Severe Neutropenia and Dose Reduction: Impact on Survival of Lung cancer

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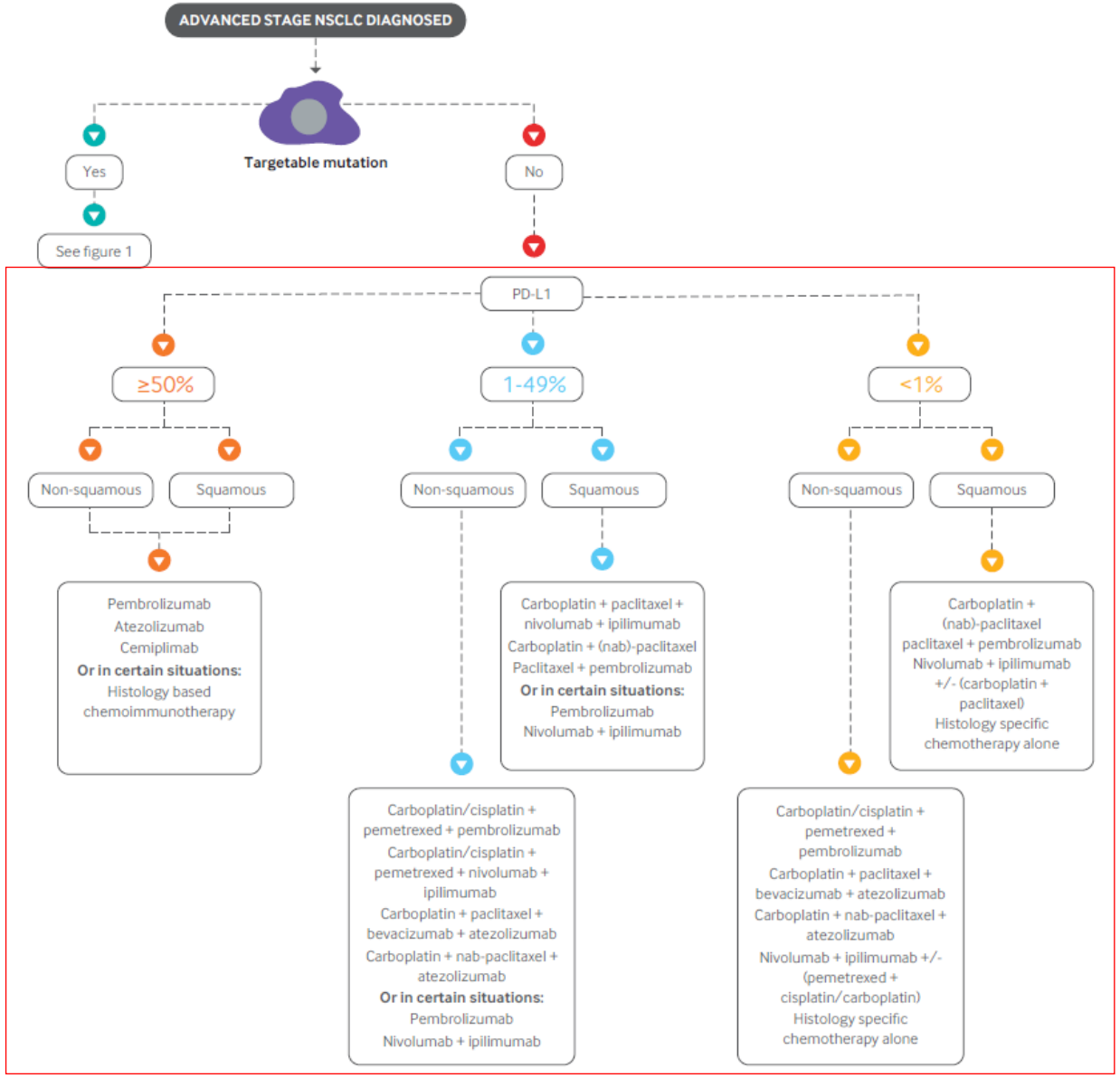
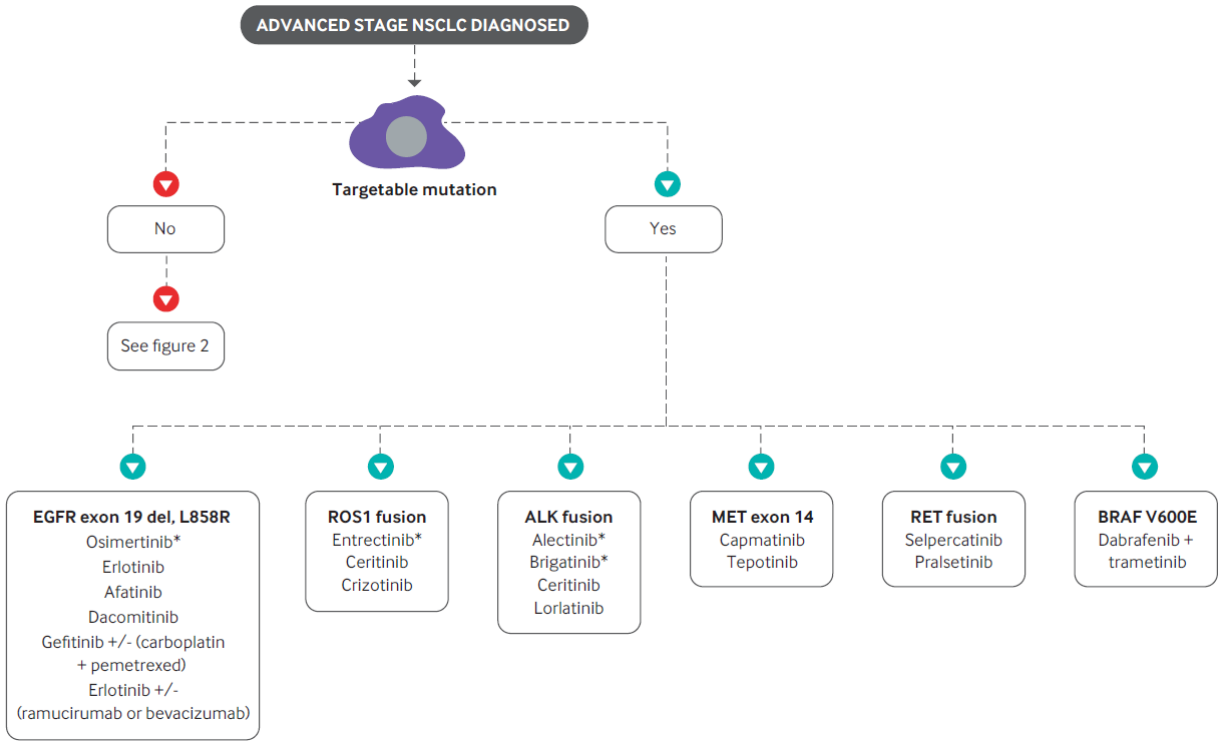
Therapeutic options in advanced stage NSCLC





BMJ 2021;375:n2363

Chemotherapy-induced neutropenia

- **Chemotherapy-induced neutropenia (CIN)**
  - One of the most common dose-limiting toxicities associated with cytotoxic effects
  - Onset and duration of neutropenia vary widely by agent, dose, frequency of dosing, and host-related factors
  - Presence of neutropenia predisposes patients to infection
  - Greatest risk of severe CIN, including febrile neutropenia (FN), is in the first cycle of chemotherapy

