GRUPO de ESTUDOS do CANCRO do PULMÃO

Terapêutica após progressão do CPNPC precoce ou localmente avançado tratado com QT

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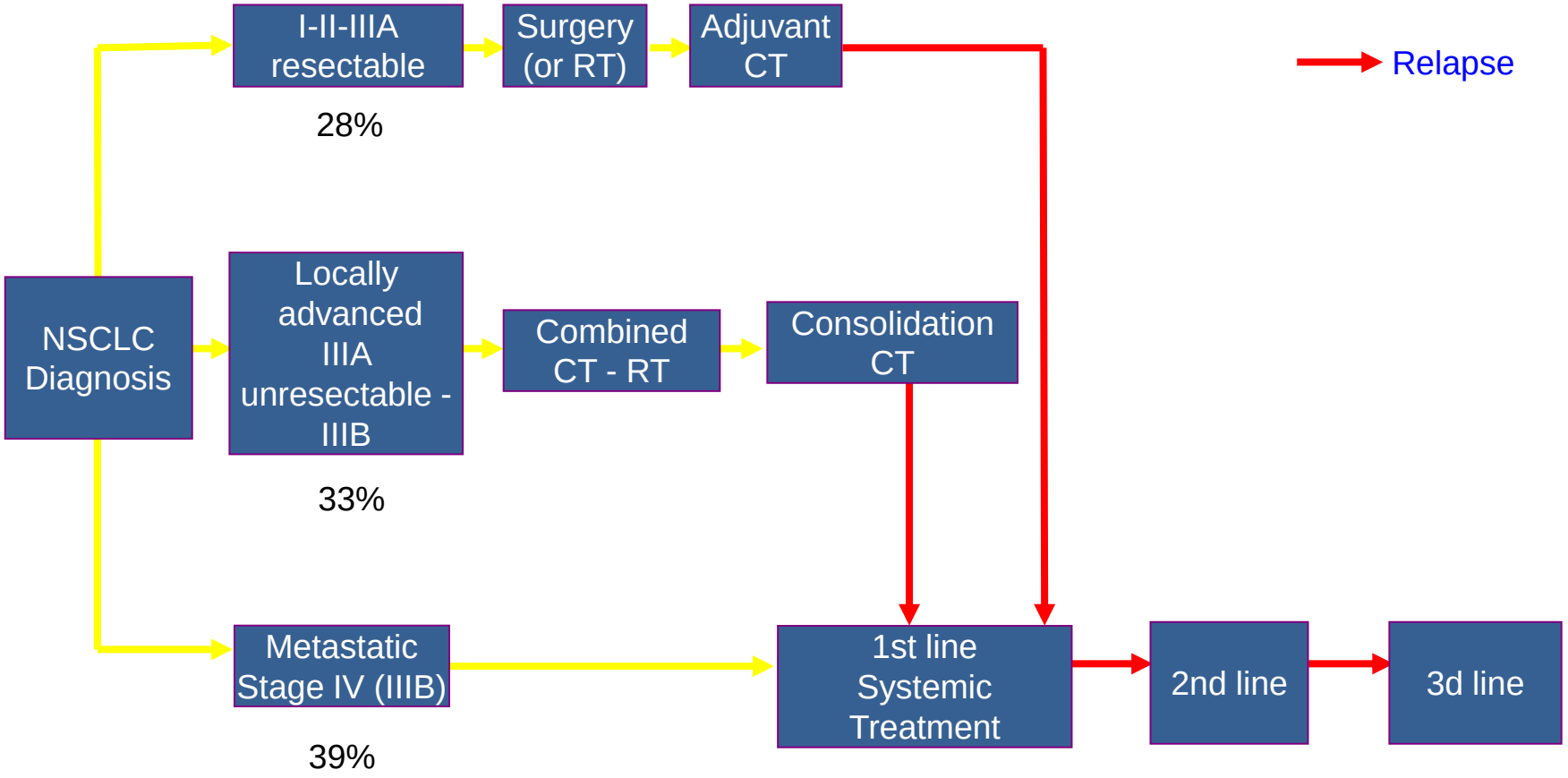
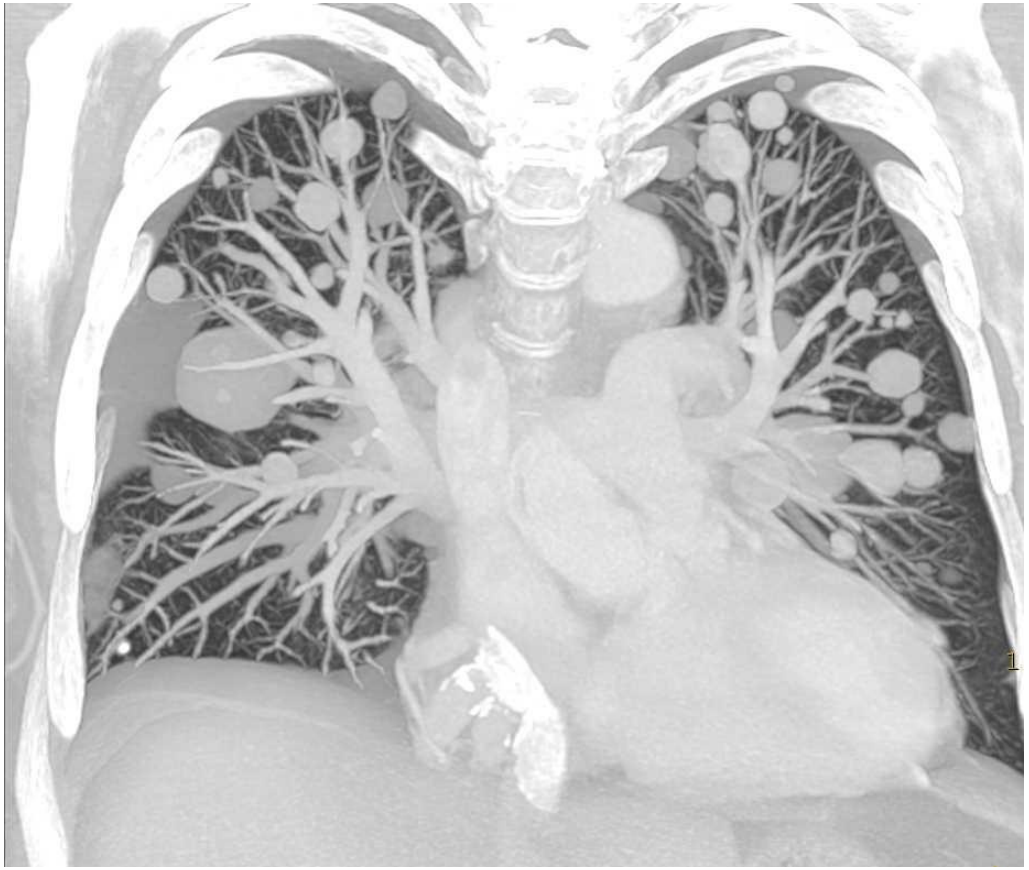
Tomar, 17 de Maio de 2014

