SERVIZIO SANITARIO REGIONALE
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Policlinico S. Orsola-Malpighi

ALMA MATER STUDIORUM
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# Neoplasie polmonari: Terapia ottimale nella fase neoadiuvante

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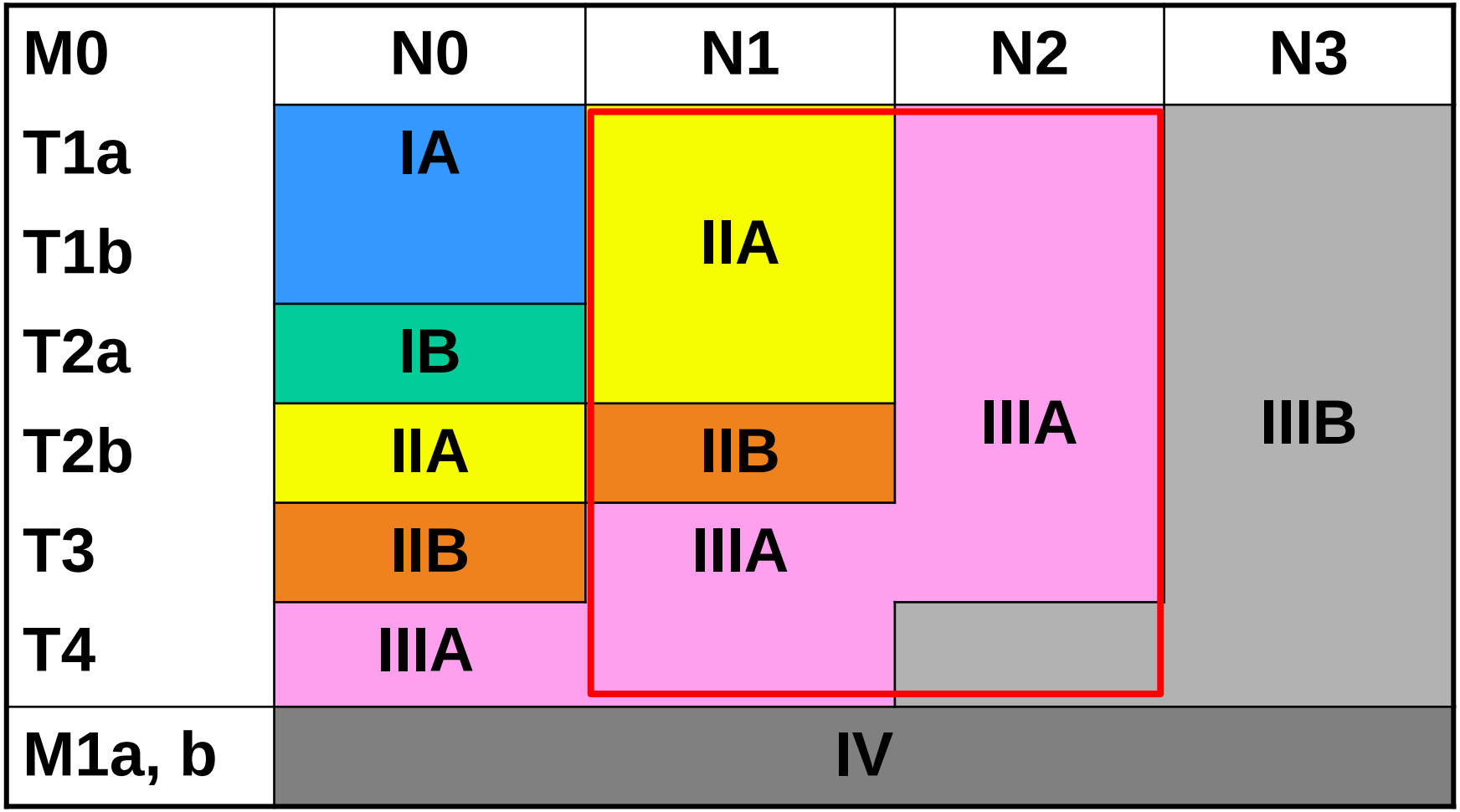
# Terapia neoadiuvante del NSCLC

- **Quali risultati**
- **Quali pazienti/stadi**
- **Neoadiuvante vs adiuvante**
- **Quale e quanta CT**
- **Quale terapia locoregionale post-CT**

