

8 Appendix: Statistical Tables and Figures

Table 1: Survival and hazard ratio estimates for study CA139-165.

Arm	Median survival (months)	95% CI survival (months)	p-value*
Cisplatin/etoposide	7.4	(6.5, 8.6)	—
Taxol/cisplatin	9.3	(8.0, 10.4)	0.125
Taxol/cisplatin/G-CSF	10.0	(8.9, 11.7)	0.079
Arm (vs. Cisp/etop)	Hazard ratio	97.5% CI hazard ratio	
Taxol/cisplatin	1.18	(0.93, 1.51)	
Taxol/cisplatin/G-CSF	1.21	(0.95, 1.53)	

* Stratified log-rank, comparison vs. cisp/etop.

Table 2: Survival and hazard ratio estimates for study CA139-165 with both Taxol arms pooled.

Arm	Median survival (months)	95% CI survival (months)	p-value*
Cisplatin/etoposide	7.4	(6.5, 8.6)	—
Pooled Taxol group	9.7	(8.8, 10.6)	0.049
Arm (vs. Cisp/etop)	Hazard ratio	95% CI hazard ratio	
Pooled Taxol group	1.21	(0.95, 1.53)	

* Stratified log-rank, comparison vs. cisp/etop.

Table 3: Cox regression parameter estimates and p-values on survival for all patients in study CA139-165.

Variable	Parameter est.	Std. Err.	p-value*
Trt (Txl/cisp) vs. cisp/etop	-0.15	0.11	0.169
Trt (Txl/cisp/G-CSF) vs. cisp/etop	-0.18	0.11	0.094
Gender (male)	0.10	0.09	0.303
LDH	0.25	0.09	0.007
Pr. Radiotherapy (yes)	0.13	0.11	0.233
Histology (not squam.)	-0.01	0.11	0.945

* Stratified Cox regression, adjusting for all covariates.

Table 4: Progression frequencies for study CA139-165 across treatment arms.

	Taxol/cisp	Taxol/cisp/G-CSF	cisp/etop
Progressed	173	170	174
Disease progression	156	152	161
Death	17	18	13
Censored	25	31	26
Not relapsed	3	5	4
Sec. Thrpy - Chemo	7	10	10
Sec. Thrpy - Radio	8	11	7
Sec. Thrpy - Surgery	2	1	
Never Treated	2	4	4
Wrong primary cell type	2		1
Lost to followup	1		
Total	198	201	200

Table 5: Median time to progression (in months) for study CA139-165 across treatment arms.

	Taxol/cisp	Taxol/cisp/G-CSF	cisp/etop
Time to Prog. and 95% CI	4.3 (3.3, 5.1)	4.9 (4.0, 5.8)	2.7 (2.2, 3.2)
vs. cisp/etop (log-rank)	p = 0.0504	p = 0.004	—

Table 6: Cox regression parameter estimates and p-values for time to progression in study CA139-165.

Variable	p-value log-rank (strat.)	p-value Cox adj.*	Hazard ratio
Gender	0.344	0.469	1.07 (0.89, 1.30) (Female/male)
Histology	0.077	0.101	0.83 (0.66, 1.04) (Squam/other)
LDH	0.009	0.016	1.27 (1.05, 1.53) (normal/other)
Pr. Radiotherapy	0.317	0.497	1.08 (0.86, 1.36) (no/other)
Txl/cisp/G-CSF	0.0504	0.005	1.25 (1.00, 1.55) (vs. cisp/etop)
Txl/cisp	0.004	0.060	1.37 (1.10, 1.70) (vs. cisp/etop)

* Stratified Cox regression, adjusting for all covariates.

Table 7: Seven patients in CA139-165 classified as having "tumor progression," although there was no evidence of progression on these patients' case-report forms.

Center	Subject No.	Arm
139165005		Cisplatin/Etoposide
139165007		Cisplatin/Etoposide
139165012		Cisplatin/Etoposide
139165012		Cisplatin/Etoposide
139165026		Cisplatin/Etoposide
139165013		Taxol/Cisplatin/G-CSF
139165009		Taxol/Cisplatin/G-CSF

Table 8: Time to progression (in months) for study CA139-165 across treatment arms. This analysis categorizes seven patients with no documented reason for progression as having been censored.

