Oncology Center of Excellence Virtual Public Workshop Presents:

Non-Muscle Invasive Bladder Cancer (NMIBC)

Day 1: November 18, 2021, 9am - 1pm, ET

Day 2: November 19, 2021, 9am - 12pm, ET

Cystectomy: Clinical Context

@MariaJRibal

Uro-Oncology Unit. Hospital Clinic. University of Barcelona

#eauguidelines Office

Short and Long-Term Complications in Radical Cystectomy

Reporting Complications

Disparity in the quality of surgical complication reporting in urologic oncology makes it impossible to compare the morbidity of surgical techniques and outcomes.

Terms such as major and minor complication have little meaning, particularly if not clearly defined or consistent.

The lack of standardisation is hampering the progress of improving morbidity and mortality associated with RC.

EAU Guidelines on

Reporting and Grading of Complications after Urologic Surgical Procedures

D. Mitropoulos (chair), W. Artibani, M. Graefen, M. Remzi, M. Rouprêt, M.C. Truss

Grades	Definitions
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Acceptable therapeutic regimens are: drugs such as antiemetics, antipyretics, analgesics, diuretics and electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than those allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade III-a	Intervention not under general anaesthesia
Grade III-b	Intervention under general anaesthesia
Grade IV	Life-threatening complication (including CNS complications: brain haemorrhage, ischaemic stroke, subarachnoid bleeding, but excluding transient ischaemic attacks) requiring IC/ICU management
Grade IV-a	Single organ dysfunction (including dialysis)
Grade IV-b	Multi-organ dysfunction
Grade V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of discharge the suffix "d" (for disability) is added to the respective grade of complication. This label indicates the need for a follow-up to evaluate the complication fully.

Prevention and Management of Complications Following Radical Cystectomy for Bladder Cancer

Nathan Lawrentschuk[a,], Renzo Colombo[b], Oliver W. Hakenberg[c], Seth P. Lerner[d], Wiking Månsson[e], Arthur Sagalowsky[f], Manfred P. Wirth[g]*

BMJ Open

Short-term morbidity and mortality following radical cystectomy: a systematic review

BMJ Open 2021;**11**:e043266. doi:10.1136/bmjopen-2020-043266

Sophia Liff Maibom ,[1,2] Ulla Nordström Joensen,[1,2] Alicia Martin Poulsen,[3] Henrik Kehlet,[2,4] Klaus Brasso,[1] Martin Andreas Røder[1,2]

Outcome	Complication rate, weighted average (%-range)
In-hospital complication rate	34.9%* (28.8–68.8)
30-day complication rate	39.0%† (27.3–80.0)
CD grade I	9.2% (6.0–16.1)
CD grade II	29.8% (20.6–52.5)
CD grade IIIa+b	6.9% (5.6–14.4)
CD grade IVa+b	7.8% (0.7–11.0)
CD grade V	1.7% (0.0–2.1)
Minor complication rate‡ (%)	40.0% (19.9–77.4)
Major complication rate§	15.5% (4.9–24.8)
90-day complication rate	58.5%¶ (36.1–80.5)
CD grade I	15.0% (4.0–31.6)
CD grade II	38.9% (27.0–67.4)
CD grade IIIa+b	20.5% (8.5–39.2)
CD grade IVa+b	3.0% (0.2–8.5)
CD grade V	3.5% (0.1–3.9)
Minor complication rate‡	38.2% (19.0–80.8)
Major complication rate§	16.9% (13.4–32.0)
Reoperation rate	
30 days	5.8% (3.0–8.7)
90 days	12.3% (9.3–18.9)

	Mortality rate, weighted average (%-range)
In-hospital mortality	2.4% (0.9–4.7)
30-day mortality	2.1% (0.0–3.7)
90-day mortality	4.7% (0.0–7.0)

Category/type	Rate, weighted average (%-range)
Gastrointestinal	29.0% (6.7–42.7)
Ileus	16.5% (3.8–33.7)
Small bowel obstruction	4.6% (1.7–9.0)
Constipation	3.3% (0.5–11.4)
Clostridium difficile colitis	2.3% (0.7–3.8)
Diarrhoea	1.7% (0.6–5.6)
Anastomotic bowel leak	1.1% (0.3–1.9)
Gastrointestinal bleeding	1.0% (0.3–1.3)
Infectious	26.4% (10.9–46.2)
UTI/pyelonephritis	14.1% (1.1–29.7)
Sepsis	4.2% (1.5–8.5)
Fever of unknown origin	3.1% (0.6–4.8)
Pelvic/intra-abdominal abscess	2.4% (0.1–4.3)
Genitourinary	16.0% (6.0–23.5)
Ureter stenosis	3.2% (1.7–7.0)
Ureter leakage	3.1% (0.4–5.3)
Wound	13.1% (5.6–27.0)
Dehiscence	4.0% (1.3–4.9)
Fascial dehiscence	1.6% (0.4–3.5)
Infection	10.5% (2.4–19.3)
Cardiac	6.1% (0.6–16.9)
Myocardial infarction	1.1% (0.2–3.5)
Arrhythmia	4.2% (0.2–14.4)
Bleeding	3.5% (0.5–17.8)
Haematoma	0.9% (0.7–1.2)
Transfusion	23.2% (8.1–45.3)
Respiratory	5.0% (1.3–11.5)
Pneumonia	2.8% (0.6–5.9)
Thromboembolic	3.6% (0.2–8.1)
Neurological	2.8% (0.6–7.7)
Renal failure	2.3% (0.5–6.7)
Other	
Fistula	1.1% (0.6–1.4)
Lymphocele	2.1% (1.3–4.7)

Robot-assisted radical cystectomy versus open radical cystectomy in patients with bladder cancer (RAZOR): an open-label, randomised, phase 3, non-inferiority trial

Dipen J Parekh, Isildinha M Reis, Erik P Castle, Mark L Gonzalgo, Michael E Woods, Robert S Svatek, Alon Z Weizer, Badrinath R Konety, Mathew Tollefson, Tracey L Krupski, Norm D Smith, Ahmad Shabsigh, Daniel A Barocas, Marcus L Quek, Atreya Dash, Adam S Kibel, Lynn Shemanski, Raj S Pruthi, Jeffrey Scott Montgomery, Christopher J Weight, David S Sharp, Sam S Chang, Michael S Cookson, Gopal N Gupta, Alex Gorbonos, Edward M Uchio, Eila Skinner, Vivek Venkatramani, Nachiketh Soodana-Prakash, Kerri Kendrick, Joseph A Smith Jr, Ian M Thompson

Summary

Background Radical cystectomy is the surgical standard for invasive bladder cancer. Robot-assisted cystectomy has

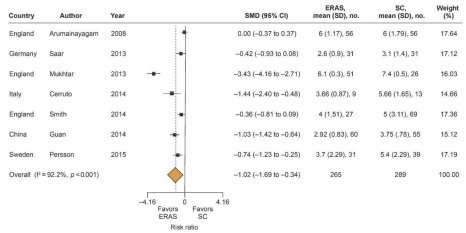
Lancet 2018; 391: 2525–36

	Robotic cystectomy (n=150)	Open cystectomy (n=152)	Difference (95% CI)	p value
Patients with blood loss data	148 (99%)	149 (98%)	..	..
Blood loss, mL	300 (200–500)	700 (500–1000)	..	<0·0001
Perioperative transfusion	35/143 (24%)	65/143 (45%)	−21·0 (−31·8 to −10·2)	0·0002
Units of blood transfused	3 (2–5)	4 (2–5)	..	0·46
Intraoperative transfusion	18/139 (13%)	46/136 (34%)	−20·8 (−30·6 to −11·2)	<0·0001
Postoperative transfusion	33/132 (25%)	54/135 (40%)	−15·0 (−26·1 to −3·9)	0·0089
Hospital stay ≤5 days	40/139 (29%)	27/146 (18%)	10·3 (0·5 to 20·1)	0·0407
Length of stay, days	6 (5–10)	7 (6–10)	..	0·0216
Operating time, min	428 (322–509)	361 (281–450)	..	0·0005
Surgical complications within 90 days*				
0	49 (33%)	47 (31%)	..	0·80
I	24 (16%)	20 (13%)	..	..
II	44 (29%)	51 (34%)	..	..
III	29 (19%)	28 (18%)	..	..
IV	0	2 (1%)	..	..
V	4 (3%)	4 (3%)	..	..
Grades I–V *vs* 0	101 (67%)	105 (69%)	−1·8 (−12·3 to 8·8)	0·75
Grades III–V *vs* 0–II	33 (22%)	34 (22%)	−0·4 (−9·0 to 9·8)	0·94

Enhanced Recovery Pathways Versus Standard Care After Cystectomy: A Meta-analysis of the Effect on Perioperative Outcomes

Mark D. Tyson [a,b,*], *Sam S. Chang* [b]

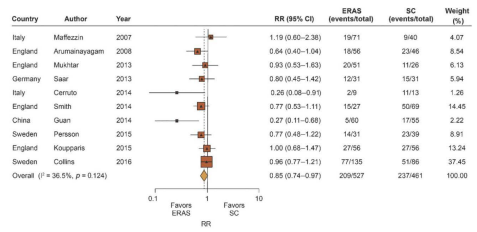
[a] *Department of Urology, Mayo Clinic Hospital, Phoenix, AZ, USA;* [b] *Department of Urologic Surgery, Vanderbilt University Medical Center, Nashville, TN, USA*



Country	Author	Year	SMD (95% CI)	ERAS, mean (SD), no.	SC, mean (SD), no.	Weight (%)
England	Arumainayagam	2008	0.00 (−0.37 to 0.37)	6 (1.17), 56	6 (1.79), 56	17.64
Germany	Saar	2013	−0.42 (−0.93 to 0.08)	2.6 (0.9), 31	3.1 (1.4), 31	17.12
England	Mukhtar	2013	−3.43 (−4.16 to −2.71)	6.1 (0.3), 51	7.4 (0.5), 26	16.03
Italy	Cerruto	2014	−1.44 (−2.40 to −0.48)	3.66 (0.87), 9	5.66 (1.65), 13	14.66
England	Smith	2014	−0.36 (−0.81 to 0.09)	4 (1.51), 27	5 (3.11), 69	17.36
China	Guan	2014	−1.03 (−1.42 to −0.64)	2.92 (0.83), 60	3.75 (.78), 55	15.12
Sweden	Persson	2015	−0.74 (−1.23 to −0.25)	3.7 (2.29), 31	5.4 (2.29), 39	17.19
Overall	(I^2 = 92.2%, p <0.001)		−1.02 (−1.69 to −0.34)	265	289	100.00

−4.16 0 4.16
Favors ERAS
Favors SC
Risk ratio

Fig. 4 – Forest plot displaying a random-effects meta-analysis of the effect of enhanced recovery after surgery (ERAS) on time to bowel function after cystectomy. Weights are from random-effects analysis.
CI = confidence interval; SC, standard care; SMD, standardized mean difference.



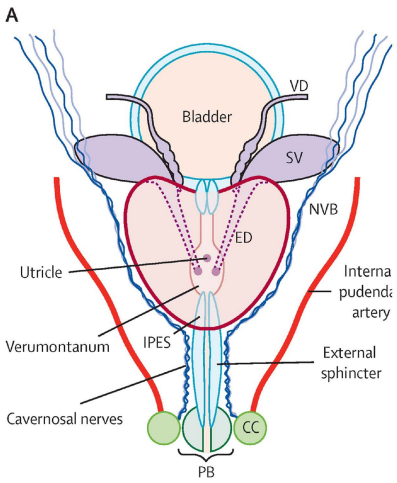
Country	Author	Year	RR (95% CI)	ERAS (events/total)	SC (events/total)	Weight (%)
Italy	Maffezzin	2007	1.19 (0.60–2.38)	19/71	9/40	4.07
England	Arumainayagam	2008	0.64 (0.40–1.04)	18/56	23/46	8.54
England	Mukhtar	2013	0.93 (0.53–1.63)	20/51	11/26	6.13
Germany	Saar	2013	0.80 (0.45–1.42)	12/31	15/31	5.94
Italy	Cerruto	2014	0.26 (0.08–0.91)	2/9	11/13	1.26
England	Smith	2014	0.77 (0.53–1.11)	15/27	50/69	14.45
China	Guan	2014	0.27 (0.11–0.68)	5/60	17/55	2.22
Sweden	Persson	2015	0.77 (0.48–1.22)	14/31	23/39	8.91
England	Koupparis	2015	1.00 (0.68–1.47)	27/56	27/56	13.24
Sweden	Collins	2016	0.96 (0.77–1.21)	77/135	51/86	37.45
Overall	(I^2 = 36.5%, p = 0.124)		0.85 (0.74–0.97)	209/527	237/461	100.00

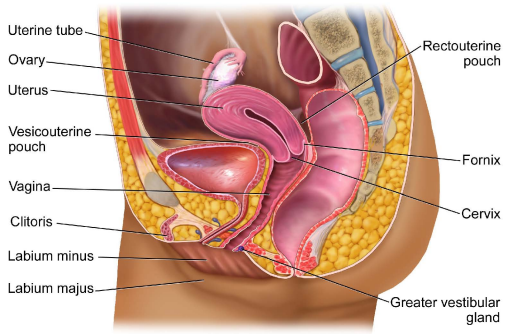
0.1 1 10
Favors ERAS
Favors SC
RR

Fig. 2 – Forest plot displaying a fixed-effects meta-analysis of the effect of enhanced recovery after surgery (ERAS) on complication rates after cystectomy
CI = confidence interval; RR = risk ratio; SC = standard care.

