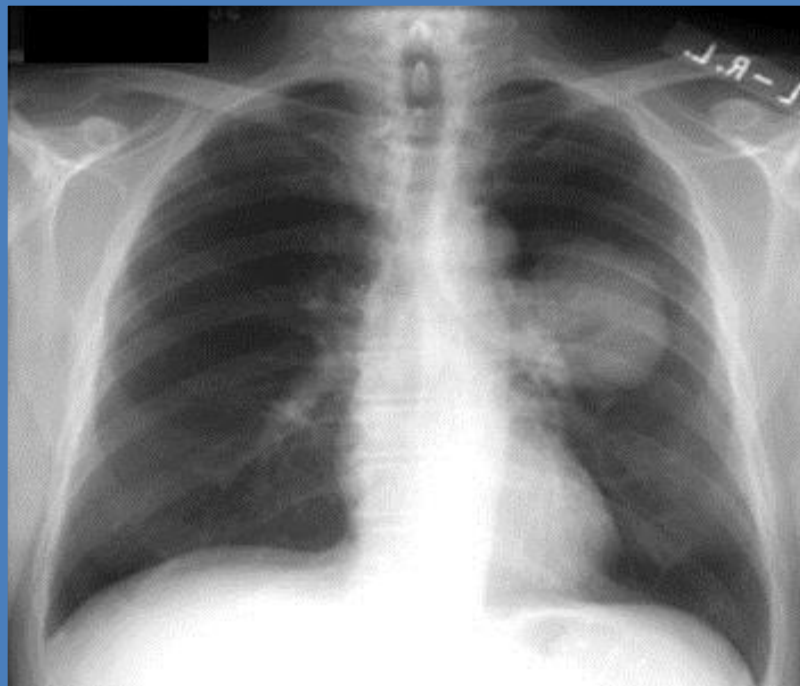
26-29 March 2014, Geneva, Switzerland

Organisers



- **Smoking along lung cancer history**
- Perceptions among thoracic oncology providers
- Overall impact of smoking cessation on lung cancer outcomes (all pathological types / all stages)
- In patients treated with curative intent
- In metastatic lung cancer
- Guidelines

