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Concurrent Chemotherapy in Non Small Cell Lung Cancer

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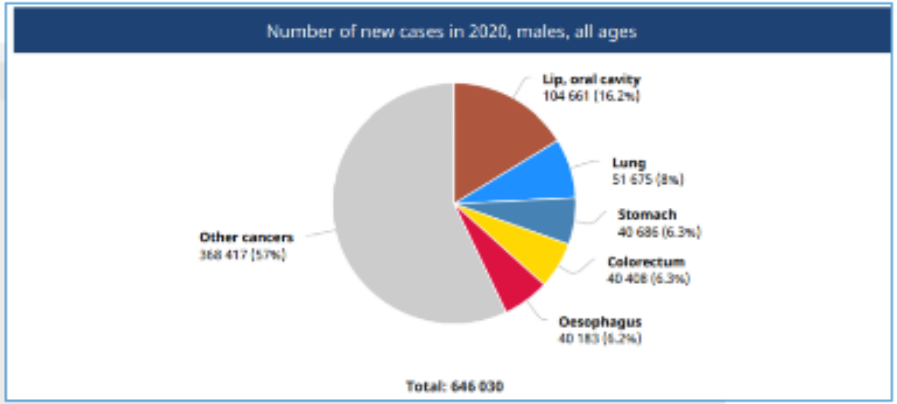
The burden of lung cancer in India

Incidence / death	
Total lung cancer incidence (N)	88,831*
Total lung cancer deaths (N)	80,523
Incidence / death (%)	9.3%



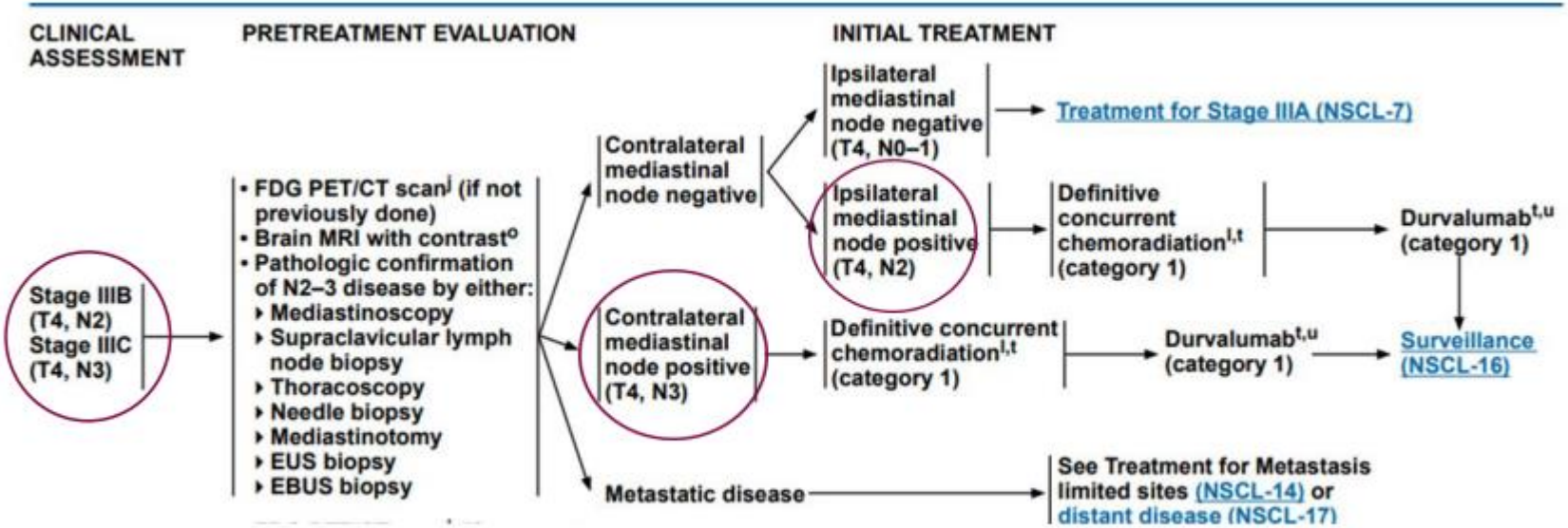
2nd Most common cause in Males

* 2021 projection: https://gco.iarc.fr/today/data/factsheets/populations/356-india-fact-sheets.pdf