Algorithm for the treatment of NSCLC in 2014

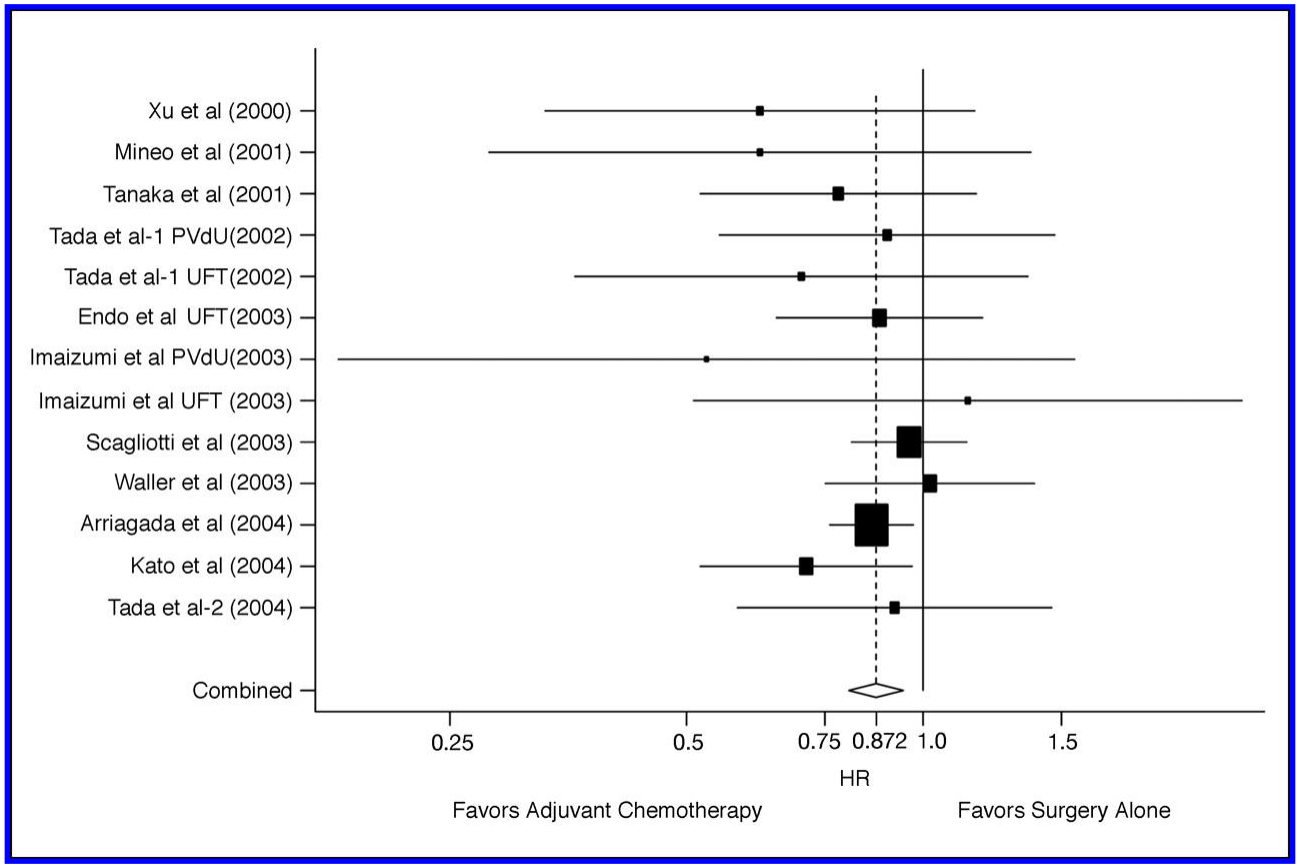


Non-Small Cell Lung Cancer (NSCLC)