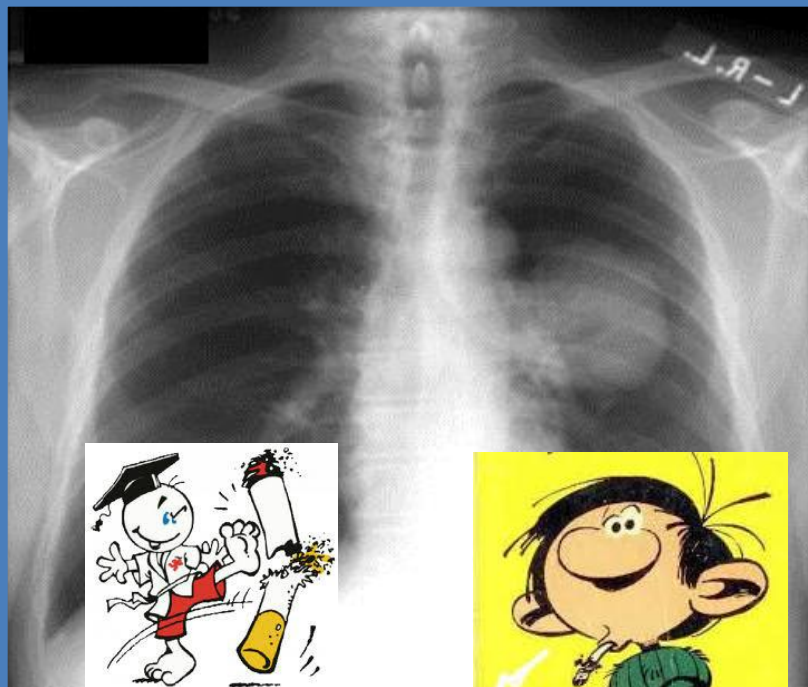
# Smoking along Lung Cancer History



Ferketich, Cancer 2013  
Cox, Cancer 2003

50% + 35%

# Smoking along Lung Cancer History

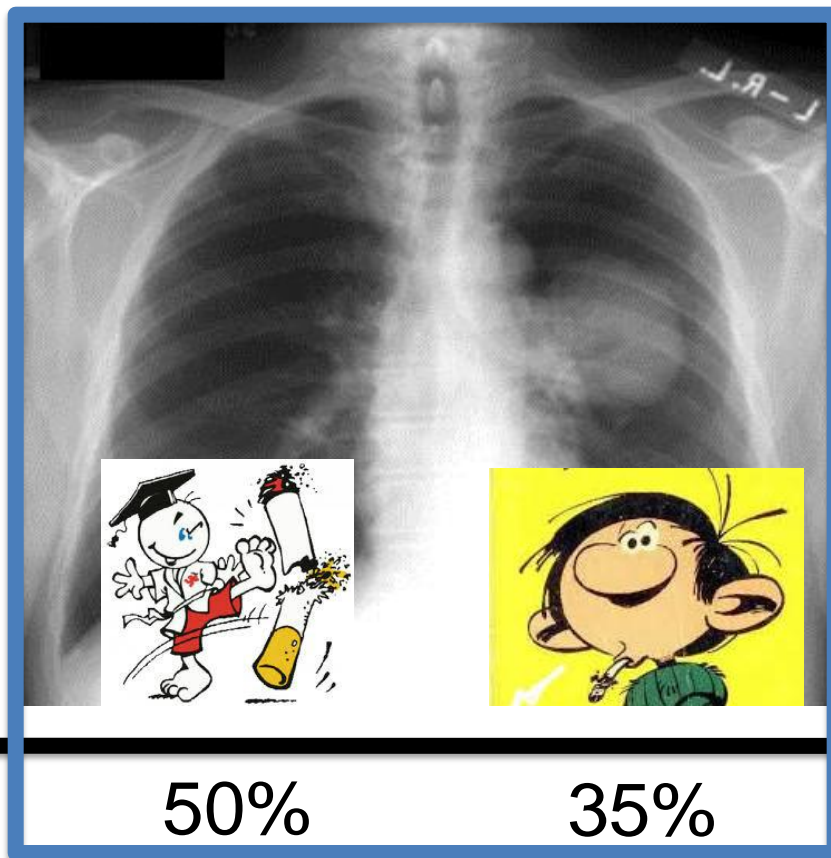


50%

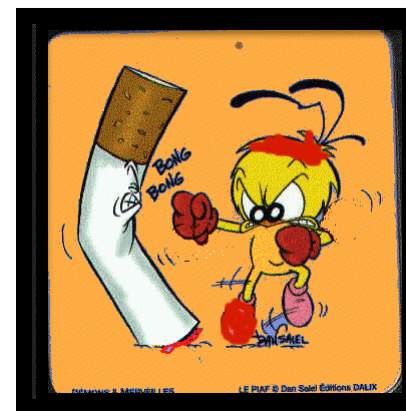
35%

Ferketich, Cancer 2013  
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# Smoking along Lung Cancer History



Ferketich, Cancer 2013  
Cox, Cancer 2003



14-55%

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# Perception among Thoracic Oncology Providers

**TABLE 5.** Physician Respondent Perceptions of Barriers to Providing Tobacco Cessation Interventions in Cancer Patients who Currently Smoke or Use Tobacco

Question		Strongly Agree (%)	Agree (%)	No Opinion or Neutral (%)	Disagree (%)	Strongly Disagree (%)
Inability to get patients to quit tobacco use		154 (11.7)	615 (46.7)	266 (20.2)	212 (16.1)	69 (5.2)
Waste of time—cessation does not affect outcomes in cancer patients		18 (1.4)	138 (10.5)	150 (11.4)	491 (37.3)	519 (39.4)
<b>Overall</b>	<b>Category</b>	<b>Respondents (%)</b>	523 (39.7)	295 (22.4)	321 (24.4)	108 (8.2)
			342 (26.0)	485 (36.9)	291 (22.1)	130 (9.9)
			720 (54.7)	218 (16.6)	172 (13.1)	40 (3.0)
			559 (42.5)	313 (23.8)	299 (22.7)	77 (5.9)
			1507 (40.5)			
			504 (33.4)	526 (40.0)	260 (19.8)	339 (25.8)
			282 (18.7)			92 (7.0)
			133 (8.8)			
			366 (24.3)			
			222 (14.7)			
Specialty	Medical oncology	504 (33.4)	526 (40.0)	260 (19.8)	339 (25.8)	92 (7.0)
	Pulmonary medicine	282 (18.7)				
	Radiation oncology	133 (8.8)				
	Surgery	366 (24.3)				
	Other	222 (14.7)				

Warren, J Thorac Oncol 2013

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Warren, J Thorac Oncol 2013

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Warren, J Thorac Oncol 2013

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# Prognostic Value of Smoking Cessation in Lung Cancer Patients

Prospective study, Roswell Park Cancer Institute, 1982-1998

Table 4. Mortality analyses in men

Disease site	Current <i>versus</i> recent quit			
	Model 1		Model 2	
	HR	(95% CI)	HR	(95% CI)
Overall mortality				
Lung	1.40	(1.09, 1.80)	1.38	(1.06, 1.79)

← within 1 month of diagnosis

Table 5. Mortality analyses in women

Disease site	MP	Current <i>versus</i> recent quit			
		Model 1		Model 2	
		HR	(95% CI)	HR	(95% CI)
Overall mortality					
Lung	All	0.95	(0.72, 1.26)	0.97	(0.73, 1.29)

Warren,  
IJC 2013

# Effectiveness or Comorbidity?

## Disease-specific mortality

Men 1.32 (1.02, 1.72)

Women 0.86 (0.63, 1.17)

