

Neoadjuvant and Adjuvant chemotherapy in Bladder Cancer

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Prechemo



3 x Cis-Gem



60 yr / female

Neoadj chemo → chemoRT

Prechemo



2 x Cis-Gem



61 yr / male “locally unresectable”

Neoadj chemo (4 x Cis-Gem) → cystectomy: pT4N2 (2/17)

→ adj chemo (2 x Cis-Gem)

TABLE 1. *Survival after radical cystectomy according to pathological (pT) stage⁶*

References	No. Pts	% pT0*	% Operative Mortality	% 5-Yr Survival		
				pT2	pT3	pT4
Richie	134	8	8.5	40	20	—
Braedel	174	—	4	51	25	18
Mathur	58	7	3	77	33	29
Skinner	197	10	2	64	44	36
Montie	99	10	9	69	57	—
Giuliani	202	—	12	56	19	0
Totals	864	9	7	60	33	21
Roehrborn	280	—	2	63	36	24
Pagano	261	9	2	57	15	21
Wishnow	188	5	1	79	46	33
Waehre	227	25	—	61	36	29
Vieweg	686	8	2	58	22	15
Stein	633	6	3	72	48	33
Dalbagni	284	10	—	59	29	25
Studer	507	—	4.5	74	52	36
Grossman	154	15	0.6	75	—	28
Totals	3,220	12	2.2	67	35	27

* No residual tumor in cystectomy specimen.

Radical surgery alone provides excellent local control of the primary tumor.

Despite improvements in surgical techniques and perioperative care a sobering analysis of cystectomy series before and after 1985 revealed only modest gains in survival.

<u>cystectomy 5Y OS</u>	<u>historical</u>	<u>contemporary</u>
pT2	60%	67%
pT3	33%	35%
pT4	21%	27%

Metastatic failure rates

pT2	20% - 30%
pT3	40% - 60%
pT4	70% - 90%

Treatment in addition to radical cystectomy is needed for all clinical stages even in patients with the most favorable organ confined (pT0-2) and node negative (N0) invasive tumors.

Table 3. Recurrence-Free and Overall Survival After Radical Cystectomy

Pathologic Stage*	No. of Patients	Probability of Surviving and Remaining Recurrence-Free (<i>P</i> ± SE)			
		Recurrence-Free		Overall Survival	
		5 Years	10 Years	5 Years	10 Years
P ₀ , P _a , P _{is}					
N- [#]	208	.89 ± .02	.85 ± .03	.85 ± .03	.67 ± .04
N+ ^s	5	.60 ± .22	.60 ± .22	.40 ± .22	.40 ± .22
All Pts P ₀ P _a P _{is}	213	.88 ± .02	.85 ± .03	.84 ± .03	.67 ± .04
P1					
N-	194	.83 ± .03	.78 ± .04	.76 ± .03	.52 ± .04
N+	14	.43 ± .13	.43 ± .13	.50 ± .13	.42 ± .13
All Pts P1	208	.80 ± .03	.75 ± .04	.74 ± .03	.51 ± .04
P2					
N-	94	.89 ± .03	.87 ± .04	.77 ± .04	.57 ± .06
N+	21	.50 ± .11	.50 ± .11	.52 ± .11	.52 ± .11
All Pts P2	115	.81 ± .04	.80 ± .04	.72 ± .04	.56 ± .05
P3 _a					
N-	98	.78 ± .05	.76 ± .05	.64 ± .05	.44 ± .06
N+	35	.41 ± .09	.37 ± .09	.40 ± .08	.26 ± .08
All Pts P3 _a	133	.68 ± .04	.65 ± .05	.58 ± .04	.39 ± .05
P3 _b					
N-	135	.62 ± .05	.61 ± .05	.49 ± .04	.29 ± .05
N+	113	.29 ± .05	.29 ± .05	.24 ± .04	.12 ± .04
All Pts P3 _b	248	.47 ± .04	.46 ± .04	.38 ± .03	.22 ± .03
P4 _a					
N-	79	.50 ± .06	.45 ± .07	.44 ± .06	.23 ± .06
N+	58	.33 ± .07	.33 ± .07	.26 ± .06	.20 ± .05
All Pts P4 _a	137	.44 ± .05	.41 ± .05	.33 ± .04	.22 ± .04
Organ-confined†					
N-	594	.85 ± .02	.82 ± .02	.78 ± .02	.56 ± .02
N+	75	.46 ± .06	.44 ± .06	.45 ± .06	.37 ± .06
All Pts	669	.80 ± .02	.77 ± .02	.74 ± .02	.54 ± .02
Extravesical‡					
N-	214	.58 ± .04	.55 ± .04	.47 ± .04	.27 ± .04
N+	171	.30 ± .04	.30 ± .04	.25 ± .04	.17 ± .03
All Pts	385	.46 ± .03	.44 ± .03	.37 ± .03	.22 ± .03
LN- Pts	808	.78 ± .02	.75 ± .02	.69 ± .02	.49 ± .02
LN+ Pts	246	.35 ± .03	.34 ± .03	.31 ± .03	.23 ± .03
Total group	1,054	.68 ± .02	.66 ± .02	.60 ± .02	.43 ± .02

NOTE. Estimated probabilities of recurrence-free and overall survival at 5 and 10 years in 1,054 patients undergoing cystectomy, according to pathologic stage (with or without lymph node involvement) and pathologic subgroups. Probabilities of recurrence-free and overall survival are based on Kaplan-Meier estimates.¹⁵ Plus-minus values are estimates of the SE calculated using Greenwood's formula.¹⁶

Abbreviations: N-, without lymph node involvement (node-negative); N+, with lymph node involvement (node-positive); Pts, patients.

*Pathologic stage is based on 1987 TNM system.¹³

†Organ confined, including P₀, P_a, P_{is}, P1, P2, and P3_a bladder tumors.

‡Extravesical, including P3_b and P4 bladder tumors.

