Current Treatment Approaches and Integration of Checkpoint Inhibitors into the Treatment of Urothelial Bladder Cancer

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Disclosures

No relevant conflicts of interest to disclose.

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Module 1

- Role of perioperative systemic treatment
- Use of neoadjuvant systemic therapy in pts not eligible for cisplatin
- Identification of pts with potentially curable UBC who should undergo cystectomy; optimal monitoring and follow-up
- Common sites of recurrence and optimal integration of salvage therapy into the bladder cancer management algorithm
- Role of the urologist in timely referral to a medical oncologist for consideration of treatment with an anti-PD-1/PD-L1 antibody

Introduction

- 25% of patients with bladder cancer either present with or later develop metastases.
- **Systemic chemotherapy** is standard approach for inoperable locally advanced or metastatic urothelial malignancies.
- Initial response rates are high however:
  - Median survival 15 months
  - 5YS <15%
- 2nd line chemotherapy has very limited role

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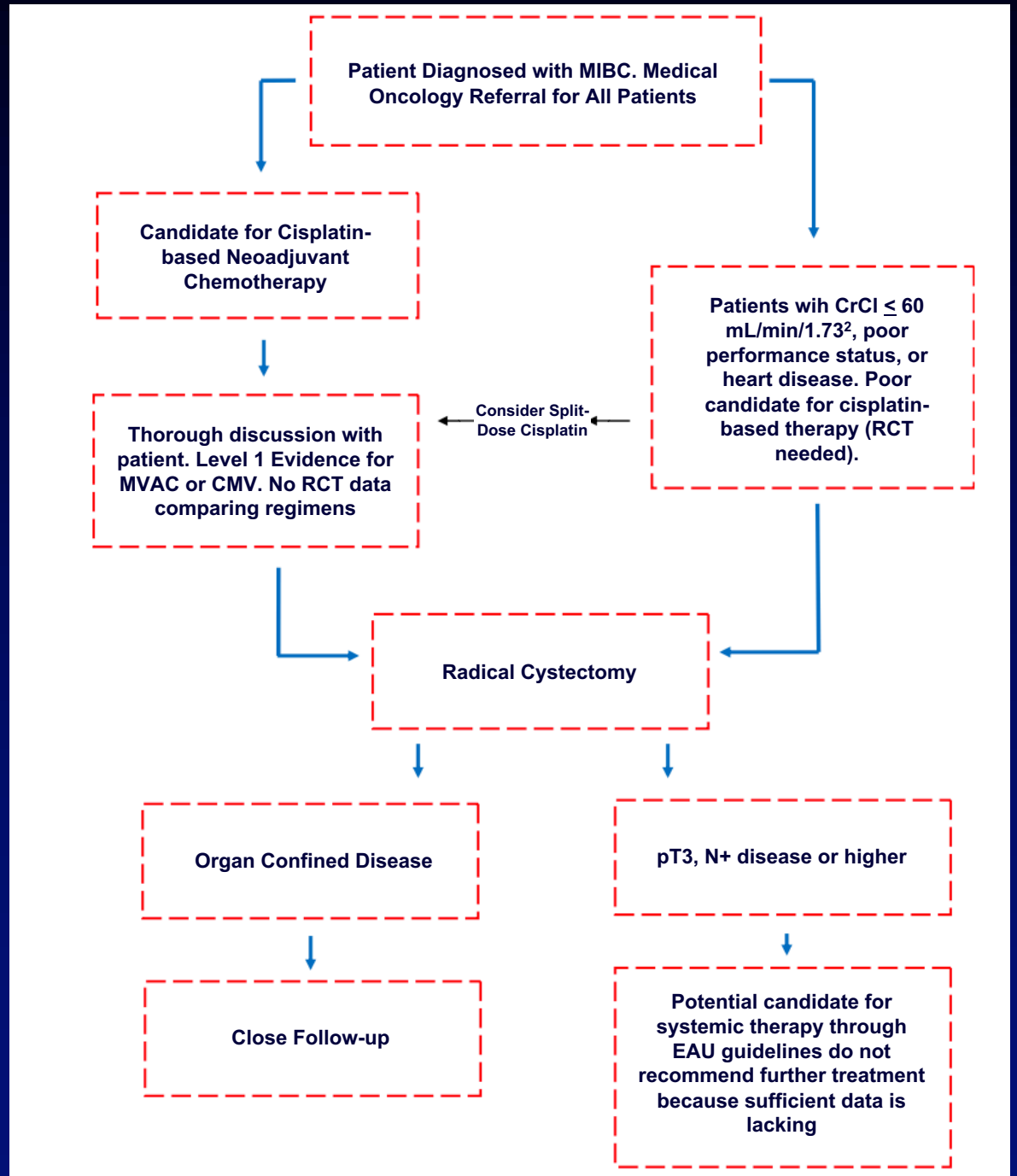

Flow-chart of current management paradigm for patients with MIBC. RCT = Randomized Controlled Trial.

Current and recent clinical trials for perioperative systemic therapy for muscle invasive bladder cancer: a systematic review.

Vashistha, DI Quinn, T Dorff, S Daneshmand. *BMC Cancer* 2014;14:966.