	Taxol/cisp	Taxol/cisp/G-CSF	cisp/etop
Time to Prog. and 95% CI	5.1 (4.2, 5.8)	4.3 (3.3, 5.1)	2.8 (2.3, 3.2)
vs. cisp/etop (log-rank)	p = 0.091	p = 0.007	—

Table 9: Clinical response across treatments for study CA139-165.

	Taxol/cisp.	Taxol/cisp/G-CSF	cisp/etop
Measurable Disease	174	169	177
Complete response	4	3	1
Partial response	42	48	23
Stable disease	84	72	94
Progressive disease	38	36	51
Early Death	6	10	8
Non-measurable	18	28	16
Non-evaluable	6	4	7

Table 10: Quality of life questionnaire compliance for CA139-165.

Time Point	Cisp/etop	Taxol/cisp	Taxol/cisp/G-CSF
Baseline	182	188	183
Week 6	113	133	139
Week 12	88	107	98
Week 25	58	64	77

Table 11: Results from quality of life longitudinal analysis of CA139-165.

Var.	Group	Taxol/cisp		TxI/G-CSF		Cisp/etop	
		Est.*	SE	Est.*	SE	Est.*	SE
Physical	Dropouts	-1.32	0.93	-1.07	0.72	-2.10	0.67
Functioning	Completers	-0.44	0.11	-0.56	0.13	-0.47	0.12
Funct.	Dropouts	-0.51	0.91	-0.97	0.70	-0.93	0.81
Well Being	Completers	-0.30	0.12	-0.34	0.12	-0.18	0.12
Lung Cancer	Dropouts	0.17	0.83	0.02	0.66	-2.16	0.64
Specific	Completers	0.09	0.12	-0.05	0.13	-0.31	0.12

* Estimated slopes and standard errors for the GEE model outlined in Section 3.2.

Table 12: Survival and hazard ratio estimates for study CA139-103.

Arm	Median survival (months)	95% CI survival (months)	p-value*
Teniposide/cisplatin	9.9	(8.2, 12.0)	—
Taxol/cisplatin	9.5	(8.2, 11.7)	0.802
Arm (vs. Tenip/cisp)	Hazard ratio	95% CI hazard ratio	
Taxol/cisplatin	1.03	(0.80, 1.33)	

* Stratified log-rank, comparison vs. tenip/cisp.

Table 13: Cox regression parameter estimates and p-values on survival for study CA139-103.

Variable	p-value log-rank (strat.)	p-value Cox adj.*	Hazard ratio
Gender	0.014	0.002	0.62 (0.46, 0.83) (Female/male)
Histology	0.164	0.008	0.66 (0.48, 0.90) (Squam/other)
Wt. Loss	0.003	0.017	0.71 (0.54, 0.94) (< 5%/other)
Pr. Radiotherapy	0.001	0.001	0.53 (0.36, 0.78) (no/other)
Hemoglobin	0.0001	0.0001	0.47 (0.33, 0.66) (normal/other)
Treatment arm	0.802	0.789	1.04 (0.80, 1.33)

* Stratified Cox regression, adjusting for all covariates.

Table 14: Progression frequencies for study CA139-103 across treatment arms.

	Taxol/cisp	tenip/cisp
Progressed	130	127
Disease progression	120	111
Death	10	16
Censored	36	39
Sec. Thrpy - Chemo	6	0
Sec. Thrpy - Radio	8	21
Sec. Thrpy - Surgery	4	6
Never Treated	6	1
Not relapsed	11	10
Other	1	1
Total	166	166

Table 15: Median time to progression (in months) for study CA139-103 across treatment arms.

	Taxol/cisp	tenip/cisp
Time to Prog. and 95% CI	5.1 (4.3, 5.9)	5.0 (3.7, 5.8)
vs. tenip/cisp (log-rank)	p = 0.608	—

Table 16: Cox regression parameter estimates and p-values for time to progression in study CA139-103.