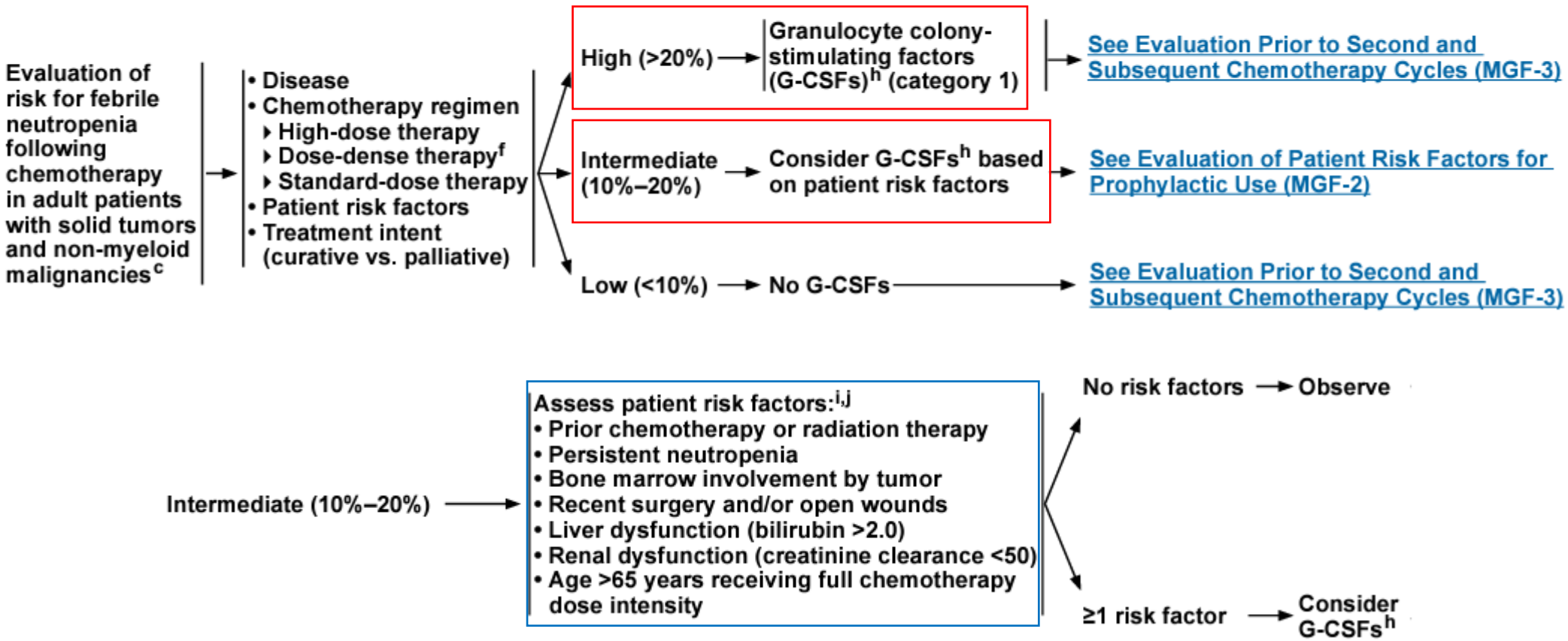
NCI CTACE ver 5.0 hematologic toxicity

Blood element	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neutrophils	<LLN to 1,500	1000 to 1500	500 to 1000	<500	
Platelets	<LLN to 75,000	50,000 to 75,000	25,000 to 50,000	< 25,000	
Hemoglobin	<LLN to 10g/dL	8.0 to 10.0 g/dL	<8.0 g/dL	Life-threatening consequence; urgent intervention indicated	Death
Febrile neutropenia			ANC <1000/microL with a single temperature >38.3°C (100.4°F) or a sustained temperature ≥38°C (100°F) for more than one hour	Life-threatening consequence; urgent intervention indicated	Death

In general, toxicity is graded as mild (Grade 1), moderate (Grade 2), severe (Grade 3), or life-threatening (Grade 4), with specific parameters according to the organ system involved.

Management of neutropenia

EVALUATION PRIOR TO FIRST CHEMOTHERAPY CYCLE[a,b]	RISK ASSESSMENT[d] FOR FEBRILE NEUTROPENIA[e]	OVERALL FEBRILE NEUTROPENIA RISK	PROPHYLACTIC USE OF G-CSFs FOR FEBRILE NEUTROPENIA CURATIVE/ADJUVANT OR PALLIATIVE SETTING[g]



NCCN guideline ver1. 2022

Management of neutropenia

Chemotherapy regimens with a high risk for febrile neutropenia (>20%)

- Small cell lung cancer
  - Topotecan

Chemotherapy regimens with an intermediate risk for febrile neutropenia (10-20%)

- Non-small cell lung cancer
  - Cisplatin/paclitaxel
  - Cisplatin/vinorelbine
  - Cisplatin/docetaxel
  - Cisplatin/etoposide
  - Carboplatin/paclitaxel
  - Docetaxel

NCCN guideline ver1. 2022

Management of neutropenia

- Optimal outcomes are achieved with standard chemotherapy regimens
- Chemotherapy dose delays and dose reductions result in poorer disease-free, progression-free, and overall survivals among patients with curable malignancies receiving adjuvant and neoadjuvant therapies

→ Maintaining full-dose chemotherapy on the planned schedule in clinical practice as a means to improve patient outcomes

JNCCN 2015

Management of neutropenia

- The use of CSF support is particularly important for delivery of dose dense chemotherapy

- However, in other patients, dose escalation of standard chemotherapy regimens has not improved survival

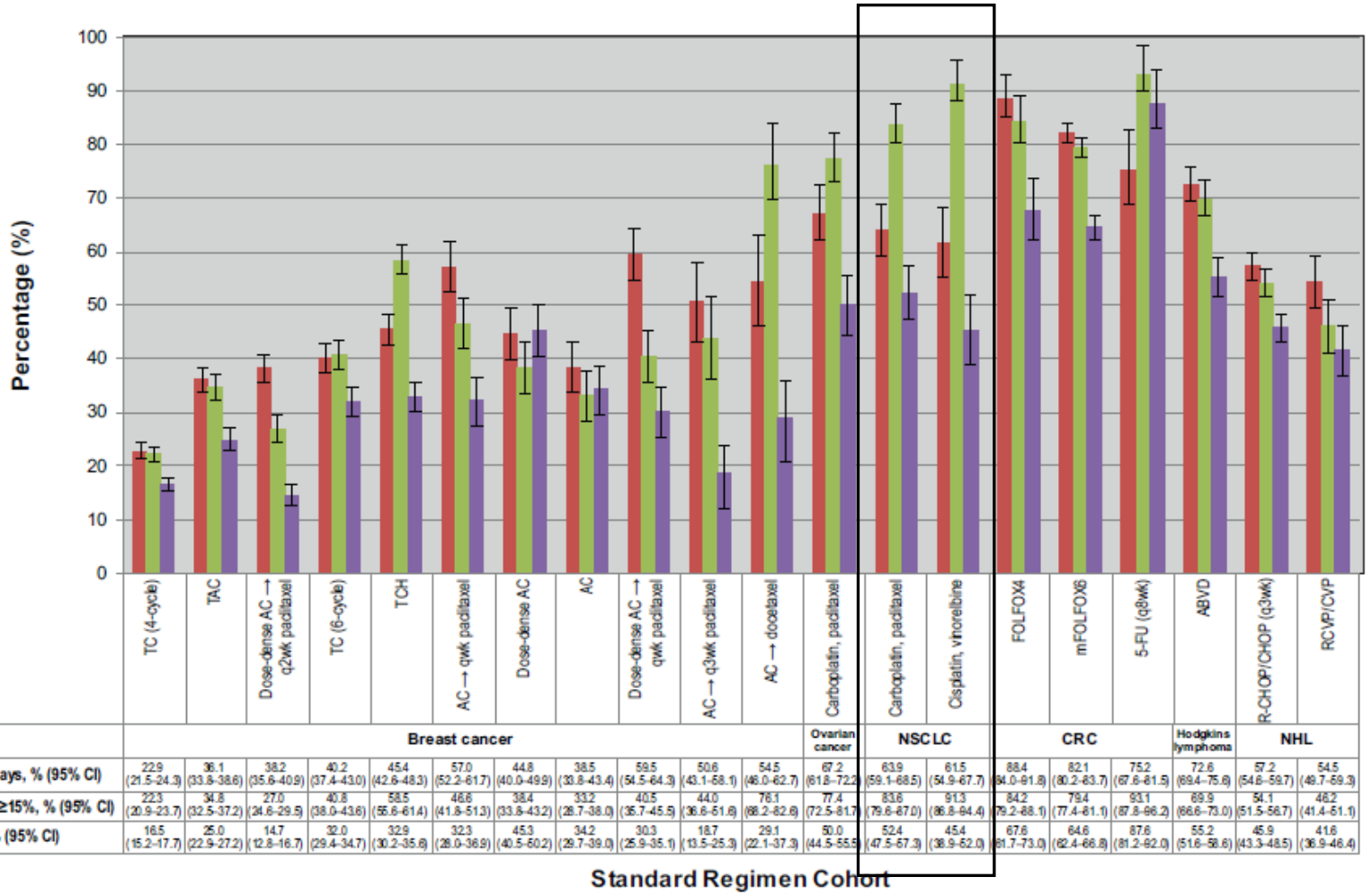
  : Dose-intense regimens in NSCLC have not yet shown any survival benefit and are not recommended

→ Dose reduction without the prophylactic use of CSF is a feasible and generally preferred option, particularly in patients receiving palliative care

n engl j med 368;12, 2013
J Thorac Oncol. 2010;5: 1397–1403

Dose delays, dose reductions, and reduced RDI by tumor type

- US, Adjuvant or Neoadjuvant Chemotherapy in Community Oncology Practices
- N=16,233, 6 different tumor types, 1 of 20 chemotherapy regimens



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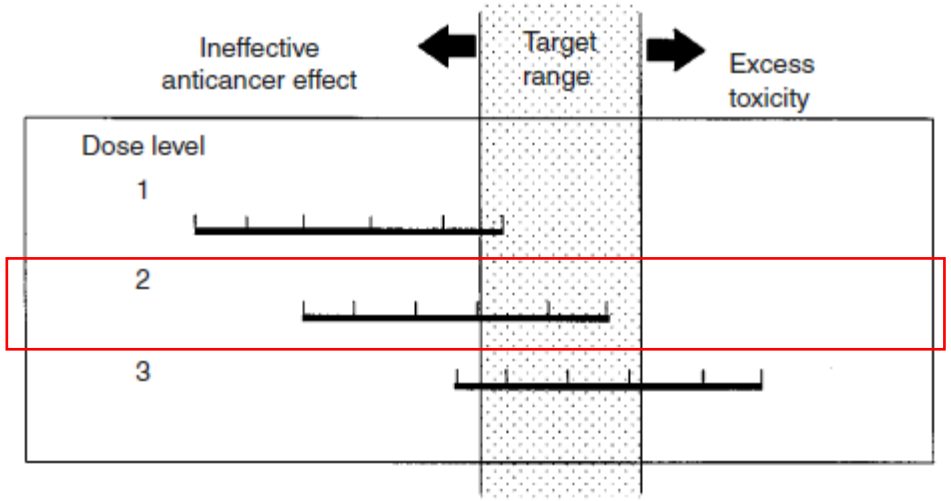
Neutropenia and Survival

