Xray One

Poggio Rusco
(MN)
17 marzo 2018

Con il Patrocinio
Ordine dei Medici di Mantova
Sistema Socio Sanitario
Regione Lombardia
ATS Val Padana

AGGIORNAMENTI IN UROLOGIA:
SPECIALISTI E MMG A CONFRONTO

LE NEOPLASIE UROTELIALI: terapia chirurgica ma non solo

www.urochirurgia.com

Dr. Maurizio Simone

UroChirurgia

UROTELIOMI: *FACTS!*

- Ca vescicale (BC):
  - 9° per frequenza
  - 4° per *cancer death*
  - 70-75% NON MIOINVASIVO alla diagnosi

- Ca uroteliale dell' alta via escretrice (UTUC):
  - 5-8% di tutti i TCC
  - 5% di tutti i tumori renali
  - > 90% di tutti i tumori dell' alta via escretrice
  - 2-5% ricorrerà controlateralmente nel tempo

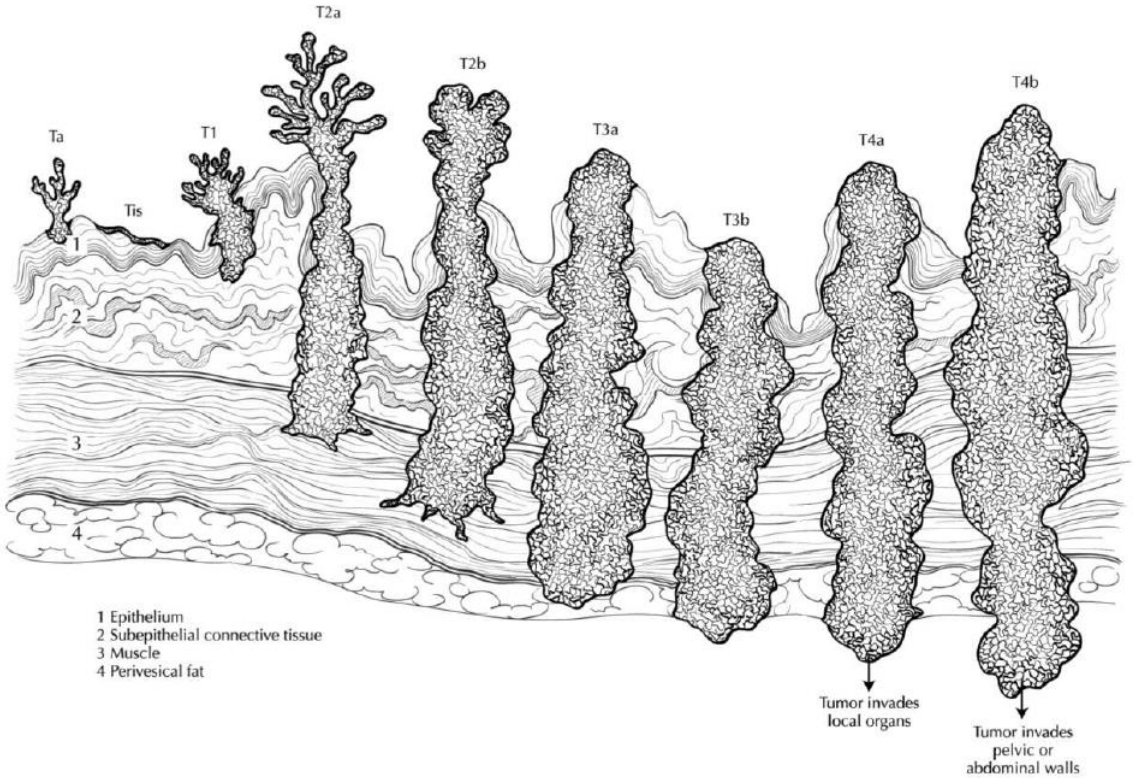