Variable	p-value log-rank (strat.)	p-value Cox adj.*	Hazard ratio
Gender	0.671	0.262	0.85 (0.64, 1.13)
Histology	0.034	0.013	0.67 (0.49, 0.92)
Weight Loss	0.387	0.321	0.87 (0.66, 1.15)
Baseline Hemoglob.	0.001	0.001	0.53 (0.37, 0.76)
Pr. Radiotherapy	0.202	0.244	0.79 (0.53, 1.17)
Treatment	0.723	0.767	1.04 (0.81, 1.34)

* Stratified Cox regression, adjusting for all covariates.

Table 17: Clinical response across treatments for study CA139-103.

	Taxol/cisp.	tenip/cisp
Measurable Disease	159	161
Complete response	2	0
Partial response	56	41
Stable disease	70	74
Progressive disease	23	31
Early Death	8	15
Non-measurable	0	4
Non-evaluable	7	5

Table 18: Quality of life questionnaire compliance for CA139-103. The numerator in each case is the number of questionnaires completed and the denominator is the number of patients alive at the beginning of each period.

Week	teniposide/cisplatin	Taxol/cisplatin
Baseline	50/86 (58%)	50/82 (61%)
Week 6	53/85 (62%)	46/79 (58%)
Week 12	32/74 (43%)	37/71 (52%)
Week 18	23/66 (35%)	22/66 (33%)
Week 24	16/62 (26%)	14/63 (22%)

Table 19: Results from quality of life longitudinal analysis of CA139-103. A positive trend for Global Health, Physical, Role and Social Functioning corresponds to an improvement, whereas a positive trend in Peripheral Neuropathy and Pain corresponds to worsening of symptoms.

Var.	Taxol/cisp		Tenip/cisp		p-val.
	Est.*	SE	Est.*	SE	
Global Health	-1.71	1.51	-1.05	1.41	0.74
Phys. Func.	-2.55	1.11	-6.06	1.15	0.03
Periph. Neurop.	13.33	2.16	8.55	2.15	0.12
Pain	1.67	1.91	-0.20	3.39	0.63
Role Func.	-2.17	3.37	-4.16	1.88	0.61
Social Func.	-0.94	1.71	2.86	2.36	0.12

* Estimated slopes and standard errors for the GEE model outlined in Section 3.2.

Table 20: Survival and hazard ratio estimates for study CA139-208.

Arm	Median survival (months)	95% CI survival (months)	p-value*
HD Cisplatin	8.6	(7.1, 10.3)	—
Taxol/cisplatin	8.1	(7.3, 9.2)	0.862
Arm (vs. HD Cisp)	Hazard ratio	95% CI	
Taxol/cisplatin	0.98	(0.79, 1.22)	

* Stratified log-rank, comparison vs. HD cisp.

Table 21: Median time to progression (in months) for study CA139-208 across treatment arms.

	Taxol/cisp	HD Cisp
Time to Prog. and 95% CI	4.3 (3.5, 4.6)	3.2 (2.4, 3.9)
vs. HD Cisp (log-rank)	p = 0.085	—

Table 22: Cox regression parameter estimates and p-values for time to progression in study CA139-208.

Variable	p-value log-rank (strat.)	p-value Cox adj.*	Hazard ratio (95% CI)
Gender	0.949	0.917	1.02 (0.77, 1.35) (Female/male)
Histology	0.895	0.789	0.97 (0.76, 1.23) (Squam/other)
Wt. Loss	0.407	0.504	0.93 (0.74, 1.16) (< 5%/other)
Base. Hemoglob.	0.408	0.683	0.93 (0.67, 1.31) (normal/other)
Baseline LDH	0.097	0.125	0.84 (0.66, 1.05) (normal/other)
Pr. Radiotherapy	0.465	0.532	0.88 (0.59, 1.32) (no/other)
Treatment arm	0.085	0.056	1.24 (1.00, 1.54)

* Stratified Cox regression, adjusting for all covariates.

Table 23: Clinical response across treatments for study CA139-208.