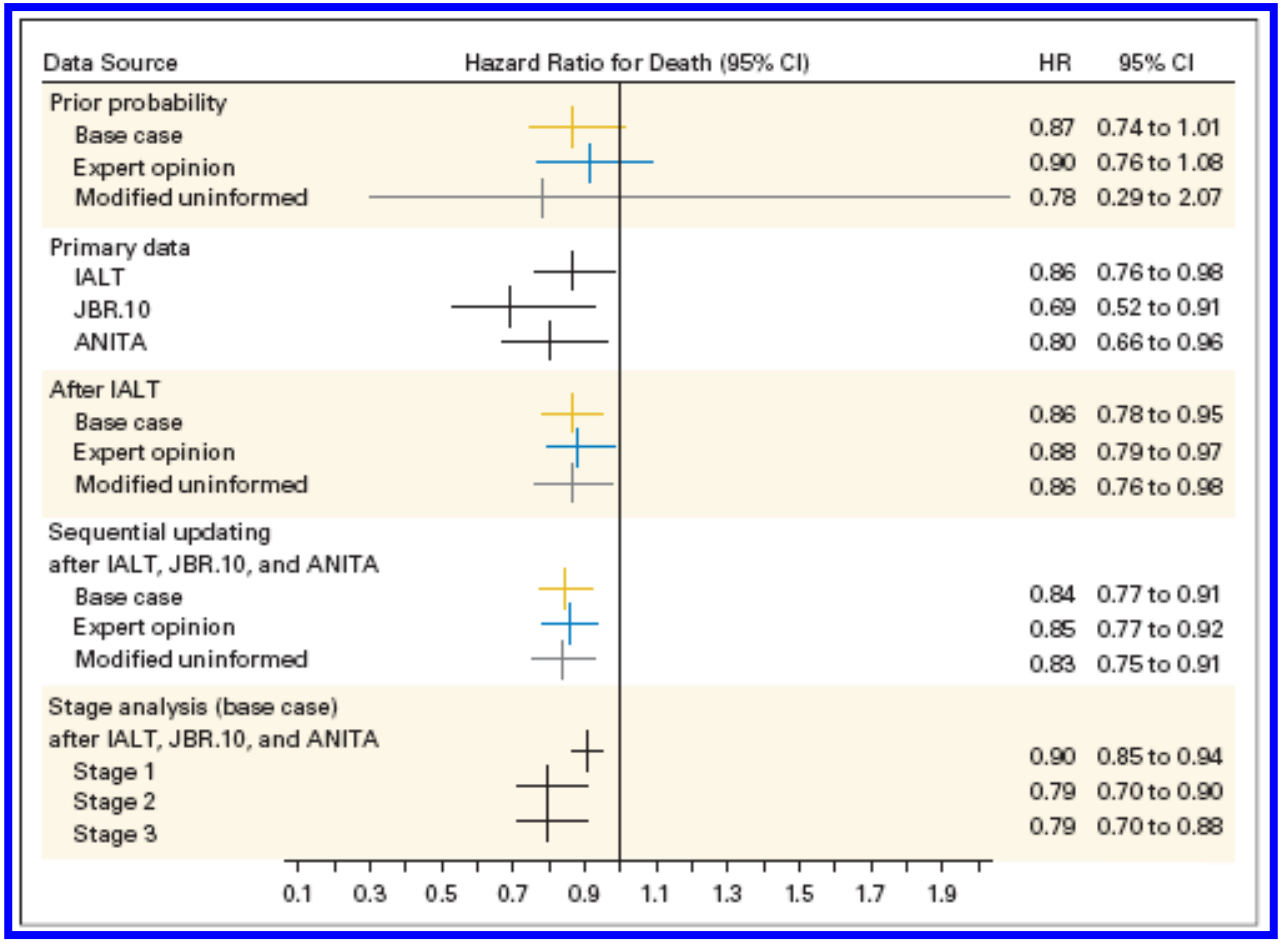
Stages IB to IIIA

Surgery *versus* Surgery and adjuvant CT (Overall Survival)



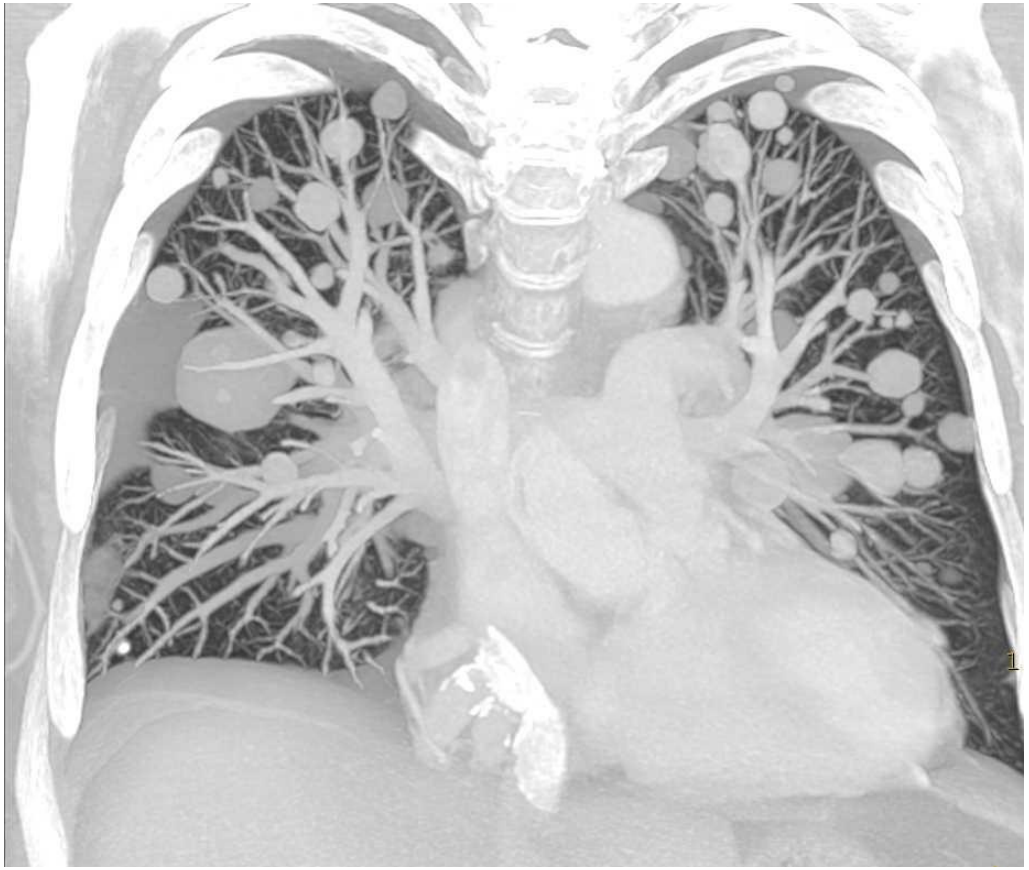
Hotta, K. et al. J Clin Oncol 22:3860-3867, 2004

Adjuvant CT regimens
(Meta-analysis of Overall Survival)



Miksad RA et al. J Clin Oncol 27:2245-2252, 2009

Non-Small Cell Lung Cancer (NSCLC)