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A Multi-Institutional Analysis of Outcomes of Patients with Clinically Node Positive Urothelial Bladder Cancer Treated with Induction Chemotherapy and Radical Cystectomy

KZ Shoshtari, K Zargar, Y Lotan, JB Shah, BW van Rhijn, Siamak Daneshmand, Philippe E. Spiess and Peter C. Black

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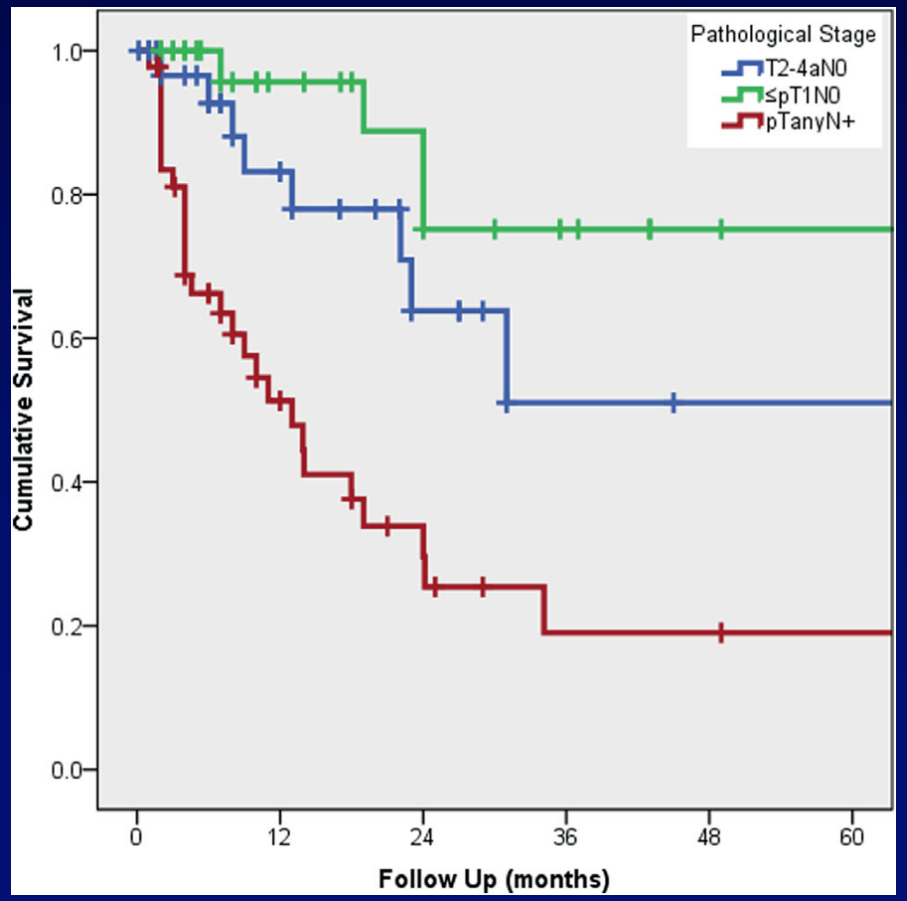
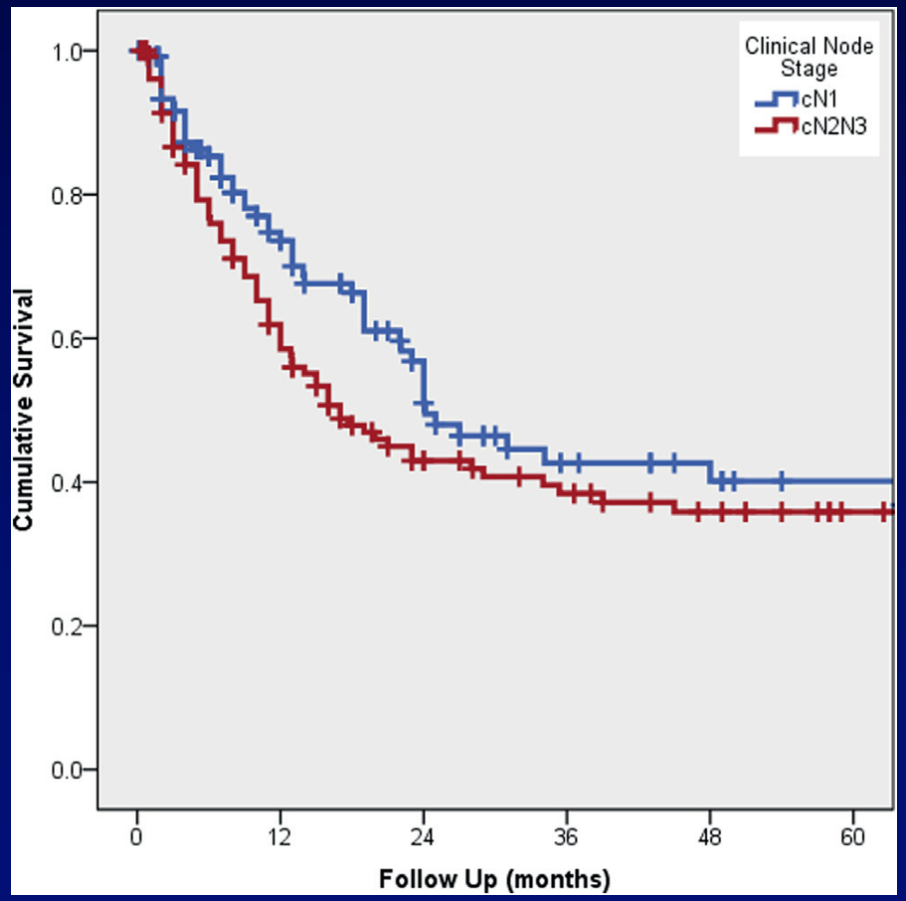


