National Cancer Institute

Overview of Bladder Cancer

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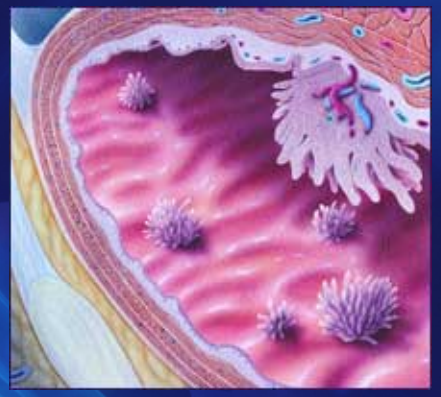
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Epidemiology



- 4th most common malignancy in men and the 9th most common in women
- Estimated 70,530 new cases and 14,680 deaths in the year 2010
- Median age is 68 years
- 90% over age 55, > 50% over age 73
- 3:1 male to female ratio

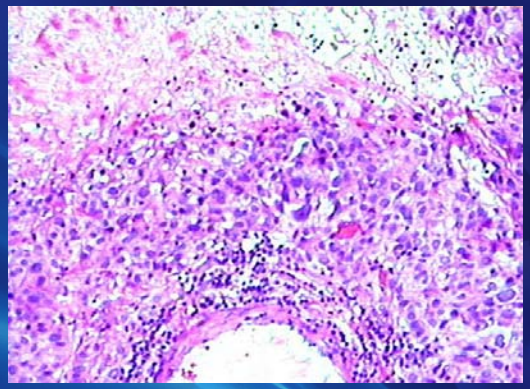
Risk Factors

- Smoking: accounts 50% in US, 3-5 folds higher risk in smokers.
- Aromatic amines, certain occupations: leather/rubber/painting (analine dyes, vinyl, etc)
- Prior pelvic irradiation
- Prior cyclophosphamide
- Schistosomiasis (squamous cell carcinoma and TCC)
- Chronic cystitis (squamous cell ca)
- HNPCC (with upper tract tumors)

Molecular Genetics

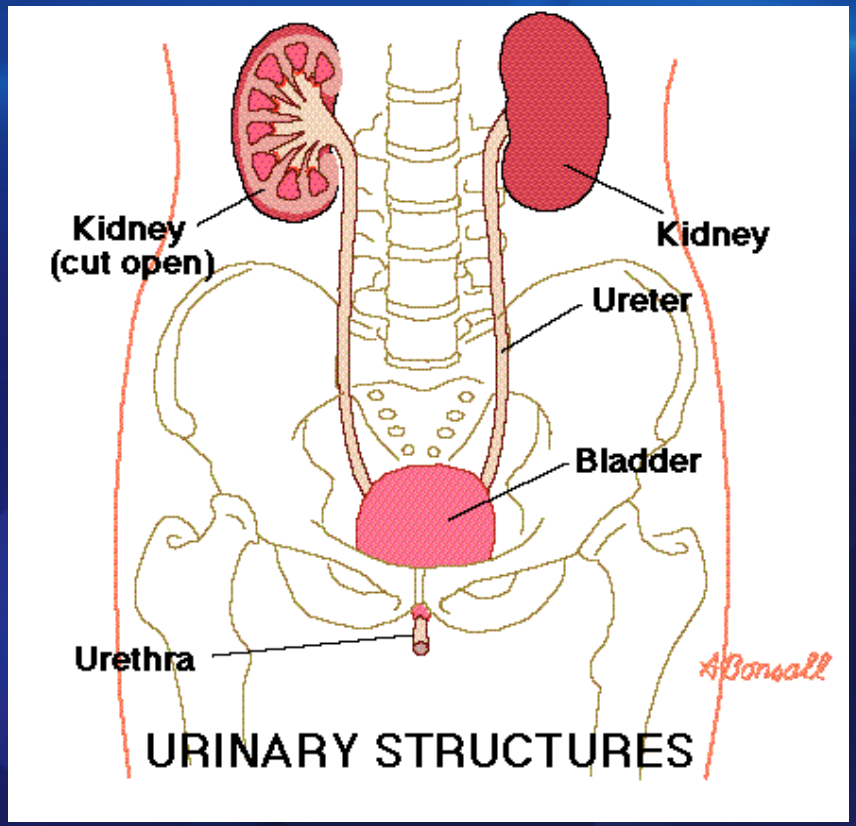
- No specific genetic abnormality that is diagnostic of bladder cancer
- Involved in tumorogenesis:
  - p53 mutations
  - Rb
  - deletions on chromosome 9
  - overexpression of c-erb-B2
  - H-*ras* mutations

Histology



Transitional Cell Carcinoma	90%
Squamous Cell Carcinoma	5%
Adenocarcinoma	0.5-2%
Small Cell Carcinoma	<1%

Urothelial Carcinoma



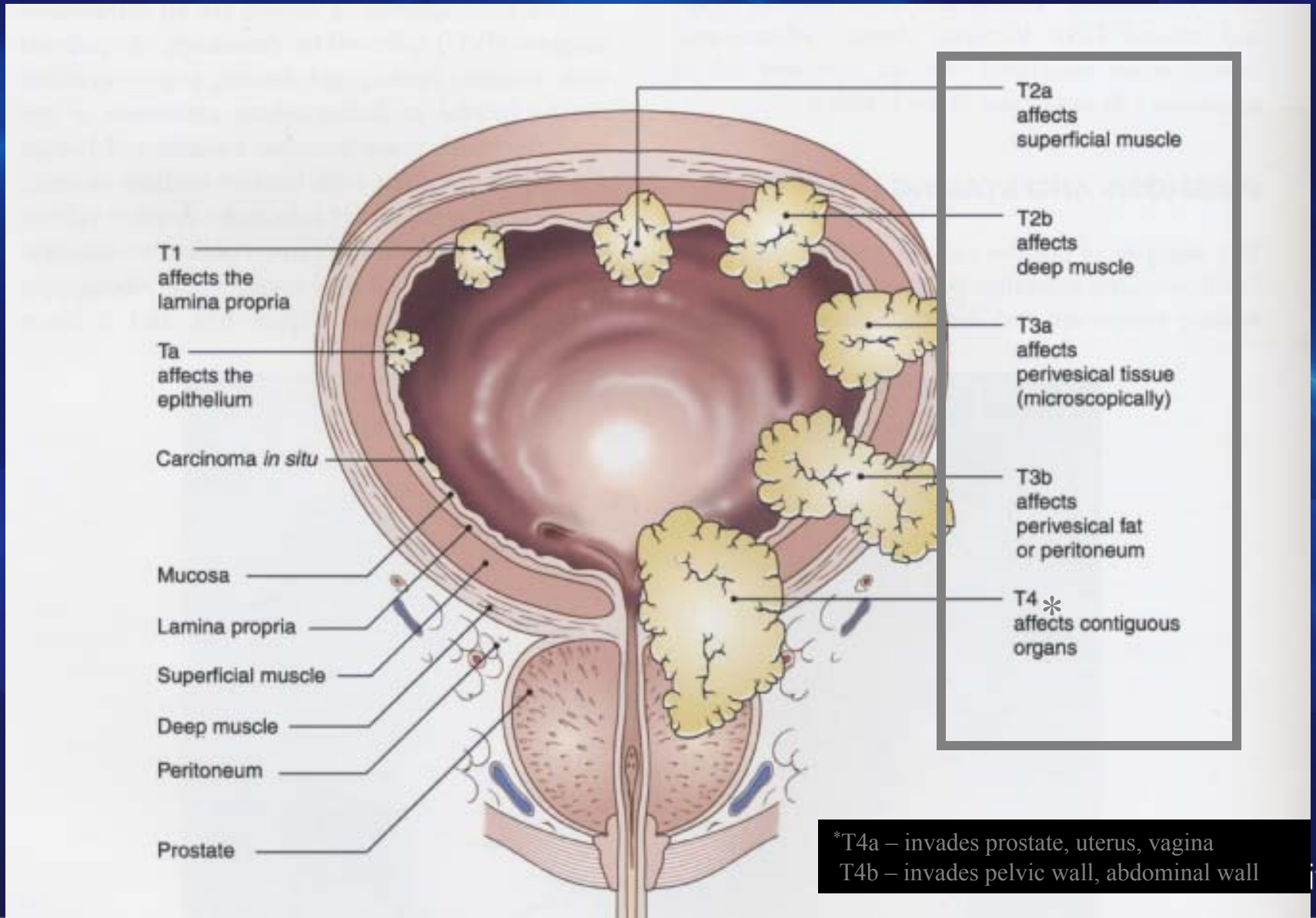
Transitional Cell Carcinoma

Includes:

- Bladder
- Ureter
- Renal pelvis (5-10% of all renal tumors)

Have a similar natural history and similar management principles may be applied to each.

Staging


T2a
affects
superficial muscle
T2b
affects
deep muscle
T3a
affects
perivesical tissue
(microscopically)
T3b
affects
perivesical fat
or peritoneum
T4 *
affects contiguous
organs
T1
affects the
lamina propria
Ta
affects the
epithelium
Carcinoma *in situ*
Mucosa
Lamina propria
Superficial muscle
Deep muscle
Peritoneum
Prostate
*T4a – invades prostate, uterus, vagina
T4b – invades pelvic wall, abdominal wall

Staging

	T1	T2ab	T3ab	T4ab
N0	I	IIA IIB	IIIA IIIB	IIIB IV
N123	IV	IV	IV	IV
M1	IV	IV	IV	IV

N1 – single LN < 2cm
N2 – single LN > 2cm - 5cm; or multiple LNs, none > 5cm
N3 – LN(s) > 5cm

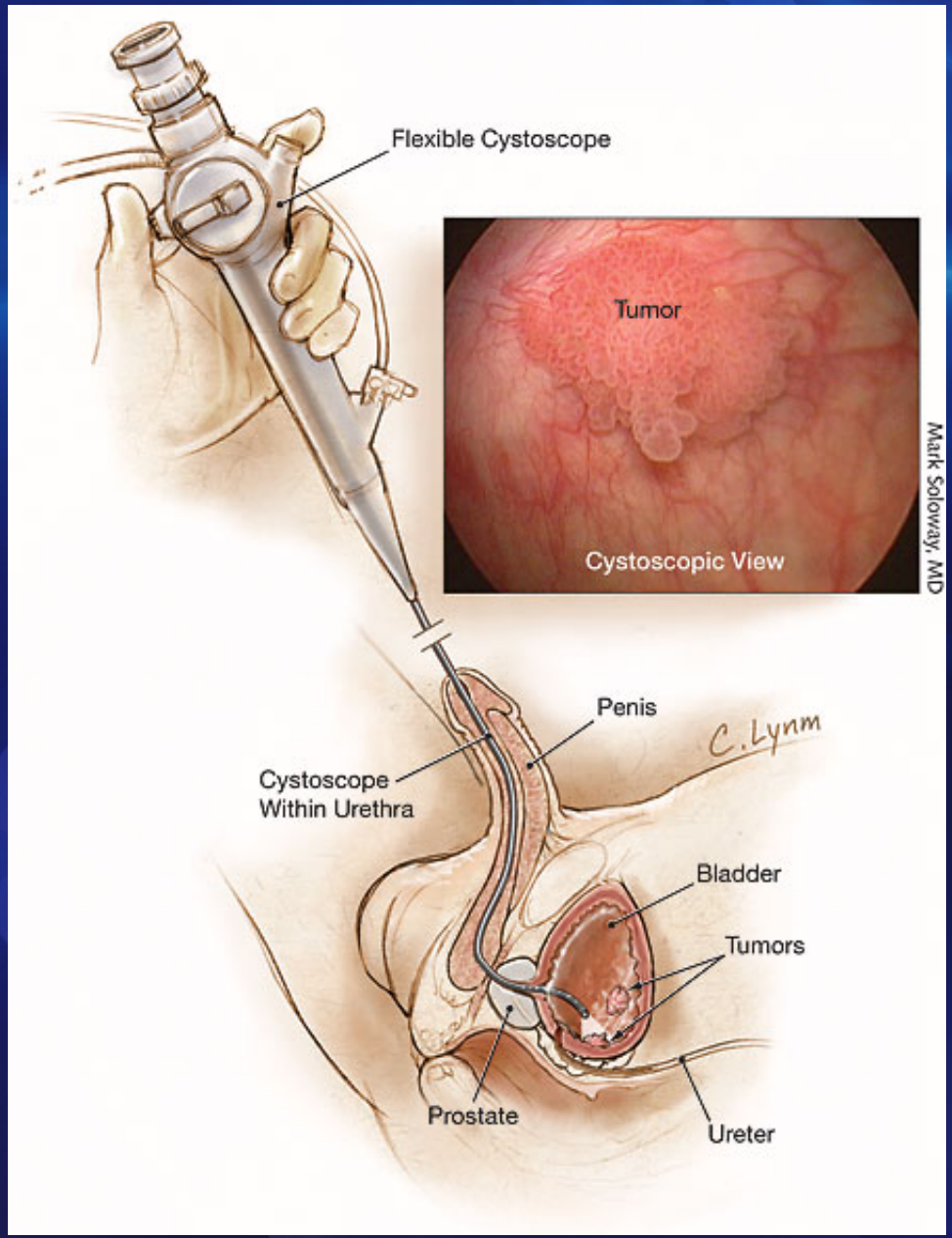
Clinical presentation

- Painless gross hematuria 80%
- Irritative symptoms 20%: urinary frequency, urgency and dysuria, suggesting Cis and muscle invasive dx.
- Some asymptomatic: microscopic hematuria.
- Advanced dx: urinary obstruction or invovled organ symptoms.

Workup and Diagnosis

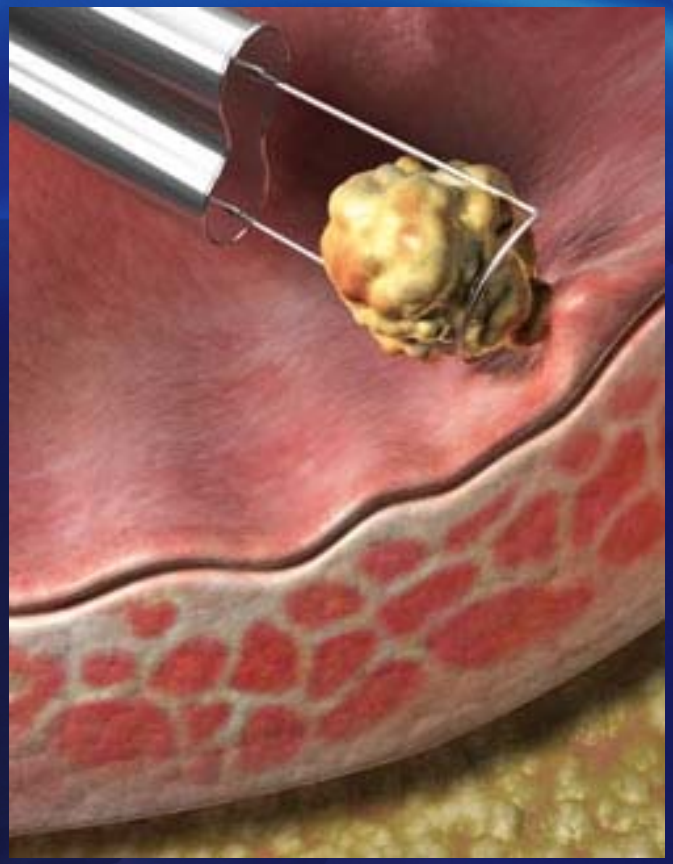
- Urinalysis, urine cytology (sensitivity 40-60%) and cystoscopy
- CT scan (with contrast) to establish patency of urinary tract and to assess pelvic and RP LNs
- CT chest with locally advanced disease
- Bone scan if complaints c/w osseous metastases
- PET/CT is currently being investigated

Cystoscopic Evaluation



Transurethral resection (TUR) of the bladder is a surgical procedure that is used both to diagnose bladder cancer and to remove cancerous tissue from the bladder

