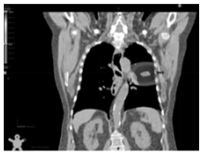
Meta-analysis in Lung Cancer



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Today's Roadmap

- **Part I: The Basics**
  - Epidemiology, Screening, and Staging
- **Part II: Non-Small Cell Lung Cancer**
  - Stage I
  - Stage II/III – Resectable and Unresectable
  - Stage IV
    - Oligometastases
- **Part III: Small Cell Lung Cancer**

Lung Cancer: A Public Health Problem

Lung cancer is the leading cause of cancer death in the world.

Alberg, CHEST 2013; 143(5)(Suppl):e1S–e29S

A Public Health Problem

A Public Health Problem

Risk Factors

- **Active Cigarette Smoking**
- **Other causal agents**: Secondhand smoke, ionizing radiation (including radon), occupational exposures (arsenic, chromium, nickel, asbestos), indoor and outdoor pollution
- **Additional risk indicators**: Age, male sex, family history, acquired lung disease (e.g. IPF)

143(5)(Suppl):e1S–e29S

Alberg, CHEST 2013

Screening

- At least 6 large RCTs evaluated lung cancer screening with CXR, and none showed a mortality benefit to screening
- Refinements in low-dose CT technology led to the NLST
  - Average dose 2 mSv.
- Eligible patients:
  - 55-74 years
  - 30 pack years of smoking; if quit, then within 15 years
  - 53,454 randomized to 3 annual LDCTs vs. 3 annual CXRs

NEJM Aug 2011: 365(5)

Screening

NEJM Aug 2011: 365(5)

Screening

- 20% relative reduction in lung cancer mortality
- 6.7% relative reduction in all-cause mortality
- Subsequent NEJM publication: ICER= $81,000 per QALY

NEJM Aug 2011: 365(5)

Staging Investigations

- History, Physical, Appropriate Labs, PFTs
- CXR, CE-CT chest/upper abdomen
- Whole body PET/CT
  - 2 RCTS show that use of PET (or PET/CT) avoids unnecessary surgery in ~10-20%
  - MRI head for stage III/IV

Getting Tissue from the Thorax

- Sputum cytology
- Bronchoscopy
- Endobronchial ultrasound
- Esophageal ultrasound
- Transthoracic biopsy
- Mediastinoscopy
- Electromagnetic navigation
- VATS

- Notes:
  - When nodes are positive on imaging, nodal biopsy is preferred first attempt at tissue as it provides diagnosis and stage
  - Histopathology preferred over cytology

Addressing the Mediastinum

Needle or Surgical Approach?

Surgical Approaches
Cervical: 1, 2, 3, 4, 7, +/- 10
Anterior: predominantly 5, 6

Needle vs. Surgical

- 241 patients with resectable NSCLC in whom mediastinal staging was indicated
- Randomized to surgical staging vs. combined EUS-FNA and EBUS-TBNA followed by surgical staging if negative

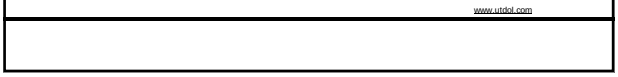
Annema et al , JAMA 2010

Needle vs. Surgical

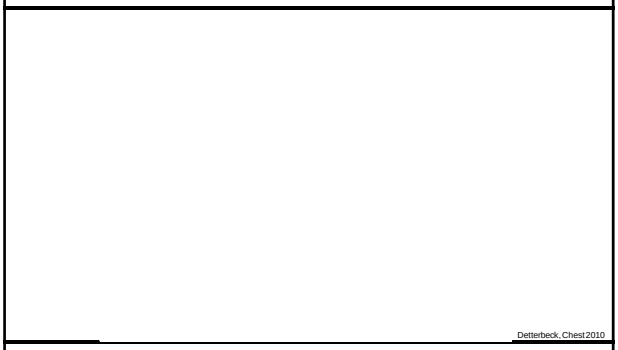
- 47% in EUS/EBUS arm avoided surgical staging

Annema et al , JAMA 2010

Staging System

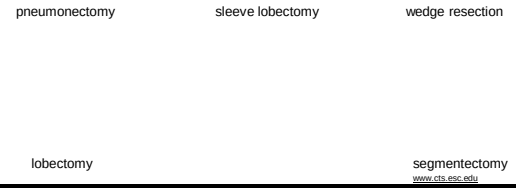


Staging System



Management: Stage I NSCLC

Types of Surgical Resections



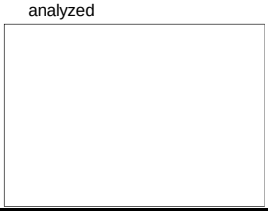
Types of Surgical Resections

- ❑ Lobectomy is the standard surgery for operable NSCLC.
- ❑ Various randomized /non randomized studies has shown survival advantage over limited resection [(1)]
- ❑ however several recent studies and metanalysis have compared sub lobar resection with lobectomy in appropriately selected early-stage NSCLC with mixed results [(2-5)]

1. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg 1995;60(3):615–623
2. Christopher Cao et al.Meta-analysis of intentional sublobar resections versus lobectomy for early stage non-small cell lung cancer : CORE group STUDY, Ann cardiothoracic surgery, 2014
3. Amgad El-Sherif,Outcomes of Sublobar Resection Versus Lobectomy for Stage I Non–Small Cell Lung Cancer: A 13-Year
Analysis, Ann Thorac Surg 2006; 82:408 –16
4.Okada M et al. Radical sublobar resection for small-sized NSCLC: a multicenter study. J Thorac Cardiovasc Surg 2006;132:769-75
5. Watanabe A et al. Feasibility of VATS segmentectomy for selected peripheral lung carcinomas. Eur J Cardiothorac Surg 2009;35:775-80

Stage I: Surgery Preferred

- 247 patients with T1N0 NSCLC analyzed



Annals of Thoracic Surgery 1995

Modern Sublobar Resection Outcomes

LR was defined as recurrence within the primary tumor lobe at the staple line (local progression), recurrence within the primary tumor lobe away from the staple line (involved lobe failure), or recurrence within hilar lymph nodes.

JCO 2014

World J Surg Oncol. 2014 May 1;12:138. doi: 10.1186/1477-7819-12-138.

Sublobectomy versus lobectomy for stage IA (T1a) non-small-cell lung cancer: a meta-analysis study.

Liu Y, Huang C, Liu H, Chen Y, Li S[1].