KM plot for OS and pathological response



KM plot for OS and clinical nodal stage

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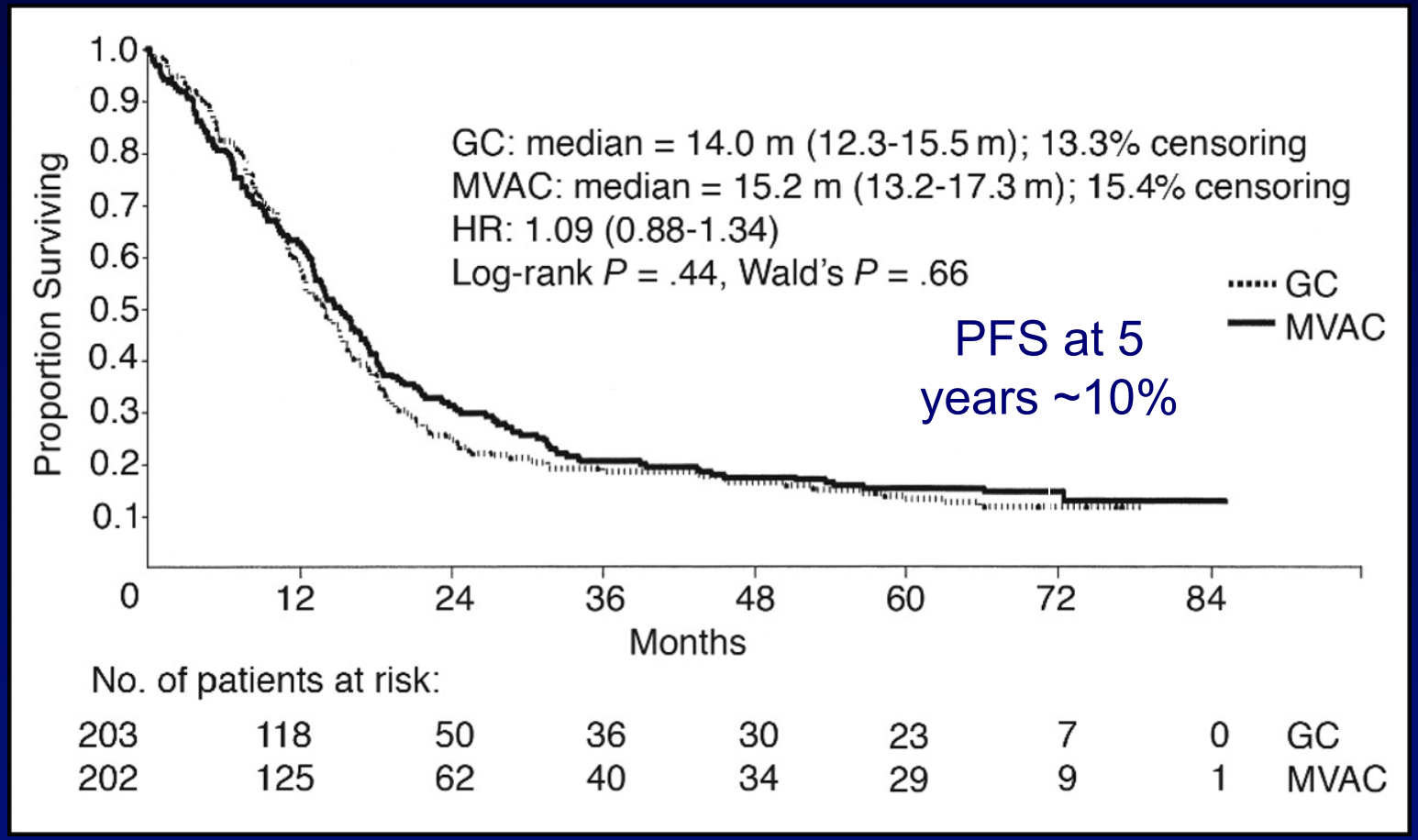
OVERALL SURVIVAL: Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, phase III study



Von der Maase H et al. EORTC *J Clin Oncol*;18:3068, 2000; Von der Maase H et al. *J Clin Oncol*; 23:4602-4608 2005.