Transurethral Resection of Bladder Tumor



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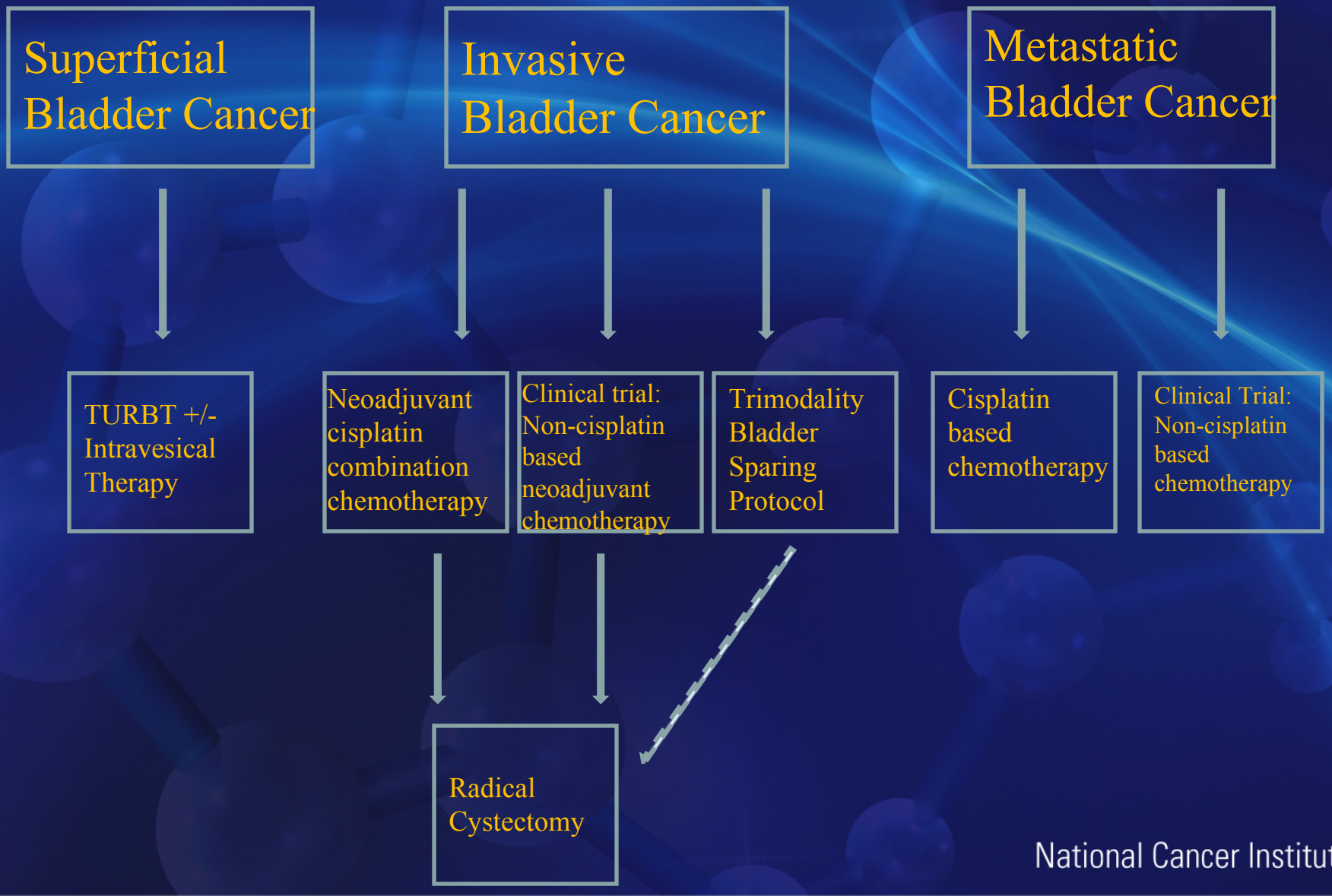
Bladder Cancer Management



Treatment Options for Superficial Bladder Cancer

- Transurethral resection
- Cystectomy
- Laser treatment
- Photodynamic therapy
- Intravesical therapy
  - Chemotherapy
  - BCG
  - Interferon
  - BCG + interferon

Primary Superficial Bladder Cancer Risk Groups
Stratified by Tumor Grade and Stage

Low Risk
- Grade I, stage Ta disease
- Single grade I, stage T1 tumor

Recurrence 37%, progression 0%, mortality 0%

Intermediate Risk
- Multiple grade I, stage T1 tumors
- Grade II, stage Ta disease
- Single grade II, stage T1 tumor

Recurrence 45%, progression 1.8%, mortality 0.73%

High Risk
- Multiple grade II, stage T1 tumors
- Grade III, stage Ta or T1 disease
- Carcinoma in situ

Recurrence 54%, progression 15%, mortality 9.5%

Millan-Rodriguez F, et al. *J Urol.* 2000;164:680.

Intravesical Therapy
Indications

- Multiple tumor recurrences or rapidly recurrent disease
- Large (>5 cm) solid bladder tumor
- Lamina propria invasion
- Multifocal disease
- High-grade Ta disease or any grade T1 disease
- Carcinoma in situ
- Extravesical involvement (prostatic urethra)
- Postresection positive cytology (after negative workup of upper urinary tracts)

BCG Is More Effective Than Chemotherapy for Reducing Rate of Recurrence and Progression

Agent	Patients/ series/sig	Recurrence (%)			Progression (%)		
		Ctrl	Rx	Benefit	Ctrl	Rx	*P* Value
Thiotepa	1007/10/6	56	44	12	6	4	NS
Doxorubicin	1241/5/3	47	34	13	8	9	NS
Mytomycin C	1157/6/2	50	35	15	7	4	NS
BCG	496/5/4	72	32	40	23	13	.03

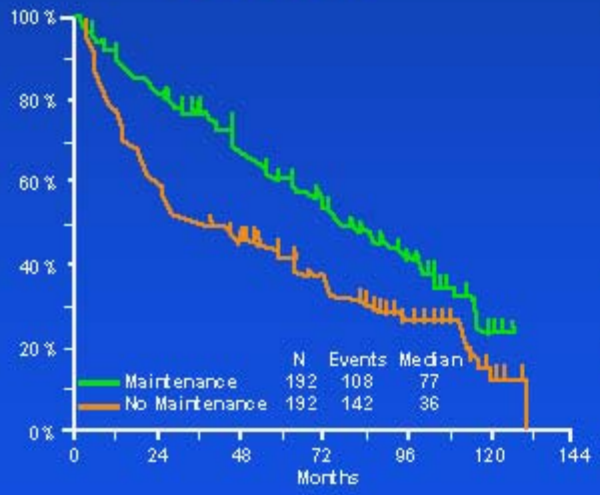
Series = Number of controlled studies; sig = Number of controlled studies statistically significant ($P<.05$), as reported by the authors. NS = not significant.

Lamm DL. *Eur Urol*. 1995;27(suppl 1):2. Reprinted with permission from S Karger AG.

Maintenance Therapy Improves Outcomes
SWOG Study

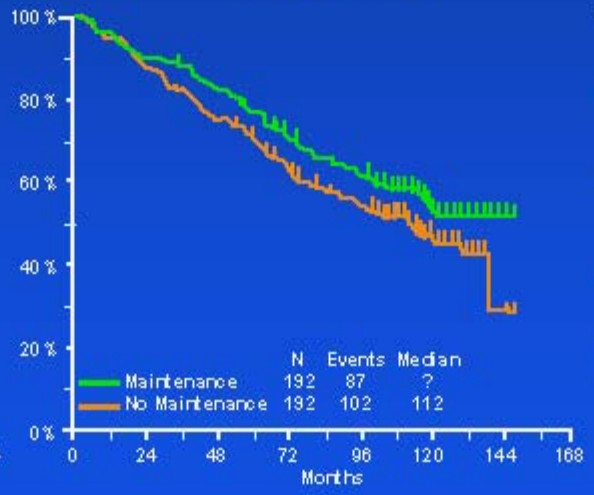
- N = 384 disease free after induction BCG (Connaught strain)
- Maintenance: full dose for 3 weeks at 3 and 6 months, then q6mo for 3 years

Recurrence-Free Survival



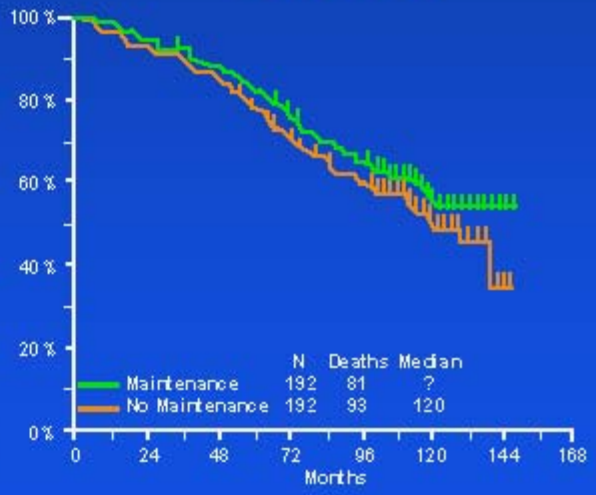
P<.0001

Progression-Free Survival



P = .04

Survival



P = .08

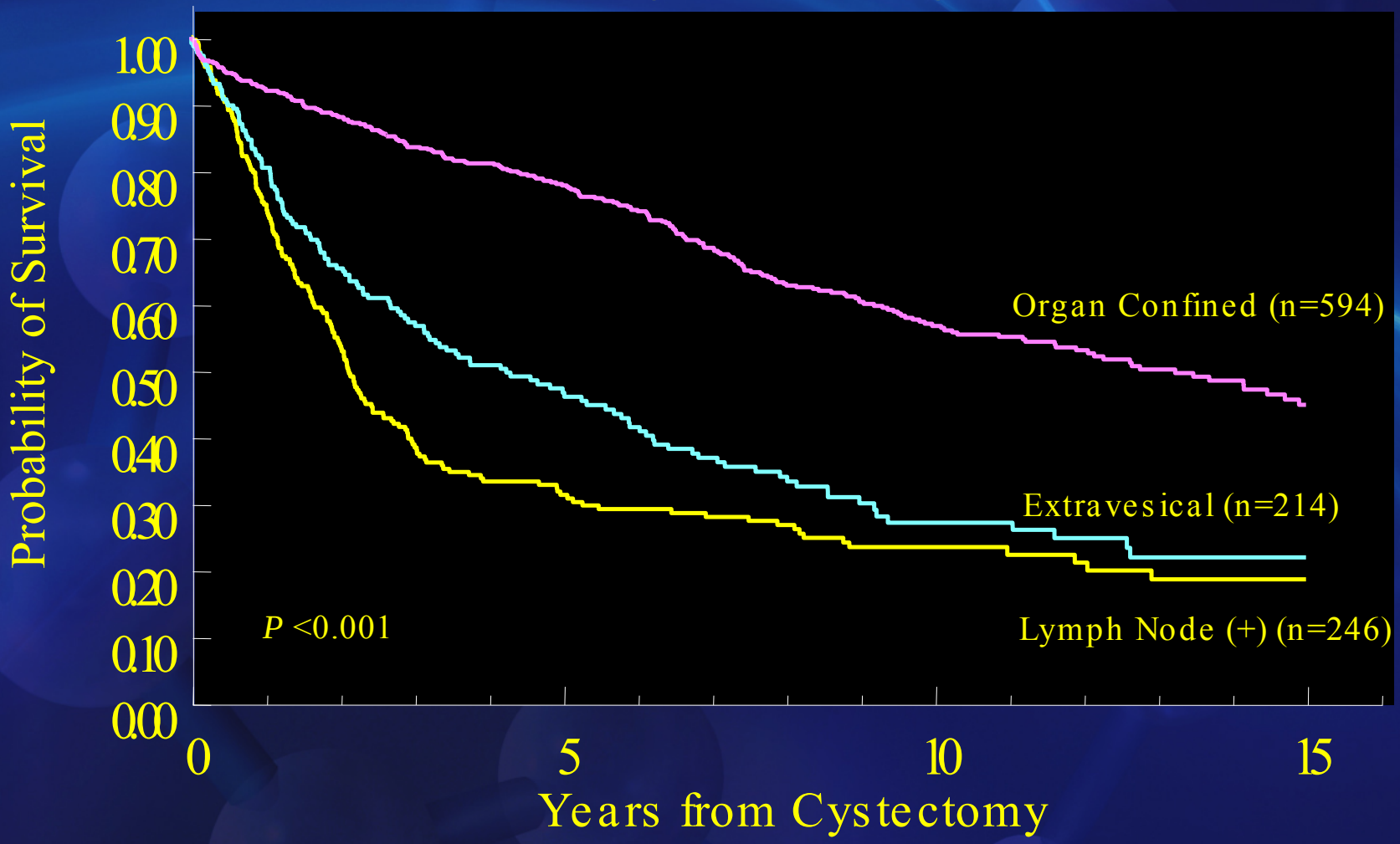
Reprinted from Lamm DL, et al. *J Urol.* 2000;163(4):1124.

Muscle-invasive BC

- Radical cystectomy with bilateral LND, standard in US, mortality ~5%.
- Over 90% local control.
- Very high metastatic potential, 50% develop metastatic dx in 2 yrs.
- Most important prognostic factor for survival is pathologic stage.

USC/Norris Bladder Cancer Experience in 1054 Patients

Probability of Survival According to Pathologic Groups



J Clin Oncol 2001;19:666

National Cancer Institute

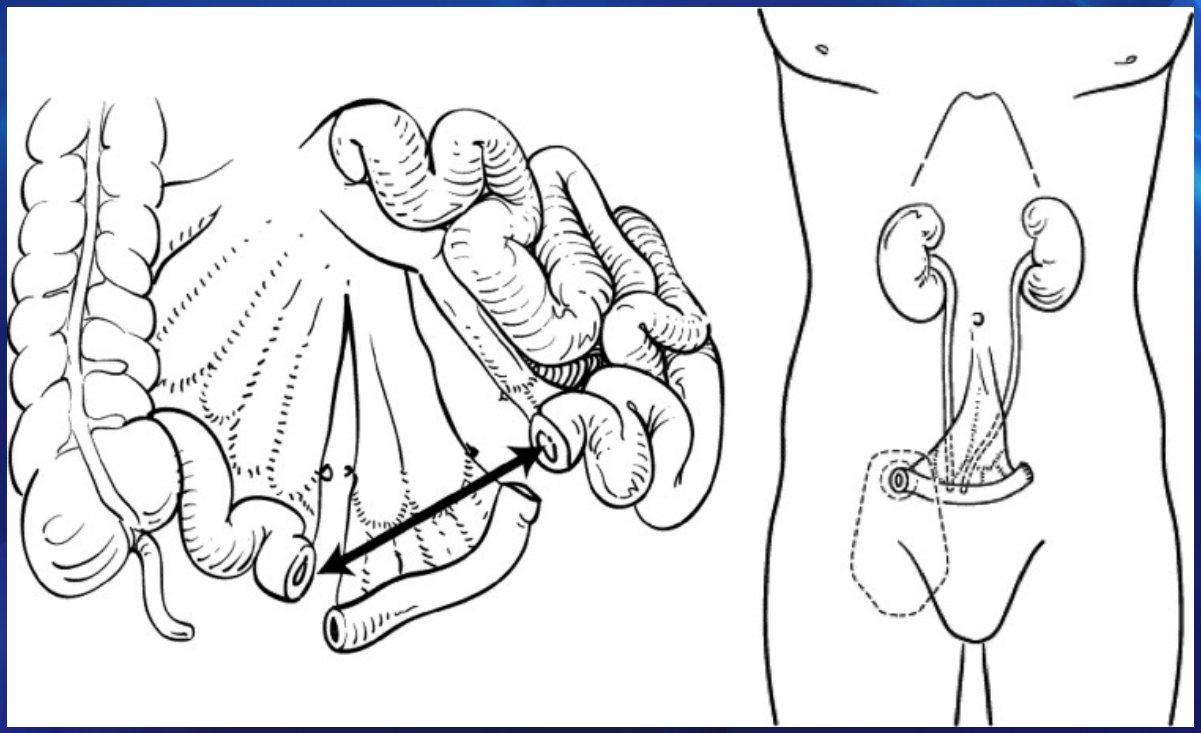
Muscle Invasive Disease

- Radical cystectomy (includes bladder, regional pelvic LNs, distal ureters)
  - in men, prostate gland, seminal vesicles, and proximal urethra are included
  - in women, the urethra, uterus, fallopian tubes, anterior vaginal wall and surrounding fascia are included