How to calculate the dose of chemotherapy

- **Body surface area (BSA)-dosing method**
  - " Old habits die hard"
  - 4 ~ 10-fold variation in cytotoxic drug clearance between individuals due to differing activity of drug elimination processes related to genetic and environmental factors



→ Wide distribution of systemic exposure is skewed towards the ineffective range when dose is calculated using BSA

British Journal of Cancer (2002) 86, 1297 – 1302

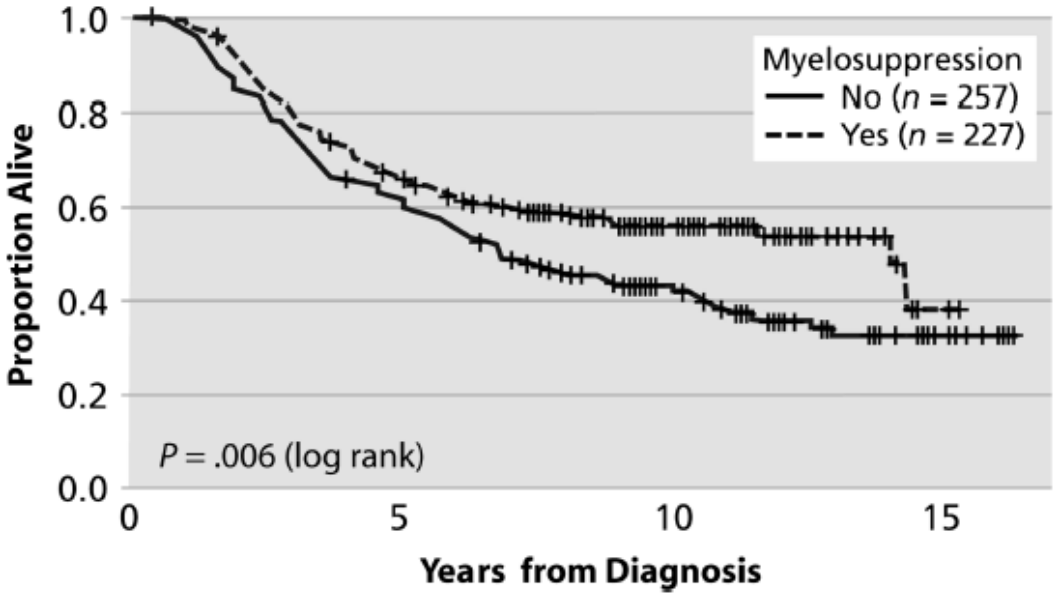
How to calculate the dose of chemotherapy

- Under-dosing
  - Can the lack of effect on normal tissue (i.e. toxicity) be used to identify a lack of effect in neoplastic tissue?
  - Dose – toxicity and dose – response relationships

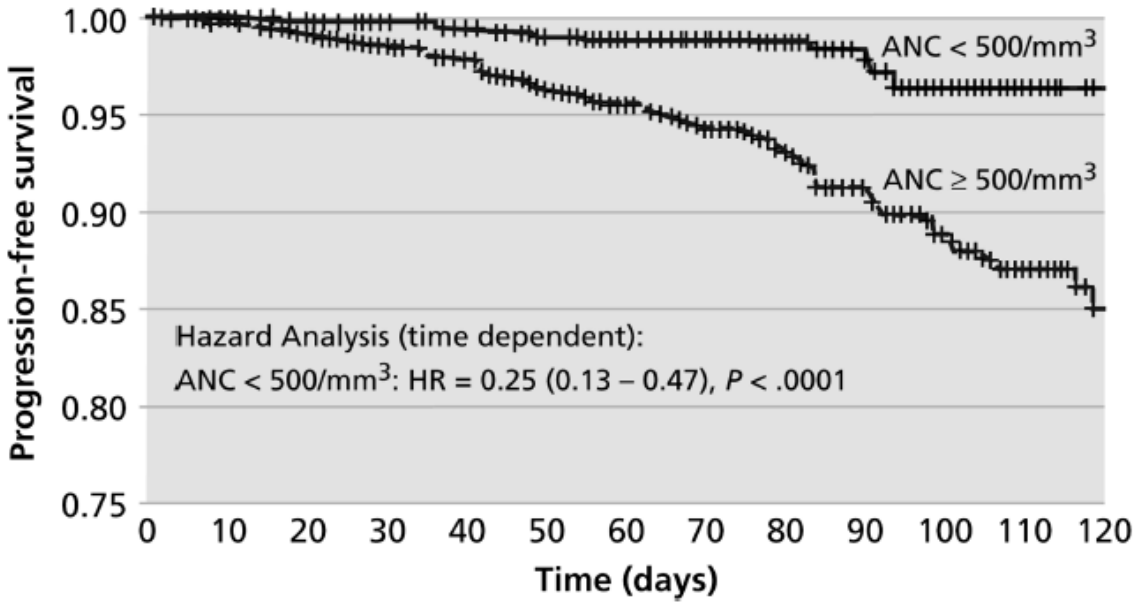
→ **Myelosuppression** is considered a surrogate for chemotherapy dose intensity, suggesting a strong association between dose intensity and clinical efficacy

British Journal of Cancer (2002) 86, 1297 – 1302
JNCCN 2009;7:99–108

Relationship between myelosuppression and anticancer effect (curative setting)



Retrospective evaluation based on whether myelosuppression occurred during chemotherapy. Shown is the Kaplan-Meier plot of overall survival from diagnosis among women with early-stage breast cancer receiving adjuvant chemotherapy



Results from a prospective observational study of nearly 2500 unselected patients with early-stage (1–3) cancers of the breast, colorectum, ovary, or lung and malignant lymphoma.
Shown is the Kaplan-Meier survival plot of patients experiencing one or more episodes of severe neutropenia during systemic chemotherapy in the initial course of treatment

J Natl Compr Canc Netw 2007;5:188–102.

Relationship between myelosuppression and anticancer effect (curative setting)

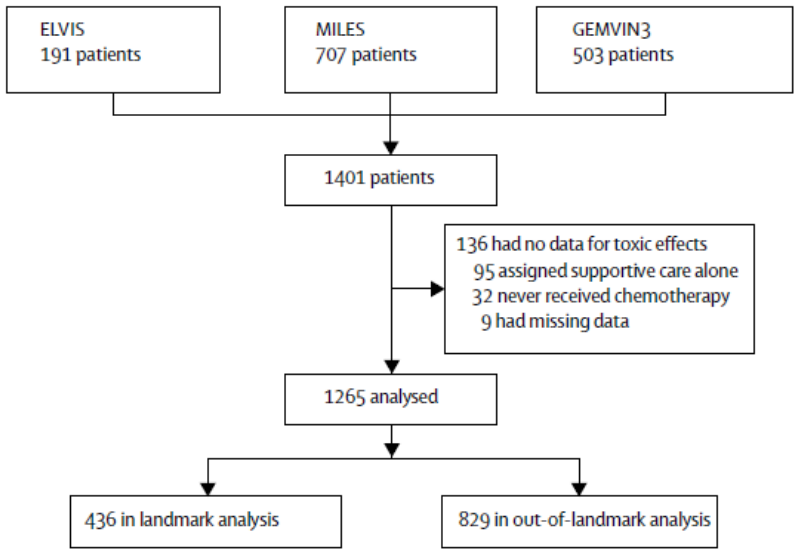
Reference	Tumour type	Outcome
Carpenter *et al*, 1982	Stage 2 breast cancer randomised between melphalan or CMF	In patients with 1 to 3 nodes, a nadir WCC of $<3 \times 10^9$ per litre was significant predictor of disease free survival in multivariate analysis
Poikonen *et al*, 1999	Stage 2 breast cancer treated with CMF	Low nadir leukocyte associated with longer distant disease free survival.
Horwich *et al*, 1997	Testis cancer treated with carboplatin, etoposide and bleomycin	Patients with nadir WCC $<2 \times 10^9$ per litre and or platelets $<90 \times 10^9$ per litre had lower relapse rate. 14% *vs* 28%, $P=0.04$
Rankin *et al*, 1992	Advanced ovarian cancer. Carboplatin plus chlorambucil *vs* carboplatin	Worse progression-free survival for patients who had grade 0 WCC nadir ($P<0.001$)
Gurney *et al*, (unpublished)	Aggressive lymphoma treated with CEOP	Worse progression free survival for patients with neutrophil count nadir of $>1 \times 10^9$ per litre ($P=0.04$)

CMF=cydophosphamide, methotrexate, 5FU. CAF=cyclophosphamide, doxorubicin, 5FU. CEOP=cyclophosphamide, epirubicin, vincristine, prednisolone.