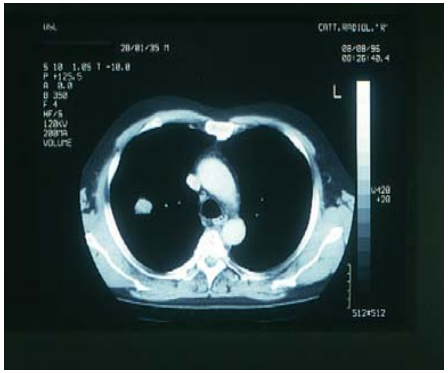
# Alcuni avvertimenti

- **Studi vecchi (non ci sono novità recenti)**
- **La stadiazione TNM cambia continuamente**
- **Strumenti per stadiazione in evoluzione (recente uso PET e EBUS -> stage migration)**
- **Teoria vs pratica**
- **Applicazione in clinica molto influenzata dal setting in cui si opera**

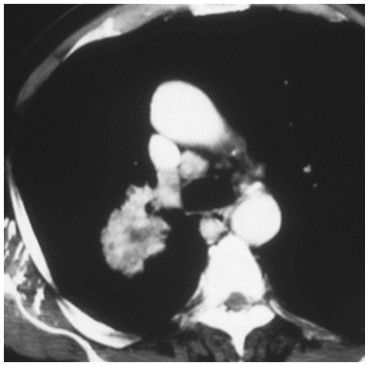
# TNM 7 Clinical Stage



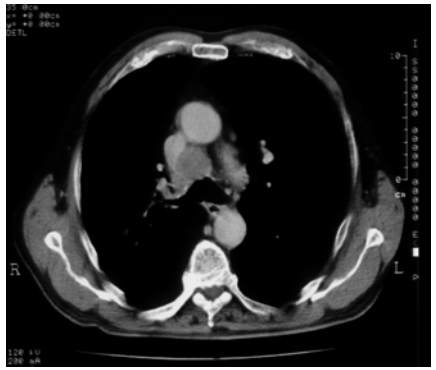
# NSCLC stadio III A



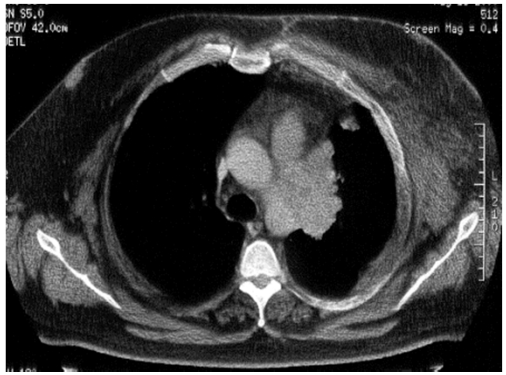
**N2 minimo (IIIA)**



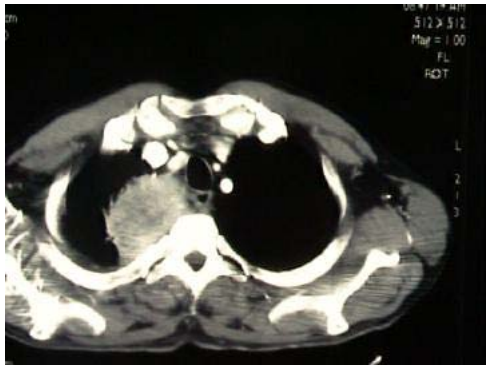
**N2 non- bulky (IIIA)**



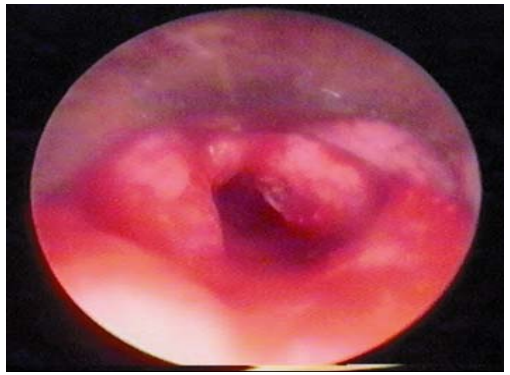
**N2 bulky (IIIA)**



**T4 (infiltrazione mediastinica)**



**T4 (infiltrazione parete toracica)**



**T4 (infiltrazione tracheale)**

# Clinicopathological 5 Y Survival*

| % (*95% CI*) | C | P |
|---|---|---|
| **I** | **45 (*43-47*)** | **54 (*51-56*)** |
| **II** | **34 (*30-38*)** | **38 (*34-41*)** |
| **IIIA** | **35 (*31-40*)** | **23 (*19-26*)** |
| **IIIB** | **27 (*17-38*)** | **17 (*12-23*)** |
| **All** | **41 (*39-43*)** | |