Urinary Diversion

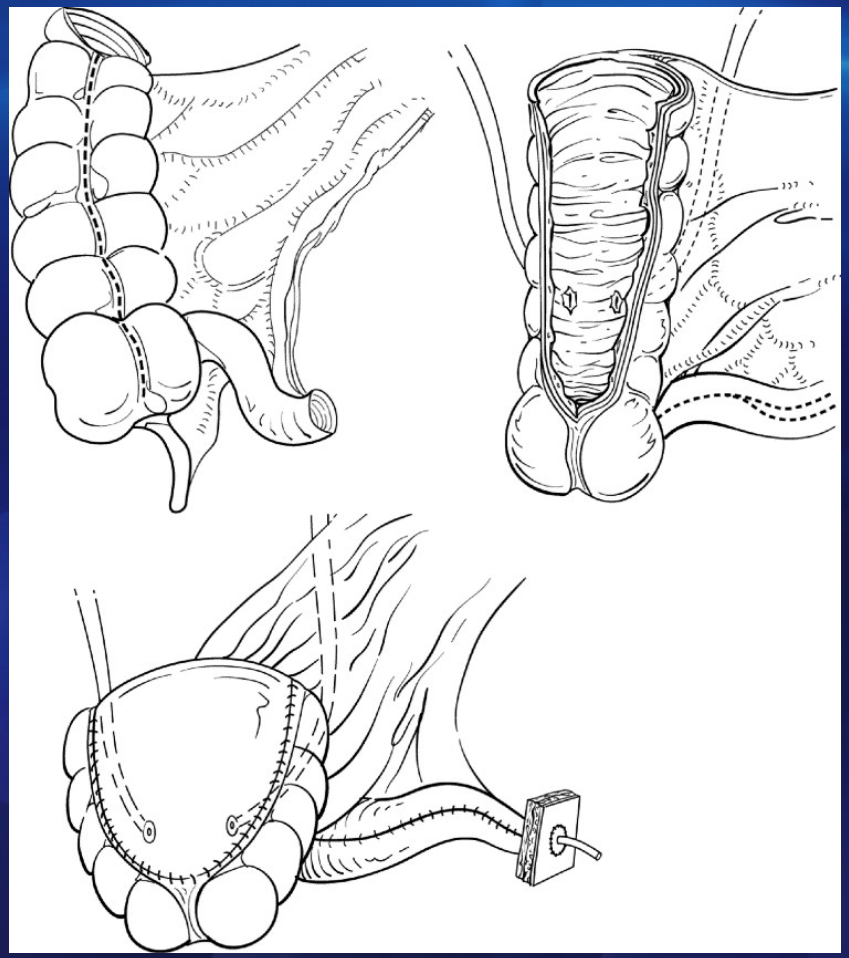
- Ileal conduit
- Continent cutaneous reservoir
- Orthotopic urethral diversions (neobladder)

Ileal conduit



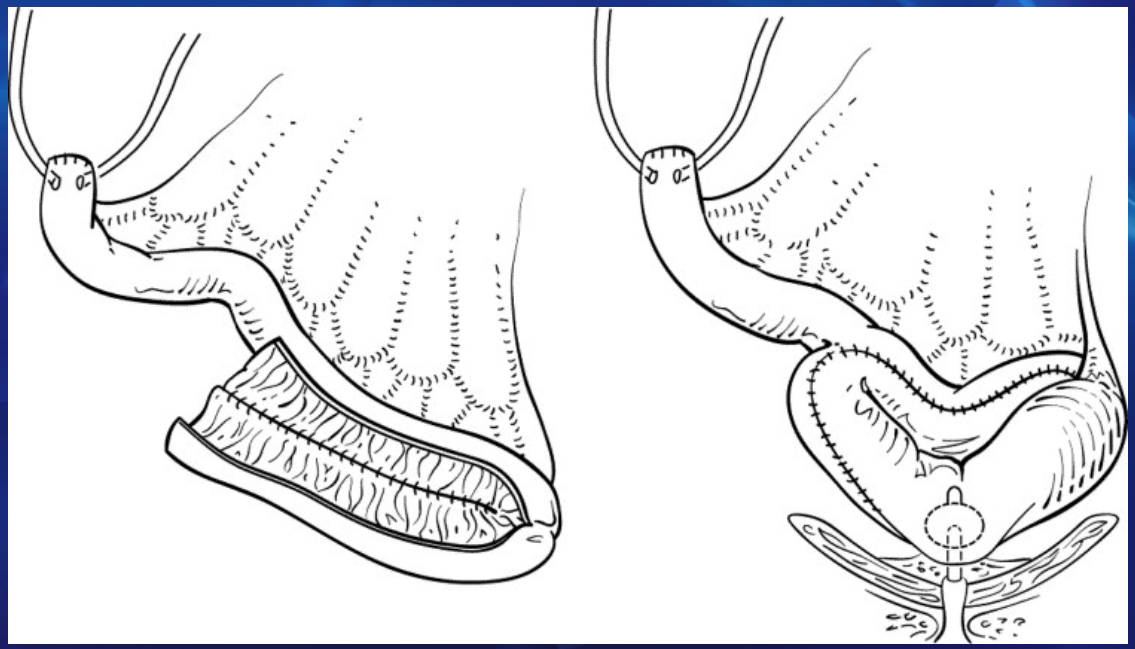
An isolated segment of the ileum is exteriorized in the form of a stoma through the abdominal wall with an appliance secured for continuous drain of urine.

Continent cutaneous reservoirs



- A pouch is made of detubularized bowel for urinary storage
- A tapered bowel segments connects to skin
- Requires intermittent clean self catherization

Orthotopic urethral diversions (neobladder)



- Spherical pouch is made from detubularized bowel for urinary storage
- Ureters are anastomized to the pouch which is then anastomized to native urethra

FAQ's on Muscle-Invasive Bladder Cancer

- Is there a benefit to neoadjuvant chemotherapy?
- Is there a benefit to adjuvant chemotherapy?
- What should be the standard of care?
- What about GC vs MVAC as neoadjuvant or adjuvant chemotherapy?

Potential impact of postoperative early complications on the timing of adjuvant chemotherapy in patients undergoing radical cystectomy

Complications within 90 days of surgery using a 5-grade system.

Grade 1-	oral medication/bedside care
Grade 2-	IV therapy, transfusion, hyperalimentation, enteral feedings
Grade 3-	intubation, interventional radiology, or re-operative intervention
Grade 4-	organ resection or chronic disability
Grade 5-	death

- 30% of pts experienced a grade 2-5 complication potentially interfere with the administration of adjuvant chemotherapy

Donat SM et al Eur Urol. 2009 Jan;55(1):177-85

All Complications Grades 2-5							
		0-30 days post RC		30-60 days post RC		60-90 days post RC	
Complication Category	N=611 pts (%)	Complication Category	N=547 pts (%)	Complication Category	N=97 pts (%)	Complication Category	N=54 pts (%)
GI	242 (40%)	GI	214 (39%)	Infection	53 (55%)	Infection	28 (52%)
Infection	240 (39%)	Infection	175 (32%)	GU	22 (23%)	GI	16 (30%)
Cardiac	115 (19%)	Cardiac	103 (19%)	GI	19 20%)	GU	8 (15%)
Bleeding	99 (16%)	Bleeding	90 (16%)	DVT/PE	14 (14%)	Wound	6 (11%)
DVT/PE	92 (15%)	DVT/PE	76 (14%)	Wound	12 (12%)	Bleeding	4 (7%)
Wound	88 (14%)	Wound	71 (13%)	Cardiac	12 (12%)	DVT/PE	3 (6%)
GU	85 (14%)	Pulmonary	63 (12%)	Pulmonary	5 (5%)	Pulmonary	2 (4%)
Pulmonary	68 (11%)	GU	59 (11%)	Neurologic	5 (5%)	Neurologic	2 (4%)
Neurologic	29 (5%)	Neurologic	21 (4%)	Bleeding	5 (5%)	Misc	2 (4%)
Misc	13 (2%)	Misc	9 (2%)	Misc	2 (2%)	Surgical	1 (2%)
Surgical	7 (1%)	Surgical	6 (1%)	Surgical	0 (0%)	Cardiac	1 (2%)

Randomized Trials of Adjuvant Therapy

Author	Year	Chemotherapy	No.Pts	Survival benefit
Skinner	1991	cisplatin, cyclophosphamide, and doxorubicin	102	Yes
Studer	1994	cisplatin	77	No
Stockle	1995	cisplatin, methotrexate, vinblastine, doxorubicin or epirubicin)	49	Yes
Freiha	1996	cisplatin, methotrexate, vinblastine	55	No
Bono	1997	cisplatin, methotrexate	93	No
Otto	2001	cisplatin, methotrexate, vinblastine, epirubicin	108	No

Randomized Trials of Adjuvant Therapy

- Hampered by serious methodological flaws
- Major deficiencies observed:
  - small sample size
  - early stopping of patient entry
  - statistical analyses
  - pts in chemo group that did not receive Rx were moved to non-chemo group for analysis
  - pts who relapsed did not routinely receive chemotherapy

European Urology

European Urology 48 (2005) 189–201

Review—Bladder Cancer

Adjuvant Chemotherapy in Invasive Bladder Cancer: A Systematic Review and Meta-Analysis of Individual Patient Data

Advanced Bladder Cancer (ABC) Meta-analysis Collaboration

The power of this metaanalysis is clearly limited

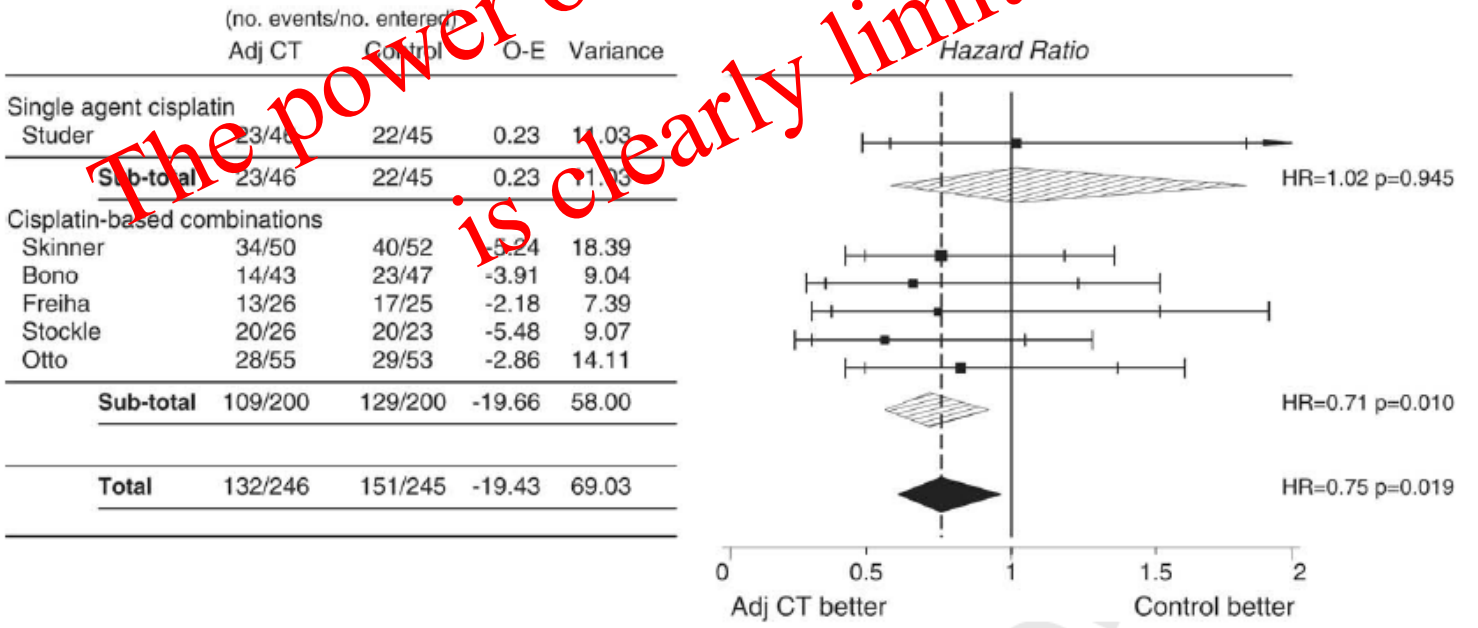


Fig. 1. Hazard ratio plot for survival, each individual trial is represented by a square, the centre of which denotes hazard ratio for that trial; extremities of horizontal bars denote 99% CI and inner bars mark 95% CI. Size of square is directly proportional to amount of information in trial. The black 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)

Cognetti et al. ASCO 2008 Phase III Study of Adjuvant Cisplatin and Gemcitabine (GC) vs Observation in Patients With Bladder Cancer at High Risk After Radical Cystectomy

randomize

Arm I: GC randomized to 1 of 2 schedules.

- *GC2:* cisplatin on day 2 and gemcitabine on days 1, 8, and 15.
- *GC15:* cisplatin on day 15 and gemcitabine on days 1, 8, 15.

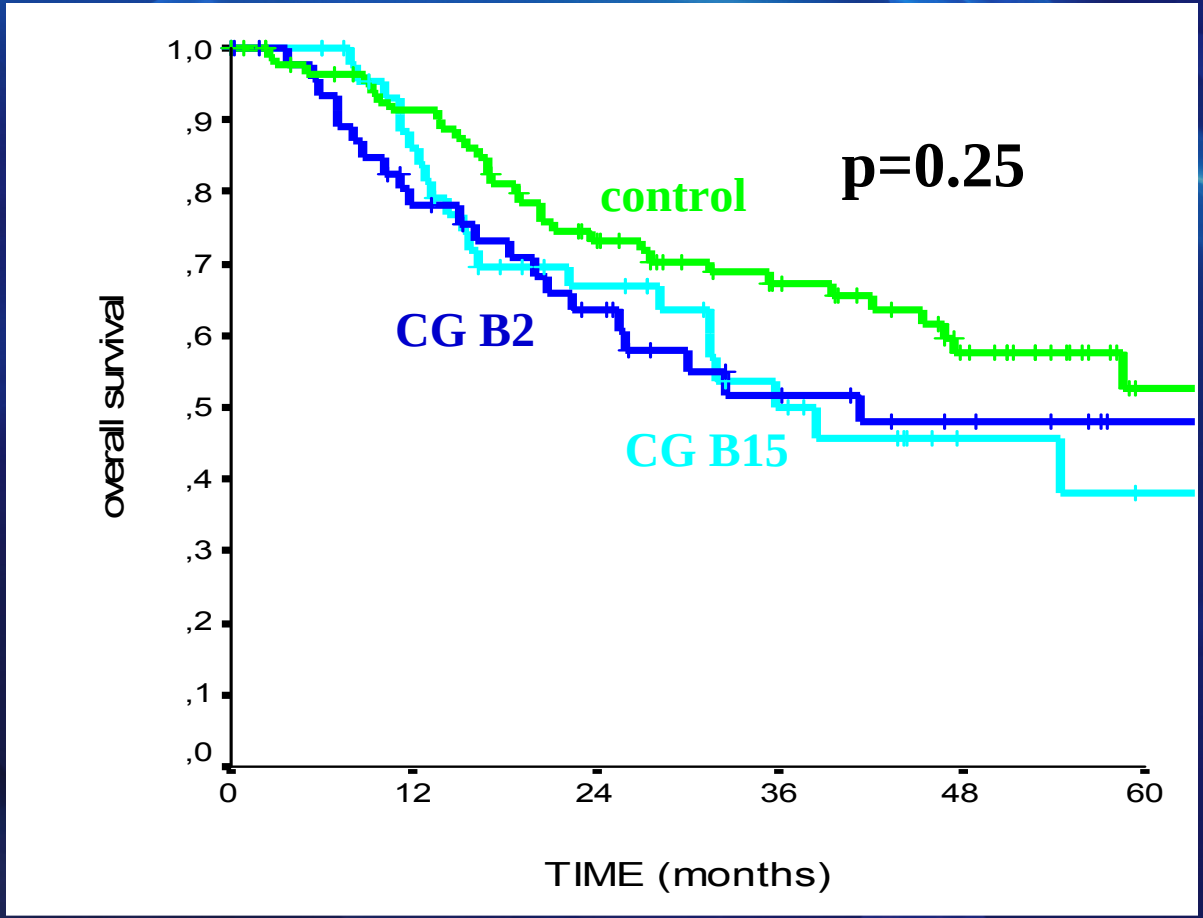
194 patients randomized

Arm II: Patients undergo observation followed by GC at relapse.

Design: 610 patients to detect 10% difference in 5 yr survival
Treatment in both regimens repeats every 28 days for 4 courses.
(T2 [G3 only] or T3-4 [any G], N0-2 vs any T, N1-2, M0).