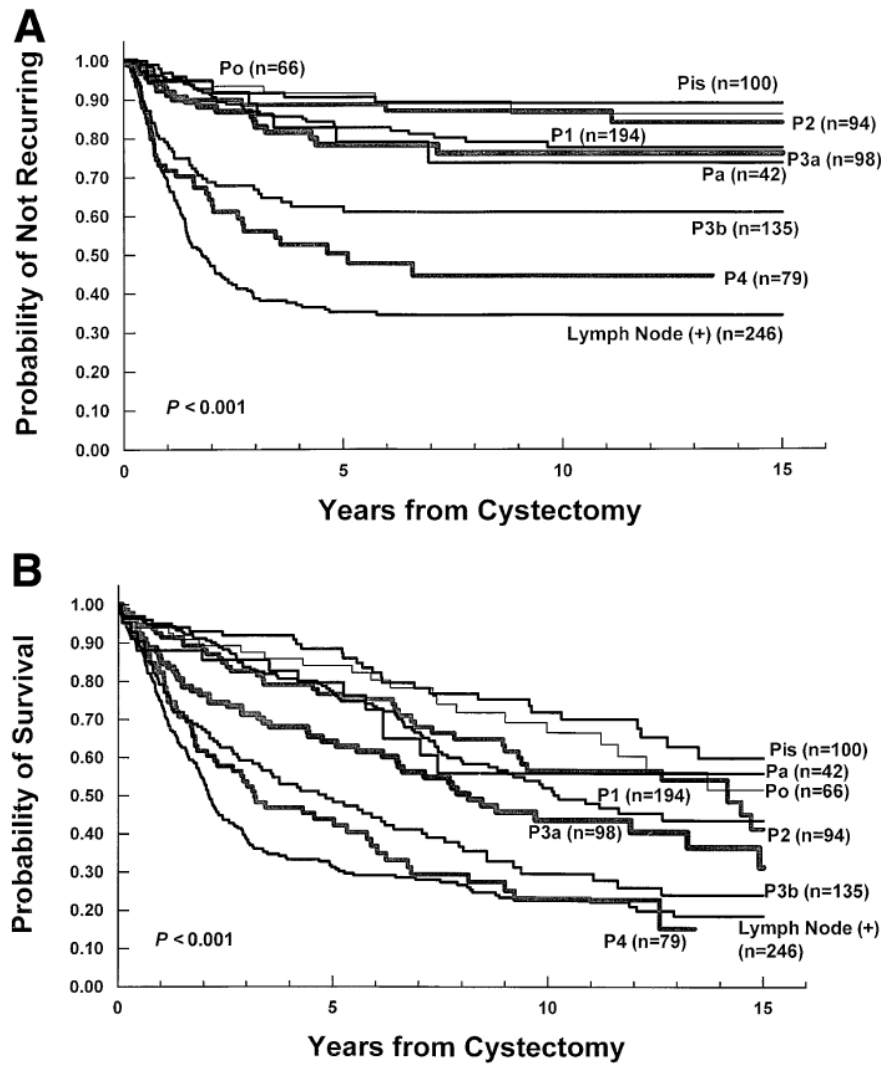


Fig 2. (A) Recurrence-free survival and (B) overall survival in 1,054 patients after radical cystectomy stratified by pathologic stage and lymph node status.

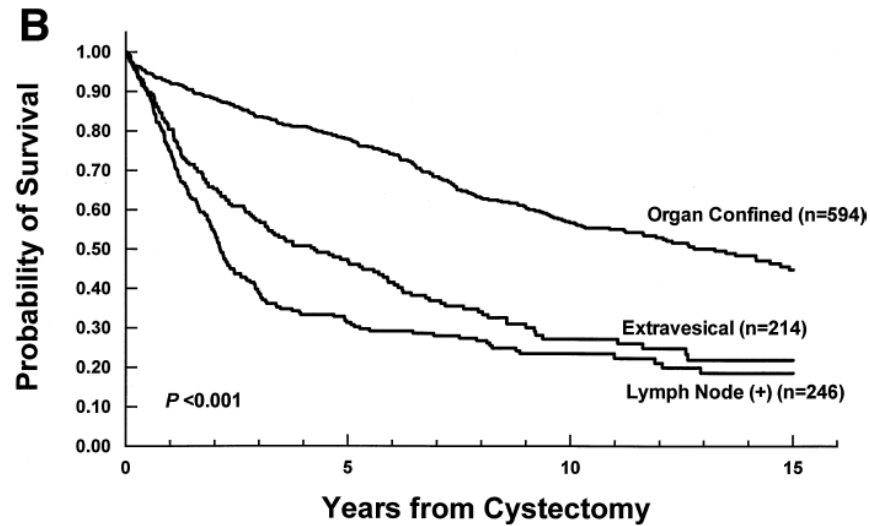
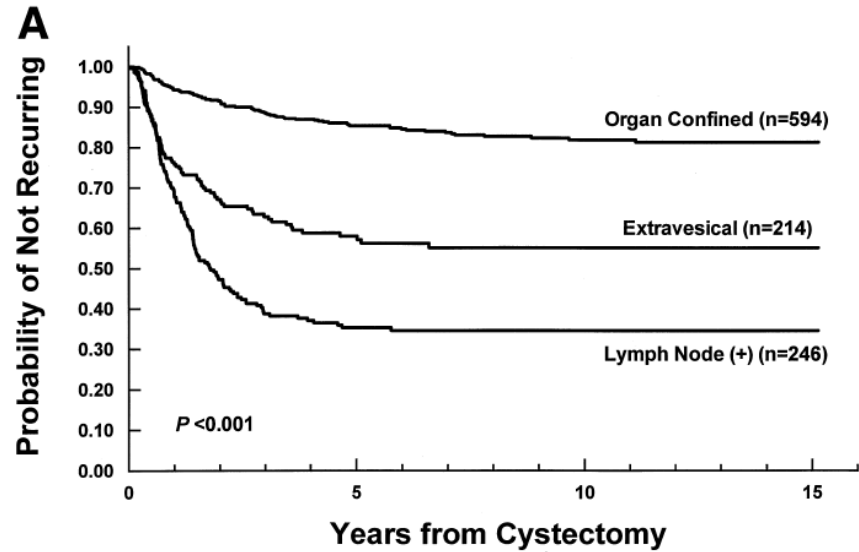


Fig 3. (A) Recurrence-free survival and (B) overall survival in 1,054 patients after radical cystectomy stratified by pathologic subgroups (organ confined, extravesical, and lymph node positive).

“Chemotherapy is now standard practice for localized colon and breast cancer, although it is less effective for these metastatic tumors than for metastatic bladder cancer.”

Metastatic TCC: randomised trials

<u>Author</u>	<u>Chemo</u>	<u>n</u>	<u>RR(%)</u>	<u>med S</u>	<u>Comments</u>
Loehrer	MVAC	126	39	12.5	MVAC > CDDP
	CDDP	120	12	8.2	
Logothesis	MVAC	65	65	12.6	MVAC > CISCA
	CISCA	55	46	10.0	
Von der Maase	MVAC	202	46	14.8	MVAC ~ GC
	GC	203	49	13.8	
Bamias	MVAC	109	54	14.2	MVAC
	DC	111	37	9.3	
Sternberg	HD MVAC	134	72	15.1	HD MVAC > MVAC
	MVAC	129	58	14.9	
Bellmunt	GCP	312	57 (cr15)	15.7	GCP better RR, OS ns
	GC	315	46 (cr10)	12.8	

Metastatic: hi-dose vs classic MVAC

<u>N 263</u>	HD MVAC	MVAC Classic	P
RR %	62	50	.06
CR %	21	9	.009
Alive %	25	13	
Med PFS (mo)	9.5	8.1	
2yS %	37	26	
5yS %	22	14	
Med S (mo)	15.1	14.9	
Cancer death %	65	76	
Mort HR	0.76		borderline sig
Mucositis	10%	17%	
Neut fever	10%	26%	
Thrombocytopenia	20%	17%	

Metastatic: MVAC vs Cis-Gem

	Cis-Gem	MVAC	
OS	13.8 mo	14.8 mo	HR 1.04 (0.82-1.32)
TTP	7.4 mo	7.4 mo	
RR	49%	46%	Sim
G4-3 neutropenia	71%	82%	
Neutropenic fever	2%	14%	
Neutropenic sepsis	1%	12%	
G3-4 mucositis	1%	22%	
Toxic death	1%	3%	
G3-4 anemia	More		No clinical sequelae
G3-4 thrombocytopenia	More		
Hospital admissions (no.)	9	49	
Hospital admissions (days)	33	272	
QOL	Surprisingly similar except better fatigue index for cis-gem.		