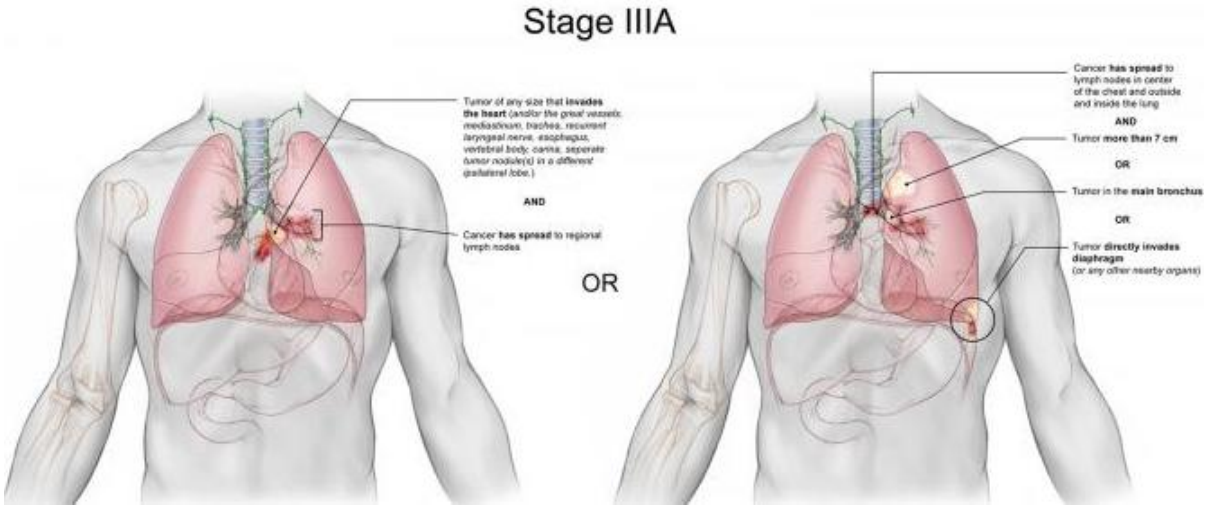


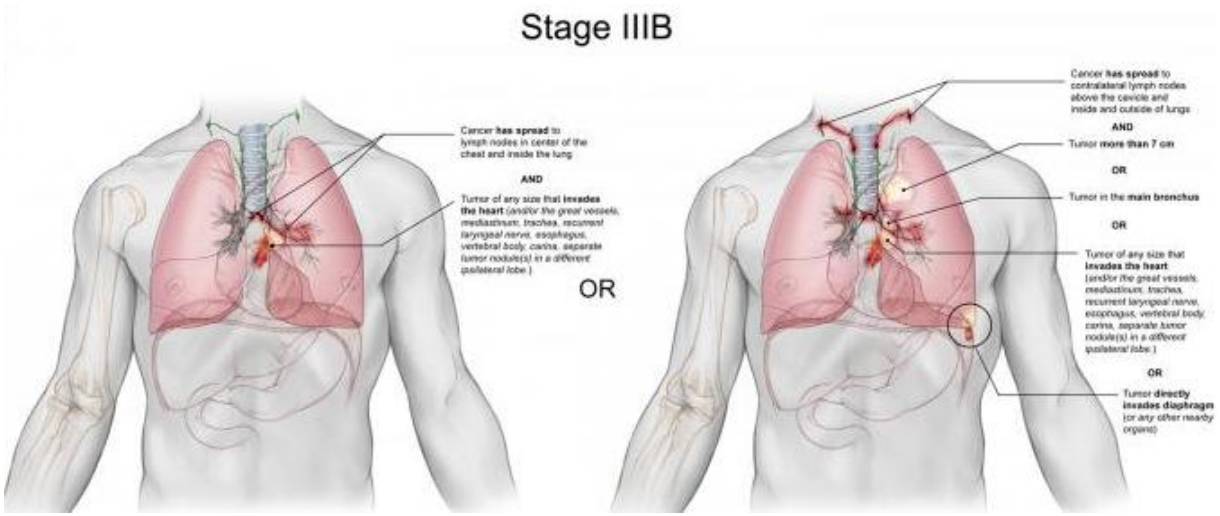
Stages IIIA and IIIB

Stages IIIA and IIIB

Represents very different diseases

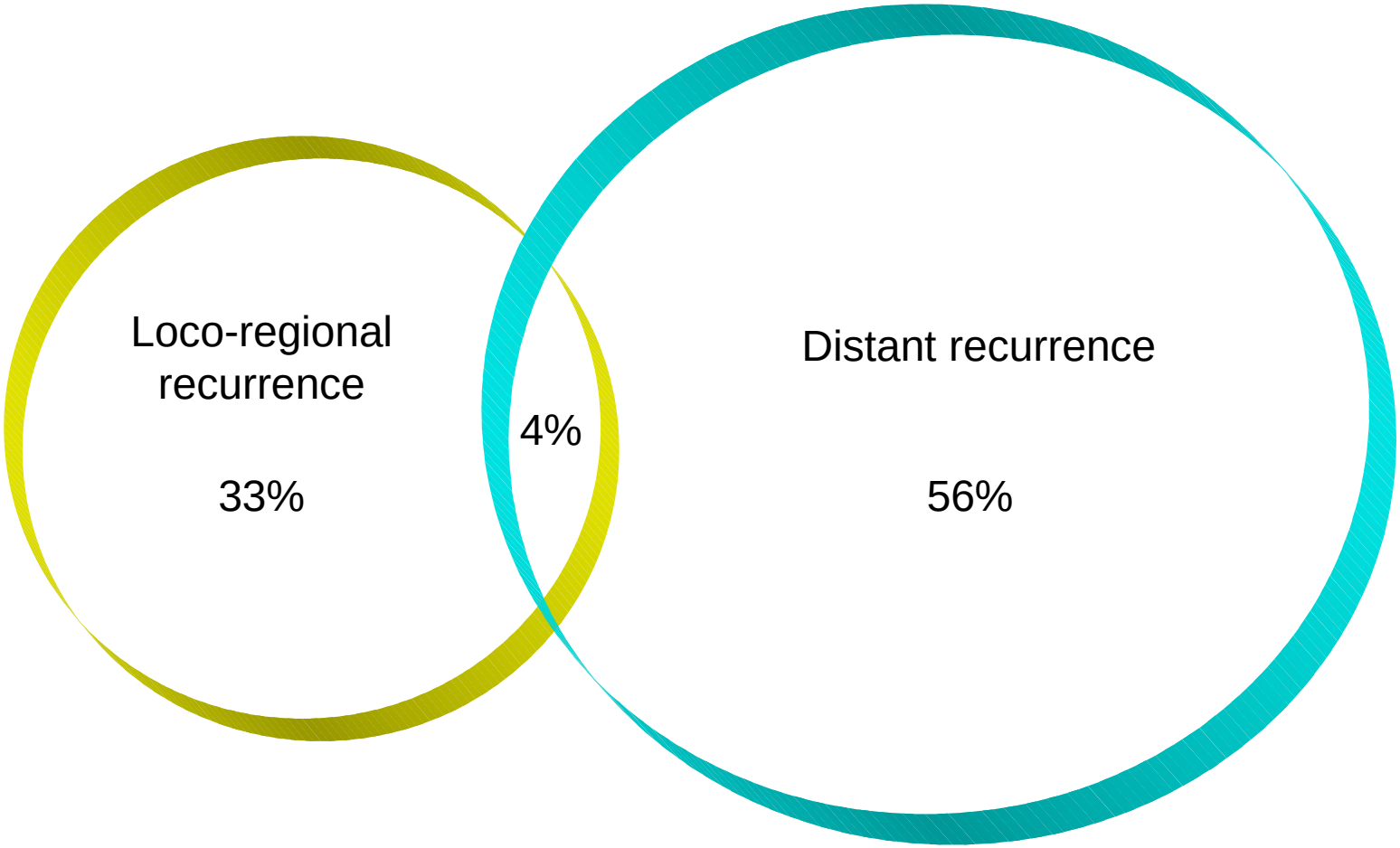
Stage IIIA	**T1a**	**N2**	**M0**
	T1b	**N2**	**M0**
	T2a	**N2**	**M0**
	T2b	**N2**	**M0**
	T3	**N1**	**M0**
	T3	**N2**	**M0**
	T4	**N0**	**M0**
	T4	**N1**	**M0**
Stage IIIB	**T1a**	**N3**	**M0**
	T1b	**N3**	**M0**
	T2a	**N3**	**M0**
	T2b	**N3**	**M0**
	T3	**N3**	**M0**
	T4	**N2**	**M0**
	T4	**N3**	**M0**