Cognetti et al. Adjuvant gemcitabine and cisplatin in patients with muscle-invasive bladder cancer

Overall Survival



Paz-Ares et al. ASCO 2010: Randomized phase III trial comparing adjuvant paclitaxel/gemcitabine/cisplatin (PGC) to observation in patients with resected invasive bladder cancer: SOGUG 99/01 study

Eligibility
- TCC
- Post-cystectomy
- pT3-4 and/or pN+
- PS 0-1
- CrCl> 50ml/min

r a n d o m i z e

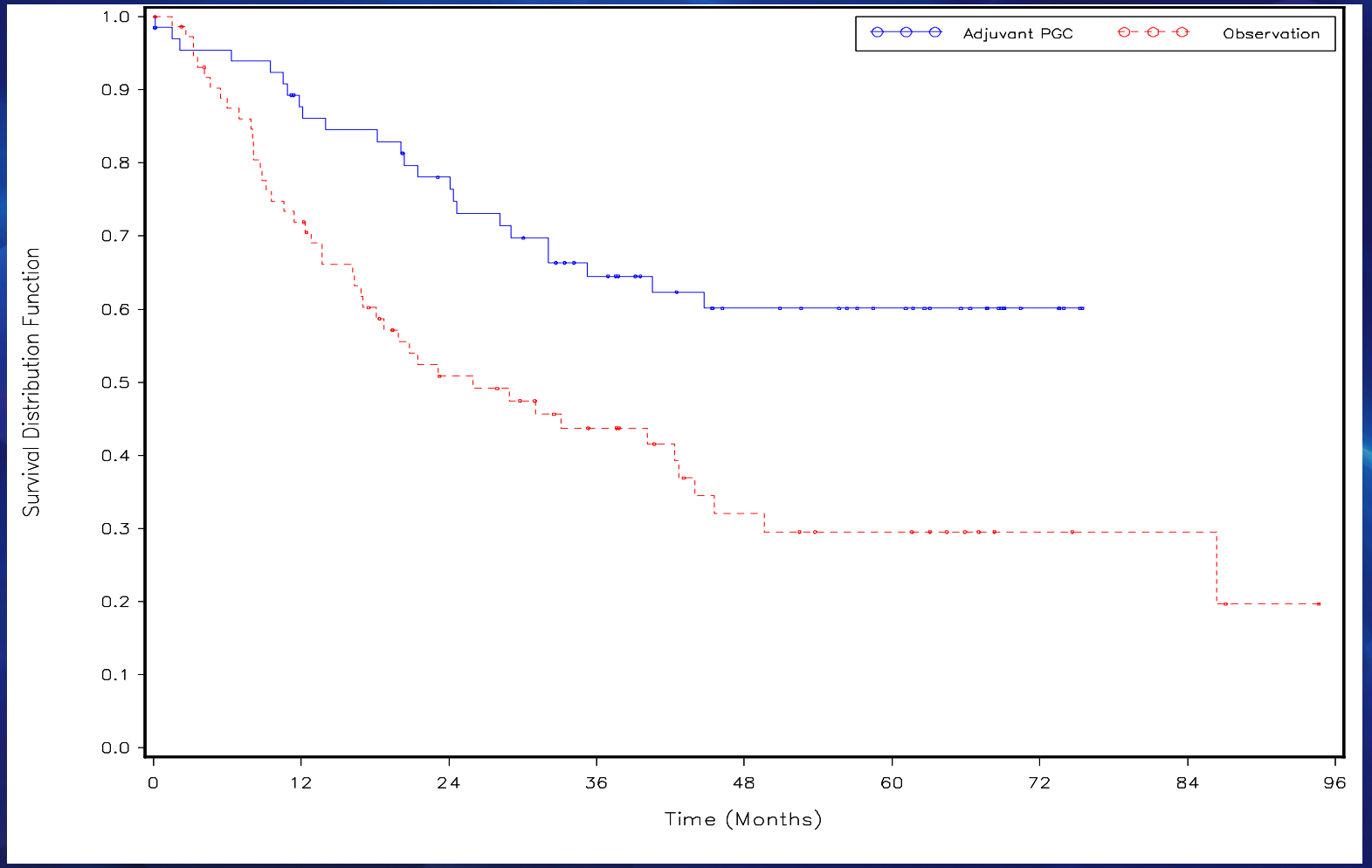
PGC x4

142 patients randomized

Observation

N=340 to detect 15% increase
In 2 years OS (50% -> 65%
Alpha 0.05 and beta 0.2

Overall Survival - ITT



HR: 0.44 ; P< 0.0009

HR: 0.378 (95% CI: 0.649-0.221) **P<0.0004 Adjusted - Cox Multivariate**

Treatment at Relapse

	PGC N=30	Observation N=54
Further Chemo	16 (53%)	38 (70%)
Platinum-based	13 (43%)	33 (61%)
Non-platinum-based	3 (10%)	5 (9%)

Paz-Ares et al. ASCO 2010

EORTC Early vs Delayed Chemotherapy after Cystectomy pT3-pT4, and/or N+M0

Randomize

Gem-Cis x 4 or
M-VAC x 4 or
HD-M-VAC x 4

Therapy at relapse

Increase in 5 yr survival from
35 to 42%. (7% increase)
Alpha .05; Beta .20:
644 pts closed June 2008 298 accrued

Randomized Trials of Adjuvant Therapy

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Skinner	1991	cisplatin, cyclophosphamide, and doxorubicin	102	Yes
Studer	1994	cisplatin	77	No
Stockle	1995	cisplatin, methotrexate, vinblastine, doxorubicin or epirubicin)	49	Yes
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Bono	1997	cisplatin, methotrexate	93	No
Otto	2001	cisplatin, methotrexate, vinblastine, epirubicin	108	No
Cognetti	2008	cisplatin, gemcitabine	192	No
Stadler	2009	cisplatin, methotrexate, vinblastine, doxorubicin	114	No
Paz-Ares	2010	cisplatin, paclitaxel, gemcitabine	142	Yes

Adjuvant Chemotherapy

- Meta-analyses need to be updated to include these large randomized trials
- Insufficient evidence to support the routine use of adjuvant chemotherapy
- All patients should be informed about neoadjuvant chemotherapy benefits derived from data on over 3000 randomized patients on 12 randomized trials
- If the patient refuses, then adjuvant chemotherapy should be considered but the data are less compelling

What are the Neoadjuvant Chemotherapy Data?

Series	ChemoRx	Pts	Primary Rx	Survival Benefit
Shearer	MTX	376	RT/cyst	No
Wallace	Cisplatin	225	RT	No
Martinez-Piniero	Cisplatin	121	Cyst	No
Nordic-2	MTX-Cisplatin	317	Cyst	No
Vitale	Cis/FU/RT	104	Cyst	No
Shipley	CMV	121	Cisplatin-RT	No
Pellegrini	MVEC	171	Cyst	No
Malmstom	Doxorubin/Cis	325	RT/cyst	T3,T4
Hall	CMV	975	RT/Cyst/Both	Yes
Grossman	MVAC	317	Cyst	Yes

Neoadjuvant MRC/EORTC Trial

- Largest published trial to date
- 976* pts (CMV versus no chemotherapy)
- At 4 yrs, non-significant trend towards improved overall survival
- At 7.4 yrs, significant 6% absolute survival benefit
- Short course of chemotherapy (9 weeks) and inclusion of leucovorin rescue may have led to suboptimal eradication of micrometastases

*planned sample size sufficient to detect a 10% improvement in OS

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Neoadjuvant Chemotherapy plus Cystectomy Compared with Cystectomy Alone for Locally Advanced Bladder Cancer

H. Barton Grossman, M.D., Ronald B. Natale, M.D., Catherine M. Tangen, Dr.P.H., V.O. Speights, D.O., Nicholas J. Vogelzang, M.D., Donald L. Trump, M.D., Ralph W. deVere White, M.D., Michael F. Sarosdy, M.D., David P. Wood, Jr., M.D., Derek Raghavan, M.D., Ph.D., and E. David Crawford, M.D.

N Engl J Med 349;9 859-66 August 28, 2003

Table 4. Stratified and Unstratified Survival Analysis.*

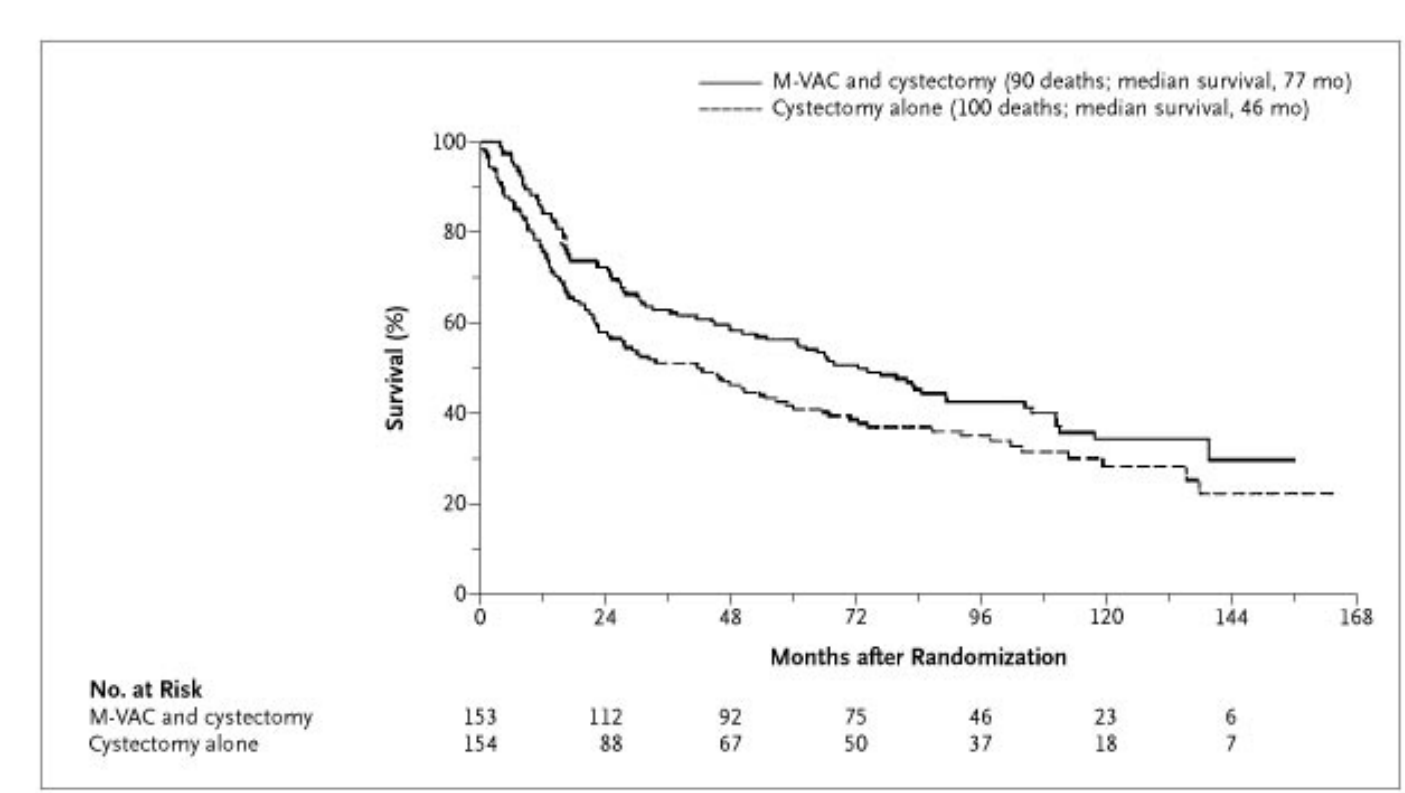
Variable	Median Survival		P Value†
	M-VAC and Cystectomy	Cystectomy Alone	
	months		
Unstratified	77	46	0.05
Primary analysis, stratified according to age and tumor stage			0.06
Stratified according to age			0.05
Age <65 yr	104	67	
Age ≥65 yr	61	30	
Stratified according to tumor stage			0.05
T2	105	75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

* There were 90 deaths in the combination-therapy group after a median follow-up of 8.7 years. There were 100 deaths in the cystectomy group after a median follow-up of 8.4 years. M-VAC denotes methotrexate, vinblastine, doxorubicin, and cisplatin.

† The log-rank test was used to calculate P values.

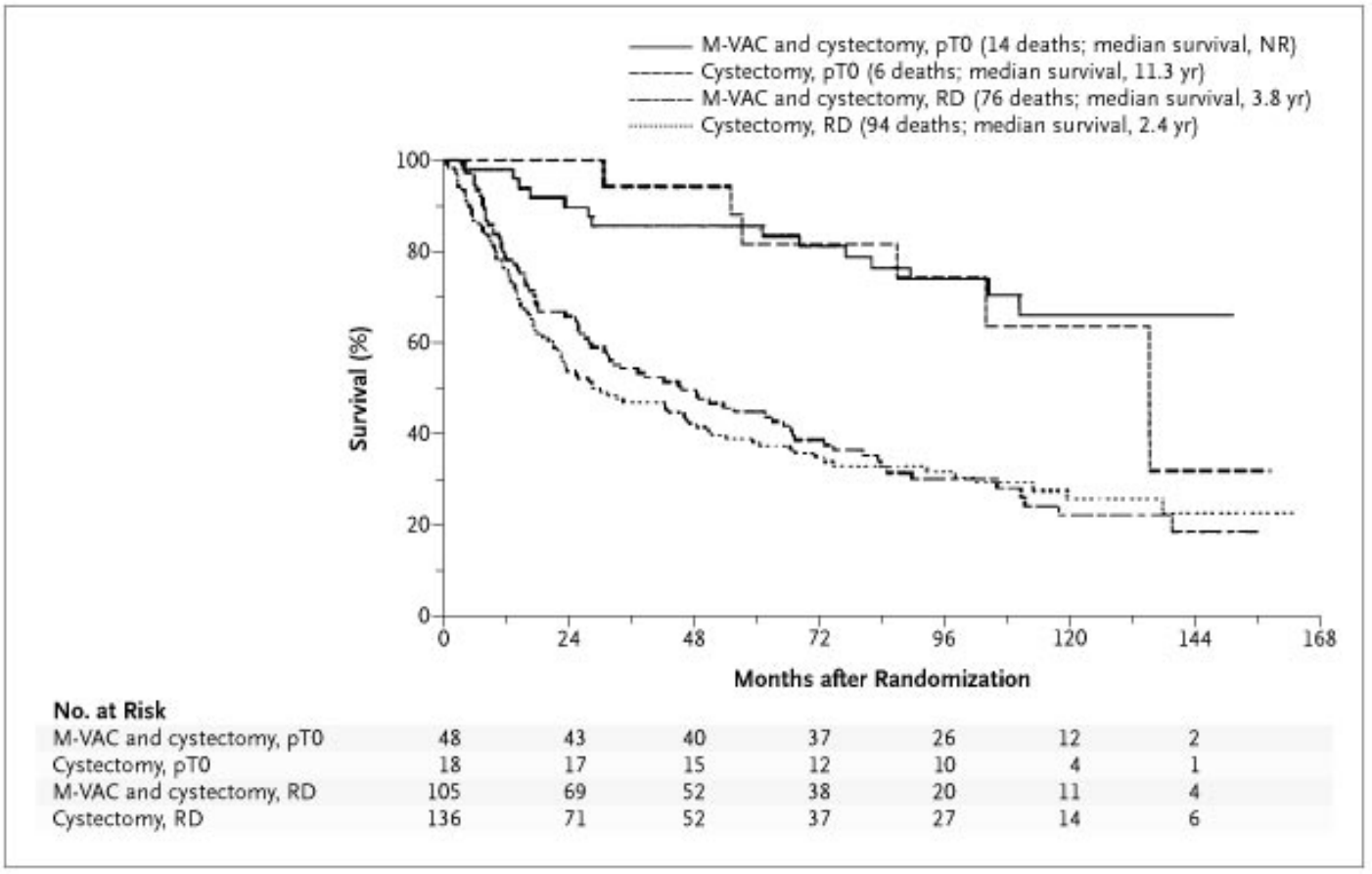
N Engl J Med 349;9 859-66 August 28, 2003

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



Grossman, H. B. et. al. N Engl J Med 2003;349:859-866

Survival According to Treatment Group and Whether Patients Were Pathologically Free of Cancer (pT0) or Had Residual Disease (RD) at the Time of Cystectomy



No. at Risk							
M-VAC and cystectomy, pT0	48	43	40	37	26	12	2
Cystectomy, pT0	18	17	15	12	10	4	1
M-VAC and cystectomy, RD	105	69	52	38	20	11	4
Cystectomy, RD	136	71	52	37	27	14	6

Grossman, H. B. et. al. N Engl J Med 2003;349:859-866

Conclusions

- Median survival of cystectomy alone was 46 mo c/w 77 mo for combination therapy (p=0.06 by two-sided stratified log rank test)
- In both groups, improved survival associated with the absence of residual cancer in the cystectomy specimen
- Significantly more patients in the combination group had no residual disease than patients in the cystectomy group (38% vs. 15%, p=<0.001)

N Engl J Med 349;9 859-66 August 28, 2003

Conclusions[3]

- The 38% rate of p0 achieved in this study and the significant survival of this subset of patients provides a strong rationale for considering a bladder-sparing approach in future studies.
  - » Can radical cystectomy be deferred?
  - » Can cystoscopy and urinary biochemical and molecular studies effectively identify and monitor patients achieving p0?