Neoadjuvant

PROS

- Tolerance is better than adjuvant
- Does not increase periop morbidity vs adjuvant
- In vivo drug sensitivity testing
 - Prognostication based on response
 - Further adjuvant rx ?
- May downstage tumors, allowing for technically easier surgery.
- Evidence: 2 large randomised trials, 1 meta-analysis

CONS

- Evaluating response is difficult
- Discrepancy between clinical and pathologic staging
 - expected in 30%
- Delay in cystectomy/RT in patients who do not respond or progress.
 - an interval >12 wk between diagnosis & cystectomy a/w poorer outcome

Table 1 – Randomized phase 3 trials of neoadjuvant chemotherapy

Study group	Neoadjuvant arm	Standard arm	Patients (n)	Survival
Australia/United Kingdom [54]	DDP/RT	RT	255	No difference
Canada/NCIC [55]	DDP/RT or preop RT + Cyst	RT or preop RT + Cyst	99	No difference
Spain (CUETO) [56]	DDP/Cyst	Cyst	121	No difference
EORTC/MRC [14]	CMV/RT or Cyst	RT or Cyst	976	5.5% difference in favor of CMV
SWOG [57]	M-VAC/Cyst	Cyst	298	Trend in benefit with M-VAC ($p = 0.06$)
Italy (GUONE) [18]	M-VAC/Cyst	Cyst	206	No difference
Italy (GISTV) [58]	M-VEC/Cyst	Cyst	171	No difference
Genoa [59]	DDP/5FU/RT/Cyst	Cyst	104	No difference
Nordic 1	ADM/DDP/RT/Cyst	RT/Cyst	311	No difference, 15% benefit with ADM + DDP in T3-T4a
Nordic 2 [19]	MTX/DDP/Cyst	Cyst	317	No difference
Abol-Enein et al [60]	CarboMV/Cyst	Cyst	194	Benefit with CarboMV

5FU = fluorouracil; ADM = doxorubicin (Adriamycin); CarboMV = carboplatin, methotrexate, and vinblastine; CMV = cisplatin, methotrexate, and vinblastine; CUETO = Club Urológico Español de Tratamiento Oncológico; Cyst = cystectomy; DDP = cisplatin; EORTC = European Organization for Research and Treatment of Cancer; GISTV = Gruppo Italiano per lo Studio dei Tumori della Viscica (ie, Italian Bladder Cancer Study Group); GUONE = Gruppo Uro-Oncologico del Nord Est (ie, Northeast Uro-oncological Group); MRC = Medical Research Council; MTX = methotrexate; M-VAC = methotrexate, vinblastine, doxorubicin (Adriamycin), and cisplatin; M-VEC = methotrexate, vinblastine, epirubicin, and cisplatin; NCIC = National Cancer Institute of Canada; RT = radiation therapy; SWOG = Southwest Oncology Group.

Neoadjuvant: SWOG/INT

Table 4. Stratified and Unstratified Survival Analysis.*

Variable	Median Survival		P Value†
	M-VAC and Cystectomy	Cystectomy Alone	
	<i>months</i>		
Unstratified	77	46	0.05
Primary analysis, stratified according to age and tumor stage			0.06
Stratified according to age			0.05
Age <65 yr	104	67	
Age ≥65 yr	61	30	
Stratified according to tumor stage			0.05
T2	105	75	
T3 or T4a	65	24	

