

Bladder Cancer

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Bladder Cancer Demographics

- Estimated Worldwide Annual Incidence:
 - 261,000 new cases
 - 115,000 deaths
- Peak incidence in the 7th decade
- Male to Female ratio of 3:1

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Bladder Cancer as a Proportion of All Cancers (in each country)

- Cyprus 7.5%
- Israel (Jews) 5.9%
- Israel (Arabs) 5.0%
- Egypt 10.1%
- Jordan 5.7%
- U.S. SEER 4.3%

Bladder Cancer is one of the most common cancers in the Middle East

Bladder Cancer Histology (worldwide)

- 90%-95% transitional cell carcinoma (TCC)
- 3%-7% squamous,
- 1%-2% adenocarcinoma,
- Other less common histologies are small cell, carcinosarcoma and sarcoma

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Histologic Distribution

Histology	Egypt	Jordan	U.S.
• Squamous Cell	25.5%	1.8%	1.5%
• Transitional Cell	62.9	90.8%	94.9%
• Adenocarcinoma	5.7%	3.8%	1.2%
• Other/Unspecified	5.3%	3.4%	1.6%
• Sarcoma	0.4%	-	0.2%

Bladder Cancer Risk

Industries associated with higher risk:

- aluminum,
- paint dye
- petroleum,
- rubber
- textile
- hairdressers

Bladder Cancer Risk

- Risk factors for transitional cell carcinoma:
 - Smoking
 - Arylamines, Amides and Azodyes
 - Water chlorination byproducts
 - Arsenic
 - Chemotherapies (Cyclophosphamide, Ifosfamide)
 - Chronic inflammation
 - Radiation

Bladder Cancer and Parasitic Schistosomiasis

- *S. Haematobium* causes chronic inflammation which can lead to bladder cancer
 - 60% to 90% of cancers are Squamous Cell
 - 5% to 15% are adenocarcinoma
 - A small proportion are transitional cell carcinoma

Bladder Cancer and Parasitic Schistosomiasis

- S. Haematobium control programs have lowered the prevalence of the infection in Egypt
- In 1983, the prevalence was 35%
- In 2003, the prevalence was 1.7%

– Egyptian Ministry of Health and Population, 2002

Treatment of Metastatic or Unresectable Transitional Cell Carcinoma

- The most widely accepted therapy is MVAC administered in a 28 day cycle
 - Methotrexate 20mg/m² day 1, 15, 21
 - Velban 3mg/m² day 2, 15, 21
 - Adriamycin 30mg/m² day 2
 - Cisplatin 70mg/m² day 2
- MVAC and other bladder cancer therapies such as gemcitabine/cisplatin are commonly used to treat other histologies although clinical trials data are scarce

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Treatment of Metastatic or Unresectable Transitional Cell Carcinoma

- MVAC in stage 4 disease
 - Complete and Partial Response 36%-65%
 - Median Survival 12.5 to 14.8 Months
 - Toxic Deaths 3% to 5%

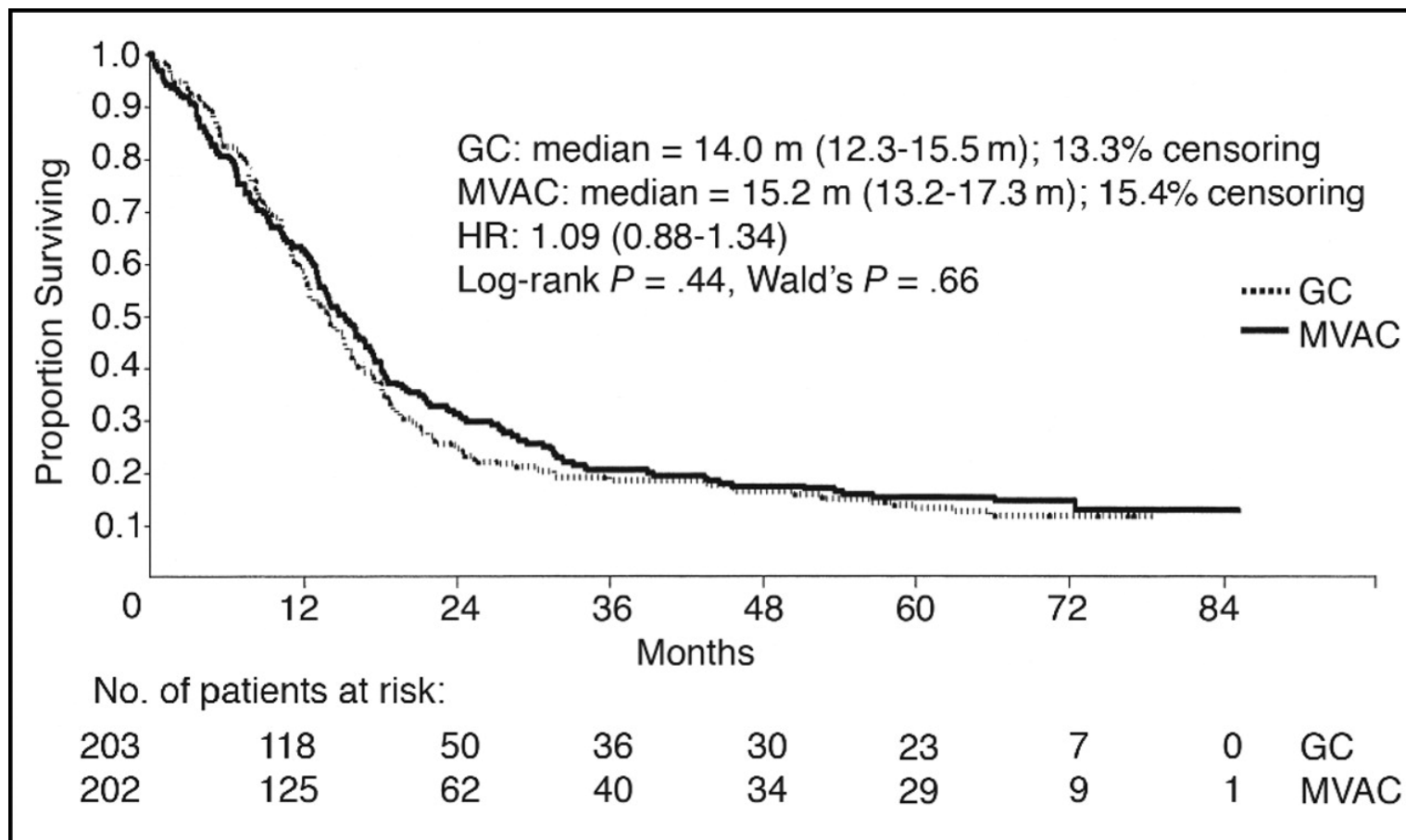
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Treatment of Metastatic or Unresectable Transitional Cell Carcinoma Gemcitabine and Cisplatin vs MVAC