Author information

Abstract

BACKGROUND: Although lobectomy is considered the standard surgical treatment for the majority of patients with non-small-cell lung cancer (NSCLC), the operation project for patients with stage IA NSCLC (T1a, tumor diameters≤2 cm) remains controversial. Sublobectomy is appropriate only in certain patients as many doctors consider it to be overtreatment. We evaluated the five-year overall survival rate of sublobectomy and lobectomy for stage IA NSCLC (T1a, tumor diameters≤2 cm) through a meta-analysis.

METHODS: The five-year overall survival rate (OS) of stage IA (T1a) NSCLC after sublobectomy (including wedge resection and segmentectomy) and lobectomy were compared. We also compared the OS of stage IA (T1a) NSCLC after segmentectomy and lobectomy. The log (hazard ratio, ln (HR)) and its standard error (SE) were used as the outcome measure for data combining.

RESULTS: There were 12 eligible studies published between 1994 and 2013 in which the total number of participants was 18,720. When compared to lobectomy, there was a statistically significant difference of sublobectomy on OS of stage IA (T1a) NSCLC patients (HR 1.38; 95% confidence interval (95% CI), 1.19 to 1.61; P<0.0001). For the comparison between segmentectomy and lobectomy, there was also a statistically significant difference of segmentectomy alone on OS of stage IA (T1a) NSCLC patients (HR 1.48; 95% CI: 1.27 to 1.73; P<0.00001) CONCLUSIONS: We have concluded that in stage IA (T1a) patients sublobectomy, including segmentectomy and wedge resection, causes a lower survival rate than lobectomy.

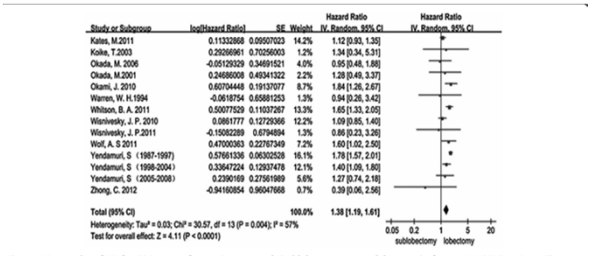


Figure 1 Forest plot of HR for OS impact of operative approach (sublobectomy versus lobectomy) of stage IA NSCLC patients. The combined HR displayed in this figure when compared with sublobectomy suggested that there was a significant benefit of lobectomy on OS of stage IA patients with tumors no larger than 2 cm, (HR 1.38; 95% CI, 1.19 to 1.61; *P* <0.0001) [5,9,12,16-24]. CI, confidence interval; df, degree of freedom; HR, hazard ratio, OS, overall survivalNSCLC,non-small cell lung cancer; SE, standard error

Conclusion: sublobectomy (including wedge resection and segmentectomy) causes lower OS in stage IA (T1a) NSCLC patients. Hence lobectomy is the best optimal choice

Systematic Review and Meta-Analysis of Randomized and Nonrandomized Trials on Safety and Efficacy of Video-Assisted Thoracic Surgery Lobectomy for Early-Stage Non–Small-Cell Lung Cancer

Tristan D. Yan, Deborah Black, Paul G. Bannon, and Brian C. McCaughan

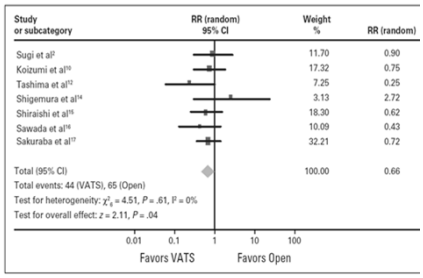
VATS vs open thoracic surgery meta analysis

- 21 studies; 2641 patients
- Two randomized trials
- 1391 VATS resections
- 1250 open resections

J Clin Oncol 27:2553-2562. © 2009 by American Society of Clinical Oncology

All cause mortality

Improved 5-year mortality rate of VATS (P = .04).



CONCLUSION:
Both randomized and nonrandomized trials suggest that VATS lobectomy is an appropriate procedure for selected patients with early-stage NSCLC when compared with open surgery

PLoS One. 2014 Oct 8;9(10):e109979. doi: 10.1371/journal.pone.0109979. eCollection 2014.

Mediastinal lymph node dissection versus mediastinal lymph node sampling for early stage non-small cell lung cancer: a systematic review and meta-analysis.

Huang X[1], Wang J[1], Chen Q[1], Jiang J[1].

First author, year, location	Participants	Study Group	Patients, n	Men, n	Age, y, median	Outcomes (MLND/MLNS)
Darling [10], 2011, USA	N0 or N1 NSCLC	MLND	525	272	67	Overall survival (52.4%/50.9%); local recurrence (5.7%/4.8%); distant metastasis (21.7%/22.3%)
		MLNS	498	257	68	
Allen [17], 2006, USA	N0 or N1 NSCLC	MLND	525	272	67	Complications (e.g., arrhythmia, prolonged air leakage, and pneumonia)
		MLNS	498	257	68	
Izbicki [18], 1998, Germany	In stage I–IIIA NSCLC	MLND	76	52	ND	Overall survival (70.6%/47.9%); local recurrence (28.9%/34.4%); distant metastasis (26.3%/31.2%)
		MLNS	93	73		
Izbicki [19], 1994, Germany	In stage I–IIIA NSCLC	MLND	82	56	58.5	Complications (e.g., arrhythmia, prolonged air leakage, and pneumonia)
		MLNS	100	80	60.9	
Sugi [20], 1998, Japan	Peripheral NSCLC<2 cm diameter	MLND	59	31	64.7±1.2	Overall survival (81.4%/83.9%); local recurrence (3.4%/3.6%); distant metastasis (10.2%/8.9%); complications (e.g., arrhythmia, prolonged air leakage, and pneumonia)
		MLNS	56	26	66.7±2.6	
Wu [21], 2002, China	In stage I–IIIA NSCLC	MLND	240	182	57	Overall survival (48.37%/36.98%); local recurrence (2.9%/4.8%); distant metastasis (22.5%/30.7%)
		MLNS	231	184	57	

Conclusion

- There was no statistically significant difference in overall survival, local recurrence, and distant metastasis between MLND and MLNS in early stage NSCLC patients.
- Furthermore, no evidence was found that MLND increased complications compared with MLNS.
- However, due to **significant staging heterogeneity** between RCTs, whether or not MLND is superior to MLNS remains to be determined.

