Concurrent Chemotherapy in Lung cancer

Regimen Selection, Results Efficacy, Complications, Compliance

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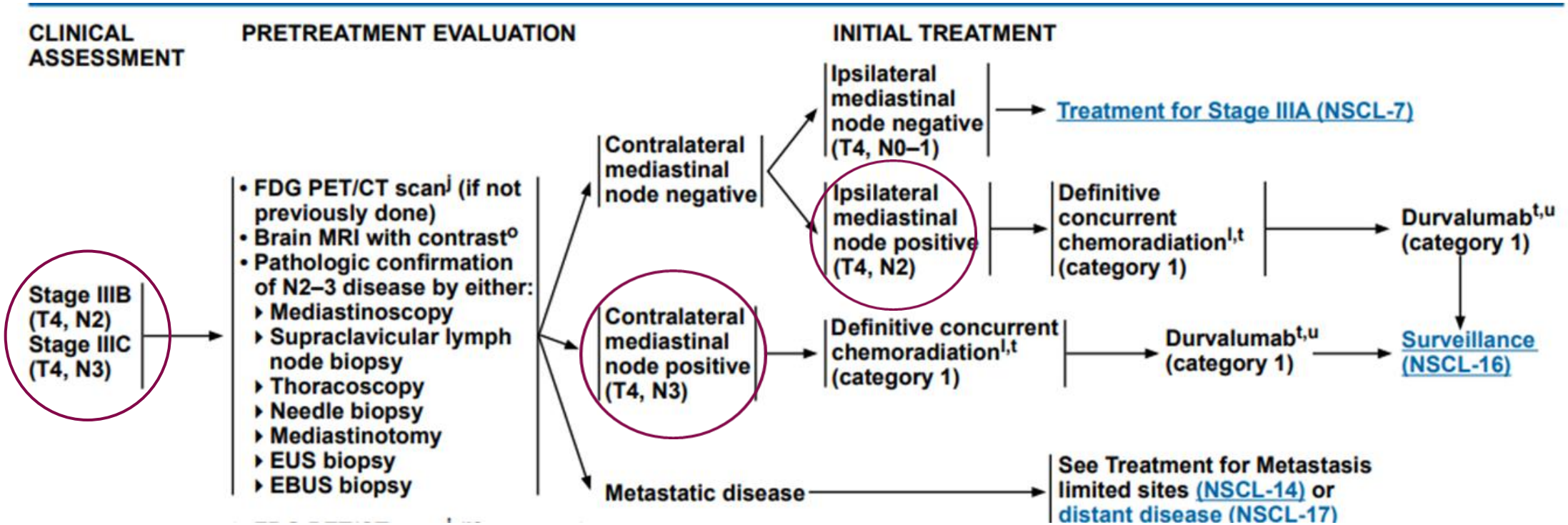
Schema-

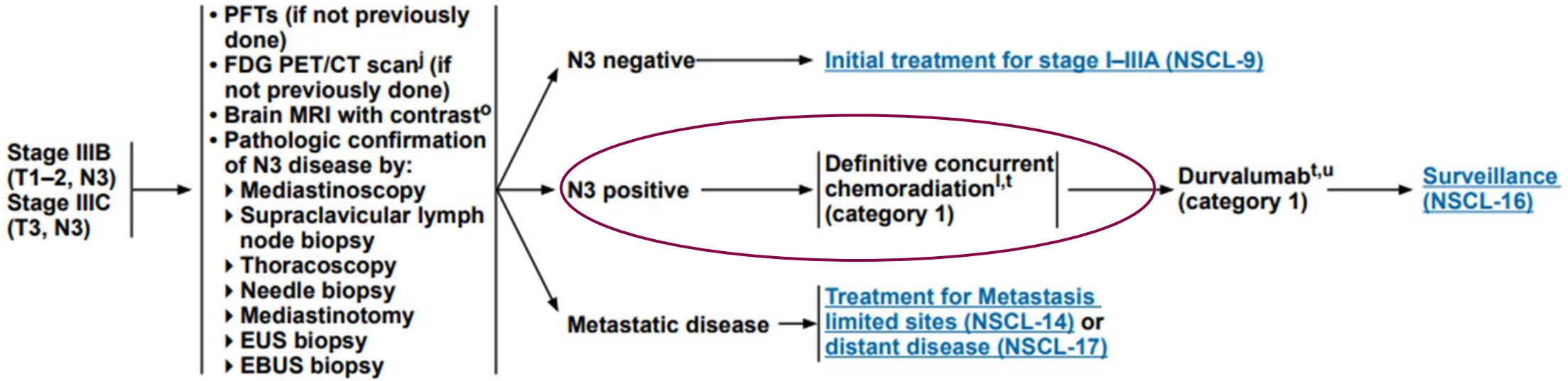
- Concurrent chemoradiation in NSCLC- when to give
- Benefit over radiation alone
- Regimens and available evidence for them
- Comparison between various concurrent chemotherapy regimens in terms of efficacy, safety etc

- Concurrent chemoradiotherapy
- Sequential chemoradiotherapy

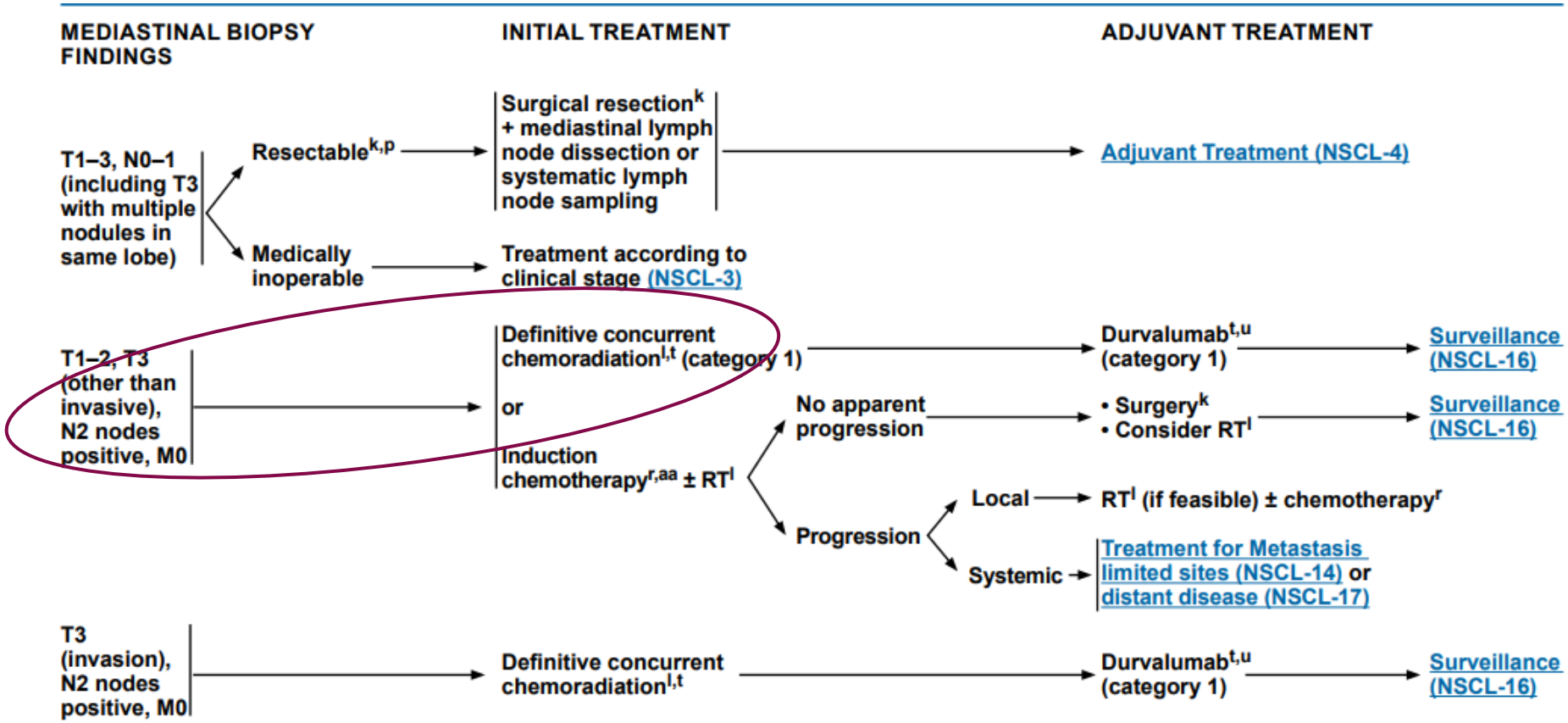
Concurrent chemotherapy in NSCLC- where is the role