	Taxol/cisp.	Cisp.
Measurable Disease	200	196
Complete response	3	1
Partial response	47	33
Stable disease	98	95
Progressive disease	32	51
Early Death or Tox	10	17
Non-evaluable	6	3
Not measurable	11	7

Table 24: Quality of life questionnaire compliance for CA139-208. The numerator in each case is the number of questionnaire completed and the denominator is the number of patients alive at the beginning of each period.

Week	Cisplatin	Taxol/cisplatin
Baseline	190/207 (92%)	178/207 (86%)
Week 5	159/206 (77%)	172/202 (85%)
Week 8	134/173 (77%)	151/181 (83%)
Week 11	91/138 (66%)	121/164 (74%)
Week 14	67/99 (68%)	96/127 (76%)
Week 17	51/82 (62%)	86/104 (83%)
Week 20	26/57 (46%)	36/74 (49%)
Week 23	13/23 (57%)	13/27 (48%)
Week 26	3/12 (25%)	9/16 (56%)
Week 34	4/4 (100%)	1/4 (25%)

Table 25: Summary table of the p-values of the three QOL analyses for study CA139-208

Subscale	W-J p-value	W-L p-value	Mixed* p-value	Favorable arm
Physical Funct.	0.054	0.062	0.073	Taxol/cisplatin
Nausea/Vomiting	< 0.001	< 0.001	< 0.001	Taxol/cisplatin
Appetite Loss	0.020	0.015	0.025	Taxol/cisplatin
Constipation -	0.032	0.030	0.015	Taxol/cisplatin
Periph. Neuropathy	< 0.001	< 0.001	< 0.001	Cisplatin
Hair Loss	< 0.001	< 0.001	< 0.001	Cisplatin

* Mixed model with period and treatment as fixed effects with banded longitudinal covariance matrix.

CA139-165 Physical Functioning QOL Subscale

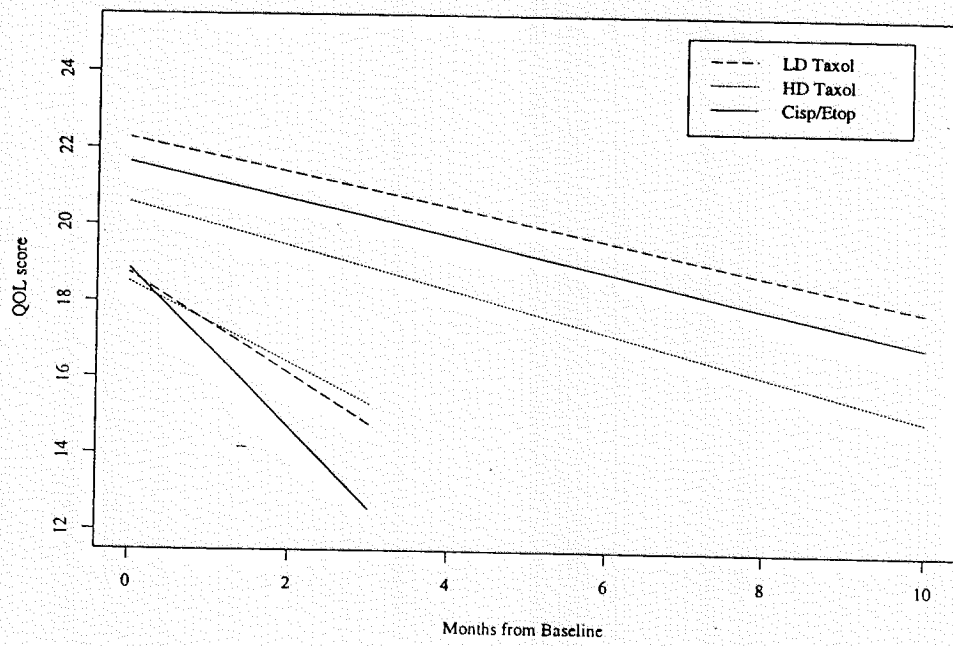


Figure 1: Study 165 QOL Physical Functioning subscale linear estimates for trend. The shorter set of lines represents the "Dropouts" and the longer set represents the "Completers." Note that the slopes for cisplatin/etoposide are different, implying a non-ignorable dropout mechanism.