Adverse Event	GemCis	MVAC
Neutropenic Sepsis	1%	12%
Admission Fever-Neutropenia	9%	49%
Use of Colony Stimulating Factors	6%	21%
Severe Mucositis	1%	22%
Death	1%	3%
Complete and Partial Remission	50%	46%
Complete Remission	12%	12%

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Fig 1. Kaplan-Meier curves for overall survival



von der Maase, H. et al. J Clin Oncol; 23:4602-4608 2005

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Doublets in Phase II Trials of advanced TCC

Regimen	Pts	CR	OR	Survival (mos)
Cisplatin/Gemcitabine	121	20%	44%	13.2
Cisplatin/Paclitaxel	81	11%	54%	10-13
Cisplatin/Docetaxel	91	15%	54%	8-13.6
Carboplatin/Paclitaxel	210	13%	45%	8.5-9.5
Carboplatin/Gemcitabine	63	13%	59%	Not Reported

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Carboplatin vs Cisplatin Response (R) in Advanced Bladder Cancer

	Complete R		Overall R	
	Cis	CBDCA	Cis	CBDCA
MVAC versus CBDCA, MTX, VLB	17%	0%	52%	39%
MVEC versus MVE- CBDCA	25%	11%	71%	41%
Cis-Gem vs CBDCA-Gem	23%	9%	66%	59%

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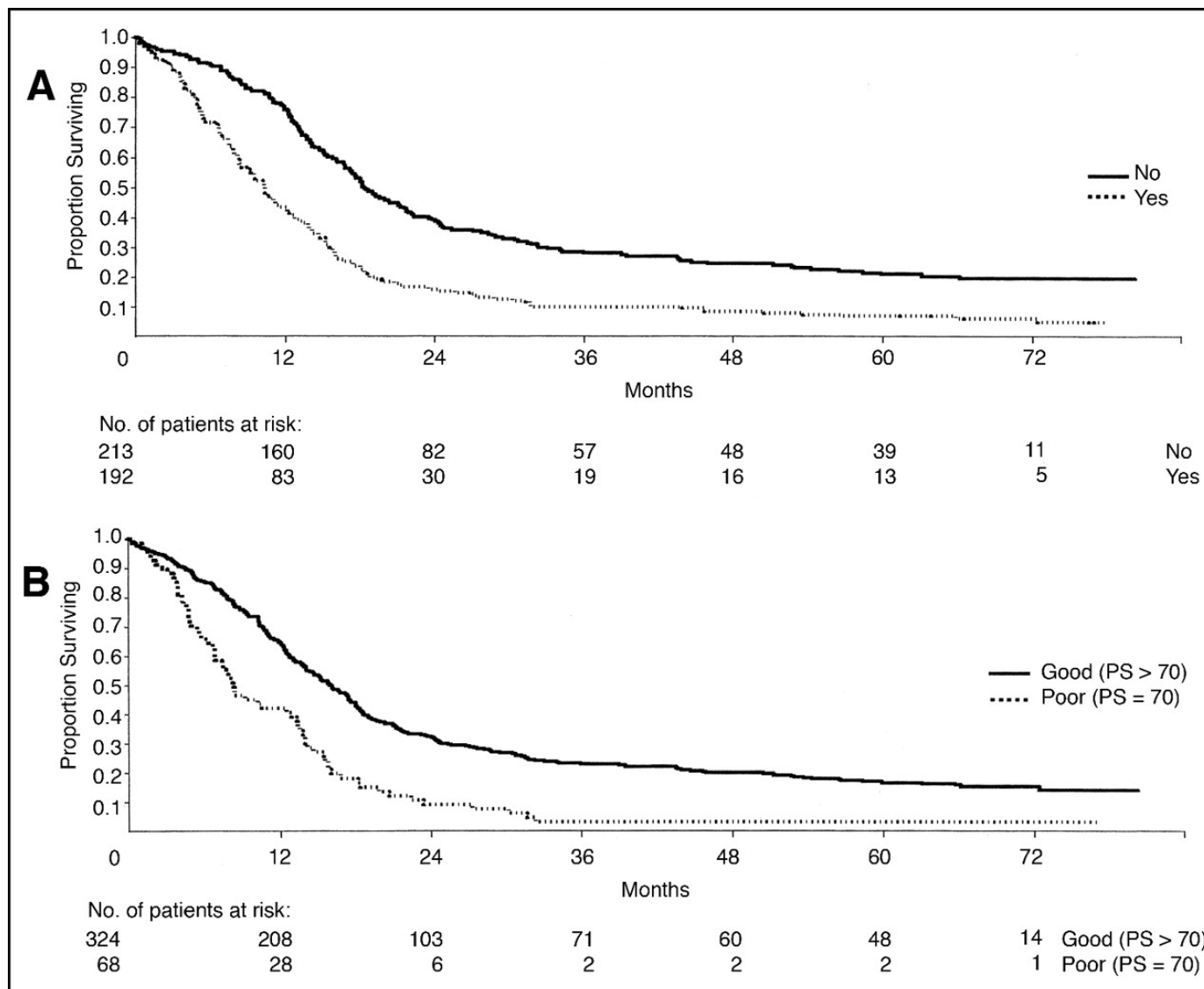
Non Platinum Therapies

Study	Agents	Patients	Complete Response	Overall Response
Kaufman	Pac/Gem	18	11%	39%
Meluch	Pac/Gem	16	9%	57%
Gitlitz	Gem/Doc	14	14%	13%
Neri	Gem/Epi	26	26%	16%

Prognostic Factors

- **Patients with good performance status do better**
- **Patients with disease restricted to lymph nodes (no visceral metastases) do better**
- **Patients with a good performance status and no visceral metastases can have a ten year survival rate of 24%, indeed some can be cured with chemotherapy**
- **Patients with poor performance status and visceral metastases do not do well**