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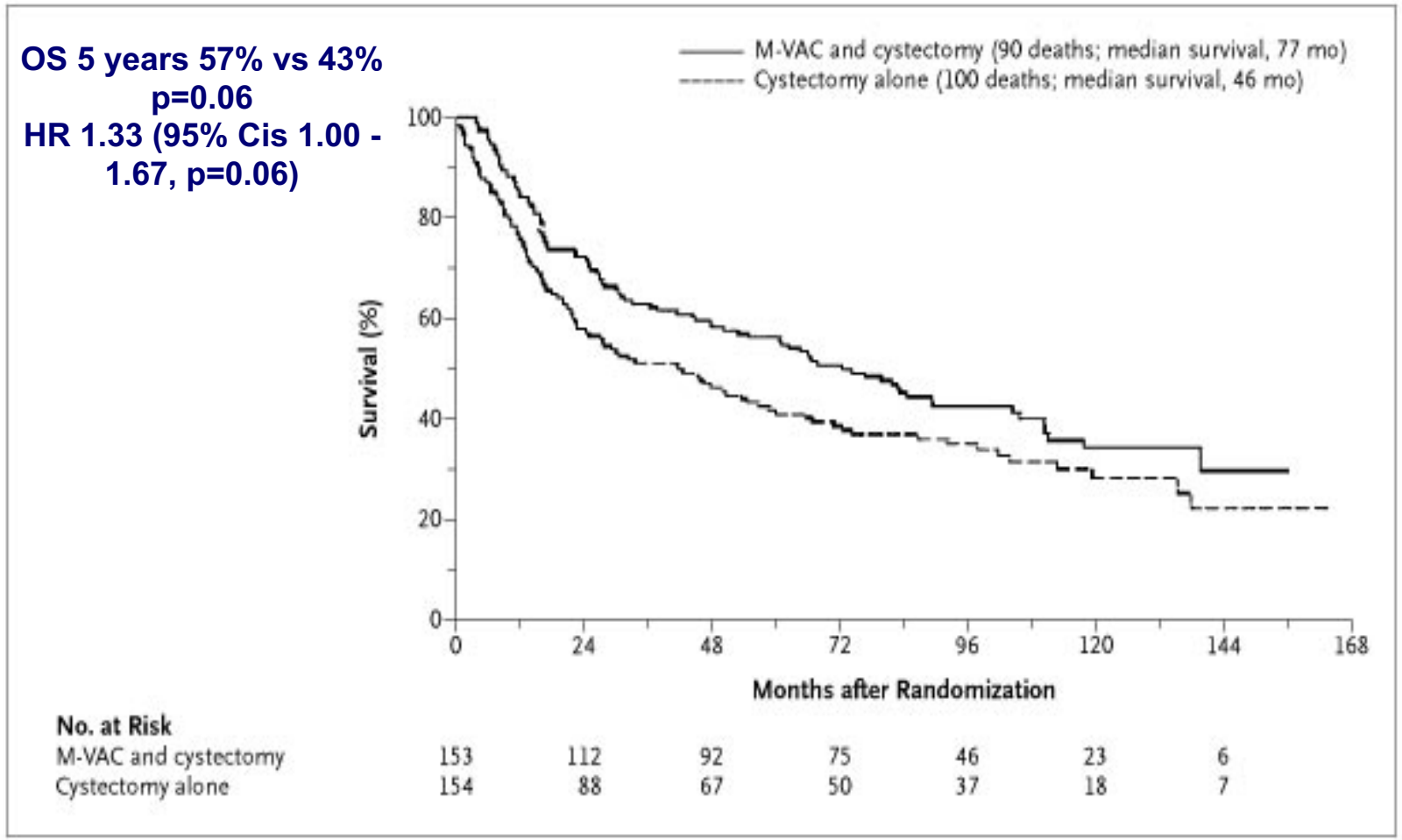
Survival among Patients Randomly Assigned to Receive Methotrexate, Vinblastine, Doxorubicin, and Cisplatin (M-VAC) Followed by Cystectomy or Cystectomy Alone, According to an Intention-to-Treat Analysis

OS 5 years 57% vs 43%
p=0.06
HR 1.33 (95% Cis 1.00 - 1.67, p=0.06)