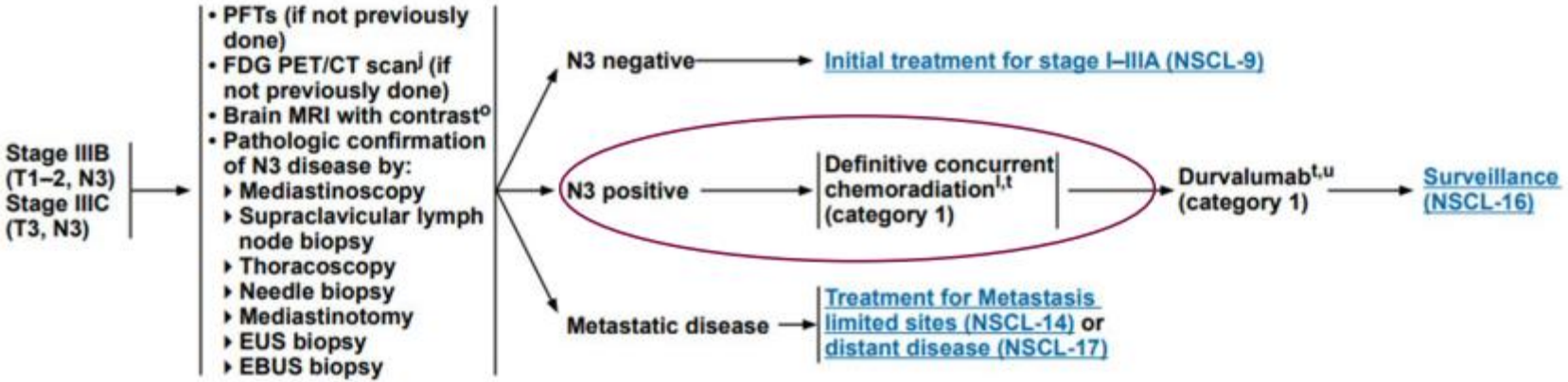
Concurrent Chemotherapy in NSCLC

- When to use it
- Benefits over RT alone
- Regimens available
- Comparing the efficacy and safety

NCCN GUIDELINES



NCCN GUIDELINES



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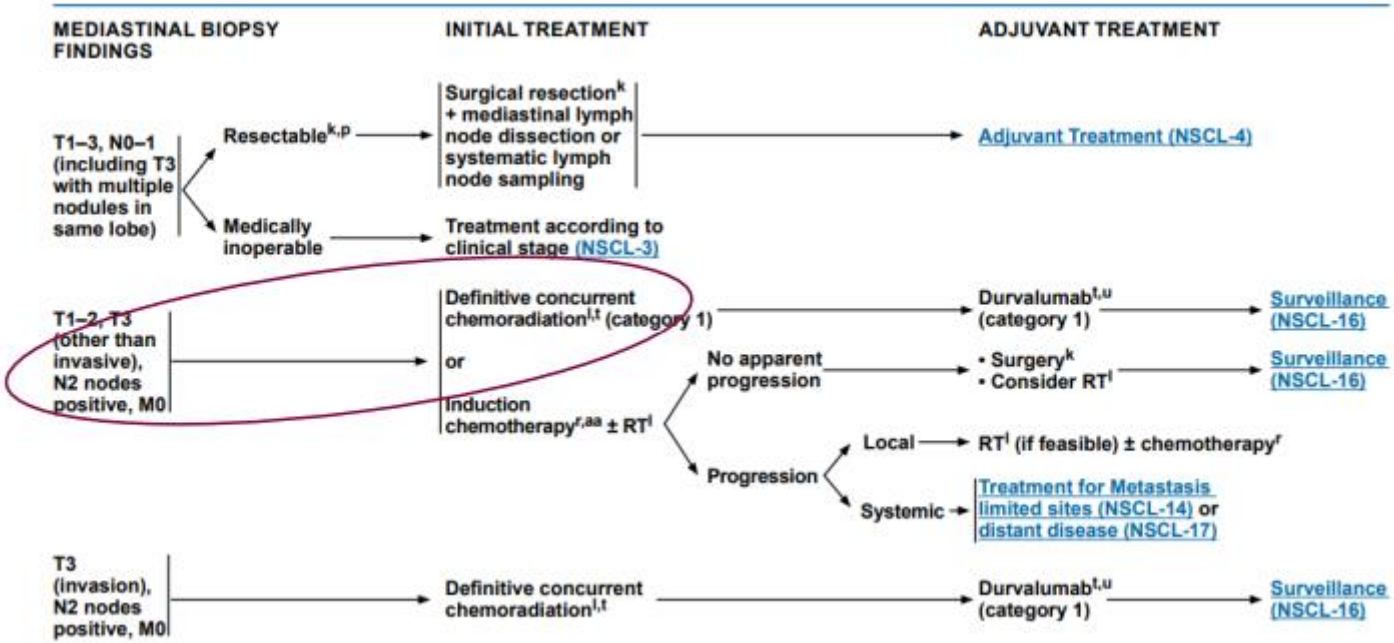