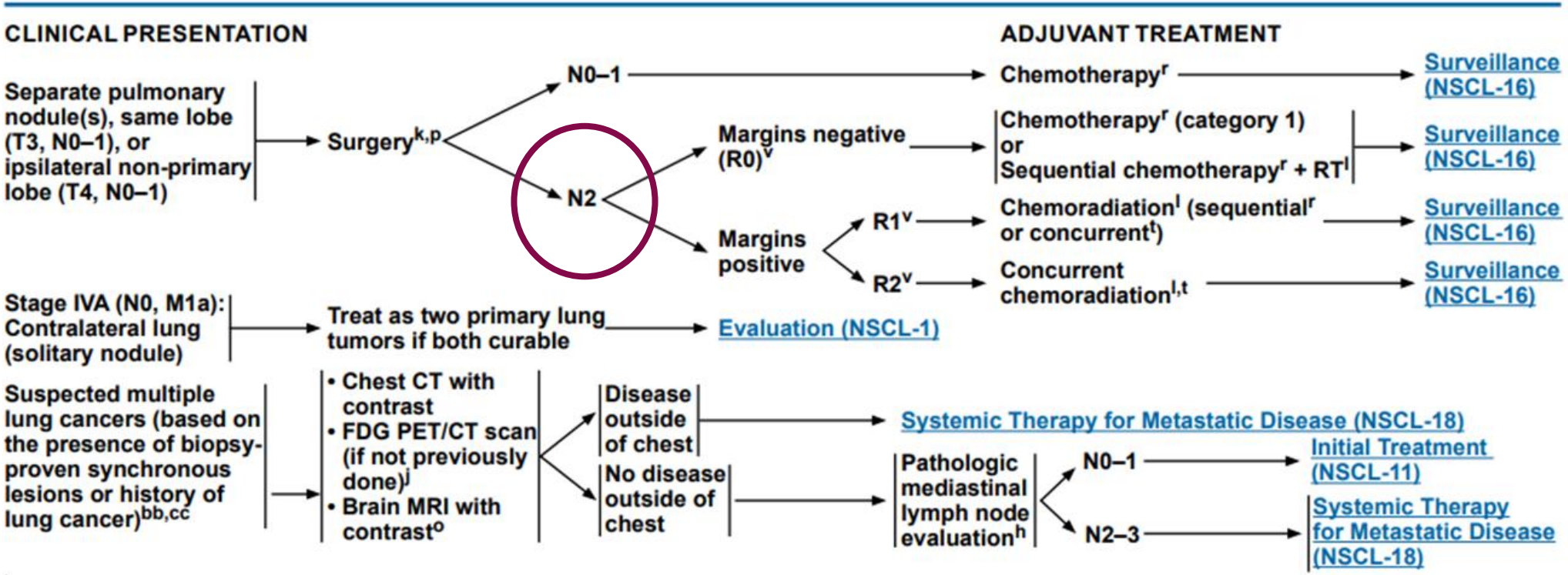
Concurrent chemotherapy in NSCLC- where is the role



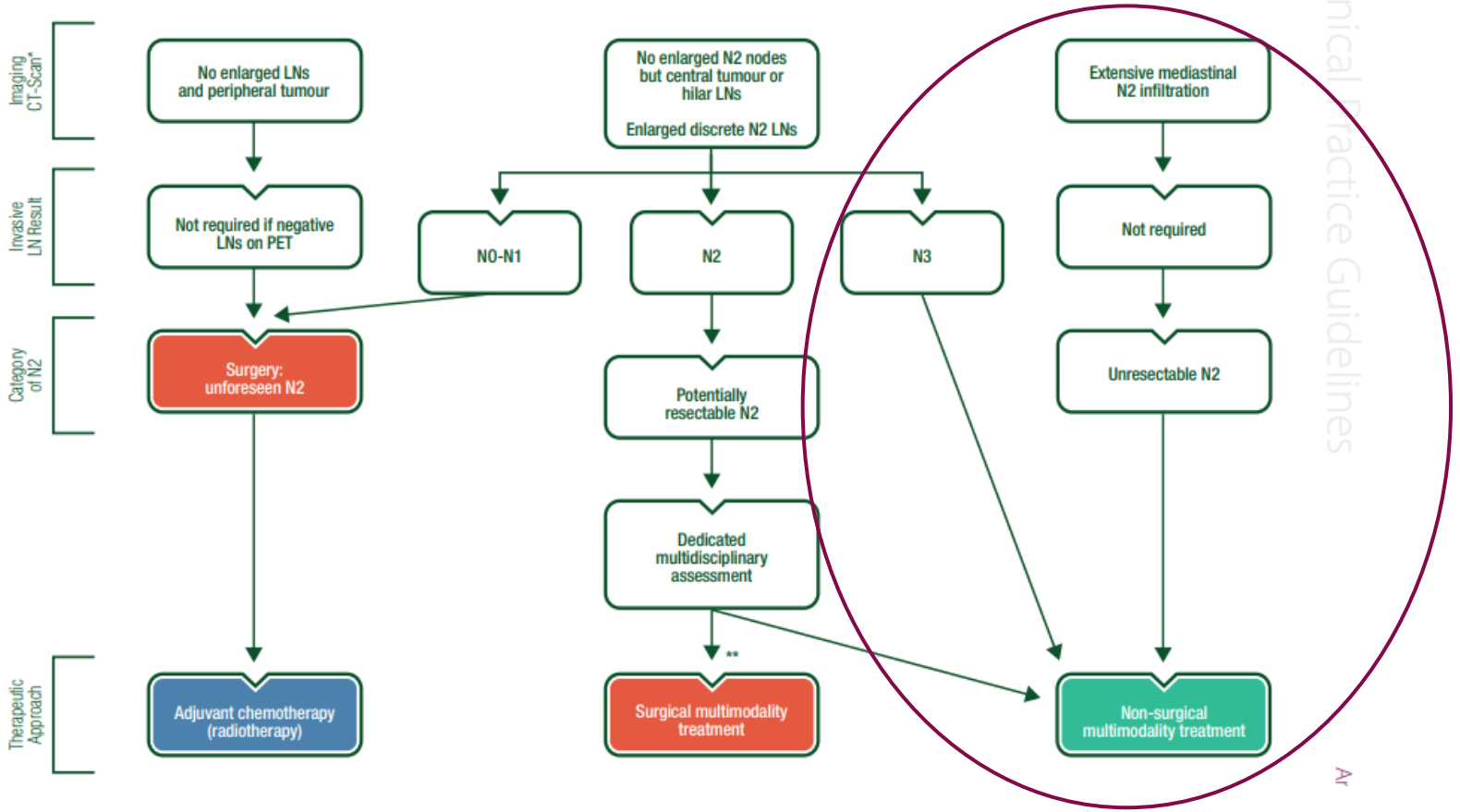
Concurrent chemotherapy in NSCLC- where is the role



Concurrent chemotherapy in NSCLC- where is the role



Concurrent chemotherapy in NSCLC- where is the role



Concurrent CTRT Vs Definitive RT alone

- Until the 1990's radiotherapy alone was the standard treatment for patients with inoperable NSCLC, however the 5-year survival rate was poor (under 10%).[1]

- However, current standard of care for locally advanced NSCLC- combination chemotherapy and radiotherapy, as studies have shown survival benefit with this strategy compared to RT alone.

- **Principle of combined Chemoradiation strategy-** The idea is that chemotherapy will reduce the risk of distant metastasis and radiotherapy will maintain loco-regional control. The chemotherapeutic drug may also increase radio-sensitivity and increase the effectiveness of the radiation treatment.[2,3]

1. Hung MS, Wu YF, Chen YC. Efficacy of chemoradiotherapy versus radiation alone in patients with inoperable locally advanced non–small-cell lung cancer: a meta-analysis and systematic review. Medicine. 2019 Jul;98(27).
2. Le Chevalier T, Arriagada R, Quoix E, Ruffie P, Martin M, Douillard JY, Tarayre M, Lacombe-Terrier MJ, Laplanche A. Radiotherapy alone versus combined chemotherapy and radiotherapy in unresectable non-small cell lung carcinoma. Lung cancer. 1994 Mar 1;10:S239-44.
3. Blackstock AW, Govindan R. Definitive Chemoradiation for the Treatment of Locally Advanced Non–Small-Cell Lung Cancer. Journal of clinical oncology. 2007 Sep 10;25(26):4146-52.

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.

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.

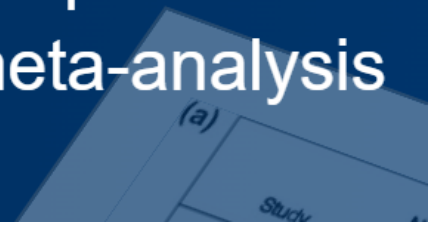
Randomized trials of radiotherapy alone versus combined chemotherapy and radiotherapy in stages IIIa and IIIb nonsmall cell lung cancer. A meta-analysis

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.