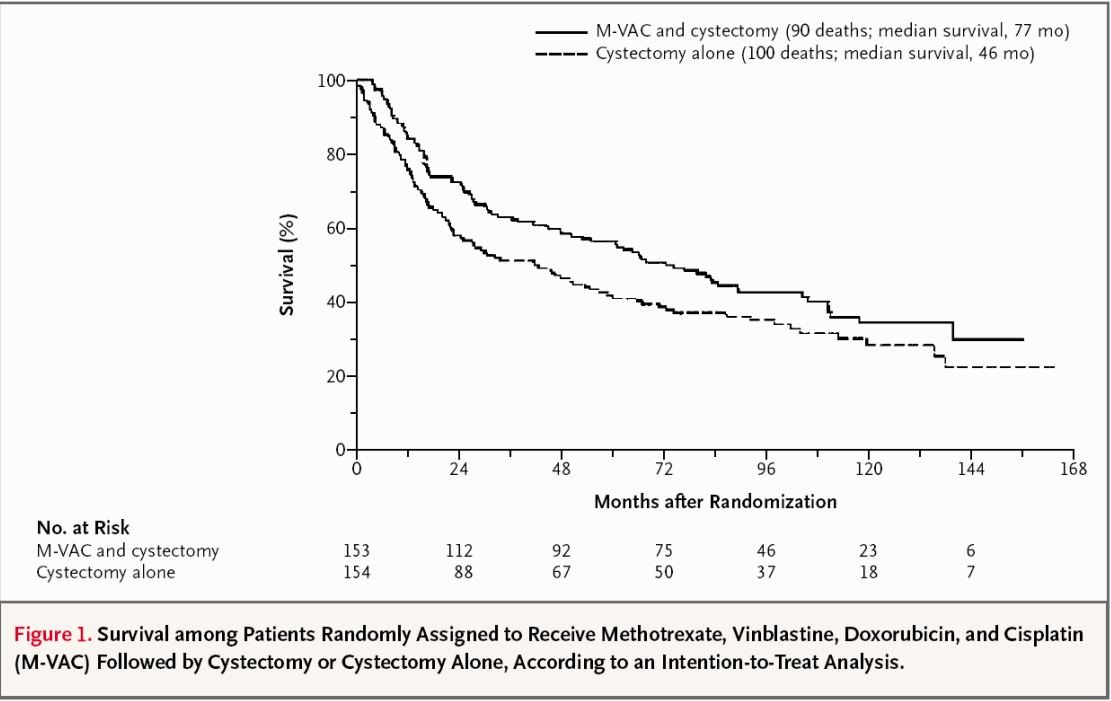


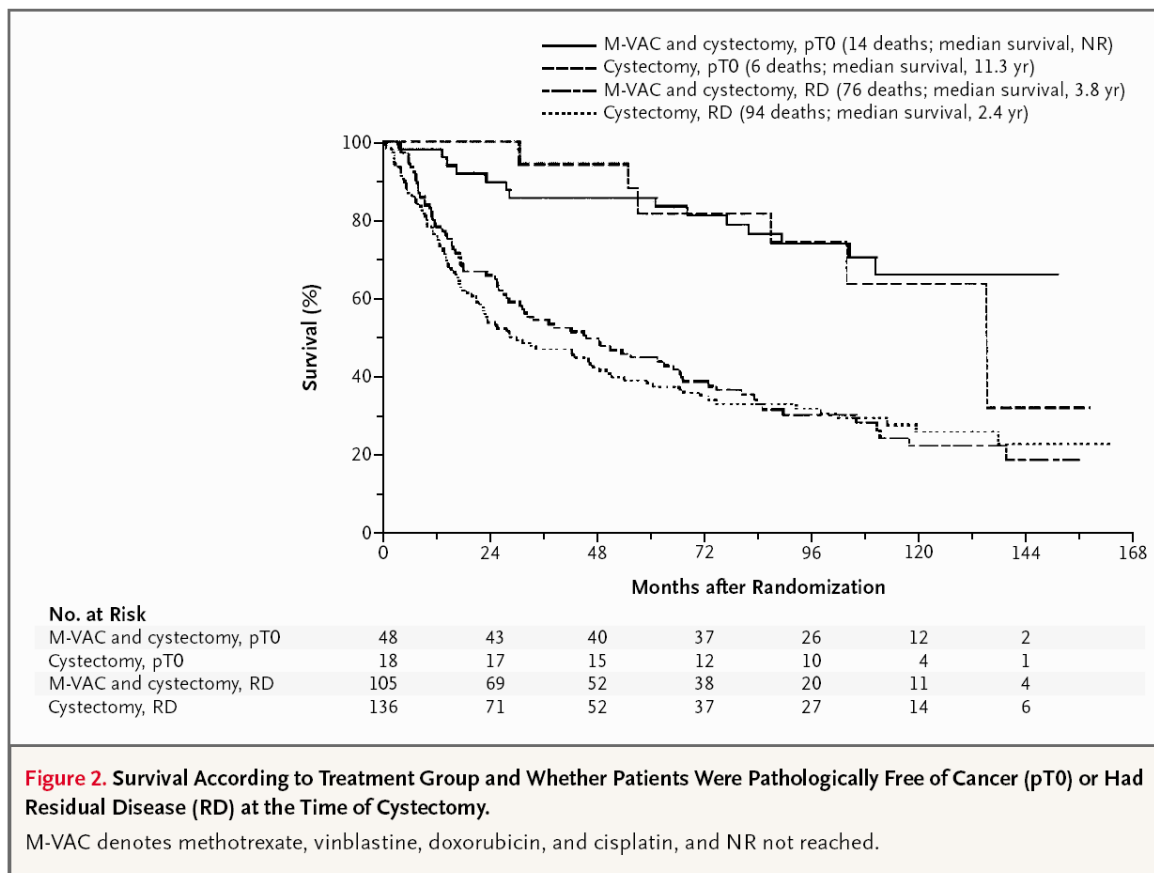
Figure 1. Survival among Patients Randomly Assigned to Receive Methotrexate, Vinblastine, Doxorubicin, and Cisplatin (M-VAC) Followed by Cystectomy or Cystectomy Alone, According to an Intention-to-Treat Analysis.

*chemo did not affect ability to proceed with op or post op cx's

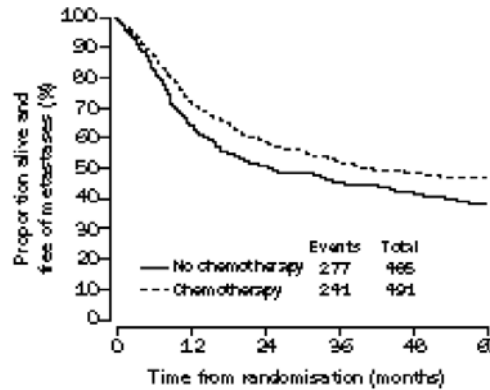
Neoadjuvant: SWOG/INT

In both groups, improved survival was associated with the absence of residual cancer in the cystectomy specimen.

Significantly more patients in the combination-therapy group had no residual disease than patients in the cystectomy group (38 percent vs. 15 percent, $P < 0.001$).



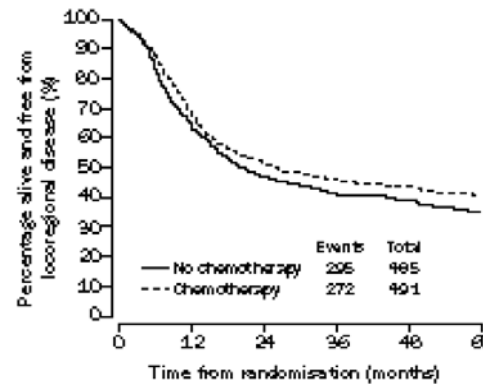
Neoadjuvant: MRC/EORTC



Patients at risk

	0	12	24	36	48	60
No chemotherapy	465	299	229	169	121	75
Chemotherapy	491	337	260	190	134	61

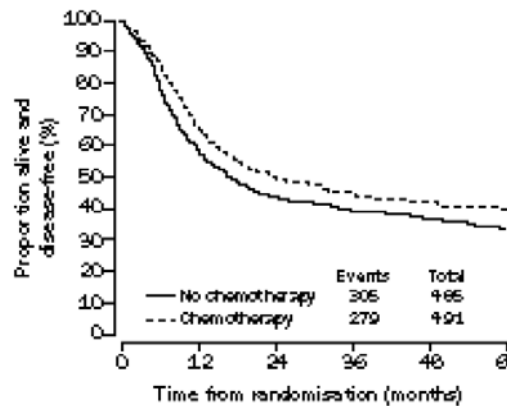
Figure 4: Metastasis-free survival



Patients at risk

	0	12	24	36	48	60
No chemotherapy	465	301	209	154	109	61
Chemotherapy	491	324	232	168	119	71

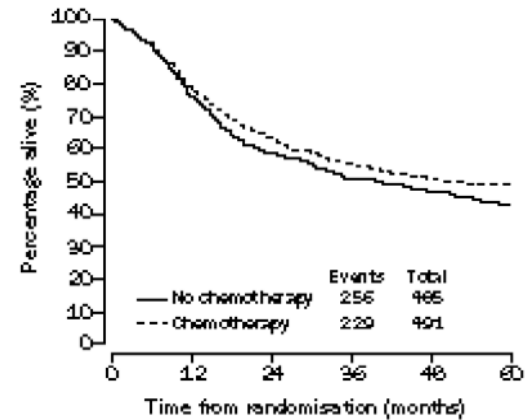
Figure 5: Locoregional disease-free survival



Patients at risk

	0	12	24	36	48	60
No chemotherapy	465	271	192	145	102	61
Chemotherapy	491	308	222	163	116	71

Figure 6: Disease-free survival



Patients at risk

	0	12	24	36	48	60
No chemotherapy	465	355	257	187	132	60
Chemotherapy	491	372	283	200	139	93

Figure 3: Overall survival

Neoadjuvant: MRC/EORTC

	<u>LANCET 99</u>	<u>ASCO UPDATE 2002</u>	
Median follow-up	4.0 years	7.4 years	
Total Deaths	485		
	78.6% of deaths due to TCC		
Chemo mortality	1%		
Cystectomy mort	3.7%.		
Survival	<u>3Y OS</u>	<u>5Y OS</u>	<u>8Y OS</u>
Chemo	55.5%	50%	43%
no chemo	50.0%	44%	37%
difference	5.5%	maintained	
95% CI	0.5-11.0		
	p=0.075	p=0.048	
Med S	Chemo 44 mo		
	no-chemo 37.5 mo		
No tumor on Cystectomy	Chemo 32.5%		
	no chemo 12%		
Neoadj chemo did not increase rate of			
	- postop complications.		
	- morbidity during/immediately after RT		

Neoadjuvant: MRC/EORTC

The improvement was slightly less than the magnitude originally sought in the trial.