British Journal of Cancer (2002) 86, 1297 – 1302

Relationship between myelosuppression and anticancer effect (Lung cancers-metastatic setting)

- Italy, 1996~2001



	Treatment (trial)						
	Vinorelbine (ELVIS) n=24	Vinorelbine (MILES) n=84	Gemcitabine (MILES) n=80	Gemcitabine and vinorelbine (GEMVIN3) n=87	Gemcitabine and vinorelbine (MILES) n=83	Cisplatin and vinorelbine (GEMVIN3) n=35	Cisplatin and gemcitabine (GEMVIN3) n=43
Age, years							
Median (range)	74 (70–80)	73 (69–80)	72 (69–81)	63 (42–70)	73 (69–84)	61 (36–69)	63 (47–70)
Sex							
Men	21	72	62	61	64	33	32
Women	3	12	18	26	19	2	11
Performance status							
0–1	21	75	71	78	72	33	37
2	3	9	9	9	11	2	6
Stage							
IIIB	6	29	25	21	22	8	8
IV	18	55	55	66	61	27	35
Histological subtype							
Squamous	0	29	30	19	38	13	16
Adenocarcinoma	0	33	30	42	31	17	18
Other	0	22	20	26	14	5	9
Unknown	24	0	0	0	0	0	0

Table 1: Landmark analysis: characteristics of patients

Lancet Oncol 2005; 6: 669–77

Relationship between myelosuppression and anticancer effect (Lung cancers-metastatic setting)

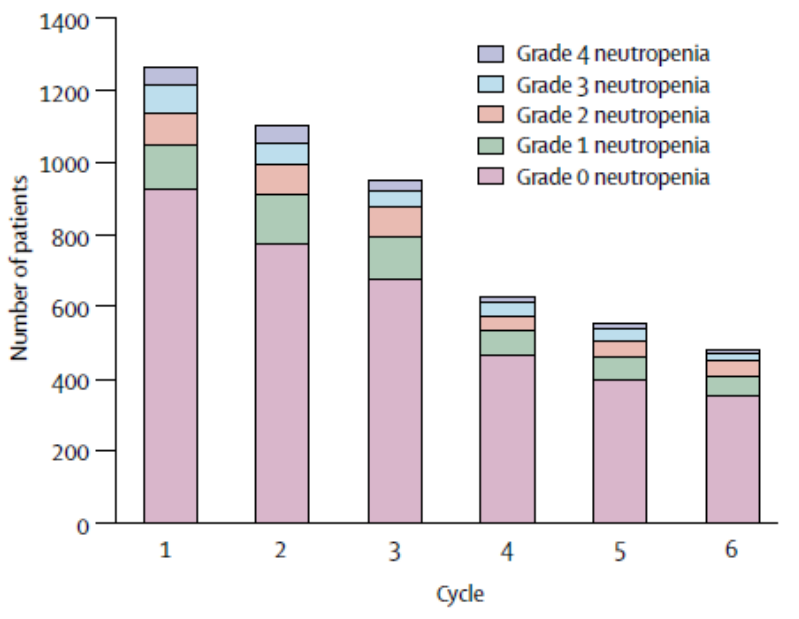


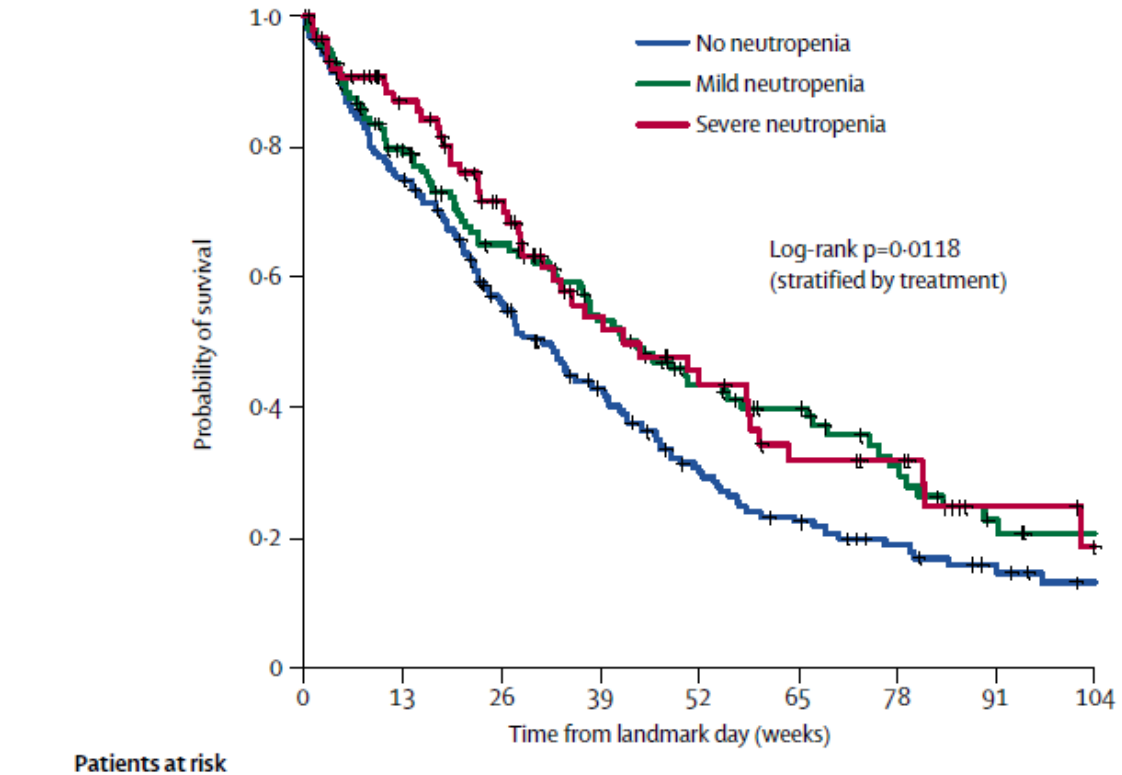
Figure 2: Worst grade of neutropenia recorded by cycle of chemotherapy in 1265 patients analysed

	Treatment (trial)						
	Vinorelbine (ELVIS) n=24	Vinorelbine (MILES) n=84	Gemcitabine (MILES) n=80	Gemcitabine and vinorelbine (GEMVIN3) n=87	Gemcitabine and vinorelbine (MILES) n=83	Cisplatin and vinorelbine (GEMVIN3) n=35	Cisplatin and gemcitabine (GEMVIN3) n=43
Grade 0	15 (62%)	35 (42%)	47(59%)	48 (55%)	33 (40%)	13(37%)	17 (40%)
Grade 1	2 (8%)	14 (17%)	13 (16%)	8 (9%)	16 (19%)	4 (11%)	8 (19%)
Grade 2	3 (13%)	11 (13%)	13 (16%)	16 (18%)	16 (19%)	6 (17%)	8 (19%)
Grade 3	3 (13%)	19 (23%)	7 (9%)	9 (10%)	12 (14%)	3 (9%)	6 (14%)
Grade 4	1 (4%)	5 (6%)	0	6 (7%)	6 (7%)	9 (26%)	4 (9%)

Table 2: Landmark analysis: worst neutropenia by treatment

Lancet Oncol 2005; 6: 669–77

Relationship between myelosuppression and anticancer effect (Lung cancers-metastatic setting)



	Hazard ratio of death (95% CI)	p
Neutropenia		
1–2 *vs* 0	0·74 (0·56–0·98)	0·0362
3–4 *vs* 0	0·65 (0·46–0·93)	0·0182
Age		
Increasing	1·00 (0·97–1·02)	0·8025
Sex		
Women *vs* men	1·01 (0·74–1·39)	0·9529
Performance status		
2 *vs* 0–1	1·05 (0·72–1·53)	0·7956
Stage		
IV *vs* IIIB	0·94 (0·73–1·23)	0·6654
Histological subtype		
Adenocarcinoma *vs* squamous	0·82 (0·61–1·10)	0·1815
Other *vs* squamous	0·80 (0·57–1·12)	0·1982

***Table 3*: Landmark analysis: multivariable Cox model stratified by treatment**

Lancet Oncol 2005; 6: 669–77

Relationship between myelosuppression and anticancer effect (Lung cancers-metastatic setting)

- Japan multinational trial organization LC00-03, 2001~2005, n=393
- Vinorelbine+Gemcitabine, followed by Docetaxel vs. Paclitaxel+Carboplain

Table 1 The incidence of neutropenia according to treatment cycle ($n = 387$). Values indicate number (%) of patients

