Management of Stage III NSCLC

Dr Aman Sharma,

Assistant Professor, NCI-AIIMS-Jhajjar

Management Stage III NSCLC

- Stage III nonsmall cell lung cancer (NSCLC) comprises about one-third of NSCLC patients and is very heterogeneous with varying and mostly poor prognosis.
- It is also called “locoregionally or locally advanced disease”.
- Due to its heterogeneity a general schematic management approach is not appropriate.
- Usually a combination of local therapy (surgery or radiotherapy, depending on functional, technical and oncological operability) with systemic platinum-based doublet chemotherapy and, recently, followed by immune therapy is used.

Management Stage III NSCLC

- Locally advanced nonsmall cell lung cancer (NSCLC) is classified according to the TNM staging system as stage III with subclassification into stage IIIA, IIIB and IIIC (TNM 8),
- Prognosis for stage III disease has an intermediate position between stage I–II disease and stage IV disease.
- Overall, the prognosis is poor with failures occurring in the majority of the patients both locally and at distant sites.
- Therefore, optimal local control as well as systemic treatment are essential.
- Stage III patients are still a very heterogeneous group ranging from individuals presenting with multiple nodules in the lungs, tumours invading mediastinal structures, unilateral mediastinal lymph nodes and contralateral nodes without a detectable primary tumour.

The TNM staging system, version 8, demonstrating the heterogeneity of stage III

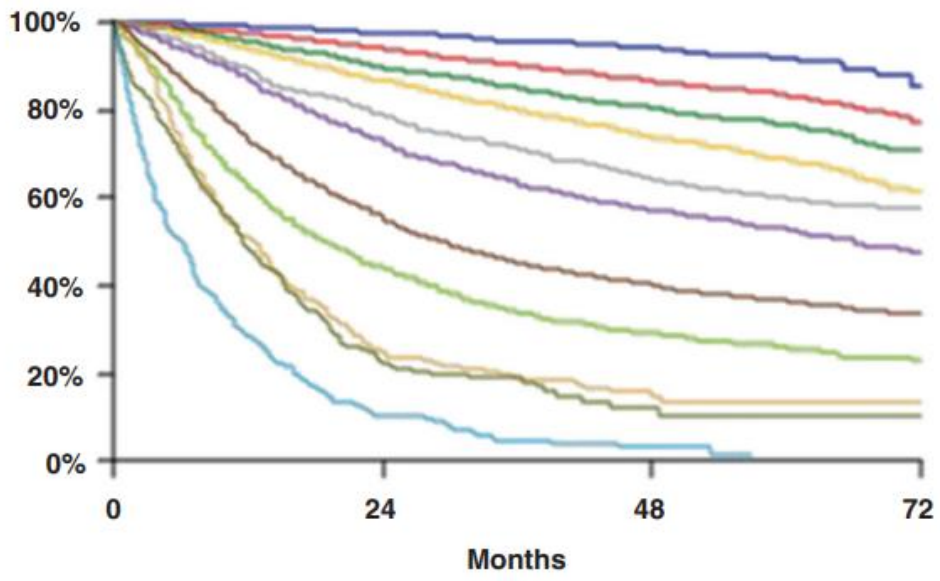
TABLE 1 The TNM staging system, version 8, demonstrating the heterogeneity of stage III

T/M and label	Description	N0	N1	N2	N3
T1					
T1a	⩽1 cm	I A1	II B	III A	III B
T1b	>1–2 cm	I A2	II B	III A	III B
T1c	>2–3 cm	I A3	II B	III A	III B
T2					
T2a	Central, visceral and pleura	I B	II B	III A	III B
	>3–4 m	I B	II B	III A	III B
T2b	>4–5 cm	II A	II B	III A	III B
T3	>5–7 cm	II B	III A	III B	III C
	Invasive	II B	III A	III B	III C
	Satellite	II B	III A	III B	III C
T4	>7 cm	III A	III A	III B	III C
	Invasive	III A	III A	III B	III C
	Ipsilateral nodes	III A	III A	III B	III C
M1					
M1a	Contralateral nodes	IV A	IV A	IV A	IV A
	Pleura disseminated	IV A	IV A	IV A	IV A
M1b	Single	IV A	IV A	IV A	IV A
M1c	Multi	IV B	IV B	IV B	IV B

The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer

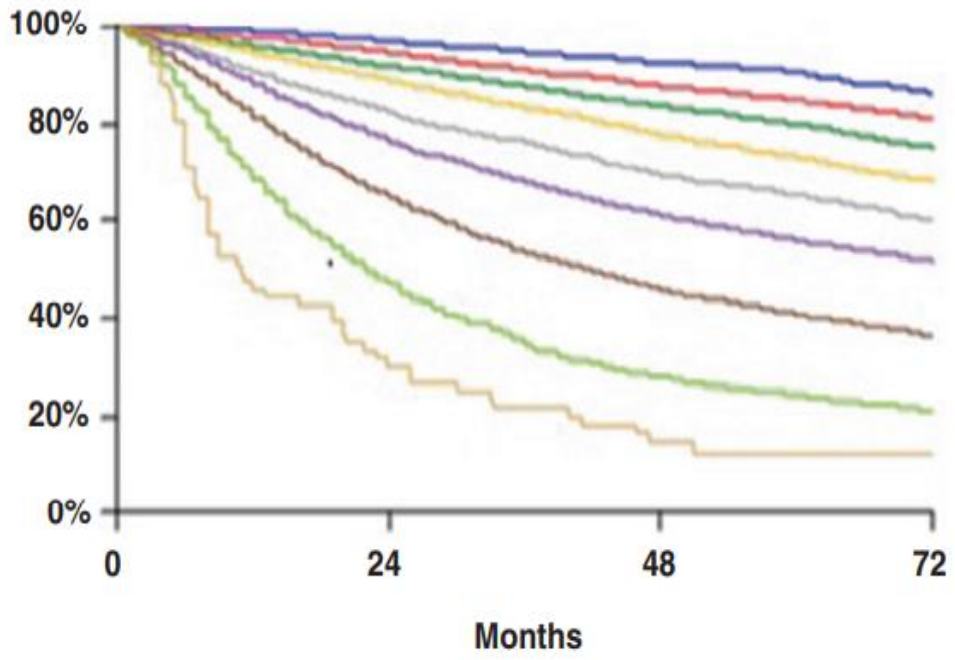
- The IASLC Staging and Prognostic Factors Committee has collected a new database of **94,708** cases donated from **35 sources** in **16 countries** around the globe.
- This has now been analysed by our statistical partners at Cancer Research And Biostatistics and, in close collaboration with the members of the committee proposals have been developed for the T, N, and M categories of the 8th edition of the TNM.

Overall survival graph and 2- and 5-year overall survival rates for 8th Edition clinical stages



	Events/N	MST	24 months	60 months
IA1	68/781	NR	97%	92%
IA2	505/3105	NR	94%	83%
IA3	546/2417	NR	90%	77%
IIB	560/1928	NR	87%	68%
IIA	215/585	NR	79%	60%
IIB	605/1453	66.0	72%	53%
IIIA	2052/3200	29.3	55%	36%
IIIB	1551/2140	19.0	44%	26%
IIIC	831/986	12.6	24%	13%
IVA	336/484	11.5	23%	10%
IVB	328/398	6.0	10%	0%

Overall survival graph and 2- and 5-year overall survival rates for 8th Edition pathological stages

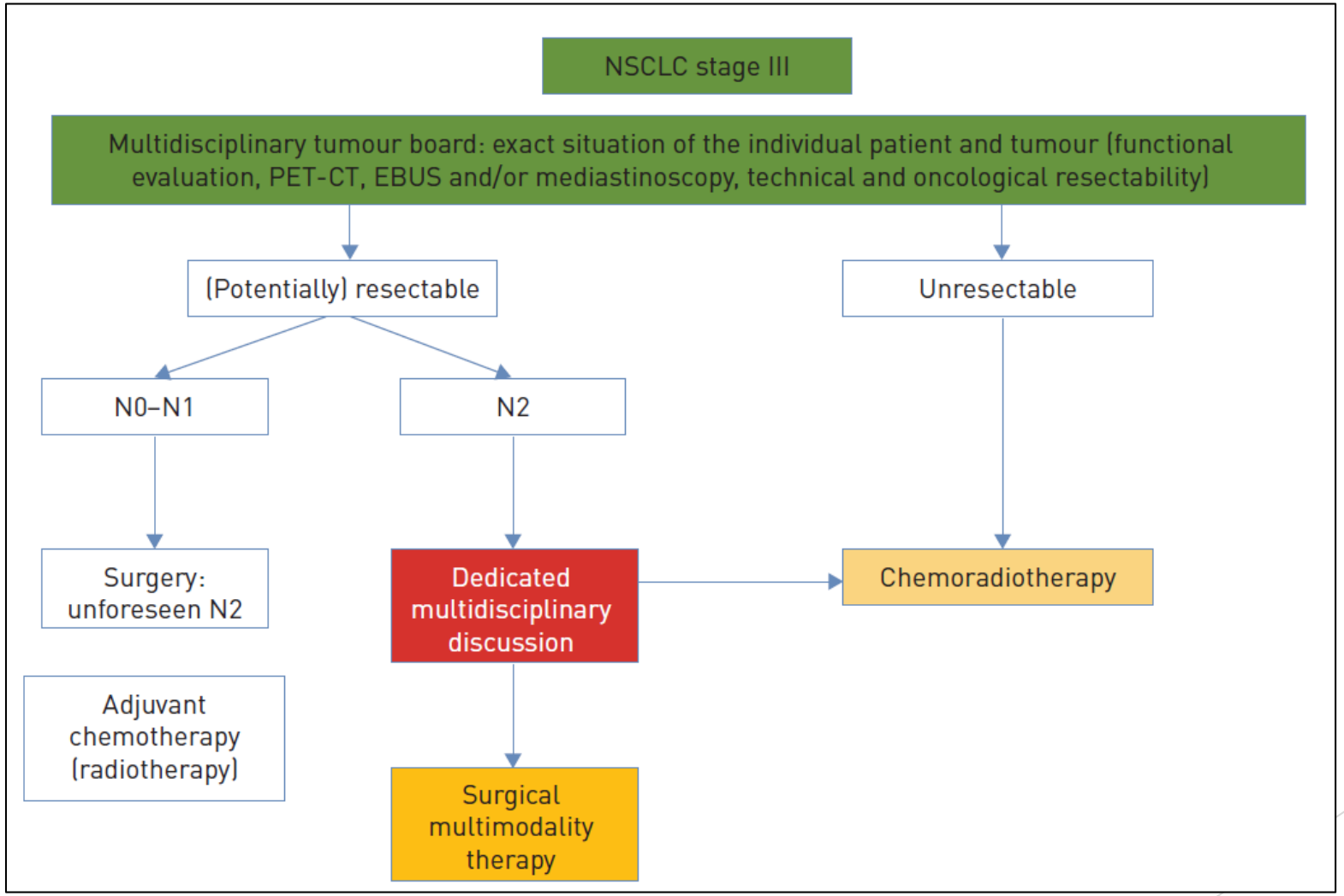


	Events/N	MST	24 months	60 months
IA1	139/1389	NR	97%	90%
IA2	823/5633	NR	94%	85%
IA3	875/4401	NR	92%	80%
IB	1618/6095	NR	89%	73%
IIA	556/1638	NR	82%	65%
IIB	2175/5226	NR	76%	56%
IIIA	3219/5756	41.9	65%	41%
IIIB	1215/1729	22.0	47%	24%
IIIC	55/69	11.0	30%	12%