Non-Surgical Patients: Older XRT

Qiao et al, Lung Cancer 2003

Stereotactic Radiation

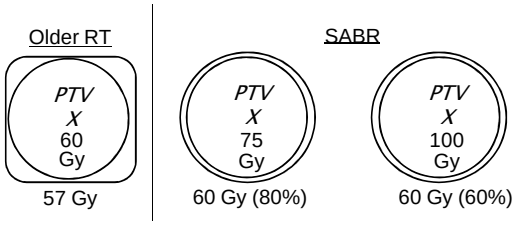
SBRT
Stereotactic Body Radiation Therapy

SABR
Stereotactic Ablative Radiation Therapy

Features of Lung SABR

- Accounting for Motion
  - •4D Planning
- Small tumour volumes
  - • Small margins
- Many Beam Directions
  - •7-11 Beams / Arc Therapy
- Steep dose gradients
  - • Inhomogeneous target dose
- Accurate Targeting
  - • CBCT pre-RT
- High dose per fraction
  - • Short total treatment duration

60 Gy in a Different Way



Senan, Palma, Lagerwaard, J Thorac Dis 2011

RTOG 0236

JAMA 2010

- Multicenter phase II trial
- Equivalent of 54 Gy in 3 fractions
- Primary tumor control 98%
- Lobar control 91%

- 2014 ASTRO update -- 5-year outcomes: primary tumor recurrence 7%, involved lobar recurrence 20%, regional recurrence 38% and distant recurrence 31%.

SABR Outcomes: VUMC Amsterdam

5 yr LC 89.5% 5 yr RC 87.3% 5 yr DC 80.1%

Senthi et al Lancet Oncology 2012

Dose: How much and where?*

Central Tumors

60/8

60/3

- Meta-analysis (Senthi 2012):
- BED_{10} ≥ 100 to maximize local control
- BED_3 ≤ 240 to keep risk of fatal toxicity to 1%.

Timmerman et al JCO 2006
Haasbeek et al JTO 2011

Still need to be cautious

Corradeeti, Haas, Rengan NEJM 2012

Still need to be cautious

- Awaiting RTOG 0813

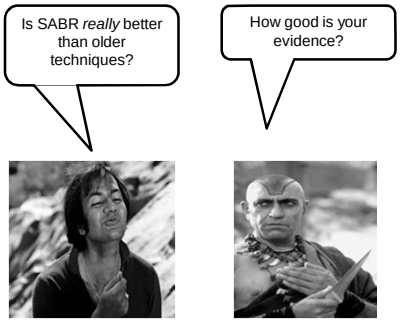
- Be aware of 'central' vs. 'ultra-central' locations (ASTRO 2014)

Overall, the SABR Evidence Looks Exciting!

We have excellent outcomes!

Let's SABR!

The Naysayers



Is SABR better than older techniques?

Timmerman J Clin Oncol 32:2847-2854

SABR Implementation: Population Data

- *Using the Amsterdam Cancer Registry, elderly patients divided into 3 time periods after the routine introduction of FDG-PET:*
  - *Period A (1999-2001): pre-SABR*
  - *Period B (2002-2004): some SABR availability*
  - *Period C (2005-2007): SABR fully available*

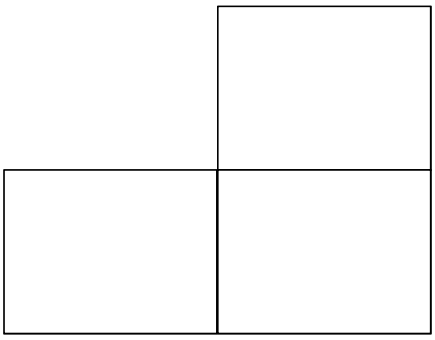
Palma et al JCO 2010
t al JC

SABR implementation

p<0.01

Palma et al JCO 2010

SABR implementation



Palma et al JCO 2010

SABR vs. older techniques

- At least two other population-based studies with similar results
  - Haasbeek, Netherlands, Annals of Oncology 2011
  - Shirvani, SEER-Medicare, IJROBP 2012
- At least 3 RCTs launched comparing SABR with standard or less-hypofractionated regimens
  - SPACE (Sweden) - completed
  - CHISEL (Australia)
  - LUSTRE (Canada)

RCT #1: SPACE

Comparison
66 Gy in 3 fractions (0.5 – 1 cm margin)
vs. 70 Gy in 35 fractions (2 cm margin)

Major Inclusion Criteria
- T1-2 N0 M0
- Medically Inoperable or Refusing Surgery
- WHO 0-2
- Biopsy proven or growing on CT with positive PET

Nyman et al, ESTRO 2014, OC-0565

SPACE

Variable	*SABR N=49*	*Conventional N=53*
Median Age	*72.7*	*75.3*
Male	*45%*	*36%*
COPD	*71%*	*64%*
T2	*47%*	*25%*
SCC	*18%*	*28%*
Adenocarcinoma	*45%*	*36%*

Nyman et al, ESTRO 2014, OC-0565

SPACE

- No differences in local control or survival outcomes

Variable	*SABR N=49*	*Conventional N=53*
Pneumonitis (any)	*16%*	*34%*
Esophagitis (any)	*9%*	*32%*
Any toxicity G3-5	*18%*	*16%*

- SAB[illegible] to old[illegible]

Nyman et al, ESTRO 2014, OC-0565

Stage I Inoperable: Summary

- SABR has been widely adopted as standard treatment for inoperable patients
- Non-randomized comparisons suggest better local control, better survival than with conventional treatments
- Convenience of SABR probably improves access to care
- Preliminary randomized data (SPACE) suggests that long-course treatments can also achieve good local control
- More randomized data is coming

Operable Patients

Onishi et al IJROBP 2011

SEER-Medicare: SABR vs. other techniques

- 10,923 patients aged 66+ with stage I NSCLC, 2001-2007
- Five treatment strategies: lobectomy (59%), sublobar (12%), conventional radiation (15%), observation (13%), SABR (1%).
  - Propensity matched
- Individual-level PET and co-morbidity data

Taljic

What is a Propensity Score?

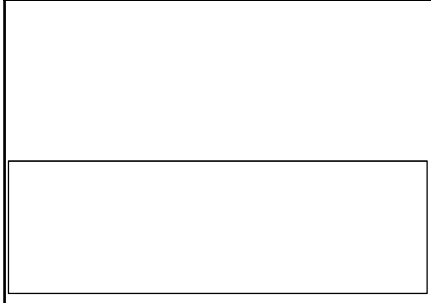
- A number assigned to an individual patient that takes into account numerous baseline confounders
- ‘Fitness Score’: 0 is poor, 100 is very good
  - Two patients may have same score but very different baseline characteristics
- Logistic model where the dependent variable is treatment allocation

$\ln[PS/(1-PS)] = \beta_0 + \beta_1(ECOG) + \beta_2(T\text{-stage}) + \beta_3(FEV_1) + \ldots$

SEER-Medicare: SABR vs. other techniques

t al JC

SABR vs. VATS lobectomy



Annals of Oncology Mar 2013

SABR vs. Wedge Resection

- 124 patients with stage I NSCLC not fit for anatomic lobectomy
- 69 wedge, 55 SABR
- SABR patients significantly older, higher Charlson scores

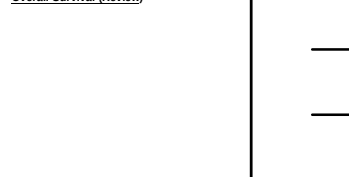
SABR vs. Wedge Resection

- SABR patients had **better** local control
- No differences in other types of recurrence or DSS
- SABR worse OS due to non-cancer deaths

"[SABR] may be equivalent, if not superior to, wedge resection for recurrence and CSS."