European Urology

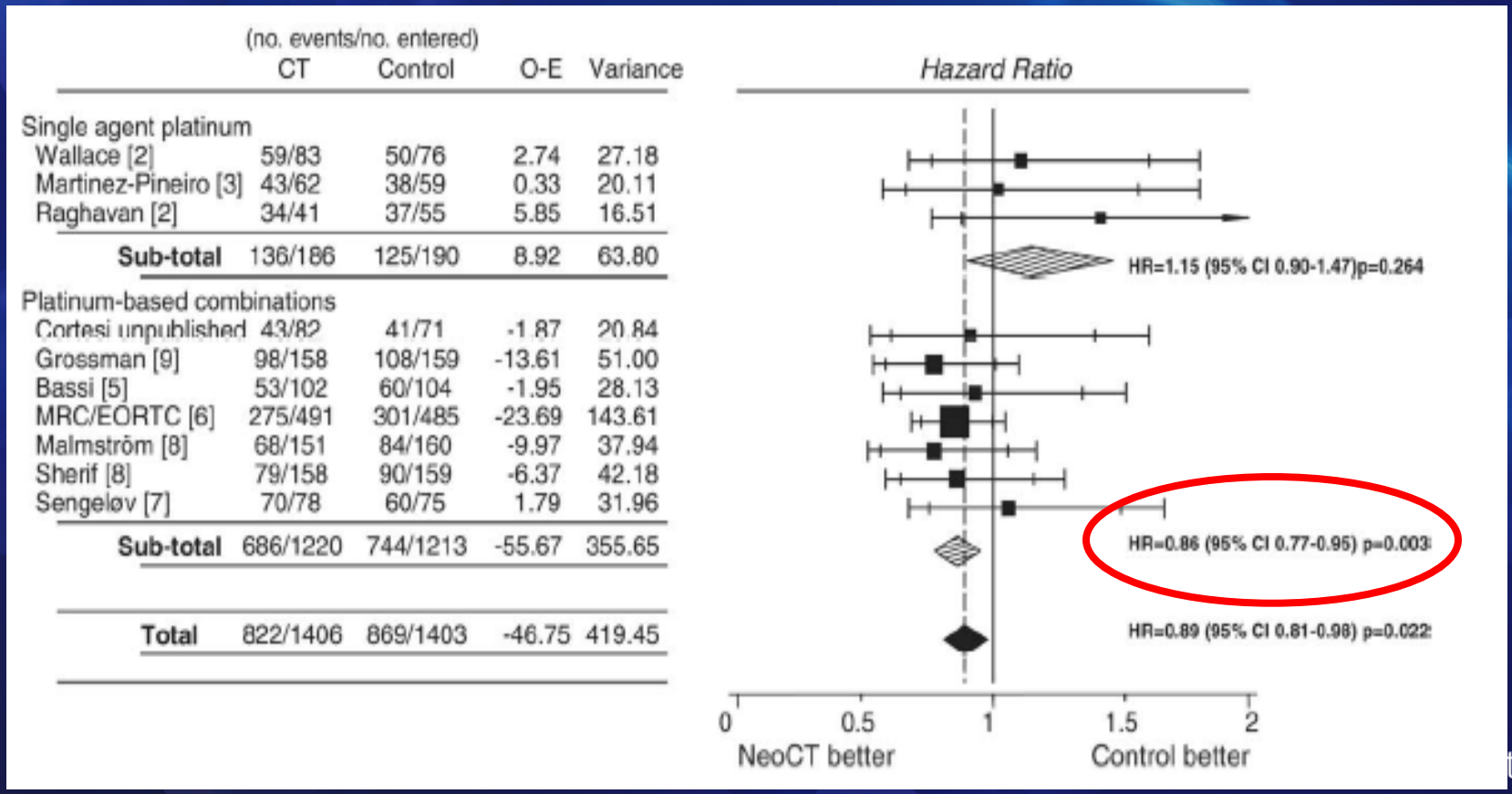
European Urology 48 (2005) 202–206

Review—Bladder Cancer

Neoadjuvant Chemotherapy in Invasive Bladder Cancer: Update of a Systematic Review and Meta-Analysis of Individual Patient Data

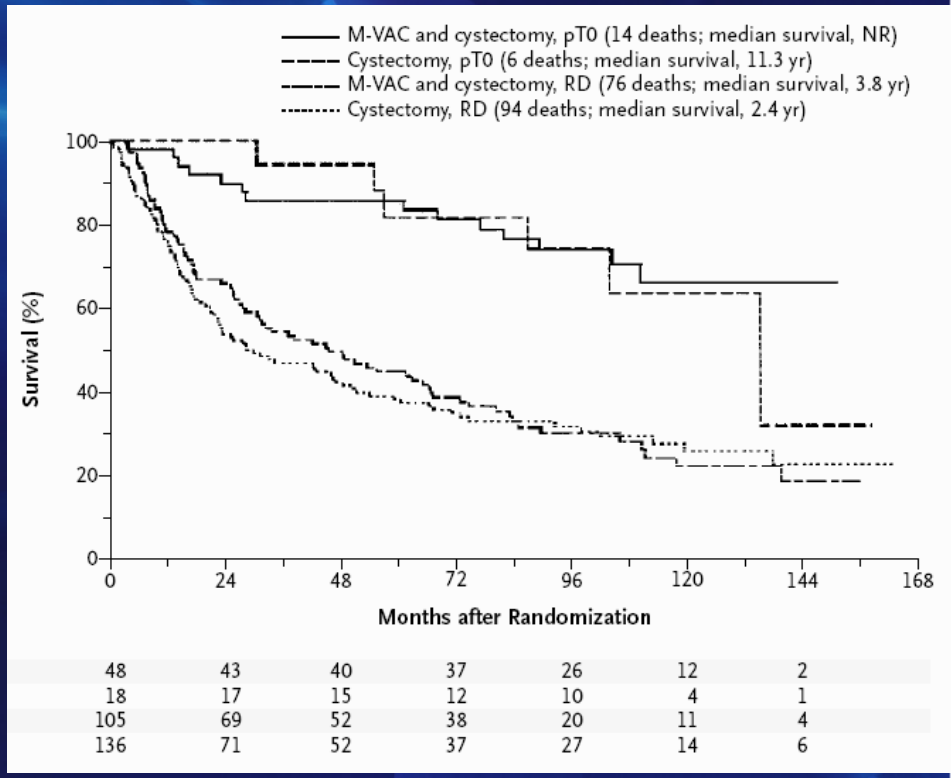
Advanced Bladder Cancer (ABC) Meta-analysis Collaboration

Meta-analysis Group, Medical Research Council Clinical Trials Unit, 222 Euston Road, London NW1 2DA, UK



Dash et al. Neoadjuvant gemcitabine plus cisplatin (GC) in muscle-invasive TCC

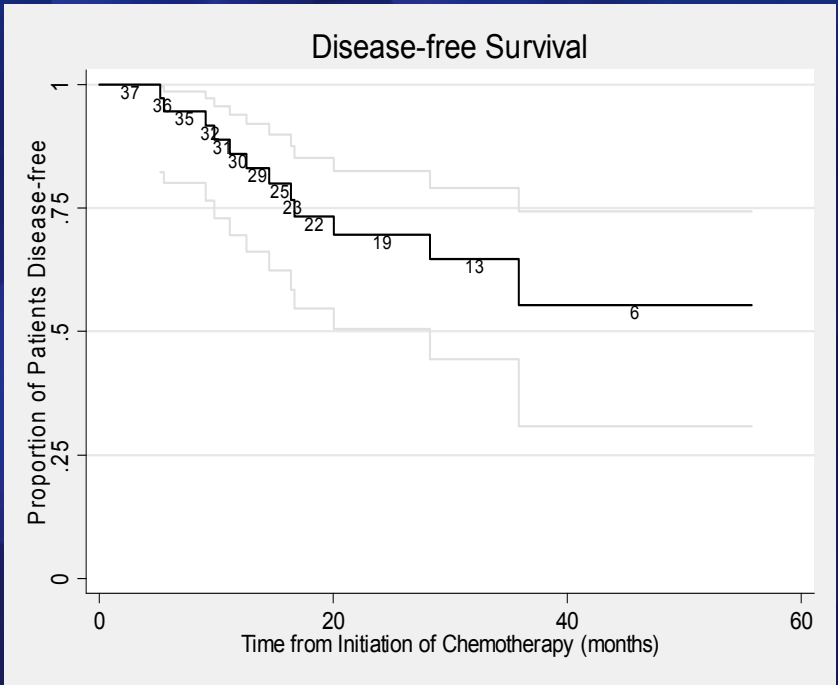
- Neoadjuvant chemotherapy confers a survival benefit and 85% achieving pT0 are alive at 5 years (Grossman, NEJM 2003)
- Downstaging to ≤ pT1 or pT0 disease confers the greatest survival benefit (Splinter, JU 1992)



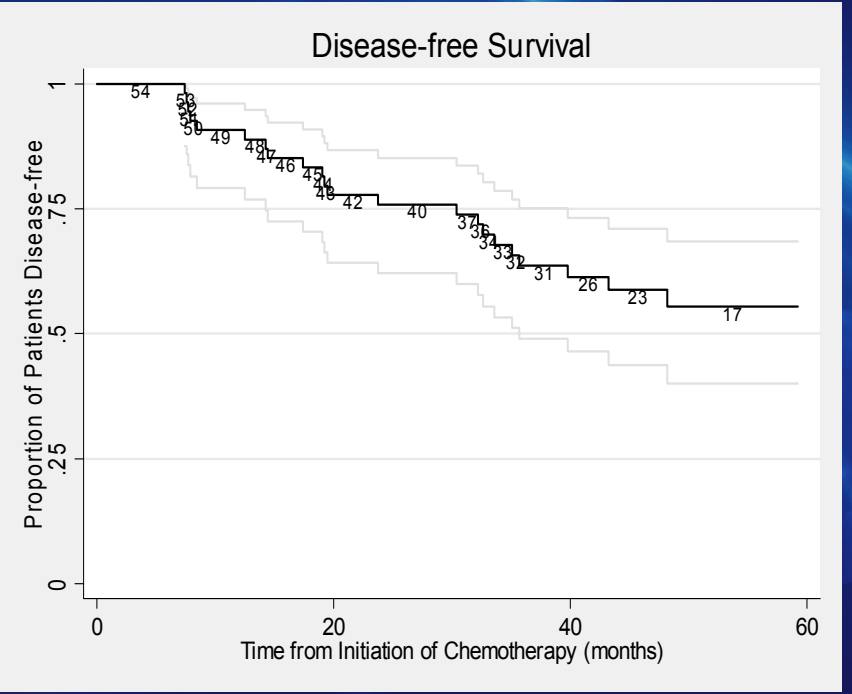
- Gemcitabine and Cisplatin (GC)
  less toxic than MVAC with comparable survival (JCO 2005)
- GC has evolved into the standard regimen for neoadjuvant chemotherapy in muscle-invasive urothelial carcinoma of the bladder but no data on efficacy

Comparison of Outcomes

	GC (n=42)	MVAC (n=55)
pT0	26% (95% CI 14, 42)	27% (95% CI 16, 41)
≤ pT1	36% (95% CI 21, 52)	36% (95% CI 24, 50)
LN positive	26% (95% CI 14, 42)	22% (95% CI 12, 35)



Median f/u survivors 30 months



Median f/u survivors 40 months

Median DFS 71 months (95% CI 52, 88)

Muscle-invasive TCC
Neo-adjuvant chemotherapy is now a standard of care

What does this mean for patients?

1. All patients should be informed about neoadjuvant chemotherapy benefits derived from data on over 3000 randomized patients on 12 randomized trials.
2. Patients tolerant of cisplatin-combination chemotherapy should get 3 months of neoadjuvant chemotherapy.
3. If the patient refuses, then adjuvant chemotherapy should be considered but the data are less compelling and derived from 150 patients on randomized 2 phase trials.

What does this mean for physicians practicing evidenced-based medicine?

1. Chemotherapy does not substitute for surgery; this is combined modality like testicular, ovarian and breast cancer
2. A "little chemotherapy" or a "couple of cycles" doesn't make sense in solid tumors

Review of 7,161 cases of stage III bladder cancer from the National Cancer Database in 1998-2003. Neo-adjuvant chemotherapy given in 1.2% of cases and Adjuvant chemotherapy in 10.4% of of cases. Small difference between 1998 and 2003 (David et al. *J Urol* 2007)

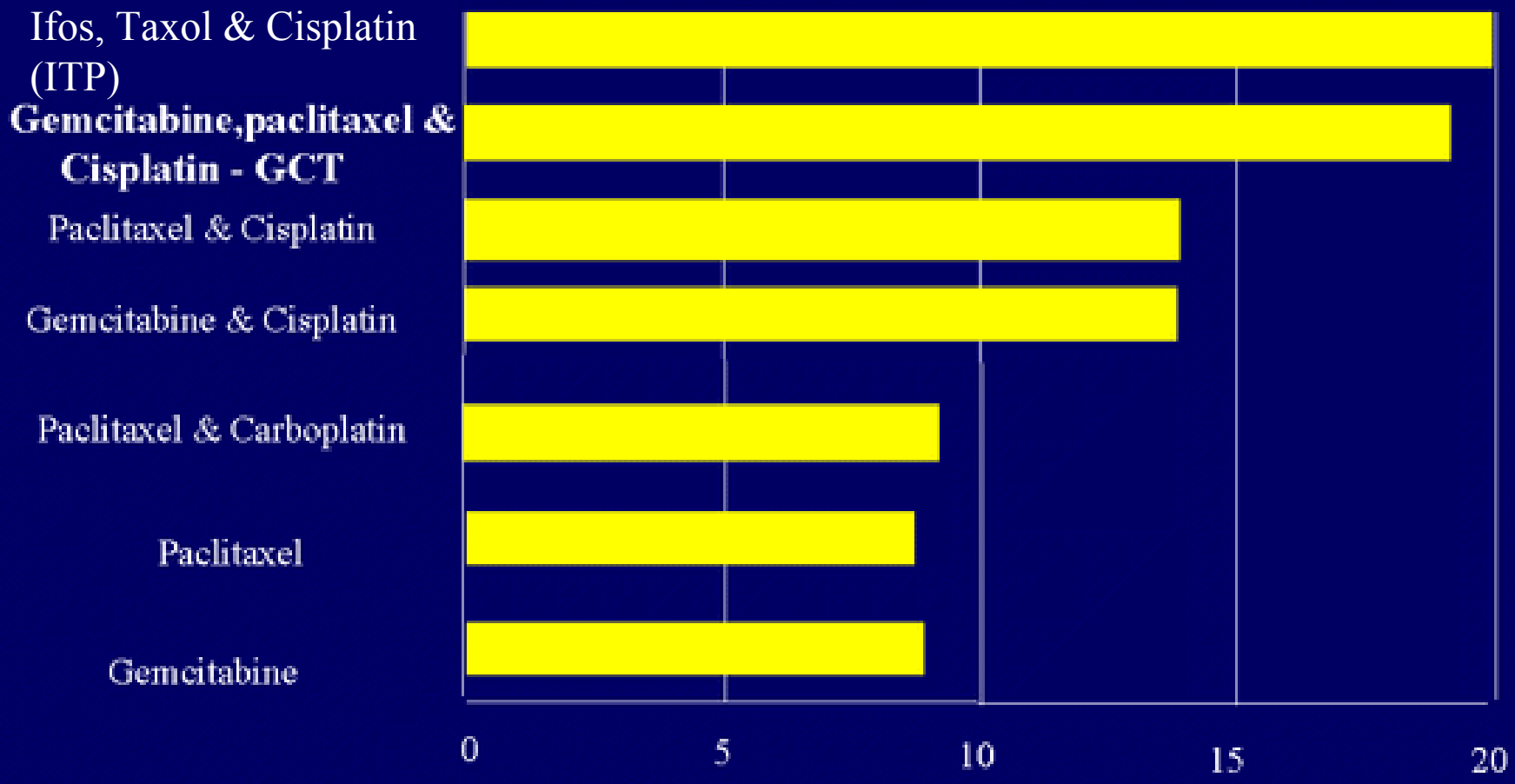
Metastatic Bladder Cancer
Sites of Metastases