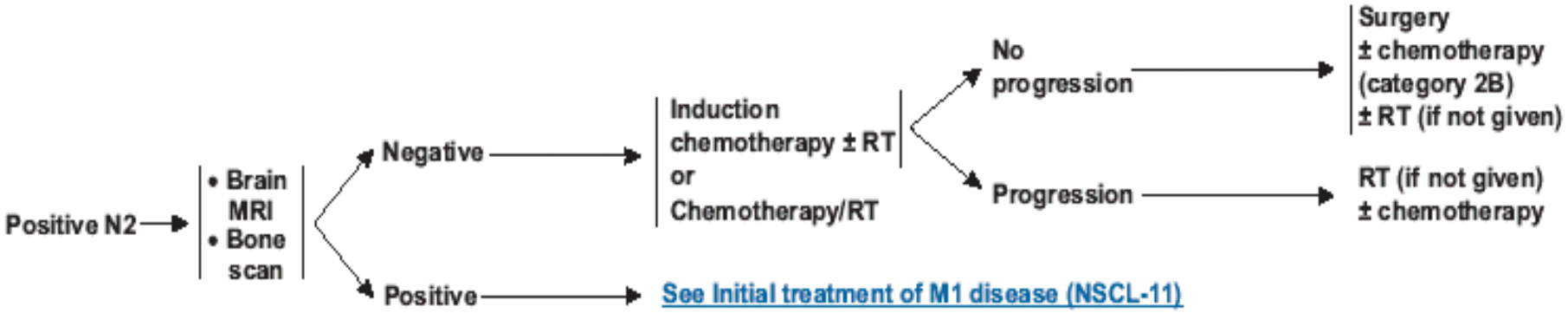
* N = 3275 patients in IASLC database with matched c-p data

*Van Meerbeeck, 2008*

NCCN National Comprehensive Cancer Network

Clinical Practice Guidelines in Oncology – v.1.2002

Neoadjuvant chemotherapy with surgery and/or chest radiation therapy should be considered for patients with good performance status who have stage IIIA NSCLC.



# Neoadjuvant = Preoperative chemotherapy

| Strenghts | Weaknesses |
| --- | --- |
| **-Early effect on micromet's** | **-Delay of surgery** |
| Improve survival | **-Increase in operative morbidity & mortality** |
| **-Better tolerance** | **-Late toxicity** |
| Improve compliance | Non-lung cancer mortality |
| **-Tumor shrinkage** | **-Based on cTNM** |
| Increase operability | Less reliable |
| Lesser resection | |
| Assesment of benefit | |

# CT neoadiuvante del NSCLC: Evidenze disponibili

- **10 studi randomizzati (3 su N2)**
- **3 meta-analisi dati pubblicati**
- **1 meta-analisi su dati individuali**
- **Nessuno studio randomizzato negli stadi III inoperabili**
- **2 studi randomizzati sulla migliore terapia locale (RT vs CH)**
- **1 studio di CT vs CT-RT neoadiuvante**

# Preoperative chemotherapy for non-small cell lung cancer: a systematic review and meta-analysis of individual participant data

*NSCLC Meta-analysis Collaborative Group**

# Treatment characteristics

| | |
|---|---|
| **Neoadjuvant only:** | **10/15 trials** |
| Peri operative: | 5 |
| PORT: | 8 |
| **Platinum-based:** | **14/15** |
| Cisplatin | 7 |
| Carboplatin | 4 |
| Both | 3 |
| Doublet | 9 |
| 3rd generation | 6 |
| 3 cycles | 8 |