High Risk Patients: Severe COPD

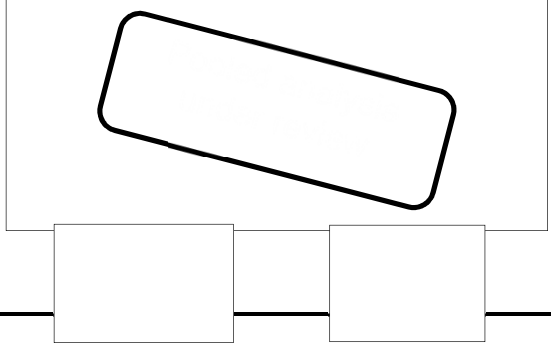
- Systematic Review of the Literature
  - Only 4 papers reported with subgroups of patients with severe/very severe COPD or ppo-FEV1<40%
  - All reported local control of ≥89%
  - 30 day mortality: all SABR studies = 0%, surgical average = 10%



Palma et al IJROBP 2011

In Search of Level 1 Evidence…

Randomized Trials



Summary: Stage I treatment

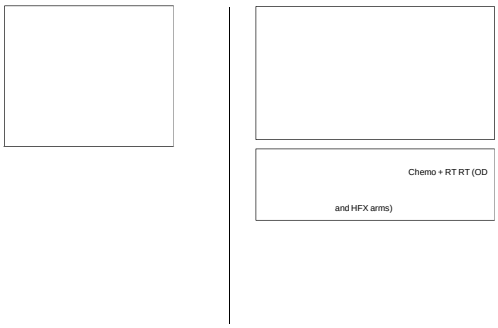
- Surgery remains standard of care, but non-randomized data suggests that SABR can achieve comparable outcomes
- Some randomized data expected in 2015. Trials being launched through VA system and in China
- SABR beats 3D-CRT on convenience and toxicity, but early RCT data suggests that good local control can also be achieved with very prolonged fractionation schedules

Management: Stage III NSCLC

Unresectable: RT alone

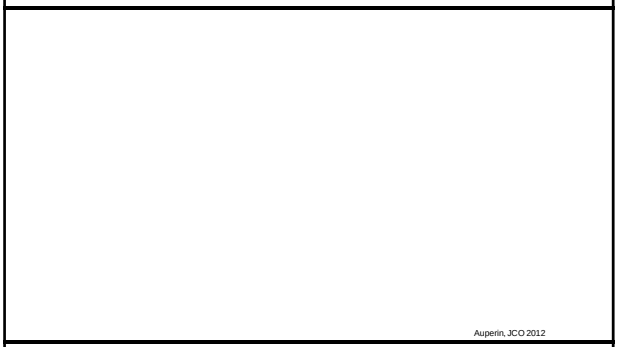
- Perez et al RTOG RCT (IJROBP 1986) established 60 Gy in 30 fractions based on highest rates of local control (no survival differences vs. 40 or 50 Gy).
- Altered fractionation provides a 2.5% benefit in 5-year survival (meta-analysis JCO 2012) at the expense of increased esophagitis

Chemo + RT vs. RT alone



JNCI 1995 and 1996
Chest 2000

Chemo: Concurrent vs. Sequential



Auperin, JCO 2012

NSCLC| Chemotherapy: Meta-analysis

Meta-analysis of 8 trials (778 patients) using cisplatin-based chemotherapy[1]

- **–Absolute improvement in survival of 10% at 1 yr**[1]
- –Median survival, BSC vs chemo: 4 vs 8+ mos, respectively

- Median survival now 12+ mos in more recent trials
  - –VEGF-targeted therapy plus platinum doublet[2]
- **Quality-of-life benefit from chemotherapy[3]**

1. NSCLC Collaborative Group, et al. BMJ. 1995;311:899-909.
2. Herbst R, et al. Clin Lung Cancer. 2009;10:20-27
3. Klastersky J, et al. Lung Cancer. 2001;34(suppl 4):S95-S101.
4. Chambers et al. BMC Cancer. 2012; 12: 184

Optimal Chemotherapy Unknown

- Most common options in U.S. are carboplatin/paclitaxel and cisplatin/etoposide
- No phase III data to compare these
  - Pneumonitis rates appear higher with carbo/paclitaxel
  - Phase II survival data favors cisplatin/etoposide
- Cis-Vinca alkaloid also reasonable

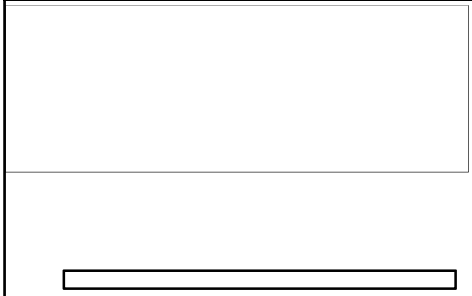
NSCLC| Initial Systemic Therapy: Doublets

Meta-analysis: 65 trials (N = 13,601) between 1980-2001
–Compared efficacy of
- Doublet vs single-agent regimens
- Triplet vs doublet regimens

Survival Outcome	Doublet vs Single-Agent Regimens	Triplet vs Doublet Regimens
1-yr OS	Doublet > single-agent ▪ OR: 0.80; 95% CI: 0.70-0.91; *P* < .001 ▪ 5% absolute benefit	Triplet = doublet ▪ OR: 1.01; 95% CI: 0.85-1.21; *P* = .88
Median OS	Doublet > single-agent ▪ MR: 0.83; 95% CI: 0.79-0.89; *P* < .001	Triplet = doublet ▪ MR: 1.00; 95% CI: 0.94-1.06; *P* = .97

Delbaldo C, et al. JAMA. 2004;292:470-484.

STRIPE Pneumonitis Meta-analysis



IJROBP 2011

Cis/Etoposide or Carbo/Paclitaxel?

Lung Cancer 2012

Cis/Etoposide or Carbo/Paclitaxel?