CA139-165 Functional Well Being QOL Subscale

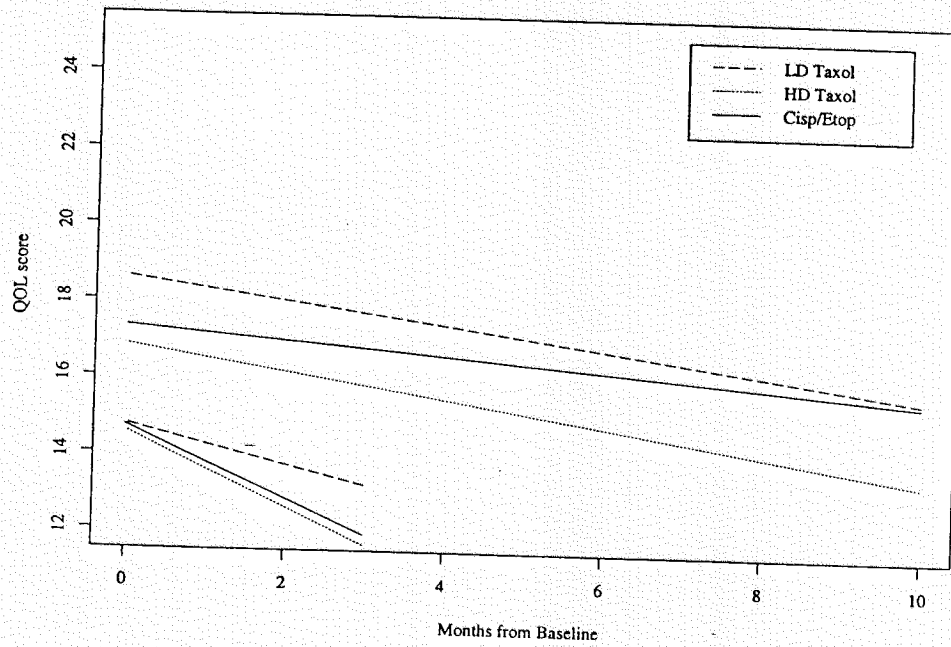


Figure 2: Study 165 QOL Functional Well Being subscale linear estimates for trend. The shorter set of lines represents the "Dropouts" and the longer set represents the "Completers." Note that the slopes for cisplatin/etoposide are different, implying a non-ignorable dropout mechanism.