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.

Table 2

The protocol of radiotherapy and chemoradiotherapy.

Study name First author (yr)	CT dosage/ intervals	RT dosage/ intervals	Median of follow-up time (months)
Jeremic B (2015)	up to 3 cycles of **platinum**-based CHT	low dose palliative RT (10 Gy in a single fraction or 16 Gy in 2 fractions given with one week split	4.15 yr
Atagi (2012)	30 mg/m^2 (30 min iv) of **carboplatin** 1 h before every RT, for the first 20 fractions	60 Gy in 30 fractions over 6 weeks	19.4
Nawrocki (2010)	2 cycles (**cisplatin** 80 mg/m^2 on day 1, **Navelbine** 25 mg/m^2 on days 1 and 8)	30 Gy/10 fractions	41
Huber (2006)	60 mg/m^2 of **paclitaxel** weekly over 6 weeks, up to 6 hours before RT,	60 Gy	13.6
Komaki R (1997)	**Cisplatin** 100 mg/m^2 days1 and 29 with **vinblastine** 5mg/m^2 weekly for 5 weeks	60 Gy at 2.0 Gy per day	6 years
Dillman (1996)	**Vinblastine**5 mg/m^2 for 5 week iv on days1,8,15,22,29 and**cisplatin** 100mg/m^2 given monthly iv over a 30-to 60-min period on days1 and 29	60 Gy in 20 fractions over a 4-week period to the original tumor volume/10 fractions over a 2 week period to the boost volume.	84
Le Chevalier T (1994)	3 monthly cycles of VCPC (**vindesine**, 1.5 mg/m^2 on days 1 and 2; **lomustine**50 mg/m^2 on day 2,25 mg/m^2 on day 3; **cisplatin** 100 mg/m^2 on day 2; **cyclophosphamide** 200 mg/m^2 on days 2-4).	65 Gy	61
Crino_ L (1993)	**Cisplatin** 100 mg/m^2 given intravenously over 30 min on day 1 and **etoposide**120 mg/m^{2}given intravenously over 45 min on day 1-2-3.	The daily fractionation was 2000 cGy for a total dose of 5600 to 6000 cGy within 6 weeks	6 years
Simpson JR (1989)	**Misonidazole** 400 mg/m^2 2–4 h prior to RT daily for 5–6 weeks to a maximum dose of 12 g/m^2 or until tumor progression).	50 Gy large field and 10 Gy boost	minimum of 4.0 years or untildeath.

CT = chemotherapy; RT = radiotherapy; iv = intravenous injection; Gy = gray.

Results: Ultimately, 13 RCT studies were included in the systematic review and meta-analysis. The 13 studies included a total of 1936 patients with incurable/inoperable stage III NSCLC, of which 975 received RT alone and 961 received RT+CT combination therapy. The average age ranged from 54 to 77 years. At 1 and 2 years after treatment, the pooled data reveal that patients receiving CT+RT combination therapy had higher overall survival (pooled hazard ratio (HR), 0.72; 95% CI, 0.62–0.84; $P < .001$; 1-yr: HR, 0.67; 95% CI, 0.54–0.84; $P < .001$; 2-year: HR, 0.57; 95% CI, 0.45–0.73; $P < .001$), higher PFS (pooled HR, 0.73, 95% CI, 0.60–0.89; $P = .002$; 1-year: HR, 0.36; 95% CI, 0.24–0.53; $P < .001$; 2-year: HR, 0.38; 95% CI, 0.23–0.63; $P < .001$).

Various concurrent chemotherapy Regimens-

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.

what is the optimal chemotherapy to be given to stage III disease patients?

cisplatin or carboplatin in combination with radiotherapy

Recommendation 5.1: In the absence of contraindications, the optimal chemotherapy to be combined with radiation in stage III NSCLC should be based on cisplatin. There are no firm conclusions supporting single agent carboplatin as a radiation sensitiser [I, A].

Eberhardt WE, de ruysscher D, weder W, le pechoux C, de leyn P, hoffmann H, westeel V, stahel R, felip E, peters S, members P. 2nd ESMO consensus conference in lung cancer: locally advanced stage III non-small-cell lung cancer. Annals of oncology. 2015 aug 1;26(8):1573-88.

Phase-2 trials of concurrent chemoradiation

CISPLATIN-ETOPOSIDE

Regimens	Evidence available	Compared with	Chemo dose	RT dose	Outcomes	AEs
Etoposide-Cisplatin	Phase-II study	Single arm	Cisplatin 20 mg/m2 D1-D5 Etoposide 50 mg/m2 D1-D5 Every 4 weekly for 4 cycles	60 Gy	ORR- 84% CR-68% Median survival- 18 months	Hematologic toxicities- 24% pts

Clinical Trial > Int J Radiat Oncol Biol Phys. 1996 May 1;35(2):343-50.
doi: 10.1016/0360-3016(96)00087-9.

Concurrent cisplatin, etoposide, and radiotherapy for unresectable stage III nonsmall cell lung cancer: a phase II study

F Reboul [1], Y Brewer, P Vincent, B Chauvet, C F Faure, M Taulelle

Methods and materials: Between February 1992 and April 1993, 50 patients with either medically or technically **inoperable Stage III NSCLC** were treated with concurrent chemoradiotherapy. Thoracic radiotherapy was administered to a total dose of **60 Gy**. Concurrent chemotherapy consisted of **cisplatin 20 mg/m2/day plus etoposide 50 mg/m2/day**, from day 1 through day 5, every 4 weeks for four cycles.

Results- ORR- 84% (68% CR). Median overall survival- 18 months.
Overall survival was 70% at 1 year, 39.7% at 2 years, and 34.7% at 3 years.
Patients achieving CR (n = 34) had a 2-year survival of 58.4% compared to 0% for nonresponders ($p < 0.0001$).
Actuarial local control was 63.4% at 1 year, and 58.5% at 2 and 3 years, respectively.
Major hematologic toxicity occurred in 24% of the patients.

Phase-2 trials of concurrent chemoradiation

PACLITAXEL-CARBOPLATIN

Regimens	Evidence available	Compared with	Chemo dose	RT dose	Outcomes	AEs
Paclitaxel-carboplatin	Phase-II (39 pts)	single arm	Weekly paclitaxel (50 mg/m2)/ carboplatin (AUC = 2) with RT followed by 2 cycles of paclitaxel (200 mg/m2)/carboplatin (AUC = 6)	66 Gy	Median OS- 20.5 m 1 yr OS- 56% 2 Yrs OS- 38% Median PFS- 9 months ORR- 75.7%	Gd ¾ esophagitis 46%
Paclitaxel-carboplatin	Phase-II randomized non comparative study	3 arms	**Arm-1 sequential-** Paclitaxel (200 mg/m2) + Carboplatin AUC-6 q 3 weekly x 2 cycles followed by sequential thoracic RT **Arm-2 induction/concurrent-** Paclitaxel (200 mg/m2) + Carboplatin AUC-6 q 3 weekly x 2 cycles followed by Paclitaxel 45 mg/m2 and carboplatin AUC-2 weekly with RT **Arm-3 concurrent/consolidation-** weekly paclitaxel (45 mg/m2)/ carboplatin (AUC = 2) with RT followed by 2 cycles of paclitaxel (200 mg/m2)/carboplatin (AUC = 6)	63 Gy	Median OS Arm-1- 13.0 months Arm-2- 12.7 months Arm-3- 16.3 months	Most common locoregional Gd ¾ toxicity during and after RT was esophagitis Arm-2- 19% Arm-3- 28%
Paclitaxel-carboplatin	Phase-II (34 pts)	Single arm	Weekly twice paclitaxel (30 mg/m2)/ carboplatin (AUC = 1.5) with RT followed by 2 cycles of paclitaxel (200 mg/m2)/carboplatin (AUC = 6)	61 Gy	ORR- 71% Median OS- 17 months	Gd ¾ toxicity Esophagitis- 38% Neutropenia- 12%

Phase-2 single arm study, JCO 1998

Multiinstitutional Phase II Trial of Paclitaxel, Carboplatin, and Concurrent Radiation Therapy for Locally Advanced Non–Small-Cell Lung Cancer

By H. Choy, W. Akerley, H. Safran, S. Graziano, C. Chung, T. Williams, B. Cole, and T. Kennedy

Purpose: **Combined modality therapy for non–small-cell lung cancer (NSCLC) has produced promising results. A multiinstitutional phase II clinical trial was conducted to evaluate the activity and toxicity of paclitaxel, carboplatin, and concurrent radiation therapy on patients with locally advanced NSCLC.**