Country	Author	Year	SMD (95% CI)	ERAS, mean (SD), no.	SC, mean (SD), no.	Weight (%)
USA	Pruthi	2003	−0.93 (−1.43 to −0.44)	5.2 (6.67), 40	11.2 (6.08), 30	8.94
Italy	Maffezzin	2007	−0.65 (−1.05 to −0.26)	20.5 (6.67), 71	25.3 (8.25), 40	9.37
England	Arumainayagam	2008	−0.87 (−1.26 to −0.48)	13.7 (4.55), 56	18.3 (6.08), 56	9.41
England	Mukhtar	2013	−0.13 (−0.61 to 0.34)	11.5 (12.4), 51	12.9 (4.29), 26	9.06
Germany	Saar	2013	−0.02 (−0.52 to 0.48)	18 (5.1), 31	18.1 (6.3), 31	8.95
Italy	Cerruto	2014	−0.78 (−1.66 to 0.10)	14.7 (0.87), 9	15.3 (0.83), 13	7.05
England	Smith	2014	−0.97 (−1.44 to −0.51)	8.77 (5.74), 27	16 (7.97), 69	9.09
USA	Daneshmand	2014	−1.41 (−1.71 to −1.12)	6.5 (2.4), 110	11.5 (4.4), 110	9.73
China	Guan	2014	−2.37 (−2.85 to −1.89)	6.9 (1.1), 60	10 (1.5), 55	8.30
Sweden	Collins	2016	−0.60 (−0.88 to −0.33)	8 (2.99), 135	10 (3.77), 86	9.79
Sweden	Persson	2015	0.54 (0.06–1.02)	34.5 (23.8), 31	24.5 (12.6), 39	9.02
USA	Xu	2015	−2.03 (−2.37 to −1.68)	6.75 (2.17), 124	15.5 (6.33), 81	9.58
Overall	(I^2 = 92.8%, $p \leq 0.001$)		−0.87 (−1.31 to −0.42)	745	636	100.00

−2.85 0 2.85
Favors ERAS
Favors SC
Risk ratio





Study ID	Type of surgery	Number of patients			Type of study		Country	Recruitment period
		Entire study	Intervention	Control				
De Vries *et al.* 2009/ Mertens *et al.* 2014 [240, 277]	Prostate sparing vs. RC	126	63	63	Comparative	Retrospective (Matched pair)	Netherlands	1994-2006
Gotsadze *et al.* 2008 [278]	Prostate sparing	87	87		Non-comparative	Retrospective	Georgia	1991-2005
Basiri *et al.* 2012 [279]	Capsule sparing vs. RC	50	23	27	Comparative	Retrospective (Matched pair)	Iran	2003-2008
Wang *et al.* 2008 [280]		36	27	9	Comparative	Retrospective	China	2000- 2006
Moon *et al.* 2005 [281]		35	17	18	Comparative	Retrospective	Korea	1999-2003
Rozet *et al.* 2008 [282]	Capsule sparing	108	108		Non-comparative	Retrospective	France	1992-2004
Muto *et al.* 2014 [283]		91	91		Non-comparative	Retrospective	Italy	1990-2009
Vilaseca *et al.* 2013 [284]		44	11	33	Comparative	Retrospective	Spain	2006-2009
El-Bahnasawy *et al.* 2006 /Hekal 2009 [285, 286]	Nerve sparing vs. RC	60	30	30	Comparative	Retrospective	Egypt	2003-2005
Kessler *et al.* 2004 [287]		331	256	75	Comparative	Retrospective	Switzerland	1985-2003
Intervention vs. Intervention								
Jacobs *et al.* 2015 (RCT) [288]	Capsule sparing vs. Nerve sparing	40	20	20	RCT	Prospective	USA	2007-2011
Colombo *et al.* 2015 [289]	Capsule sparing vs. Seminal sparing vs. Nerve sparing	90	CS:36 SS:19 NS:35		Comparative	Retrospective	Italy	1997-2012

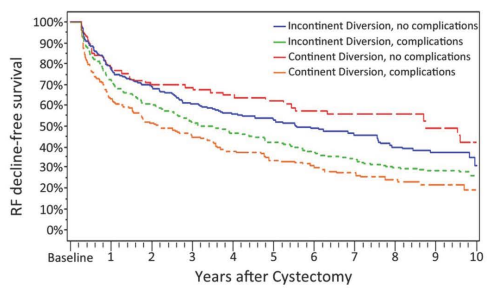
Recommendations	Strength rating
Offer sexual-preserving techniques to men motivated to preserve their sexual function since the majority will benefit.	Strong
Select patients based on: • organ-confined disease; • absence of any kind of tumour at the level of the prostate, prostatic urethra or bladder neck.	Strong
Do not offer sexual-preserving cystectomy as standard therapy for muscle-invasive bladder cancer.	Strong

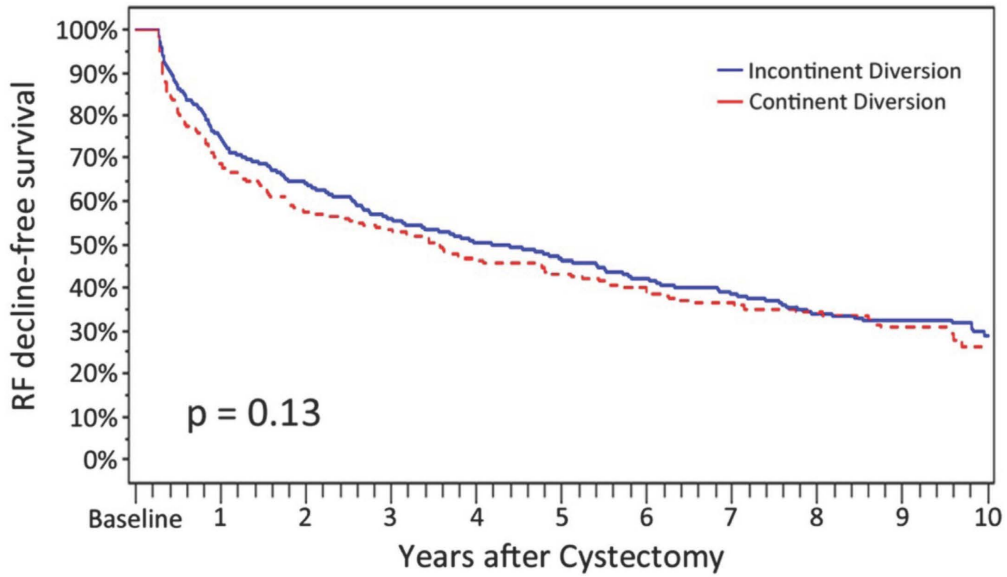
References	No. pts assessed	Age, yr (mean, range)	Type of diversion	Mean duration of follow-up	Baseline evaluation	Measure	Sexual activity	Satisfaction	FSFI score (mean)
Neymeyer J *et al.* 2009 [293]	86	NR	Neobladder	36 mo (6-54)	No	Interview	89.5%	95.3%	NR
Ali-el-Dein B *et al.* 2013 [299]	12/15	42 (25-54)	Hautmann neobladder	70 mo (37-99)	No	FSFI	100%	100%	18
Horenblas S *et al.* 2001 [300]	2/3	55 (38-71)	Neobladder	42 mo (24-72)	No	Interview	NR	100%	NR
Bhatt A *et al.* 2006 [298]	6/13	55.9 (52-59)	Neobladder	13.2 mo (12-14)	Yes	FSFI	100%	80%	22.3
Rouanne M *et al.* 2014 [295]	31/46	64.8 (43-86)	Z-shaped neobladder	68 mo (6-204)	No	Contilife	58%	NR	NR
Wishahi M *et al.* 2015 [303]	13/13	37.9 (20-54)	U-shaped neobladder	132 mo (60-180)	No	FSFI	92.3%	NR	23.7

Long-Term Renal Function Outcomes after Radical Cystectomy

Manuel S. Eisenberg, R. Houston Thompson, Igor Frank,* Simon P. Kim, Katherine J. Cotter, Matthew K. Tollefson, Dharam Kaushik, Prabin Thapa, Robert Tarrell and Stephen A. Boorjian†

From the Departments of Urology (MSE, RHT, IF, MKT, DK, SAB) and Health Sciences Research (PT, RT), Mayo Clinic, Rochester and Department of Urology, University of Minnesota (KJC), Minneapolis, Minnesota, and Department of Urology, Yale University (SPK), New Haven, Connecticut





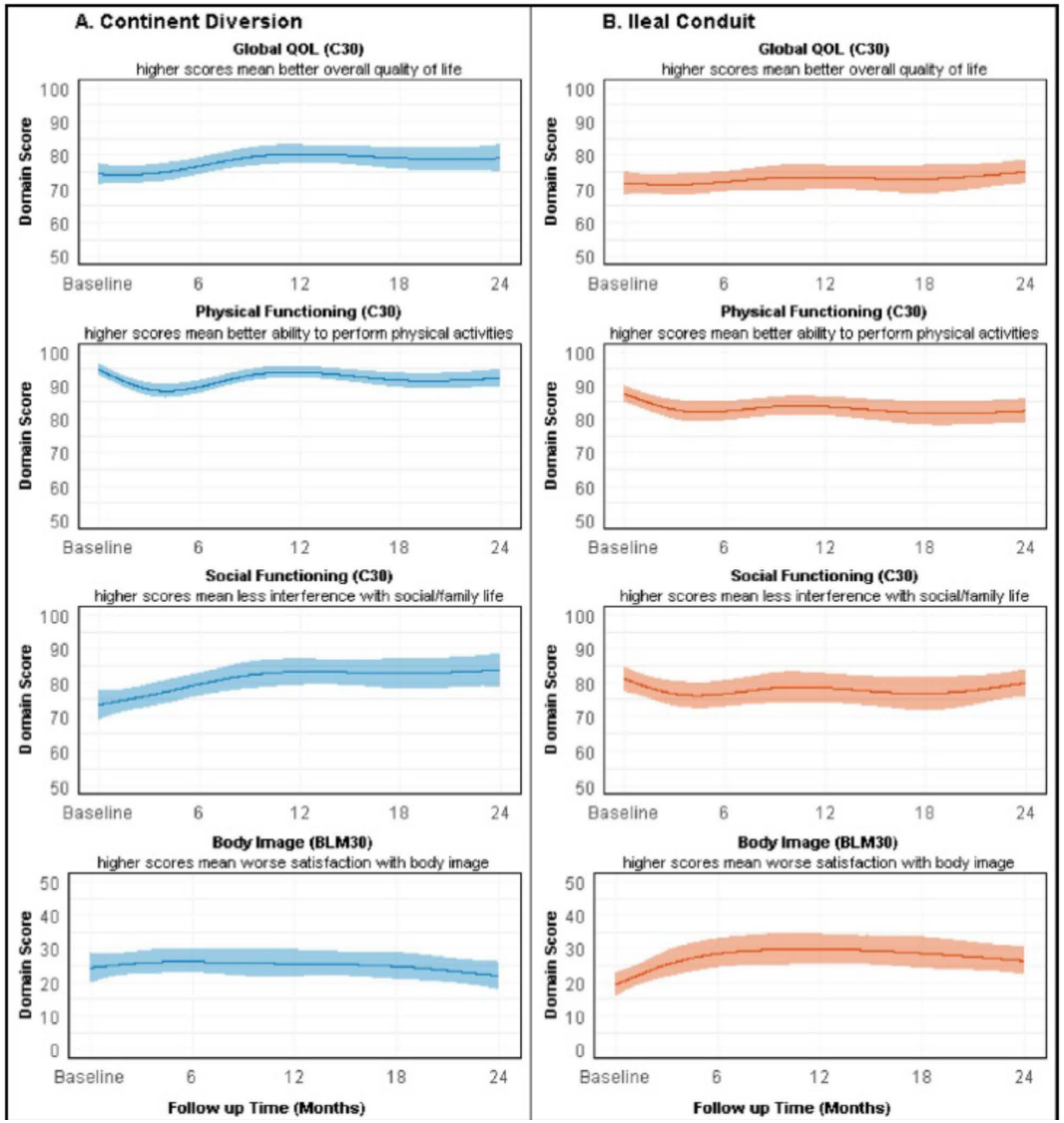
- No large, observable detriments to HRQOL by 3 or 6 mo postoperatively.
- With the exception of sexual functioning and body image in ileal conduit patients, average reported scores across most domains typically recovered to baseline or better.