NSCLC| Bevacizumab

E4599

- Advanced NSCLC (stage IIIB or IV)- non- squamous
  - –Randomised to paclitaxel/ carboplatin or paclitaxel/carboplatin + bevacizumab
  - –Excluded brain mets and haemoptysis

	Median PFS	Median OS	RR	Significant Bleeding
PC	4.5	10.3	15%	0.7%
PCB	6.2	12.3	35%	4.4%
P-value	< 0.001	0.003	< 0.001	< 0.001

AVAiL

- Advanced NSCLC (stage IIIB or IV)- non- squamous
  - – Randomised to cisplatin/gemcitabine + placebo/low dose bevacizumab/ high dose bevacizumab
  - – Excluded brain mets and haemoptysis
  - – Confirmed outcome with less spectacular results

Reck M, et al. J Clin Oncol. 2009;27:1227-1234..
Sandler A, et al. N Engl J Med. 2006;355:2542-2550.

Optimal RT Dose – RTOG 0617

Optimal Dose – RTOG 0617

- **Factors predictive of OS**: Radiation dose (60 Gy), maximum esophagitis grade, PTV size, heart V5 and V30

Unresectable Stage III – Summary

- Concurrent chemoradiotherapy is preferred
  - Optimal chemotherapy is an open question
- Randomized evidence best supports a total dose of 60 Gy in 2 Gy daily fractions with chemotherapy
- Sequential chemoradiation, and radiation alone are options in less-fit patients

Resectable Stage III NSCLC

- Options for curative-intent treatment:

Surgery ⟹ Chemo ± RT

Chemo ⟹ Surgery ⟹ ± RT

ChemoRT ⟹ Surgery

Concurrent ChemoRT

Others: sequential chemoRT
RT alone

Sobering quote:
"While there are many potential treatment options, none yields a high probability of cure."

– Schild et al, utdol.com

Option 1: Surgery first

- In carefully selected patients with limited stage IIIA disease that can be completely resected, initial surgery is often the treatment of choice
  - Examples include T3N1 disease, or T4 disease due to multiple tumor nodules in one lung.
- Superior sulcus (Pancoast) tumors are a special case
  - SWOG 9416 evaluated neoadjuvant chemoRT for T3-T4 N0/1 superior sulcus tumors (45 Gy with concurrent cis/eto then resection)
  - 2-year survival 55%

Surgery first? Then what…?

JCO 2008

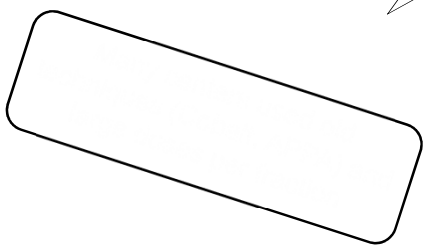
INDICATIONS – Post OP Radiotherapy

- Completely resected R0
- Stage I & II –no role.
- Stage IIIA- may benefit

- Other indications
  - Stage I & II – close/positive margins.
  - Stage IIIA
  - Close margin (<5mm),
  - Positive margin,
  - N2 disease,
  - Nodal ECE

Post-Operative Radiotherapy: PORT

PORT = Pretty Old Radiotherapy



Lancet 1998

Post-Operative Radiotherapy: PORT

Lancet 1998

PORT meta-analysis Trialist Group

- 2128 patients.
- 9 randomised trials of S +PORT vs Surgery
- 21% relative increase in the risk of death with RT
- 2 yr reduced OS from 55% to 48%
- Adverse effect was greatest for Stage I,II
- Stage.III (N2): no clear evidence of an adverse effect
- CRITICISM:
  - 25% pts were pN0
  - no quality control in the radiotherapy

Role Of PORT Called Into Question

Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials. PORT Meta-analysis Trialists Group. *Lancet* 1998;352(9124):257–263.

Post-Operative Radiotherapy: PORT

- Several subsequent observational studies suggest some value for PORT
  - Data sources:
    - ANITA trial (post hoc analysis – IJROBP 2008)
    - SEER (JCO 2006)
    - National Cancer Database (JTO 2014)
- PORT in N2 disease is the current topic of the Phase III European LUNG-ART randomized trial (EORTC 22055) – dose is 54 Gy in 30 fractions

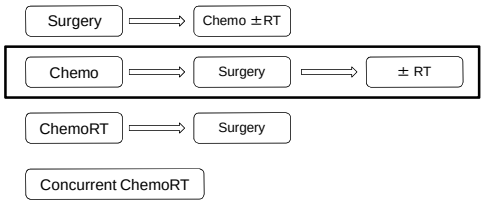
Lancet 1998

Where to treat? LUNG-ART guideline

Spoelstra, IJROBP

Resectable Stage III NSCLC

- Options for curative-intent treatment:



Option 2: Chemo before surgery

- Pre-operative chemotherapy improves survival compared to surgery alone (Meta-analysis, Lancet 2014).
- But, compared to post-operative chemotherapy, outcomes are similar (NATCH RCT).
- Induction chemotherapy may be considered in patients planned for surgery who have low volume/microscopic mediastinal disease

JNCI 2007

Option 2: Chemo before surgery

- If choosing induction therapy before surgery, no clear benefit to chemoradiation vs. chemo.
  - SAKK16/00 Phase III RCT: ASCO 2013
    - Randomized to cis-doc vs. cis-doc-RT (44Gy) before surgery
    - No benefits in RT group
  - 2 older RCTs showed similar results

JNCI 2007

Option 2: Chemo before ~~surgery~~ RT

60-62.5 Gy

JNCI 2007

Option 2: Chemo before ~~surgery~~ RT

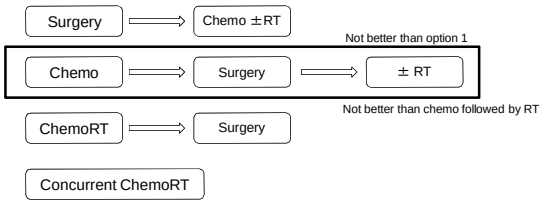
PFS OS

"In view of its low morbidity and mortality, radiotherapy should be
considered the preferred locoregional treatment."