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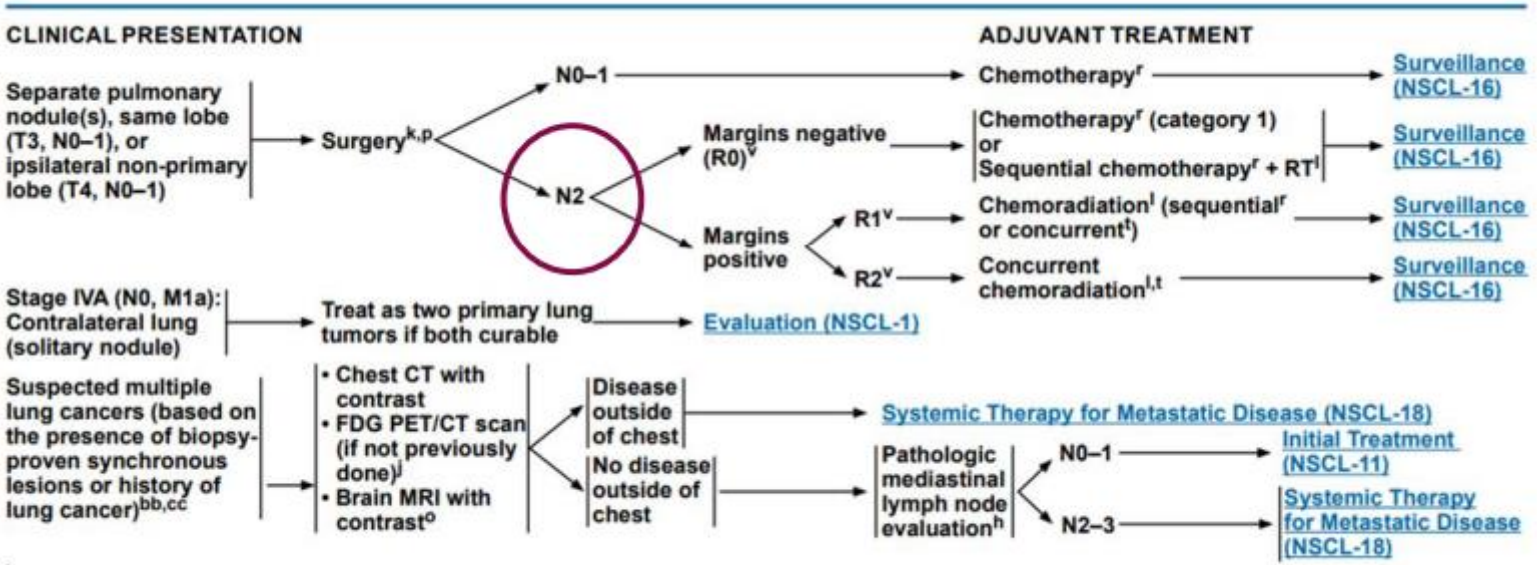
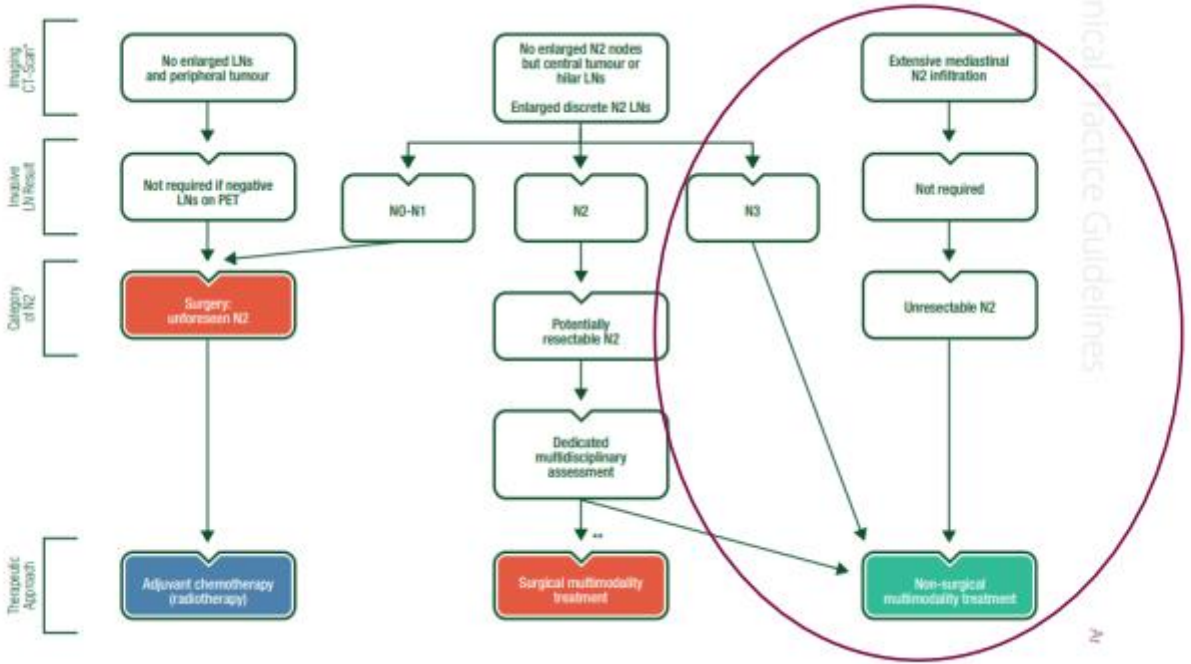