5-year survival rates of the different stages: average overall survival in the International Association for the Study of Lung Cancer (IASLC) global database of patients receiving a diagnosis between 1999 and 2010

	Clinical stage	Pathological stage
I A1	92	90
I A2	83	85
I A3	77	80
I B	68	73
II A	60	65
II B	53	56
III A	36	41
III B	26	24
III C	13	12
IV A	10	
IV B	0	

Principal management of patients with nonsmall cell lung cancer (NSCLC) in stage III



Management Stage III NSCLC

- The main local treatment modalities for patients with NSCLC in stage III are surgery and radiotherapy.
- As the leading site of relapse is outside the thorax, systemic treatment is usually combined with these treatments.
- Concurrent treatment with platinum-based chemotherapy and thoracic radiotherapy (CCRT) is the current standard of care for patients with unresectable stage III NSCLC and recently the addition of durvalumab for 12 months after completion of CCRT.
- Randomised clinical trials favor the combination chemoradiotherapy compared with radiotherapy alone.
- Meta-analyses of individual patient data from these studies indicate moderate but statistically significant improvements in overall survival with chemoradiotherapy versus radiotherapy alone (HR 0.89; p=0.02) and with concomitant versus sequential chemoradiotherapy (HR 0.84; p=0.004).
- In concurrent chemoradiotherapy there is an increased risk of acute, but not late, irreversible oesophageal toxicity compared with both sequential treatment and radiotherapy alone and not for pneumonitis.
- However, many patients are considered unsuitable for chemoradiotherapy due to poor performance status or the presence of serious comorbidities.

Considerations in the multidisciplinary tumour board for the various local treatment options in stage III nonsmall cell lung cancer

Resection as primary local treatment

- Adequate pulmonary and cardiovascular function
- Tumours without multi-zone mediastinal lymph node involvement
- Bulky, necrotic tumours with possible complications
- Multiple nodules in the same lobe
- Adequate technical operability, no pneumonectomy necessary
- Local experience and outcome date
- Patient's preferences

Radiotherapy as primary local treatment

- Not adequately resectable disease
- Reasonable dose affections of lung and heart
- (Small) tumours with multiple mediastinal lymph node involvement
- Local experience and outcome date
- Patient's preferences

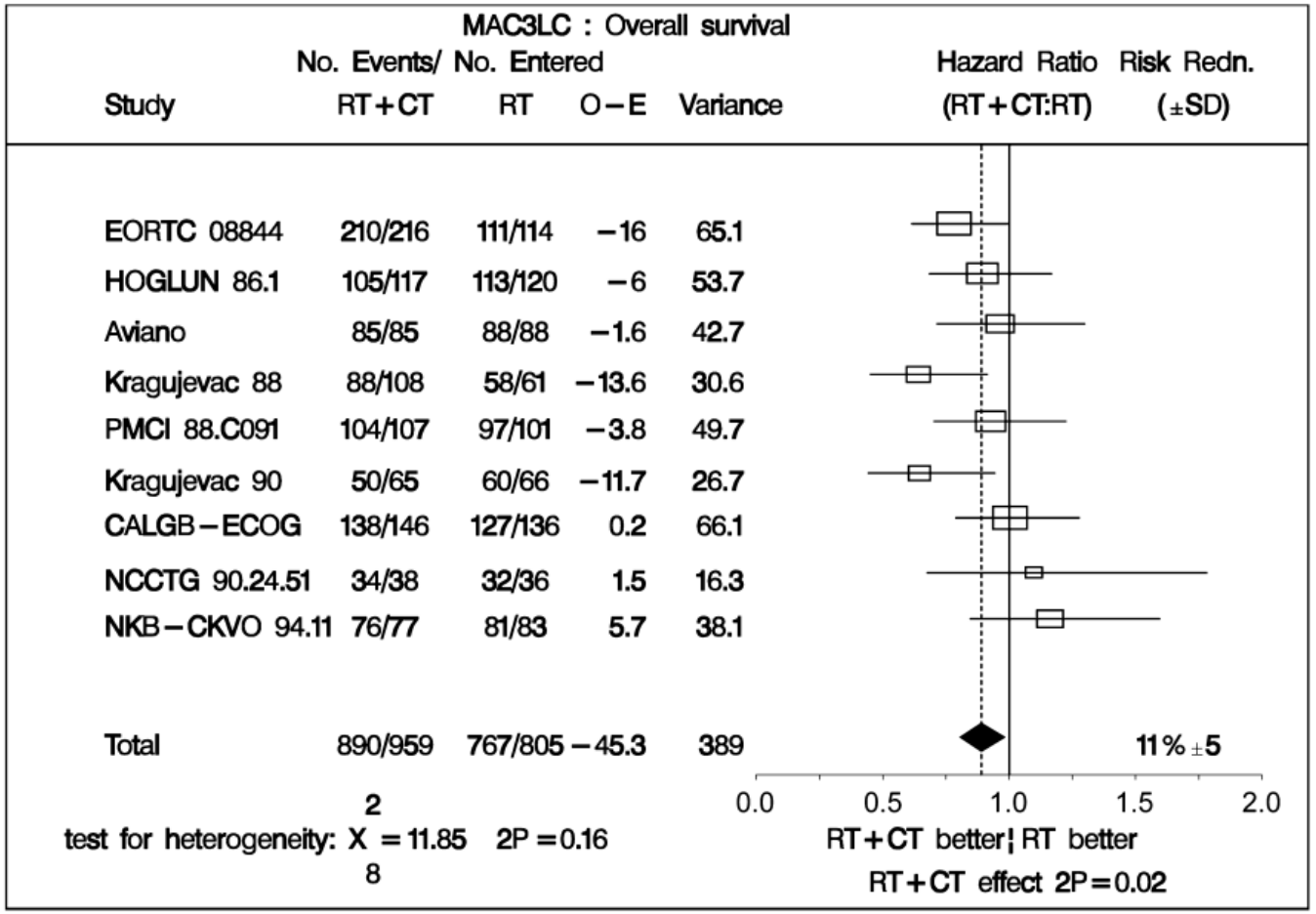
Radiotherapy and surgery

- Local tumour control is very important
- Locally invasive tumours with slim possible resection margins (*e.g.* superior sulcus tumours)

Management Stage III NSCLC

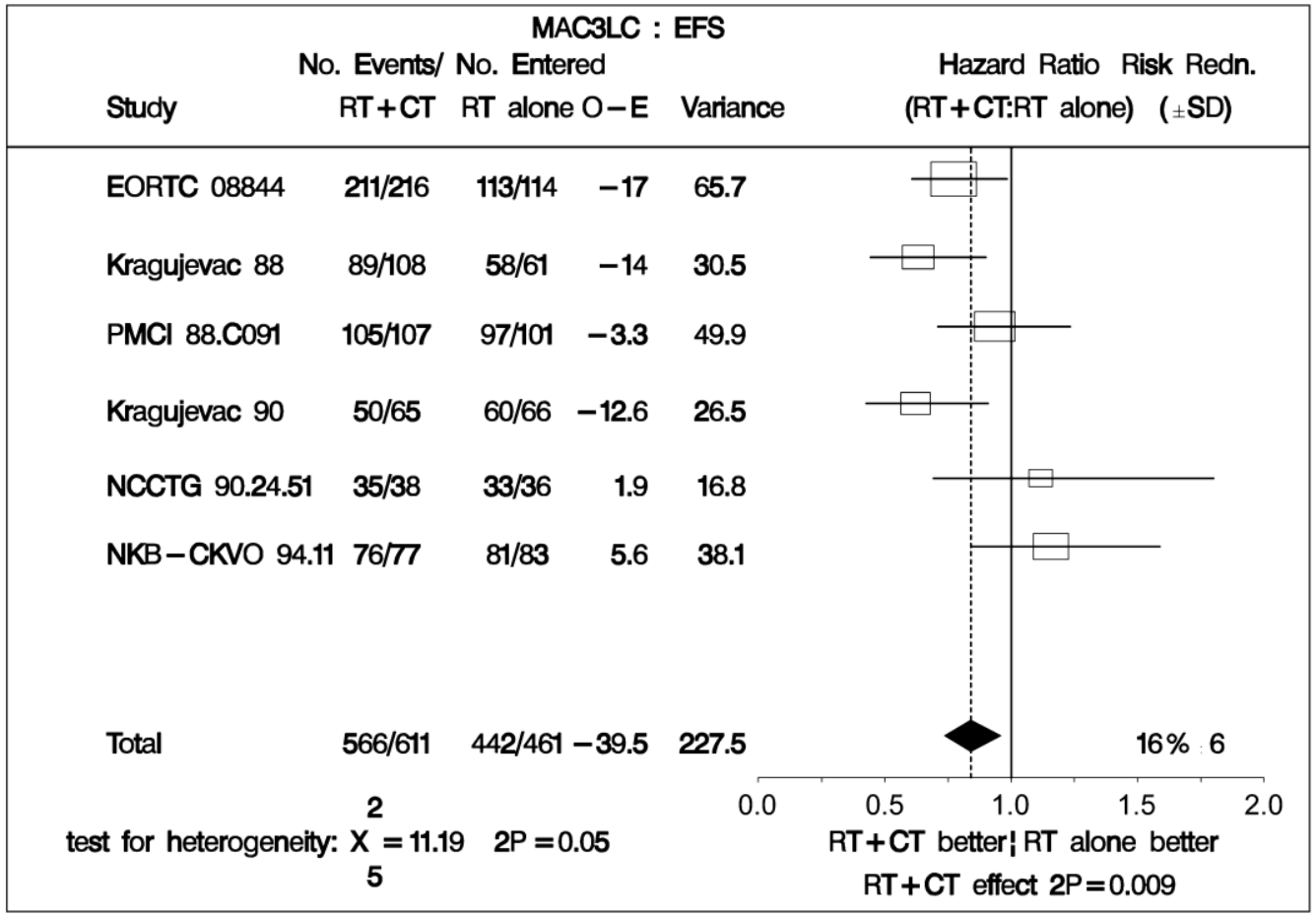
- The optimal strategy for radiotherapy is still under investigation.
- Studies have administered different radiation doses and fractions according to different schedules, including hyperfractionated accelerated radiotherapy.
- In the non-concurrent setting, shortening the overall treatment time of radiotherapy led to a significant increase in 5-year overall survival.
- In concurrent chemoradiotherapy, no regimen has been shown to be superior to 60 Gy delivered in 30 daily fractions of 2 Gy.
- Dose escalation >60 Gy in 30 daily fractions by adding 2 Gy fractions up to 74 Gy was detrimental for survival.