Fig 3. Kaplan-Meier curves showing effect of (A) visceral metastases and (B) Karnofsky performance score (PS) on overall survival



von der Maase, H. et al. J Clin Oncol; 23:4602-4608 2005

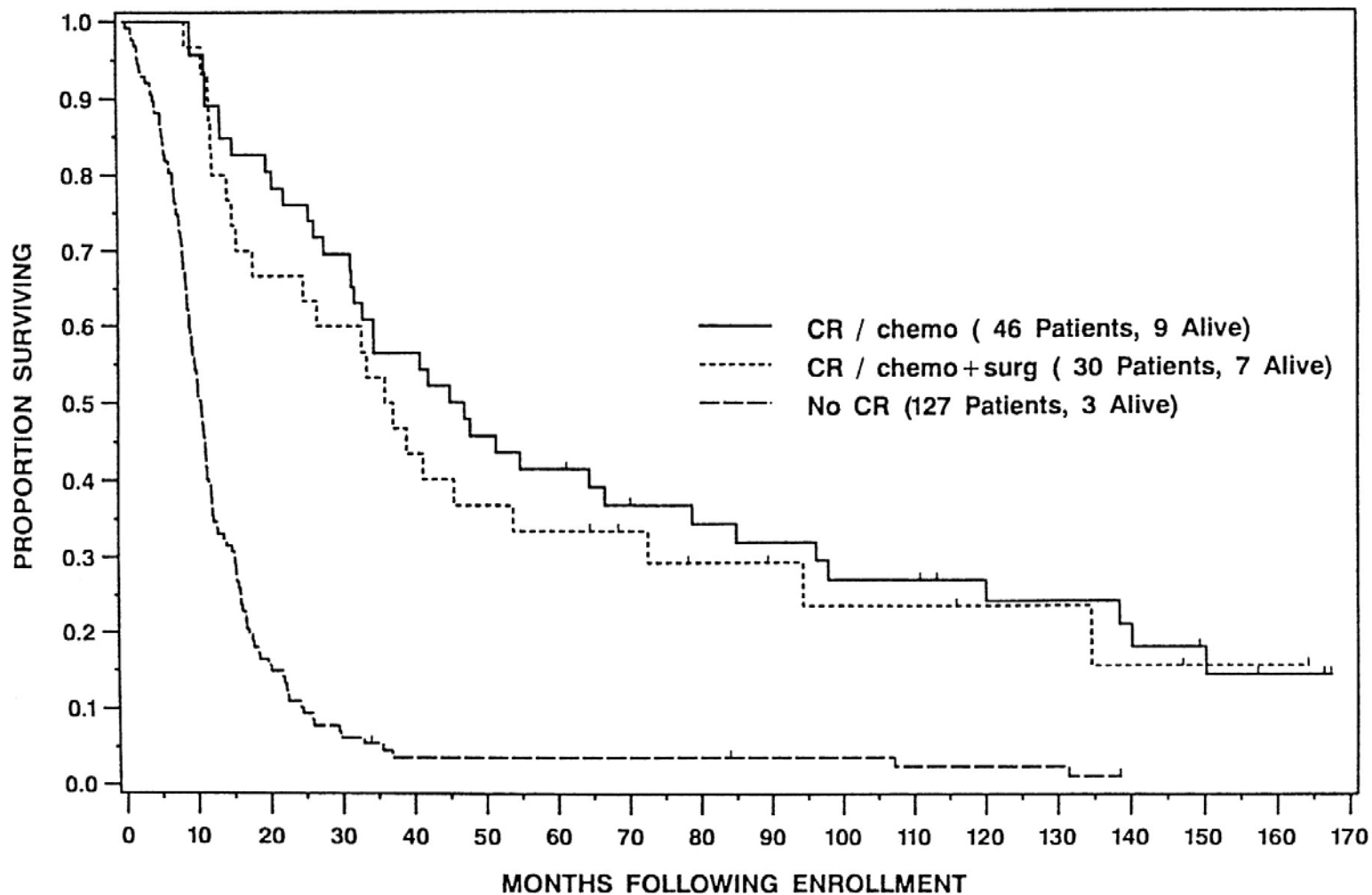
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Treatment Scheme Advanced TCC of the Bladder

- A patient with good performance status with good renal function is treated with MVAC plus G-CSF or Cis/Gem
- A patient with poor performance status or poor renal function is treated with a carboplatin combination
- A patient with two or more risk factors (visceral metastasis, poor performance status or poor renal function) is a candidate for a non-platinum doublet

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Fig 1. Survival of complete responders