ESMO GUIDELINES



CCRT vs RT alone

➢Until 1990s RT alone was the SOC for inoperable NSCLC, with poor 5 years survival <10%

➢Adding chemotherapy has a dual effect
❖Increases the radio-sensitivity – increases local control
❖Decreases the risk of distant metastasis

➢Hence now it has become the SOC.

Clinical Trial > Cancer. 1995 Aug 15;76(4):593-601.
doi: 10.1002/1097-0142(19950815)76:4<593::aid-cncr2820760409>3.0.co;2-n.

Randomized trials of radiotherapy alone versus combined chemotherapy and radiotherapy in stages IIIa and IIIb nonsmall cell lung cancer. A meta-analysis

Results: Survival probabilities at 1, 2, 3, and 5 years, as estimated from published survival curves, were considered as the endpoints of interest. For survival at 3 and 5 years, the point estimates and the confidence intervals were used. Quality scoring of the studies also was performed. Fourteen trials were selected, comprising 1887 patients in the meta-analysis. For the cisplatin-based group, the estimated pooled odds ratio of death at 1 and 2 years was 0.76 (0.6-0.9 CI) and 0.70 (0.5-0.9 CI), with a reduction in mortality of 24% and 30%, respectively. For the noncisplatin-based group, the estimated pooled odds ratio at 1 and 2 years was 1.05 (0.7-1.5 CI) and 0.82 (0.5-1.3 CI), with a reduction in mortality of 5% and 18%, respectively. However, no significant differences were found between the percentage of survival and the CI at 3 and 5 years using the point estimates.

Conclusions: These results favor combined cisplatin-based chemotherapy and radiotherapy, although it was not so at 3 and 5 years of survival. These data must, however, be considered in the light of their clinical relevance and of the balance between quality of life, toxicity, and costs of chemotherapy.

Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials

BMJ 1995 ; 311 doi: https://doi.org/10.1136/bmj.311.7010.899 (Published 07 October 1995)

LOCALLY ADVANCED DISEASE Radical radiotherapy v radical radiotherapy plus chemotherapy

Data were available from 22 trials (3033 patients and 2814 deaths) (table IV). Five trials used long term alkylating agents, mainly cyclophosphamide or nitrosourea in combination with methotrexate. Three used vinca alkaloids or etoposide, and three used "other" regimens, which in this comparison were mostly based on doxorubicin. Eleven trials (1780 patients, 1696 deaths) used chemotherapy regimens containing cisplatin, of which two used the regimen of cisplatin, doxorubicin, and cyclophosphamide and seven used a combination of cisplatin plus a vinca alkaloid or etoposide. Intended doses of cisplatin ranged from 40mg/m^2 to 120mg/m^2 per cycle and total doses from 120mg/m^2 to 800mg/$m.^2$ The intended radiation dose forcisplatin based trials ranged from 50 Gy in 20 fractions to 65 Gy in 30 fractions. Ten of these trials started chemotherapy before radiotherapy.

the risk of death, but no firm conclusions can be drawn. Trials using cisplatin based chemotherapy provided the most information (more than 50%) and the strongest evidence for an effect in favour of chemotherapy (figures 5 and 6). The hazard ratio of 0.87 (P=0.005), or 13% reduction in the risk of death, was equivalent to absolute benefits of 4% (95% confidence interval 1% to 7%) at two years and 2% (1% to 4%) at five years. However, no firm evidence exists that the results of the trials using regimens containing vinca alkaloids or etoposide or of those using other regimens of modern drugs were any different from those using cisplatin based chemotherapy.

ORIGINAL ARTICLE LUNG CANCER | VOLUME 17, ISSUE 3, P473-483, MARCH 01, 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

Based on individual patient data from published and unpublished randomised trials which compared radiotherapy alone with the same radiotherapy combined with concomitant cisplatin- or carboplatin-based chemotherapy.

Analysis was based on 9 trials including 1764 patients. Median follow-up was 7.2 years. The hazard ratio of death among patients treated with radio-chemotherapy compared to radiotherapy alone was 0.89 (95% confidence interval, 0.81–0.98; $P = 0.02$) corresponding to an absolute benefit of chemotherapy of 4% at 2 years.

Concomitant platin-based radio-chemotherapy may improve survival of patients with locally advanced NSCLC.

Chemotherapy Regimens Used With Radiotherapy in NSCLC

Concurrent Regimens

Treatment	Study	Population	Radiation Dose, Gy
Cisplatin, etoposide (two 4-week cycles)[1]	PROCLAIM	Nonsquamous stage IIIA/B NSCLC (n=297)	60-66
Cisplatin, vinblastine (5-week cycle)[2]	RTOG 9410	Untreated, inoperable stage II/III NSCLC (n=204)	63
Cisplatin, pemetrexed (three 3-week cycles)[1]	PROCLAIM	Nonsquamous stage IIIA/B NSCLC (n=301)	60-66
Paclitaxel, carboplatin (weekly ± 2 cycles of consolidation)[3]	RTOG 0617	Stage IIIA/B NSCLC (n=228)	60
Paclitaxel, carboplatin (7-week cycle)[4]	CALGB 39801	Untreated, inoperable stage III NSCLC (n=182)	66
Cisplatin, etoposide (two 1-week cycles)[5]	HOG and US Oncology	Unresected stage III NSCLC (n=74)	59.4
Cisplatin, etoposide (four 1-week cycles)[6]	—	Stage IIIA NSCLC (n=194)	61
Paclitaxel, carboplatin (two 3-week cycles)[7]	LAMP	Unresectable stage IIIA/B NSCLC (n=91)	63

- 1. Senan S, et al. J Clin Oncol. 2016;34:953-962. 2. Curran WJ Jr, et al. J Natl Cancer Inst. 2011;103:1452-1460. 3. Bradley JD, et al. Lancet Oncol. 2015;16:187-199.
4. Vokes EE, et al. J Clin Oncol. 2007;25:1698-1704. 5. Hanna N, et al. J Clin Oncol. 2008;26:5755-5760. 6. Albain KS, et al. Lancet. 2009;374:379-386.
7. Belani CP, et al. J Clin Oncol. 2005;23:5883-5891.