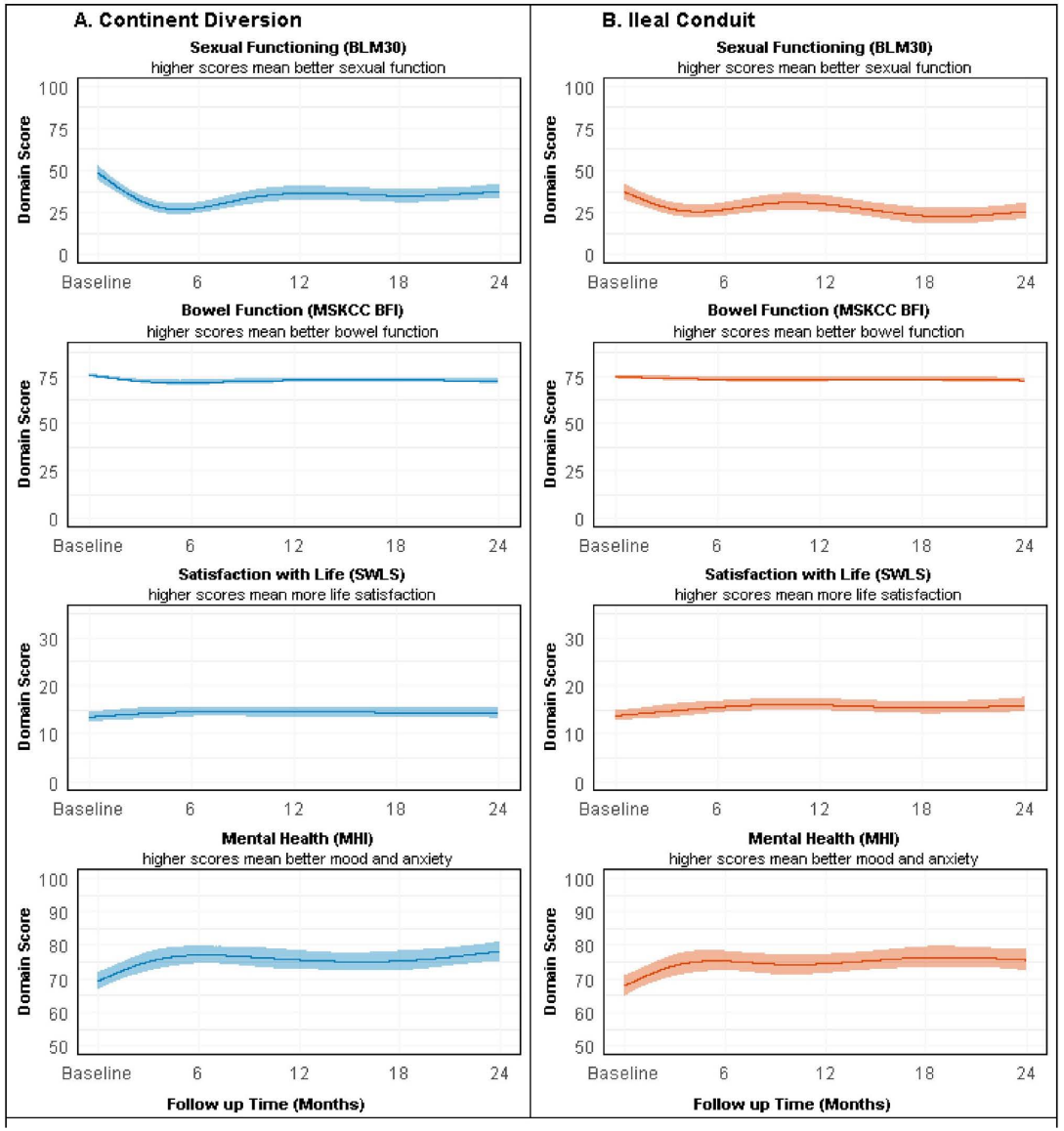
Bladder Cancer

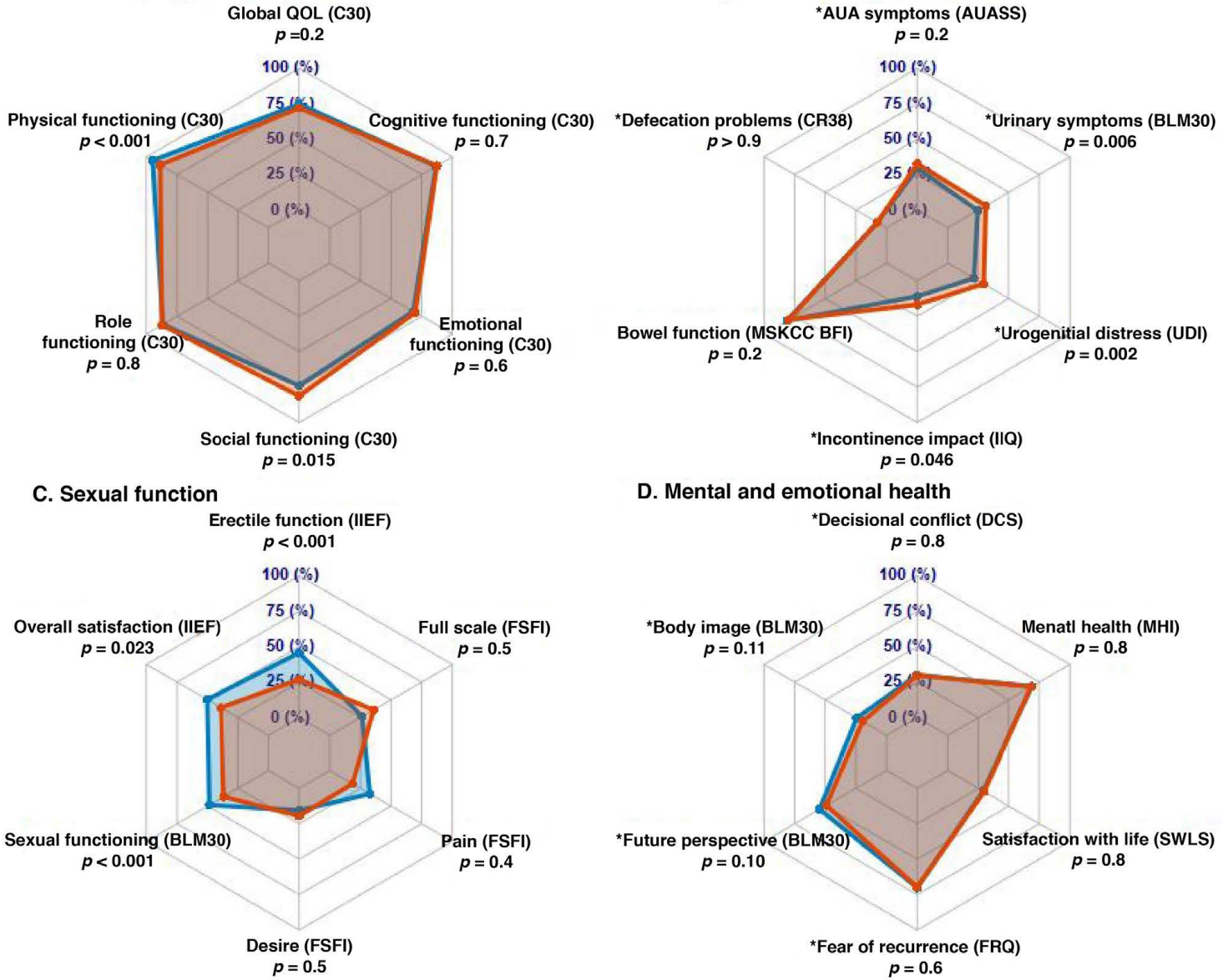
Health-related Quality of Life for Patients Undergoing Radical Cystectomy: Results of a Large Prospective Cohort

Matthew B. Clements[a], *Thomas M. Atkinson*[b], *Guido M. Dalbagni*[a], *Yuelin Li*[b], *Andrew J. Vickers*[c], *Harry W. Herr*[a], *S. Machele Donat*[a], *Jaspreet S. Sandhu*[a], *Daniel S. Sjoberg*[c], *Amy L. Tin*[c], *Bruce D. Rapkin*[d], *Bernard H. Bochner*[a,*]

[a] *Urology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA;* [b] *Department of Psychiatry and Behavioral Sciences, Memorial Sloan Kettering Cancer Center, New York, NY, USA;* [c] *Department of Epidemiology & Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA;* [d] *Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY, USA*


A. Continent Diversion
B. Ileal Conduit
Global QOL (C30)
higher scores mean better overall quality of life
Physical Functioning (C30)
higher scores mean better ability to perform physical activities
Social Functioning (C30)
higher scores mean less interference with social/family life
Body Image (BLM30)
higher scores mean worse satisfaction with body image
Domain Score
Baseline
6
12
18
24
Follow up Time (Months)


A. Continent Diversion
B. Ileal Conduit
Sexual Functioning (BLM30)
higher scores mean better sexual function
Bowel Function (MSKCC BFI)
higher scores mean better bowel function
Satisfaction with Life (SWLS)
higher scores mean more life satisfaction
Mental Health (MHI)
higher scores mean better mood and anxiety
Domain Score
Baseline
6
12
18
24
Follow up Time (Months)


Global QOL (C30)
p =0.2
100 (%)
75 (%)
50 (%)
25 (%)
0 (%)
Physical functioning (C30)
p < 0.001
Cognitive functioning (C30)
p = 0.7
Role
functioning (C30)
p = 0.8
Emotional
functioning (C30)
p = 0.6
Social functioning (C30)
p = 0.015
*AUA symptoms (AUASS)
p = 0.2
*Defecation problems (CR38)
p > 0.9
*Urinary symptoms (BLM30)
p = 0.006
Bowel function (MSKCC BFI)
p = 0.2
*Urogenitial distress (UDI)
p = 0.002
*Incontinence impact (IIQ)
p = 0.046
C. Sexual function
Erectile function (IIEF)
p < 0.001
Overall satisfaction (IIEF)
p = 0.023
Full scale (FSFI)
p = 0.5
Sexual functioning (BLM30)
p < 0.001
Pain (FSFI)
p = 0.4
Desire (FSFI)
p = 0.5
D. Mental and emotional health
*Decisional conflict (DCS)
p = 0.8
*Body image (BLM30)
p = 0.11
Menatl health (MHI)
p = 0.8
*Future perspective (BLM30)
p = 0.10
Satisfaction with life (SWLS)
p = 0.8
*Fear of recurrence (FRQ)
p = 0.6

Indications for Radical Cystectomy

European Association of Urology

T2-T4a. N0-Nx, M0

BCG refractory, relapsing, unresponsive

High risk non muscle invasive tumors

Recurrence after bladder sparing treatment

Salvage cystectomy in non-responders to conservative therapy

Extensive papillary disease

Palliative intervention (fistula formation, pain, hematuria)

T2-T4a N0-Nx

- Is the standard indication for RC
- Neoadjuvant chemotherapy could achieve 5% increase in survival
- Radical cystectomy + adequate lymph node dissection

Offer RC to patients with T2–T4a, N0M0 disease or high-risk non-muscle-invasive bladder cancer.	Strong
Perform a lymph node dissection as an integral part of RC.	Strong

Radical Cystectomy for Urothelial Carcinoma of the Bladder Without Neoadjuvant or Adjuvant Therapy: Long-Term Results in 1100 Patients

Richard E. Hautmann [a,*], *Robert C. de Petriconi* [a], *Christina Pfeiffer* [b], *Bjoern G. Volkmer* [a,b]

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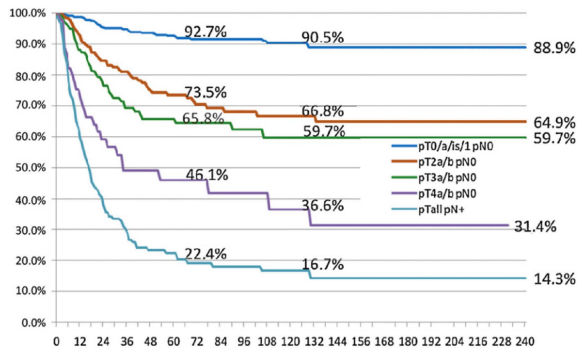
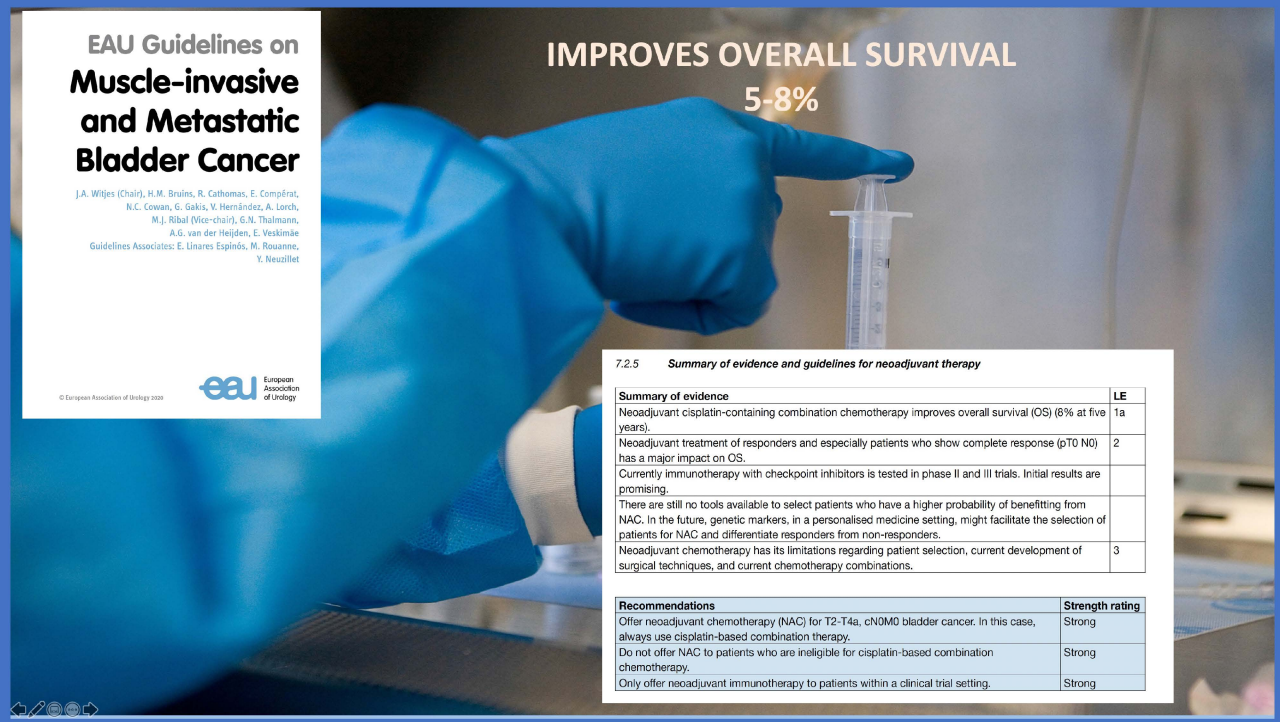


Fig. 2 – Disease-specific survival rates according to the tumor stage of the cystectomy specimen.



EAU Guidelines on

Muscle-invasive and Metastatic Bladder Cancer

J.A. Witjes (Chair), H.M. Bruins, R. Cathomas, E. Compérat, N.C. Cowan, J.A. Efstathiou, R. Fietkau, G. Gakis, V. Hernández, A. Lorch, M.I. Milowsky, M.J. Ribal (Vice-chair), G.N. Thalmann, A.G. van der Heijden, E. Veskimäe
Guidelines Associates: E. Linares Espinós, M. Rouanne, Y. Neuzillet

European Association of Urology

Summary of evidence	LE
In a highly selected patient population, long-term survival rates of multimodality treatment are comparable to those of early cystectomy.	2b

Recommendations	Strength rating
Offer surgical intervention or multimodality treatments (MMT) as primary curative therapeutic approaches since they are more effective than radiotherapy alone.	Strong
Offer MMT as an alternative to selected, well-informed and compliant patients, especially for whom radical cystectomy is not an option.	Strong

*7.6.4.2 EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer [5, 6]**

Consensus statement
Candidates for curative treatment, such as cystectomy or bladder preservation, should be clinically assessed by at least an oncologist, a urologist and a neutral HCP such as a specialist nurse.
An important determinant for patient eligibility in case of bladder preserving treatment is absence of carcinoma *in situ*.
An important determinant for patient eligibility in case of bladder preserving treatment is absence or presence of hydronephrosis.
When assessing patient eligibility for bladder preservation, the likelihood of successful debulking surgery should be taken into consideration (optimal debulking).
Bladder urothelial carcinoma with small cell neuroendocrine variant should be treated with neoadjuvant chemotherapy followed by consolidating local therapy.
In case of bladder preservation with radiotherapy, combination with a radiosensitiser is always recommended to improve clinical outcomes, such as cisplatin, 5FU/MMC, carbogen/nicotinamide or gemcitabine.
Radiotherapy for bladder preservation should be performed with IMRT and IGRT to reduce side effects.
Dose escalation above standard radical doses to the primary site in case of bladder preservation, either by IMRT or by brachytherapy, is not recommended.

**Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as ≥ 70% agreement and ≤ 15% disagreement, or vice versa).*
HCP = healthcare professional; IGRT = image-guided radiotherapy; IMRT = intensity-modulated radiotherapy; 5FU = 5-fluorouracil; MMC = mitomycin-C.

Approved by the AUA Board of Directors December 2020

Authors' disclosure of potential conflicts of interest and author/staff contributions appear at the end of the article.

The Practice Guidelines Committee would like to acknowledge the contributions of Drs. Christopher Anderson and John Gore to the 2020 Guideline Amendment.

American Urological Association (AUA) / American Society of Clinical Oncology (ASCO) / American Society for Radiation Oncology (ASTRO) / Society of Urologic Oncology (SUO)

TREATMENT OF NON-METASTATIC MUSCLE-INVASIVE BLADDER CANCER: AUA/ASCO/ASTRO/SUO GUIDELINE (AMENDED 2020)

Sam S. Chang, MD, MBA; Bernard H. Bochner, MD, FACS; Roger Chou, MD; Robert Dreicer, MD, MS, MACP, FASCO; Ashish M. Kamat, MD, MBBS, FACS; Seth P. Lerner, MD, FACS; Yair Lotan, MD; Joshua J. Meeks, MD, PhD; Jeff M. Michalski, MD, MBA; Todd M. Morgan, MD; Diane Z. Quale; Jonathan E. Rosenberg, MD; Anthony L. Zietman, MD; Jeffrey M. Holzbeierlein, MD, FACS

Purpose

BLADDER PRESERVING APPROACHES

PATIENT SELECTION

A multi-modal bladder preserving approach with its merits and disadvantages should be discussed in each individual case. The studies that support bladder preserving strategies generally have highly select patient populations. There are currently no randomized trials comparing NAC and radical cystectomy versus multi-modality bladder preserving therapies. In reviewing the available studies regarding multi-modal bladder preserving protocols that employ TURBT, radiation therapy, and chemotherapy for carefully selected patients, the Panel found no strong evidence to determine whether or not immediate cystectomy improved survival when compared to initial bladder sparing protocols that employ salvage cystectomy as therapy for persistent bladder cancer.[127-135] In addition, no high quality evidence directly compares QOL between the different treatment options; instead a number of studies report on health-related QOL outcomes and draw comparisons to other therapies. The Panel also recognizes that other non-multi-modal bladder–preserving regimens, although having less oncologic efficacy as well as less data, do exist and may be a reasonable option for certain patients, especially those who have poorer performance status.

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#eauguidelines

BCG- unresponsive NMIBC

EAU Guidelines on Non-muscle-invasive Bladder Cancer (TaT1 and CIS)

M. Babjuk (Chair), M. Burger (Vice-chair), E. Compérat, P. Gontero, F. Liedberg, A. Masson-Lecomte, A.H. Mostafid, J. Palou, B.W.G. van Rhijn, M. Rouprêt, S.F. Shariat, R. Sylvester
Guidelines Associates: O. Capoun, D. Cohen, J.L. Dominguez Escrig, T. Seisen, V. Soukup

European Association of Urology

Table 7.2: Categories of high-grade recurrence during or after BCG

Whenever a MIBC is detected during follow-up.
BCG-refractory tumour
1. If T1G3/HG tumour is present at 3 months [196, 291, 294] (LE: 3). 2. If TaG3/HG tumour is present after 3 months and/or at 6 months, after either re-induction or first course of maintenance [43] (LE: 4). 3. If CIS (without concomitant papillary tumour) is present at 3 months and persists at 6 months after either re-induction or first course of maintenance. If patients with CIS present at 3 months, an additional BCG course can achieve a complete response in > 50% of cases [43, 44, 284] (LE: 1b). 4. If HG tumour appears during BCG maintenance therapy*.
BCG-relapsing tumour
Recurrence of G3/HG (WHO 1973/2004) tumour after completion of BCG maintenance, despite an initial response [288] (LE: 3).
BCG unresponsive tumour
BCG unresponsive tumours include all BCG refractory tumours and those who develop T1Ta/HG recurrence within 6 months of completion of adequate BCG exposure** or develop CIS within 12 months of completion of adequate BCG exposure [292] (LE: 4).
BCG intolerance
Severe side effects that prevent further BCG instillation before completing treatment [266].

** Patients with low-grade recurrence during or after BCG treatment are not considered to be a BCG failure.*

*** Adequate BCG is defined as the completion of at least 5 of 6 doses of an initial induction course plus at least 2 out of 6 doses of a second induction course or 2 out of 3 doses of maintenance therapy.*

Urol Clin N Am 47 (2020) 119–128

Salvage Therapy for Non–muscle-invasive Bladder Cancer: Novel Intravesical Agents

Dunia Khaled, MD[a], John Taylor, MD[b], Jeffrey Holzbeierlein, MD[a,*]

Table 2
Summary disease-free and recurrence-free survival for current salvage therapies

Treatment	RFS	
Standard of care: radical cystectomy	5-y CSS 80%	
Target rates based on consensus panels	50% RFS at 6 mo, 30% at 12 mo, 25% at 18 mo	
Gemcitabine	21%–28% RFS at 12 mo	21% RFS at 24 mo
Docetaxel	40% RFS at 12 mo	
Valrubicin	18%–21% RFS at 6 mo	16% RFS at 12 mo
Abraxane	36% RFS at 12 mo	
Gemcitabine/Docetaxel	54% RFS at 12 mo	34% RFS at 24 mo
Gemcitabine/MMC	48% RFS at 12 mo	38% RFS at 24 mo
BCG/INFα		45% RFS at 24 mo
BCG/INFα/IL-2/GM-CSF	55% RFS at 12 mo	53% RFS at 24 mo
Chemohyperthermia	Range 44–92 RFS at 12 mo	Range 50%–68.9% RFS at 24 mo
Chemoradiation		54% RFS at 24 mo
EMDA	53% RFS at 3 mo	58% RFS at 6 mo

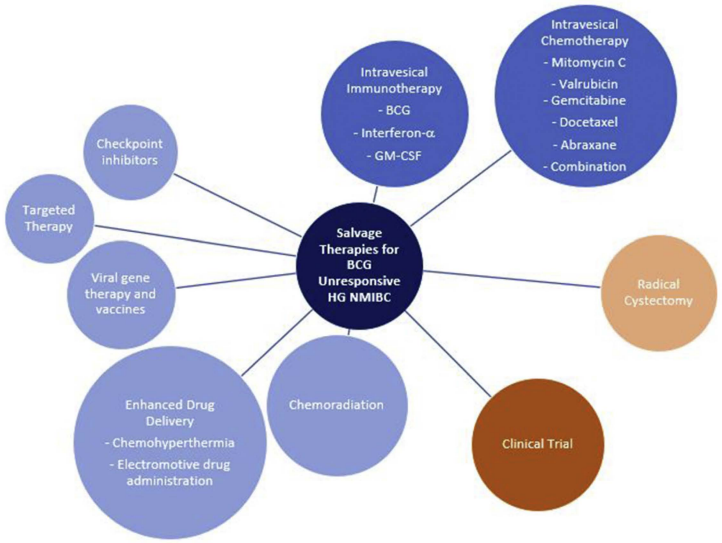

Fig. 1. Salvage intravesical therapy options. HG, high grade.

7.4.4 *Summary of evidence - treatment failure of intravesical therapy*

Summary of evidence	LE
Prior intravesical chemotherapy has no impact on the effect of bacillus Calmette-Guérin (BCG) instillation.	1a
Treatments other than radical cystectomy must be considered oncologically inferior in patients with BCG unresponsive tumours.	3

EAU Guidelines on Non-muscle-invasive Bladder Cancer (TaT1 and CIS)

M. Babjuk (Chair), M. Burger (Vice-chair), E. Compérat, P. Gontero, F. Liedberg, A. Masson-Lecomte, A.H. Mostafid, J. Palou, B.W.G. van Rhijn, M. Rouprêt, S.F. Shariat, R. Sylvester
Guidelines Associates: O. Capoun, D. Cohen, J.L. Dominguez Escrig, T. Seisen, V. Soukup

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HIGH RISK NON MUSCLE INVASIVE BLADDER CANCER

EAU Guidelines on

Non-muscle-invasive Bladder Cancer (TaT1 and CIS)

M. Babjuk (Chair), M. Burger (Vice-chair), E. Compérat, P. Gontero, F. Liedberg, A. Masson-Lecomte, A.H. Mostafid, J. Palou, B.W.G. van Rhijn, M. Rouprêt, S.F. Shariat, R. Sylvester

Guidelines Associates: O. Capoun, D. Cohen, J.L. Dominguez Escrig, T. Seisen, V. Soukup

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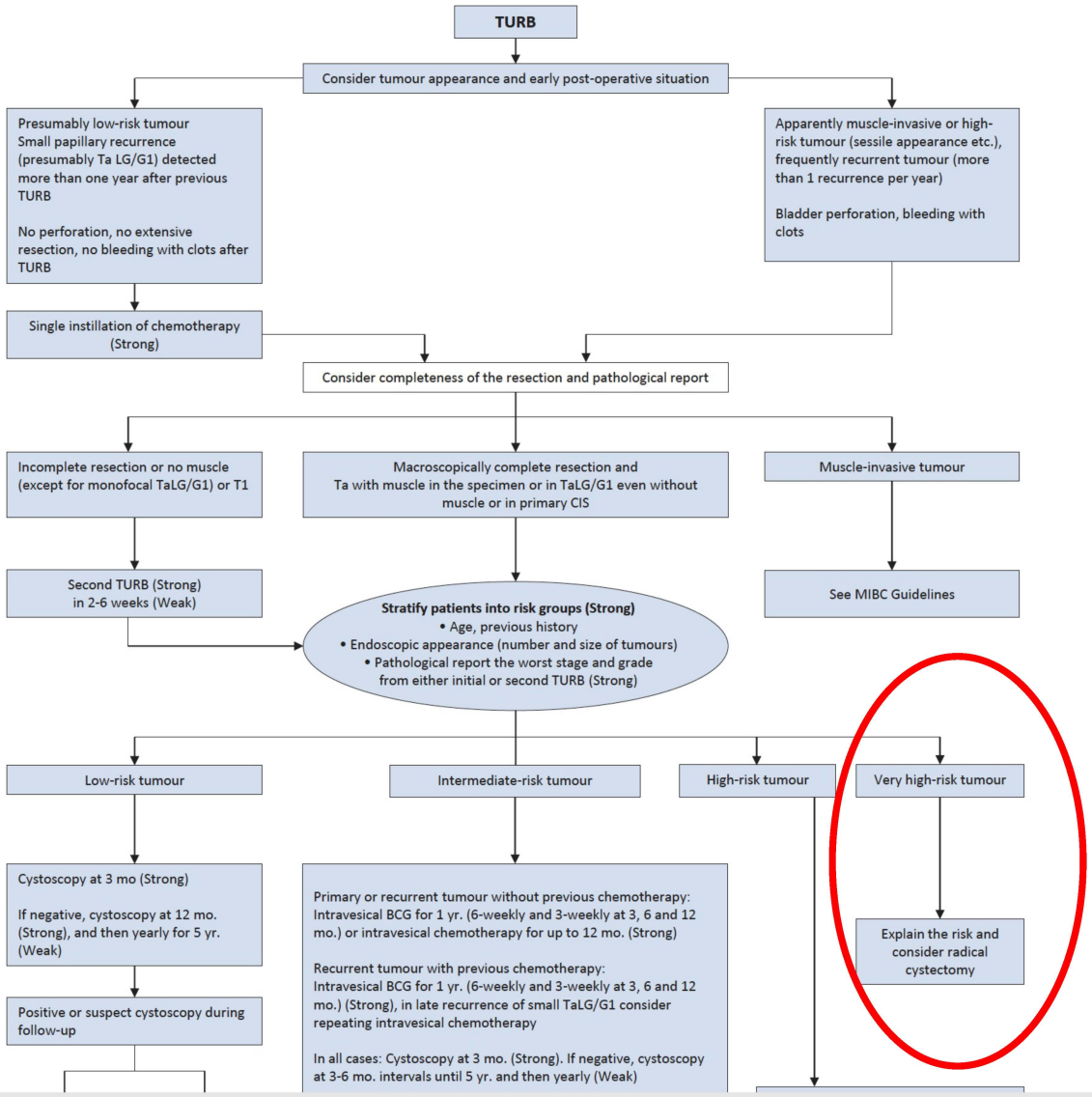
Figure 7.1: Treatment strategy in primary or recurrent tumour(s) without previous BCG*



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Approved by the AUA Board of Directors May 2020

Authors' disclosure of potential conflicts of interest and author/staff contributions appear at the end of the article.

The Practice Guidelines Committee would like to acknowledge the contributions of Drs. Christopher Anderson and John Gore to the 2020 Guideline Amendment.