Concomitant radio-chemotherapy based on platin compounds in patients with locally advanced non-small cell lung cancer (NSCLC): A meta-analysis of individual data from 1764 patients



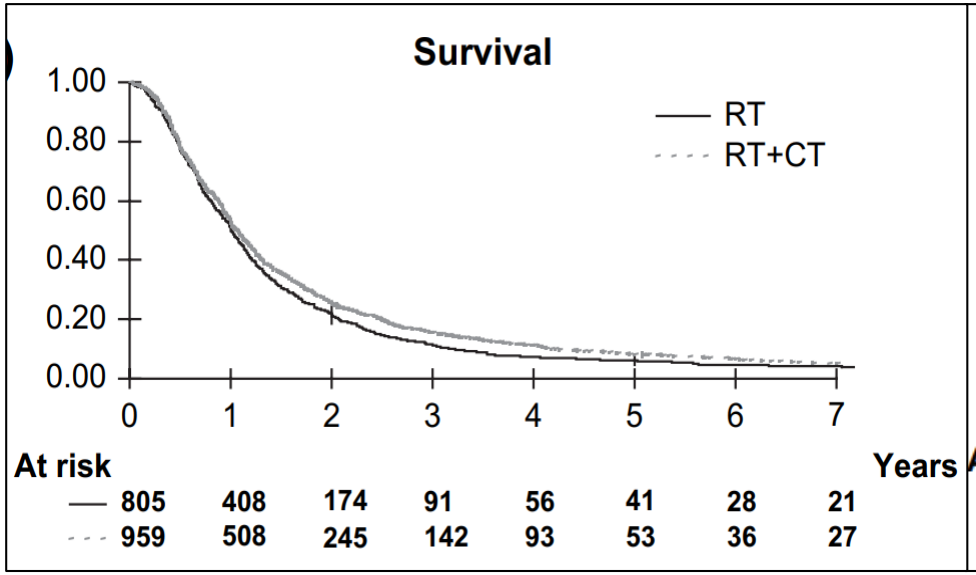
Auperin et al Annals of Oncology 2006

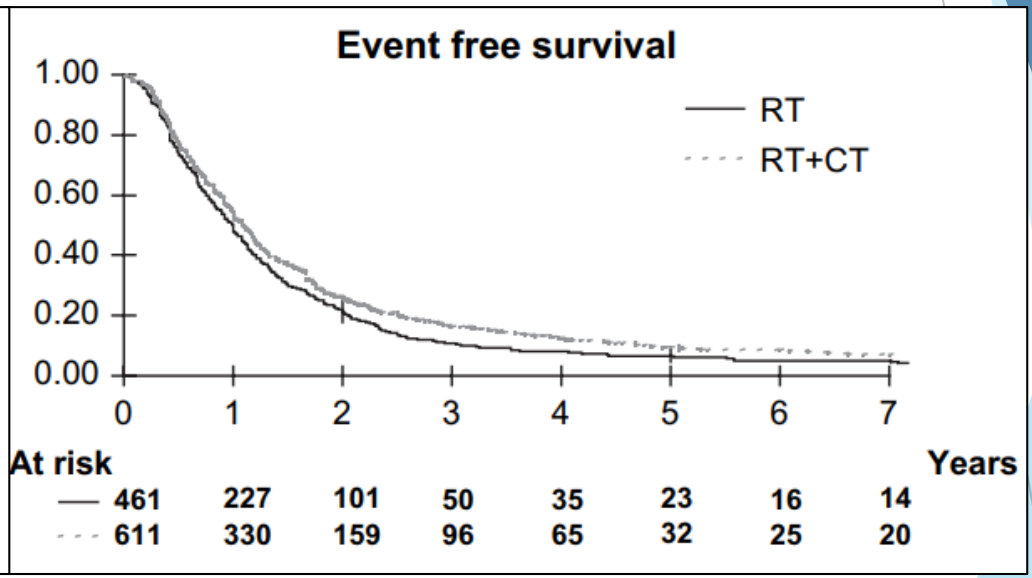
Concomitant radio-chemotherapy based on platin compounds in patients with locally advanced non-small cell lung cancer (NSCLC): A meta-analysis of individual data from 1764 patients



Auperin et al Annals of Oncology 2006

Concomitant radio-chemotherapy based on platin compounds in patients with locally advanced non-small cell lung cancer (NSCLC): A meta-analysis of individual data from 1764 patients

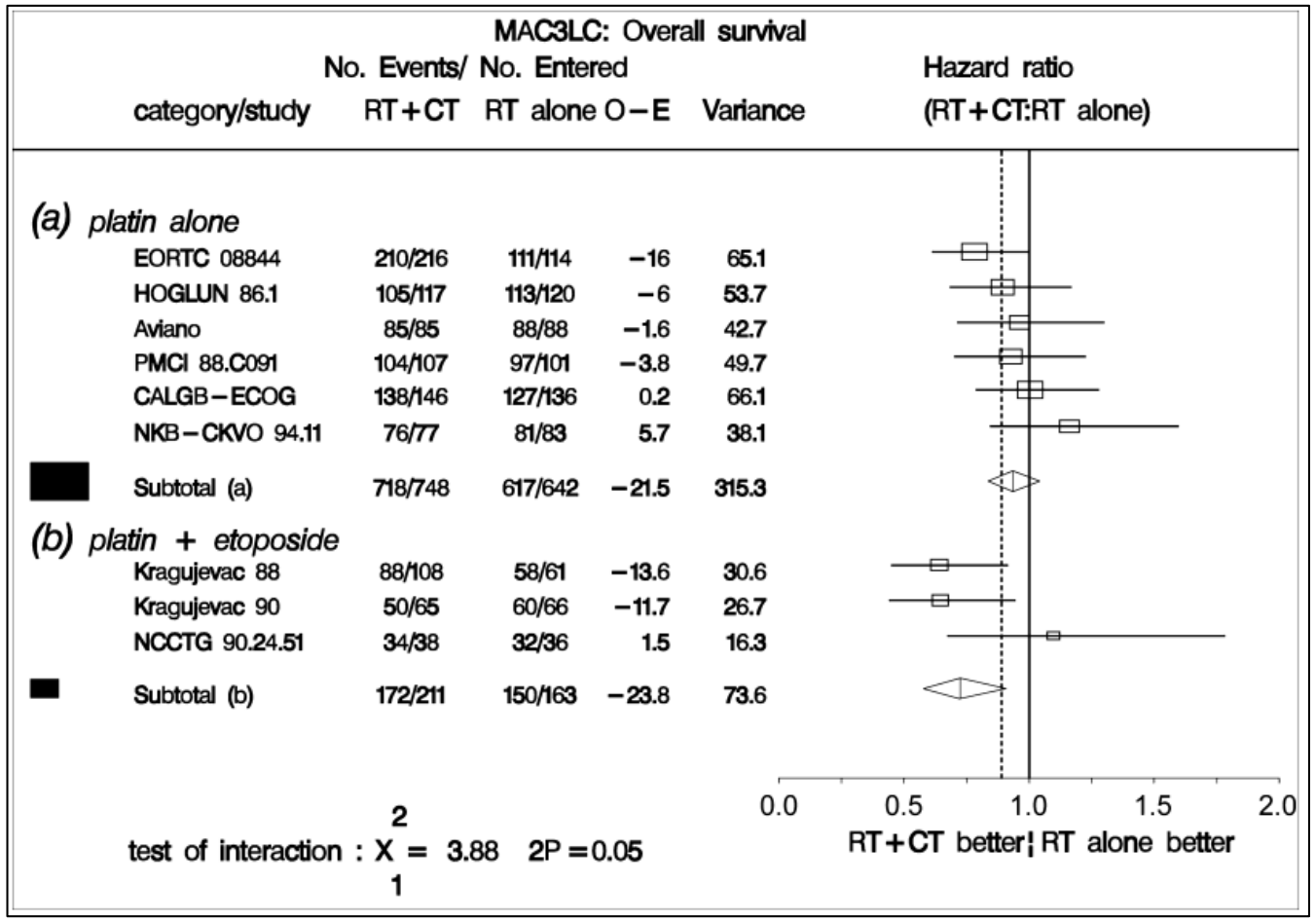




- The HR of death among patients treated with radio-chemotherapy compared to radiotherapy alone was 0.89 (95%CI 0.81–0.98; P = 0.02).
- An absolute benefit of chemotherapy of **4% at 2 years** and **2.2% at 5** years, increasing respectively the 2- and 5-year survival rates from 21.4% to 25.4%, and from 6.0% to 8.2%