VARIOUS CHEMOTHERAPY REGIMENS USED IN CCRT

Preferred regimen for nonsquamous NSCLC-

- Carboplatin AUC5 (Day-1), pemetrexed 500 mg/m2 (Day-1) every 21 days for 4 cycles with concurrent thoracic RT
- Cisplatin 75 mg/m2 (Day-1), pemetrexed 500 mg/m2 (Day-1) every 21 days for 4 cycles with concurrent thoracic RT +/- additional 4 cycles of pemetrexed 500 mg/m2 every 3 weekly
- Paclitaxel 45-50 mg/m2 weekly, Carboplatin AUC-2 with concurrent thoracic RT +/- additional 2 cycles every 21 days of paclitaxel 200 mg/m2 and carboplatin AUC-6
- Cisplatin 50 mg/m2 on Day-1, 8, 29, 36 and Etoposide 50 mg/m2 D1-D5, D29-D33 with concurrent thoracic RT.

Preferred regimen for squamous NSCLC-

- Paclitaxel 45-50 mg/m2 weekly, Carboplatin AUC-2 with concurrent thoracic RT +/- additional 2 cycles every 21 days of paclitaxel 200 mg/m2 and carboplatin AUC-6
- Cisplatin 50 mg/m2 on Day-1, 8, 29, 36 and Etoposide 50 mg/m2 D1-D5, D29-D33 with concurrent thoracic RT.

HOW TO CHOOSE THE BEST REGIMEN

- Patient related factors
  - Age
  - Co-morbidities
  - Nutrition
  - Lung Function
  - Performance Status
  - Platinum Eligibility

- Therapy related factor – the toxicity profile.

Liu et al. Radiation Oncology (2019) 14:55
https://doi.org/10.1186/s13014-019-1239-7

Radiation Oncology

RESEARCH Open Access

Comparative efficacy and safety for different chemotherapy regimens used concurrently with thoracic radiation for locally advanced non-small cell lung cancer: a systematic review and network meta-analysis

Tingting Liu†, Zheng He†, Jun Dang* and Guang Li

Background: It remains unknown which is the most preferable regimen used concurrently with thoracic radiation for locally advanced non-small cell lung cancer (NSCLC). We performed a network meta-analysis to address this important issue.

Methods: PubMed, Embase, Cochrane Library, Web of Science and major international scientific meetings were searched for relevant randomized controlled trials (RCTs). Overall survival (OS) data was the primary outcome of interest, and progression-free survival (PFS), and serious adverse events (SAEs) were the secondary outcomes of interests, reported as hazard ratio (HR) or odds ratio (OR) and 95% confidence intervals (CIs).

Table 1 Characteristics of included trials

From: Comparative efficacy and safety for different chemotherapy regimens used concurrently with thoracic radiation for locally advanced non-small cell lung cancer: a systematic review and network meta-analysis

Trial	Design	Time Range	Region	Primary Endpoint	Treatment	Median follow-up (months)	Sample Size	Median Age	Histology(%) (SCC/non-SCC)	Consolidation Chemotherapy	Radiotherapy Dose(Gy)	Radiotherapy Technology
Oh/2013 [12]	III	2005–2007	Korea	ORR	PC	Over 36	33	64	72.7/27.3	63.6%	60–66	3D
					DP		29	61.5	69/31	65.5%		
					GP		31	64	64.5/35.5	64.5%		
Segawa/2010 [13]	III	2000–2005	Japan	OS	MVP	NR	101	NR	52.5/37.5	NR	60	2D
					DP		99	NR	44.4/55.6	NR		
Takiguchi/2018 [14]	II	2011–2014	Japan	OS	SP	48	53	NR	26.4/73.6	NR	60	NR
					DP		53	NR	20.8/79.2	NR		
Yamamoto/2010 [15]	III	2001–2005	Japan	OS	MVP	NR	146	63	47.9/52.1	41%	60	2D
					IC		147	62	42.2/57.8	29.3%		
					PC		147	63	48.3/51.7	49.7%		
Senan/2016 [16]	III	2008–2012	USA	OS	PP	22	301	59.5	100	76%	60–66	3D
					EP	23	297	58.7	100	74.3%		
Govindan/2011 [17]	II	2005–2008	USA	OS	PP	32	48	65	35/65	69.8%	70	3D
					PP-Cet		53	66	34/66	85.4%		

Abbreviations: *OS* overall survival, *ORR* overall response rate, *SP* S-1-cisplatin, *UP* UFT-cisplatin, *NP* vinorelbine-cisplatin, *EP* etoposide-cisplatin, *MVP* mitomycin-vindesine-cisplatin, *DP* docetaxel-cisplatin, *PC* paclitaxel-cisplatin/carboplatin, *PP* pemtrexed-cisplatin/carboplatin, *IC* irinotecan-carboplatin, *GP* gemcitabine-cisplatin, *Cet* cetuximab, *SCC* squamous cell carcinoma, *2D* two-dimensional radiotherapy, *3D* three-dimensional conformal radiotherapy, *NR* not reported

Abstract

Background: It remains unknown which is the most preferable regimen used concurrently with thoracic radiation for locally advanced non-small cell lung cancer (NSCLC). We performed a network meta-analysis to address this important issue.