Patients and Methods: **Forty previously untreated patients with inoperable locally advanced NSCLC entered onto a phase II study from March 1995 to December 1996. On an outpatient basis for 7 weeks, patients received paclitaxel 50 mg/m² weekly over1 hour; carboplatin at (area under the curve) AUC 2 weekly; and radiation therapy of 66 Gy in 33 fractions. After chemoradiation therapy, patients received an additional two cycles of paclitaxel 200 mg/m² over 3 hours and carboplatin at AUC 6 every 3 weeks.**

Results: **Thirty-nine patients were eligible for the study. The survival rates at 12 months were 56.3%, and at 24 months, 38.3%, with a median overall survival of 20.5 months. The progression-free survival rates at 12 months were 43.6%, and at 24 months, 34.7%, with a median progression-free survival of 9.0 months. Two patients did not receive more than 2 weeks of concurrent chemoradiotherapy and were not assessable for toxicity and response. The overall response rate (partial plus complete response) of 37 assessable patients was 75.7%. The major toxicity was esophagitis. Seventeen patients (46%) developed grade 3 or 4 esophagitis. However, only two patients developed late esophageal toxicity with stricture at 3 and 6 months posttreatment.**

Conclusion: **Combined modality therapy with paclitaxel, carboplatin, and radiation is a promising treatment for locally advanced NSCLC that has a high response rate and acceptable toxicity and survival rates. A randomized trial will be necessary to fully evaluate the usefulness of these findings.**

J Clin Oncol 16:3316-3322.

JCO- 2005

Phase-II study

3 arms

All with Paclitaxel-carboplatin in various sequences

Combined Chemoradiotherapy Regimens of Paclitaxel and Carboplatin for Locally Advanced Non–Small-Cell Lung Cancer: A Randomized Phase II Locally Advanced Multi-Modality Protocol

Chandra P. Belani, Hak Choy, Phil Bonomi, Charles Scott, Patrick Travis, John Haluschak, and Walter J. Curran Jr

A B S T R A C T

Purpose
This phase II noncomparative randomized trial was conducted to determine the optimal sequencing and integration of paclitaxel/carboplatin with standard daily thoracic radiation therapy (TRT), in patients with locally advanced unresected stage III non–small-cell lung cancer (NSCLC). Survival data were compared with historical standard sequential chemoradiotherapy data from the Radiation Therapy Oncology Group.

Patients and Methods
Patients with unresected stages IIIA and IIIB NSCLC, with Karnofsky performance status ≥ 70% and weight loss ≤ 10%, received two cycles of induction paclitaxel (200 mg/m^2)/carboplatin (area under the plasma concentration time curve [AUC] = 6) followed by TRT 63.0 Gy (arm 1, sequential) or two cycles of induction paclitaxel (200 mg/m^2)/carboplatin (AUC = 6) followed by weekly paclitaxel (45 mg/m^2)/carboplatin (AUC = 2) with concurrent TRT 63.0 Gy (arm 2, induction/concurrent), or weekly paclitaxel (45 mg/m^2)/carboplatin (AUC = 2)/TRT (63.0 Gy) followed by two cycles of paclitaxel (200 mg/m^2)/carboplatin (AUC = 6; arm 3, concurrent/consolidation).

Results
With a median follow-up time of 39.6 months, median overall survival was 13.0, 12.7, and 16.3 months for arms 1, 2, and 3, respectively. During induction chemotherapy, grade 3/4 granulocytopenia occurred in 32% and 38% of patients on study arms 1 and 2, respectively. The most common locoregional grade 3/4 toxicity during and after TRT was esophagitis, which was more pronounced with the administration of concurrent chemoradiotherapy on study arms 2 and 3 (19% and 28%, respectively).

Conclusion
Concurrent weekly paclitaxel, carboplatin, and TRT followed by consolidation seems to be associated with the best outcome, although this schedule was associated with greater toxicity.

Phase-II single arm study, JCO-2001

Twice-Weekly Paclitaxel and Weekly Carboplatin With Concurrent Thoracic Radiation Followed by Carboplatin/ Paclitaxel Consolidation for Stage III Non–Small-Cell Lung Cancer: A California Cancer Consortium Phase II Trial

By Derick Lau, Bryan Leigh, David Gandara, Martin Edelman, Robert Morgan, Valerie Israel, Primo Lara, Richard Wilder, Janice Ryu, and James Doroshow

Purpose: **Recent studies have suggested the superiority of concurrent chemoradiotherapy and the efficacy of paclitaxel/carboplatin in advanced non–small-cell lung cancer (NSCLC). In view of those results, we sought to examine the safety and efficacy of administration of radiosensitizing paclitaxel twice weekly and carboplatin weekly with concurrent thoracic radiation therapy (XRT) followed by consolidation paclitaxel and carboplatin for stage III NSCLC in a multi-institutional phase II trial.**

Patients and Methods: **Induction chemoradiotherapy consisted of paclitaxel 30 mg/m^2 delivered intravenously (IV) for 1 hour twice weekly for 6 weeks, carboplatin at a dose based on an area under the concentration-time curve (AUC) of 1.5 mg/mL × min, given IV once weekly for 6 weeks, and concomitant XRT of 1.8 to 2.0 Gy daily for a total of 61 Gy. Patients who achieved a complete response, partial response, or stable disease received two 21-day cycles of consolidation chemotherapy consisting of paclitaxel 200 mg/m^2 IV for 3 hours and carboplatin at a dose based on an AUC of 6 mg/mL × min.**

Results: **Thirty-four patients were eligible. Their median age was 62 years (range, 39 to 73 years), 59% were female, 41% were male, 94% had a performance status of 0 or 1, 38% had stage IIIA NSCLC, and 62% had stage IIIB NSCLC. Common grade III and IV toxicities during the induction chemoradiation phase included esophagitis (38%) and neutropenia (12%). The most common adverse reaction during consolidation chemotherapy was grade III neutropenia in five patients (15%). The overall response rate was 71%, which was achieved in the induction phase. The median follow-up was 20 months, the median survival was 17 months, and 2-year actuarial survival rate was 40% (95% confidence interval, 20% to 65%).**

Conclusion: **This regimen is tolerable and results are promising. We recommend further evaluation of this regimen in a phase III trial.**

J Clin Oncol 19:442-447.

Phase-2 trials of concurrent chemoradiation

DOCETAXEL-CARBOPLATIN/CISPLATIN

Regimens	Evidence available	Compared with	Chemo dose	RT dose	Outcomes	AEs
Docetaxel-carboplatin	**Phase-II study (67 patients)**	Single arm	weekly Docetaxel (20 mg/m2)/ carboplatin (AUC = 2) with RT followed by 2 cycles of Docetaxel (75 mg/m2)/ carboplatin (AUC = 6)	63 Gy	Median OS- 12 months Median PFS- 8 months 1 yr PFS- 27%	Gd ¾ toxicity Esophagitis- 22%
Docetaxel-Cisplatin	**Phase-II study (42 patients)** Segawa et al	Single arm	Docetaxel 40 mg/m2 and Cisplatin 40 mg/m2 on D1, D8, D29, D36	60 Gy over 6 weeks	ORR 79%	Gd ¾ toxicity Esophagitis- 19%

A Phase II Study of Concurrent Chemoradiation with Weekly Docetaxel, Carboplatin, and Radiation Therapy Followed by Consolidation Chemotherapy with Docetaxel and Carboplatin for Locally Advanced Inoperable Non-small Cell Lung Cancer (NSCLC)

Anshu K. Jain, BS, Randall S. Hughes, MD,† Alan B. Sandler, MD,‡ Afshin Dowlati, MD,§ Lee S. Schwartzberg, MD,‖ Tracy Dobbs, MD,¶ Larry Schlabach, MD,# Jean Wu, MSN,* Nancy J. Muldowney, BSN, RN,‡ and Hak Choy, MD**

Introduction: The current standard of care for good performance status patients with locally advanced non-small cell lung carcinoma is concurrent chemoradiation, although a clearly superior regimen has not been identified. Docetaxel has been shown to possess good single-agent activity against non-small cell lung cancer (NSCLC) and radiosensitizing properties, both alone and synergistically with carboplatin. We undertook this phase II study to determine the safety and efficacy of weekly docetaxel-carboplatin and concurrent radiation therapy followed by docetaxel-carboplatin consolidation for the treatment of locally advanced NSCLC.

Methods: Sixty-seven patients having previously untreated stage IIIA or IIIB unresectable NSCLC were enrolled, with 61 patients evaluated for endpoints. Docetaxel 20 mg/m^2 IV infusion over 30 minutes followed by carboplatin area under the curve = 2 over 30 minutes was administered weekly during concurrent thoracic radiotherapy. After 3 week rest, consolidation docetaxel 75 mg/m^2 IV infusion over 60 minutes and carboplatin area under the curve = 6 over 30 minutes was administered every 3 weeks for two cycles. Concurrent thoracic radiation consisted of 45 Gy (1.8 Gy fractions 5 d/wk for first 5 weeks) followed by 18 Gy boost (2.0 Gy fractions 5 d/wk for 2 weeks) for a total dose of 63 Gy.