Auperin et al Annals of Oncology 2006

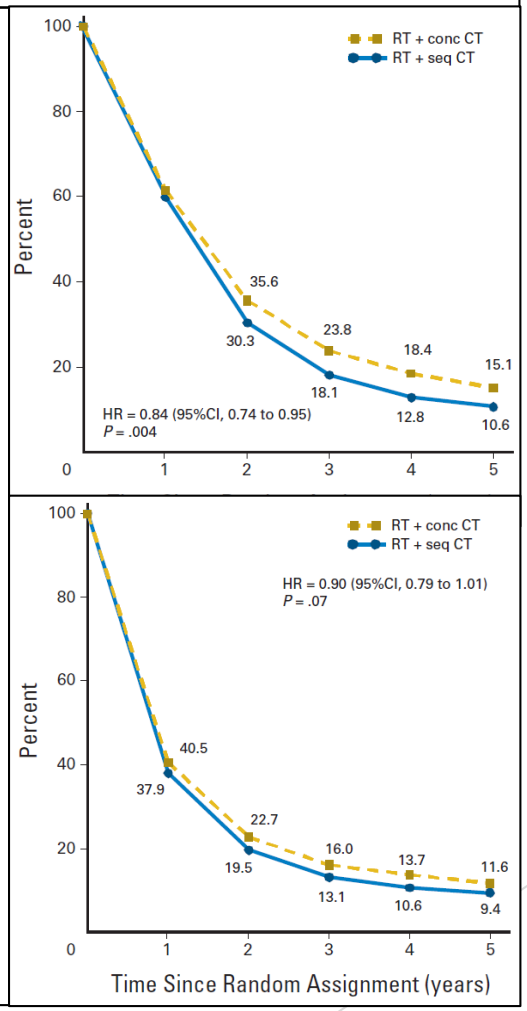
Concomitant radio-chemotherapy based on platin compounds in patients with locally advanced non-small cell lung cancer (NSCLC): A meta-analysis of individual data from 1764 patients



Auperin et al Annals of Oncology 2006

Meta-Analysis of Concomitant Versus Sequential Radiochemotherapy in Locally Advanced Non–Small-Cell Lung Cancer

- N= 6 trials were received (1,205 patients).
- Median follow-up was 6 years.
- There was a significant benefit of CRT on OS(**HR, 0.84**; 95% CI, 0.74 to 0.95; ***P* = .004**)
- An absolute benefit of **5.7%** (from 18.1% to 23.8%) at 3 years and **4.5% at 5 years**.
- For progression-free survival, the **HR was 0.90** (95% CI, 0.79 to 1.01; ***P* = .07**).
- Concomitant treatment decreased locoregional progression (**HR, 0.77**; 95% CI, 0.62 to 0.95; *P* = .01)
- CRT was not different than sequential treatment on distant progression (HR, 1.04; 95% CI, 0.86 to 1.25; *P* = .69).
- CRT increased acute esophageal toxicity (grade 3-4) from **4% to 18%** with a **relative risk of 4.9** (95% CI, 3.1 to 7.8; *P*= .001). There was no significant difference regarding acute pulmonary toxicity.



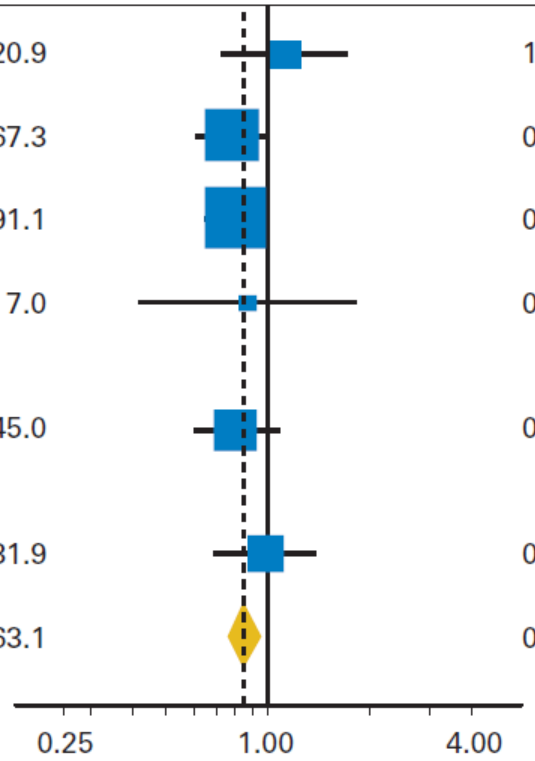
Auperin et al JCO 2010

Meta-Analysis of Concomitant Versus Sequential Radiochemotherapy in Locally Advanced Non–Small-Cell Lung Cancer

A

Trial	No. Deaths / No. Entered RT + Conc CT	RT + Seq CT	O-E	Variance	HR (95% CI)
CALGB 8831	45/46	39/45	2.4	20.9	1.12 (0.73 to 1.72)
WJLCG	131/156	142/158	-16.8	67.3	0.78 (0.61 to 0.99)
RTOG 9410	180/204	189/203	-20.5	91.1	0.80 (0.65 to 0.98)
GMMA Ankara 95	15/15	15/15	-1.0	7.0	0.87 (0.41 to 1.82)
GLOT-GFPC NPC	87/102	96/103	-9.9	45.0	0.80 (0.60 to 1.07)
EORTC 08972	63/80	66/78	-0.5	31.9	0.98 (0.69 to 1.39)
Total	521/603	547/602	-46.4	263.1	0.84 (0.74 to 0.95)

Test for heterogeneity:
$\chi^2_5 = 3.24$, $P = .66$, $I^2 = 0\%$



RT + conc CT effect: Log-rank test = 8.19, $P = .004$

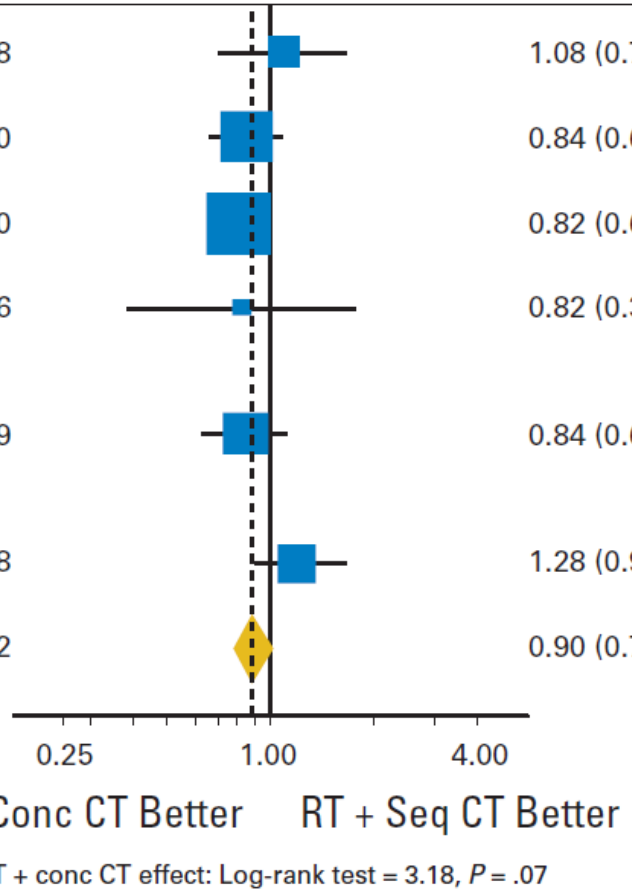
Auperin et al Annals of Oncology 2006

Meta-Analysis of Concomitant Versus Sequential Radiochemotherapy in Locally Advanced Non–Small-Cell Lung Cancer

B

Trial	No. Events / No. Entered RT + Conc CT	RT + Seq CT	O-E	Variance	Hazard Ratio	HR (95% CI)
CALGB 8831	45/46	39/45	1.7	20.8		1.08 (0.70 to 1.66)
WJLCG	128/148	132/145	-11.0	64.0		0.84 (0.66 to 1.08)
RTOG 9410	189/204	192/203	-18.8	94.0		0.82 (0.67 to 1.00)
GMMA Ankara 95	13/15	14/15	-1.3	6.6		0.82 (0.38 to 1.76)
GLOT-GFPC NPC	88/102	97/103	-8.0	44.9		0.84 (0.63 to 1.12)
EORTC 08972	70/80	67/78	8.4	33.8		1.28 (0.92 to 1.80)
Total	533/595	541/589	-29.0	264.2		0.90 (0.79 to 1.01)

Test for heterogeneity:
$\chi^2_5 = 6.37$, $P = .27$, $I^2 = 22\%$



RT + conc CT effect: Log-rank test = 3.18, $P = .07$

Auperin et al Annals of Oncology 2006

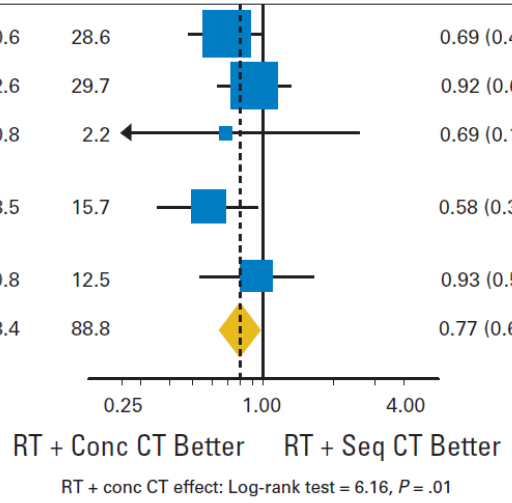
Meta-Analysis of Concomitant Versus Sequential Radiochemotherapy in Locally Advanced Non–Small-Cell Lung Cancer