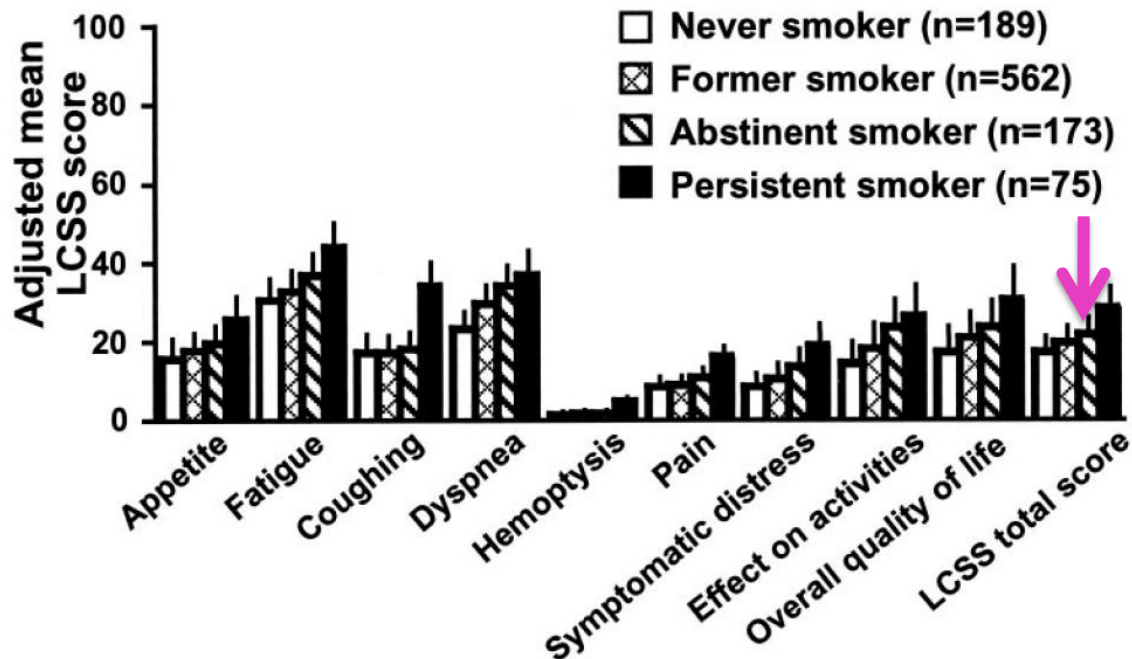
Warren, Int J Cancer 2013

Retrospective study, 1155  
lung cancer patients  
Henry Ford Health System  
Tammemagi, Chest 2004

variables	Model B, Adjusted for Baseline Covariates and Comorbidities
Smoking status (current vs former/never)	1.38 (1.18–1.60, < 0.001)
Age (per 10 yr)	1.36 (1.26–1.47, < 0.001)
Gender (male vs female)	1.12 (0.95–1.31, 0.18)
Illicit drug use	1.82 (1.09–3.04, 0.02)
Stage I	1.00 (referent group)
Stage II	2.28 (1.47–3.53, < 0.001)
Stage III	3.21 (2.48–4.15, < 0.001)
Stage IV	7.17 (5.55–9.27, < 0.001)
Stage, NOS	2.78 (1.98–3.91, < 0.001)
Histology, SqCC	1.00 (referent group)
Histology, adenocarcinoma	1.20 (0.98–1.48, 0.08)
Histology, BAC	0.52 (0.23–1.15, 0.11)
Histology, SCLC	1.51 (1.17–1.95, 0.002)
Histology, other defined types pooled	0.97 (0.61–1.53, 0.88)
Histology, NOS	1.43 (1.15–1.77, 0.001)
Symptoms, adverse ( $\geq 1$ vs 0)*	1.90 (1.57–2.30, < 0.001)
HIV/AIDS	3.20 (1.40–7.33, 0.006)
Tuberculosis, active or current	2.57 (0.62–10.68, 0.19)
Previous metastatic cancer	1.94 (1.06–3.56, 0.03)
Thyroid/glandular (nondiabetic)†	1.09 (0.81–1.47, 0.57)
Electrolyte/mineral imbalance	1.64 (0.89–3.02, 0.11)
Anemia (pretreatment)†	1.06 (0.79–1.42, 0.72)
Blood disorder (other than anemia)	3.27 (1.50–7.14, 0.003)
Dementia	2.00 (1.05–3.83, 0.04)
Neurologic disorder	1.86 (1.10–3.14, 0.02)
CHF	1.26 (0.97–1.63, 0.08)
COPD	1.19 (1.00–1.41, 0.05)
Asthma	1.35 (0.94–1.94, 0.10)
Pulmonary fibrosis	5.58 (2.00–15.53, 0.001)
Liver disease†	1.32 (0.85–2.05, 0.22)
GI hemorrhage	1.93 (1.08–3.45, 0.02)
Renal disease	1.48 (1.09–2.00, 0.01)
Musculoskeletal/connective tissue	1.28 (1.07–1.52, 0.006)
Osteoporosis	1.51 (0.93–2.46, 0.09)