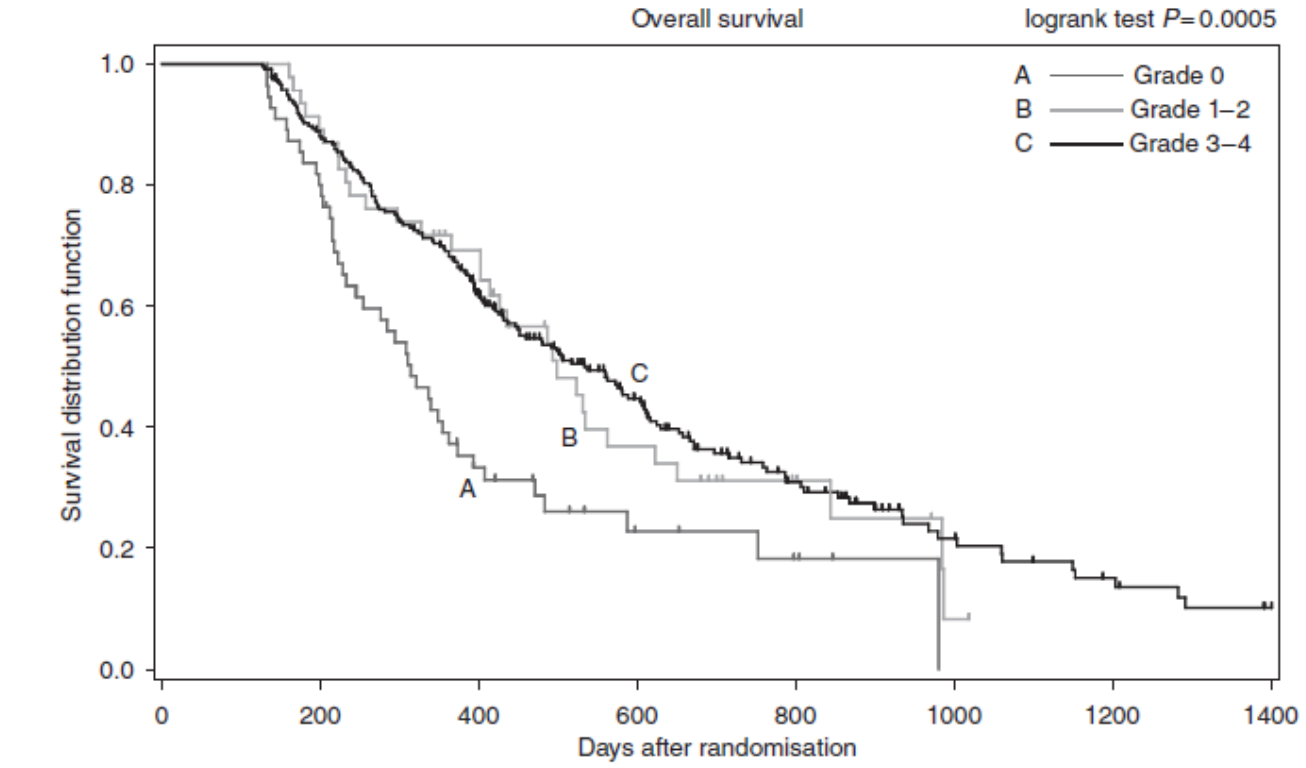
Treatment cycle	1	2	3	4	5	6	1–6
Number of patients	387	350	300	242	181	155	387
Grade 0	140 (36)	123 (35)	113 (38)	90 (37)	73 (40)	81 (52)	79 (26)
Grade 1	26 (7)	31 (9)	26 (9)	16 (7)	11 (6)	4 (3)	20 (5)
Grade 2	42 (11)	50 (14)	30 (10)	33 (14)	19 (10)	18 (12)	38 (10)
Grade 3	89 (23)	87 (25)	79 (26)	53 (22)	43 (24)	30 (19)	97 (25)
Grade 4	90 (23)	59 (17)	52 (17)	50 (21)	35 (19)	22 (14)	153 (40)
Grades 1–4	247 (64)	227 (65)	187 (62)	152 (63)	108 (60)	74 (48)	308 (80)

Table 3 Association between worst grade of neutropenia and number of treatment cycles received

	Number of treatment cycles			
	All patients ($n = 372$)		Patients in landmark analysis ($n = 337$)	
Worst grade of neutropenia	*n*	Mean ± s.d.	*n*	Mean ± s.d.
Grade 0	70	3.4 ± 1.9	55	3.9 ± 1.9
Grade 1	19	4.0 ± 1.7	18	3.9 ± 1.7
Grade 2	33	4.2 ± 1.9	28	4.6 ± 1.7
Grade 3	97	4.5 ± 1.6	90	4.7 ± 1.5
Grade 4	153	4.5 ± 1.7	146	4.6 ± 1.6

British Journal of Cancer (2009) 101(9), 1537 – 1542

Relationship between myelosuppression and anticancer effect (Lung cancers-metastatic setting)



No. at risk								
Grade 0	55	44	16	6	3			
Grade 1–2	46	41	28	13	6	1		
Grade 3–4	236	205	135	74	37	18	10	4

British Journal of Cancer (2009) 101(9), 1537 – 1542

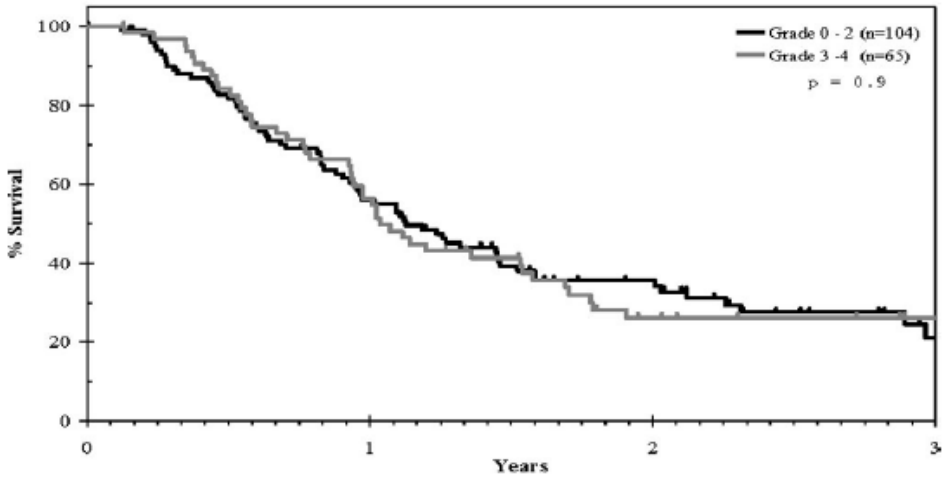
Relationship between myelosuppression and anticancer effect (Lung cancers-metastatic setting)

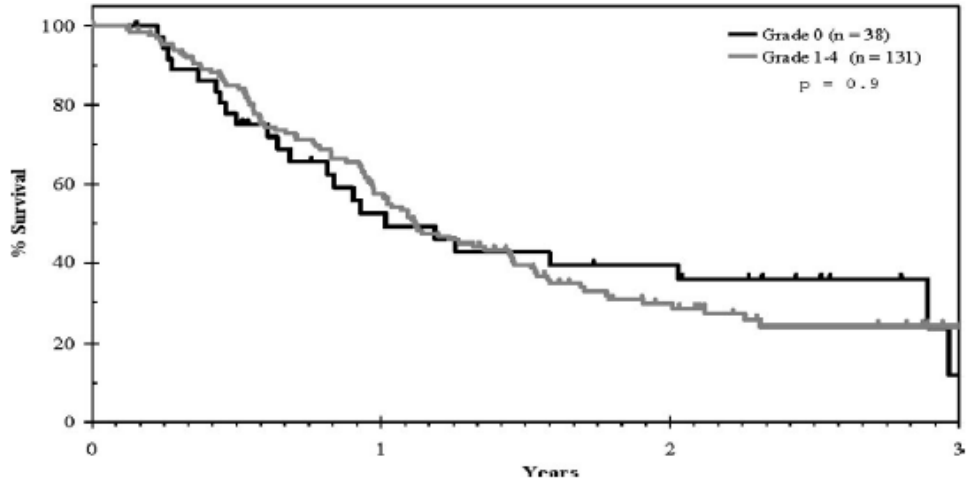
- UK, retrospective study, advanced stage NSCLC, n=169

TABLE 3. Rates of Neutropenia Across All Four Chemotherapy Groups

Worst Grade of Neutropenia	Carboplatin + Gemcitabine (%)	Carboplatin + Vinorelbine (%)	Cisplatin + Gemcitabine (%)	Cisplatin + Vinorelbine (%)	Total (%)
Grade 0	7 (18.9)	21 (28.8)	4 (30.8)	6 (13)	38 (22.5)
Grade 1	5 (13.5)	12 (16.4)	1 (7.7)	10 (21.7)	28 (16.6)
Grade 2	11 (27.9)	15 (20.5)	3 (23.1)	9 (19.6)	38 (22.5)
Grade 3	9 (24.3)	10 (13.7)	3 (23.1)	8 (17.4)	30 (17.8)
Grade 4	5 (13.5)	15 (20.5)	2 (15.4)	13 (28.3)	35 (20.7)
Total	37 (100)	73 (100)	13 (100)	46 (100)	169 (100)

The worst grade of neutropenia for each chemotherapy doublet in the first four cycles of treatment is shown. No significant differences between groups are demonstrated.