CMV inferior to MVAC ? - no randomised comparison

Local therapy included radiation (?inferior to cystectomy):

chemotherapy	42%
no chemo	43%

There was no evidence to suggest that the effect of chemotherapy was more or less for patients treated with cystectomy than for those treated with RT. (exploratory subgroup analysis)

Neoadjuvant: Meta-analysis

11 trials, 3005 patients;
98% of all patients from known eligible randomised controlled trials.

Results provide the best available evidence in support of the use of neoadjuvant platinum-based combination chemotherapy

Table 1

Results for survival and disease-free survival overall and for trials grouped by chemotherapy type

Endpoint	Chemotherapy type	Number of patients/events	HR (95% CI)	Effect <i>p</i> -value	Absolute benefit at 5 yrs (95% CI)	Interaction <i>p</i> -value
Overall survival	Single agent platinum	261/376	1.15 (0.90–1.47)	0.26	–5% (–14% to 4%)	0.029
	Platinum based combinations	1430/2433	0.86 (0.77–0.95)	0.003	5% (2% to 9%)	
	All trials	1691/2890	0.89 (0.81–0.98)	0.022	4% (0% to 7%)	
Disease-free survival	Single agent platinum	166/217	1.14 (0.83–1.55)	0.42	–5% (–16% to 7%)	0.024
	Platinum based combinations	1681/2629	0.78 (0.71–0.86)	<0.0001	9% (5% to 12%)	
	All trials	1847/2846	0.81 (0.74–0.89)	<0.0001	8% (4% to 11%)	

Neoadjuvant: Meta-analysis

	(no. events/no. entered)		O-E	Variance
	CT	Control		
Single agent platinum				
Wallace [2]	59/83	50/76	2.74	27.18
Martinez-Pineiro [3]	43/62	38/59	0.33	20.11
Raghavan [2]	34/41	37/55	5.85	16.51
Sub-total	136/186	125/190	8.92	63.80
Platinum-based combinations				
Cortesi unpublished	43/82	41/71	-1.87	20.84
Grossman [9]	98/158	108/159	-13.61	51.00
Bassi [5]	53/102	60/104	-1.95	28.13
MRC/EORTC [6]	275/491	301/485	-23.69	143.61
Malmström [8]	68/151	84/160	-9.97	37.94
Sherif [8]	79/158	90/159	-6.37	42.18
Sengeløv [7]	70/78	60/75	1.79	31.96
Sub-total	686/1220	744/1213	-55.67	355.65
Total	822/1406	869/1403	-46.75	419.45

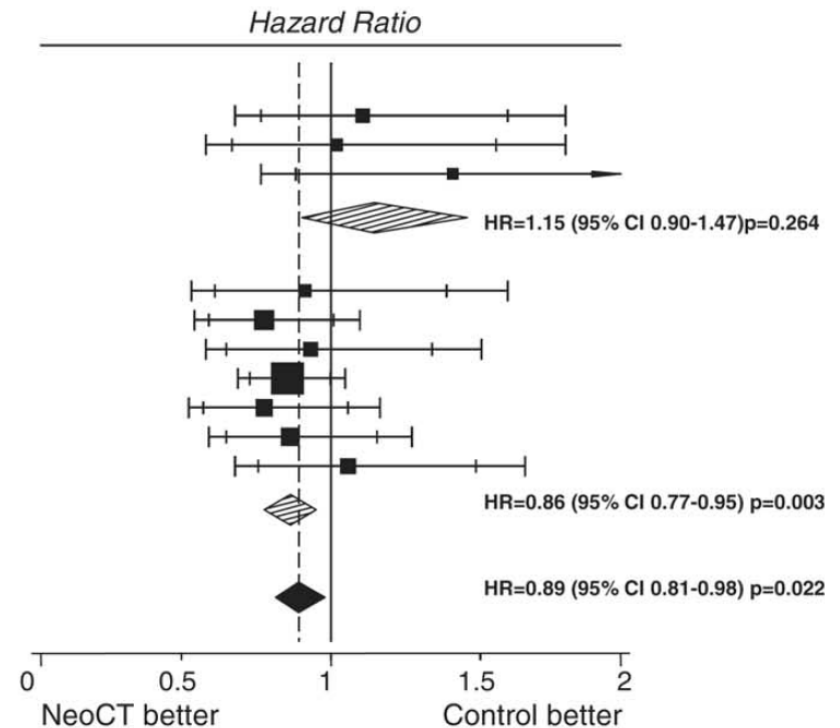
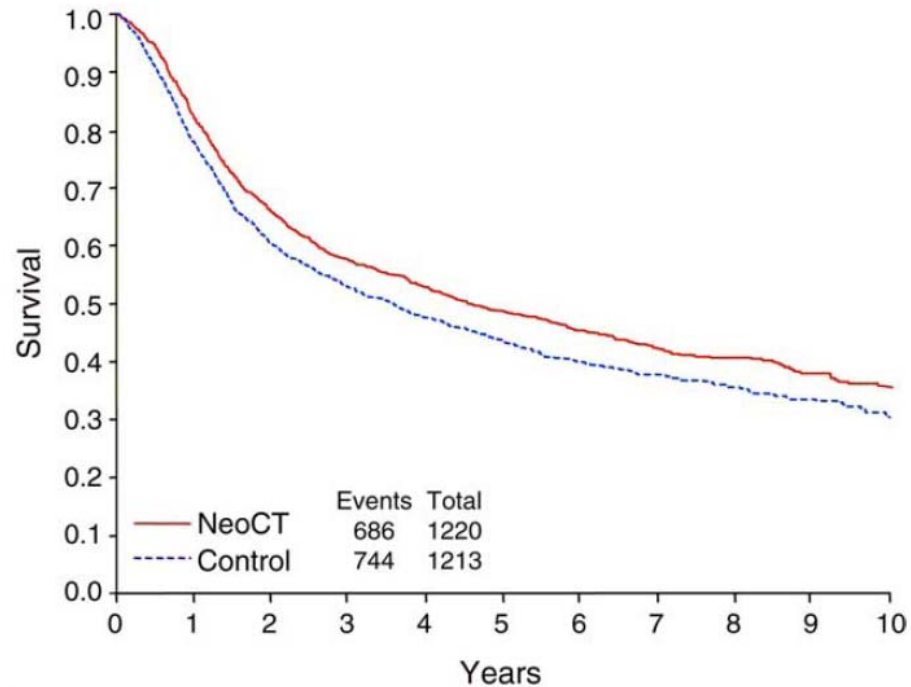


Fig. 1. Hazard ratio plot for overall survival CT = chemotherapy. O-E = observed minus expected events. Each trial is represented by a square, the centre of which gives the hazard ratio for that trial. Size of the square is proportional to the information in that trial. Ends of horizontal bars denote the 99% CI and inner bars mark the 95% CI. Trials are ordered chronologically by start date (oldest first). The black diamond gives the overall hazard ratio for the combined results of all trials; the centre denotes the hazard ratio, the extremities the 95% CI. The shaded diamonds denote the hazard ratios for the trial groups; the centre denotes the hazard ratio, the extremities the 95% CI. Single-agent platinum: Heterogeneity $\text{Chi}^2 = 1.11$ ($p = 0.57$); Inconsistency $I^2 = 0\%$ Platinum-based combinations Heterogeneity $\text{Chi}^2 = 2.81$ ($p = 0.83$); Inconsistency $I^2 = 0\%$ All trials: Heterogeneity $\text{Chi}^2 = 8.67$ ($p = 0.57$); Inconsistency $I^2 = 0\%$.