Loco-regional control

C

Trial	No. Events / No. Entered RT + Conc CT	RT + Seq CT	O-E	Variance	HR (95% CI)
WJLCG	50/148	65/145	-10.6	28.6	0.69 (0.48 to 1.00)
RTOG 9410	58/204	61/203	-2.6	29.7	0.92 (0.64 to 1.31)
GMMA Ankara 95	4/15	5/15	-0.8	2.2	0.69 (0.19 to 2.57)
GLOT-GFPC NPC	24/101	40/103	-8.5	15.7	0.58 (0.35 to 0.95)
EORTC 08972	24/80	26/78	-0.8	12.5	0.93 (0.54 to 1.63)
Total	160/548	197/544	-23.4	88.8	0.77 (0.62 to 0.95)

Test for heterogeneity:
$\chi^2_4 = 2.96$, $P = .56$, $I^2 = 0\%$



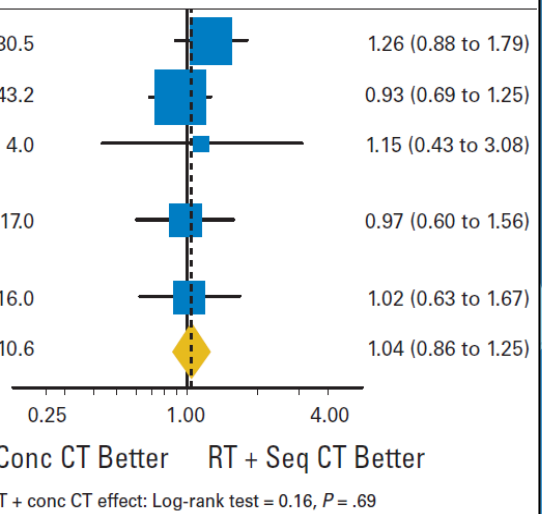
RT + conc CT effect: Log-rank test = 6.16, $P = .01$

Distant metastases

D

Trial	No. Events / No. Entered RT + Conc CT	RT + Seq CT	O-E	Variance	HR (95% CI)
WJLCG	67/148	55/145	7.0	30.5	1.26 (0.88 to 1.79)
RTOG 9410	85/204	88/203	-3.1	43.2	0.93 (0.69 to 1.25)
GMMA Ankara 95	8/14	8/14	0.5	4.0	1.15 (0.43 to 3.08)
GLOT-GFPC NPC	34/101	36/103	-0.5	17.0	0.97 (0.60 to 1.56)
EORTC 08972	32/80	32/78	0.3	16.0	1.02 (0.63 to 1.67)
Total	226/547	219/543	4.2	110.6	1.04 (0.86 to 1.25)

Test for heterogeneity:
$\chi^2_4 = 1.76$, $P = .78$, $I^2 = 0\%$

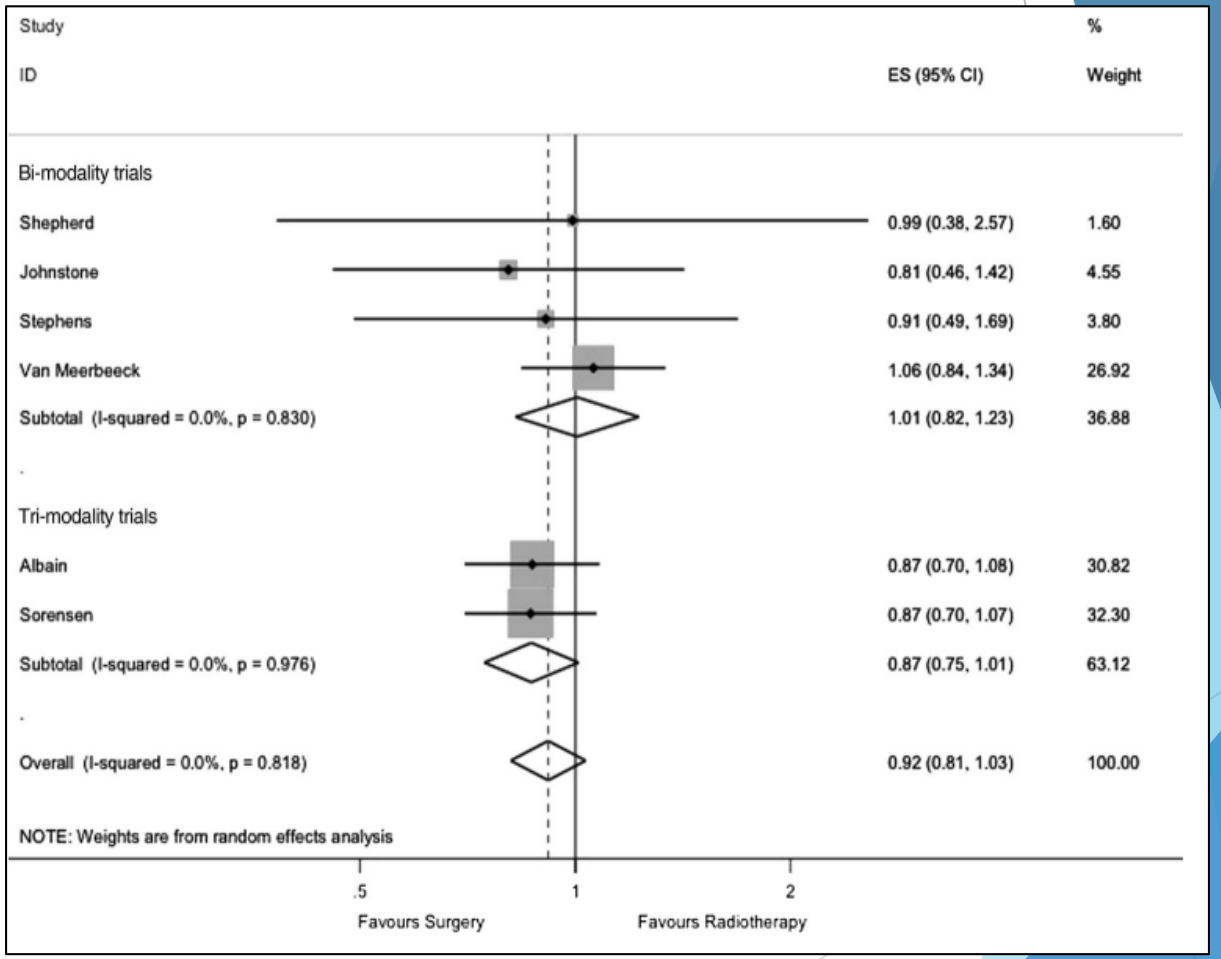


RT + conc CT effect: Log-rank test = 0.16, $P = .69$

Auperin et al Annals of Oncology 2006

Outcome of surgery versus radiotherapy after induction treatment in patients with N2 disease: systematic review and meta-analysis of randomised trials

- N= six trials 868 patients.
- In four trials, patients received induction chemotherapy and in two trials patients received induction chemoradiotherapy.
- **HR surgery after chemotherapy** =1.01 (95% CI 0.82 to 1.23; p=0.954)
- **HR surgery after chemoradiotherapy** =0.87 (0.74 to 1.02; p=0.078).
- **The overall HR of all pooled trials**
- =0.92 (0.81 to 1.04; p=0.179).
- **Conclusions:** In trials where patients received surgery as part of bimodality (with chemotherapy) or trimodality (with chemoradiotherapy) treatment, **overall survival was not significantly better than RT (with chemotherapy) or chemoradiotherapy alone**.



McElnay PJ, et al. Thorax 2015

Definitive radiochemotherapy versus surgery within multimodality treatment in stage III non-small cell lung cancer (NSCLC) - a cumulative meta-analysis of the randomized evidence

Trial (Period of Recruitment)	Inclusion Criteria	Treatment	median OS [mo]	long-term OS	Hazard Ratio	*P*
RTOG 89-01 (1990-1994)	IIIA N2	[R]* (1) 2x CDDP/VBL (MMC) → S (2) 2x CDDP/VBL (MMC) → RT [64 Gy]	19.4 17.4	22.0% [4Y] 22.0%	n.g.	0.46
NCI Canada (closed 1995)	IIIA N2	[R] (1) 2x CDDP/VBL → S (2) ---------- → RT [60 Gy]	18.7 16.2	n.g.	n.g.	NS
MRC (1995-1999)	IIIA	[R] (1) 4x CDDP/MMC/IFO or VBL → S (2) ---------- → RT [40-60 Gy]	13.8 11.2	n.g.	0.91 [0.49-1.72]	0.78
EORTC 08941 (1994-2002)	IIIA N2	(1) 3x CDDP/ 3rd gen drug →[R]° → S [+PORT 56 Gy] (2) 3x CDDP/ 3rd gen drug → RT [60-62.5 Gy]	16.4 17.5	15.7% [5Y] 14.0%	1.06 [0.84-1.35]	0.596
Nordic TOG (1998-2009)	IIIA N2	[R] (1) 3x carboplatin/paclitaxel → S [+PORT 60 Gy] (2) 3x carboplatin/paclitaxel → RT [60 Gy]	17.3 14.9	19.0% [5Y] 17.0%	0.866	0.218
INT 0139 (1994-2001)	IIIA N2	[R] (1) 2x CDDP/ETOII45 Gy/1.8 Gy qd → S → 2x CDDP/ETO (2) 2x CDDP/ETOII45 Gy/1.8 Gy qd → RT [61 Gy]→2x CDDP/ETO	23.6 22.2	27.0% [5Y] 20.0%	0.87 [0.7-1.1]	0.24
ESPATUE (2004-2012)	IIIA N2 selected IIIB	(1) 3x CDDP/paclitaxel→CDDP/VINII45 Gy (AHF)→[R]→ S (2) 3x CDDP/paclitaxel→CDDP/VINII45 Gy (AHF) → RT [20-26 Gy→65-71 Gy] +CDDP/VIN	49.3 34.8	44.0% [5Y] 40.0%	0.81 [0.5-1.3]	0.34

Pöttgen PJ, et al. Oncotarget 2017

Definitive radiochemotherapy versus surgery within multimodality treatment in stage III non-small cell lung cancer (NSCLC) - a cumulative meta-analysis of the randomized evidence

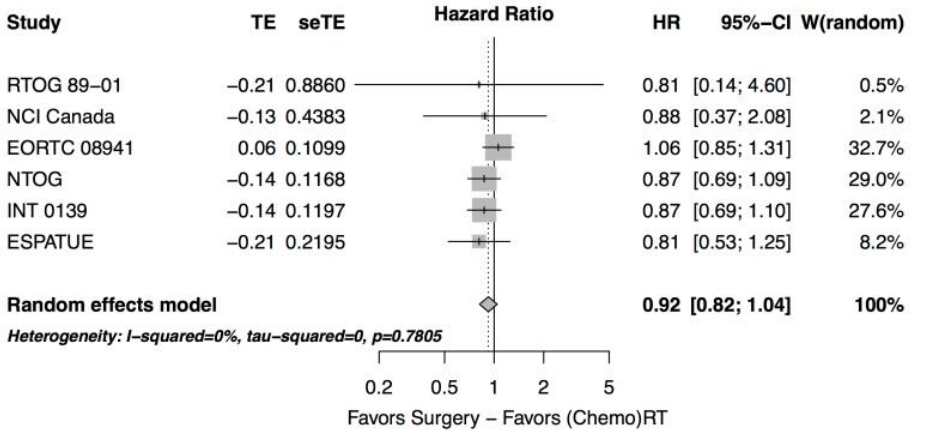


Figure 1: Forest plot: overall survival - randomized prospective studies, experimental: treatment arm with surgery.