UROTELIOMI: *FACTS!*

- BC → UTUC
  - 2-4 %
- UTUC → BC
  - 50 %

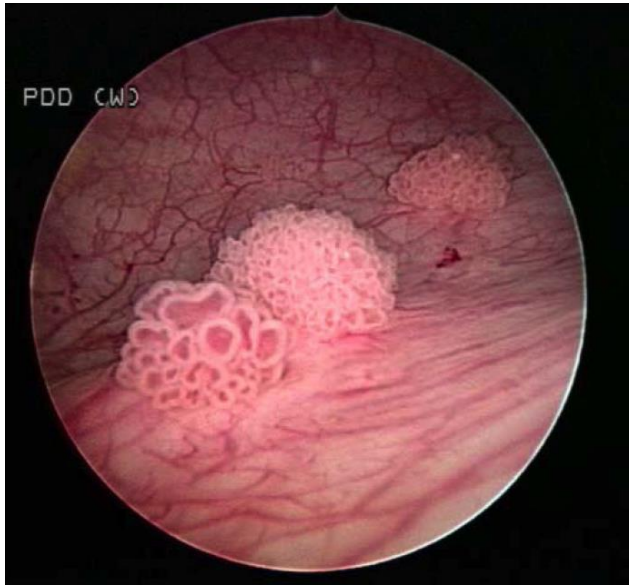
- UTUC M+ alla diagnosi
  - 19 %

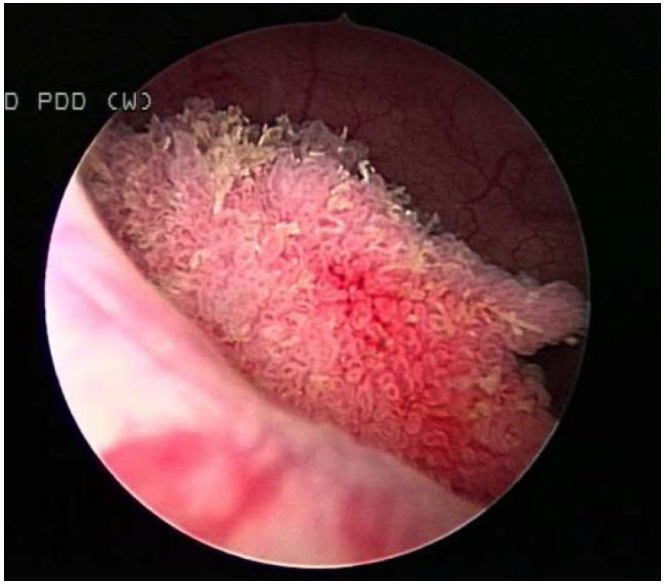
CARCINOMA VESCICALE

1. Non-mioinvasivo
2. Mioinvasivo


T2a
T2b
T4b
Ta
T1
T3a
T4a
Tis
T3b
1
2
3
4
1 Epithelium
2 Subepithelial connective tissue
3 Muscle
4 Perivesical fat
Tumor invades local organs
Tumor invades pelvic or abdominal walls

NON-MIOINVASIVO



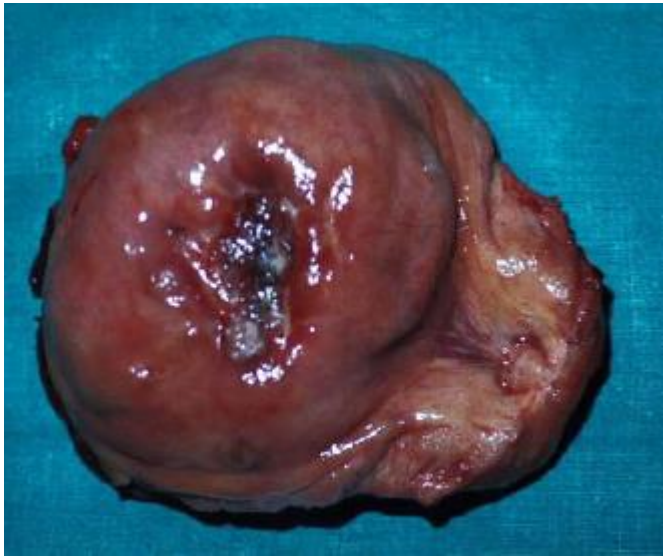


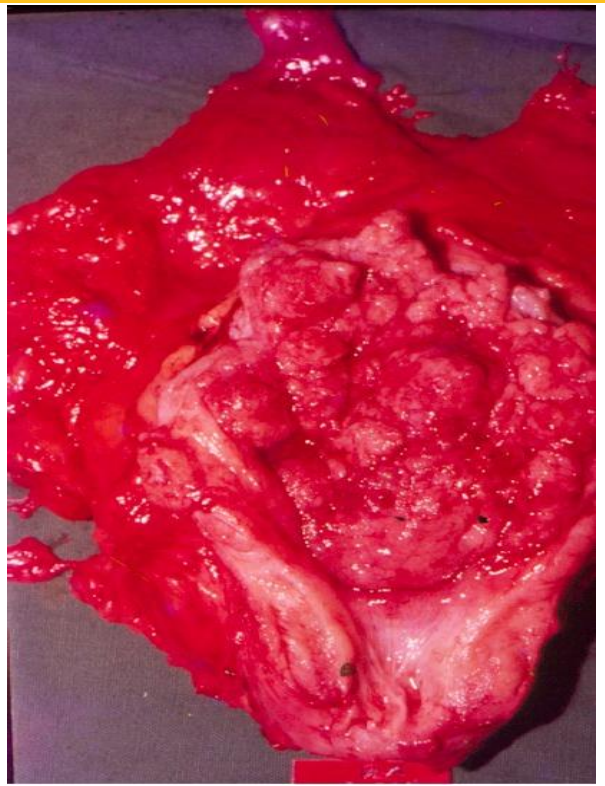
Non Muscle-Invasive Bladder Cancer

- alla presentazione → 70-80 % NMIBC [1]
- probabilità (a 5 anni) di:
  - recidiva: 31 - 78 %
  - progressione: <1 - 45 % [2]