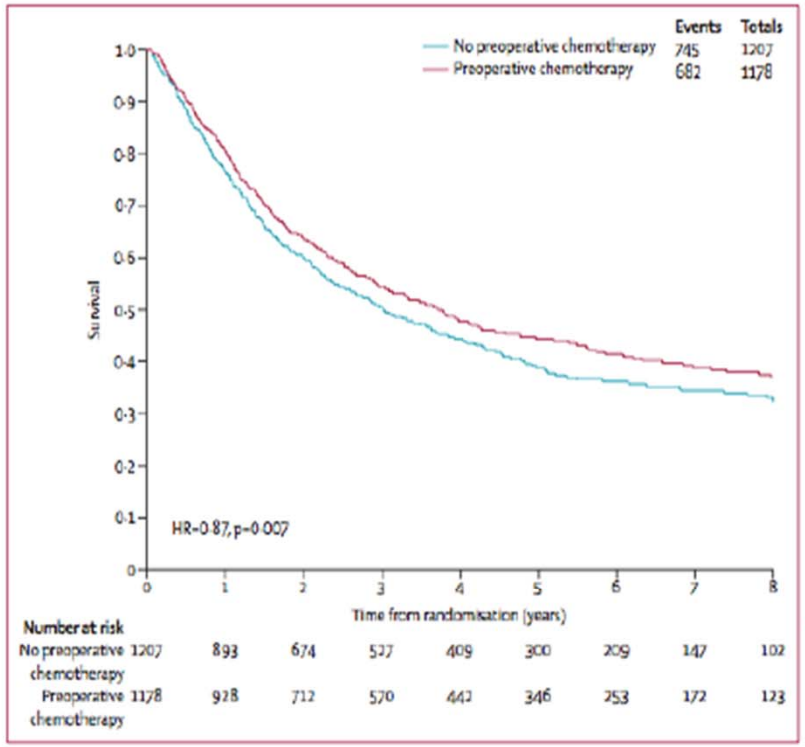
*NSCLC coll, Lancet 2014*

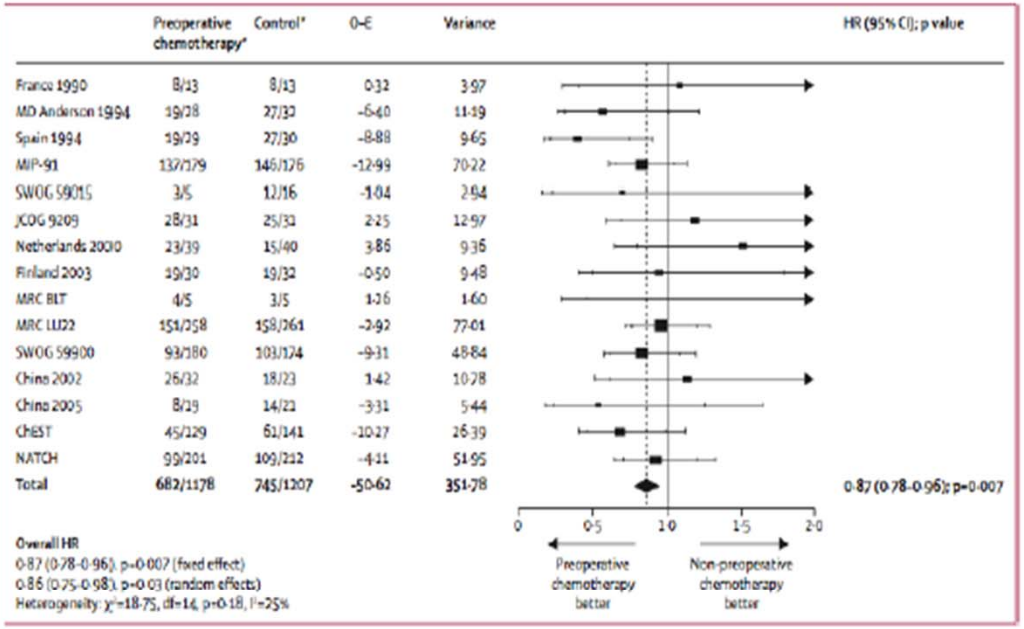
# Patient characteristics

| | S | CT-S |
|---|---|---|
| **N** | **1194** | **1165** |
| **Median age** | **62 (24-89)** | |
| **Male (%)** | **81** | **79** |
| **cIA (%)** | **5** | **6** |
| **cIB (%)** | **46** | **43** |
| **cIIA (%)** | **2** | **3** |
| **cIIB (%)** | **26** | **24** |
| **cIIIA (%)** | **21** | **24** |
| **PS 0-1 (%)** | **89** | **88** |
| **Squamous cell (%)** | **52** | **49** |