Stages IIIA and IIIB

Patterns of recurrence post RT / CT



Furuse K et al. J Clin Oncol 17:2692-2699, 1999

Stages IIIA and IIIB

Factors influencing the choice of treatment

Stage of disease

Age

Performance status

Weigth loss

Co-morbidities

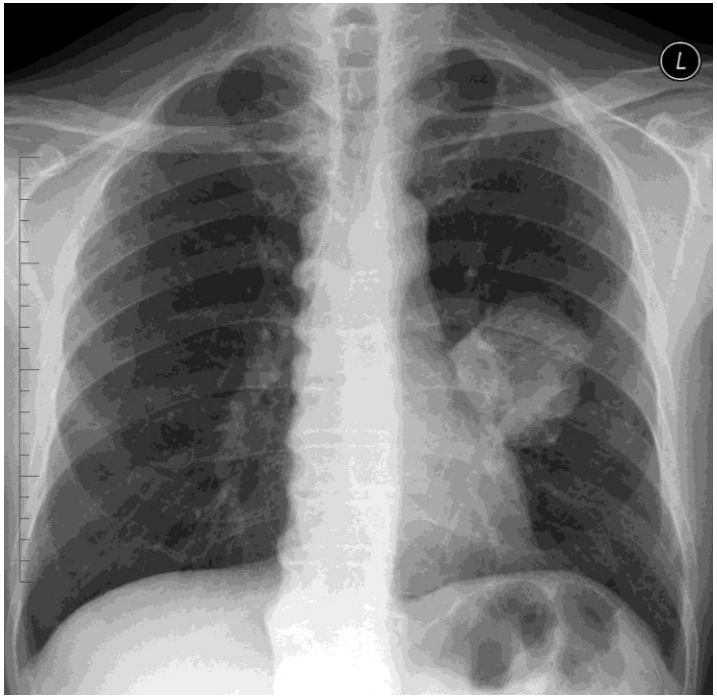
Structural conditions of the Center

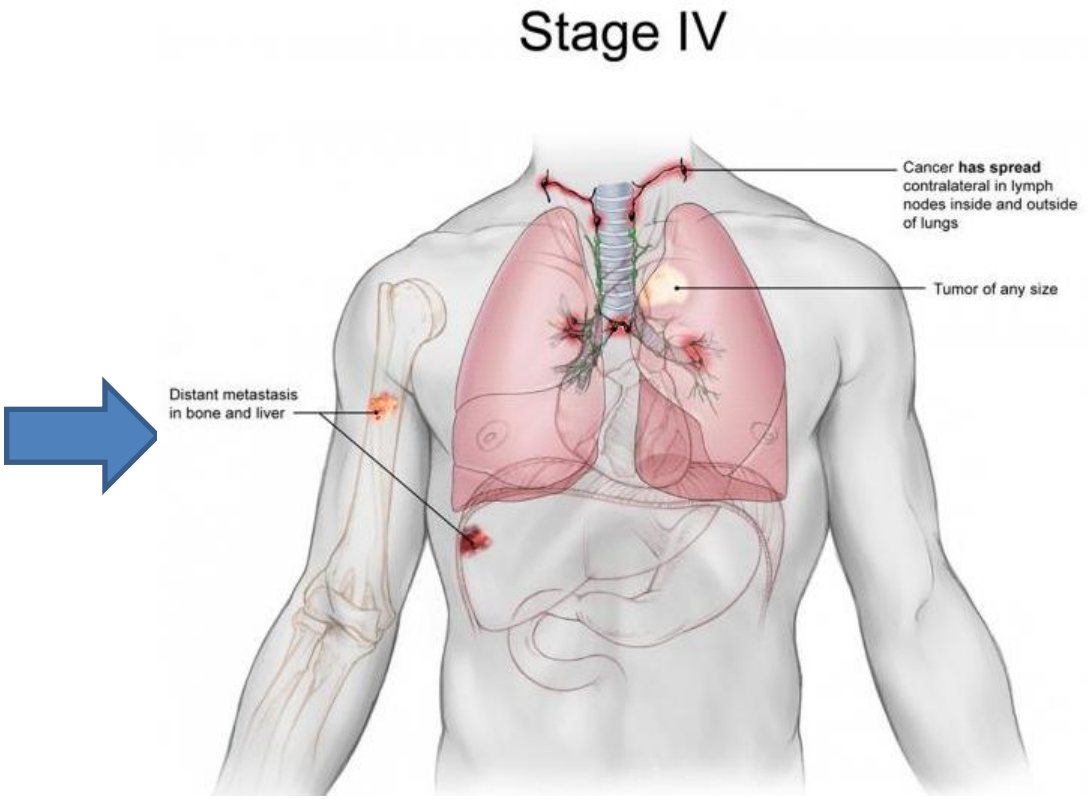
Stages IIIA and IIIB

Progress achieved

Trial	Median OS	3-Y OS
CALGB 8433 RT	9.6 mo	10%
CALGB 8433 Seq C - RT	13.7 mo	24%
RTOG 9410 Seq C (Vinb/CisP) - RT	14.6 mo	31%
RTOG 9410 Con C (Vinb/CisP) - RT	17.1 mo	37%
RTOG 9410 Con C (Etop/CisP) - RT	19.6 mo	40%
SWOG 9504 Con C - RT → D	27.0 mo	40%