- Regional lymph nodes
- Bone
- Lung
- Liver
- Skin
- CNS (seen in chemotherapy treated pts)

Metastatic Bladder Cancer

- Many chemotherapy agents with activity in TCC e.g. CDDP, carboplatin, MTX, doxorubicin, vinblastine, ifosfamide, gemcitabine, paclitaxel and docetaxel
- MVAC found to improve OS c/w CDDP alone or CISCA
- A small proportion of patients (3-7%) can be cured with MVAC
- MVAC with significant toxicity

Chemotherapy for Metastatic Bladder Cancer: Median Survivals



Randomized Phase III Study In Metastatic Bladder Cancer

GC

- Gemzar 1000 mg/m^2 day 1, 8 and 15
- Cisplatin 70 mg/m^2 day 2

MVAC

- Methotrexate 30 mg/m^2 day 1, 15 and 22
- Vinblastine 3 mg/m^2 day 2, 15 and 22
- Adriamycin 30 mg/m^2 day 2
- Cisplatin 70 mg/m^2 day 2

Patient Characteristics

	G-C	MVAC
Randomized pts	203	202
Median age	63 years	63 years
PS $\geq$ 80	82.5%	81.1%
T_{any} N_{any} M1	69.5%	62.9%
Visceral Mets	48.8%	46.0%
High Alk Phos	28.6%	26.0%
$\geq$ 4 ds sites	20.7%	17.3%

GC versus MVAC

Most important toxicity differences

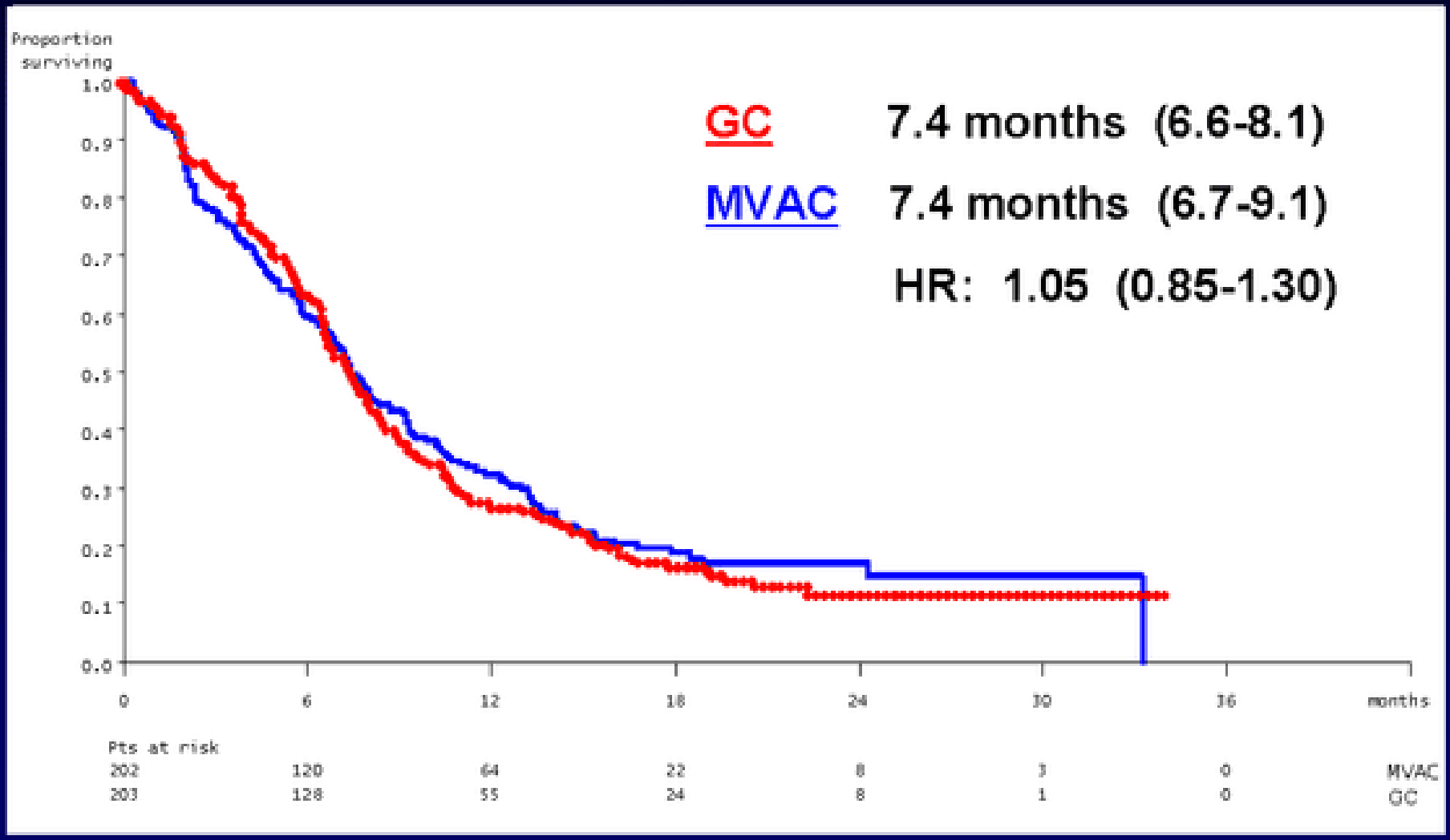
Toxicity	GC	MVAC
Neutropenic fever	2%	14%
Neutropenic sepsis	1%	12%
Mucositis (grade 3/4)	1%	22%
Toxic deaths	1%	3%

GC versus MVAC Survival Analysis

	G-C	MVAC
Overall Survival	13.8 months	14.8 months
Response Rate	49.4%	45.7%
CR	12.2%	11.9%
PR	37.2%	33.8%
SD	33.5%	32.5%
Median TTP	7.4 months	7.4 months
Median TTF	5.8 months	4.6 months

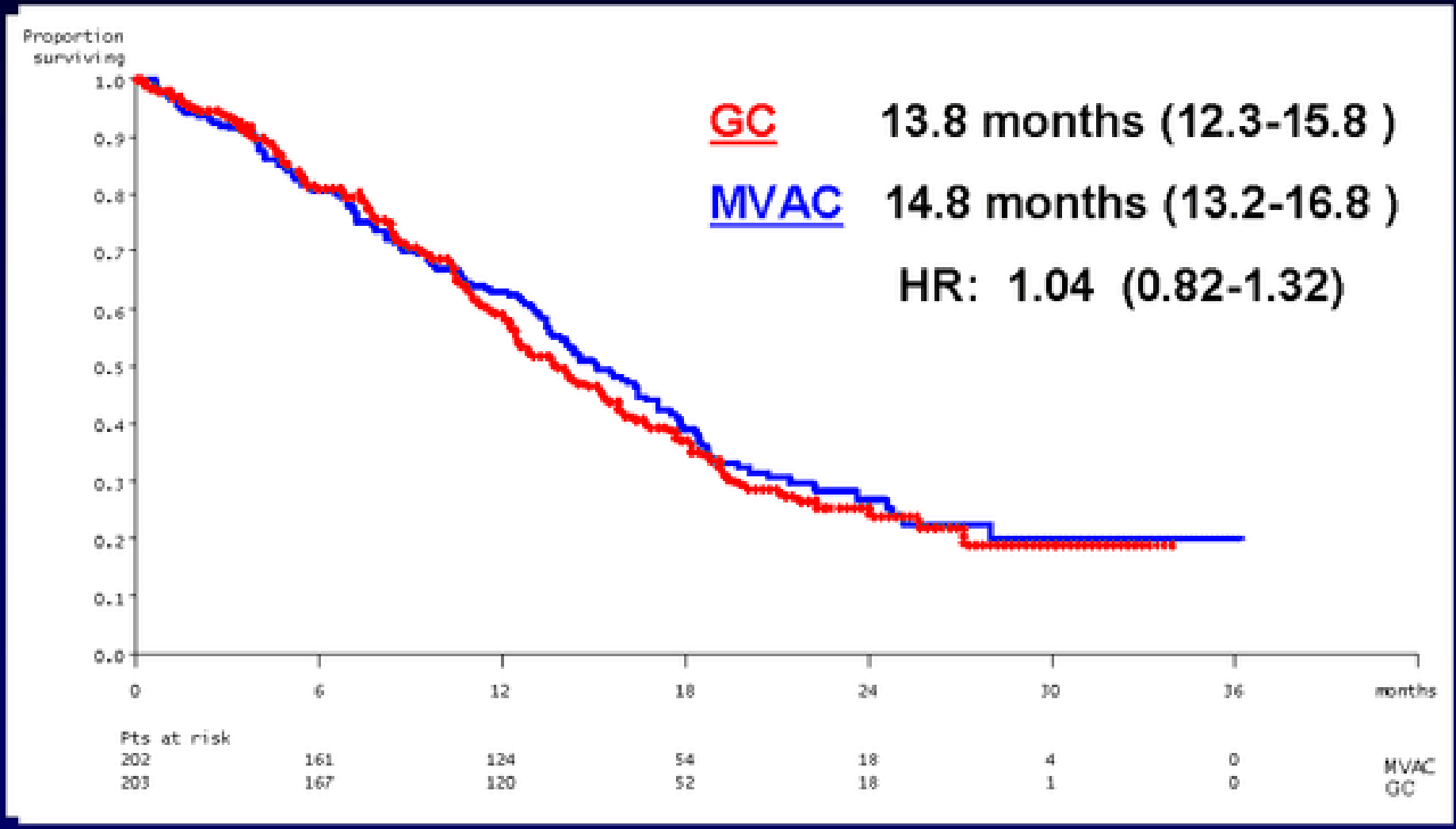
GC versus MVAC

Time to progressive disease



GC versus MVAC

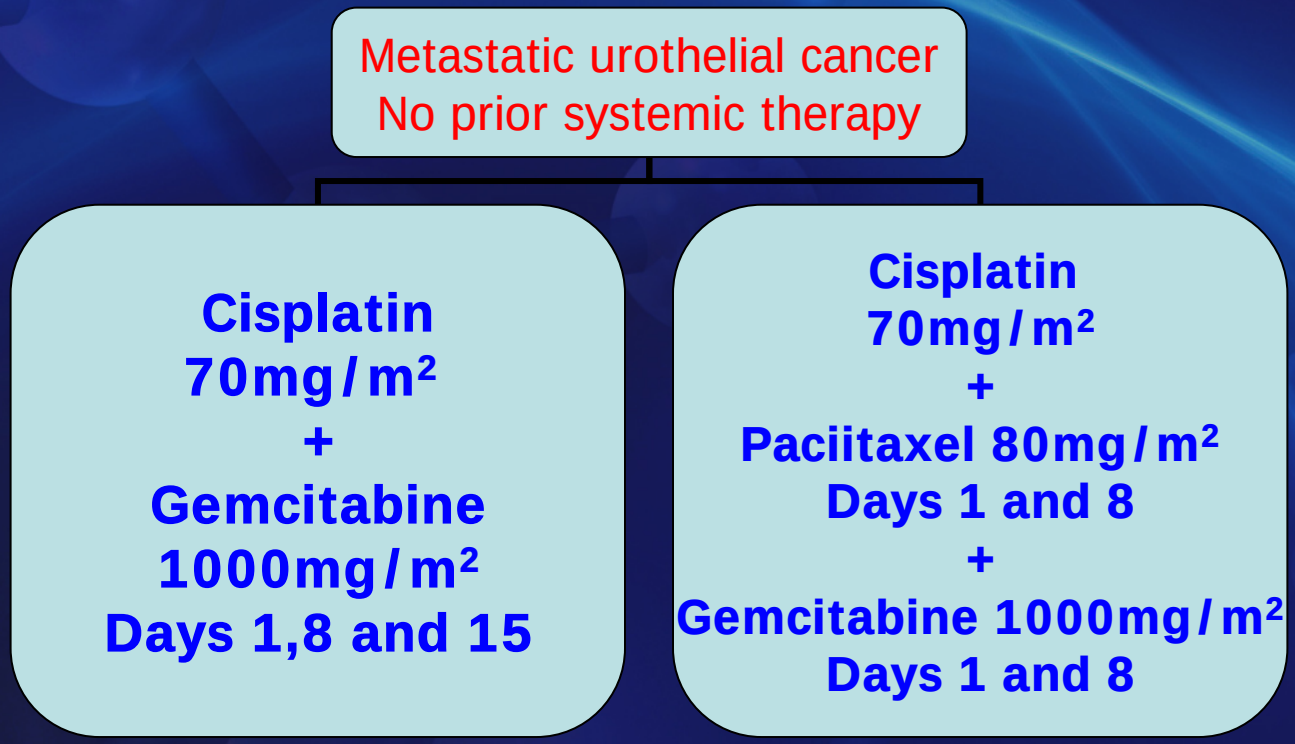
Overall survival



Urothelial Cancer EORTC/Intergroup Study

[Bellmunt et al. Abstract # LBA5030, ASCO 2007]

- Phase III trial



Results (627 patients)

	Cis+Gem	Cis+Tax+Gem
Med PFS	7.7 mos	8.8 mos
RR CR	46% 10%	57% (p=0.02) 15%
Med surv	12.8 mos	15 mos (p=0.10)
Febrile Neutropenia	3.8%	12.5%

Conclusion

- Triplet therapy improved response rates in metastatic bladder cancer
- Subset analysis revealed significant benefit for bladder primary and patients with 0 or 1 poor risk factors (PS of 1, or visceral mets)
- No statistically significant improvement in overall survival
- Hence current standard regimen remains cis+gem in metastatic disease

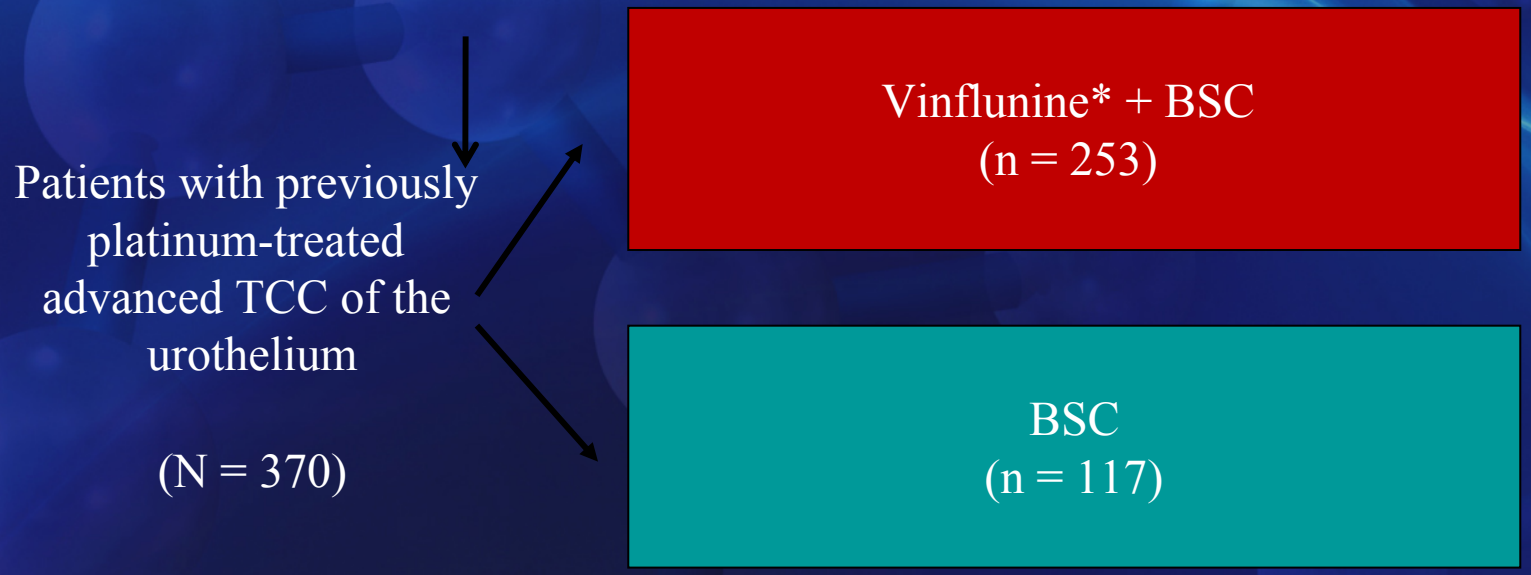
Therapies in metastatic disease after cisplatin based regimens

- Currently no established therapy in this setting

- As we use cisplatin and gem in neo/adjuvant setting, the evaluation of novel agents in frontline metastatic disease is even more important since we are likely treating disease refractory to this regimen.