CA139-165 Lung Cancer Specific Symptoms QOL Subscale

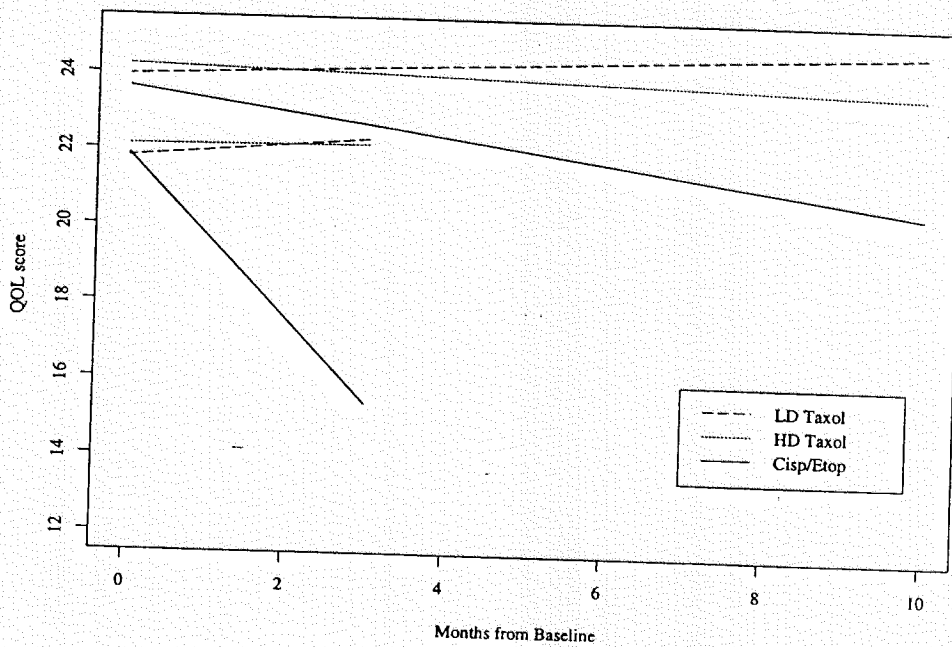


Figure 3: Study 165 QOL Lung Cancer Specific Symptoms subscale linear estimates for trend. The shorter set of lines represents the "Dropouts" and the longer set represents the "Completers." Note that the slopes for cisplatin/etoposide are different, implying a non-ignorable dropout mechanism.