*NSCLC coll*, Lancet *2014*

# Efficacy of neoadjuvant chemotherapy



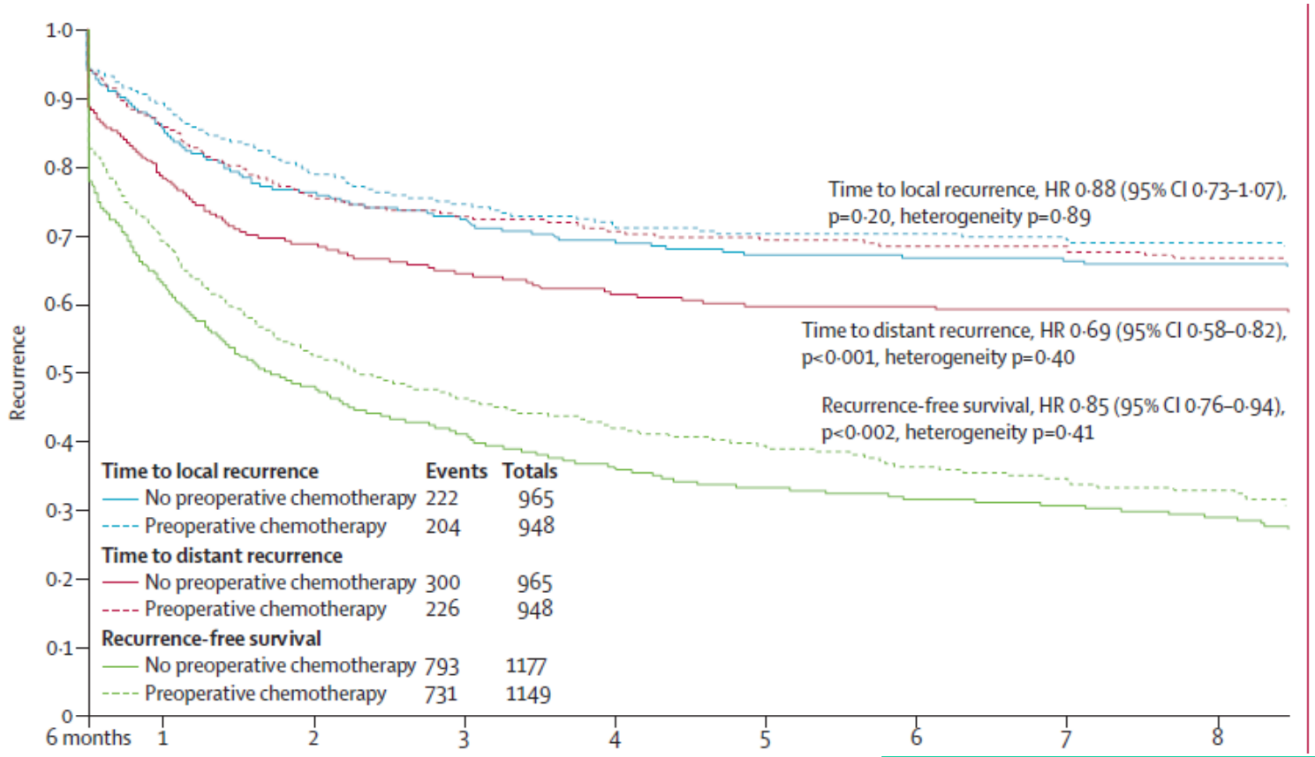




Improvement 5 year survival: 5% (40 – 45%)



NSCLC Metaanalysis Collaborative Group, Lancet 2014; 383: 1561-72

# Effect of pre-operative chemotherapy on time to loco-regional recurrence, time to distant recurrence, and recurrence-free survival




| Number at risk | | | | | | |
|---|---|---|---|---|---|---|
| **Time to local recurrence** | | | | | | |
| No preoperative chemotherapy | 965 | 594 | 422 | 334 | 265 | 212 |
| Preoperative chemotherapy | 948 | 628 | 459 | 387 | 317 | 269 |
| **Time to distant recurrence** | | | | | | |
| No preoperative chemotherapy | 965 | 569 | 420 | 342 | 268 | 214 |
| Preoperative chemotherapy | 948 | 617 | 462 | 391 | 319 | 269 |
| **Recurrence-free survival** | | | | | | |
| No preoperative chemotherapy | 1177 | 710 | 518 | 418 | 321 | 250 |
| Preoperative chemotherapy | 1149 | 771 | 572 | 474 | 379 | 305 |

| Absolute improvement % @ 5 y |
|---|
| + 3% |
| +10% (60 ->70) |
| +6% (30 -> 36) |

*NSCLC coll, Lancet 2014*

# Meta-Analysis of Neoadjuvant CT : Conclusions

- **Improved outcome (+5% at 5y) mainly due to an effect on micrometastatic disease**
- **No stage-specific effect**
- **Acceptable toxicity (no data on late toxicity)**
- **High compliance (2-3 cycles)**
- **Does not increase operative mortality**
- **Equivocal effect on downstaging**
- **No clear effect on extent and completeness of resection or loco regional recurrence**