# Quality of Life

- 1,506 lung cancer survivors treated between 1999-2002 (Mayo Clinic)
- Prospective QoL at 6 mo., 1 yr, /yr for 5 yr
- Mean LCSS scores :
  - 22.1 (SD 4.03) in patients who quit at diagnosis
  - 28.7 (SD 5.09) in persistent smokers



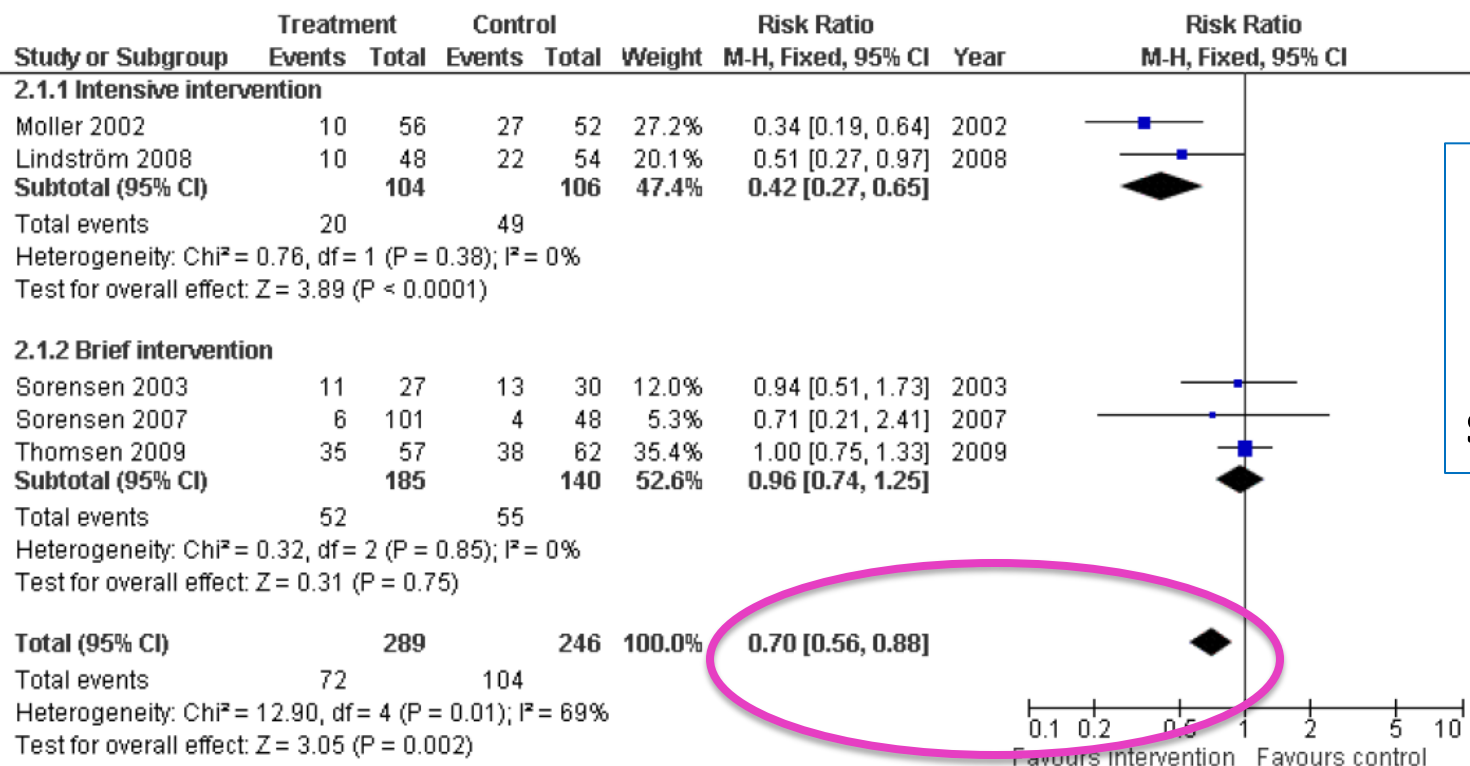
Adjusted on age, diagnosis, gender, stage, time of follow-up; Trend ( $p=0.0003$ )

Garces, Chest 2004



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# Reduction in Any Postoperative Complication



**8 RCT  
(0 lung  
cancer  
surgery)**

Thomsen, Cochrane 2010

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# Stopping Smoking Shortly Before Surgery