Dodd, P. M. et al. J Clin Oncol; 17:2546 1999

Investigation

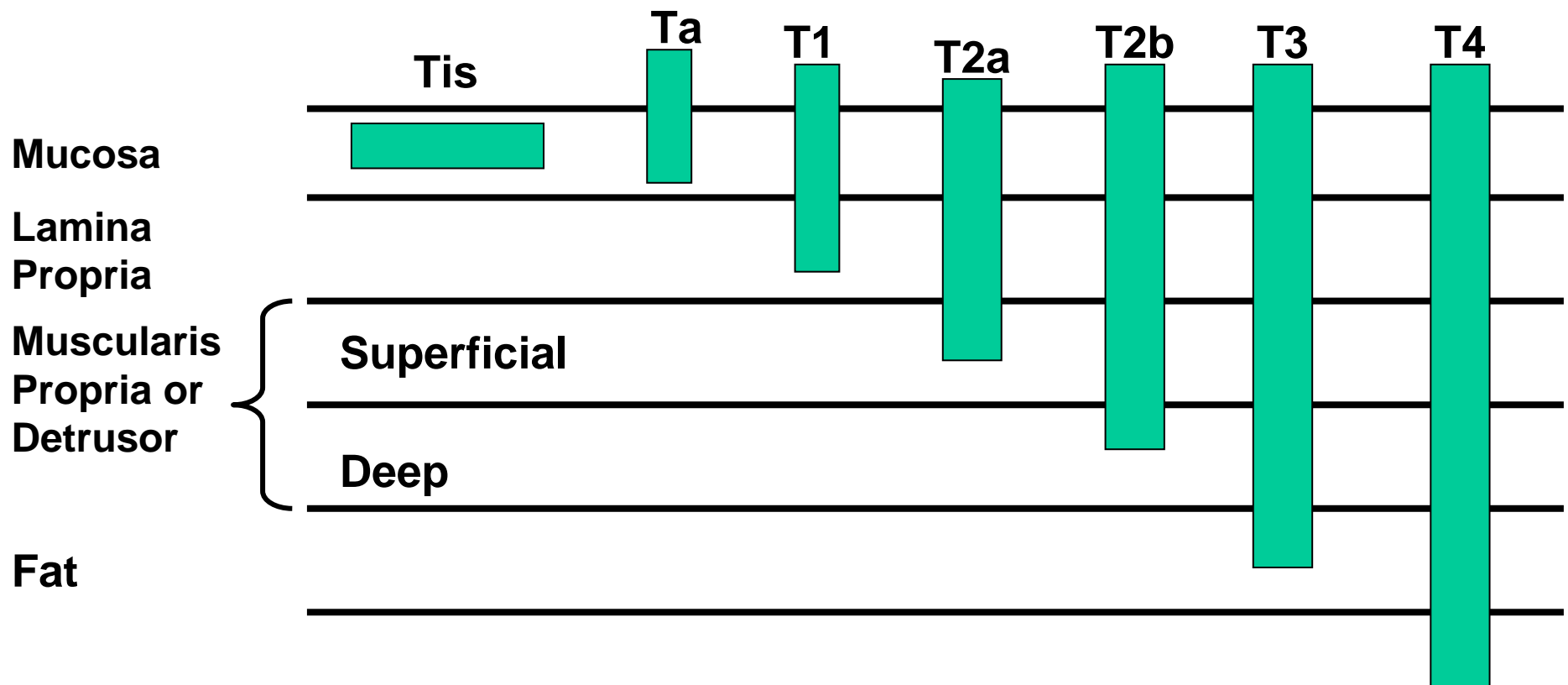
- Three and four drug regimens other than MVAC are under investigation and are not yet accepted.
- Targeted therapy using trastuzumab targeted to HER 2 neu is of interest and is being studied.
 - HER 2 positive urothelial carcinoma appears to be more aggressive and more likely to form visceral metastases

Investigation

- Gem/Cis with and without Paclitaxel
- Gem/Cis with Bevacizumab
- Etoposide
- Herceptin
- Pemetrexed
- Irinotecan
- Sorafenib

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Bladder Cancer Staging



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Five Year Survival Based on Pathologic Stage

Pathologic T2	59%
Pathologic T3	33%
Pathologic T4	25%

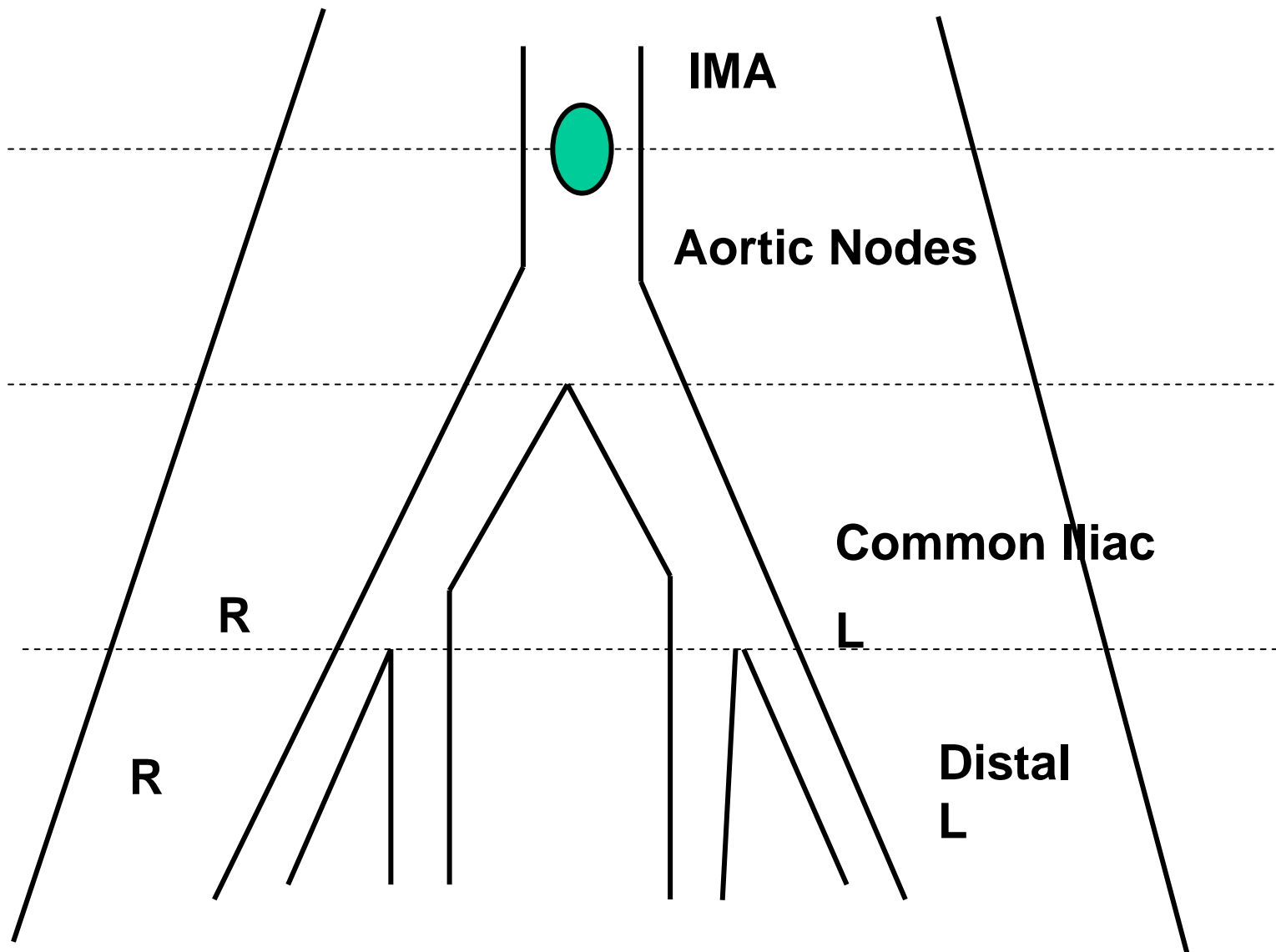
The Bladder Cancer Operation

- Male resection is a cysto-prostatectomy and a bilateral pelvic lymph node dissection
- Female resection is cystectomy, resection of a portion of the vaginal vault and a total abdominal hysterectomy, bilateral salpingo-oophorectomy and a bilateral pelvic lymph node dissection
- Diversion of the ureter can be with an ileal conduit or a neobladder connected to the urethra