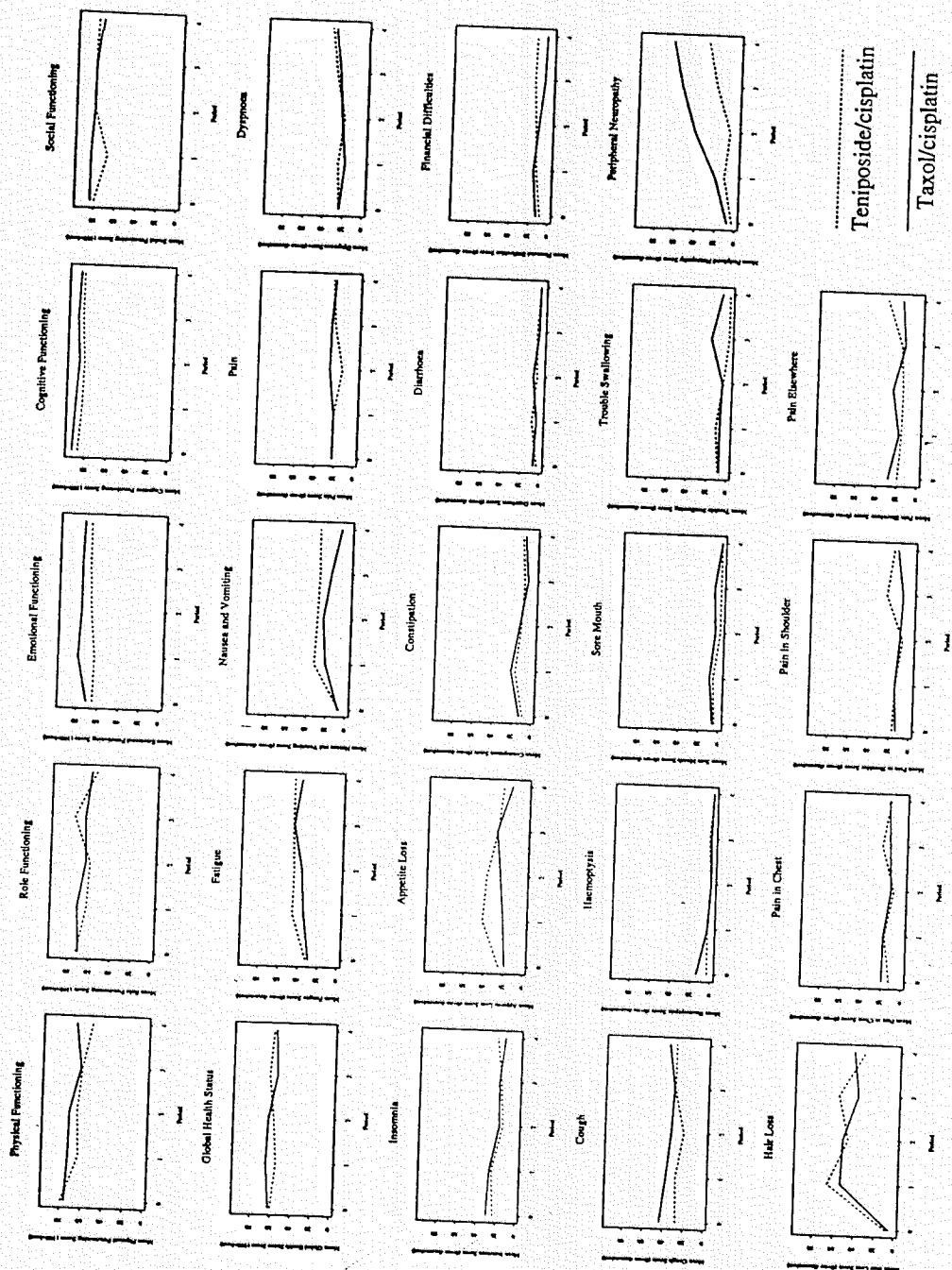


Figure 4: Means by followup period for the 24 QOL endpoints examined in CA139-103. Note that the vertical axis is not interpreted in the same manner across these endpoints.