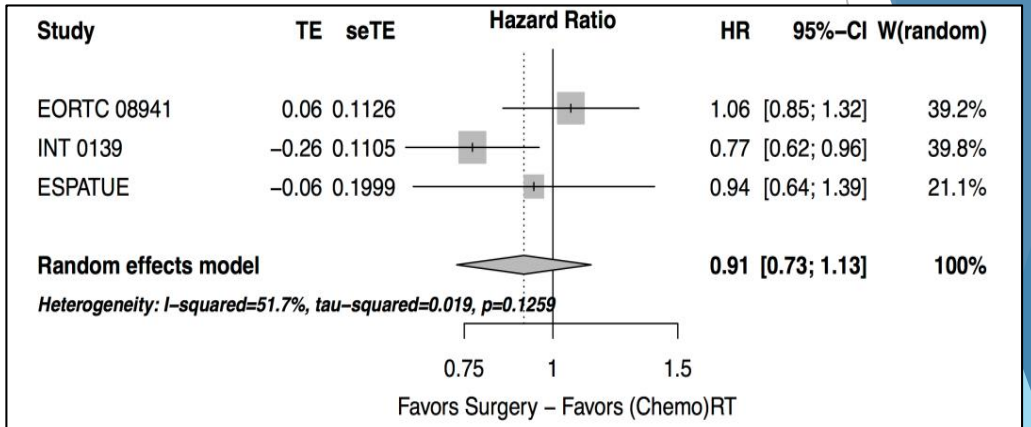
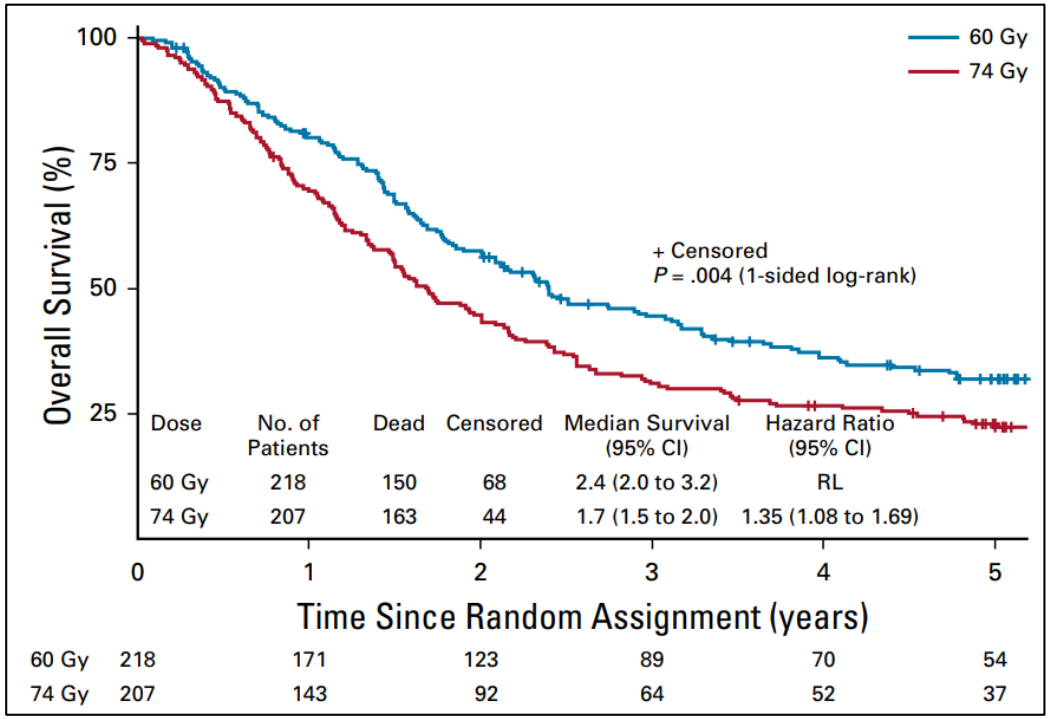


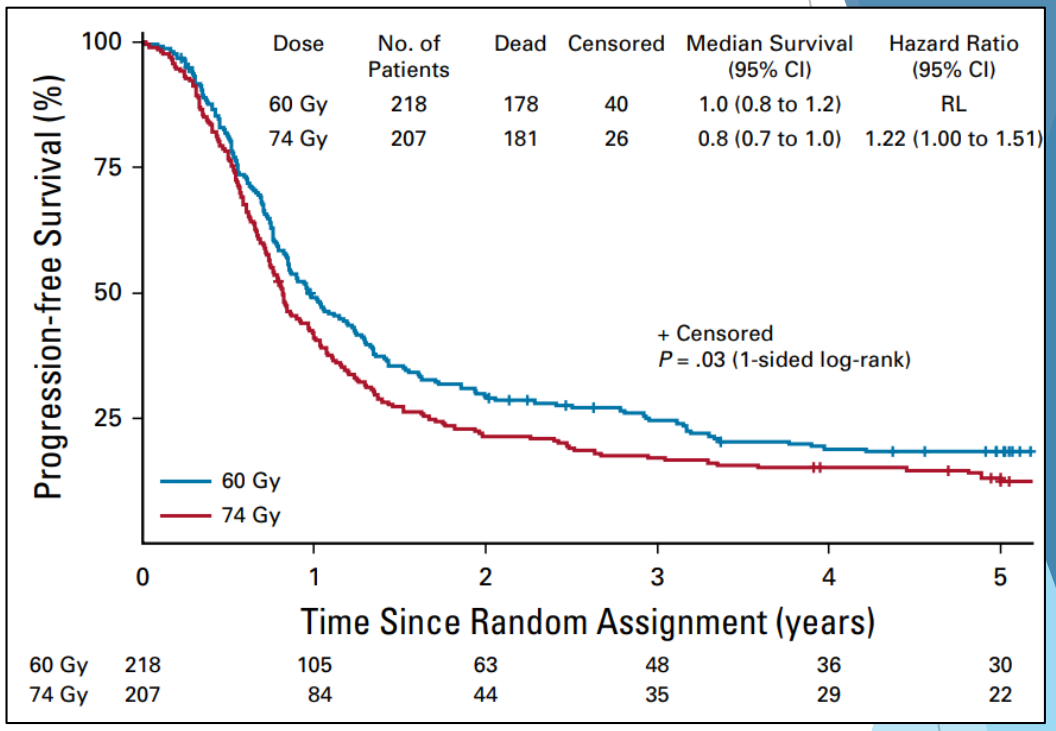
Figure 2: Forest plot: progression-free survival - randomized prospective studies with published progression-free survival rates, experimental: treatment arm with surgery.

- **OS was not significantly different between surgical and definitive radiotherapy arms** (HR=0.92 [95%CI 0.82-1.04], p=0.19, χ2-test).
- Trials using **concurrent radiochemotherapy (ccRT/CT) showed better survival at 2 years** (risk ratio of death=0.80 [95%CI 0.73-0.88], *p*<0.0001).
- In ccRT/CT trials, survival in **surgical arms tended to have excess early mortality before 6 months** of follow-up and **a lesser hazard rate in comparison to definitive ccRT/CT thereafter (HR=0.78 [95%CI 0.63-0.98]).**
- Over all trials, **treatment associated mortality was higher in the surgical arms** (risk ratio=3.56 [95% CI: 1.65-7.72], *p*=0.0005).
- With respect to **progression-free survival, no significant differences were found** (HR=0.91 [95%CI: 0.73 - 1.13])

Pöttgen PJ, et al. Oncotarget 2017

Long-Term Results of NRG Oncology RTOG 0617: Standard- Versus High-Dose Chemoradiotherapy With or Without Cetuximab for Unresectable Stage III Non–Small-Cell Lung Cancer





- RTOG 0617 compared standard-dose (SD 60 Gy) vs high-dose (HD 74 Gy) radiation with concurrent chemotherapy & determined efficacy of cetuximab
- Median follow-up was 5.1 years.
- There were **3** grade 5 adverse events (AEs) in the SD arm and **9** in the HD arm.
- Grade ≥3 **dysphagia** and **esophagitis** occurred in 3.2% and 5.0% SD arm v 12.1% and 17.4% in HD arm (P = .0005 and = .0001).
- Median OS was 28.7 v 20.3 months (P = .0072) in the SD and HD arms
- 5-year OS and progression-free survival (PFS) rates were 32.1% and 23% and 18.3% and 13% (P = .055), respectively

Bradley et al JCO 2019

Cardiac Toxicity After Radiotherapy for Stage III Non–Small Cell Lung Cancer: Pooled Analysis of Dose-Escalation Trials Delivering 70 to 90 Gy

- N=127 patients with stage III NSCLC received dose-escalated RT to 70 to 90 Gy (median, 74 Gy) in six trials.
- Primary end point: **symptomatic cardiac events**
  - *Pericardial effusion*
  - *Acute coronary syndrome*
  - *Pericarditis*
  - *Arrhythmia*
  - *Heart failure*.
- Median follow-up for surviving patients was 8.8 years.
- **Twenty-six patients (23%)** had one or more events at a median of 26 months to first event (effusion [n = 7], myocardial infarction [n = 5], unstable angina [n = 3], pericarditis [n = 2], arrhythmia [n = 12], and heart failure [n = 1]).
- **Heart dose** remained significant on MVA
- Two-year competing risk–adjusted event rates for patients with heart mean dose **10 Gy, 10 to 20 Gy, or >20 Gy were 4%, 7%, and 21%,** respectively.
- Cardiac events are relatively common after high-dose thoracic RT and were independently associated with both heart dose and baseline cardiac risk.
- RT-associated cardiac toxicity after treatment of stage III NSCLC may occur earlier than historically understood, and heart doses should be minimized.