The Bladder Cancer Operation

- The lymph node dissection should go up to the area of the common iliacs and preferably to the aortic region
- A large number of bladder cancer operations do not sample the iliac and aortic nodes adequately

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The Bladder Cancer Operation

- The proportion of lymph nodes positive for cancer has prognostic value. In some series:
 - Those with less than 20% of lymph nodes positive for cancer had a five year survival of 50%.
 - Those with more than 20% positive had a five year survival of less than 10%

Bladder Preservation

- Tumor size
- Tumor stage
- Multi-focality and Location
- Associated CIS and past history of disease
- Histology (not for Squamous, Adeno or Small Cell)
- Age and comorbidities
- Patient Compliance

Bladder Preservation Muscle Invasive Disease

- Partial Cystectomy for a small T2 or T3 tumor in a redundant area of the bladder
- Trans Urethral Resection (TUR) alone or with intravesicular therapy for a patient with a small amount of muscle involvement
- Larger tumors, even T3, may be treated with TUR and Chemo or TUR and XRT with radiosensitizer

Bladder Preservation Muscle Invasive Disease

- Small solitary tumor - No mass on exam under anesthesia
- No ureteral obstruction
- Visibly complete transurethral resection
- No residual T1 or T2 disease on restaging TUR usually done at 7 to 10 weeks
- CR with Chemo +/- XRT with TUR and cytology
- Cystoscopy is done on regular basis

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Bladder Preservation T2 Muscle Invasive Disease

- TUR, Chemotherapy (usually cisplatin) plus radiation to 66 Gray
 - **90% complete treatment**
 - **50% have complete response**
- At five years
 - **30% alive with bladder in place**
 - **40% alive without bladder**
 - **30% die of disease**

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Bladder Preservation Muscle Invasive Disease

Multi Modality Therapy (TUR Chemo XRT)

- **10-20% unable to complete therapy**
- **50-60% of complete responses develop new tumors in the bladder**
- **5% severe bladder difficulties due to radiation**
- **38-50% 5 year survival with intact bladder**
- **At risk for extravesical relapse especially in the ureter**

Neoadjuvant Therapy for TCC

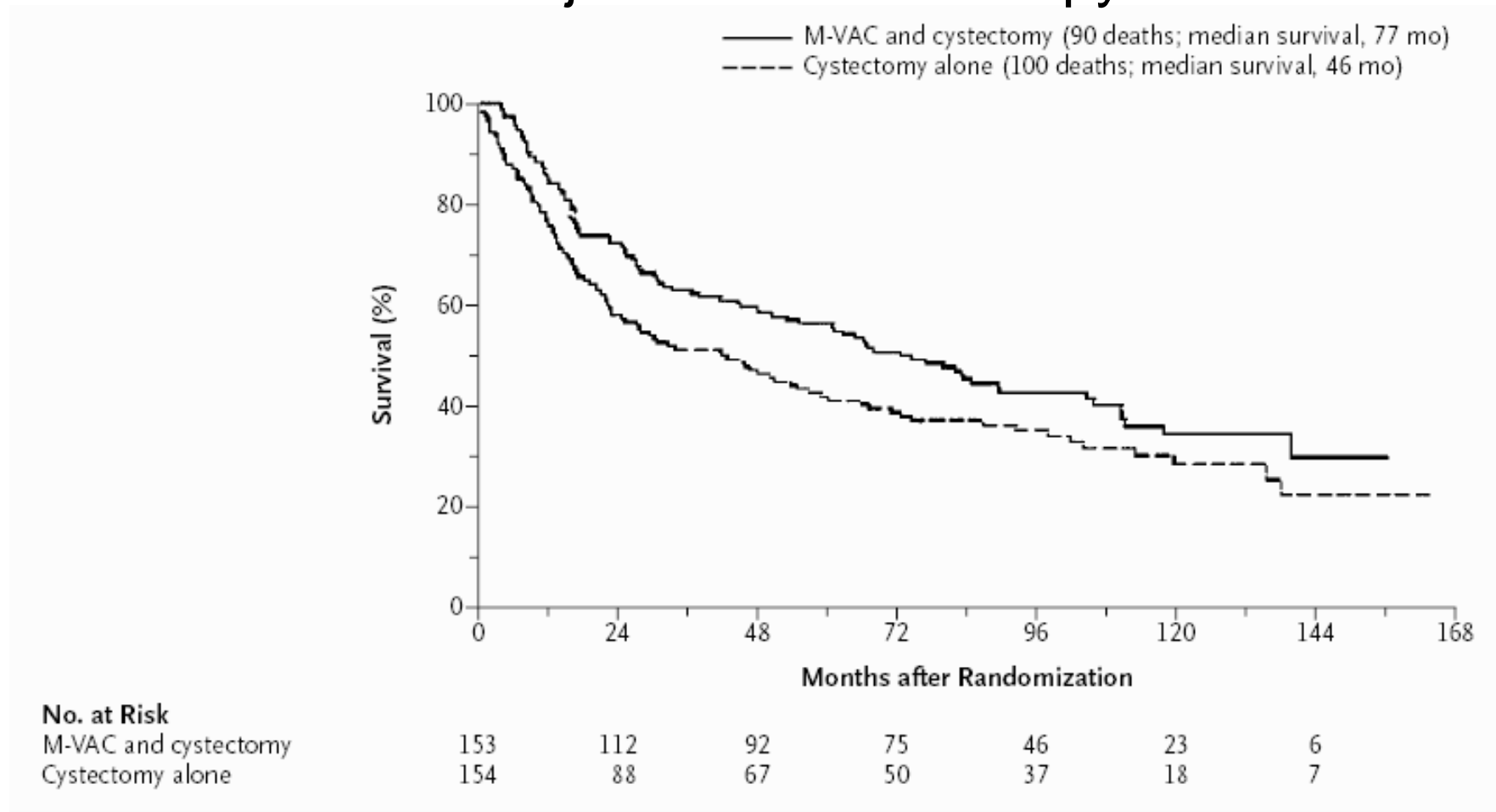
- SWOG 8710 Trial n=307
 - 3 cycles MVAC plus cystectomy vs cystectomy alone