Grossman HB et al. NEJM 2003;349:859-866

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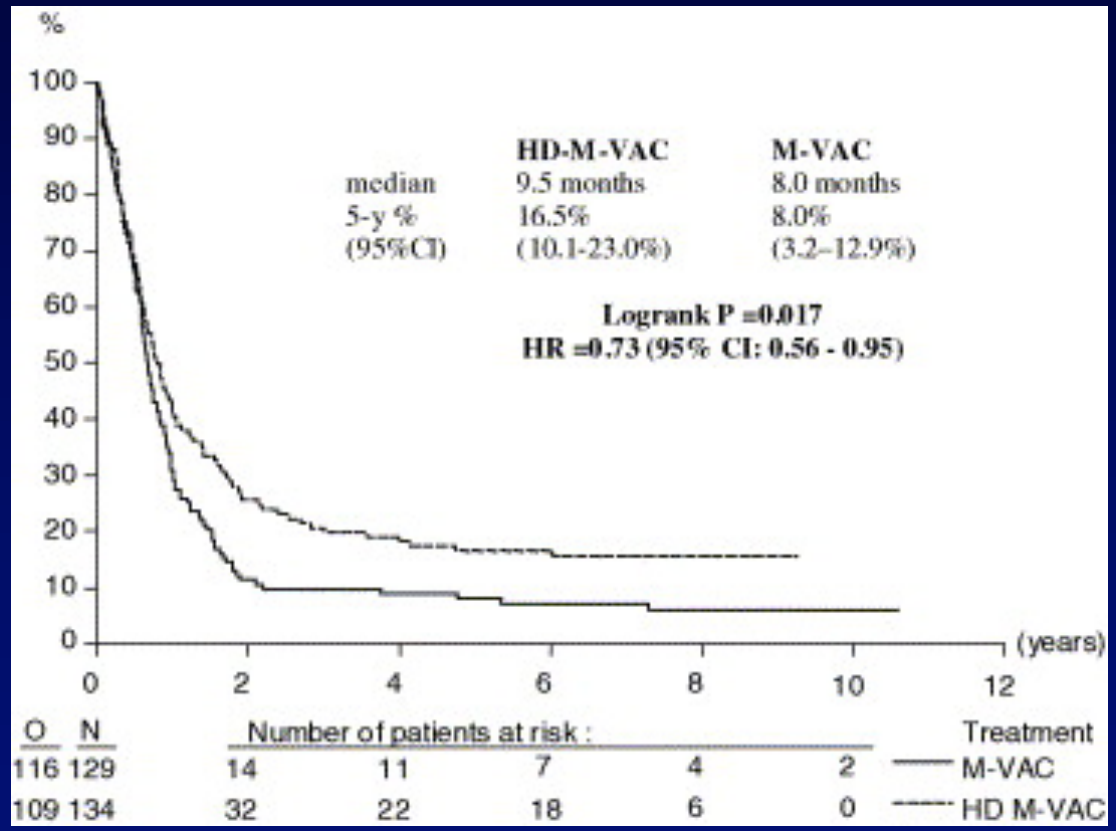
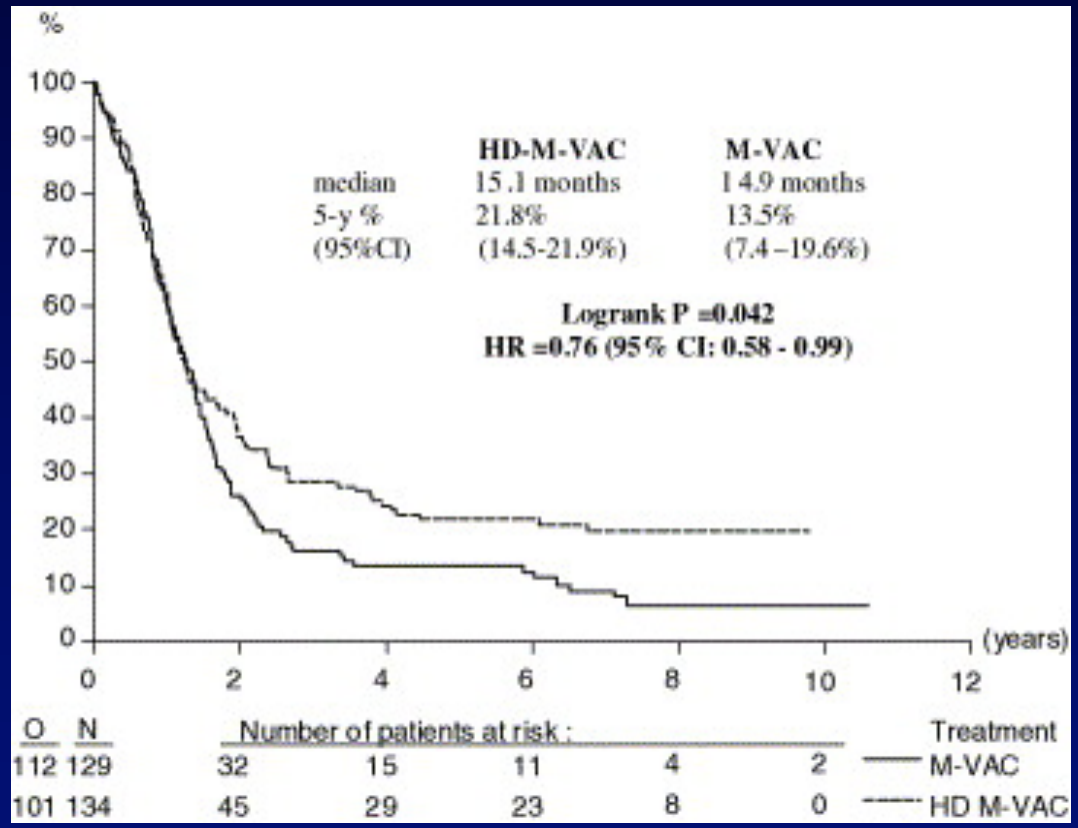
Seven year update of an EORTC phase III trial of high-dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC in advanced urothelial tumours C.N. Sternberg, et al and the EORTC Genito-Urinary Cancer Group