Progression after therapy





Adjuvant CT regimens

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2014
Non-Small Cell Lung Cancer

NCCN Guidelines Index
NSCLC Table of Contents
Discussion

CHEMOTHERAPY REGIMENS FOR NEOADJUVANT AND ADJUVANT THERAPY

- Cisplatin 50 mg/m² days 1 and 8; vinorelbine 25 mg/m² days 1, 8, 15, 22, every 28 days for 4 cycles[a]
- Cisplatin 100 mg/m² day 1; vinorelbine 30 mg/m² days 1, 8, 15, 22; every 28 days for 4 cycles[b,c]
- Cisplatin 75-80 mg/m² day 1; vinorelbine 25-30 mg/m² days 1 + 8, every 21 days for 4 cycles
- Cisplatin 100 mg/m² day 1; etoposide 100 mg/m² days 1-3, every 28 days for 4 cycles[b]
- Cisplatin 80 mg/m² days 1, 22, 43, 64; vinblastine 4 mg/m² days 1, 8, 15, 22, 29 then every 2 wks after day 43, every 21 days for 4 cycles[b]
- Cisplatin 75 mg/m² day 1; gemcitabine 1250 mg/m² days 1, 8, every 21 days for 4 cycles
- Cisplatin 75 mg/m² day 1; docetaxel 75 mg/m² day 1 every 21 days for 4 cycles[d]
- Cisplatin 75 mg/m² day 1, pemetrexed 500 mg/m² day 1 for adenocarcinoma and large cell carcinoma and NSCLC NOS (without specific histologic subtype) every 21 days for 4 cycles

Chemotherapy Regimens for patients with comorbidities or patients not able to tolerate cisplatin

Paclitaxel 200 mg/m² day 1, carboplatin AUC 6 day 1, every 21 days[e]

CHEMOTHERAPY REGIMENS USED WITH RADIATION THERAPY

Concurrent Chemotherapy/RT Regimens

- Cisplatin 50 mg/m² on days 1, 8, 29, and 36; etoposide 50 mg/m² days 1-5, 29-33; concurrent thoracic RT[a] (preferred)*
- Cisplatin 100 mg/m² days 1 and 29; vinblastine 5 mg/m²/weekly x 5; concurrent thoracic RT[b] (preferred)
- Carboplatin AUC 5 on day 1, pemetrexed 500 mg/m² on day 1 every 21 days for 4 cycles; concurrent thoracic RT[c] (nonsquamous)
- Cisplatin 75 mg/m² on day 1, pemetrexed 500 mg/m² on day 1 every 21 days for 3 cycles; concurrent thoracic RT[d] (nonsquamous)

Sequential Chemotherapy/RT Regimens

- Cisplatin 100 mg/m² on days 1 and 29; vinblastine 5 mg/m²/weekly on days 1, 8, 15, 22, and 29; followed by RT[b]
- Paclitaxel 200 mg/m² over 3 hours on day 1; carboplatin AUC 6 over 60 minutes on day 1 every 3 weeks for 2 cycles followed by thoracic RT[e]

Concurrent Chemotherapy/RT Followed by Chemotherapy

- Paclitaxel 45-50 mg/m² weekly; carboplatin AUC 2, concurrent thoracic RT followed by 2 cycles of paclitaxel 200 mg/m² and carboplatin AUC 6[e]
- Cisplatin 50 mg/m² on days 1, 8, 29, and 36; etoposide 50 mg/m² days 1-5, 29-33; concurrent thoracic RT followed by cisplatin 50 mg/m² and etoposide 50 mg/m² x 2 additional cycles (category 2B)[a]

Adjuvant CT regimens

clinical practice guidelines

Annals of Oncology 24 (Supplement 6): vi89–vi98, 2013
doi:10.1093/annonc/mdt241
Published online 16 July 2013

Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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These Clinical Practice Guidelines are endorsed by the Japanese Society of Medical Oncology (JSMO)

Treatment of early stages I and II

- Surgery should be offered to patients with stage I or II NSCLC who are willing to accept procedure-related risks [III, A].
- Anatomical resection (lobectomy) is preferred over lesser resections such as wedge or segment resection [I, A].
- Lymph node dissection should conform to IASLC specifications for staging [III, A].
- Either open thoracotomy or VATS access can be utilised as appropriate to the expertise of the surgeon [III, A].
- Adjuvant chemotherapy should be offered to patients with resected stage II or III NSCLC [I, A] and can be considered in patients with resected stage IB disease and a primary tumour >4 cm [II, B]. However, pre-existing co-morbidity and postoperative recovery need to be taken into account in this decision.
- For adjuvant chemotherapy, a two-drug combination with cisplatin is preferable [I, A]. In randomised studies, the attempted cumulative cisplatin dose was up to 300 mg/m², delivered in three to four cycles. The most frequently studied regimen is cisplatin–vinorelbine.