Neoadjuvant: Meta-analysis



Patients at risk		0	1	2	3	4	5	6	7	8	9	10
NeoCT	1220	972	770	659	585	510	403	284	201	140	92	
Control	1213	922	705	608	527	448	338	241	171	116	77	

Fig. 2. Overall survival curve (platinum based combination chemotherapy trials only).

Neoadjuvant: evidence

Author	ph/n.	entry	rx	outcomes	P
Hall '02 MRC/ EORTC	III,976	T2(G3), T3, T4a, N0/NX	neoadj CMVx3 +localrx vs localrx (RT/cystect/both)	TTP improved by 8% 3/5/8yS better by 5.5% Survival improved locoreg/mets control better pCR 33 v 12%	.048
Grossman '03 INT 0080	III, 307	T2-T4a	neoadj MVACx3 +cystec vs cystec	pCR 38 v 15% medS 77 v 46mo 5yS 57 v 43%	<.001 .06 .06
ABC collab '05	meta-analys 11rTrials n 3005 (updated to include INT 0080)		neoadj chemo + localrx vs localrx	Platinum-based combination chemo: Improved OS HR 0.86 (0.77-0.99) 5% OS benefit at 5y (45->50%) 9% DFS benefit at 5y	.003

Adjuvant

PROS

- Path staging
 - Selection of highest risk patients
 - Avoid overtreatment of lower risk patients
- Immediate surgery
 - Acceptable morbidity, improved techniques/QOL (orthotopic neobladder)
 - May not respond or even progress on chemo
- Molecular prognostic or predictive markers

CONS

- Cannot tell 'response': clinical end-point is time to recurrence
- Difficult to give post-op e.g. elderly
- Delay in treatment of micromets
- Only tested in -ve surg margins
- Relative lack of evidence
 - Small trials
 - Inappropriate early stopping
 - Inappropriate statistical analyses
 - Suboptimal chemo
- Difficult accrual !

Table 3 – Adjuvant chemotherapy trials following cystectomy

Investigator	Year	Regimen	Chemo	No chemo	Results
Logothetis et al [42]	1988	CISCA	62	71	Benefit but not randomized
Skinner et al [41]	1991	CAP	47	44	Benefit few patients received therapy
Stockle et al [45,46]	1992	M-VAC/M-VEC	23	26	Benefit no treatment at relapse
Studer et al [47]	1994	DDP	40	37	No benefit
Bono et al [43]	1995	CM	48	35	No benefit for N0
Freiha et al [48]	1996	CMV	25	25	Benefit in relapse-free survival
Otto et al [44]	2001	M-VEC	55	53	No benefit
Cognetti et al [49]	2008	GC	97	86	No benefit for N0 or N+

CAP = cyclophosphamide, doxorubicin (Adriamycin), and cisplatin; CISCA = cisplatin, cyclophosphamide, and doxorubicin (Adriamycin); CM = cisplatin and methotrexate; CMV = cisplatin, methotrexate, and vinblastine; DDP = cisplatin; GC = gemcitabine and cisplatin; M-VAC = methotrexate, vinblastine, doxorubicin (Adriamycin), and cisplatin; M-VEC = methotrexate, vinblastine, epirubicin, and cisplatin.

Adjuvant: evidence for

Author	ph/n.	entry	rx	outcomes	P	
Lehmann (Stockle) '06 Germany	rand,49	pT3b,pT4a pN1-2	cystec->3x MVAC/MVEC vs cystec	10yPFS 44 v 13% 10yDSS 42 v 17% 10yOS 27 v 17% LN+ : 27 v 92% progression	HR 2.84 HR 2.52 HR 1.75	.002 .007 .069
Skinner '91 California	rand,91	pT3-4, pN+	cystec->4x chemo vs cystec (cis-doxo-cycloph, others)	3yDF 70 v 46% medS 4.3 v 2.4 y 3yS 66 v 50%		.001 .006 .09

Adjuvant: evidence against

Author	ph/n.	entry	rx	outcomes	P
Studer '94 Swiss	rand, 77		cystec->3 x cisplatin vs cystec	no difference in survival	
Freiha '96 Stanford	rand,50	p3b-4 NO-1	cystec->4 x CMV	FFP 37 v 12mo medS 63 v 36mo relapse 52 v 75%	.01 .32

Adjuvant: evidence against

Adjuvant chemotherapy (AC) with cisplatin + gemcitabine (CG) versus chemotherapy (CT) at relapse (CR) in patients (pts) with muscle-invasive bladder cancer (MIBC) submitted to radical cystectomy (RC). An Italian multicenter randomised phase III trial.

2001-2007, 194 pts, pT2G3, pT3-4, N0-2 TCC bladder
Stratified according to site and pN status (pN0 vs pN1-2).
Primary endpoint OS, secondary endpoint DFS
median follow up 32.5 months (range 25.5-39)

	<u>No chemo (n 92)</u>	<u>Chemo (n 102, 4 x Cis-Gem)*</u>
Baseline characteristics	similar in the 2 arms: median age 64 yrs pT1-2 28%, pT3-4 72% pN0 53%, pN1 21%, pN2 26%.	64% of pts received 4 courses and 77% at least 3. No CT-related death.
3-year OS	67% (\pm 6% SE)	48% (\pm 6% SE)
3-year DFS	47% (\pm 6% SE)	35% (\pm 6% SE)

No significant difference in OS and DFS between arm A and B were found.

Conclusions: These preliminary results seem to indicate that AC did not improve OS and DFS in these pts.

*Further randomized in 2 subgroups with G 1,000 mg/m² day 1,8 and 15 + C 70 mg/m² day 2 (Arm B2: 50 pts) or G as above + C 70 mg/m² day 15(Arm B15: 52 pts). Q4 wk cycles.
Main toxicities were also similar in the two CT arms except for thrombocytopenia Gr 3-4 25 vs 5% (p = 0.01) for arm B2 and B15 respectively.