Results: One and 2 years overall survival rates were 45 and 20%, respectively. Progression free survival at 1 year was 27%. Median survival time was 12 months. Median time to progression was 8 months. The primary hematologic toxicity was leukopenia. The primary nonhematologic toxicity was esophagitis.

Conclusion: The administered regimen of weekly docetaxel-carboplatin and concurrent radiation therapy followed by docetaxel-carboplatin consolidation has acceptable toxicity profile. However, the overall survivals at 1 and 2 years are somewhat disappointing.

Phase-2 study
Single arm

J Thoracic Onco 2009

Randomized Phase-2/Phase-3 trials of concurrent chemoradiation

Regimens	Evidence available	Compared with	Chemo dose	RT dose	Outcomes	AEs
Paclitaxel-carboplatin (PC arm)	Phase-II study Randomized (Total 65 pts)	Concurrent Etoposide-Cisplatin (PE arm)	Cisplatin 50 mg/m2 on D1, D8, D29, D36 Etoposide 50 mg/m2 (D1-D5, D29-D33) Paclitaxel- 45 mg/m2 weekly Carboplatin AUC-2 weekly	60 Gy	3 Year OS PE- 33%, PC- 13%	Gd ¾ neutropenia PE- 78%, PC- 51% Radiation pneumonitis (Gd 2 or more) PE- 25%, PC- 48%
Paclitaxel-carboplatin (PC arm)	Phase-III study Randomized (Total 200 pts)	Concurrent Etoposide-Cisplatin (PE arm)	Cisplatin 50 mg/m2 on D1, D8, D29, D36 Etoposide 50 mg/m2 (D1-D5, D29-D33) Paclitaxel- 45 mg/m2 weekly Carboplatin AUC-2 weekly	60-66 Gy	Median survival PE- 23.3 months PC- 20.9 months	Gd ¾ esophagitis PE- 20%, PC- 6% Radiation pneumonitis (Gd 2 or more) PE- 19%, PC- 33%
Paclitaxel-carboplatin (Arm C)	Phase- III study Randomized (440 pts)	3 arms A. Cisplatin, Vindesine, MMC B. Irinotecan, Carboplatin C. Paclitaxel, Carboplatin	-	60 Gy	Similar long term outcomes	Paclitaxel carboplatin has a safer toxicity profile
Docetaxel-cisplatin	Phase III study Randomized (200 pts)	2 arms 1. Doceaxel-Cisplatin 2. MVP	DP (docetaxel 40 mg/m2 and cisplatin 40 mg/m2 on days 1, 8, 29, and 36)		ORR- 78.8% Vs 70.3% 2 year survival 60% Vs 48%	Gd ¾ neutropenia DP- 22%, MVP- 39% Gd ¾ esophagitis DP- 14%, MVP- 6%

LUNG CANCER

FULL LENGTH ARTICLE | VOLUME 77, ISSUE 1, P89-96, JULY 01, 2012

Randomized phase II study of concurrent cisplatin/etoposide or paclitaxel/carboplatin and thoracic radiotherapy in patients with stage III non-small cell lung cancer

Luhua Wang • Shixiu Wu • Guangfei Ou • Nan Bi • Wenfeng Li • Hua Ren • Jianzhong Cao • Jun Liang • Junling Li • Zongmei Zhou • Jima Lv • Xiangru Zhang • Show less

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Objective: To evaluate the activity and safety of concurrent thoracic radiotherapy (TRT) plus weekly paclitaxel/carboplatin (PC) regimen compared with widely used cisplatin/etoposide (PE) regimen in patients with unresectable stage III non-small cell lung cancer (NSCLC).

Patients and methods: Patients were randomly assigned to receive the following treatments: PE arm, cisplatin (50mg/m(2)) on days 1, 8, 29, and 36 and etoposide (50 mg/m(2)) on days 1-5 and 29-33 plus 60 Gy of TRT; PC arm, weekly concurrent carboplatin (AUC = 2) and paclitaxel (45 mg/m(2)) plus 60 Gy of TRT.

Results: A total of 65 patients were randomized (PE arm, n = 33; PC arm, n = 32). The 3-year overall survival (OS) was significantly better in the PE arm than in the PC arm (33.1% vs. 13%, P = .04). The incidence of Grade 3/4 neutropenia was 78.1% in the PE arm and 51.5% in the PC arm (P = .05). The rate of Grade 2 or greater radiation pneumonitis was 25% in the PE arm and 48.5% in the PC arm (P = .09).

Conclusions: Compared to PE regimen, weekly PC regimen cannot be recommended since it failed to achieve an improvement in either OS or PFS.

Etoposide and cisplatin versus paclitaxel and carboplatin with concurrent thoracic radiotherapy in unresectable stage III non-small cell lung cancer: a multicenter randomized phase III trial

Patients and methods: Patients were randomly received 60–66 Gy of thoracic radiation therapy concurrent with either etoposide 50 mg/m2 on days 1–5 and cisplatin 50 mg/m2 on days 1 and 8 every 4 weeks for two cycles (EP arm), or paclitaxel 45 mg/m2 and carboplatin (AUC 2) on day 1 weekly (PC arm). The primary end point was overall survival (OS).

Results- With a median follow-up time of 73 months, the 3-year OS was significantly higher in the EP arm than that of the PC arm. The estimated **difference was 15.0%** (95% CI 2.0%–28.0%) and P value of 0.024. Median survival times were 23.3 months in the EP arm and 20.7 months in the PC arm (log-rank test P ¼ 0.095, HR 0.76, 95%CI 0.55–1.05). The incidence of Grade 2 radiation pneumonitis was higher in the PC arm (33.3% versus 18.9%, P ¼ 0.036), while the incidence of Grade 3 esophagitis was higher in the EP arm (20.0% versus 6.3%, P ¼ 0.009).

Phase III Study Comparing Second- and Third-Generation Regimens With Concurrent Thoracic Radiotherapy in Patients With Unresectable Stage III Non–Small-Cell Lung Cancer: West Japan Thoracic Oncology Group WJTOG0105

Table 4. Objective Response

Response	Arm A (n = 146)		Arm B (n = 147)		Arm C (n = 147)	
	No.	%	No.	%	No.	%
CR	3	2.1	4	2.7	5	3.4
PR	94	64.4	79	53.7	88	59.9
SD	16	11.0	32	21.8	32	21.8
PD	19	13.0	19	12.9	16	10.9
NE	14	9.6	13	8.8	6	4.1
Response rate, CR + PR*	97	66.4	83	56.5	92	63.0

Clinical Trial > JAMA Oncol. 2021 Jun 1;7(6):904-909. doi: 10.1001/jamaoncol.2021.0113.

Effect of Second-generation vs Third-generation Chemotherapy Regimens With Thoracic Radiotherapy on Unresectable Stage III Non-Small-Cell Lung Cancer: 10-Year Follow-up of a WJTOG0105 Phase 3 Randomized Clinical Trial

Results: From September 2001 to September 2005, 440 patients (group A, n = 146 [33.2%; median (range) age, 63 (31-74) years; 18 women (12.3%)]; group B, n = 147 [33.4%; median (range) age, 63 (30-75) years; 22 women (15.0%)]; group C, n = 147 [33.4%; median (range) age, 63 (38-74) years; 19 women (12.9%)]) were enrolled. The median (range) follow-up was 11.9 (7.6-13.3) years. In groups A, B, and C, median (range) overall survival times were 20.5 (17.5-26.0), 19.8 (16.7-23.5), and 22.0 (18.7-26.2) months, respectively, and 10-year survival probabilities were 13.6%, 7.5%, and 15.2%, respectively. There were no significant differences in overall survival among treatment groups. The 10-year progression-free survival probabilities were 8.5%, 6.5%, and 11.1% in groups A, B, and C, respectively. Grade 3 or 4 late toxic effect rates were 3.4% (heart, 0.7%; lung, 2.7%) in group A, and those only affecting the lung represented 3.4% and 4.1% in groups B and C, respectively. No other cases of late toxic effects (grades 3/4) were observed since the initial report.