Progression-Free Survival



Overall Survival

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Regimen Reference	N (Cystectomy)	Pre-NAC ≤cT2N0M0	Downstaging ypT0	Downstaging ≤ ypT1	Survival
MVAC (q28d) **arm** **Grossman** et al., NEJM 2003	153	50%	**38%**	-	77 mos
DDMVAC + Bevacizumab (4 cycles) **McConkey** et al., Eur Urol 2016	44	39%	**38%**	53%	5y - 63%
MVAC vs **AMVAC** **Pouessel** et al., Eur J Cancer 2016	52 169	50% 65%	**38%** **35%**	53% 49%	-- --
AMVAC (3 cycles – split dose Cis allowed) **Plimack** et al., JCO 2014	40	36%	**38%**	52%	--
MVAC (q28d, 2 cycles) **Kitamura** et al., Ann Oncol 2014	64 (terminated early)	55%	**34%**	-	5y - 72%

Regimen, schedule reference	N	Pre-NAC ≤cT2N0M0	Downstaging ypT0	Completed planned cycles (≥3)	Survival
GC (mostly 3-weekly) vs **MVAC** (comparative effectiveness) **Galsky**, et al., Cancer 2015	146 66 (77% dose dense)	62% 62%	**31%** **29%**	90% 95%	35.5 mos 26.8 mos
GC split dose, GFR>40ml/min (Cis 35/Gem 1000 d1&8, q21d , 4 cycles) **Hussain** et al., Oncol Letters, 2012	23	48%	n.a. (6 surgery, 9 RT+chemo)	81%	25.3 mos 5y – 31%

NAC, neoadjuvant chemotherapy; RT, radiotherapy; GC, Gemcitabine (G), Cisplatin (C); MVAC, Methotrexat (M), Vinblastin (V), Adriamycin (A), Cisplatin (C);

NAC, neoadjuvant chemotherapy; MVAC, Methotrexat (M), Vinblastin (V), Adriamycin (A), Cisplatin (C); DDMVAC, dose dense MVAC; AMVAC, accelerated MVAC

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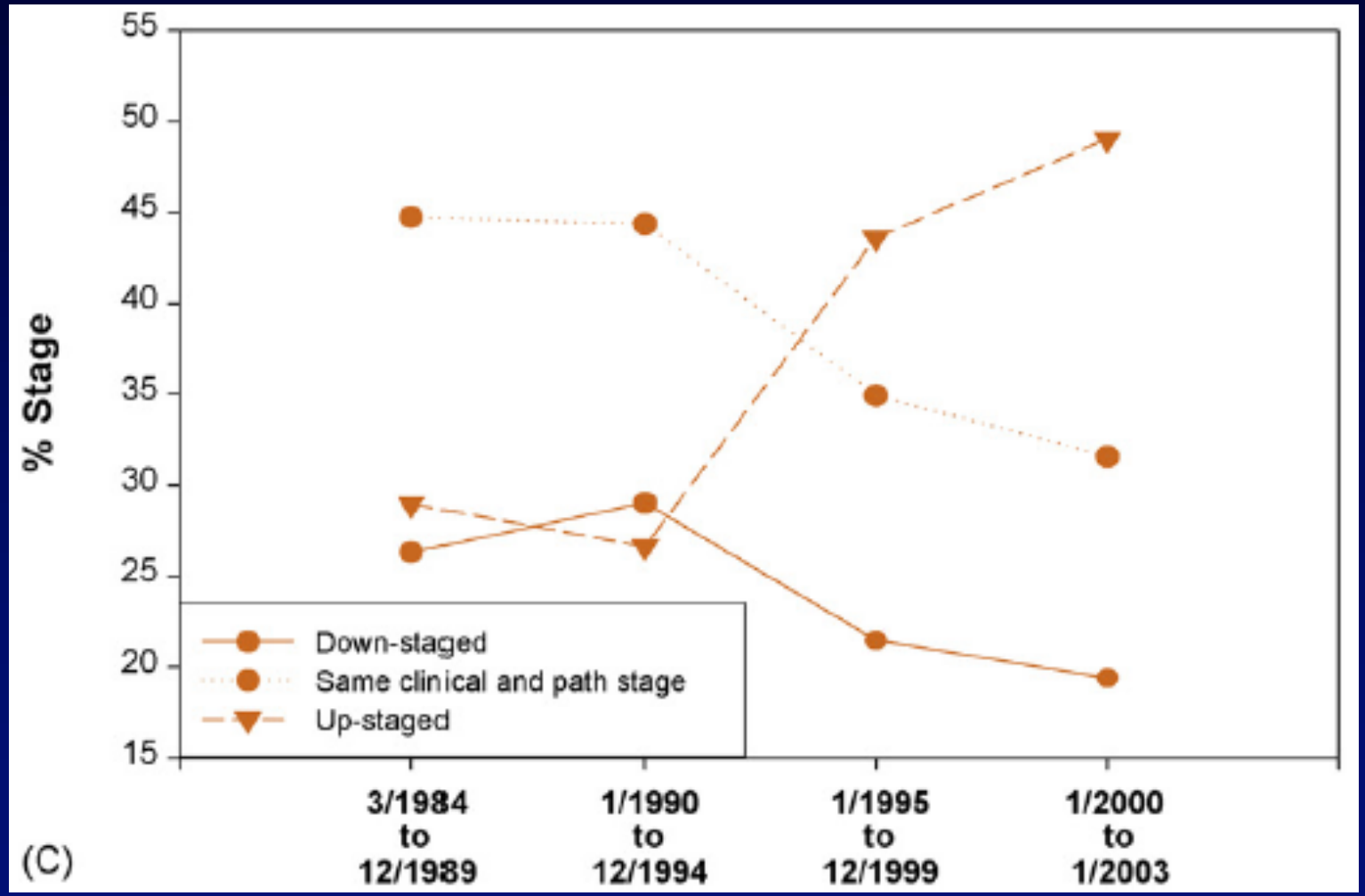
Understaging in HGMIBC