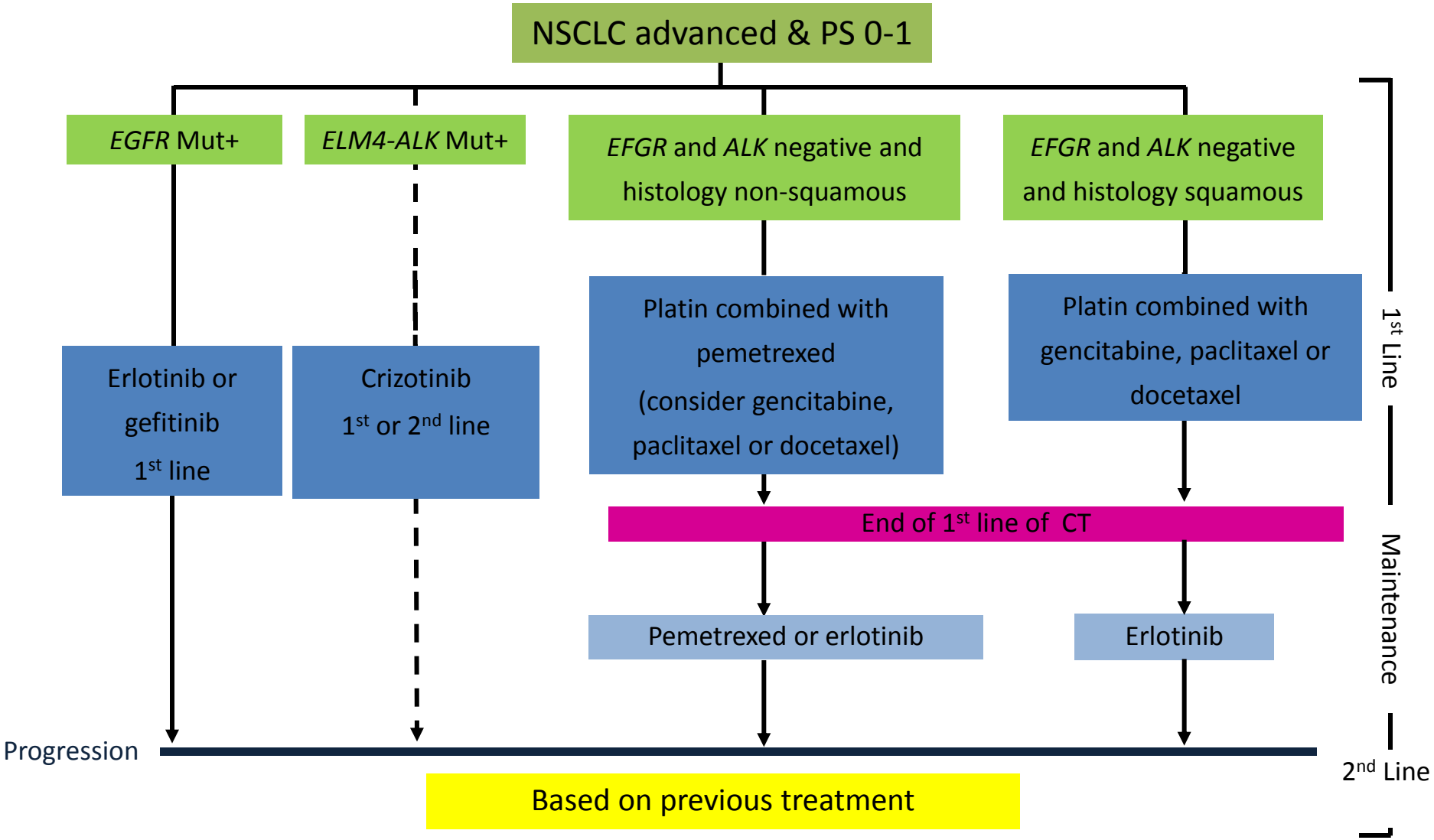
Treatment of locally advanced stage III

- Chemotherapy should be offered to all patients with LA-NSCLC who can tolerate it [I, A].
- Cisplatin-based regimens (e.g. cisplatin–etoposide or cisplatin–vinorelbine) delivered concurrently with radiotherapy have been studied most extensively, and are therefore recommended [II, A]. Studies using carboplatin–paclitaxel or other carboplatin-based combinations generally showed inferior outcomes, but may be chosen individually based on co-morbidity issues. The number of cycles ranges from two to four, and the cisplatin dose per cycle was in the range of 80 mg/m² [III, B].

Considerations for first-line therapy

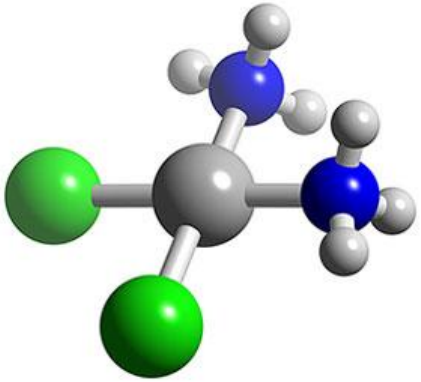
- Performance status
- Age
- Organ function, nutritional status
  - Hemoptysis
- Histology
- Molecular variables
- Other
  - CNS metastases
- Previous chemotherapy in adjuvant or locally advanced setting
  - Response and adverse events
  - Time from previous treatment

Algorithm for the treatment of advanced NSCLC in 2014



Updated from Gandara DR, et al. Clin Lung Cancer 10:392-394, 2009

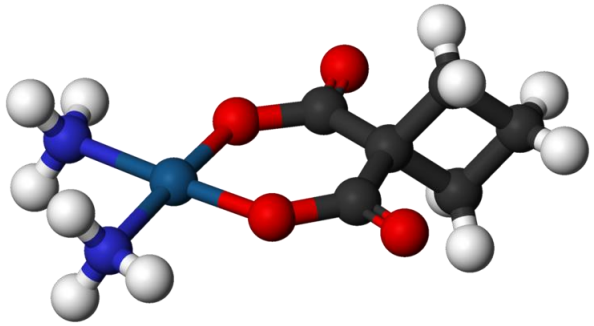
Cisplatin



- Pharmacologic category: Alkylating agent
- Mechanism of action: Inhibits DNA synthesis by the formation of DNA cross-links.