Conclusion and relevance: In this 10-year follow-up of a phase 3 randomized clinical trial, group C achieved similar efficacy and toxic effect profiles as group A 10 years after initiating treatment. These results serve as a historical control for the long-term comparisons of outcomes of future clinical trials of

Table 4. Major Toxicity Profile in Each Treatment Arm

	Treatment Arm by Toxicity Grade										
	DP arm (n = 99)					MVP arm (n = 100)					
Toxicity	Grade 3	Grade 4	Grade 5	Grade 3 or Greater No.	Grade 3 or Greater %	Grade 3	Grade 4	Grade 5	Grade 3 or Greater No.	Grade 3 or Greater %	*P*
Leukocytes	54	19	0	73	74	31	65	0	96	96	
Neutrophils	40	21	0	61	62	24	70	0	94	94	.000
Platelets	1	1	0	2	2	22	3	0	25	25	
Febrile neutropenia	22	0	0	22	22	39	0	0	39	39	.012
Dysphagia/esophagitis	13	1	0	14	14	6	0	0	6	6	.056
Pneumonitis/pulmonary infiltrates	7	1	2	10	10	7	0	0	7	7	.434

NOTE. Major toxicity was defined as any of grade 3 or greater.
Abbreviations: DP, docetaxel plus cisplatin; MVP, mitomycin plus cisplatin plus vindesine.

Phase-3 trials of concurrent chemoradiation in adenocarcinoma Lung only

PEMETREXED CISPLATIN

PROCLAIM: Randomized Phase III Trial of Pemetrexed-Cisplatin or Etoposide-Cisplatin Plus Thoracic Radiation Therapy Followed by Consolidation Chemotherapy in Locally Advanced Nonsquamous Non–Small-Cell Lung Cancer

Suresh Senan, Anthony Brade, Lu-hua Wang, Johan Vansteenkiste, Shaker Dakhil, Bonne Biesma, Maite Martinez Aguillo, Joachim Aerts, Ramaswamy Govindan, Belén Rubio-Viqueira, Conrad Lewanski, David Gandara, Hak Choy, Tony Mok, Anwar Hossain, Neill Iscoe, Joseph Treat, Andrew Koustenis, Bélen San Antonio, Nadia Chouaki, and Everett Vokes

ABSTRACT

Purpose

The phase III PROCLAIM study evaluated overall survival (OS) of concurrent pemetrexed-cisplatin and thoracic radiation therapy (TRT) followed by consolidation pemetrexed, versus etoposide-cisplatin and TRT followed by nonpemetrexed doublet consolidation therapy.

Patients and Methods

Patients with stage IIIA/B unresectable nonsquamous non–small-cell lung cancer randomly received (1:1) pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 intravenously every 3 weeks for three cycles plus concurrent TRT (60 to 66 Gy) followed by pemetrexed consolidation every 3 weeks for four cycles (arm A), or standard therapy with etoposide 50 mg/m^2 and cisplatin 50 mg/m^2 intravenously, every 4 weeks for two cycles plus concurrent TRT (60 to 66 Gy) followed by two cycles of consolidation platinum-based doublet chemotherapy (arm B). The primary objective was OS. The study was designed as a superiority trial with 80% power to detect an OS hazard ratio of 0.74 with a type 1 error of .05.

Results

Enrollment was stopped early because of futility. Five hundred ninety-eight patients were randomly assigned (301 to arm A, 297 to arm B) and 555 patients (283 in arm A, 272 in arm B) were treated. Arm A was not superior to arm B in terms of OS (hazard ratio, 0.98; 95% CI, 0.79 to 1.20; median, 26.8 *v* 25.0 months; $P = .831$). Arm A had a significantly lower incidence of any drug-related grade 3 to 4 adverse events (64.0% *v* 76.8%; $P = .001$), including neutropenia (24.4% *v* 44.5%; $P < .001$), during the overall treatment period.

Conclusion

Pemetrexed-cisplatin combined with TRT followed by consolidation pemetrexed was not superior to standard chemoradiotherapy for stage III unresectable nonsquamous non–small-cell lung cancer.

J Clin Oncol 34:953-962.

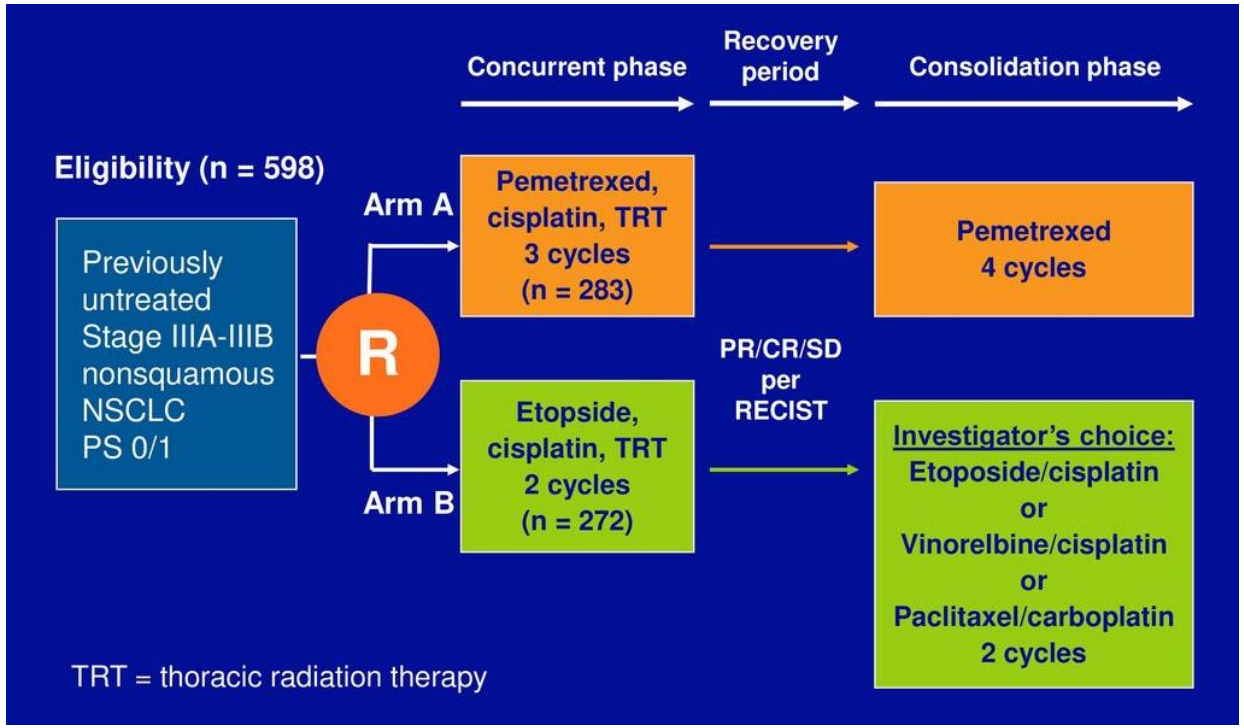

Table 4. Possible Treatment-Related Treatment-Emergent Adverse Events During the Overall Study and Concurrent Phases (any grade) That Occurred in ≥ 10% of Patients in Either Arm