Vinflunine + BSC vs BSC Alone in TCC of the Urothelium

Randomized 2:1



*Vinflunine dose based on ECOG PS and previous treatment
PS 0: 320 mg/m² every 3 weeks
PS 1 or PS 0 with previous pelvic irradiation: 280 mg/m² escalated to 320 mg/m²

Bellmunt J, et al. ASCO 2008. Abstract 5028.

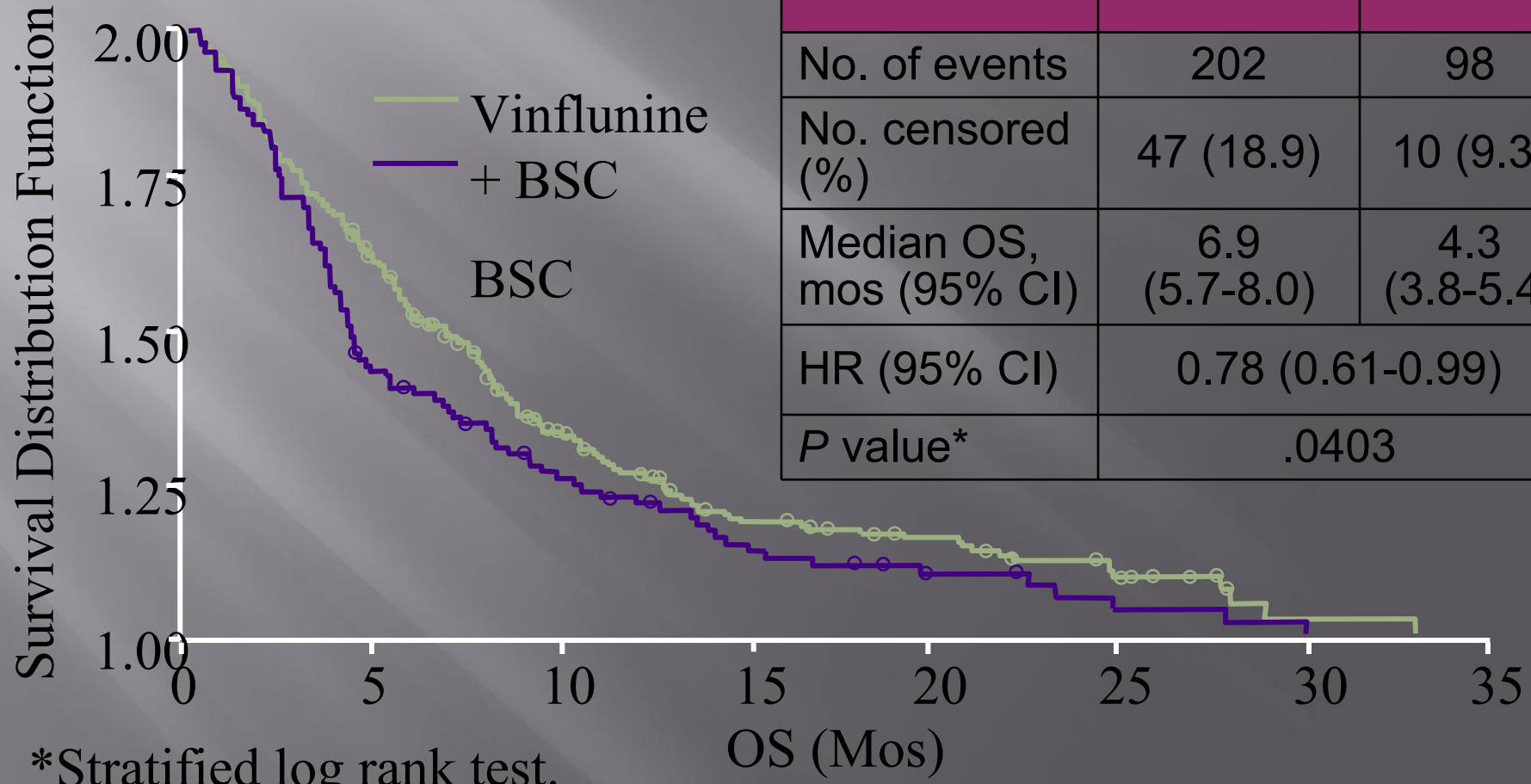
Efficacy Results: Secondary Endpoints

Number of Randomized Patients	Vinflunine + BSC (n = 253)		BSC (n = 117)
ORR (IRC) evaluable patients N (%) 95% CI	n = 185 16 (8.6) 5.0-13.7	*P* = .0063	n = 85 0
Disease control (%) IRC 95% CI	104 (41.1) 35.0-47.4	*P*= .0024	29 (24.8) 17.3-3.6
Median duration of response, mos IRC 95% CI	7.4 4.5-17.0	-	-
Median duration of disease control, mos IRC 95% CI	5.7 5.0-6.3	-	4.2 3.8-4.9
Median PFS, mos IRC 95% CI	3.0 2.1-4.0	*P* = .0012	1.5 1.4-2.3

Bellmunt J, et al. ASCO 2008. Abstract 5028.

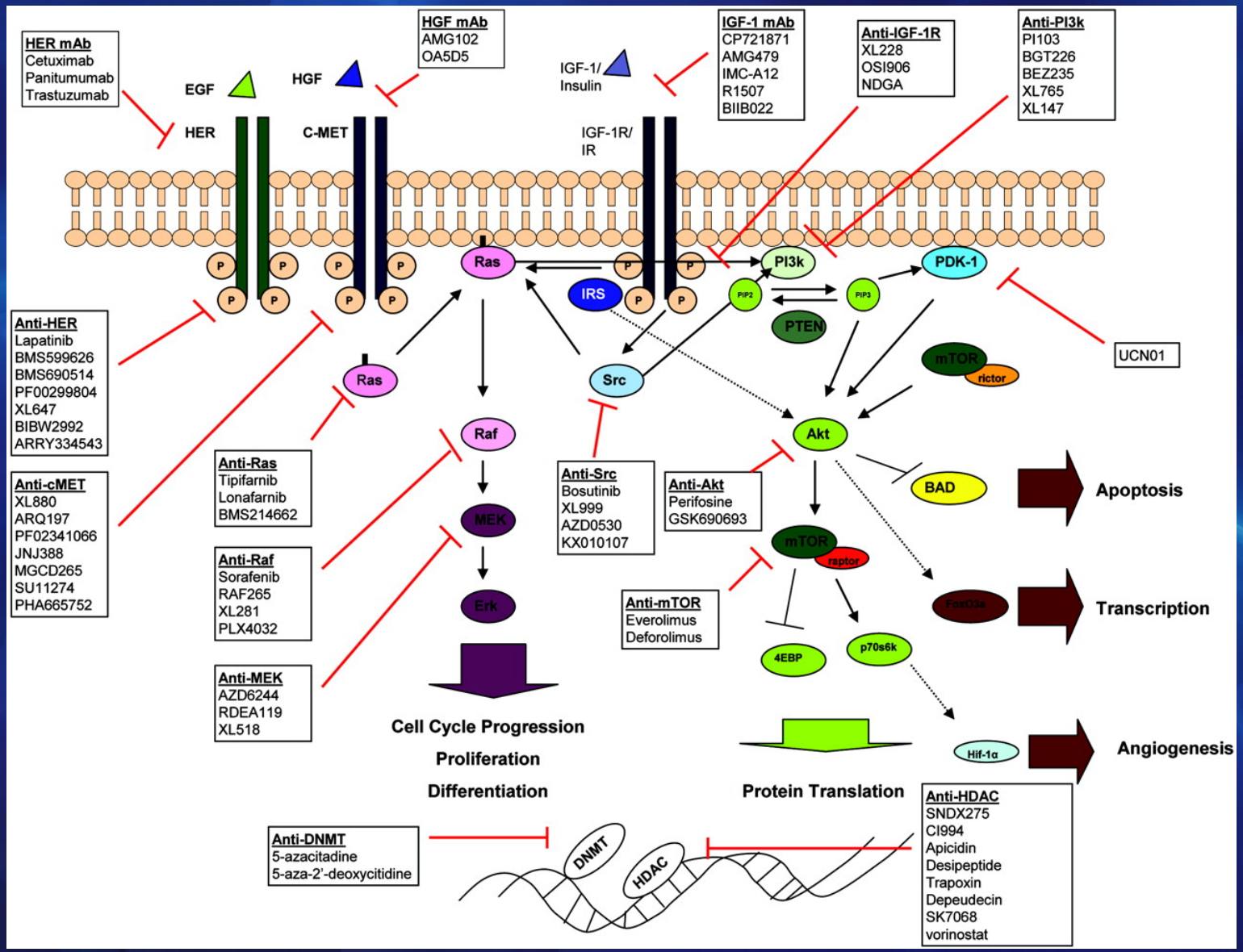
OS Results: Eligible Patients

	Vinflunine + BSC (n = 249)	BSC (n = 108)
No. of events	202	98
No. censored (%)	47 (18.9)	10 (9.3)
Median OS, mos (95% CI)	6.9 (5.7-8.0)	4.3 (3.8-5.4)
HR (95% CI)	0.78 (0.61-0.99)	
P value*	.0403	



*Stratified log rank test.

Bellmunt J, et al. ASCO 2008. Abstract 5028.



Ma et al. CA Cancer J Clin; 59:111-137 2009

National Cancer Institute

VEGF expression and signaling in UC

- Microvessel density, a histological measure of angiogenesis, has been correlated with stage, recurrence and survival.
- Increased expression of VEGF occurs in the tissue, serum, and urine in UC patients and correlates with stage and prognosis.
- Inhibitors of angiogenesis are active in UC preclinical models.

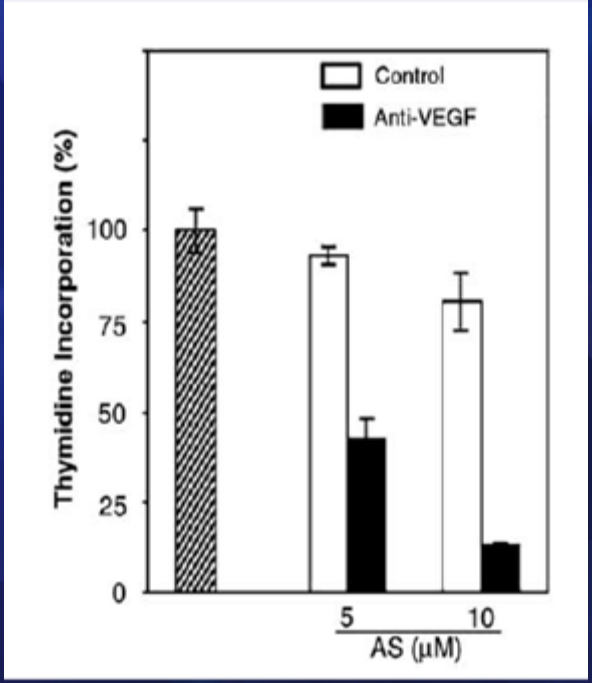


Figure 3 An autocrine function of VEGF in T24 cells. Inhibition of T24 cell proliferation by blocking endogenous VEGF expression. Cells were treated with anti-VEGF antisense oligonucleotide for 3 days. [^{3}H]thymidine (1 μCi/ml) was added to the culture during the last 4 h of incubation and cell proliferation determined by measuring the incorporation of [^{3}H]thymidine into DNA. The experiment was conducted with triplicate samples and repeated at least twice with similar results. In all, 5 and 10 μM of anti-VEGF antisense oligonucleotide significantly reduces the [^{3}H]thymidine incorporation in T24 cells compared with scrambled control oligonucleotide ($P<0.0005$ and $P<0.00004$, respectively)

Wu et al. Oncogene; 22: 3361–3370 2003.

ASCO 2010: Phase 2 first-line study of GC + bevacizumab (Hahn et al) – Abstract 4051

Key Eligibility Criteria

- Metastatic UC (mUC)
- ECOG PS 0-1
- Cr < 1.5 mg/dl
- No prior CTx for mUC
- No anticoagulation
- No CNS mets

→

ENROLLMENT

→

Cisplatin
70 mg/m^2 iv d1

Gemcitabine*
1000-1250 mg/m^2 iv d1,8

Bevacizumab
15 mg/kg iv d1

Cycle length = 21 days

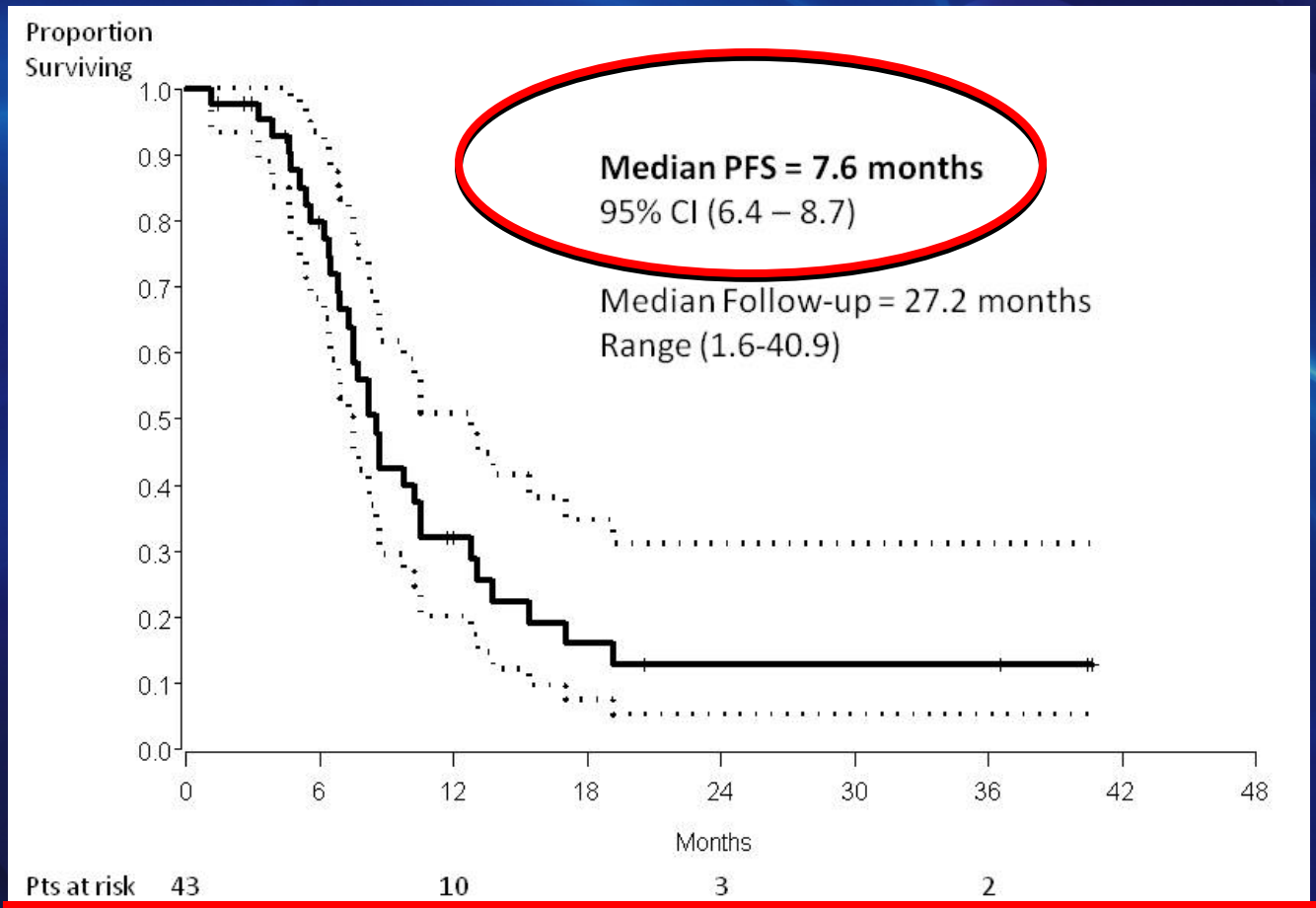
Update on phase 2 first-line study of GC + bevacizumab (Hahn et al)