Wang et al JCO 2017

Cardiac Toxicity After Radiotherapy for Stage III Non–Small Cell Lung Cancer: Pooled Analysis of Dose-Escalation Trials Delivering 70 to 90 Gy

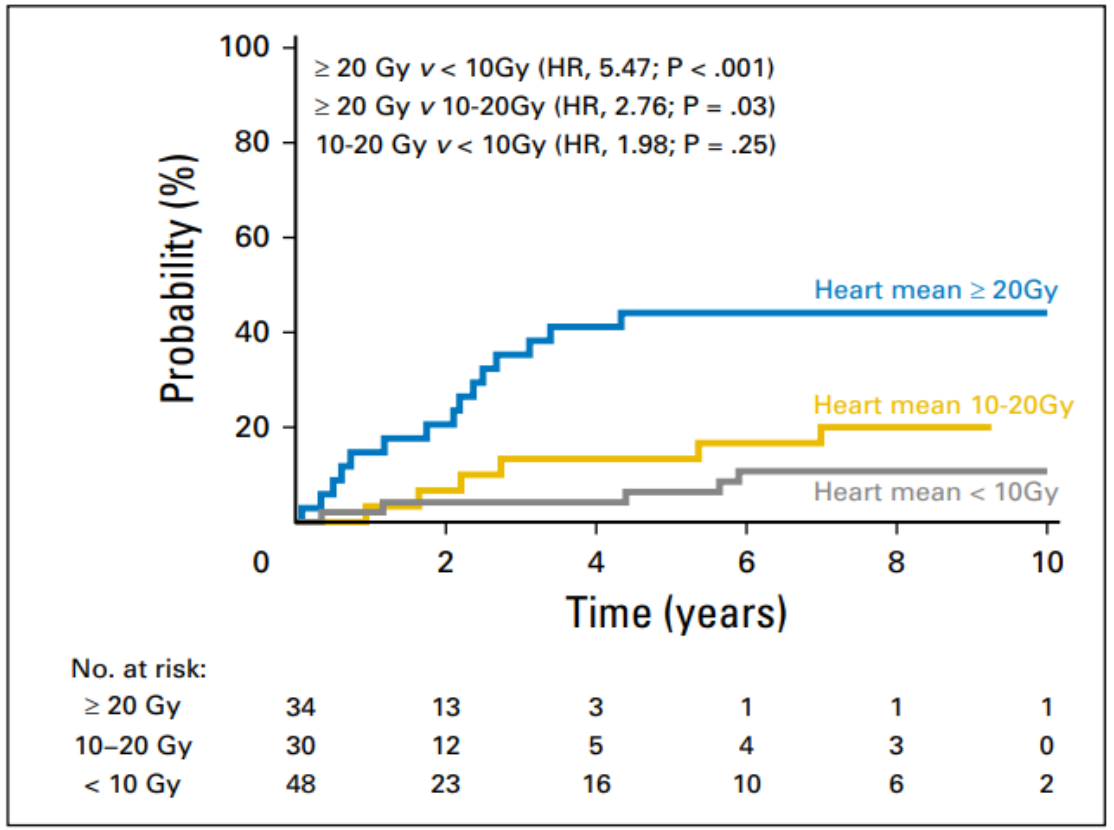


Fig 2. Cumulative incidence of competing risk–adjusted symptomatic cardiac events in patients with heart mean dose ≥ 20 Gy (blue), 10 to 20 Gy (gold), and < 10 Gy (gray).

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Cardiac Toxicity of Thoracic Radiotherapy: Existing Evidence and Future Directions

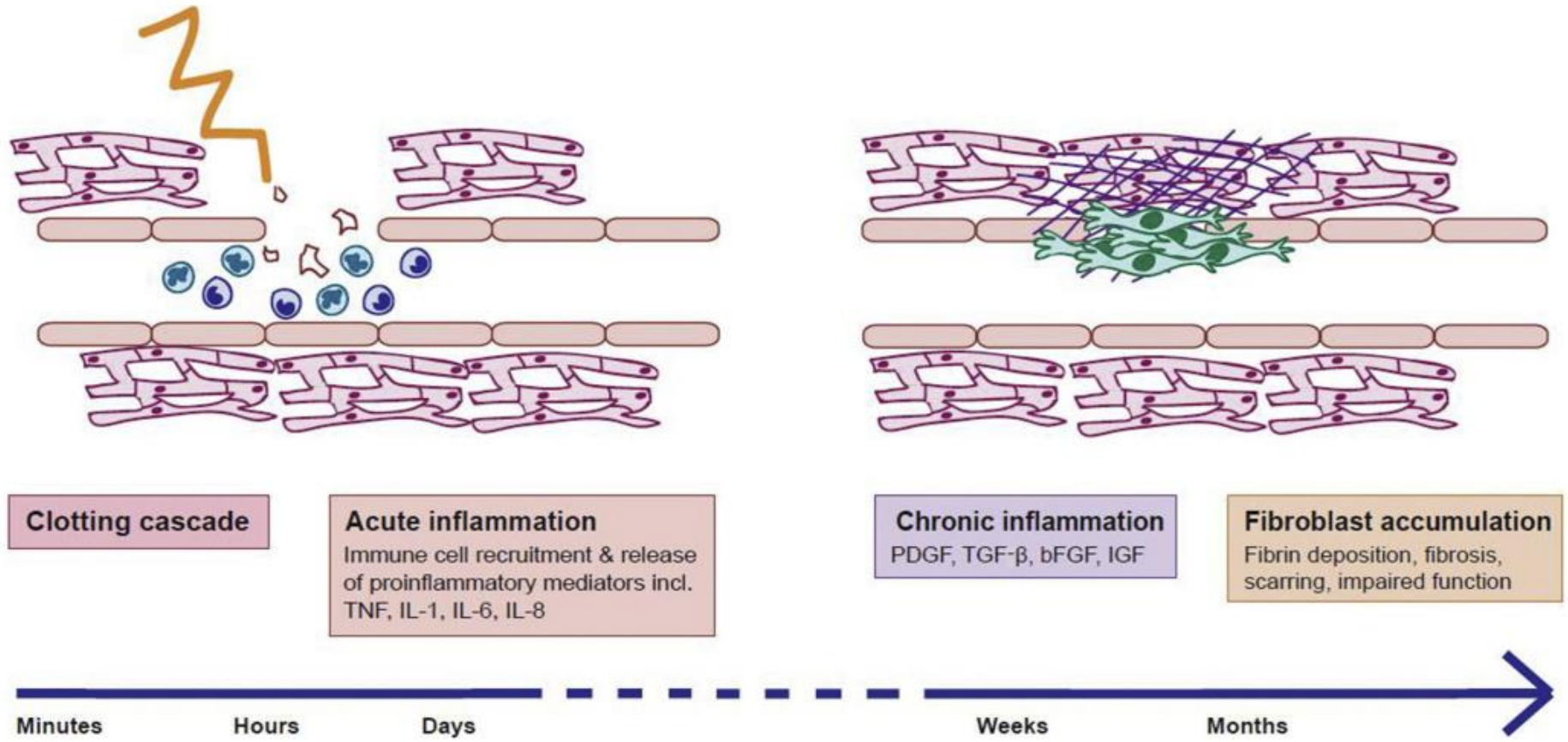
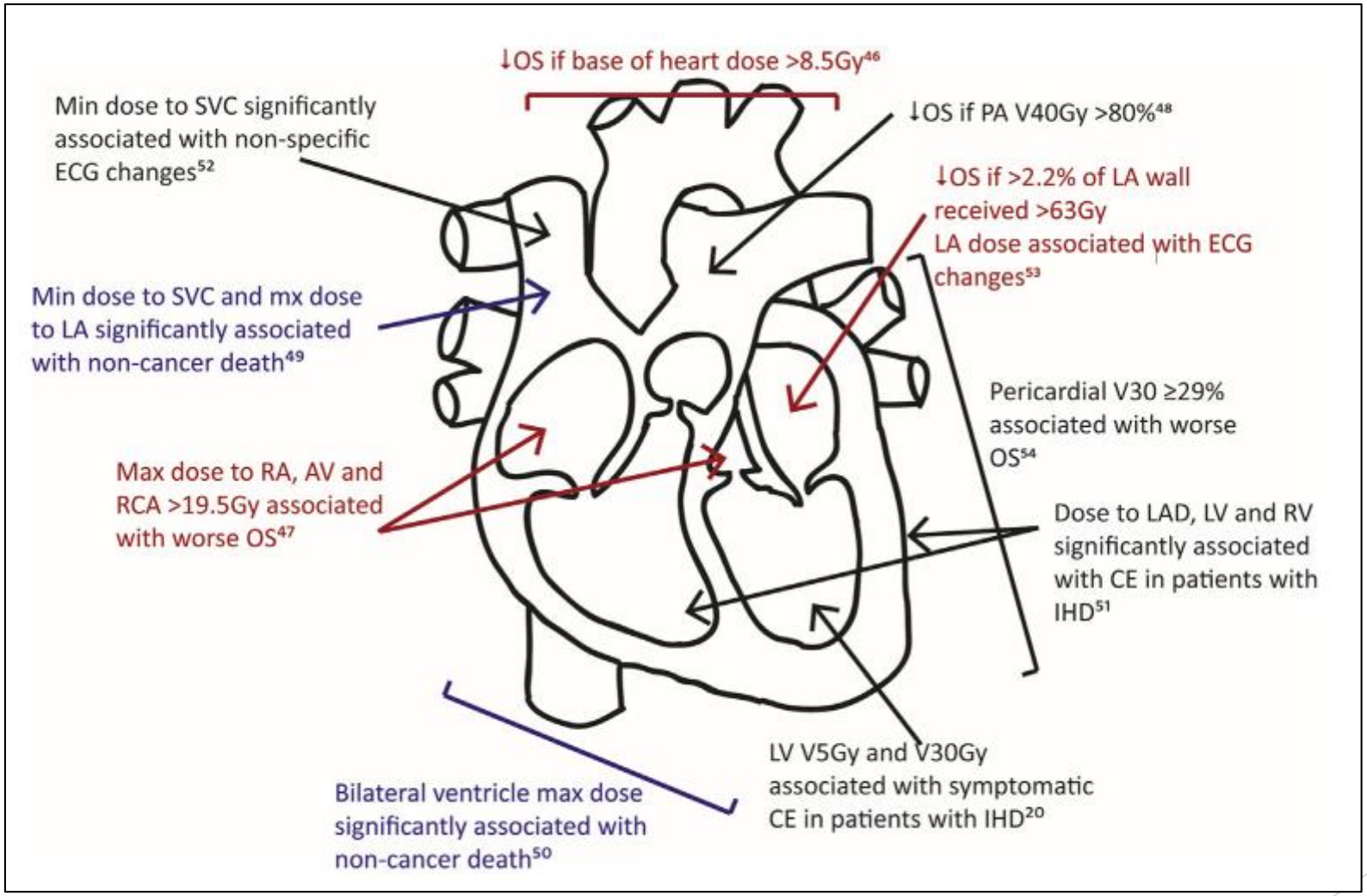