CTCAE Term	Overall Study				Concurrent Phase			
	Arm A (n = 283)		Arm B (n = 272)		Arm A (n = 283)		Arm B (n = 272)	
	Any Gr*	Gr 3–4	Any Gr*	Gr 3–4	Any Gr†	Gr 3–4	Any Gr†	Gr 3–4
≥ 1 CTCAE	281 (99.3)	181 (64.0)	269 (98.9)	**209 (76.8)**	278 (98.2)	160 (56.5)	265 (97.4)	173 (63.6)
Laboratory								
Neutrophils/granulocytes (ANC/AGC)	121 (42.8)	69 (24.4)	**149 (54.8)**	**121 (44.5)**	102 (36.0)	52 (18.4)	112 (41.2)	**78 (28.7)**
Hemoglobin	114 (40.3)	25 (8.8)	124 (45.6)	37 (13.6)	78 (27.6)	16 (5.7)	83 (30.5)	22 (8.1)
Leukocytes (total WBC)	104 (36.7)	64 (22.6)	111 (40.8)	82 (30.1)	96 (33.9)	53 (18.7)	99 (36.4)	69 (25.4)
Lymphopenia	61 (21.6)	51 (18.0)	52 (19.1)	40 (14.7)	57 (20.1)	48 (17.0)	47 (17.3)	37 (13.6)
Platelets	55 (19.4)	19 (6.7)	**85 (31.3)**	29 (10.7)	50 (17.7)	15 (5.3)	60 (22.1)	19 (7.0)
Potassium, serum low	18 (6.4)	8 (2.8)	29 (10.7)	9 (3.3)	13 (4.6)	7 (2.5)	21 (7.7)	8 (2.9)
Nonlaboratory								
Nausea	**170 (60.1)**	10 (3.5)	137 (50.4)	11 (4.0)	**158 (55.8)**	10 (3.5)	122 (44.9)	10 (3.7)
Fatigue	154 (54.4)	17 (6.0)	146 (53.7)	13 (4.8)	121 (42.8)	12 (4.2)	115 (42.3)	7 (2.6)
Dysphagia	143 (50.5)	23 (8.1)	115 (42.3)	18 (6.6)	135 (47.7)	19 (6.7)	110 (40.4)	16 (5.9)
Esophagitis	136 (48.1)	44 (15.5)	138 (50.7)	56 (20.6)	134 (47.3)	44 (15.5)	129 (47.4)	51 (18.8)
Vomiting	110 (38.9)	11 (3.9)	90 (33.1)	17 (6.3)	**105 (37.1)**	10 (3.5)	78 (28.7)	14 (5.1)
Anorexia	91 (32.2)	11 (3.9)	79 (29.0)	10 (3.7)	81 (28.6)	10 (3.5)	63 (23.2)	8 (2.9)
Rash: dermatitis associated with radiation‡	77 (27.2)	0 (0.0)	64 (23.5)	4 (1.5)	74 (26.1)	0 (0.0)	62 (22.8)	4 (1.5)
Constipation	71 (25.1)	1 (0.4)	72 (26.5)	4 (1.5)	65 (23.0)	0 (0.0)	59 (21.7)	1 (0.4)
Mucositis/stomatitis‡	**62 (21.9)**	3 (1.1)	40 (14.7)	5 (1.8)	47 (16.6)	3 (1.1)	36 (13.2)	5 (1.8)
Pneumonitis	**48 (17.0)**	5 (1.8)	29 (10.7)	7 (2.6)	4 (1.4)	0 (0.0)	4 (1.5)	2 (0.7)
GI pain‡	**46 (16.3)**	5 (1.8)	23 (8.5)	2 (0.7)	**38 (13.4)**	4 (1.4)	18 (6.6)	2 (0.7)
Weight loss	46 (16.3)	3 (1.1)	45 (16.5)	1 (0.4)	42 (14.8)	3 (1.1)	34 (12.5)	1 (0.4)
Cough	46 (16.3)	1 (0.4)	33 (12.1)	1 (0.4)	23 (8.1)	0 (0.0)	18 (6.6)	1 (0.4)
Infection‡	42 (14.8)	8 (2.8)	33 (12.1)	7 (2.6)	25 (8.8)	6 (2.1)	17 (6.3)	5 (1.8)
Dyspnea	**42 (14.8)**	6 (2.1)	23 (8.5)	4 (1.5)	16 (5.7)	4 (1.4)	12 (4.4)	2 (0.7)
Diarrhea	38 (13.4)	3 (1.1)	40 (14.7)	5 (1.8)	31(11.0)	3 (1.1)	30 (11.0)	4 (1.5)
Heartburn/dyspepsia	38 (13.4)	4 (1.4)	30 (11.0)	1 (0.4)	27 (9.5)	1 (0.4)	26 (9.6)	1 (0.4)
Neuropathy, sensory	37 (13.1)	0 (0.0)	**56 (20.6)**	0 (0.0)	15 (5.3)	0 (0.0)	17 (6.3)	0 (0.0)
Pulmonary/upper respiratory pain‡	35 (12.4)	6 (2.1)	34 (12.5)	5 (1.8)	22 (7.8)	3 (1.1)	28 (10.3)	2 (0.7)
Pain other than pulmonary or GI‡	33 (11.7)	1 (0.4)	**53 (19.5)**	4 (1.5)	20 (7.1)	1 (0.4)	26 (9.6)	1 (0.4)
Rash‡	33 (11.7)	0 (0.0)	27 (9.9)	1 (0.4)	27 (9.5)	0 (0.0)	19 (7.0)	1 (0.4)
Renal event‡	**30 (10.6)**	5 (1.8)	16 (5.9)	4 (1.5)	23 (8.1)	3 (1.1)	14 (5.1)	4 (1.5)
Fever (in the absence of neutropenia)	29 (10.2)	0 (0.0)	24 (8.8)	1 (0.4)	12 (4.2)	0 (0.0)	17 (6.3)	1 (0.4)
Dizziness	29 (10.2)	2 (0.7)	21 (7.7)	1 (0.4)	25 (8.8)	1 (0.4)	17 (6.3)	1 (0.4)
Dysgeusia	29 (10.2)	0 (0.0)	21 (7.7)	0 (0.0)	23 (8.1)	0 (0.0)	16 (5.9)	0 (0.0)
Alopecia	23 (8.1)	0 (0.0)	**98 (36.0)**	1 (0.4)	17 (6.0)	0 (0.0)	**90 (33.1)**	1 (0.4)
Febrile neutropenia	16 (5.7)	15 (5.3)	28 (10.3)	26 (9.6)	10 (3.5)	9 (3.2)	**22 (8.1)**	**20 (7.4)**

	95% CI	*P*
CR	—	
PR	27.7 to 38.7	
SD	32.2 to 43.5	
PD	3.9 to 9.8	
Unkno	—	
Not p	—	
ORR‡	27.7 to 38.7	.458
DCR§	65.2 to 75.8	.004

NOTE
CIs for
Abbre
*Unkr
†Not p
‡Defir
§Defir

the difference in rates. The 95%

l response; SD, stable disease.

eline assessment was available.

Complications of concurrent chemoradiation

Phase 3 trial- Cis etopo Vs Pacli-carbo

	EP arm (N= 95)							PC arm (N= 96)						
	Grade 0	**1**	**2**	**3**	**4**	**5**	**≥Grade 3**	**Grade 0**	**1**	**2**	**3**	**4**	**5**	**≥Grade 3**
Esophagitis	**12 (12·6%)**	**32 (33·7%)**	**32 (33·7%)**	**19 (20·0%)**	**0**	**0**	**19 (20·0%)**	**15 (15·6%)**	**37 (38·5%)**	**38 (39·6%)**	**6 (6·3%)**	**0**	**0**	**6 (6·3%)**
Leukopenia	4 (4·2%)	18 (18·9%)	44 (46·3%)	21 (22·1%)	8 (8·4%)	0	29 (30·5%)	7 (7·3%)	24 (25·0%)	39 (40·6%)	25 (26·0%)	1 (1·0%)	0	26 (27·0%)
Anemia	72 (75·8%)	23 (24·2%)	0	0	0	0	0	83 (86·5%)	12 (12·5%)	1 (1·0%)	0	0	0	0
Thrombocytopenia	83 (87·4%)	9 (9·5%)	3 (3·2%)	0	0	0	0	91 (94·8%)	4 (4·2%)	1 (1·0%)	0	0	0	0
Dermotological toxicity	28 (29·5%)	59 (62·1%)	7 (7·4%)	1 (1·1%)	0	0	1 (1·1%)	38 (39·6%)	51 (53·1%)	5 (5·2%)	2 (2·1%)	0	0	2 (2·1%)
Radiation pneumonitis	22 (23·2%)	55 (57·9%)	11 (11·6%)	3 (3·2%)	0	4 (4·2%)	≥Grade 2 18 (19·0%)	26 (27·1%)	38 (39·6%)	24 (25·0%)	3 (3·1%)	0	5 (5·2%)	≥Grade 2 32 (33·3%)
Gastrointestinal toxicity[a]	0	78 (82·1%)	6 (6·3%)	11 (11·6%)	0	0	11 (11·6%)	0	59 (61·5%)	18 (18·8%)	19 (19·8%)	0	0	19 20%

Phase 3 trial- MVP Vs IrinoCarbo Vs Pacli-carbo

Table 3. Grade 3 or Worse Toxicity

Toxicity	All Treatment				Concurrent Phase			
	Arm A	Arm B	Arm C	*P*	Arm A	Arm B	Arm C	*P*
Neutropenia	95.9	60.5	61.9	< .001	93.8	53.7	23.1	< .001
Leukopenia	96.6	75.5	66.0	< .001	95.9	72.1	46.9	< .001
Anemia	25.3	17.7	8.8	< .001	15.8	8.8	6.1	0.019
Thrombocytopenia	28.8	28.6	7.5	< .001	21.9	11.6	5.4	< .001
Febrile neutropenia	37.0	8.8	10.2	< .001	30.8	6.1	3.4	< .001
Nausea	21.9	4.8	4.8	< .001	21.9	3.4	3.4	< .001
Vomiting	6.8	2.7	0.7	.012	6.2	1.4	0.0	.001
Fatigue	13.0	6.1	4.8	.019	9.6	2.0	1.4	< .001
Constipation	11.6	6.1	2.7	.009	8.9	6.1	1.4	.015
Diarrhea	0.7	2.0	1.4	.606	0.7	0.7	0.7	.999
Neurogenic (sensory)	0.7	0.7	4.8	.017	0.0	0.0	0.0	—
Esophagitis	5.5	2.7	8.2	.121	4.1	2.0	7.5	.077
Infection	26.0	16.3	17.0	.066	22.6	12.2	10.2	.006
Dyspnea	6.2	5.4	6.1	.957	2.7	0.7	2.0	.406
Pneumonitis	1.4	4.1	4.1	.312	0.0	0.0	0.7	.368

Phase 3 trial- Doce Cis Vs MVP

Table 4. Major Toxicity Profile in Each Treatment Arm

	Treatment Arm by Toxicity Grade										
	DP arm (n = 99)					MVP arm (n = 100)					
Toxicity	Grade 3	Grade 4	Grade 5	Grade 3 or Greater No.	Grade 3 or Greater %	Grade 3	Grade 4	Grade 5	Grade 3 or Greater No.	Grade 3 or Greater %	*P*
Leukocytes	54	19	0	73	74	31	65	0	96	96	
Neutrophils	40	21	0	61	62	24	70	0	94	94	.000
Platelets	1	1	0	2	2	22	3	0	25	25	
Febrile neutropenia	22	0	0	22	22	39	0	0	39	39	.012
Dysphagia/esophagitis	13	1	0	14	14	6	0	0	6	6	.056
Pneumonitis/pulmonary infiltrates	7	1	2	10	10	7	0	0	7	7	.434

NOTE. Major toxicity was defined as any of grade 3 or greater.
Abbreviations: DP, docetaxel plus cisplatin; MVP, mitomycin plus cisplatin plus vindesine.