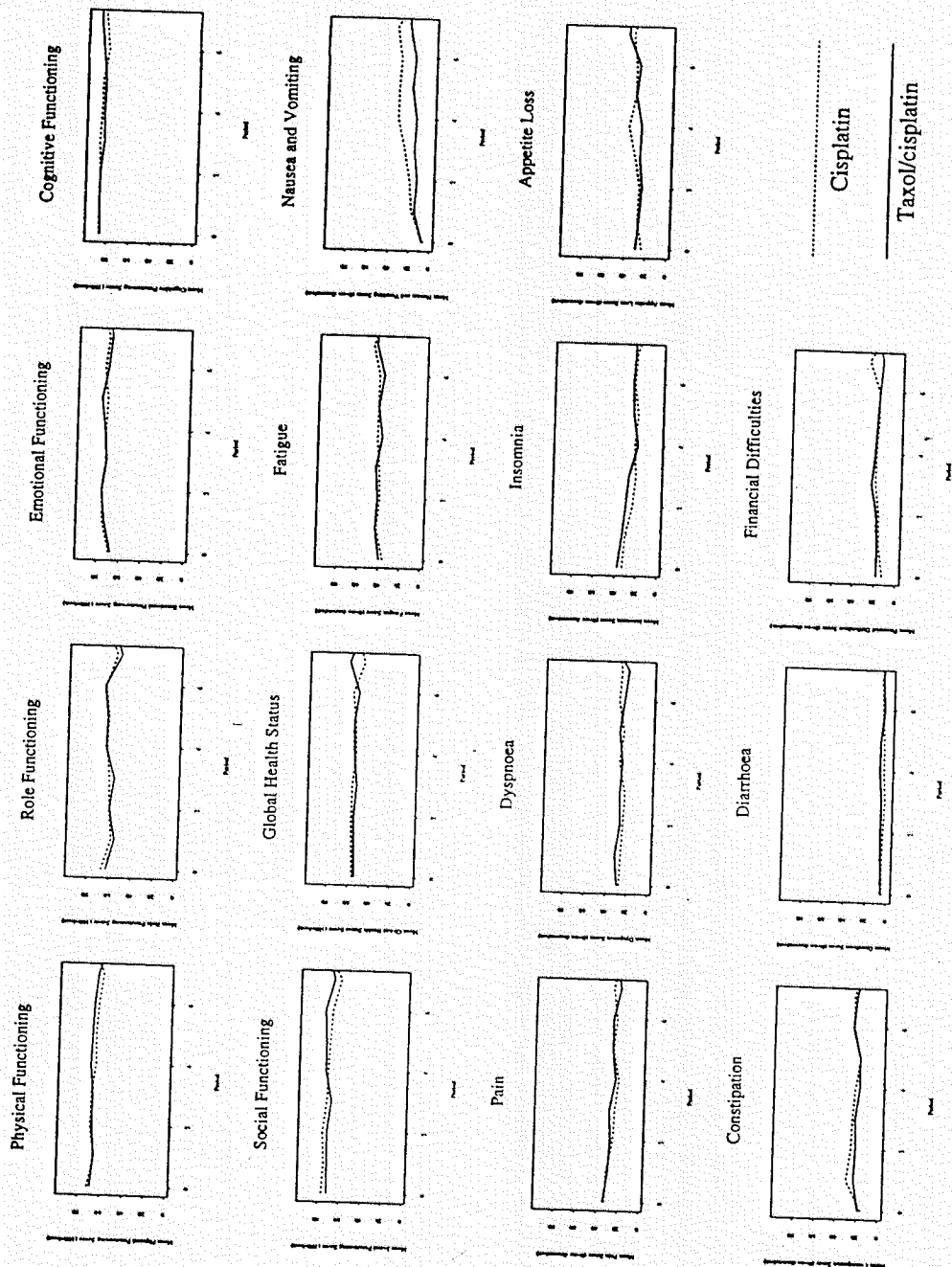


Figure 5: Means by followup period for the 24 QOL endpoints examined in CA139-208. Note that the vertical axis is not interpreted in the same manner across these endpoints.

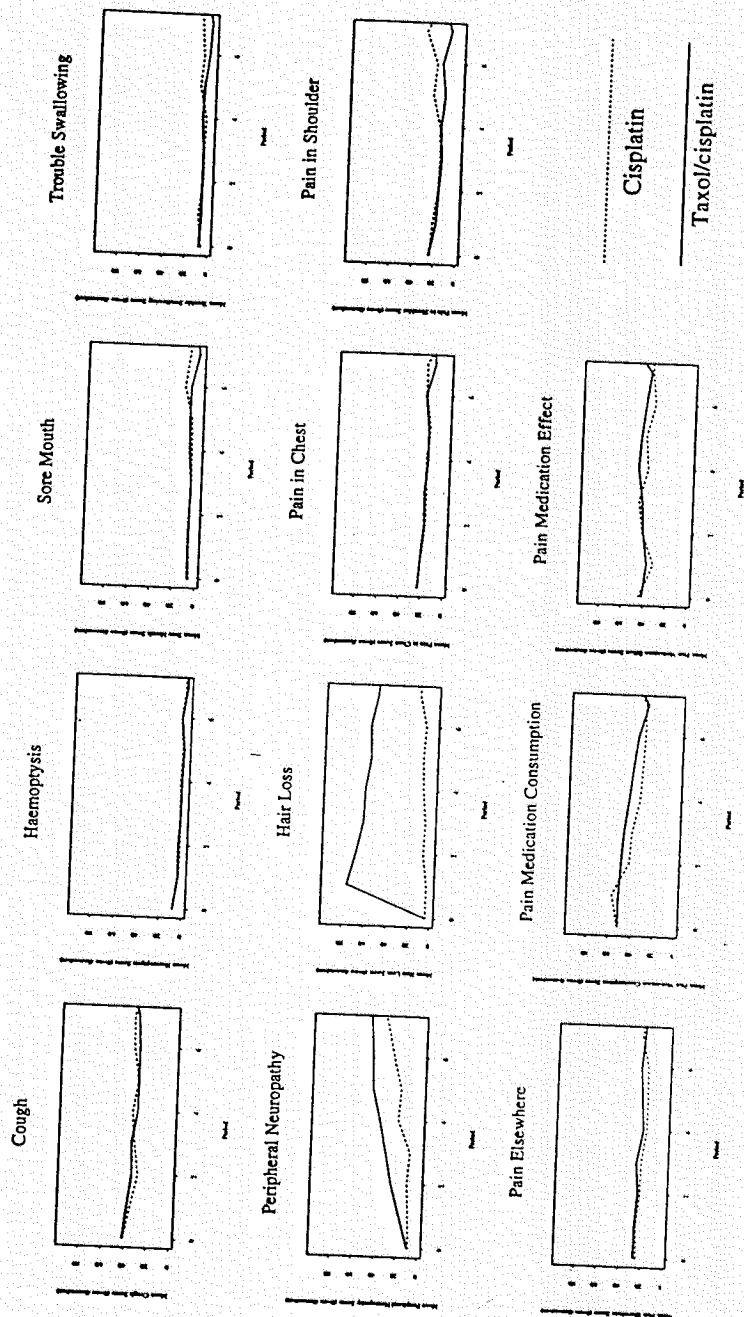


Figure 6: Means by followup period for the 24 QOL endpoints examined in CA139-208.