American Urological Association (AUA)/

Society of Urologic Oncology (SUO) Guideline

DIAGNOSIS AND TREATMENT OF NON-MUSCLE INVASIVE BLADDER CANCER: AUA/SUO GUIDELINE

2016, Amended 2020

Sam S. Chang, MD, MBA; Stephen A. Boorjian, MD; Roger Chou, MD; Peter E. Clark, MD; Siamak Daneshmand, MD; Badrinath R. Konety, MD, FACS, MBA; Raj Pruthi, MD, FACS; Diane Z. Quale; Chad R. Ritch, MD, MBA; John D. Seigne, MD; Eila Curlee Skinner, MD; Norm D. Smith, MD; James M. McKiernan, MD

Purpose

The survival rate for the majority of patients with non-muscle invasive bladder

Role of Cystectomy in NMIBC

27. In a patient with Ta low- or intermediate-risk disease, a clinician should not perform radical cystectomy until bladder-sparing modalities (staged TURBT, intravesical therapies) have failed. (Clinical Principle)

28. In a high-risk patient who is fit for surgery with persistent high-grade T1 disease on repeat resection, or T1 tumors with associated CIS, LVI, or variant histologies, a clinician should consider offering initial radical cystectomy. (Moderate Recommendation; Evidence Strength: Grade C)

29. In a high-risk patient with persistent or recurrent disease within one year following treatment with two induction cycles of BCG or BCG maintenance, a clinician should offer radical cystectomy. (Moderate Recommendation; Evidence Strength: Grade C)

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2021
Non-Muscle Invasive Bladder Cancer

NCCN Guidelines Index
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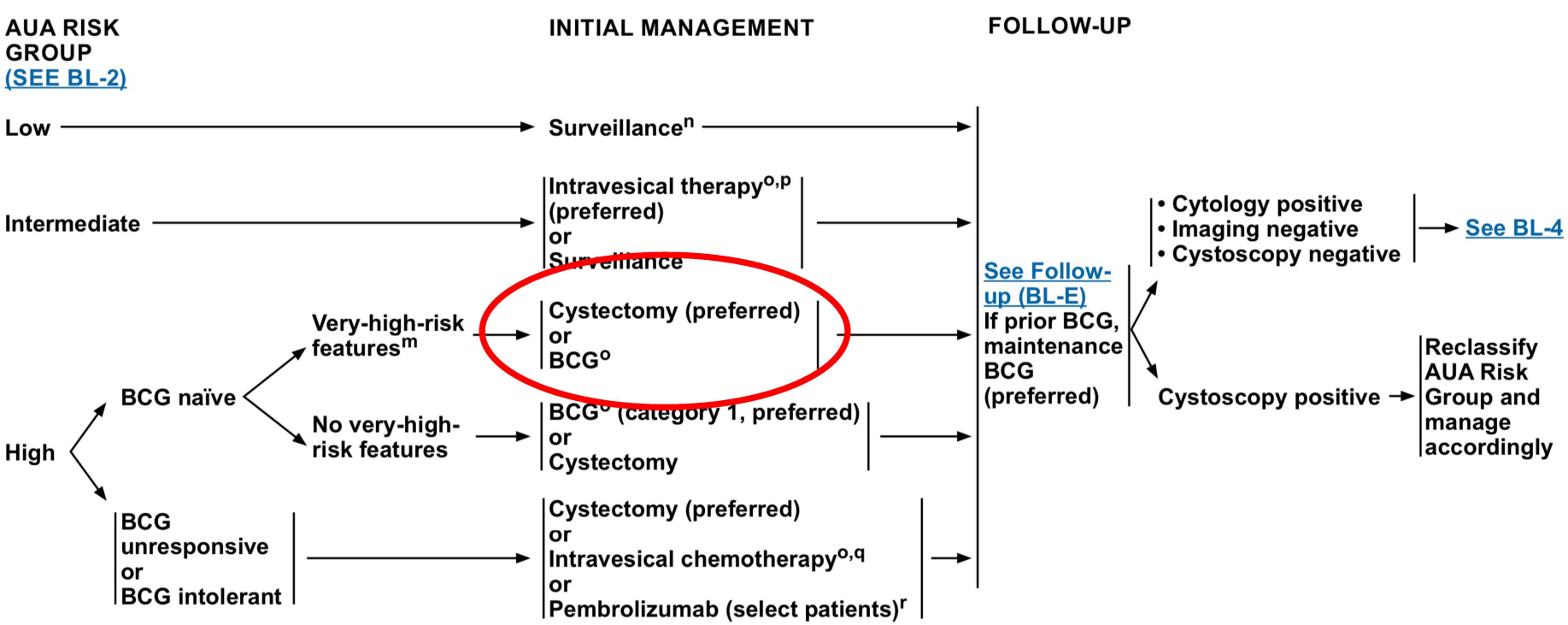
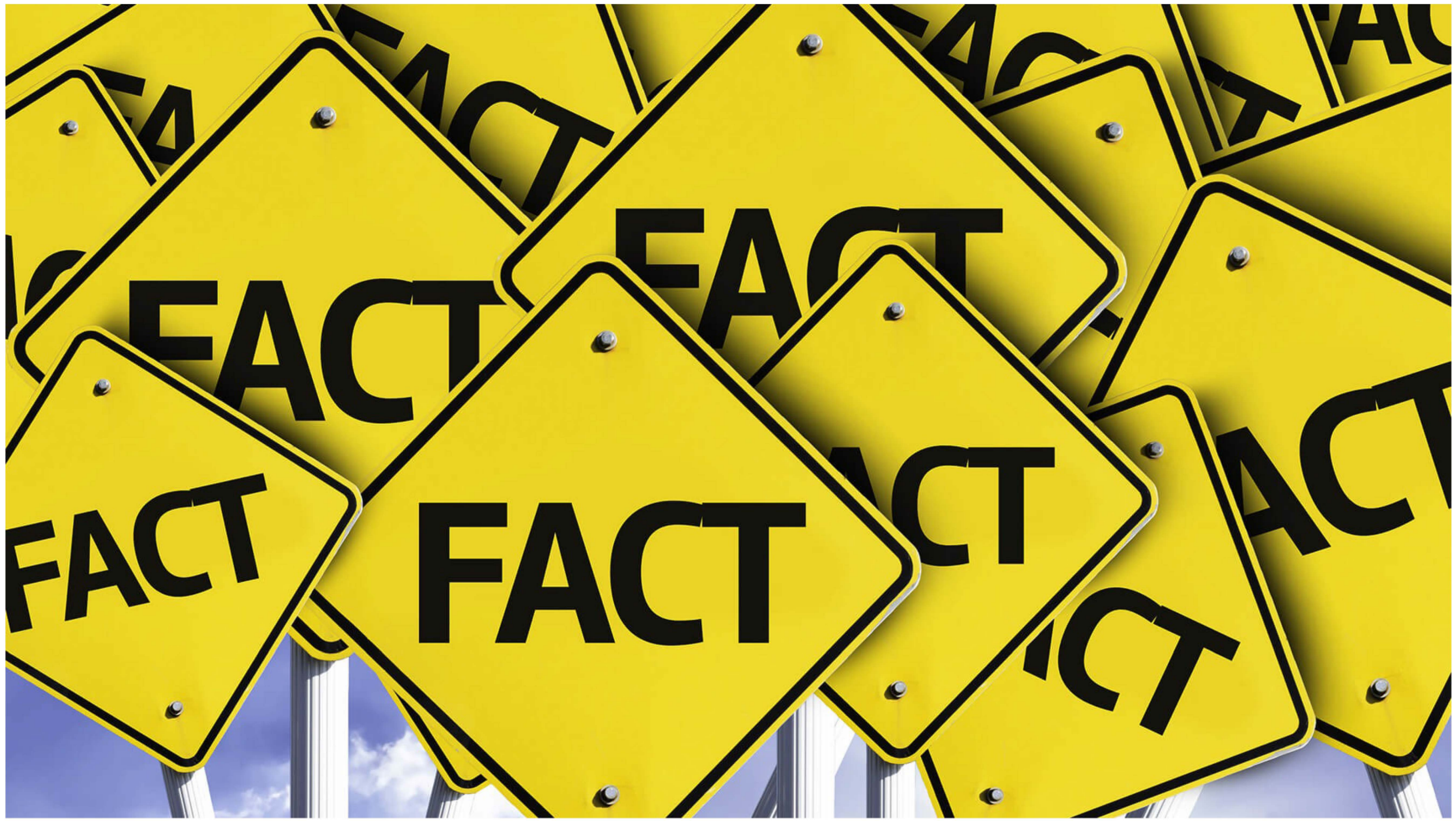
Discussion

MANAGEMENT PER NMIBC RISK GROUP



[m] Lymphovascular invasion, prostatic urethral involvement of tumor, variant histology (eg, micropapillary, plasmacytoid, sarcomatoid), T1 with extensive CIS.
[n] Should consider single perioperative instillation of intravesical chemotherapy at time of TURBT.
[o] See Principles of Intravesical Therapy (BL-F).
[p] Options for intravesical therapy for intermediate-risk disease include BCG and chemotherapy; should consider BCG availability in decision-making.
[q] Valrubicin is approved for BCG-refractory CIS.



- **BCG has demonstrated a significant impact in recurrence.**
- **Its role in progression is still controversial**
- **Even when maintenance is considered its role in progression is not well established.**
- **There is a lack of subset analysis for T1G3 tumours**

Table 1
Meta-analyses of intravesical therapy for superficial bladder cancer.

Study/aims	Included studies	Results
Shelley [7] a meta-analysis of published RCTs to compare incidence of tumour recurrence following TUR alone with TUR plus intravesical BCG	585 Patients from 6 RCTs (281 TUR alone, 304 TUR plus BCG). 4 different strains of BCG included, with doses of 78–180 mg instilled over 1–2 h	Tumour recurrence was significantly less in patients receiving TUR plus BCG (OR 0.33, 95% CI 0.21–0.43, $p < 0.0001$)
Han [8] meta-analysis of published data on BCG and tumour recurrence rate	25 Trials (RCTs and retrospective studies) comparing BCG ($n = 2,342$) versus TUR or other non-BCG intravesical therapies ($n = 2425$)	Recurrence was significantly less in BCG group (40.5% versus 49.7%, $p < 0.0001$)
Sylvester [4] determine effect of intravesical BCG on risk of disease progression.	24 RCTs comparing TUR + BCG versus TUR + non-BCG treatment (4863 Ta/T1/CIS)	BCG significantly reduced risk of progression (rate: BCG 9.8%, non-BCG 13.8%) OR 0.73 (95% CI 0.60–0.89, $p = 0.001$)
Pan [17] determine role of maintenance BCG therapy in T1G3 tumours	13 RCTS or controlled trials comparing maintenance BCG ($n = 915$) with no maintenance ($n = 733$) and reporting recurrence data	41% maintenance group recurred compared to 45% in control group (odds ratio 0.58, 95% CI 0.41–0.83, $p = 0.003$)
Bohle [3] to compare recurrence and toxicity of intravesical BCG with MMC in Ta/T 1 bladder cancer.	11 Controlled trials ($n = 2,799$) recruiting intermediate/high risk patients receiving BCG or MMC	39% of BCG group and 46% in MMC group recurred (OR 0.56, 95% CI 0.38–0.84, $p = 0.005$). Maintenance therapy appeared to be important in BCG's superiority
Shelley [30] compare the efficacy of intravesical BCG with MMC	A meta-analysis of published data from 1527 Ta/T1 patients from 6 RCTs (834 BCG versus 693 MMC)	In high risk patients BCG significantly reduced risk of recurrence (31% reduction in probability of recurrence per unit time, $p < 0.001$).
Bohle [33] to compare risk of progression of intravesical BCG with MMC in Ta/T1 bladder cancer	9 Controlled trials (7 prospective, 1 retrospective, 1 observational) comparing BCG with MMC (2410 patients).	No difference in progression rate (BCG 7.7%, MMC9.4%). However, BCG superior when BCG maintenance group compared to MMC (OR 0.66, 95% CI 0.47–0.94, $p = 0.02$)
Malmstrom [9] to compare the efficacy of BCG with MMC in terms of recurrence, progression and survival	An IPD meta-analysis from 9 RCTs (2820 patients) comparing BCG with MMC.	BCG plus maintenance superior to MMC for recurrence ($p < 0.001$) but no significant difference was observed in rates of progression and survival
Huncharek [5] determine impact of intravesical chemotherapy on tumour recurrence following complete TUR	11 RCTs (3730 patients Ta/T1G1–G3 tumours). Compared TUR versus TUR + intravesical chemotherapy (ADR, MMC, EP, thiotepa, peplomycin, neocarbarzine, mitoxantrone). Treatment varied from a single instillation to a 2 year schedule	Significant reduction in recurrence with intravesical chemotherapy. Sub-analysis indicated improved effect with longer schedules
Pawiniski [6] to evaluate the impact of prophylactic chemotherapy agents followingTUR, on recurrence, progression and survival. An individual-patient-data meta-analysis	4 EORTC and 2 MRC (2,535 patients) prophylactic RCTs in primary or recurrent Ta/T1 patients assessing TUR with (1629) or without (906) intravesical chemotherapy (thiotepa, VM-26, ADR, epodyl, Epirubicin, MMC, pyridoxine)	Adjuvant chemotherapy significantly reduced the risk the recurrence and increased the disease-free interval $P < 0.01$). There was no benefit for disease progression or survival
Sylvester [35] assess the efficacy of long-term or short-term BCG and chemotherapy for CIS	9 RCTs 700 patients with CIS. Compared BCG with intravesical chemotherapy (MMC, EP, ADR)	68% Complete response on BCG compared to 51% on chemotherapy ($p = 0.0002$). 47% on BCG disease-free, 26% on chemotherapy ($p < 0.0001$) BCG superior for CIS
Sylvester [73] assess the effect of a single immediate intravesical instillation on risk of recurrence	7 RCTs comparing TUR alone versus TUR + single post-operative cytotoxic instillation (MMC, EP, thiotepa, pirarubicin, 1476 Ta/T1).	Single instillation significantly reduced risk of recurrence (OR 0.61, 95% CI 0.49–0.75, $p = 0.0001$). More effective for single tumours

TUR – transurethral resection, RCT – randomised controlled trial, BCG – Bacillus Calmette–Guerin, OR – odds ratio, CI – confidence interval, CIS – carcinoma in situ, MMC – Mitomycin C, EP – Epirubicin, ADR – Adriamycin, CR – complete response, IPD – individual-patient-data.