J Thorac Oncol. 2010;5: 1397–1403

Dose reduction and survival

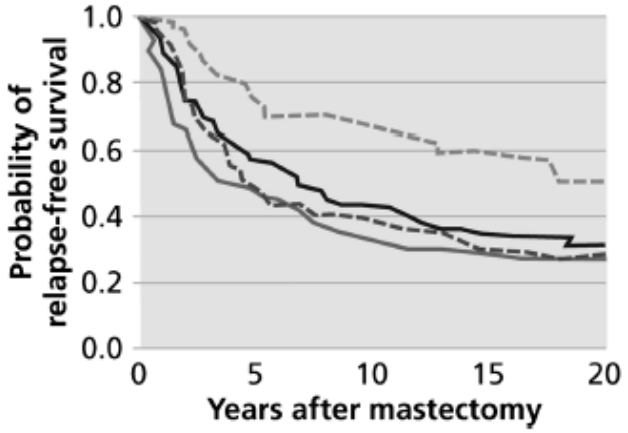
Relative dose intensity (RDI)

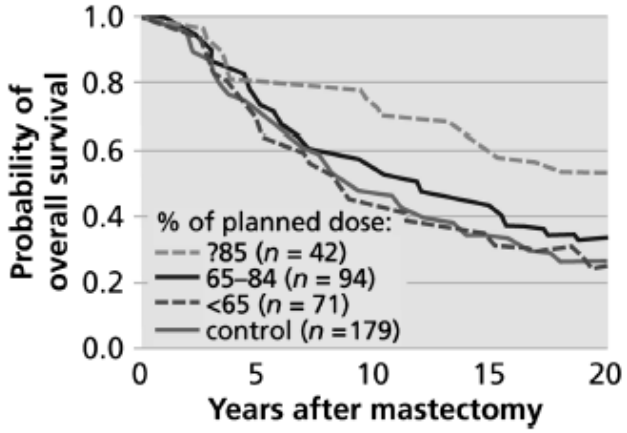
- **Relative dose intensity (RDI)**
  - Ratio of delivered dose intensity to standard or planned dose intensity
  - Commonly used to describe dose delays and/or reductions that occur within a chemotherapy course
  - RDI less than 85% is generally considered to be a clinically significant reduction from standard or planned therapy
  - Curative setting patients with cancer receiving chemotherapy at higher RDI had better clinical outcomes than those receiving treatment at lower RDI
  - However, the impact of RDI in advanced/metastatic disease remains unclear

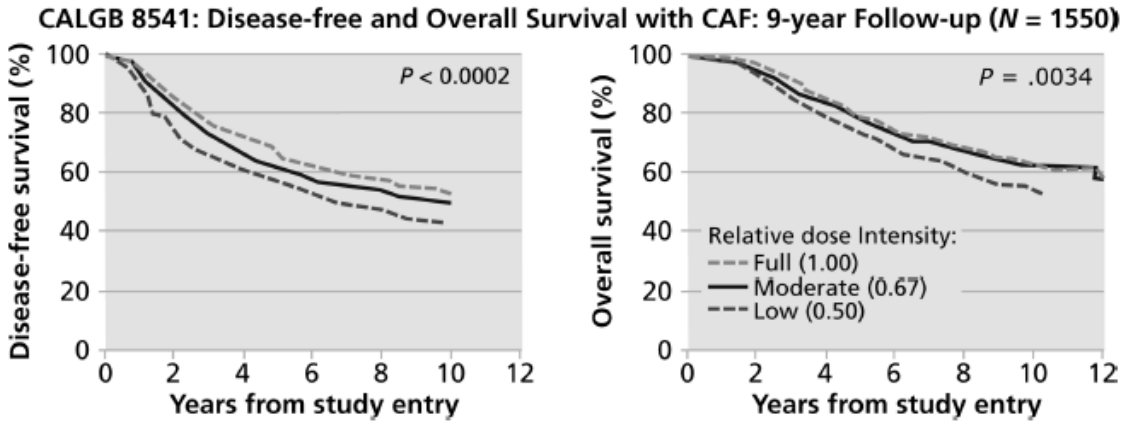
JNCCN 2015
Critical Reviews in Oncology/Hematology 93 (2015) 203–210

Relationship between dose reduction and survival (Curative setting)

[Lymph node positive early-stage breast]







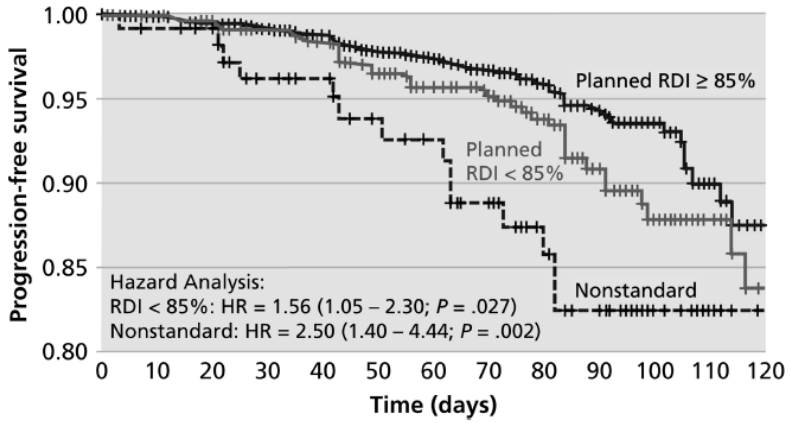


Figure 5 Results from a prospective observational study of nearly 2500 patients with early-stage (1–3) cancers of the breast, colorectum, ovary, or lung and malignant lymphoma. Shown is the Kaplan-Meier survival plot of patients through the initial course of treatment based on planned relative dose intensity (RDI) ≥ 85% or ≤ 85% of standard compared with those treated with a nonstandard regimen for which RDI could not be estimated. Data from Crawford J, Althaus B, Armitage J, et al. Clinical Practice Guidelines in Oncology: Myeloid Growth Factors. J Natl Compr Canc Netw 2007;5:188–202.

Curative setting patients with cancer receiving chemotherapy at higher RDI had better clinical outcomes than those receiving treatment at lower RDI

N Engl J Med 1995;332:904.
J Natl Cancer Inst 1998;90:1208.
J Natl Compr Canc Netw 2007;5:188–102.

Relationship between dose reduction and survival (Curative setting)

- Canada, retrospective analysis for The British Columbia Cancer Agency
- Surgically resected stage II NSCLC between 1 January 2005 and 31 December 2010

Factors affecting overall survival in all patients in British Columbia who received adjuvant chemotherapy for fully resected stage II non-small cell lung cancer diagnosed between 2005 and 2010 ($n = 158$)

	HR	*P* value	MVA HR	*P* value
Gender				
Female	1			
Male	1.368 (0.789–2.372)	0.264		
Age				
<70	1		1	
≥70	2.09 (1.225–3.568)	0.007	2.184 (1.224–3.899)	0.008
ECOG performance status				
0–1	1		1	
≥2	1.696 (0.954–3.015)	0.072	1.64 (0.846–3.179)	0.143
Charlson comorbidity score				
0–1	1		1	
≥2	2.24 (1.298–3.868)	0.004	2.416 (1.356–4.307)	0.003
Histology				
Adenocarcinoma	1			
Squamous cell carcinoma	1.036 (0.568–1.890)	0.908		
Other	1.552 (0.649–3.713)	0.323		
Smoking status				
Never	1			
Ever	1.631 (0.509–5.232)	0.41		
Weight loss				
<10%	1			
≥10%	2.037 (0.847–4.902)	0.112		
Unknown	1.546 (0.857–2.788)	0.148		
Type of platinum				
Cisplatin	1		1	
Carboplatin	1.368 (0.733–2.552)	0.325	1.139 (0.531–2.443)	0.768
Time from surgery to adjuvant chemotherapy				
<6 weeks	1		1	
6–8 weeks	1.086 (0.408–2.889)	0.869	0.768 (0.276–2.139)	0.613
8–10 weeks	1.179 (0.430–3.232)	0.749	0.961 (0.326–2.828)	0.942
>10 weeks	1.042 (0.370–2.934)	0.938	0.484 (0.154–1.520)	0.214
Dose of chemotherapy				
≥80%	1		1	
<80%	2.004 (1.159–3.463)	0.013	2.197 (1.196–4.037)	0.011

Clinical Oncology 27 (2015) 394e400.

Systematic review of RDI and survival in patients with metastatic NSCLC

Lung cancer studies evaluating overall survival by RDI.