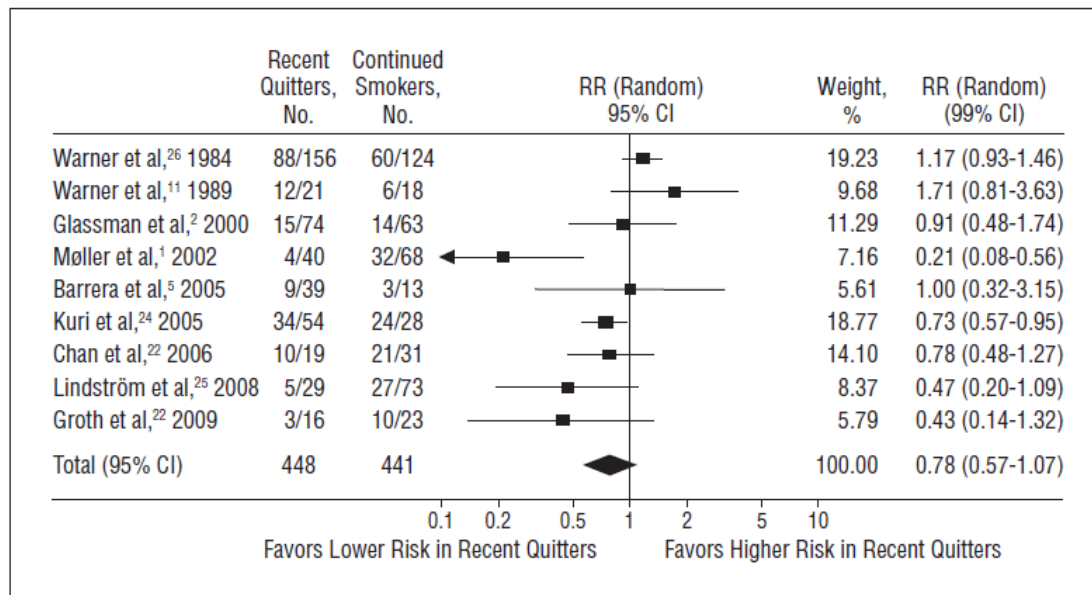
Table. Methodologic Characteristics of Included Studies

Source <b>N=9</b>	Study Period	Study Design	Definition of Recent Quitters	Type of Surgery	Complications Assessed	Validation of Smoking Abstinence
Barrera et al, <sup>5</sup> 2005	30 d post surgery	Prospective	Smoke free 1-2 wk before surgery	Thoracotomy for lung tumors	Pulmonary complications	None
Chan et al, <sup>22</sup> 2006	During hospital stay	Retrospective	Smoke free less than 4 wk before surgery	Bilateral breast reduction	Wound complications	None
Glassman et al, <sup>2</sup> 2000	During hospital stay	Retrospective	Smoke free up to 1 mo before surgery	Posterior instrumental fusion at either L4-L5 or L5-S1	Wound complications	None
Groth et al, <sup>23</sup> 2009	During hospital stay	Retrospective	Smoke free up to 1 mo before surgery	Pulmonary resection	All complications	None
Kuri et al, <sup>24</sup> 2005	During hospital stay	Retrospective	Smoke free up to 6 wk before surgery	Reconstructive head and neck surgery	Wound complications	None
Lindström et al, <sup>25</sup> 2008	30 d post surgery	Randomized controlled trial	Smoke free up to 3 wk before surgery	Hernia repair, laparoscopic cholecystectomy, hip and knee replacement	All complications	Carbon monoxide reading
Møller et al, <sup>1</sup> 2002	During hospital stay	Randomized controlled trial	Smoke free for up to 8 wk before surgery	Primary elective hip or knee alloplasty	All complications	Carbon monoxide reading
Warner et al, <sup>26</sup> 1984	30 d post surgery	Retrospective	Smoke free for up to 8 wk before surgery	Coronary artery bypass grafting	Pulmonary complications	None
Warner et al, <sup>11</sup> 1989	7 d post surgery	Prospective	Smoke free for up to 8 wk before surgery	Elective coronary artery bypass grafting	Pulmonary complications	Urinary cotinine