Figure 1. Cardiac endothelial damage caused by radiation resulting in fibrosis. bFGF, basic fibroblast growth factor; IGF, insulin-like growth factor; IL, interleukin; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor-β; TNF, tumor necrosis factor.

Cardiac Toxicity of Thoracic Radiotherapy: Existing Evidence and Future Directions



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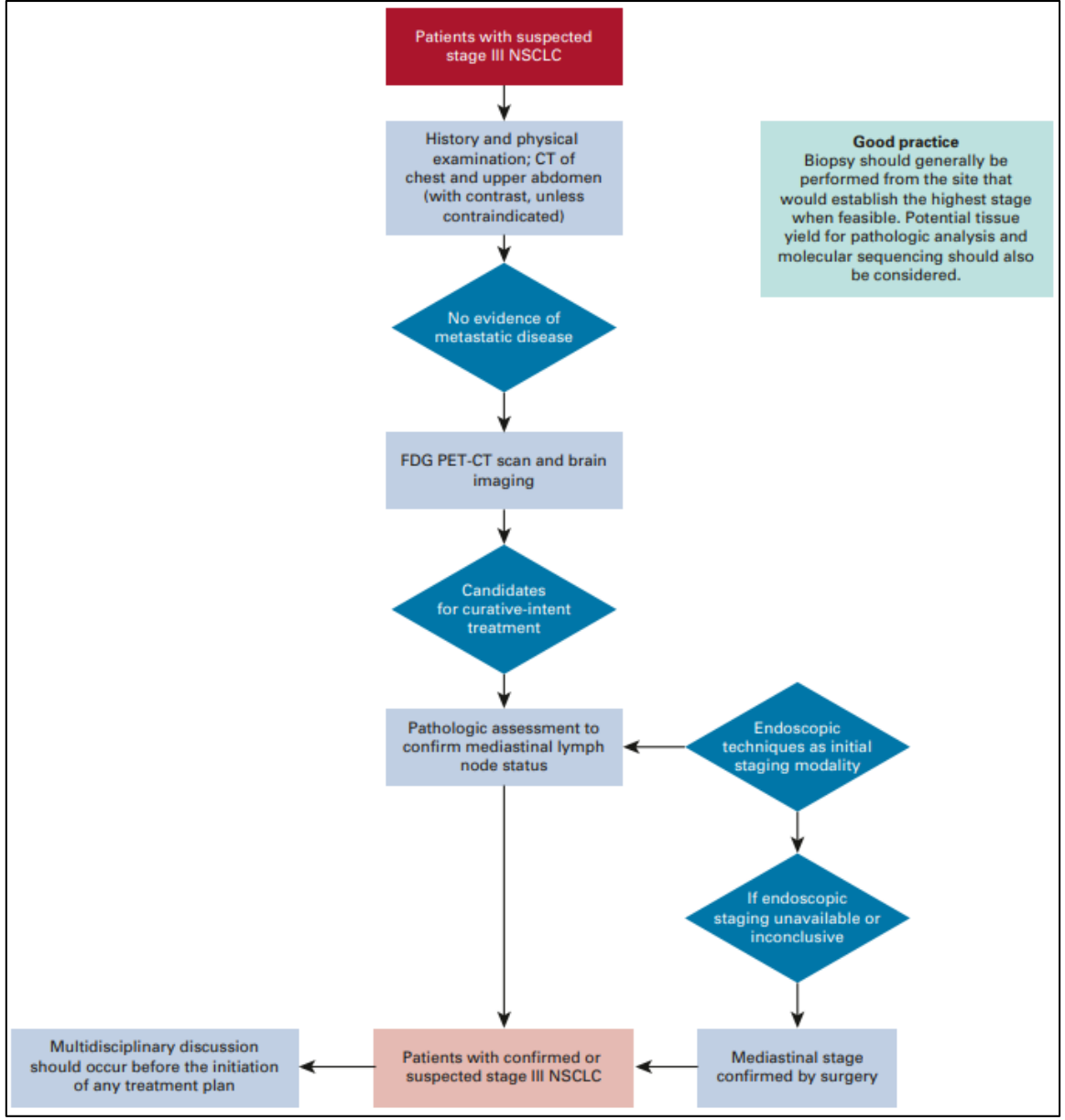
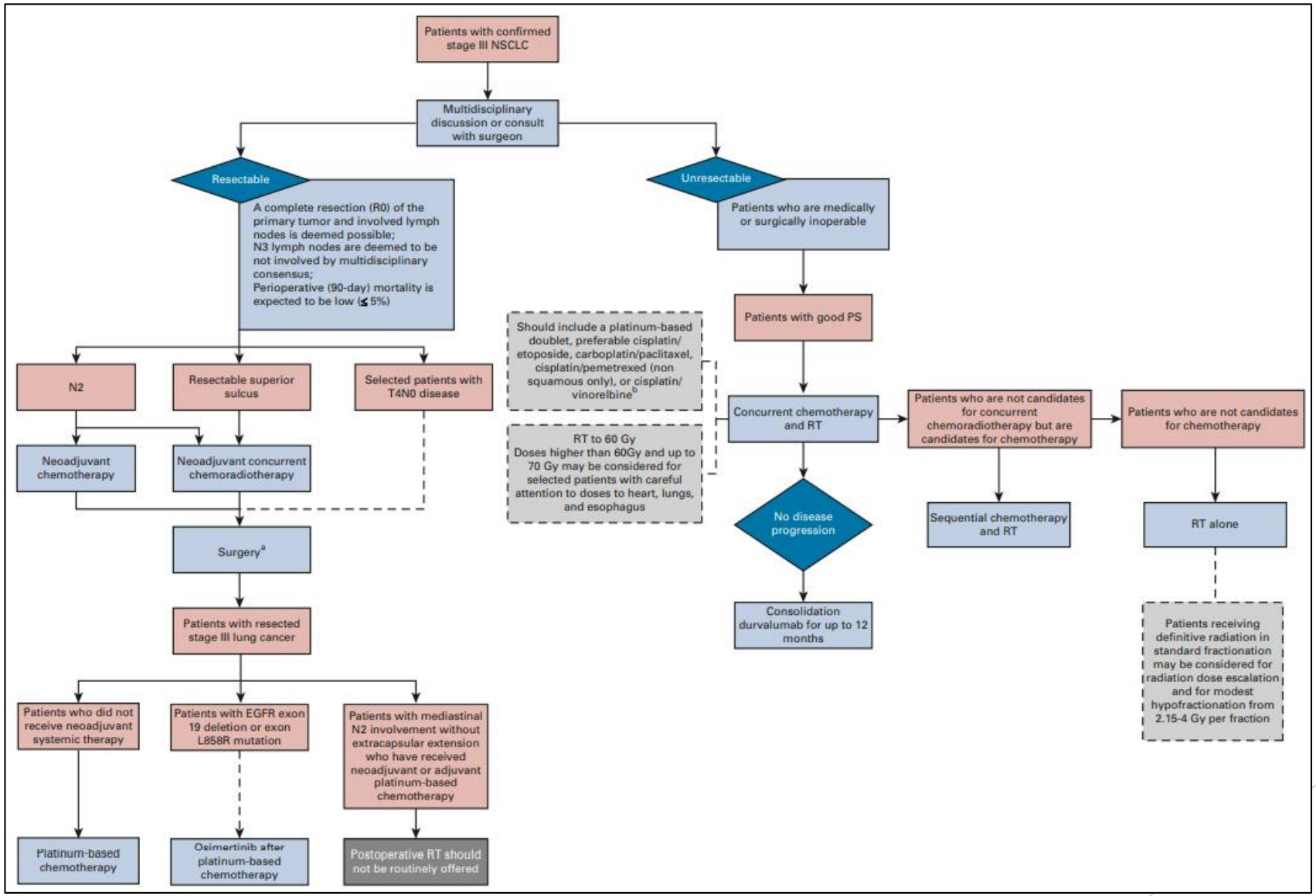
Management of Stage III Non-Small-Cell Lung Cancer: ASCO Guideline



Management of Stage III Non-Small-Cell Lung Cancer: ASCO Guideline



THANKS!