# Meta-Analysis of Neoadjuvant CT : Caveats

- **UICC TNM <7**
- **Prior to widespread use of PET-CT and EBUS staging**
- **5 trials used pre-and postop chemotherapy**
- **No predictive biomarker investigated**
- **All stages included**
- **Role of PORT not defined**

# Prospective randomized comparison of neo-adjuvant vs adjuvant CT

| | N | Outcome | Hazard ratio | P value |
|---|---|---|---|---|
| **NATCH, *Felip 2010*** | **413** | **OS** | **0.93 (*0.71-1.23*)** | **0.61** |
| | | **DFS** | **0.88 (*0.68-1.13*)** | **0.31** |
| **Yang, *Pr ASCO 2013*** | **198** | **DFS** | **0.88 (*0.58-1.33*)** | **0.54** |

# Comparison of adjuvant vs neoadjuvant CT in NSCLC

**Adjuvant**

**# pts 8447**

**HR 0.86**

**p = 0.0001**

**5YS abs. benefit + 4%**

NSCLC MACG, Lancet 2010

**Neoadjuvant**

**# pts 2385**

**HR 0.87**

**p = 0.007**

**5YS abs. benefit +5%**

NSCLC coll, Lancet 2014

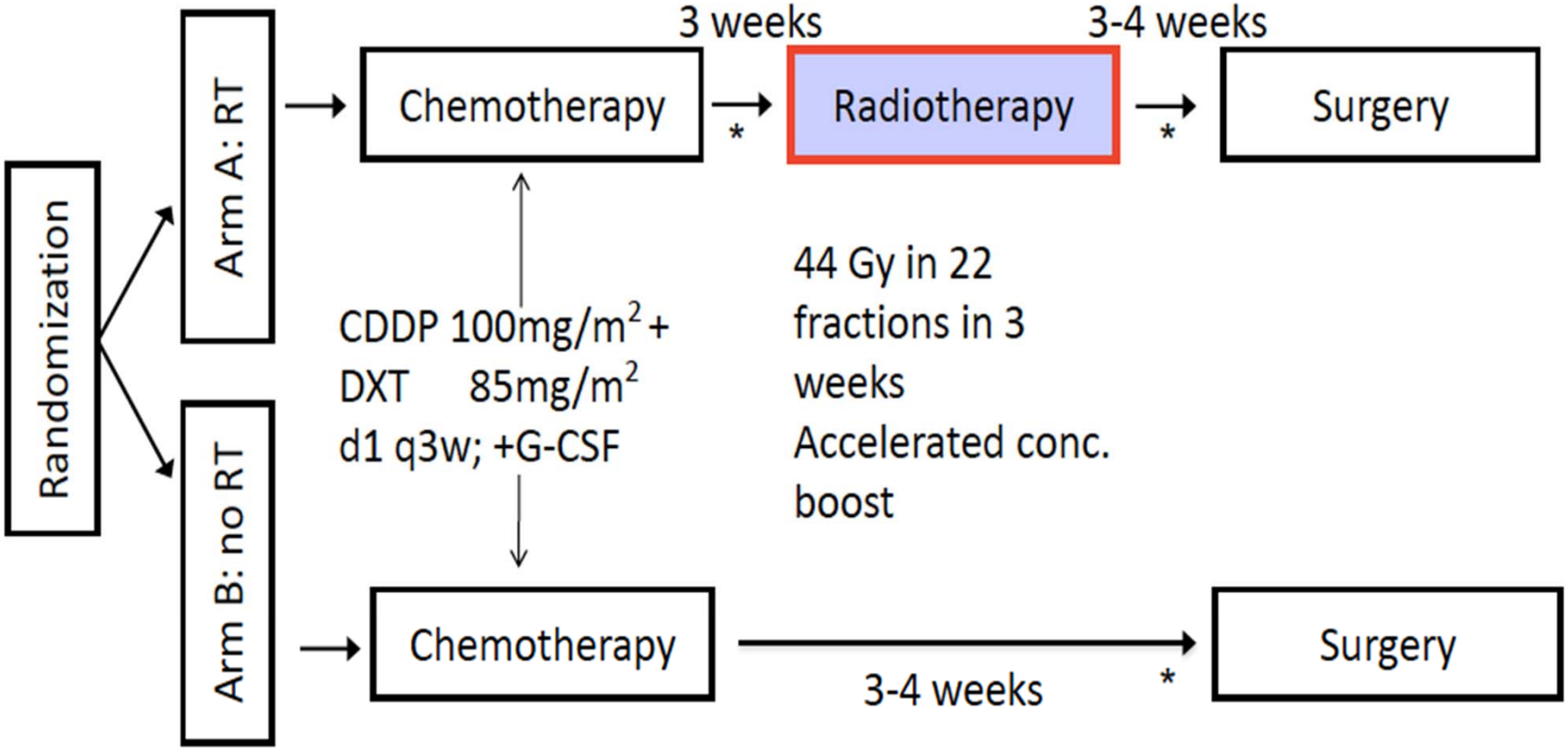
Indirect comparison meta-analisis: HR of adiuvant vs neoadiuvant = 0.96 (Lim et, JTO ’09)