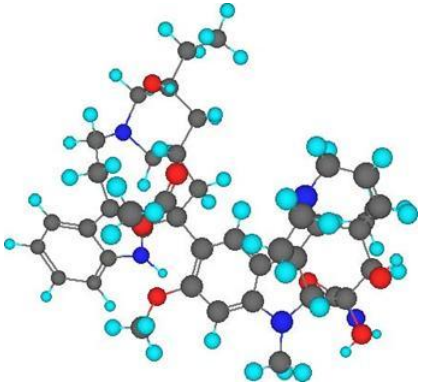
  No specific of cell cycle.
- Excretion: Urine (>90%), feces (10%)
- Frequent Adverse Reactions:
  - Nausea and vomiting
  - Myelosuppression
  - Renal impairment
  - Neurotoxicity (peripheral neuropathy is dose- and duration-dependent)
  - Endocrine & metabolic: hypokalemia, hypomagnesemia

Carboplatin



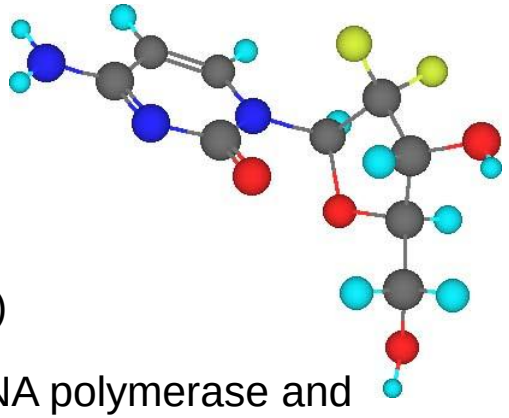
- Pharmacologic category: Alkylating agent
- Mechanism of action: Covalently binds to DNA, possible cross-linking and interfere with the function of DNA. No specific of cell cycle.
- Excretion: Urine (60 - 90%)
- Frequent Adverse Reactions:
  - Nausea, vomiting, mucositis
  - Myelosuppression (dose related and dose-limiting)
  - Renal impairment
  - Endocrine & metabolic: hypokalemia, hypomagnesemia
  - Hepatic (elevated liver function tests)

Vinorelbine



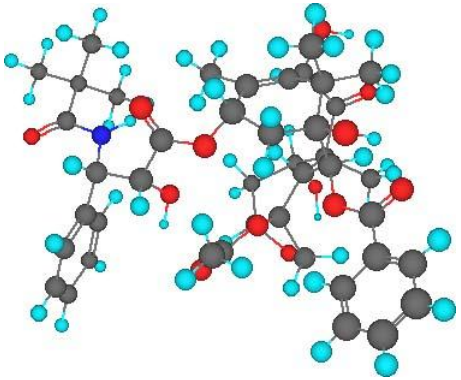
- Pharmacologic category: Vinca alkaloid
- Mechanism of action: Binds to tubulin and inhibits microtubule formation, arresting the cell at metaphase
- Excretion: Feces (46%), urine (18%)
- Frequent Adverse Reactions:
  - Nausea, vomiting
  - Myelosuppression (dose-limiting)
  - Hepatic (elevated liver function tests)
  - Neuromuscular & skeletal – weakness, peripheral neuropathy

Gemcitabine



- Pharmacologic category: Antimetabolite (pyrimidine antagonist)
- Mechanism of action: Inhibits DNA synthesis by inhibition of DNA polymerase and ribonucleotide reductase; specific for the S-phase of the cycle
- Excretion: Urine (99%), feces (>1%)
- Frequent Adverse Reactions:
  - Nausea, vomiting
  - Central nervous system: pain, fever
  - Myelosuppression (dose-limiting)
  - Hepatic (elevated liver function tests)

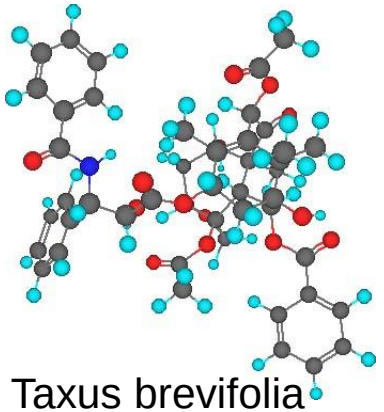
Docetaxel



- Pharmacologic category: Taxane, antimicrotubular,

  natural antineoplastic agent, isolated from the needles of the European yew.
- Mechanism of action: Promotes the assembly of microtubules from tubulin dimers, and inhibits the depolymerization of tubulin; most activity occurs during the M-phase of the cycle
- Excretion: Feces (75%), urine (6%)
- Frequent Adverse Reactions:
  - Mucositis/stomatitis (may be dose-limiting), nausea, vomiting
  - Cardiovascular – fluid retention (more common at cumulative doses ≥ 400 mg/m^2)
  - Myelosuppression
  - Hypersensitivity reactions

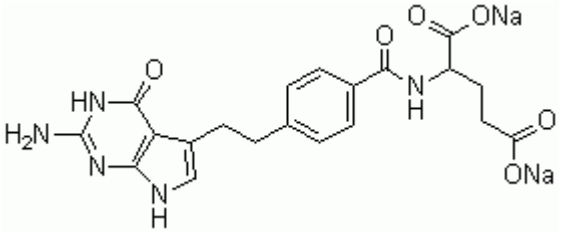
Paclitaxel



- Pharmacologic category: Taxane, antimicrotubular,

  natural antineoplastic agent, isolated from the bark of the Pacific yew, Taxus brevifolia
- Mechanism of action: Promotes the microtubules assembly by enhancing the action of tubulin dimers, and inhibiting their disassembly; interfere with the late G_2 mitotic phase; can distort mitotic spindles, resulting in the breakage of chromossomes
- Excretion: Feces (+/- 70%), urine (14%)
- Frequent Adverse Reactions:
  - Mucositis (may be dose-limiting), stomatitis (more common at doses > 390 mg/m^2)
  - Allergic (nonimmunologically mediated release of histamine and other vasoactive substances)
  - Cardiovascular – bradycardia transient
  - Myelosuppression
  - Neurotoxicity – sensory and autonomic neuropathy, myopathy and CNS toxicity – may be cumulative and dose-limiting (doses > 250 mg/m^2)

Pemetrexed



- Pharmacologic category: Antimetabolite (antifolate)
- Mechanism of action: Inhibits thymidilate synthase (TS), dihydrofolate reductase (DHFR), glycinamide ribonucleotide formyltransferase (GARFT) and aminoimidazole carboxamide ribonucleotide formyltransferase (AICARFT), enzymes involved in folate metabolism and DNA synthesis, resulting in inhibition of purine and thymidine nucleotide and protein synthesis
- Excretion: Urine (70 – 90 %)
- Frequent Adverse Reactions:
  - Cardiovascular – chest pain, edema
  - CNS - fatigue
  - Gastrointestinal – nausea, vomiting
  - Myelosuppression

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e com o doente com cancro do pulmão