Myers,  
Arch Intern  
Med 2011

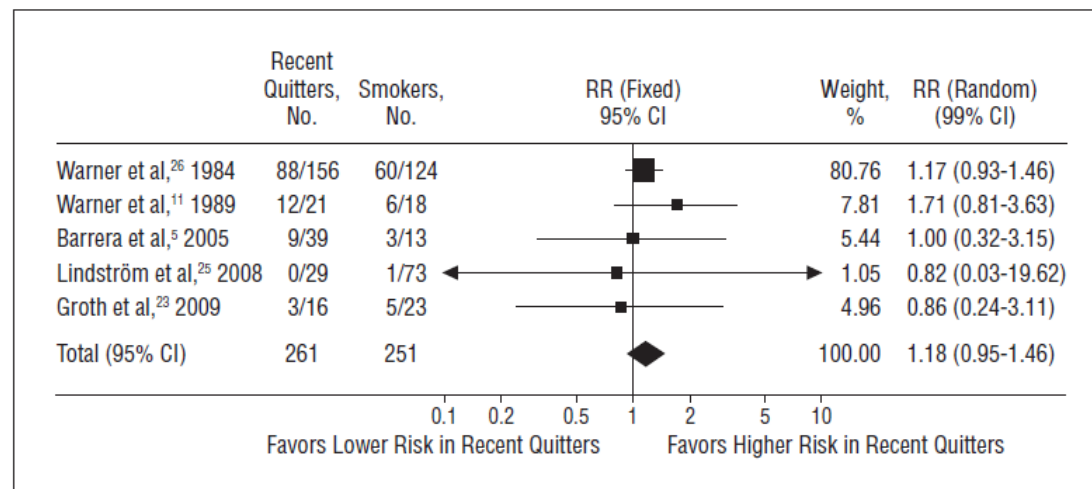
# Impact on Postoperative Complications

Any



Myers,  
Arch Intern  
Med 2011

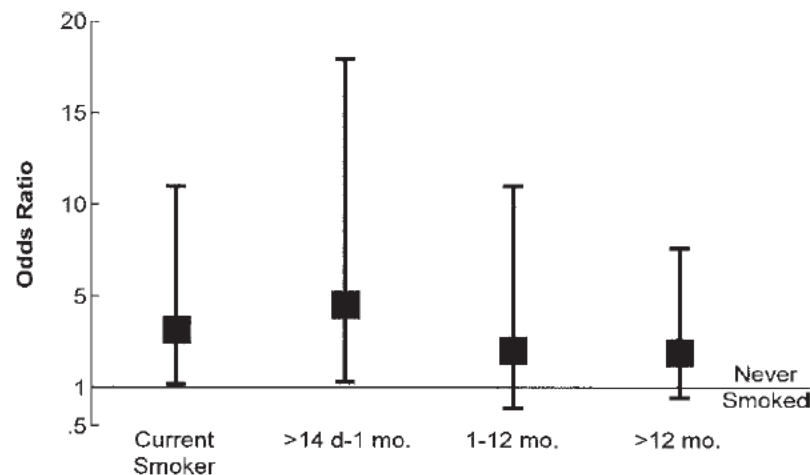
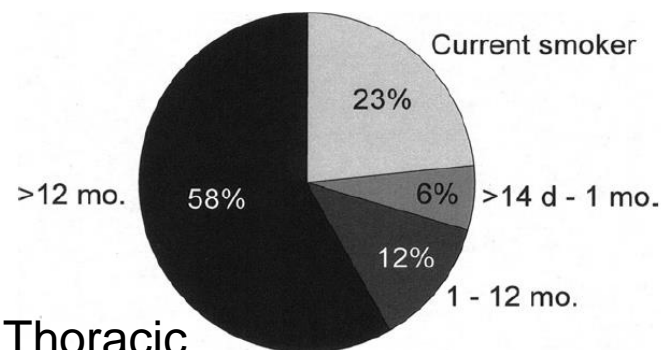
Pulmonary



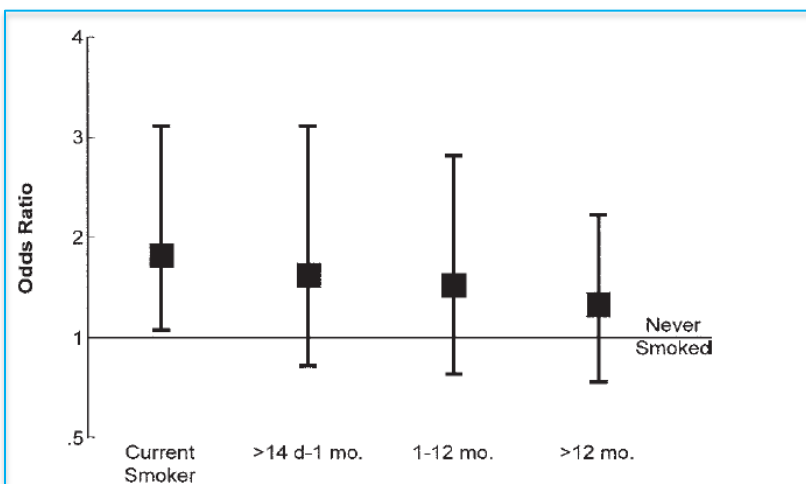
# Optimal Time of Smoking Cessation

Retrospective (Society of Thoracic Surgeons General Thoracic  
Surgery Database) (Mason, Ann Thorac Surg 2009)

7 990 lung cancer resections



Hospital mortality (Multivariate)



Pulmonary complications  
(Multivariate)

# Toxicity of Radiotherapy

- Retrospective studies
- smoking status at referral or treatment initiation

Table 2. Comparison of Toxicity-Related Treatment Breaks According to Smoking Status During Chemoradiation

215 LS-SCLC*	Smoking		Not Smoking		P
	No. of Patients	%	No. of Patients	%	
Treatment break	18	9.7	20	10.8	.49
No treatment break	61	32.8	87	46.7	
Total	79	42.5	107	57.5	