# Which local treatment after neoadjuvant CT for N2 disease?

| TRIAL | PTS | STUDY QUESTION | N | Answer | 30-day Mortality | 5-Year Survival |
|---|---|---|---|---|---|---|
| US INT 1039 | Potential resectable N2 | Surgery vs CT/RT | 429 | No difference | 8% S<br>2% RT | 27%<br>20% |
| EORTC 08941 | Unresectable N2 | Surgery vs RT | 579 | No difference | 4% S<br>NR RT | 16%<br>14% |
| ESPATUE | Potential resectable IIIAN2/IIIB | Surgery Vs CT/RT | 246 | No difference | 6% S<br>2% RT | 44%<br>40% |

# SAKK 16/00 (IIIA/pN2 NSCLC): Trial design

**Stratification factors:** Mediastinal bulk (≥5cm vs. <5cm), weight loss (≥5% vs. <5% in past 6 months), center

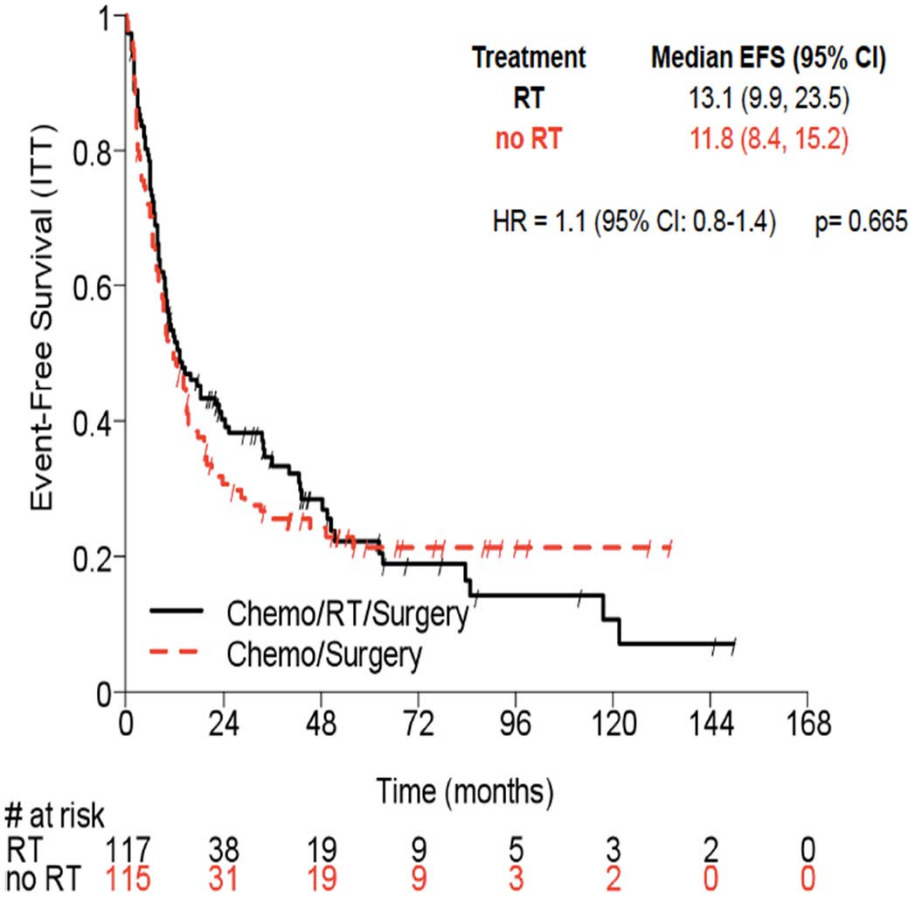



* Staging: (PET-) CT: PD went off study

SAKK

| | Induction CT-RT | Induction CT |
|---|---|---|
| ORR | 61% | 44% |
| R1/R2 | 9% | 22% |
| ypN2 | 33% | 44% |
| pCR | 16% | 12% |
| Local relapse | 24% | 35% |
| Distant relapse | 46% | 40% |