Cancer Treatment Reviews 36 (2010) 195–205

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

TUMOUR REVIEW

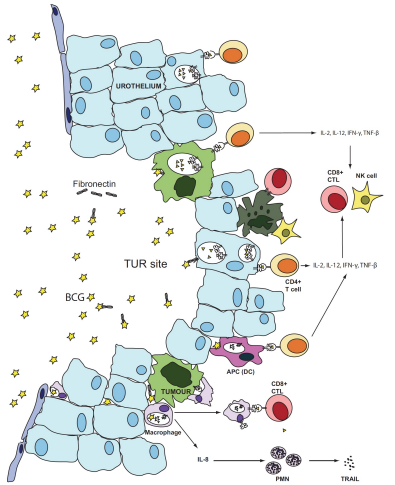
Intravesical therapy for superficial bladder cancer: A systematic review of randomised trials and meta-analyses

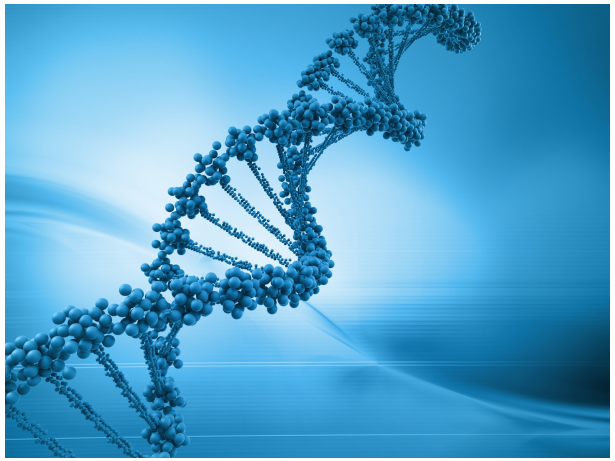
Mike D. Shelley [a,*], Malcolm D. Mason [b], Howard Kynaston [c]

- An overarching search of the literature was used to identify relevant studies to assess the clinical benefit of intravesical therapy and provide clinical guidance in a comprehensive systematic review of randomised trials and meta-analyses of intravesical therapy for superficial bladder cancer
- Intravesical BCG is superior to chemotherapy in terms of complete response and disease-free survival. However, there is no conclusive evidence that one agent is superior in terms of overall survival.

30-50% fails to respond to BCG therapy

- Compliance with the current protocol is affected by BCG-associated side effects.
- High intra- and interobserver variability among pathologists, leading to incorrect histologic staging of tumours, could explain BCG failure[8,9].
- Incomplete tumour resection, reported in 20–62% of cases, at restaging transurethral resection (TUR) could be the cause of refractory disease[10–13].
- BCG response is currently determined by refractory disease after the first or second BCG induction course or by a recurrence during maintenance therapy.
- The only strong predictive marker used to identify patients for immediate cystectomy is refractory T1 or carcinoma in situ (CIS)disease after BCG induction[14].





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Review – Bladder Cancer

Markers Predicting Response to Bacillus Calmette-Guérin Immunotherapy in High-Risk Bladder Cancer Patients: A Systematic Review

Tahlita C.M. Zuiverloon [a,b], Annemieke J.M. Nieuweboer [a], Hedvig Vékony [a], Wim J. Kirkels [b], Chris H. Bangma [b], Ellen C. Zwarthoff [a,]*

EUROPEAN UROLOGY 57 (2010) 300–309

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Urothelial Cancer

Characteristics and Outcomes of Patients with Clinical T1 Grade 3 Urothelial Carcinoma Treated with Radical Cystectomy: Results from an International Cohort

Hans-Martin Fritsche[a], Maximilian Burger[a], Robert S. Svatek[b], Claudio Jeldres[c], Pierre I. Karakiewicz[c], Giacomo Novara[d], Eila Skinner[d], Stefan Denzinger[a], Yves Fradet[e], Hendrik Isbarn[d], Patrick J. Bastian[f,k], Bjoern G. Volkmer[g], Francesco Montorsi[h], Wassim Kassouf[i], Derya Tilki[f], Wolfgang Otto[a], Umberto Capitanio[c], Jonathan I. Izawa[l], Vincenzo Ficarra[j], Seth Lerner[m], Arthur I. Sagalowsky[n], Mark Schoenberg[o], Ashish Kamat[b], Colin P. Dinney[b], Yair Lotan[n], Shahrokh F. Shariat[n,]*

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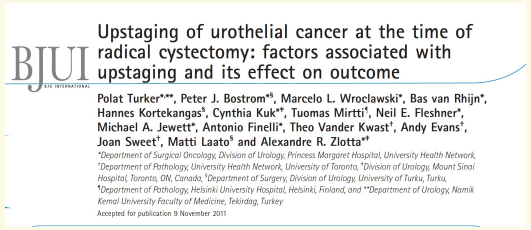
Bladder Cancer

Discrepancy between Clinical and Pathologic Stage: Impact on Prognosis after Radical Cystectomy

Shahrokh F. Shariat[a,], Ganesh S. Palapattu[b], Pierre I. Karakiewicz[c], Craig G. Rogers[b], Amnon Vazina[d], Patrick J. Bastian[b], Mark P. Schoenberg[b], Seth P. Lerner[a], Arthur I. Sagalowsky[a], Yair Lotan[a]*



BJUI

Upstaging of urothelial cancer at the time of radical cystectomy: factors associated with upstaging and its effect on outcome

Polat Turker*,**, Peter J. Bostrom*§, Marcelo L. Wroclawski*, Bas van Rhijn*, Hannes Kortekangas§, Cynthia Kuk*†, Tuomas Mirtti‡, Neil E. Fleshner*, Michael A. Jewett*, Antonio Finelli*, Theo Vander Kwast†, Andy Evans†, Joan Sweet†, Matti Laato§ and Alexandre R. Zlotta*†

*Department of Surgical Oncology, Division of Urology, Princess Margaret Hospital, University Health Network, †Department of Pathology, University Health Network, University of Toronto, ‡Division of Urology, Mount Sinai Hospital, Toronto, ON, Canada, §Department of Surgery, Division of Urology, University of Turku, Turku, ¶Department of Pathology, Helsinki University Hospital, Helsinki, Finland, and **Department of Urology, Namik Kemal University Faculty of Medicine, Tekirdag, Turkey

Accepted for publication 9 November 2011

- **The staging accuracy for T1 tumours by TURB is low with 27-51% of patients being upstaged to muscle-invasive tumour at radical cystectomy**

Systematic review

21% Risk of progression

Survival after progression: 35%

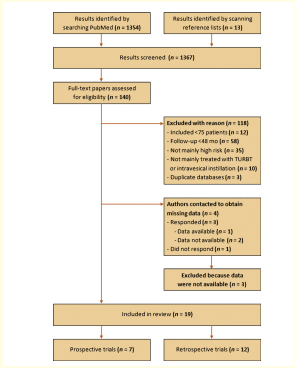
4. Conclusions

This study provides systematically gathered evidence showing a poor prognosis for patients with high-risk NMIBC and tumour progression. Progression to MIBC and BCa-related death in high-risk NMIBC are relatively early events and occur mainly within 48 mo. However, even in cases of early cystectomy, a relevant proportion of patients appears not be cured of their disease. Still, the worst outcome is seen when progression to MIBC has occurred. It remains unclear why the CSS in these patients is so much worse.

Table 1 – Included trials having a prospective design

Source	No. of patients	Median follow-up	Restaging TURBT	Proportion of Ta/T1/CIS*/cCIS**, %	Progression to MIBC, no. (%)	Death from disease, no. (%)	CSS in case of progression, %
Di Stasi et al, 2006 [30]	212	88 (IQR: 63–110)	Yes	0/100/0/27	33 (16)	23 (11)	30
Dalbagni et al, 2007 [31]	89	52 (range: 16–90)	Yes	0/100/0/38	22 (25)	15 (17)	32
Gradmark et al, 2007 [36]	250	123 (range: 46–176)	NR	42/25/33†	58 (23)	45 (18)	22
Esuvaranathan et al, 2007 [37]	80	54 (range: 6–114)	NR	24/49/27†	6 (8)	5 (6)	17
Gofrit et al, 2009 [38]	104	75	NR	38/25/37/63	22 (21)	12 (12)	45
Zieger et al, 2009 [39]	125	80 (range: 6–142)	NR	39/61/0/31	67 (54)	58 (46)	13
Sylvester et al, 2010 [5]	323	110	No	NR	50 (15)	18 (6)	64
Totals	1183	52–123	–	–	258 (22)	176 (15)	32 (range: 13–64)

TURBT = transurethral resection of the bladder tumour; CIS = carcinoma in situ; cCIS = concomitant carcinoma in situ; MIBC = muscle-invasive bladder cancer; CSS = cancer-specific survival; IQR = interquartile range; NR = not reported.
* Isolated CIS without concomitant papillary tumour.
** Papillary tumour with concomitant CIS.
† The presence of concomitant and isolated CIS were reported together.



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European Association of Urology

Review – Bladder Cancer

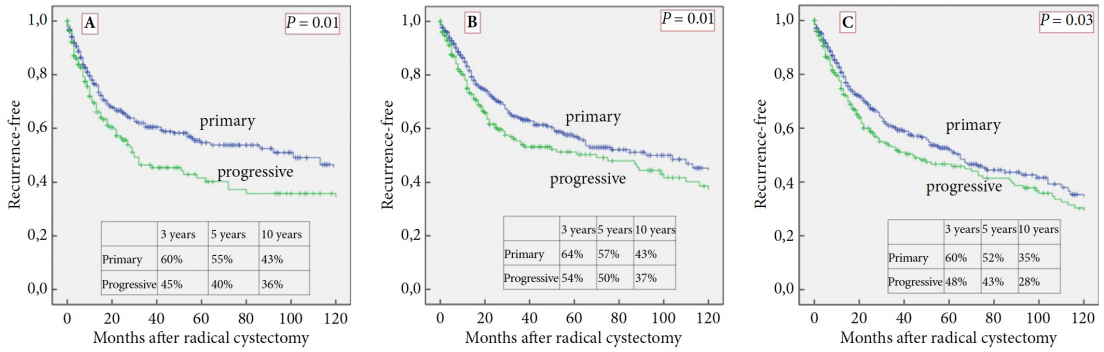
Long-term Cancer-specific Survival in Patients with High-risk, Non–muscle-invasive Bladder Cancer and Tumour Progression: A Systematic Review

Sven van den Bosch, J. Alfred Witjes *

- The 10-year RFS, CSM and OM rates for primary vs progressive status were 43 vs 36% (P = 0.01), 43 vs 37% (P = 0.01), and 35 vs 28% (P = 0.03), respectively. On multivariable Cox regression analyses, progressive status remained significantly associated with a higher rate of recurrence

- Patients who experience disease progression to MIBC have a worse prognosis than those who present “de novo” MIBC

Fig. 1 Kaplan–Meier analysis assessing (**A**) recurrence-free survival, (**B**) cancer-specific mortality (CSM)-free and (**C**) overall mortality (OM)-free rates after radical cystectomy stratified according primary or progressive status.



BJUI
BJU International

Comparing long-term outcomes of primary and progressive carcinoma invading bladder muscle after radical cystectomy

Marco Moschini*†, Vidit Sharma‡, Paolo Dell’oglio*, Vito Cucchiara*, Giorgio Gandaglia*, Francesco Cantiello†, Fabio Zattoni§, Federico Pellucchi¶, Alberto Briganti*, Rocco Damiano†, Francesco Montorsi*, Andrea Salonia* and Renzo Colombo*

BJU Int 2016; **117:** 604–610
wileyonlinelibrary.com

 | doi:10.1111/bju.13146
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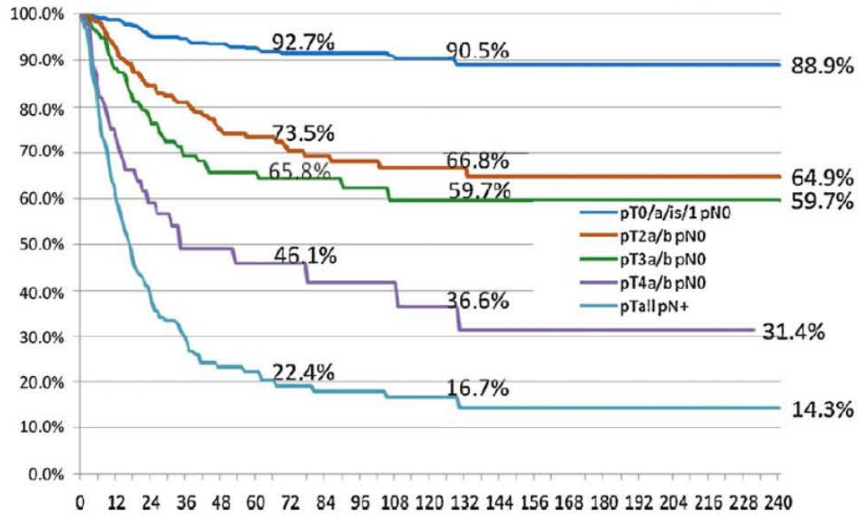

Fig. 2 – Disease-specific survival rates according to the tumor stage of the cystectomy specimen.