Adjuvant: Meta-analysis

11 randomized controlled trials of adjuvant chemo,
but individual patient survival data from only 6.
N 491, events 283
66% of all patients from eligible trials

Overall HR for survival of 0.75 (95% CI 0.60–0.96, $p = 0.019$)

25% relative reduction in the risk of death for adjuvant chemotherapy

9% improvement in absolute survival at 3 yr.

(11% improvement for cisplatin combination chemo.)

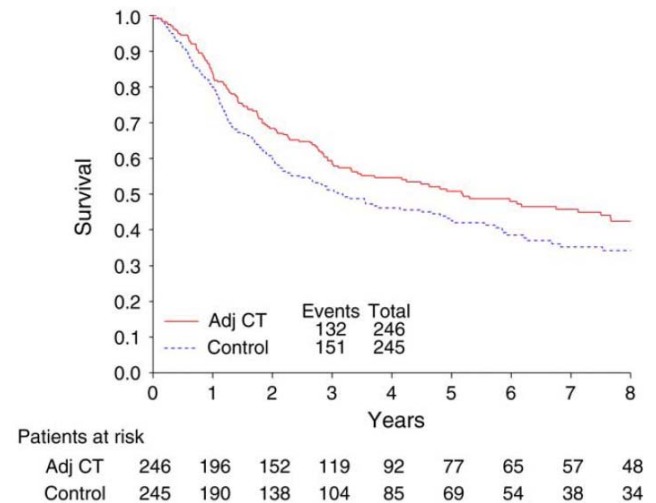


Fig. 2. Kaplan-Meier curve for survival (All trials).

Adjuvant: Meta-analysis

	(no. events/no. entered)		O-E	Variance
	Adj CT	Control		
Single agent cisplatin				
Studer	23/46	22/45	0.23	11.03
Sub-total	23/46	22/45	0.23	11.03
Cisplatin-based combinations				
Skinner	34/50	40/52	-5.24	18.39
Bono	14/43	23/47	-3.91	9.04
Freiha	13/26	17/25	-2.18	7.39
Stockle	20/26	20/23	-5.48	9.07
Otto	28/55	29/53	-2.86	14.11
Sub-total	109/200	129/200	-19.66	58.00
Total	132/246	151/245	-19.43	69.03

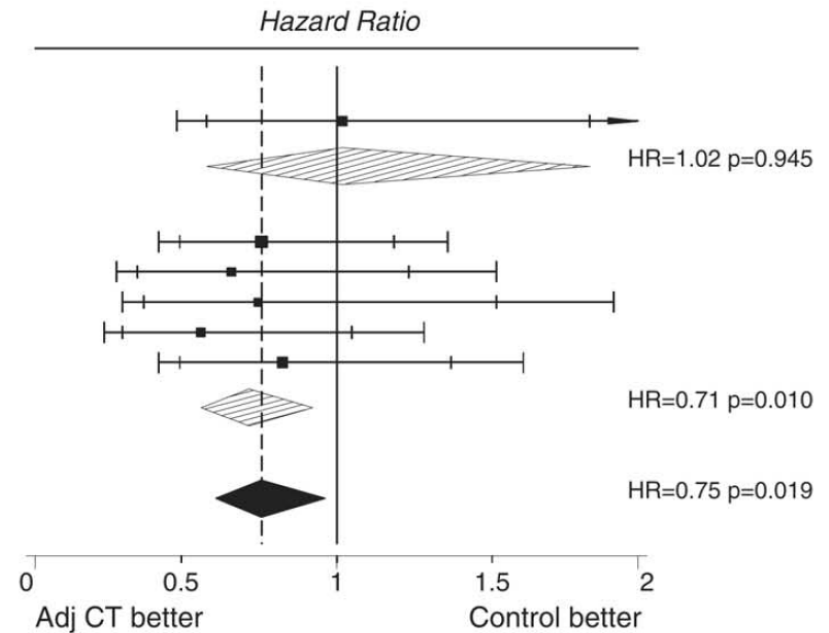


Fig. 1. Hazard ratio plot for survival. Each individual trial is represented by a square, the centre of which denotes hazard ratio for that trial; extremities of horizontal bars denote 99% CI and inner bars mark 95% CI. Size of square is directly proportional to amount of information in the trial. The black diamond gives the overall hazard ratio for combined results of all trials; the centre denotes hazard ratio and the extremities the 95% CI. The shaded diamonds represent hazard ratios for the trial groups; the centre denotes the hazard ratio and the extremities the 95% CI. Trials are ordered chronologically by date of start of trial (oldest first).

Adjuvant: Meta-analysis

But analysis hampered by underpowered survival curves, early stoppage, patients not receiving allocated treatment/salvage chemo etc.

Problems with interpretation of these results.

Best evidence available, but insufficient on which to base treatment decision.

Adjuvant: others

Author	ph/n.	entry	rx	outcomes
SWOG	III	pT1-2 stratified by p53	cystec ->3 x MVAC cystec	no difference in 5YRFS irresp of p53 or chemo
EORTC	III	pT3-4 or pN+	immed adj MVAC/GC vs sim chemo at relapse	ongoing

Neoadjuvant chemo b4 RT ?

Author	ph/n.	entry	rx	outcomes	P
Shipley '98 RTOG 8903	III,123	T2-T4aNx (T2:38,39%)	2CMV-> cis-40Gy vs cis-40Gy (cis=100mg/m ² q3wk x2) after 40Gy->assess: CR→ to 65Gy+1more cis no CR→ cystec	5yOS 48 v 49% dist mets 33 v 39% 5yS w bladder 36 v 40% no increase CR rate <u>reasons</u> ? *1. about 40% T2 2. 74% visibly complete TURBT 3. 71% total accrual 4. neoadj arm poorly tolerated (74%completion)	ns ns ns
ABC '05	meta-analy			* no evidence of a difference in the effect of platinum-based combination chemo when the trials were grouped according to whether they had used cystectomy alone, RT alone or in combination with cystectomy as the local treatment (interaction p = 0.656).	

Neoadjuvant vs Adjuvant ?

N 140 , med f/u 6.8yr

Hi risk: T2 with LVI onwards but exclude clin N+

	<u>2MVAC-->cystect</u> <u>-->3MVAC</u>	<u>cystectomy-->5 MVAC</u>	
Disease-free(med f/u)	56%	60%	NS
+ve surg margins	2%	11%	
≥2 cycles given	97%	77%	
Chemo ...	did not incr	<u>adj chemo delays</u>	
	periop morbidity	planned: <84POD	
		actual: av 103-114 POD	
	40% path no tumor (12% relapse)		
	if pLN+, relapse 86%	if pLN+, 40% survival !	
		clinical understaging common	
		- LVI on TURBT	
		- w.r.t. LNs	
		clinical overstaging uncommon	

Patients with continent diversions were generally catheterized to minimize methotrexate reabsorption.
 Patients with orthotopic neobladders were irrigated at least every 4 hours to prevent mucous plugging
 and again to minimize methotrexate reabsorption.

Neoadjuvant vs Adjuvant ?