\*Videtic, JCO 2003

- **No difference or even reduced risk of radiation pneumonitis in NSCLC and other cancers?**

(Hernando, IJROBP 2001 / Dehing-Oberije, Radiat Oncol 2009 )

- Biological rationale:
  - reduced inflammatory reaction (Bjermer L EJC 1992)
  - altered T cell response (Miller LG Chest 1982)
  - relative hypoxemia due to carboxyHb (Grau C IJROBP 1992)



# Effectiveness of Radiotherapy in NSCLC

Rades, IJROBP 2008

stage I-III  
RT +/-alone  
or combined

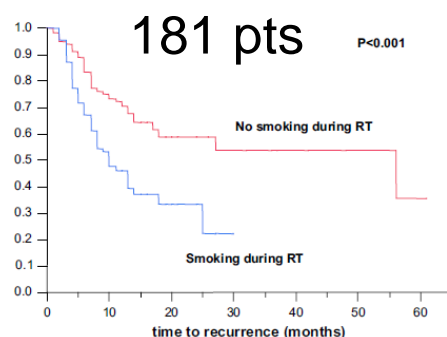


Fig. 3. Effect of smoking during radiotherapy (RT) on locoregional control.

Table 5. Multivariate analysis of factors significant for LRC on univariate analysis\*

Variable	RR	95% CI	p
KPS ( $\leq 70$ vs. $>70$ )	0.72	0.44–1.18	0.19
T stage (T1-2 vs. T3 vs. T4)	1.59	1.17–2.21	0.003 <sup>†</sup>
N stage (N0-N1 vs. N2 vs. N3)	1.24	0.93–1.69	0.15
Surgery (no vs. yes)	0.63	0.31–1.21	0.17
Respiratory insufficiency (none vs. partial vs. global)	1.27	0.78–2.09	0.34
Smoking during RT (no vs. yes)	1.74	1.06–2.89	0.029 <sup>†</sup>
Hemoglobin levels during RT ( $<12$ vs. $\geq 12$ g/dL)	0.77	0.45–1.28	0.31

Nguyen, Radiother Oncol 2010

stage I-III  
Post-op RT

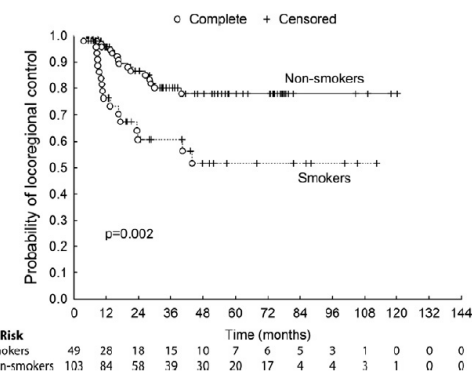


Fig. 2. Locoregional control as a function of smoking status. Data available for 103

Table 2

Multivariate analysis of clinical and treatment parameters on locoregional control.

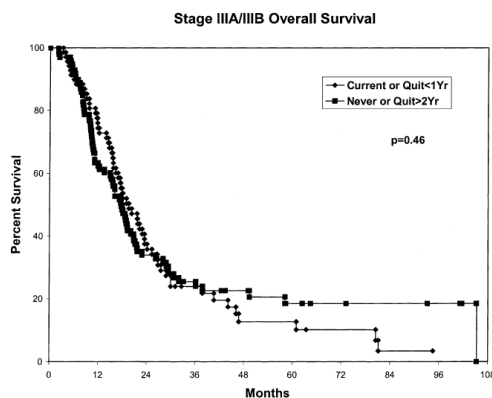
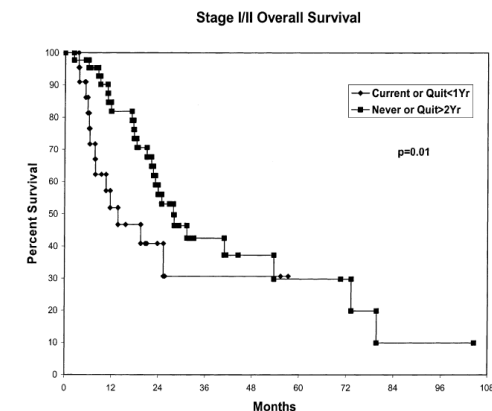
		HR	CI	p
Gender	F/M	0.77	0.35–1.7	0.5
Age	$>70/\leq 70$	1.02	0.46–2.2	0.94
N stage	N0–1/N2	0.36	0.15–0.73	0.01
Chemotherapy	No/yes	1.3	0.53–3.5	0.5
RT dose (Gy)	$\geq 45/<45$	0.56	0.23–1.37	0.2
Tobacco use	Yes/no	3.6	1.75–7.5	0.0006
Surgery	Other/pneumectomy	1.6	0.8–3.0	0.1
Margin status	Negative/positive	0.6	0.27–1.45	0.28
Histology	Adenocarcinoma/other	1.5	0.6–3.2	0.28

$p < 0.05$  is considered statistically significant.