Methods: PubMed, Embase, Cochrane Library, Web of Science and major international scientific meetings were searched for relevant randomized controlled trials (RCTs). Overall survival (OS) data was the primary outcome of interest, and progression-free survival (PFS), and serious adverse events (SAEs) were the secondary outcomes of interests, reported as hazard ratio (HR) or odds ratio (OR) and 95% confidence intervals (CIs).

Results: 14 RCTs with a total of 2975 patients randomized to receive twelve categories of treatments were included in the meta-analysis. Direct comparison meta-analysis showed that etoposide-cisplatin (EP) was more effective than paclitaxel-cisplatin/carboplatin (PC) in terms of OS (HR = 0.85, 95% CI: 0.77–0.94) and PFS (HR = 0.66, 95% CI: 0.47–0.95). In network meta-analysis, all regimen comparisons did not produce statistically significant differences in survival. Based on treatment ranking of OS and the benefit-risk ratio, S-1-cisplatin (SP) was likely to be the most preferable regimen for its best efficacy and low risk of causing SAEs. Uracil/tegafur-cisplatin (UP) and pemetrexed-cisplatin/carboplatin (PP) were ranked the second and third respectively. Gemcitabine-cisplatin (GP) and PC + Cetuximab (PC-Cet) appeared to be the worst and second-worst regimens for their poor efficacy and poor tolerability.

Conclusions: Based on efficacy and tolerability, SP is likely to be the most preferable regimen used concurrently with thoracic radiation for locally advanced NSCLC, followed by UP and PP. Further direct head-to-head studies are needed to confirm these findings.

Keywords: Locally advanced non-small cell lung cancer, Concurrent chemoradiation, Network meta-analysis

Concurrent Immunotherapy with Lung RT

Summary of ongoing randomized studies of combined radiotherapy and immunotherapy in lung cancer

Clinical trials gov identifier	Estimated enrollment (n)	Pathological types	Stage	Arms	Phase	Primary endpoint	Immunotherapy	Radiotherapy
NCT03867175	116	NSCLC	IV	RT+IO *vs.* IO	III	PFS	Pembrolizumab	SBRT
NCT03811002	506	SCLC	I-IIIC	CT+RT *vs.* CT+RT+IO	II/III	PFS OS	Atezolizumab	3D-CRT or IMRT
NCT03774732	510	NSCLC	IV	RT+IO *vs.* IO	III	OS	Nivolumab, atezolizumab or pembrolizumab	3D-CRT or SABR
NCT03540420	212	SCLC	I-III	CT+RT+IO *vs.* CT+RT	II	2-year survival	Atezolizumab	45 Gy/30 fractions
NCT03446911	20	NSCLC	I	RT+IO *vs.* RT	I/II	AE	Pembrolizumab	SABR
NCT03446547	216	NSCLC	I	RT *vs.* RT+IO	II	TTP	Durvalumab	SBRT
NCT03223155	80	SCLC	IV	RT+IO (sequential) *vs.* RT+IO (concurrent)	I	AE	Nivolumab or Ipilimumab	SBRT
NCT03110978	140	NSCLC	I-IIA NSCLC, recurrent lung cancer	RT *vs.* RT+ IO	II	EFS	Nivolumab	SBRT

TAKE HOME MESSAGE

- Platinum based Chemotherapy remains the SOC for CCRT

- Although associated with more haematological toxicity – prefer to give cisplatin based regimen – Eto + Cis

- In other patients – Taxanes + Platinum

- In near future the use of immunotherapy/TKI with RT may change the outcomes in this subset of patients

- To consolidate we have PACIFIC trial – Durvalumab
- Ongoing trial PACIFIC 8 – Durva vs Durva + Domvanalimab (Anti-TIGIT)

THANK YOU

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