	N=43	% (95% CI)
Complete Response*	8	19 (8-33)
Partial Response	23	53 (31-62)
Stable Disease	7	16 (7-31)
Progressive Disease	5	12 (4-25)

*Note: 3 patients underwent cystectomy for clinical CR. Pathologic results included – pTis N0, pT1 N2, pT3 N0

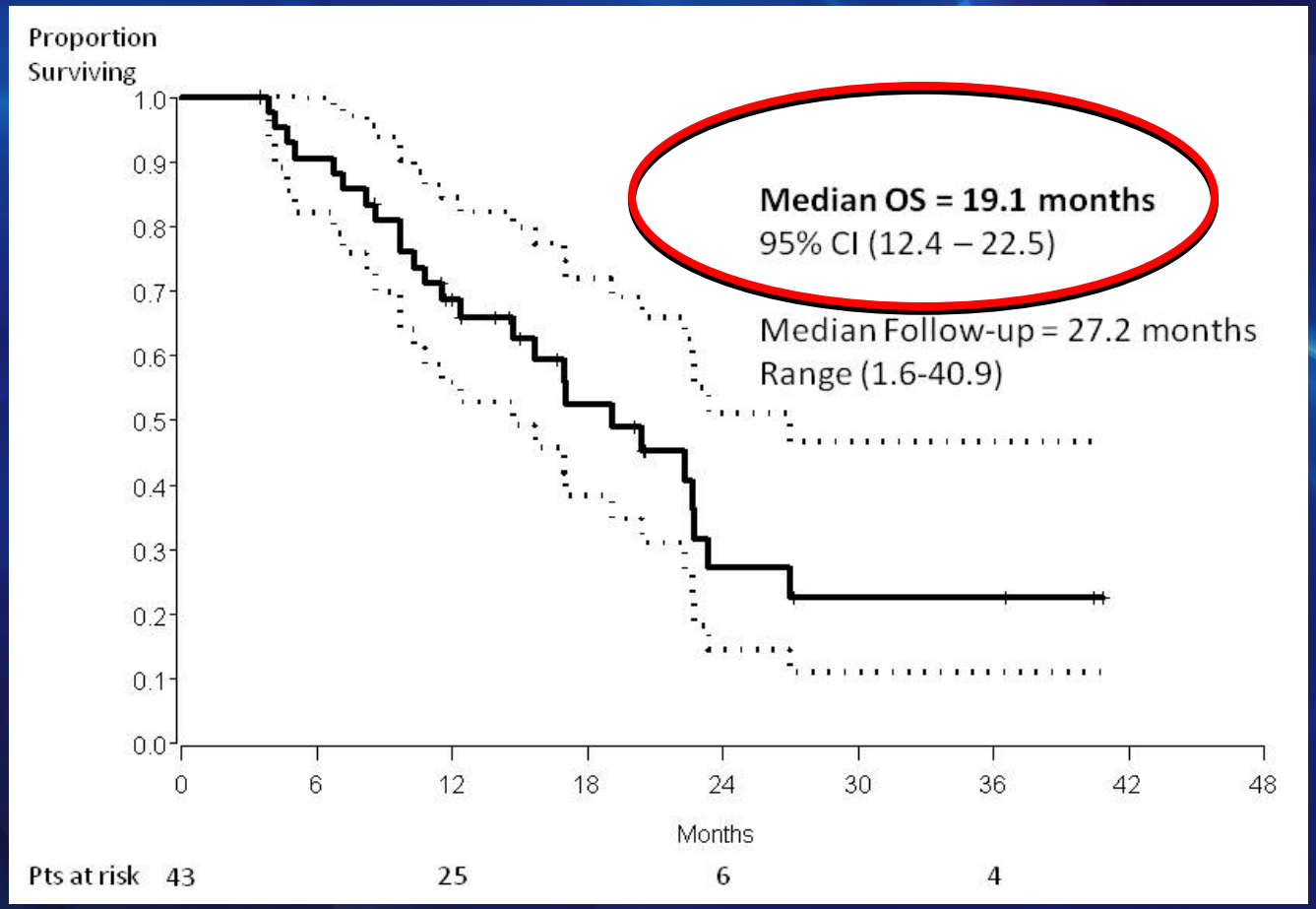
ORR = 72%

Update on phase 2 first-line study of GC + bevacizumab (Hahn et al)



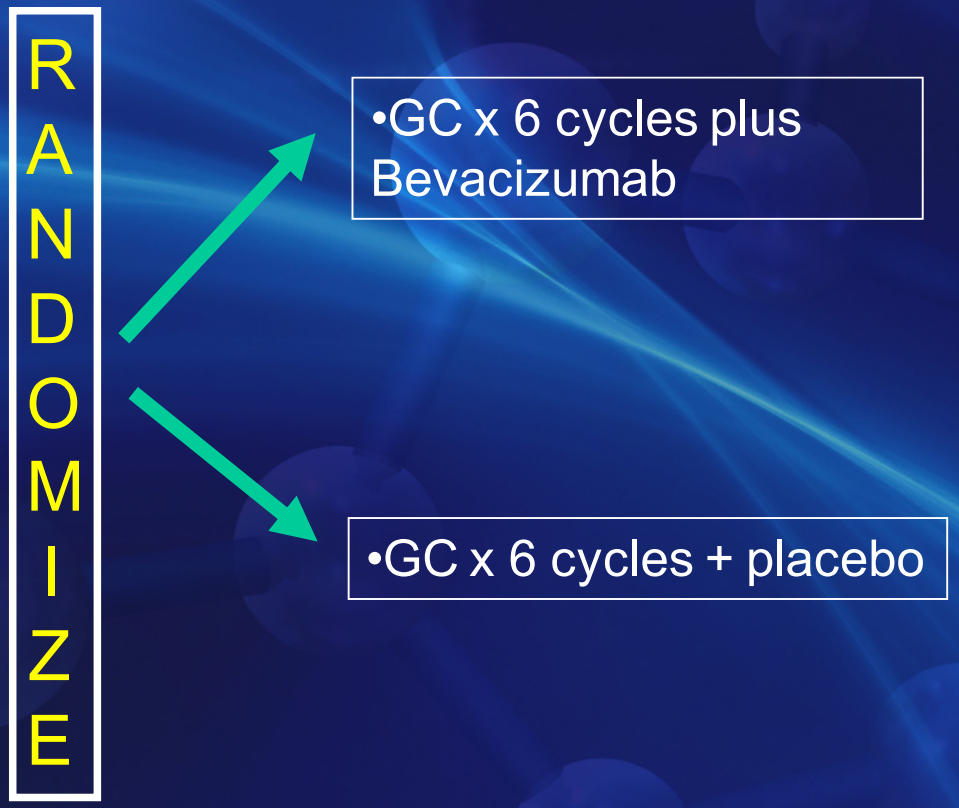
The primary study PFS endpoint was not achieved

Update on phase 2 first-line study of GC + bevacizumab (Hahn et al)



CALGB 90601TCC Trial: GC +/- Bevacizumab

- Metastatic TCC and/or
- Unresectable TCC
- Minimum CrCl 60 cc/m
- No Prior Chemotherapy

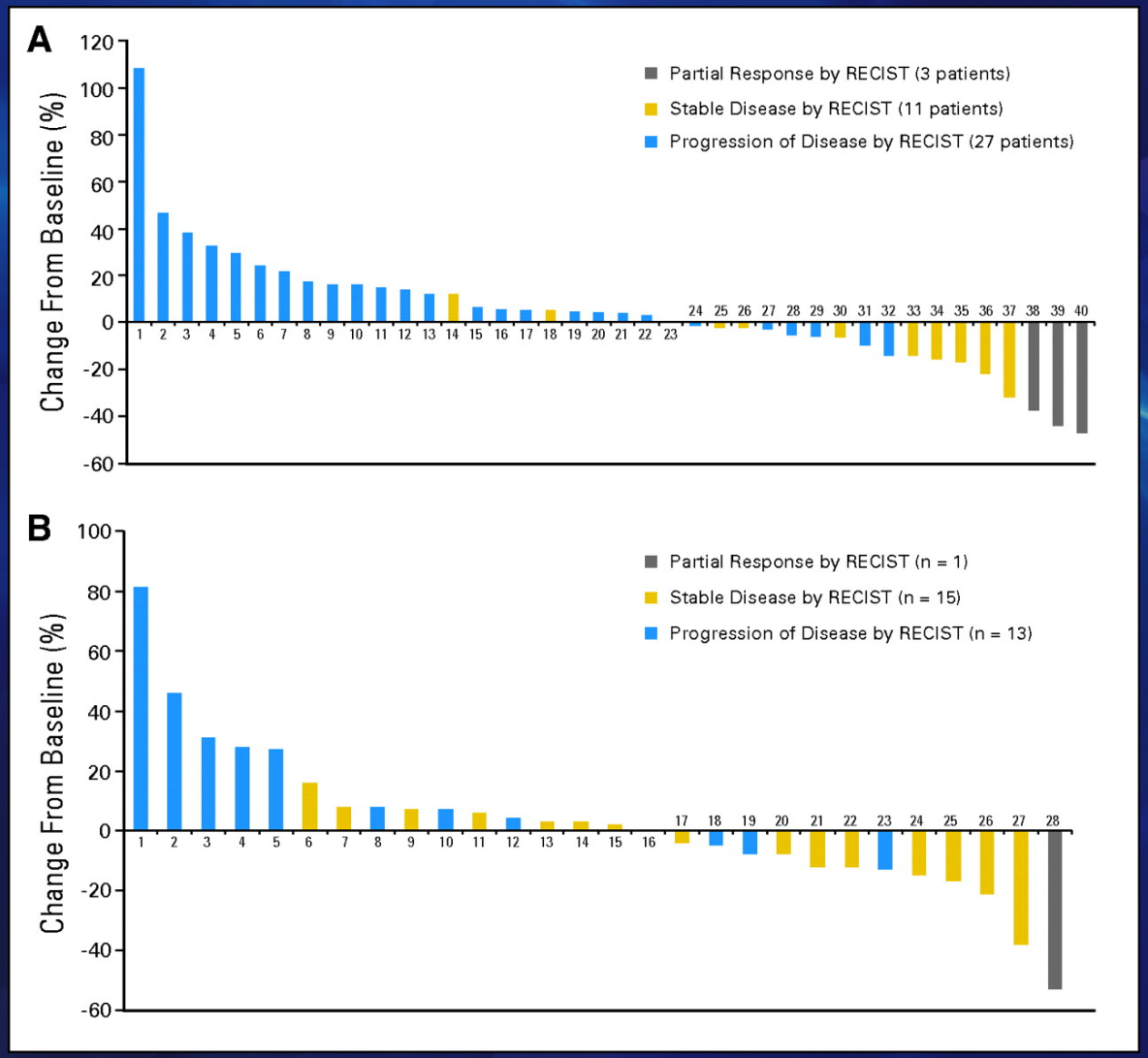


Toxicity monitoring with 5 planned analyses

PI - J. Rosenberg, MD

National Cancer Institute

Sunitinib in Second-line for Metastatic UC

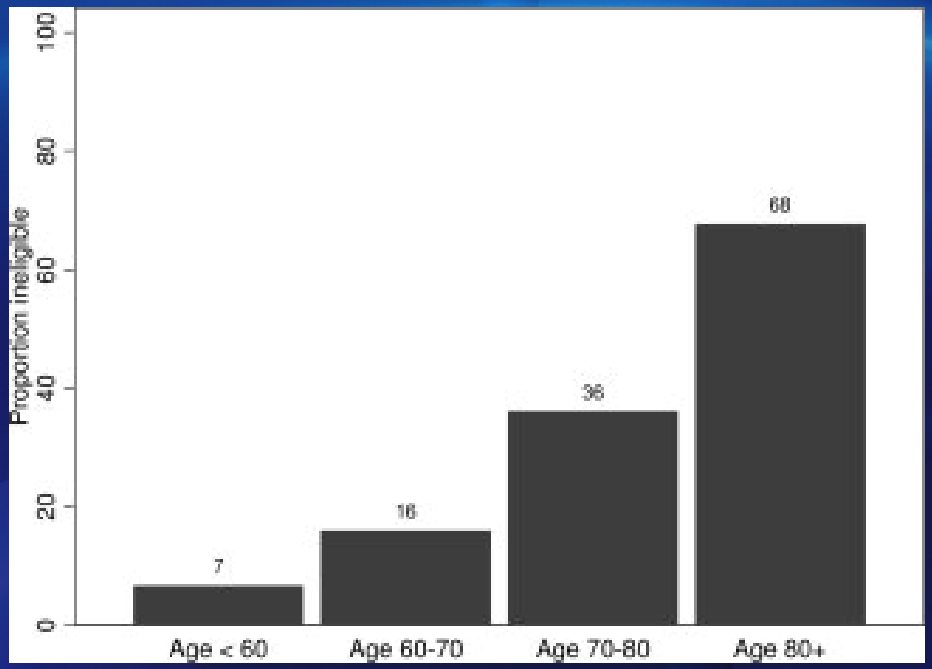


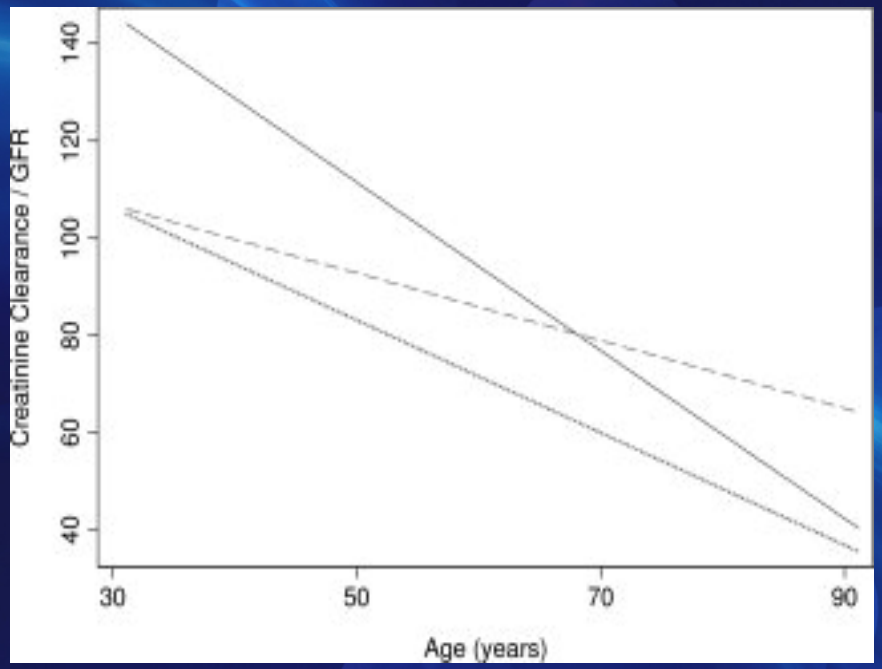
Gallagher et al. J Clin Oncol; 28:1373-1379 2010

ASCO 2010: First-line sunitinib in cisplatin ineligible pts (Bellmunt et al) – Abstract 4540

- First-line sunitinib monotherapy (n=38)
  - 50 mg/day (Schedule 4/2)
- Median age = 75
- Majority with bladder primary
- Visceral metastases (47%)
  - lung (29%), liver (10%), bone (8%)
- CDDP "unfit" criteria
  - CrCl < 60 ml/min but > 30 ml/min
- ECOG PS $\leq$ 1

Renal impairment and cisplatin eligibility





Using the CG equation, >40% of patients age >70 years are ineligible.

Dash et al. Cancer;107, 2006.

Selected Non-Cisplatin Regimens

Study	Trial	Regimen	ORR (%)	Median Survival (months)
Bellmunt et al. 1997	Phase 2	M-CAVI	39%	9
Dogliotti et al. 2007	Phase 2	Gem/Carbo	40%	9.8
Meluch et al.* 2001	Phase 2	Pac/Gem	54%	14.4
Gitlitz et al. 2003	Phase 2	Gem/Doc	33%	13
Neri et al. 2002	Phase 2	Gem/Epi	57%	16
Bellmunt et al. 2010	Phase 2	Sunitinib	9%	8.1
Quinn et al. 2010	Phase 2	Eribulin	38%	9.4

* includes previously treated patients

Summary

- Bladder cancer is one of the most common and deadly cancers
- Neoadjuvant chemotherapy improves survival in patients with muscle invasive disease
- Role and regimens of adjuvant chemo still require more studies.
- GC is an alternative and less toxic therapy than MVAC for metastatic BC.
- Newer combinations and additional targeted therapy trials are needed