## Event Free Survival

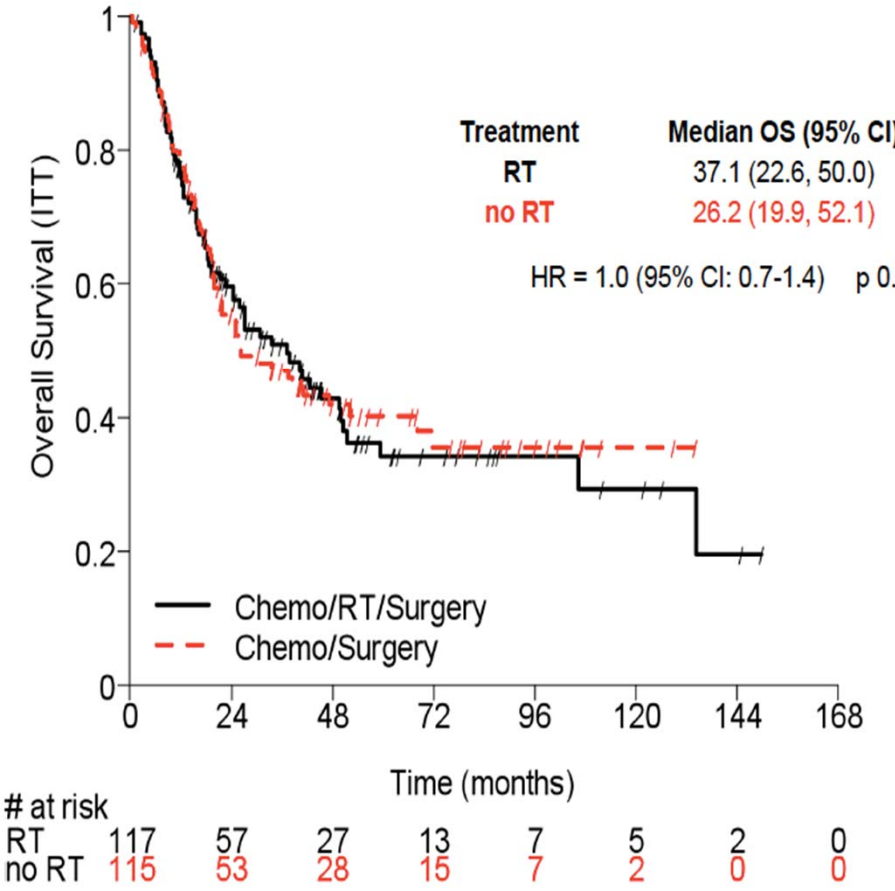



| Treatment | Median EFS (95% CI) |
|---|---|
| RT | 13.1 (9.9, 23.5) |
| no RT | 11.8 (8.4, 15.2) |

HR = 1.1 (95% CI: 0.8-1.4) p= 0.665

| # at risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| RT | 117 | 38 | 19 | 9 | 5 | 3 | 2 | 0 |
| no RT | 115 | 31 | 19 | 9 | 3 | 2 | 0 | 0 |

## Overall Survival




| Treatment | Median OS (95% CI) |
|---|---|
| RT | 37.1 (22.6, 50.0) |
| no RT | 26.2 (19.9, 52.1) |

HR = 1.0 (95% CI: 0.7-1.4) p 0.938

| # at risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| RT | 117 | 57 | 27 | 13 | 7 | 5 | 2 | 0 |
| no RT | 115 | 53 | 28 | 15 | 7 | 2 | 0 | 0 |

# CT neoadiuvante del NSCLC stadio I-III: Conclusioni

- **Complessivamente (meta-analisi) la CT neoadiuvante sembra produrre un beneficio simile a quello ottenuto con la CT adiuvante con migliore compliance**
- **Indicata in N1bulky, alcuni T3-T4, N2 non-bulky/pluristazionali**
- **3-4 cicli di un regime di terza-generazione a base di platino è lo «standard of care» (l'aggiunta di RT non migliora l'outcome)**
- **Post-CT neoadiuvante, RT e chirurgia danno risultati simili nel N2 (RT da preferire se necessaria pneumonectomia**
- **Quale strategia nei tumori «oncogene-addicted»?**

# Algoritmo terapeutico del NSCLC stadio IIB-III «inoperabile»