CI = 95% confidence interval.

# Chemo-Radiotherapy

## For stage III NSCLC?



## LS-SCLC

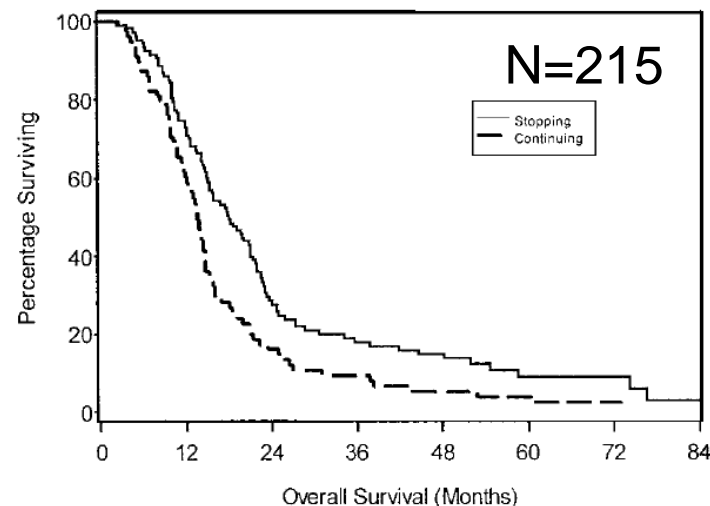


Fig 1. Actuarial overall survival according to smoking status during chemoradiotherapy ( $P = .0017$ ).

Multivariate: continued smoking  
 $HR=1.86$  ( $95\%CI=1.34-2.57$ ;  $p<0.001$ )

Videtic, JCO 2003

Fox, Lung Cancer 2004  
 Tsao, Cancer 2006

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# Risk of Second Primary cancer

- SCLC (Tucker, JNCI 1997)

Retrospective, 611 pts cancer-free >2 yr after treatment for SCLC (LS=79%) – 87 2<sup>nd</sup> primary cancers (risk x3.5/ general population)

51 lung cancer cases (NSCLC=98%)	Risk (/general population)	No RT	RT
All		X 7	X 13
Continued smoking	ND	X 5.9	X 21
Continued smoking + Alkylating agents	x 19	ND	ND

Radiation port 47%/ at the edge 18%/10% possible scatter

- NSCLC: no data

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# Metastatic Disease: Biological Background

- Pharmacokinetics:
  - drugs involving cytochrome P450 (taxanes, vinorelbine, etoposide, doxorubicin, cyclophosphamide, irinotecan / erlotinib, gefitinib) (Hamilton, Clin Cancer res 2006)
  - increased metabolic clearance, lower areas under the curve
- *In vitro* chemoresistance (squamous cell carcinoma):
  - Relative tissue **hypoxia** (nitric oxide ?)
  - **Nicotine:**
    - **Increased angiogenesis** (stimulation of endothelial nicotinic acetylcholine receptors)
    - **Reduced apoptosis** (MAP kinase and PKC pathways)
  - **Reduced immune response**

# Metastatic Disease: Treatment effectiveness?

- Randomised trials (RCT): (Mitchell, Clin Lung Cancer 2012)
  - Systematic review of 30 RCT testing first-line targeted treatments or chemotherapy for NSCLC
  - inadequate reporting of smoking status / **no conclusions**
- **Very few or indirect data:**
  - Retrospective study, 285 NSCLC + SCLC (Duarte, Lung cancer 2008)  
≥40 PY=worse response (plat-etoposide) - Mean PY= 62.5+/- 36.3 current vs 48.4+/-31.3 former smokers (p=0.003)
  - Subgroup analysis (Tammemagi, Chest 2004):  
HR adjusted for comorbidity = 1.35 in stage III-IV+ unstaged
  - Reflects a different biology?



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# Guidelines

- ACCP: « Among lung cancer patients undergoing:
  - surgery, we recommend perioperative cessation pharmacotherapy as a method for improving abstinence rates (1B)
  - chemotherapy, we recommend cessation interventions... (1B)
  - Radiotherapy, we recommend cessation interventions...(1C) »  
(Leone, Chest 2013)

## ESMO: SCLC (Früh, Ann Oncol 2014)

- The occurrence of second malignancies, particularly if smoking is continued, is of concern in survivors and smoking cessation counselling is essential

## ESMO: Stage I-III NSCLC (Vansteenkiste, Ann Oncol 2014)

- NSCLC patients should be offered smoking cessation, as this leads to superior treatment outcomes.

## ESMO: Stage IV NSCLC (Peters, Ann Oncol 2012)

In any stage of NSCLC, smoking cessation should be highly encouraged because it improves the outcome.

# Conclusions

- Strong rationale in favour of smoking cessation
- Lack of prospective high quality data
- Encourage smoking cessation, especially in patients treated with curative intent, as soon as possible
- Very few data in stage IV disease