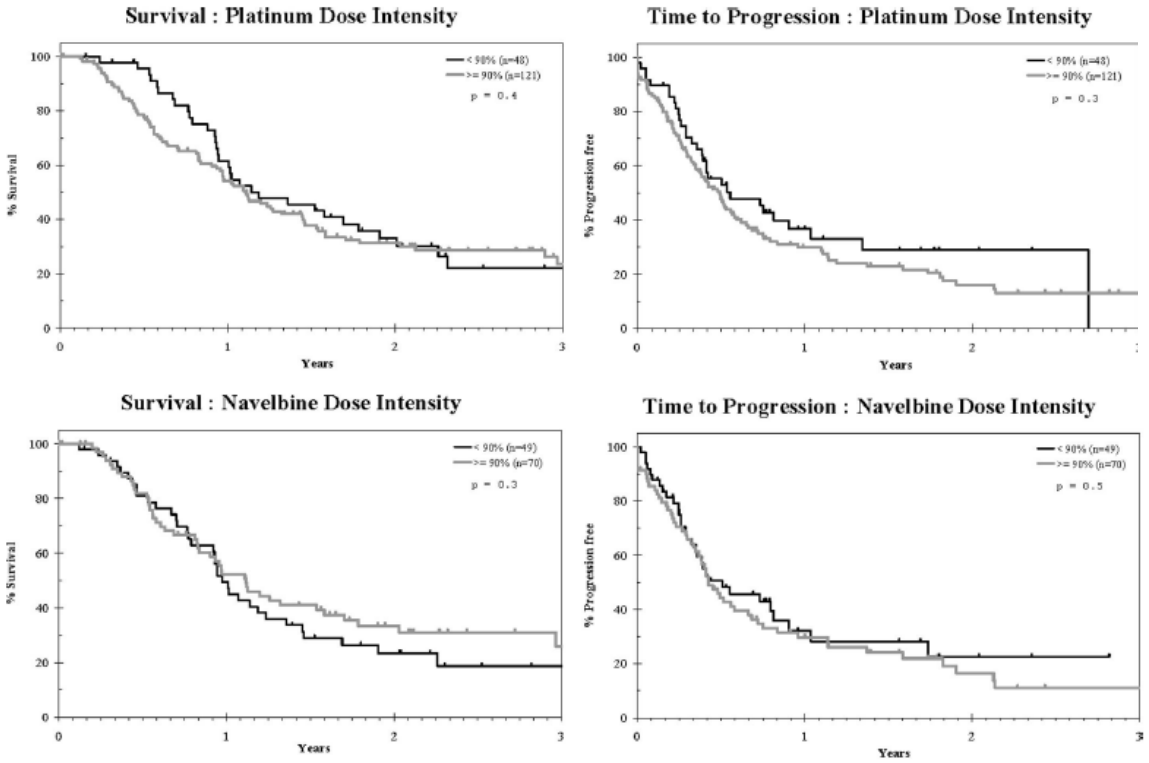
Study citation	Study type	*N*	Chemotherapy	Key findings
Brunetto et al. [13]	NSCLC, retrospective	169	Platinum[a] + vinorelbine or gemcitabine	Platinum, RDI < 90% versus RDI ≥ 90% Median (95% CI) OS: 62 (34–90) versus 58 (45–70) weeks; $P = 0.4$ Vinorelbine, RDI < 90% versus RDI ≥ 90% Median (95% CI) OS: 51 (45–56) versus 58 (45–72) weeks; $P = 0.3$ Gemcitabine, RDI < 90% versus RDI ≥ 90% Median (95% CI) OS: 79 (48–111) versus 76 (49–103) weeks; $P = 0.6$
Luciani et al [18]	NSCLC, retrospective, ≥70 years	107	Vinorelbine, gemcitabine, or vinorelbine + cisplatin	RDI ≤ 80% versus RDI > 80% Median (95% CI) OS: 7 (3.5–10.4) versus 10 (6.7–13.2) months; $P < 0.0001$

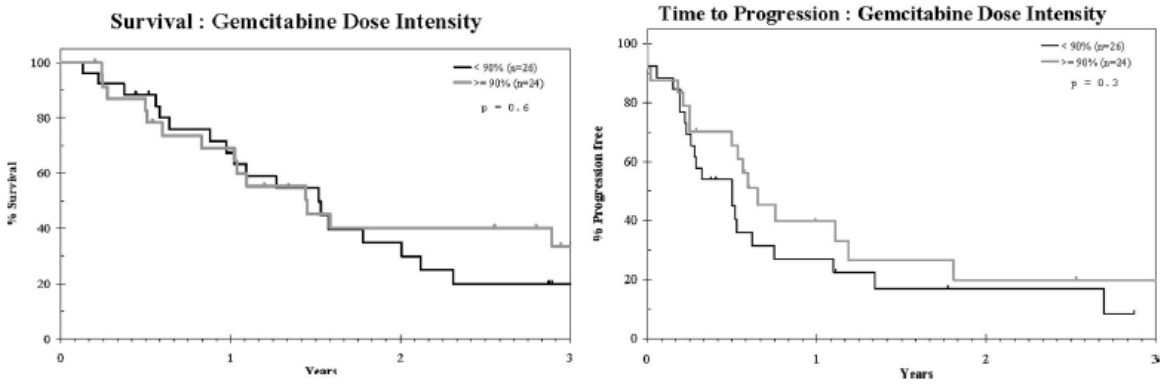
[a] Carboplatin or cisplatin. CI—confidence interval; NSCLC—non-small cell lung cancer; OS—overall survival; RDI—relative dose intensity.

Relationship between dose reduction and survival (metastatic ds)

- Brunetto, et al. UK, retrospective study, advanced stage NSCLC, n=169
- Platinum-doublet chemotherapy using a prespecified RDI threshold of 90%
- RDI across regimens was not associated with overall survival

  (platinum, *P* = 0.4; vinorelbine, *P* = 0.3; gemcitabine, *P* = 0.6)





No significant relationship between survival and dose intensity (90%), modest dose reductions (20%)

J Thorac Oncol. 2010;5: 1397–1403

Relationship between dose reduction and survival (metastatic ds)

- Luciani, et al. 1998~2007, Italy, retrospective study, n=107, elderly patients (≥ 70 years), advanced stage NSCLC
- Prespecified RDI threshold of 80%
- Patients receiving chemotherapy at a higher RDI had improved survival ($P < 0.0001$)

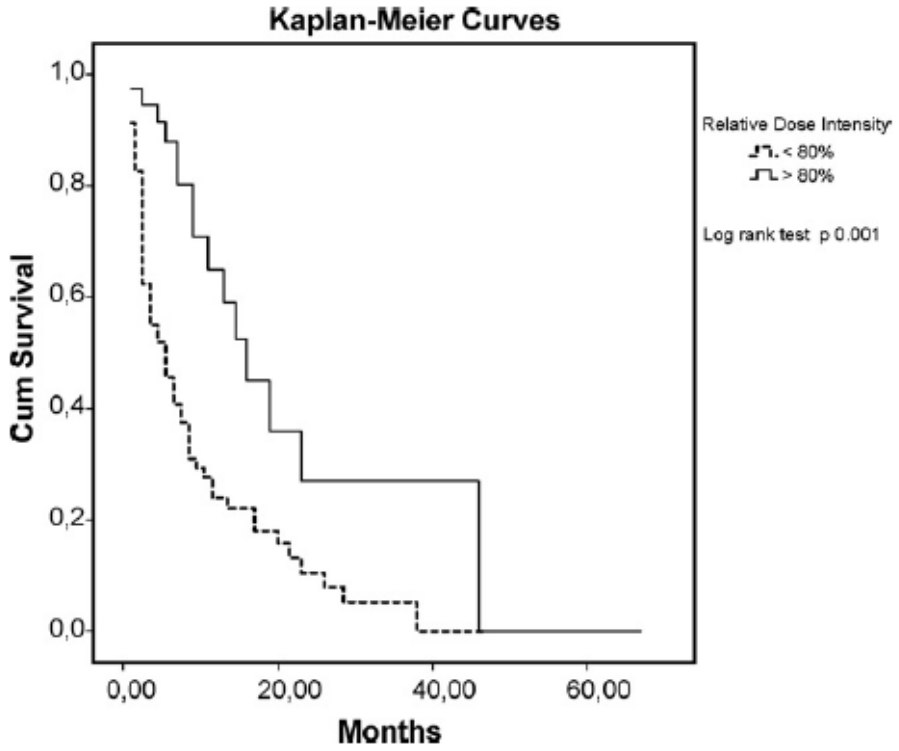


Fig. 1. Survival curves for subgroups (RDI > 80%, RDI < 80%).

Elderly patients treated with chemotherapy for advanced NSCLC an adequate dose intensity has a significant positive impact on both response rate and overall survival

Lung Cancer 66 (2009) 94–96

Relationship between dose reduction and survival (metastatic ds)

- US, retrospective study, large US community-based oncology network setting
- 2007-2010, n=3866, advanced stage NSCLC

Table 1 Standard chemotherapy regimens

Chemotherapy regimen	Standard dose
Carboplatin + paclitaxel	5 AUC/175 mg/m^2
Pemetrexed + carboplatin	500 mg/m^2/5 AUC
Bevacizumab + carboplatin + paclitaxel	15 mg/kg/5 AUC/175 mg/m^2
Pemetrexed + cisplatin	500 mg/m^2/75 mg/m^2
Pemetrexed + bevacizumab + carboplatin	500 mg/m^2/15 mg/kg/5 AUC
Carboplatin + gemcitabine	5 AUC/1000 mg/m^2 × 2

Dose delays, dose reductions, and reduced RDI were common

- Dose delay ≥ 7 days: 32.4%
- Dose reduction ≥ 15%: 50.1%
- mean (SD) RDI across all regimens : 83.9%
- RDI < 85% : 40.4%

Table 3 CSF and antibiotic use

Characteristic, *n* (%)	Patients with NSCLC *N* = 3866
CSF use	
Primary prophylaxis[a]	709 (18.3)
Secondary prophylaxis[b]	242 (6.3)
Treatment[c]	636 (16.5)
Prophylactic oral antibiotics	1200 (31.0)

Supportive Care in Cancer (2020) 28:925–932

Relationship between dose reduction and survival (metastatic ds)

Table 4 Multivariable Cox regression analysis of OS in patients with NSCLC[a]

Variable	HR (95% CI)	*P* value
RDI, < 85% vs ≥ 85%	1.176 (1.047–1.320)	0.0062
Dose delay, ≥ 7 vs < 7 days	0.710 (0.630–0.800)	< 0.0001
ECOG PS		
1 vs 0	1.316 (1.192–1.453)	< 0.0001
2 vs 0	1.654 (1.350–2.027)	< 0.0001
Hemoglobin, < 12 vs ≥ 12 g/dL	1.098 (0.993–1.213)	0.0686
Tumor subgroup		
Adenocarcinoma vs squamous	0.783 (0.698–0.877)	< 0.0001
Other vs squamous	0.932 (0.725–1.199)	0.5855

Dose delay ≥ 7 days was significantly associated with a decreased risk of death,
whereas RDI < 85% was significantly associated with an increased risk of death

→ Dose reduction alone was not a significant predictor of survival warrants further investigation.