Phase 3 trial- Pem Cis Vs Etopo Cis

Table 4. Possible Treatment-Related Treatment-Emergent Adverse Events During the Overall Study and Concurrent Phases (any grade) That Occurred in ≥ 10% of Patients in Either Arm

	Overall Study				Concurrent Phase			
	Arm A (n = 283)		Arm B (n = 272)		Arm A (n = 283)		Arm B (n = 272)	
CTCAE Term	Any Gr*	Gr 3–4	Any Gr*	Gr 3–4	Any Gr†	Gr 3–4	Any Gr†	Gr 3–4
≥ 1 CTCAE	281 (99.3)	181 (64.0)	269 (98.9)	**209 (76.8)**	278 (98.2)	160 (56.5)	265 (97.4)	173 (63.6)
Laboratory								
Neutrophils/granulocytes (ANC/AGC)	121 (42.8)	69 (24.4)	**149 (54.8)**	**121 (44.5)**	102 (36.0)	52 (18.4)	112 (41.2)	**78 (28.7)**
Hemoglobin	114 (40.3)	25 (8.8)	124 (45.6)	37 (13.6)	78 (27.6)	16 (5.7)	83 (30.5)	22 (8.1)
Leukocytes (total WBC)	104 (36.7)	64 (22.6)	111 (40.8)	82 (30.1)	96 (33.9)	53 (18.7)	99 (36.4)	69 (25.4)
Lymphopenia	61 (21.6)	51 (18.0)	52 (19.1)	40 (14.7)	57 (20.1)	48 (17.0)	47 (17.3)	37 (13.6)
Platelets	55 (19.4)	19 (6.7)	**85 (31.3)**	29 (10.7)	50 (17.7)	15 (5.3)	60 (22.1)	19 (7.0)
Potassium, serum low	18 (6.4)	8 (2.8)	29 (10.7)	9 (3.3)	13 (4.6)	7 (2.5)	21 (7.7)	8 (2.9)
Nonlaboratory								
Nausea	**170 (60.1)**	10 (3.5)	137 (50.4)	11 (4.0)	**158 (55.8)**	10 (3.5)	122 (44.9)	10 (3.7)
Fatigue	154 (54.4)	17 (6.0)	146 (53.7)	13 (4.8)	121 (42.8)	12 (4.2)	115 (42.3)	7 (2.6)
Dysphagia	143 (50.5)	23 (8.1)	115 (42.3)	18 (6.6)	135 (47.7)	19 (6.7)	110 (40.4)	16 (5.9)
Esophagitis	136 (48.1)	44 (15.5)	138 (50.7)	56 (20.6)	134 (47.3)	44 (15.5)	129 (47.4)	51 (18.8)
Vomiting	110 (38.9)	11 (3.9)	90 (33.1)	17 (6.3)	**105 (37.1)**	10 (3.5)	78 (28.7)	14 (5.1)
Anorexia	91 (32.2)	11 (3.9)	79 (29.0)	10 (3.7)	81 (28.6)	10 (3.5)	63 (23.2)	8 (2.9)
Rash: dermatitis associated with radiation‡	77 (27.2)	0 (0.0)	64 (23.5)	4 (1.5)	74 (26.1)	0 (0.0)	62 (22.8)	4 (1.5)
Constipation	71 (25.1)	1 (0.4)	72 (26.5)	4 (1.5)	65 (23.0)	0 (0.0)	59 (21.7)	1 (0.4)
Mucositis/stomatitis‡	**62 (21.9)**	3 (1.1)	40 (14.7)	5 (1.8)	47 (16.6)	3 (1.1)	36 (13.2)	5 (1.8)
Pneumonitis	**48 (17.0)**	5 (1.8)	29 (10.7)	7 (2.6)	4 (1.4)	0 (0.0)	4 (1.5)	2 (0.7)
GI pain‡	**46 (16.3)**	5 (1.8)	23 (8.5)	2 (0.7)	**38 (13.4)**	4 (1.4)	18 (6.6)	2 (0.7)
Weight loss	46 (16.3)	3 (1.1)	45 (16.5)	1 (0.4)	42 (14.8)	3 (1.1)	34 (12.5)	1 (0.4)
Cough	46 (16.3)	1 (0.4)	33 (12.1)	1 (0.4)	23 (8.1)	0 (0.0)	18 (6.6)	1 (0.4)
Infection‡	42 (14.8)	8 (2.8)	33 (12.1)	7 (2.6)	25 (8.8)	6 (2.1)	17 (6.3)	5 (1.8)
Dyspnea	**42 (14.8)**	6 (2.1)	23 (8.5)	4 (1.5)	16 (5.7)	4 (1.4)	12 (4.4)	2 (0.7)
Diarrhea	38 (13.4)	3 (1.1)	40 (14.7)	5 (1.8)	31(11.0)	3 (1.1)	30 (11.0)	4 (1.5)
Heartburn/dyspepsia	38 (13.4)	4 (1.4)	30 (11.0)	1 (0.4)	27 (9.5)	1 (0.4)	26 (9.6)	1 (0.4)
Neuropathy, sensory	37 (13.1)	0 (0.0)	**56 (20.6)**	0 (0.0)	15 (5.3)	0 (0.0)	17 (6.3)	0 (0.0)
Pulmonary/upper respiratory pain‡	35 (12.4)	6 (2.1)	34 (12.5)	5 (1.8)	22 (7.8)	3 (1.1)	28 (10.3)	2 (0.7)
Pain other than pulmonary or GI‡	33 (11.7)	1 (0.4)	**53 (19.5)**	4 (1.5)	20 (7.1)	1 (0.4)	26 (9.6)	1 (0.4)
Rash‡	33 (11.7)	0 (0.0)	27 (9.9)	1 (0.4)	27 (9.5)	0 (0.0)	19 (7.0)	1 (0.4)
Renal event‡	**30 (10.6)**	5 (1.8)	16 (5.9)	4 (1.5)	23 (8.1)	3 (1.1)	14 (5.1)	4 (1.5)
Fever (in the absence of neutropenia)	29 (10.2)	0 (0.0)	24 (8.8)	1 (0.4)	12 (4.2)	0 (0.0)	17 (6.3)	1 (0.4)
Dizziness	29 (10.2)	2 (0.7)	21 (7.7)	1 (0.4)	25 (8.8)	1 (0.4)	17 (6.3)	1 (0.4)
Dysgeusia	29 (10.2)	0 (0.0)	21 (7.7)	0 (0.0)	23 (8.1)	0 (0.0)	16 (5.9)	0 (0.0)
Alopecia	23 (8.1)	0 (0.0)	**98 (36.0)**	1 (0.4)	17 (6.0)	0 (0.0)	**90 (33.1)**	1 (0.4)
Febrile neutropenia	16 (5.7)	15 (5.3)	28 (10.3)	26 (9.6)	10 (3.5)	9 (3.2)	**22 (8.1)**	**20 (7.4)**

How to choose amongst different regimens

- Patient related factors-
  - Age
  - Comorbidities
  - Nutrition
  - Lung function- any previous predisposing factors for pneumonitis
  - Performance status
  - Platinum eligibility
- Toxicity profile of chemotherapy

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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

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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 regimen remains the standard of care for concurrent CTRT strategy.
- Although associated with more hematological toxicity, whenever feasible, should give cisplatin containing regimen, etoposide-cisplatin.
- In other patients, Taxane-platinum combination can be used.
- Combination of concurrent immunotherapy or TKIs with RT will probably change the outcomes in this set of patients.

THANK YOU