JNCI 2007

Resectable Stage III NSCLC

- Options for curative-intent treatment:



Resectable Stage III NSCLC

- Options for curative-intent treatment:

Surgery ⟹ Chemo ± RT

Chemo ⟹ Surgery ⟹ ± RT

ChemoRT ⟹ Surgery

Concurrent ChemoRT

Option 3: ChemoRT first – or alone

Lancet 2009

Albain Trial

PFS OS

- Pneumonectomy operative mortality rate: 26% (15/54)

Lancet 2009

Albain Trial – Exploratory Analysis

Lobectomy vs. Matches

Pneumonectomy vs. Matches

Lancet 2009

Resectable Stage III NSCLC

- Options for curative-intent treatment:

Surgery ⟹ Chemo ± RT

Chemo ⟹ Surgery ⟹ ± RT

ChemoRT ⟹ Surgery

Concurrent ChemoRT

Not better than concurrent chemoRT overall.
May be considered when only lobectomy needed

Resectable Stage III NSCLC

- Options for curative-intent treatment:

Surgery ⟹ Chemo ± RT

Chemo ⟹ Surgery ⟹ ± RT

ChemoRT ⟹ Surgery

Concurrent ChemoRT

Conclusion: No strong evidence as to which approach is best.
Treatment decisions must be individualized

Resectable Stage III – Summary

- Based on randomized data, outcomes appear to be similar whether the definitive local treatment is surgical or radiotherapy based
- Primary surgical patients: adjuvant chemotherapy is standard, PORT is indicated if margin positive and debatable for N2.
  - The benefit of neoadjuvant treatment in resectable cases is unclear (compared to just post-operative chemotherapy)
- Primary chemoradiotherapy: benefit of adding surgery afterward, or instead of RT, is unclear

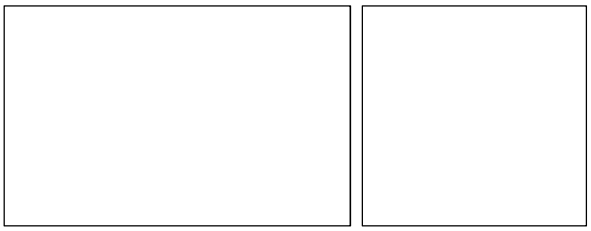
Other NSCLC Resources: Stage III

Other NSCLC Resources: Planning

JCO 2010

Oligometastatic NSCLC

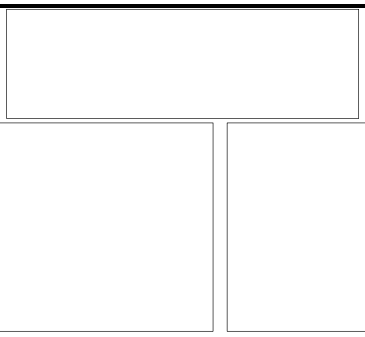
A Hot Topic Recently



A Hot Topic Recently

Back to the Case…

NSCLC Phase II Data



Prognosis: Oligometastatic NSCLC

Ashworth, Clin Lung Ca 2014

MDACC/Colorado Trial

Slide courtesy Dr. D Gomez MDACC

The COMET Trial

Principal Investigators
D. Palma, S. Senan

Target Sample Size
99

Palma et al, *BMC Cancer* 2012, **12**:305

Small Cell Lung Cancer

Epidemiology

- Approximately 15% of lung cancers – small decrease over past 30 years, higher proportion of women

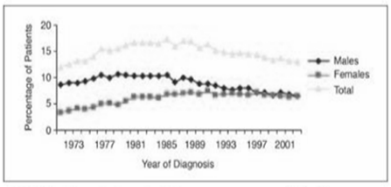
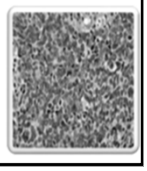


Fig 1. The diagnosis of small-cell lung cancer, as a percent of all lung cancers, over 30 years.

Pathology

- Small round blue cell tumor
- Virtually all are reactive for keratin and epithelial membrane antigen
- 75% have one more neuroendocrine markers
  - Chromogranin, synaptophysin, NSE, etc.



Staging – officially AJCC but…

NCCN Definitions

Limited Stage

- AJCC (7th edition) Stage I-III (T any, N any, M0) that can be safely treated with definitive radiation doses. Excludes T3-4 due to multiple lung nodules that are too extensive or have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan

Extensive Stage

- AJCC (7th edition) Stage IV (T any, N any, M 1a/b), or T3-4 due to multiple lung nodules that are too extensive or have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan

Stage Distribution and Survival

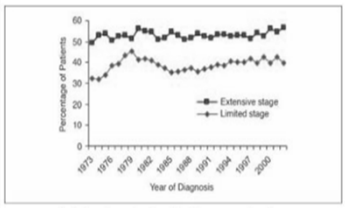


Fig 5. The diagnosis of small-cell lung cancer by stage.

Fig 10. The all-cause survival trends in limited-stage small-cell lung cancer.

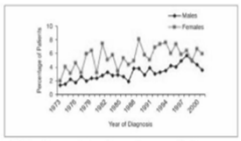


Fig 7. The all-cause survival trends in extensive-stage small-cell lung cancer.

Govindan JCO 2006

SCLC Resource

CRITICAL REVIEW

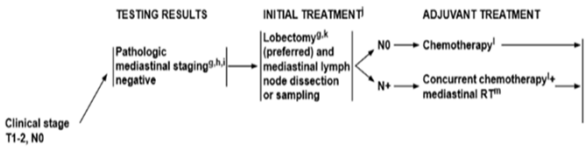
RADIOTHERAPY IN SMALL-CELL LUNG CANCER: LESSONS LEARNED AND FUTURE DIRECTIONS

BEN J. SLOTMAN, M.D., PH.D., AND SURESH SENAN, M.R.C.P., F.R.C.R., PH.D.

Department of Radiation Oncology, VU University Medical Center, Amsterdam, The Netherlands

Although chemotherapy is an essential component in the treatment of small-cell lung cancer, improvements in survival in the past two decades have been mainly achieved by the appropriate application of radiotherapy. The aim of the present study was to review the key developments in thoracic radiotherapy and prophylactic cranial radiotherapy and to discuss the rationale behind key ongoing studies in small-cell lung cancer.

Unique Scenario: T1–T2N0 lesions



- Surgery alone provides poor outcomes, but in combination with chemotherapy, outcomes are reasonable
- IASLC data: 439 patients with resected SCLC. In patients with stage I disease, 5-yr OS = 48%

The Role of Radiotherapy

- Similar data from two meta-analysis from 1992:

Pignon, NEJM: 13 trials: 5.4% OS benefit at 3-years

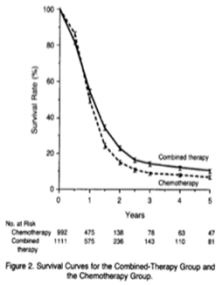
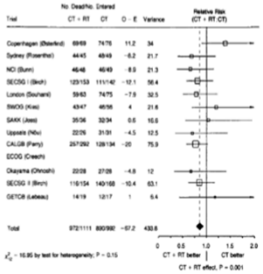


Figure 2. Survival Curves for the Combined-Therapy Group and the Chemotherapy Group.



Which Fractionation?