These results suggest that different measurements of dose variation may have different sensitivity in predicting prognosis.

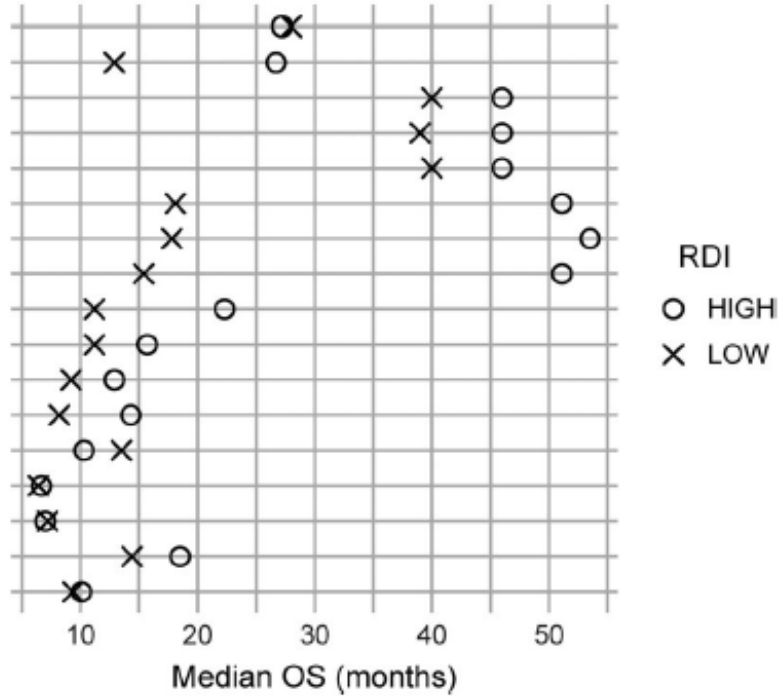
Understanding the complex effect of dose intensity on outcomes will be important for managing toxicities and improving survival

Supportive Care in Cancer (2020) 28:925–932

Relationship between dose reduction and survival

- 2013-2020, meta-analysis for association between RDI and survival (22 articles)
- Nonadjuvant-based chemotherapy regimens

Author	Year	Tumor type	Treatment	RDI threshold
Nakayama	2014	CRC	mFOLFOX6 (oxaliplatin)	79%
Nakayama*	2014	CRC	FOLFIRI (irinotecan)	80%
Au-Yeung	2014	ovarian	Paclitaxel	85%
Au-Yeung	2014	ovarian	Paclitaxel and carboplatin	85%
Au-Yeung	2014	ovarian	Carboplatin	85%
Yamashita**	2016	esophagus	Nedaplatin/5-fluorouracil	70%
Yamashita**	2016	esophagus	Nedaplatin/5-fluorouracil	60%
Yamashita**	2016	esophagus	Nedaplatin/5-fluorouracil	50%
Lee*	2017	pancreas	FOLFIRINOX	80%
Lee	2017	pancreas	FOLFIRINOX	70%
Lee**	2017	pancreas	FOLFIRINOX	55%
Kanazawa*	2017	gastric	Nab-paclitaxel	80%
Ishigaki	2017	pancreas	Nab-paclitaxel and gemcitabine	77%
Makiyama	2018	gastric	Irinotecan	80%
Fernandez	2018	pancreas	Nab-paclitaxel and gemcitabine	85%
Yoshihiro	2019	CRC	FOLFIRI	60%
Crawford	2020	NSCLC	Carboplatin or cisplatin combinations	85%



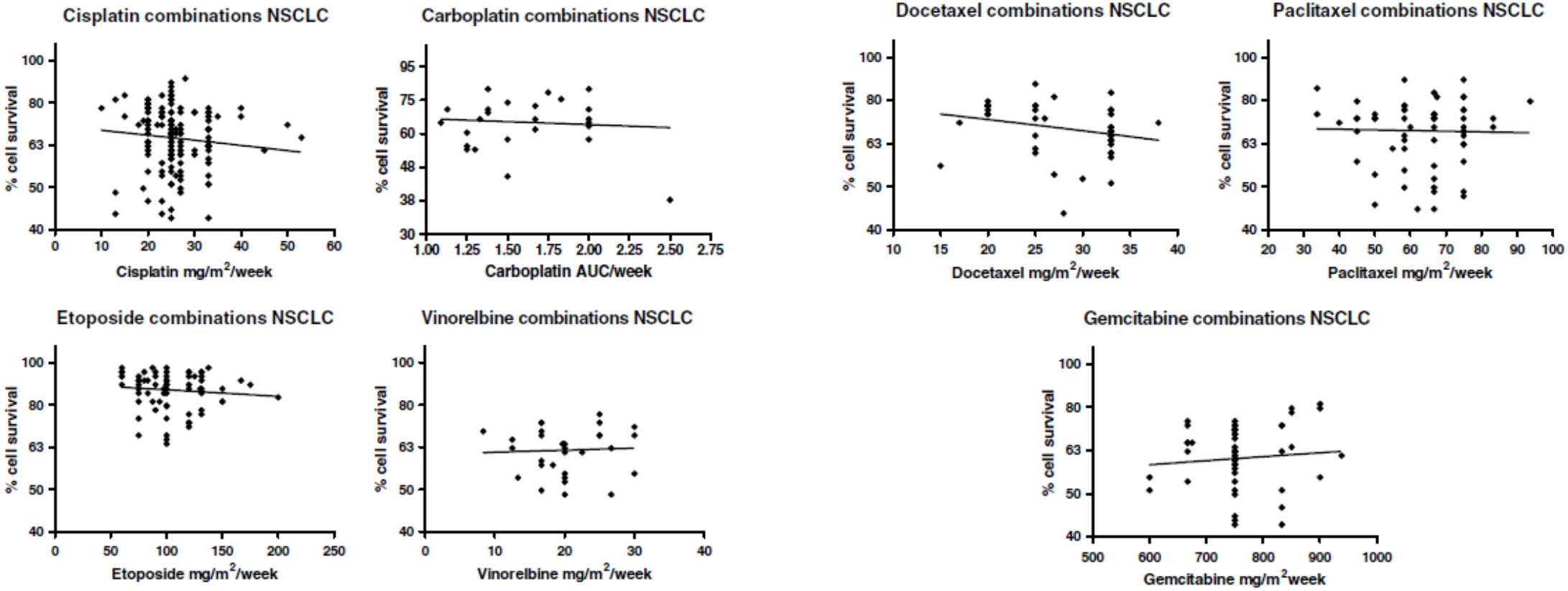
→ Longer overall survival with RDI levels of at least 80% for patients with solid tumors

managing toxicities across treatment regimens may contribute to maintenance of higher RDI and ultimately benefit overall survival.

The Oncologist 2021;26:e1609–e1618

Relationship between dose reduction and survival

Cell survival vs planned dose-intensity for agents used in combinations as therapy in NSCLC



→ For all agents, drug-response curves flattened at higher doses, suggesting efficacy is limited by saturable passive resistance

The Oncologist 2021;26:e1609–e1618

Summary

- Despite significant progress in precision medicine and immunotherapy, chemotherapy remains the cornerstone of treatment for lung cancer
- **Myelosuppression**
  - Common dose-limiting side effect of cytotoxic chemotherapy that leads to considerable morbidity and negatively impacts treatment outcomes and QoL
  - Surrogate for chemotherapy dose intensity, suggesting a strong association between dose intensity and clinical efficacy

Summary

- **Dose reduction and survival**
  - Strong evidence shows that patients with responsive and potentially curable malignancies benefit from the delivery of full-dose cancer chemotherapy
  - In the setting of palliative chemotherapy for NSCLC
    - Tumors are often chemo-resistant
    - Patient population is relatively elderly, with associated comorbidities, poor PS, and an increased risk of life-threatening complications
  - It remains unclear whether modest dose reductions or dose delays in this population are associated with adverse outcome and whether drug-induced neutropenia is necessary for improved survival

→ Managing toxicities across treatment regimens may contribute to maintenance of higher RDI and ultimately benefit overall survival

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Thank you for your attention!

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