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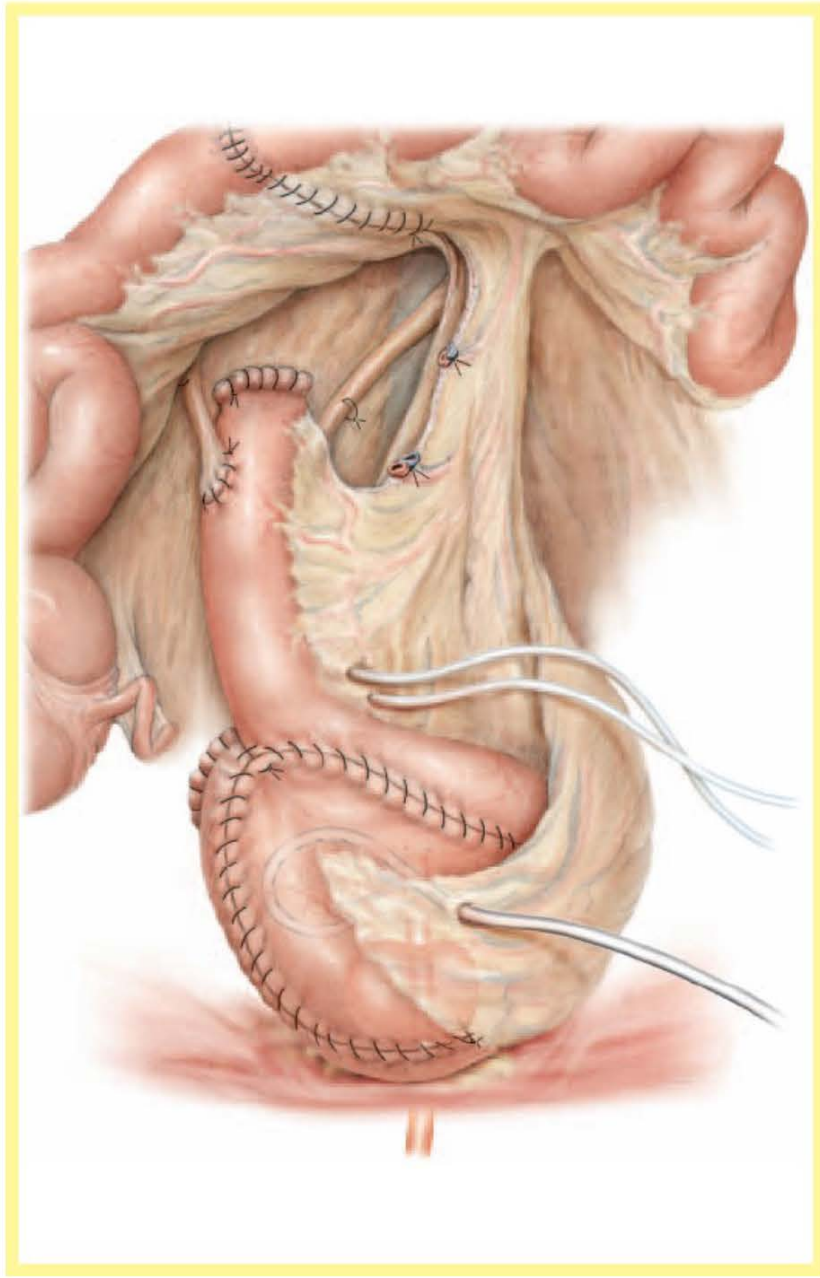
European Association of Urology

Bladder Cancer

Radical Cystectomy for Urothelial Carcinoma of the Bladder Without Neoadjuvant or Adjuvant Therapy: Long-Term Results in 1100 Patients

Richard E. Hautmann[a,*], *Robert C. de Petriconi*[a], *Christina Pfeiffer*[b], *Bjoern G. Volkmer*[a,b]



http://www.eortc.be/tools/bladdercalculator/

Prior recurrence rate:

Primary	≤ 1 per year	>1 per year

Number of tumours:

1	2 to 7	8 or more

T category:

Ta	T1

Tumour diameter:

< 3cm	≥ 3cm

Concomitant CIS:

No	Yes

Grade (WHO 1973):

G1	G2	G3

Back | Calculate

Probability of Recurrence

1 year	5 years
38.0%	62.0%

Risk of recurrence: Intermediate

Probability of Progression

1 year	5 years
17.0%	45.0%

Risk of progression: High

OK

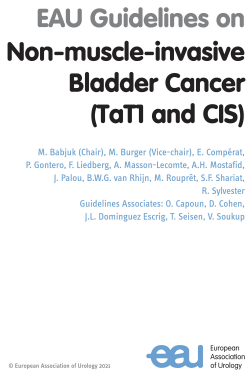
http://www.aeu.es/Cueto.html

Predicting Nonmuscle Invasive Bladder Cancer Recurrence and Progression in Patients Treated with Bacillus Calmette-Guerin: The CUETO Scoring Model Español

Factor		Score: Recurrence	Score: Progression
Gender	(•) Male	0	0
	( ) Female	3	0
Age	( ) Less than 60	0	0
	( ) 60-70	1	0
	(•) Greater than 70	2	2
Recurrent tumor	(•) No	0	0
	( ) Yes	4	2
No. tumors	( ) 3 or Less	0	0
	(•) Greater than 3	2	1
T category	( ) Ta	0	0
	(•) T1	0	2
Associated Tis	( ) No	0	0
	(•) Yes	2	1
Grade	( ) G1	0	0
	( ) G2	1	2
	(•) G3	3	6
Total scores		9	12

Recurrence and progression probabilities at 1, 2 and 5 years by total score

Time	Recurrence (7-9) Prob. (%)	Recurrence (7-9) C.I. 95% (Low-High)	Progression (>10) Prob. (%)	Progression (>10) C.I. 95% (Low-High)
1 Yr	25.36	(19.56-31.16)	13.97	(6.64-21.30)
2 Yrs	39.61	(32.93-46.29)	24.81	(15.60-34.02)
5 Yrs	47.65	(40.55-54.75)	33.57	(23.06-44.08)



Patients with the following characteristics were likewise not studied and should be included in the very high-risk group:

- The presence of CIS in the prostatic urethra is associated with a higher risk of progression [8].
- Lymphovascular invasion in TURBT specimens is associated with a higher risk of pathological upstaging to muscle-invasive disease [26–29].
- Some forms of variant histology of urothelial carcinoma (especially micropapillary, plasmacytoid, sarcomatoid, and neuroendocrine types) also have very poor prognosis [2,29–33].

INDIVIDUAL PATIENT DATA ANALYSIS FOR PIRMARY NMIBC

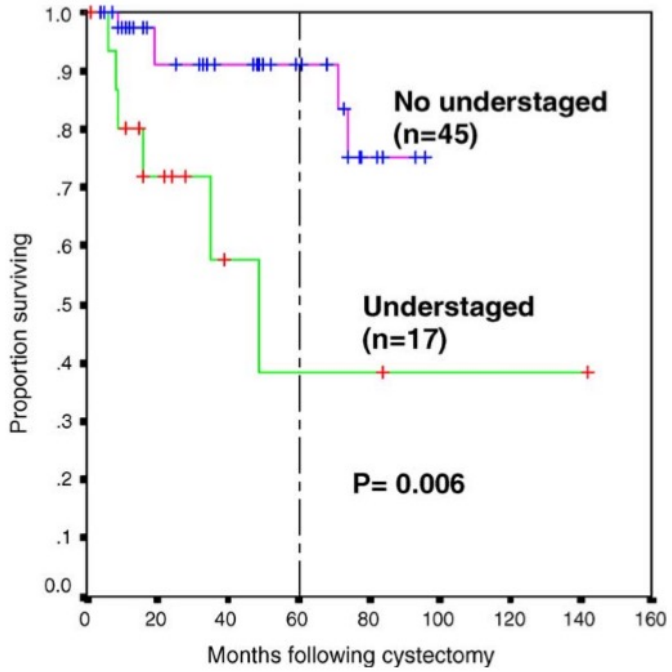
- A total of 3401 patients treated with TURBT ± intravesical chemotherapy were included.
- From the multivariable analyses, tumor stage, WHO 1973/2004–2016 grade, concomitant carcinoma in situ, number of tumors, tumor size, and age were used to form four risk groups for which the probability of progression at 5 yr varied from <1% to >40%.
- Limitations include the retrospective collection of data and the lack of central pathology review.

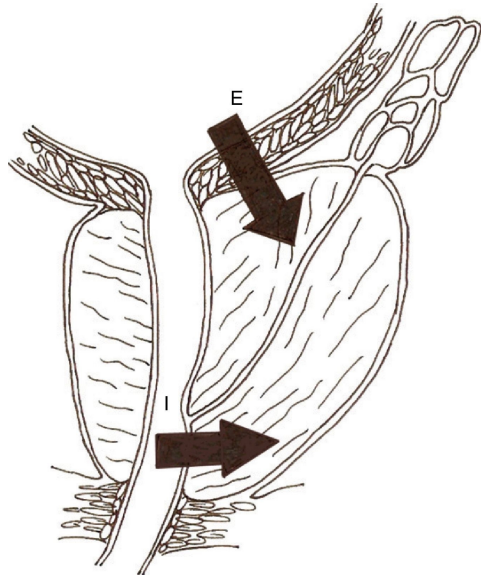
Table 6.2: Probabilities of disease progression in 1, 5 and 10 year(s) for the new EAU NMIBC risk groups [5]*

Risk group	Probability of Progression and 95% Confidence Interval (CI)		
	1 Year	5 Years	10 Years
New Risk Groups with WHO 2004/2016			
Low	0.06% (CI: 0.01%–0.43%)	0.93% (CI: 0.49%–1.7%)	3.7% (CI: 2.3%–5.9%)
Intermediate	1.0% (CI: 0.50%–2.0%)	4.9% (CI: 3.4%–7.0%)	8.5% (CI: 5.6%–13%)
High	3.5% (CI: 2.4%–5.2%)	9.6% (CI: 7.4%–12%)	14% (CI: 11%–18%)
Very High	16% (CI: 10%–26%)	40% (CI: 29%–54%)	53% (CI: 36%–73%)
New Risk Groups with WHO 1973			
Low	0.12% (CI: 0.02%–0.82%)	0.57% (CI: 0.21%–1.5%)	3.0% (CI: 1.5%–6.3%)
Intermediate	0.65% (CI: 0.36%–1.2%)	3.6% (CI: 2.7%–4.9%)	7.4% (CI: 5.5%–10%)
High	3.8% (CI: 2.6%–5.7%)	11% (CI: 8.1%–14%)	14% (CI: 10%–19%)
Very High	20% (CI: 12%–32%)	44% (CI: 30%–61%)	59% (CI: 39%–79%)

WHO = World Health Organization.
**Table 6.2 does not include patients with variant histologies, LVI, CIS in the prostatic urethra, primary CIS or recurrent patients.*

- RC should be performed prior to progression in high risk NMIBC that fail after TUR and BCG.
- In patients with clinical and pathological nonmuscle invasive disease, RC provides an excellent disease-free survival.
- One third of patients with HRSBT who underwent RC after BCG failure were understaged and had a shorter survival.
- Tumor in the prostatic urethra at endoscopic staging was the only factor associated to understaging and shorter survival.





European Urology

European Urology 48 (2005) 53–59

Bladder Cancer

Cystectomy in Patients with High Risk Superficial Bladder Tumors Who Fail Intravesical BCG Therapy: Pre-Cystectomy Prostate Involvement as a Prognostic Factor

J. Huguet[a,*], M. Crego[a], S. Sabaté[b], J. Salvador[a], J. Palou[a], H. Villavicencio[a]

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Available online 7 April 2005

Table 3
Multivariable analysis of clinical-pathological factors related to understaging

Variable	Hazard ratio	95% CI	*p*-Value
Tumor in prostatic urethra	12.2	2.2–65.5	0.003
No tumor	0.4	0.07–2.5	0.3
Size	2.3	0.4–12.01	0.3
Grade	0.7	0.1–3.4	0.6
Presence of CIS	0.3	0.08–1.7	0.2
Sex	0.1	0.01–1.5	0.1

Only the most significant variables in the bivariate analysis are included.

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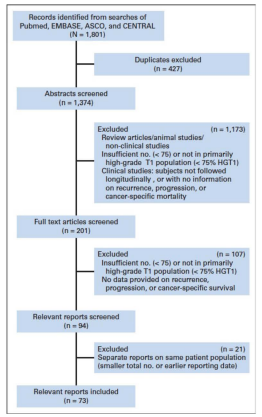
JOURNAL OF CLINICAL ONCOLOGY

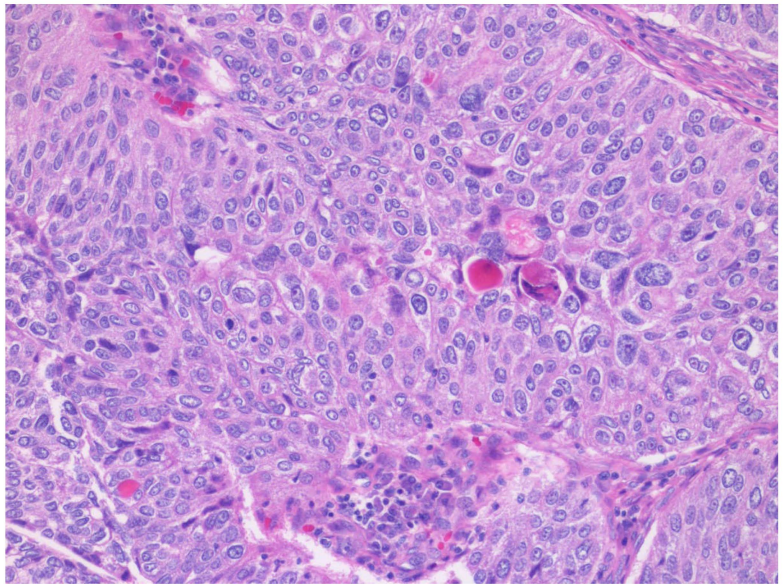
REVIEW ARTICLE

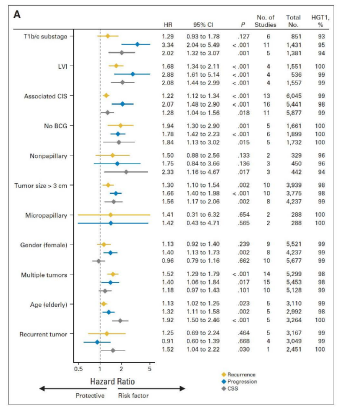
Improving Selection Criteria for Early Cystectomy in High-Grade T1 Bladder Cancer: A Meta-Analysis of 15,215 Patients

William Martin-Doyle, Jeffrey J. Leow, Anna Orsola, Steven L. Chang, and Joaquim Bellmunt

In conclusion, our meta-analysis of prognostic factors in HGT1 bladder cancer provides strong evidence that increased depth of tumor invasion is the strongest risk factor for both progression and cancer-specific survival, supporting the inclusion of depth of invasion in the TNM classification system for NMIBC. Our study also goes on to confirm the negative role associated with CIS, opening to debate whether this lesion should be actively sought by random bladder biopsies. Lymphovascular invasion, nonuse of BCG, female sex, tumor size more than 3 cm, and multiple tumors have also been validated as relevant prognostic factors. These factors should be used for patient stratification in future clinical trials, with outcomes reported by sex. These results could improve therapeutic outcomes by informing risk stratification and individualized decision making on the need for early cystectomy in recently diagnosed patients, an ongoing area of controversy. Future research should attempt to confirm these findings using individual patient data meta-analysis, which offers greater power to detect subtle effects. Combining these prognostic factors into







	Ta	T1
RESIDUAL TUMOUR	55%	51%
UPSTAGING	0,4%	8%
RECURRENCE	16% reTUR 58% control	45% reTUR 49% control
PROGRESSION	7-13%	6% reTUR 24% control
CSM		17% reTUR 31% control
OM		22-30% reTUR 26-36% control

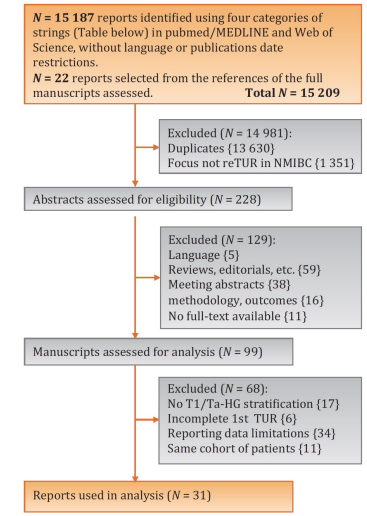


Fig. 1 – CONSORT study flow diagram. CONSORT = Consolidated Standards of Reporting Trials; NMIBC = non–muscle-invasive bladder cancer; reTUR = repeat transurethral resection; TUR = transurethral resection.