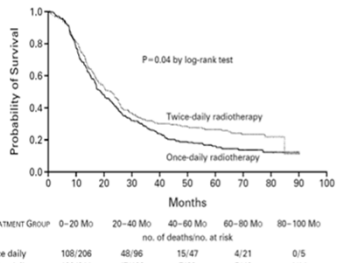
TWICE-DAILY COMPARED WITH ONCE-DAILY THORACIC RADIOTHERAPY IN LIMITED SMALL-CELL LUNG CANCER TREATED CONCURRENTLY WITH CISPLATIN AND ETOPOSIDE

ANDREW T. TURRISI, III, M.D., KYUNGMANN KIM, PH.D., RONALD BLUM, M.D., WILLIAM T. SAUSE, M.D., ROBERT B. LIVINGSTON, M.D., RITSUKO KOMAKI, M.D., HENRY WAGNER, M.D., SEENA AISNER, M.D., AND DAVID H. JOHNSON, M.D.

- 419 patients enrolled, all patients received 45 Gy starting with cycle 1 of EP: 45/30 BID vs. 45/25 OD
- Patients with CR offered PCI

NEJM 1999

Which Fractionation?



Treatment Group	0–20 Mo	20–40 Mo	40–60 Mo	60–80 Mo	80–100 Mo
	no. of deaths/no. at risk				
Once daily	108/206	48/96	15/47	4/21	0/5
Twice daily	100/211	47/109	7/62	5/42	1/14

- OS benefit at a cost of increased esophagitis
- Control arm (45/25) may be a low bar to clear

NEJM 1999

Which Fractionation?

70 GY THORACIC RADIOTHERAPY IS FEASIBLE CONCURRENT WITH CHEMOTHERAPY FOR LIMITED-STAGE SMALL-CELL LUNG CANCER: ANALYSIS OF CANCER AND LEUKEMIA GROUP B STUDY 39808

JEFFREY A. BOGART, M.D.,* JAMES E. HERNDON II, PH.D.,† ALAN P. LYSS, M.D.,‡ DOROTHY WATSON,† ANTONIUS A. MILLER,§ MICHAEL E. LEE,¶ ANDREW T. TURRISI, M.D.,§ AND MARK R. GREEN, M.D.§

- 2 cycles of paclitaxel + topotecan
- 70 Gy in 35 fractions with EP
- Phase II design, 63 patients

Table 5. Comparison of INT-0096 and CALGB 39808

Trial	INT-0096	CALGB 39808
Thoracic radiotherapy regimen	45 Gy twice daily	70 Gy every day
Patient and tumor characteristics		
Male	58%	54%
Weight loss > 5%	18%	31%
Age, years (median)	61	60
Supraclavicular adenopathy	4%	0
Toxicity profile		
Hematologic toxicity	87%	83%
Esophagitis	32%	21%
Outcome		
Median overall survival	20.3 months	22.4 months
2-year overall survival	44%	48%
2-year DFS	29%	31%

IJROBP 2004

Ongoing Trials

- Two ongoing trials:
  - CALGB 30610: 70 Gy/35 OD vs. 45 Gy/30 BID
  - CONVERT: 66 Gy/33 OD vs. 45 Gy/30 BID
- Reasonable doses include:
  - 60-70 Gy in 1.8 – 2 Gy per fraction
  - 45 Gy in 30 fractions BID (or similar short-course regimens)

When to Deliver RT?

Systematic Review Evaluating the Timing of Thoracic Radiation Therapy in Combined Modality Therapy for Limited-Stage Small-Cell Lung Cancer

Daniel B. Fried, David E. Morris, Charles Poole, Julian G. Rosenman, Jan S. Halle, Frank C. Detterbeck, Thomas A. Hensing, and Mark A. Socinski

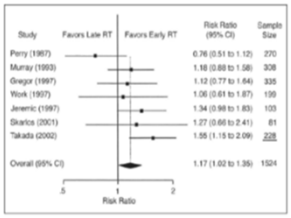
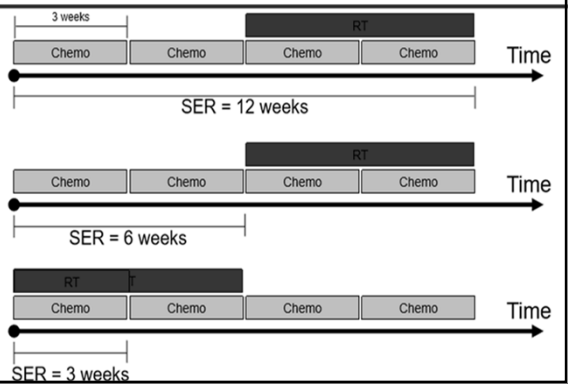


Fig 1. Two-year overall survival risk ratio forest plot for early v late thoracic radiation therapy (RT).

JCO 2007

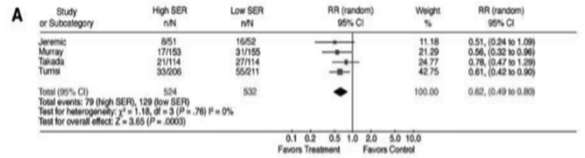
The SER: Start date to End of RT



The SER: Start date to End of RT

Time Between the First Day of Chemotherapy and the Last Day of Chest Radiation Is the Most Important Predictor of Survival in Limited-Disease Small-Cell Lung Cancer

Dirk De Ruysscher, Madelon Pijls-Johannesma, Søren M. Bentzen, André Minken, Rinus Wanders, Ludy Lutgens, Monique Hochstenbag, Liesbeth Boersma, Bradly Wouters, Guido Lammering, Johan Vansteenkiste, and Philippe Lambin



- Survival decrease of 1.86% per 1 week prolongation of SER
- Increased esophagitis with low SER

Treatment Volumes?

Multimodal Therapy for Limited Small-Cell Lung Cancer: A Randomized Study of Induction Combination Chemotherapy With or Without Thoracic Radiation in Complete Responders; and With Wide-Field Versus Reduced-Field Radiation in Partial Responders: A Southwest Oncology Group Study

By Merrill S. Kies, Joaquin O. Miro, John J. Crowley, T. Timothy Chen, Richard Pazdur, Petra N. Grosen, Saul E. Rivkin, Charles A. Coltman, Jr, John H. Ward, and Robert B. Livingston

JCO 1987

Omitting Elective Nodal Irradiation and Irradiating Postinduction Versus Preinduction Chemotherapy Tumor Extent for Limited-Stage Small Cell Lung Cancer

Interim Analysis of a Prospective Randomized Noninferiority Trial

Cancer 2011

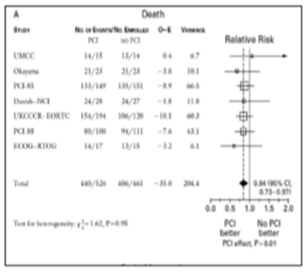
- Two RCTs have compared Pre-chemotherapy vs. Post-chemotherapy volumes
- SWOG study (started in 1979) used wide-field vs. limited-field 2-D planning
- Chinese study used 3D planning
- No differences in relapse rates or toxicity

- Dutch phase II data suggests that ENI is not required if a PET/CT is done for staging, but in the absence of PET/CT, isolated nodal relapse may be >10%.