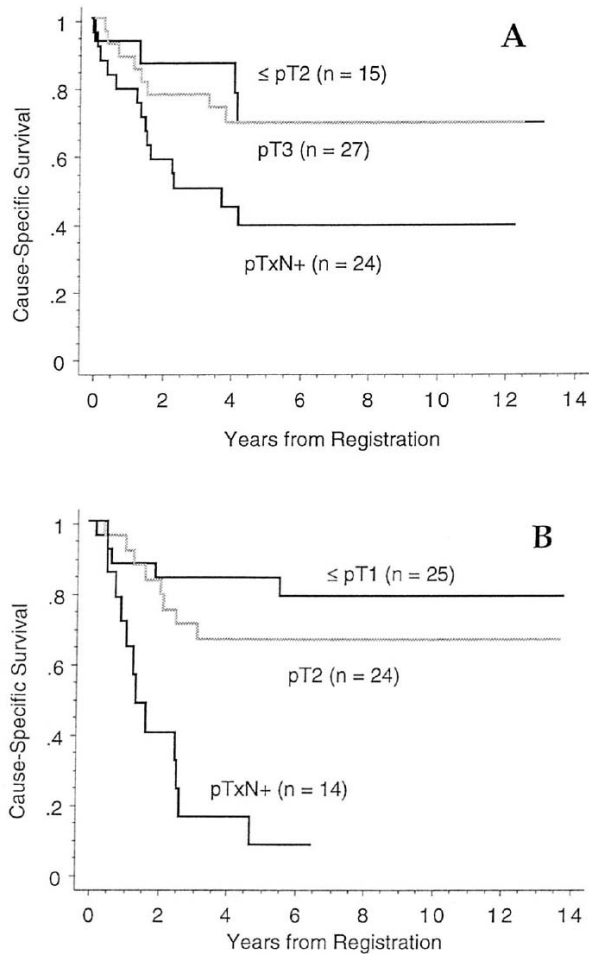


Fig 1. (A) Cause-specific survival by pathologic stage among 66 patients with bladder cancer undergoing initial surgery. For (pT2 and pT3) versus pTxN+, $P = .011$. (B) Cause-specific survival by pathologic stage among 63 patients undergoing cystectomy after 2 cycles of M-VAC chemotherapy. For stage \leq pT2 versus pTxN+, $P < .0001$.

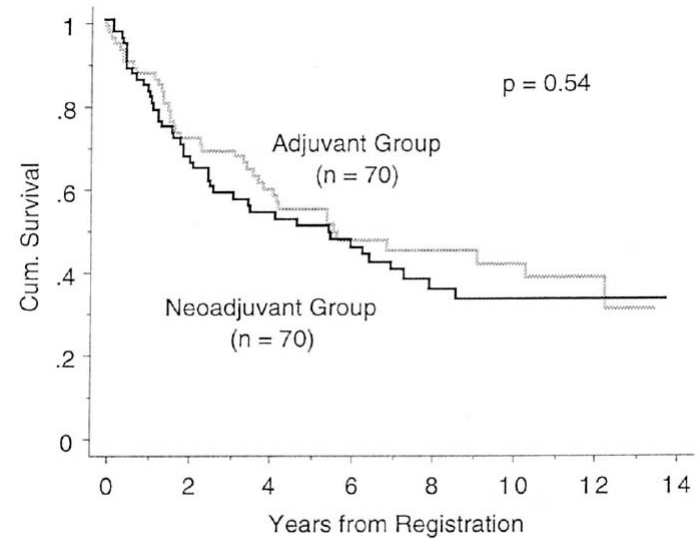


Fig 2. Overall survival of all 140 registered patients by assigned therapy.

Neoadjuvant in Locally Advanced Unresectable

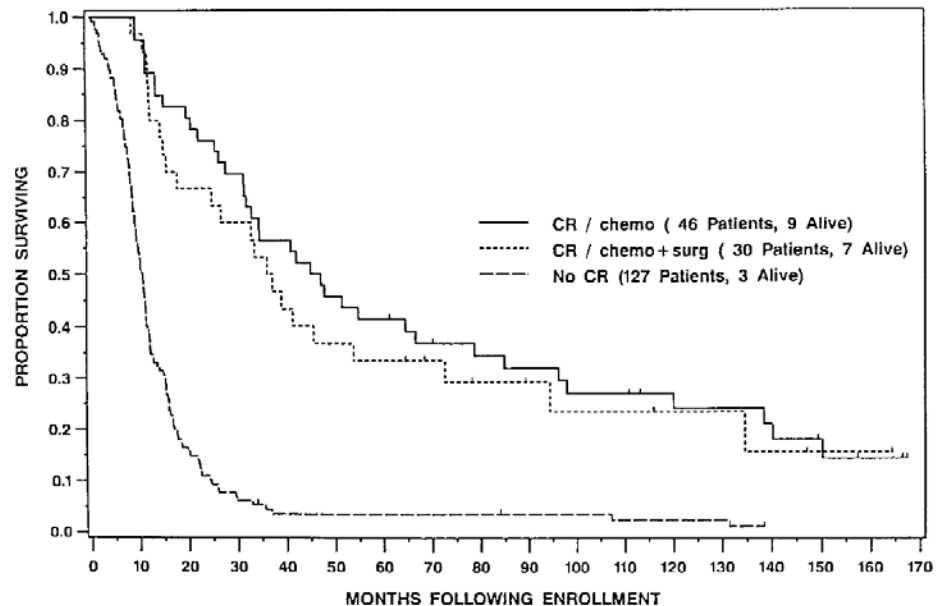
Table 3. Postchemotherapy Surgery Outcomes for Patients With Baseline Extent of Disease: Unresectable Primary Tumor (four patients)

	No. of Patients	Response to M-VAC	Surgical Procedure	Disease at Surgery	Alive at 5 Years
Residual cancer (CR-chemotherapy-plus-surgery)	3	CR (1), PR (2)	Cystectomy (3)	Primary site (3)	2/3
No residual cancer (CR-chemotherapy)	1	CR	Cystectomy (1)	0	1/1

NOTE. Numbers in parentheses indicate the number of patients.

Table 4. Postchemotherapy Surgery Outcomes for Patients With Baseline Extent of Disease: Primary Tumor Plus Regional Lymph Nodes (16 patients)

	No. of Patients	Response to M-VAC	Surgical Procedure	Disease at Surgery	Alive at 5 Years
Residual cancer (CR-chemotherapy-plus-surgery)	9	PR (7), NR (1), not assessable (1)	Cystectomy (9)	Primary site* (9), lymph node (2)	3/9
No residual cancer (CR-chemotherapy)	6	CR (3), PR (2), not assessable (1)	Cystectomy (4), partial cystectomy (2)	0	3/6
Unresectable disease	1	NR (1)	Ileal diversion (1)	T4b	0/1



Conclusions / Q&A

1. **Am I comfortable with giving Neoadjuvant chemo?**

- Yes

2. **Will Adjuvant chemo ever be proven effective?**

- Maybe not ...
- But I offer it case to case

3. **Which chemo to use?**

- Cis-Gem favorite
- I consider HD MVAC for young, fit patients with higher risk disease

4. **If bladder-sparing approach?**

- Consider neoadjuvant chemo for high risk pts