	Median Survival	Alive at 5 yrs
– Surgery	46 Months	42%
– MVAC/Surg	77 Months	57%

- P=.05
- Groosman et al. NEJM 2003

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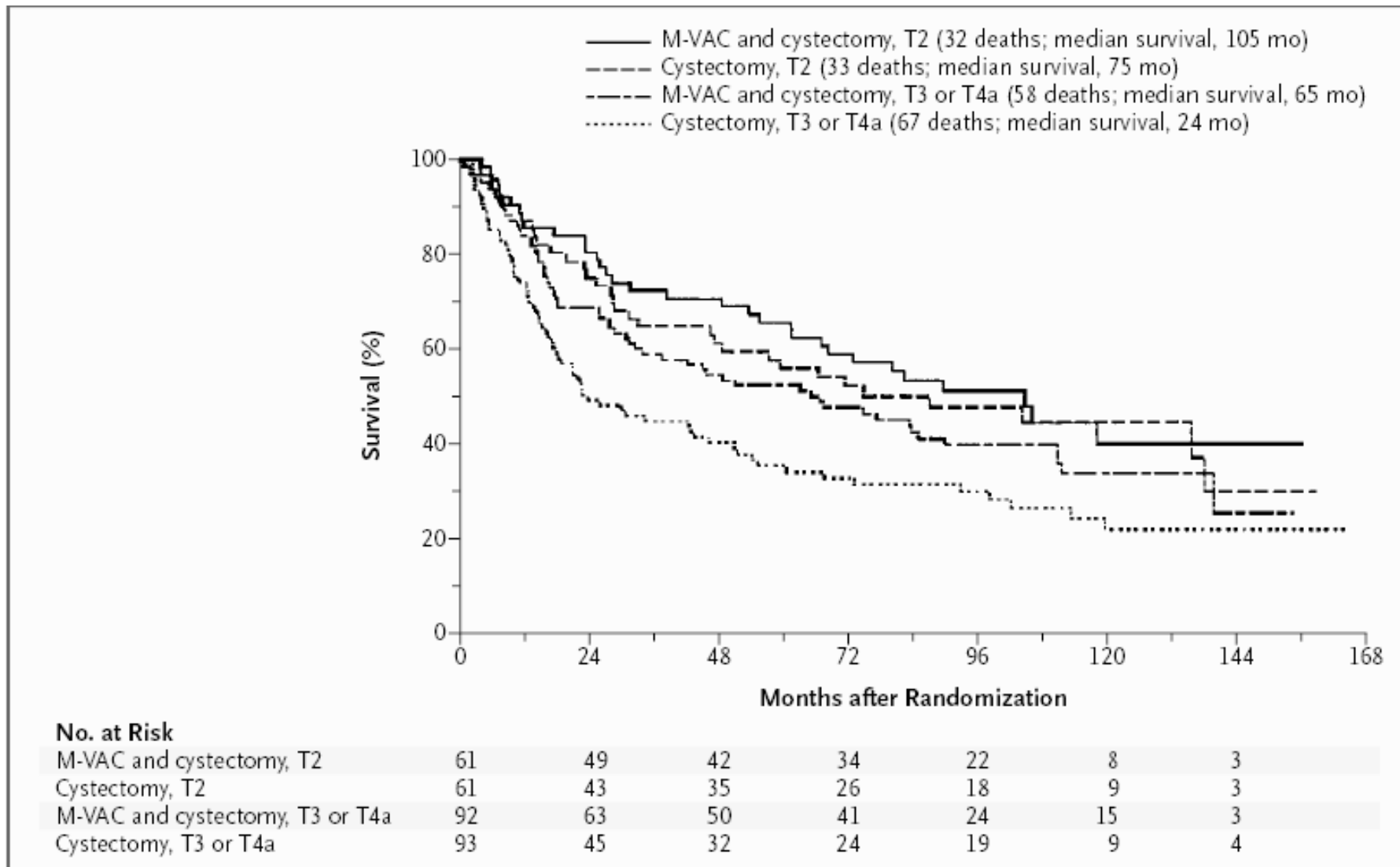
Neo-adjuvant Chemotherapy