Prophylactic Cranial Irradiation

PROPHYLACTIC CRANIAL IRRADIATION FOR PATIENTS WITH SMALL-CELL LUNG CANCER IN COMPLETE REMISSION

ANNE AUPERIN, M.D., RODRIGO ARRIAGADA, M.D., JEAN-PIERRE PIGNON, M.D., PH.D., CÉCILE LE PÉCHOUX, M.D., ANNA GREGOR, M.D., RICHARD J. STEPHENS, PAUL E.G. KRISTJANSEN, M.D., PH.D., BRUCE E. JOHNSON, M.D., HIROSHI UEOKA, M.D., HENRY WAGNER, M.D., AND JOSEPH AISNER, M.D., FOR THE PROPHYLACTIC CRANIAL IRRADIATION OVERVIEW COLLABORATIVE GROUP*



Caveats:

- In some trials, CR was defined by CXR
- A subsequent RCT showed no benefit to doses >25 Gy in 10 fractions

Extensive Stage SCLC

- Majority of SCLC patients have extensive stage disease
- Disease is highly responsive to chemotherapy, but median survival is 8-13 months
- Multiple RCTs have evaluated chemotherapy combinations and timing. Two-drug regimens are better than single-drug regimens, but >2 is not very beneficial but more toxicity
- Platinum + Etoposide (4-6 cycles) remains standard first-line in most centers
- Can radiation help improve survival?

Western UNIVERSITY · CANADA

OICR

PCI in ES-SCLC

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prophylactic Cranial Irradiation in Extensive Small-Cell Lung Cancer

- 286 patients with ES-SCLC randomized after any response to chemotherapy: PCI vs no PCI
- Several fractionations allowed: 20 Gy/5 and 30 Gy/10 most common
- Brain imaging was not part of standard staging and follow-up procedures, unless symptoms present

Slotman 2007

PCI in ES–SCLC

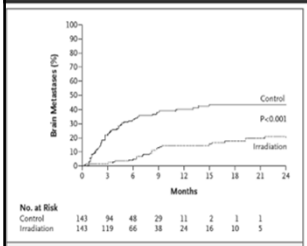


Figure 1. **Cumulative Incidence of Symptomatic Brain Metastases.**
The difference in the cumulative incidence of brain metastases between the irradiation group and the control group was significant (P<0.001, by Gray's method).

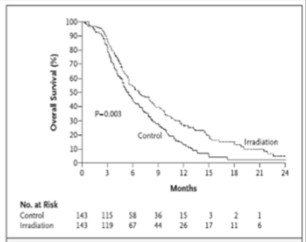


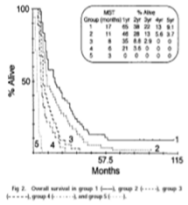
Figure 3. **Overall Survival.**
Patients in the irradiation group had a longer median overall survival (6.7 months) than did those in the control group (5.4 months) (P=0.003; hazard ratio, 0.68; 95% CI, 0.52 to 0.88).

Slotman 2007

Thoracic Radiotherapy

Role of Radiation Therapy in the Combined-Modality Treatment of Patients With Extensive Disease Small-Cell Lung Cancer: A Randomized Study

By Branislav Jeremic, Yuta Shibamoto, Nebojsa Nikolic, Biljana Milicic, Slobodan Milisavljevic, Aleksandar Dagovic, Jasna Aleksandrovic, and Gordana Radosavljevic-Asic

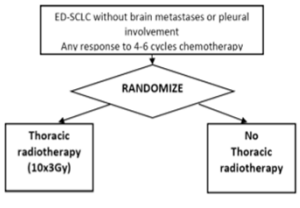


JCO 1999

Thoracic Radiotherapy

Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial

Ben J Slotman, Harm van Tinteren, John O Praag, Joost L Knegjens, Sherif Y El Sharouni, Matthew Hatton, Astrid Keijser, Corinne Faivre-Finn, Suresh Senan**



Lancet 2014

Thoracic Radiotherapy

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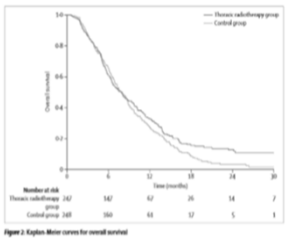

Figure 2: Kaplan-Meier curves for overall survival

1^0 Endpoint: 1-yr OS:
33% (TRT) vs. 28% (no TRT)
HR 0.84, p=0.066

2^0 Endpoint: 2-yr OS:
13% (TRT) vs. 3% (no TRT)
p=0.004

Lancet 2014

Thoracic Radiotherapy

Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial

Ben J Slotman, Harm van Tinteren, John O Praag, Joost L Knegjens, Sherif Y El Sharouni, Matthew Hatton, Astrid Keijser, Corinne Faivre-Finn*, Suresh Senan*

	Thoracic radiotherapy group (n=247)	Control group (n=248)
Cough (grade 3)	0 (0·0%)	1 (0·4%)
Dysphagia (grade 3)	1 (0·4%)	0 (0·0%)
Dyspnoea (grade 3)	3 (1·2%)	4 (1·6%)
Oesophagitis (grade 3)	4 (1·6%)	0 (0·0%)
Fatigue (grade 3)	11 (4·5%)	8 (3·2%)
Fatigue (grade 4)	0 (0·0%)	1 (0·4%)
Insomnia (grade 3)	3 (1·2%)	2 (0·8%)
Nausea or vomiting (grade 3)	1 (0·4%)	0 (0·0%)
Headache (grade 3)	3 (1·2%)	2 (0·8%)

Table 2: Grade 3 and higher toxic effects

Slotman et al Lancet 2014

SCLC: Take Home Messages

- Limited Stage
  - Chemoradiotherapy (with early RT)
  - Several reasonable radiation fractionations
    - 45/30 BID, 70/35 (CALGB), 60/30, 40/15 (NCIC BR-6)
  - PCI in responders
- Extensive Stage
  - Doublet platinum-based chemotherapy
  - In patient with a response, consider thoracic radiotherapy and PCI.

THANK YOU