4. Conclusions

Residual tumour is common after TUR for high risk NMIBC. The reTUR helps in the diagnosis of this residual cancer and may improve outcomes for cancers initially staged as T1.

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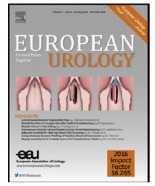

Review – Bladder Cancer

Repeat Transurethral Resection in Non–muscle-invasive Bladder Cancer: A Systematic Review

Marcus G.K. Cumberbatch[a,1,*], *Beat Foerster*[b,c,1], *James W.F. Catto*[a], *Ashish M. Kamat*[d], *Wassim Kassouf*[e], *Ibrahim Jubber*[a], *Shahrokh F. Shariat*[b,f,g], *Richard J. Sylvester*[h], *Paolo Gontero*[i]

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Bladder Cancer

Early Versus Deferred Cystectomy for Initial High-Risk pT1G3 Urothelial Carcinoma of the Bladder: Do Risk Factors Define Feasibility of Bladder-Sparing Approach?

Stefan Denzinger, Hans-Martin Fritsche, Wolfgang Otto, Andreas Blana, Wolf-Ferdinand Wieland, Maximilian Burger*

Table 2 – Univariate Cox regression analysis of factors in relation to cancer-specific death in patients with pT1G3 BC

	Adjusted HR	95%CI	p value
Gender			
Male	1.00	(Reference)	
Female	0.63	0.13–1.79	0.95
Multifocality			
Multifocality	1.00	(Reference)	
No multifocality	1.69	0.93–4.30	0.23
Tumour size			
Tumour size >3 cm	1.00	(Reference)	
Tumour size <3 cm	2.03	0.87–3.71	0.20
CIS			
No CIS	1.00	(Reference)	
CIS	3.05	1.04–15.24	**<0.001**
Treatment group			
Early cystectomy	1.00	(Reference)	
Deferred cystectomy	5.11	2.14–18.66	**<0.01**

BC, bladder cancer; HR, hazard ratio; CI, confidence interval; CIS, carcinoma in situ.
Bold face represents *p* values <0.05.

5. Conclusions

High-risk pT1G3 tumours with two or more risk factors, that is, multifocal and/or >3 cm in size and/or with concomitant CIS, should be counseled about undergoing early CX, whereas a smaller and solitary initial pT1G3 BC without CIS may be regarded for an organ-sparing approach. CIS should be considered for timely radical surgery because it relates to reduced cancer-specific survival.

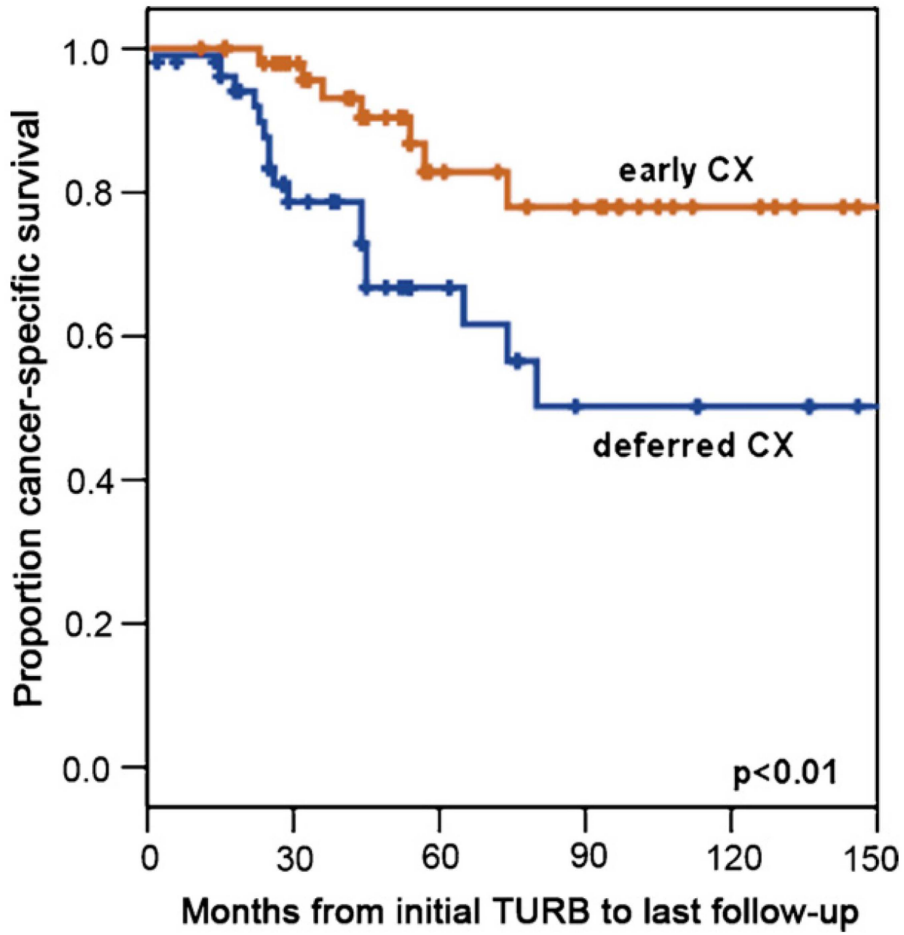

Fig. 1 – Kaplan-Meier analysis of cancer-specific survival in patients with early (orange line) versus deferred (blue line) cystectomy.

CONCLUSION

The management of patients with non-muscle invasive variant bladder tumors with intravesical immunotherapy with BCG is risky even when confirmation of diagnosis with second look biopsies and meticulous follow-up are employed. The progression rate of these patients to muscle invasive disease is high (40% at 5 years compared to 17.5% in conventional high-grade tumors). Furthermore, the chance of successful salvage after progression is lower compared to conventional high-grade tumors. A patient with a variant tumor treated with intravesical immunotherapy has a 27% chance of dying from this disease within 5 years compared to 7.5% chance for a patient with conventional high-grade carcinomas. As such, patients with variant tumors should be advised of this adverse clinical course and considerations for cystectomy strongly recommended.

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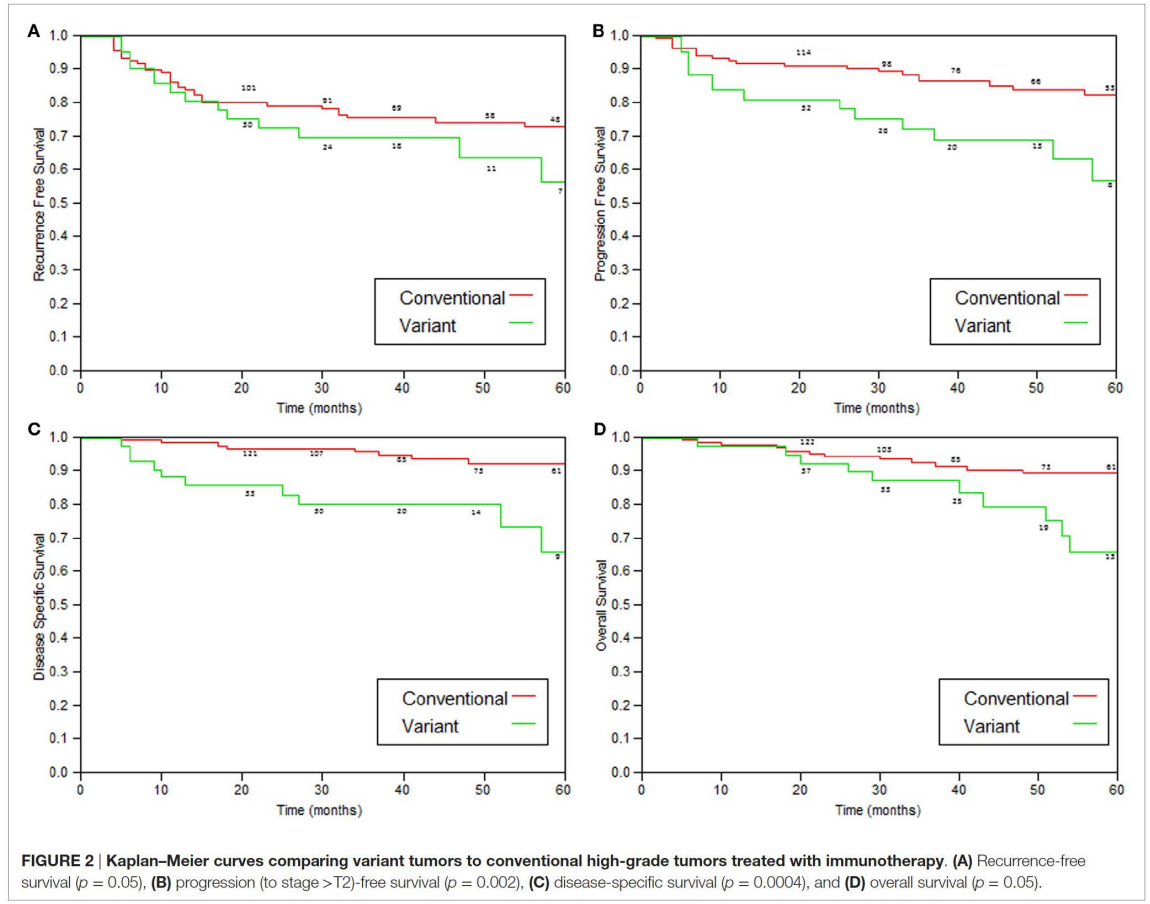

FIGURE 2 | Kaplan–Meier curves comparing variant tumors to conventional high-grade tumors treated with immunotherapy. **(A)** Recurrence-free survival ($p = 0.05$), **(B)** progression (to stage >T2)-free survival ($p = 0.002$), **(C)** disease-specific survival ($p = 0.0004$), and **(D)** overall survival ($p = 0.05$).

The Response of Variant Histology Bladder Cancer to Intravesical Immunotherapy Compared to Conventional Cancer

Ofer N. Gofrit[1], Vladimir Yutkin[1], Amos Shapiro[1], Galina Pizov[2], Kevin C. Zorn[3], Guy Hidas[1], Ilan Gielchinsky[1], Mordechai Duvdevani[1,2], Ezekiel H. Landau[1] and Dov Pode[1]*

Variant

Micropapillary
Squamous
Nested
Glandular

Table 4 – Consensus meeting statements regarding the management of bladder cancer with variant histologies.

Proposed statements[a]	Level of agreement (%)			*N*	Consensus achieved
	Disagree	Equivocal	Agree		
1. T1 high-grade bladder urothelial cancer with micropapillary histology (established after complete TURBT and/or re-TURBT) should be treated with immediate radical cystectomy and lymphadenectomy	14	0	86	29	Yes

Table 1 – Delphi survey participants according to specialty.

Specialty	Round 1, *N*	Round 2, *N*
Urology	52	45
Oncology		
Medical oncology	18	18
Radiation oncology	18	14
Other		
Nuclear medicine	3	3
Pathology	8	5
Radiology	9	7
Specialist nurse	3	3
Clinical oncology	2	2
Total	113	97

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European Association of Urology

Bladder Cancer – Editor's Choice

EAU-ESMO Consensus Statements on the Management of Advanced and Variant Bladder Cancer—An International Collaborative Multistakeholder Effort†
Under the Auspices of the EAU-ESMO Guidelines Committees

Future Markers

European Journal of Cancer 64 (2016) 127–136

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

A five-gene expression signature to predict progression in T1G3 bladder cancer

Antoine G. van der Heijden [a,1], Lourdes Mengual [b,*,1], Juan J. Lozano [c], Mercedes Ingelmo-Torres [b], Maria J. Ribal [b], Pedro L. Fernández [d], Egbert Oosterwijk [a], Jack A. Schalken [a], Antonio Alcaraz [b], J. Alfred Witjes [a]

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European Association of Urology

Bladder Cancer

Prognostic Impact of a 12-gene Progression Score in Non–muscle-invasive Bladder Cancer: A Prospective Multicentre Validation Study

Lars Dyrskjøt [a,], Thomas Reinert [a], Ferran Algaba [b], Emil Christensen [a], Daan Nieboer [c], Gregers G. Hermann [d], Karin Mogensen [d], Willemien Beukers [e], Mirari Marquez [f], Ulrika Segersten [g], Søren Høyer [h], Benedicte P. Ulhøi [h], Arndt Hartmann [i], Robert Stöhr [i], Sven Wach [j], Roman Nawroth [k], Kristina Schwamborn [l], Cane Tulic [m], Tatjana Simic [n], Kerstin Junker [o], Niels Harving [p], Astrid C. Petersen [q], Jørgen B. Jensen [r], Bastian Keck [j], Marc-Oliver Grimm [s], Marcus Horstmann [s], Tobias Maurer [k], Ewout W. Steyerberg [c], Ellen C. Zwarthoff [e], Francisco X. Real [f,t], Núria Malats [f], Per-Uno Malmström [g], Torben F. Ørntoft [a]*