Shariat SF et al. *Eur Urol* 2007 51:137

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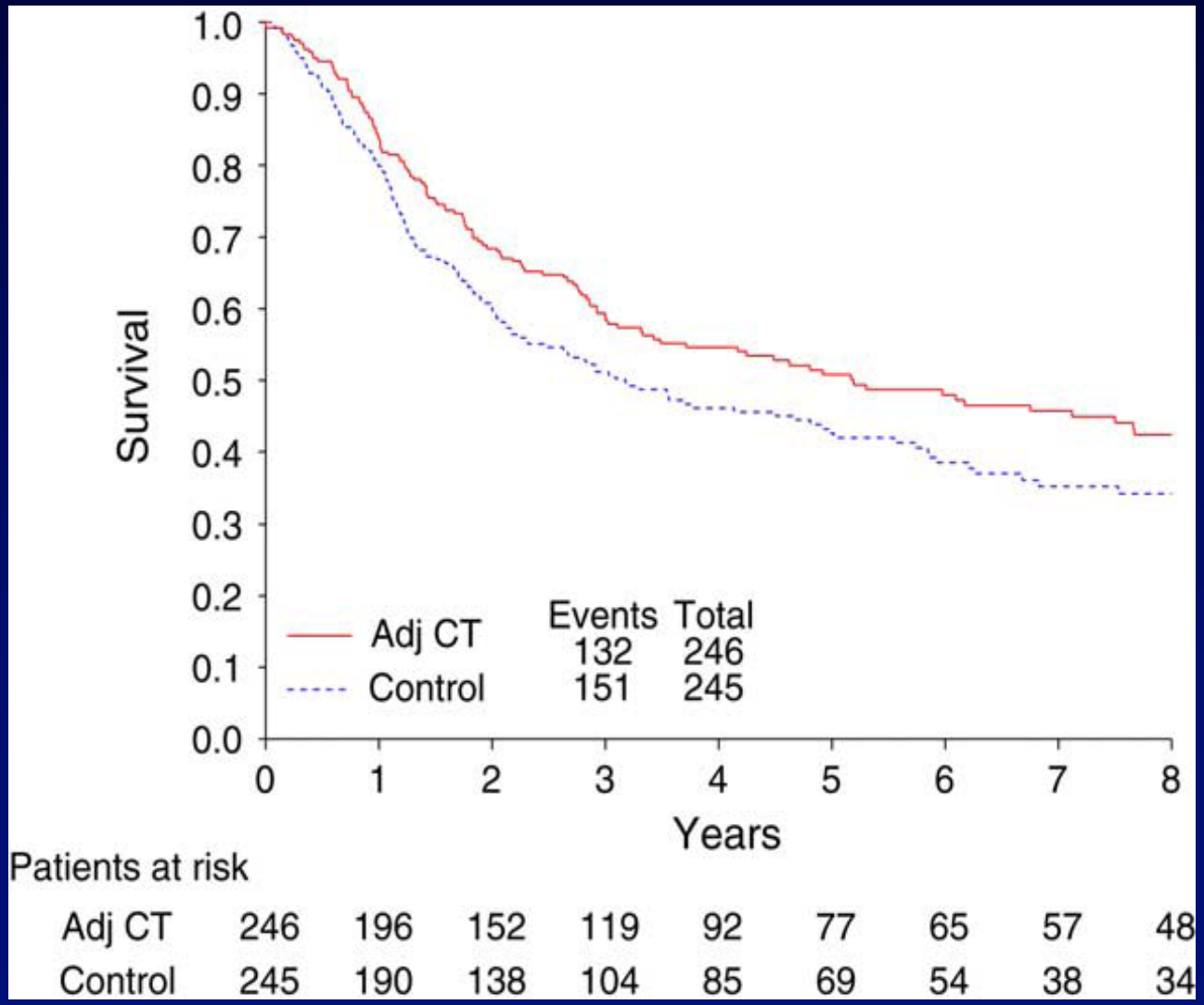

European Urology

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

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

Adj CT: 5-year overall survival: 51%

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A Systematic Review of Neoadjuvant and Adjuvant Chemotherapy for Muscle-invasive Bladder Cancer

J Meeks, J Bellmunt, BH Bochner , NW Clarke, S Daneshmand, MD Galsky, NM Hahn, SP Lerner, M Mason,T Powles, CN Sternberg, G Sonpavde