Grossman et al, NEJM 349(9):859-866, 2003

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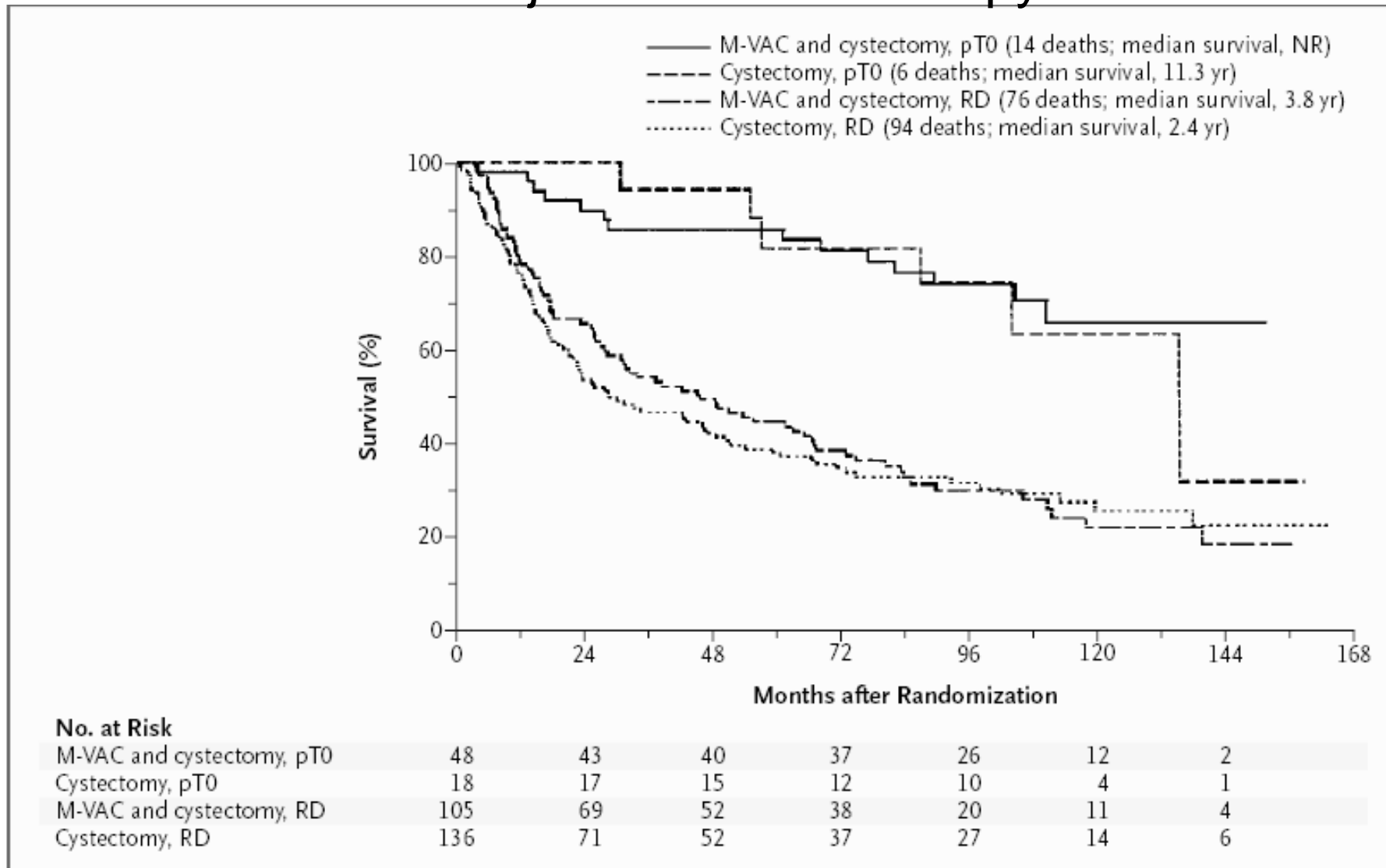
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Neo-adjuvant Chemotherapy

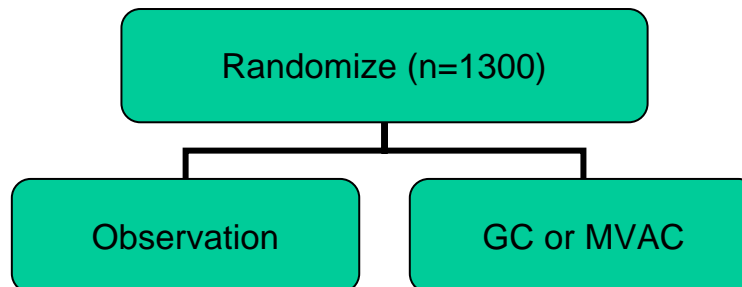


Grossman et al, NEJM 349(9):859-866, 2003

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Adjuvant Therapy TCC Bladder A Research Question

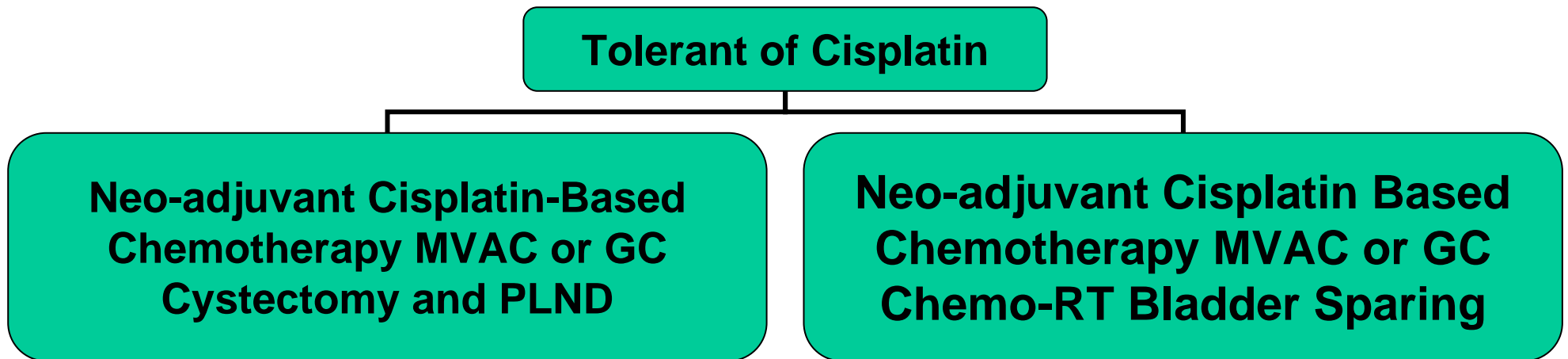
EORTC, SWOG, NCIC, and others are asking the question with patients with stage >T3 or Node positive tumors



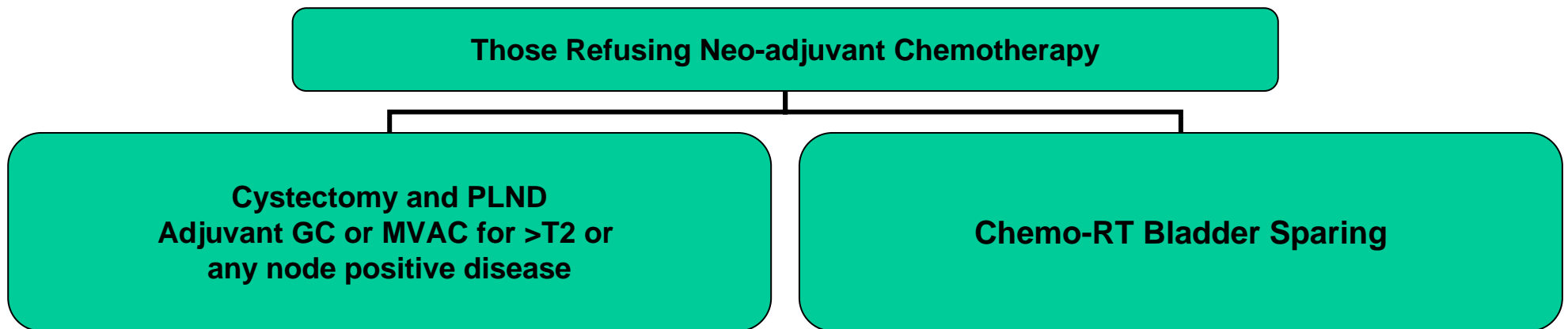
Trial assumes:

- **Adjuvant chemotherapy= neoadjuvant**
- **GC=MVAC in the adjuvant setting**

The Cystectomy Candidate (Standard Treatment)



The Cystectomy Candidate (Standard Treatment)



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Prognostic Factors for Superficial TCC

Favorable

Ta

Low grade

No dysplasia

Long tumor-free Interval

Unfavorable

T1

High grade

Carcinoma in-situ

Short tumor-free Interval

Favorable tend to “recur” in same site

Unfavorable tend to “progress” and become more invasive

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Prognostic Factors for Superficial TCC

The National Bladder Cancer Collaborative Group
probability of progression at 5 years

Probability of progression	Grade
2%	1
11%	2
45%	3

Superficial Disease

- Risk factors for progression to invasive disease
 - High grade
 - Tumor multiplicity
 - Size greater than 5 cm
 - Vascular invasion

Carcinoma in situ

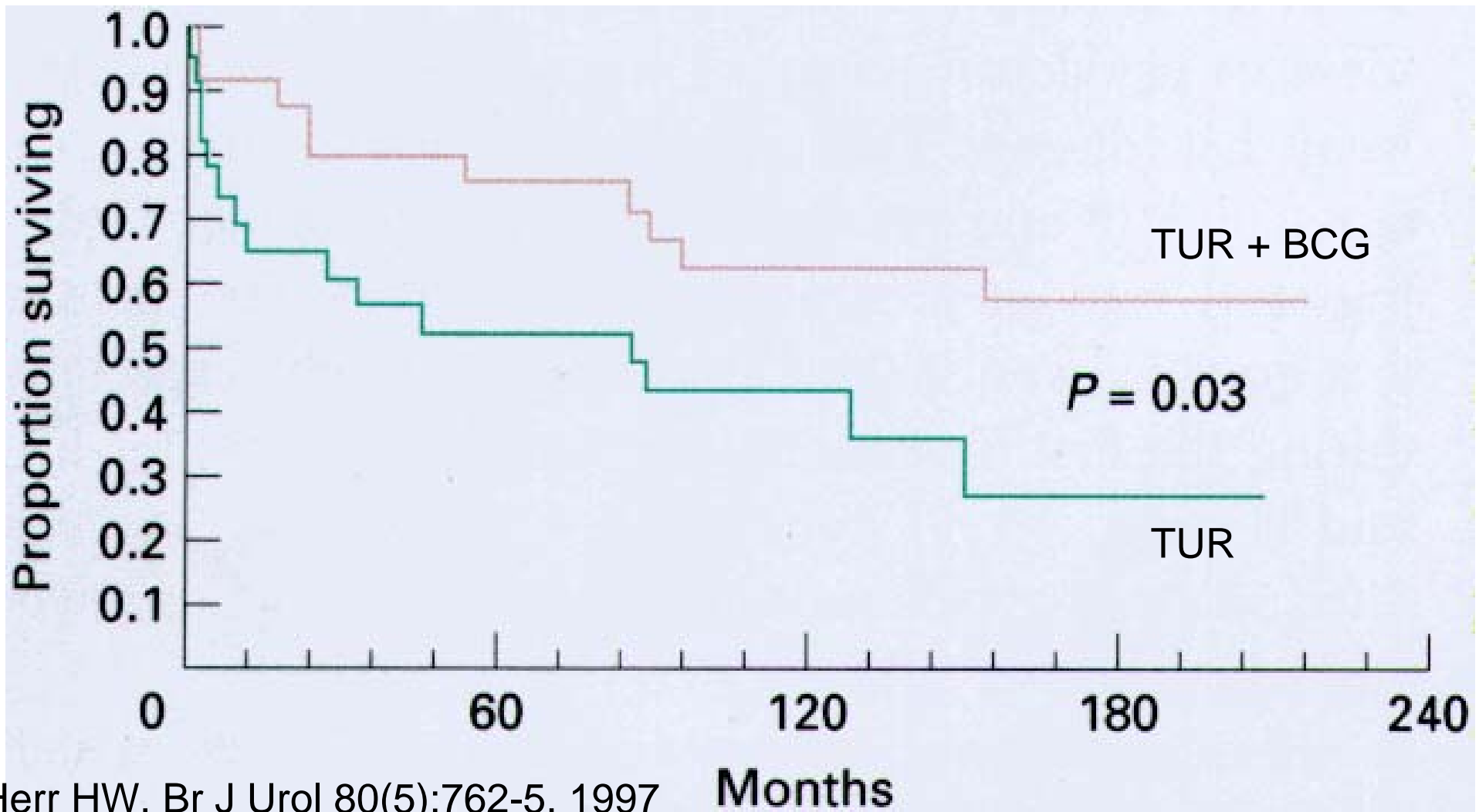
- Often (>90%) associated with papillary or nodular tumors.
- An isolated finding in less than 10% of cases
- Muscle invasion develops in more than half

Carcinoma in situ

- Symptoms include dysuria, frequency, and nocturia
- One-third are asymptomatic (commonly those with focal disease)

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Time to progression and survival of T1 bladder tumors
TUR vs TUR+BCG



Herr HW, Br J Urol 80(5):762-5, 1997

Months

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Intravesical Chemotherapy for Superficial TCC

- **BCG is superior to chemotherapy**
- **Chemotherapy has no effect on tumor progression (exception mitomycin C)**
- **Chemotherapy and BCG equally effective in papillary tumors. (Chemotherapy is used to treat papillary tumors in Europe but not U.S.)**
- **Chemotherapy reduces short term tumor recurrence. Its effect on long term tumor recurrence is unknown.**
- **Maintenance BCG or Chemotherapy of unproven benefit**
 - Akaza et al, Cancer 75(2):552-559, 1995

Treatment Scheme superficial or In-situ Carcinoma