Adjuvant chemotherapy

Institution	Patients, *n*	Regimen	Survival benefit	Completed accrual
University of Southern California [43]	91	CISCA	Yes	Yes
University of Mainz, Germany [44]	49	MVAC/MVEC	Yes	Yes
Swiss Group for Clinical Cancer Research, Switzerland [47]	77	Cisplatin	No	Yes
Stanford University [46]	55	CMV	No	Yes
US Intergroup [52]	114*	MVAC	No	No
Italian multicenter [50]	194	GC	No	No
SOGUG [51]	142	PCG	Yes	No
EORTC (NCT00028756)	242	MVAC, GC, DD-MVAC	Not reported	No

CISCA = cisplatin, doxorubicin, MVAC = methotrexate, vinblastine, doxorubicin, cisplatin; MVEC = methotrexate, vinblastine, epirubicin, cisplatin; CMV = cisplatin, methotrexate, vinblastine; GC = gemcitabine, cisplatin; PCG = paclitaxel, gemcitabine, cisplatin; SOGUG = Spanish Oncology Genitourinary Group; EORTC = European Organization for Research and Treatment of Cancer; DD-MVAC = double-dense MVAC.

* Of 521 registered patients, 499 underwent p53 assessment, 272 (55%) were positive, and 114 (42%) were randomly assigned to MVAC versus no adjuvant therapy.

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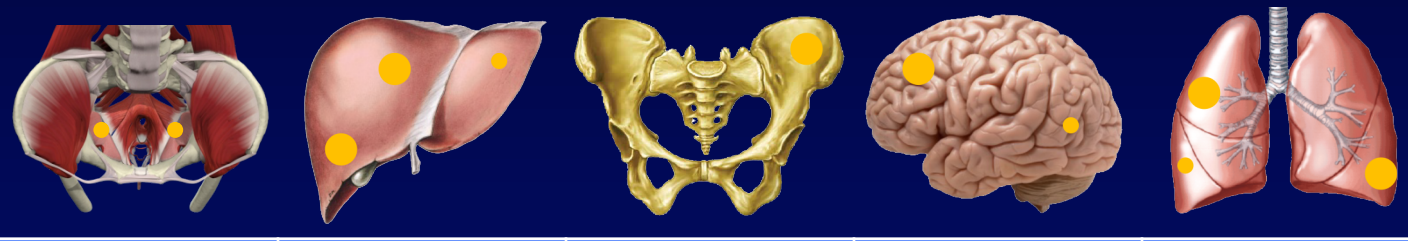
PATTERNS OF RECURRENCE

430 patients met the study criteria and had detailed documentation of recurrence sites.



	Local	Liver*	Bone*	Brain*	Lung*
n (%)	80 (19%)	86 (20%)	134 (31%)	16 (4%)	117 (27%)
Median time to recurrence (mo.)	12.5	13.8	11.7	17.9	12.9

* Non-exclusive sites of distant recurrence

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POST-RECURRENCE SURVIVAL
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Site of Recurrence	Median Post-Recurrence Survival (months)	*p**
Local	8.0	
Liver	3.4	<0.001
Bone	4.9	0.001
Brain	4.6	0.31
Lung	7.3	0.44

* Compared with local recurrence

Referral to Medical Oncology ASAP critical in improving outcomes

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2nd line therapy in met UC

- Taxol based regimens have very little efficacy
  - Docetaxel, Pemetrexed, Paclitaxel most common
- Eribulin
- Targeted therapy (ex: FGFR inhib) being studied
- Atezolizumab now approved, failed Phase III endpoint
- Nivolumab approved for those whose disease progressed during or after prior platinum-containing chemotherapy
- The news of the phase III IMvigor211 findings comes amid second-line bladder cancer approvals this month of 2 other PD-L1 inhibitors, avelumab and durvalumab.

Drug	Author	N	RR (%)	PFS/TTP (m)	OS (m)
Ifosfamide	Witte	56	20	2.4	5.5
Gemcitabine	Albers	30	11	4.9	NR
Paclitaxel	Joly	45	9	3	7
Docetaxel	McCaffrey	30	13	NR	9.0
Pemetrexed	Galsky	13	8	NR	NR
Pemetrexed	Sweeney	47	27.7	2.9	9.6
Ixabepilone	Dreicer	42	11.9	2.7	8.0
Docetaxel	Choueiri	75	11	1.6	7.0
Docetaxel	Petrylak	44	5	2.6	8.3

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Conclusions

- Locally advanced disease T3/T4, N+, M0 disease best treated with neoadjuvant chemo followed by radical cystectomy.
- Metastatic UCC of the bladder is highly lethal with dismal survival rates.
- Neoadjuvant: Gem/Cis or ddMVAC?
  - COXEN trial (SWOG S1314): try to predict which patients might benefit from MVAC vs which might benefit from GC
- Cisplatin ineligible patients should be enrolled in clinical trials or go directly for cystectomy
- Immunotherapy (PD1/PDL1 inhib) represents a major breakthrough for bladder cancer

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