1. Oosterlinck W et al., Eur Urol 2002; 41:105
2. Sylvester RJ et al., Eur Urol 2006; 49: 466

MIOINVASIVO





Muscle-Invasive Bladder Cancer

- TCC-B
  - 20 % MIBC *ab initio*
  - 10-30 % dei NMIBC progredisce dopo terapia iniziale [1, 2]
- MAX nel ♂: 78.8 – 82.7 % [3-7]
- età media: ~ 66 anni[3-7]
- MIBC non trattato: 15 % sopravvivenza a due anni[8]

1. Pashos CL et al., Cancer Pract 2002; 10: 311
2. America Cancer Society. Cancer facts & figures 2003. Atlanta, GA: American Cancer Society, 2003
3. Stein JP et al., JCO 2001; 3: 666
4. Madersbacher S et al., JCO 2003; 4: 690
5. Shariat SF et al., J Urol 2006; 176: 2414
6. Karakiewicz PI et al., Eur Urol 2006; 50: 1254
7. Hautmann RE et al., J Urol 2006; 176: 486
8. Prout G and Marshall VF. Cancer 1956; 9: 551

Recidiva

- Numero di lesioni alla diagnosi [1,2]
- Recurrence rate precedente (*max a 3 mesi*) [1,2]
- Dimensioni della neoplasia [1,2]
- Grado [1]

1. Oosterlinck w et al, GUIDELINES ON BLADDER CANCER Eur Urol 2002; 41: 105
2. Sylvester RJ et al., Eur Urol 2006; 49: 466

Progressione

- Grado [1,2]
- Stadio [1,2]
- (*Cis associato*) [2]

1. Oosterlinck w et al, GUIDELINES ON BLADDER CANCER, Eur Urol 2002; 41: 105
2. Sylvester RJ et al., Eur Urol 2006; 49: 466

… altri fattori

- Profondità di invasione
- Cistoscopia a 3 mesi
- Tecnica endoscopica
- Modalità di trattamento
  - *tratt.to endocavitario*
  - *re-TUR*

Barmoshe S and Zlotta AR, Eur Urol 2004; 3: 73

CLASSI di RISCHIO

BASSO RISCHIO	Singolo – primitivo – Ta – basso grado - ≤ 3 cm
INTERMEDIO RISCHIO	Multiplo o recidivo – basso grado - > 3 cm
ALTO RISCHIO	T1 – alto grado - Cis

- da Oosterlinck w et al, GUIDELINES ON BLADDER CANCER Eur Urol 2002; 41: 105 (mod.)

CLASSI di RISCHIO

Risk group	5-year recurrence	5-year progression
Low	31%	0.8%
Intermediate	46-62%	6-7%
High	78%	45%

Babjiuk M et al, EAU Guidelines 2008

CLASSI di RISCHIO

GESTIONE

BASSO RISCHIO	◆ Follow Up
INTERMEDIO RISCHIO	◆ CHT → MMC ◆ se recidivo dopo CHT ma non alto rischio → BCG
ALTO RISCHIO	◆ BCG

CLASSI di RISCHIO

FOLLOW UP

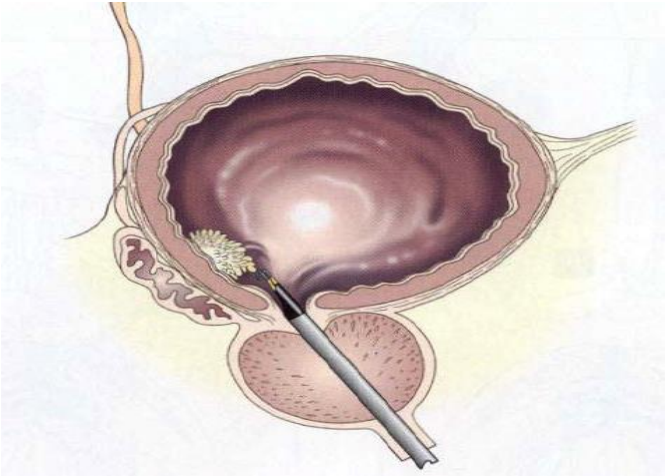
BASSO RISCHIO	◆ Cistoscopia: ➢ a 3 mesi ➢ a 9 mesi ➢ annuale *(per almeno 5 anni)* ◆ Monitoraggio alta via escretrice (AVE): non indicato necessariamente
INTERMEDIO RISCHIO	◆ Cistoscopia + Citologia ➢ a 3 mesi ➢ ogni 6 mesi fino al V° anno ➢ ogni 12 mesi in seguito ◆ AVE: controllo annuale (TC vs ECO)
ALTO RISCHIO	◆ Cistoscopia + Citologia ➢ a 3 mesi ➢ ogni 3 mesi nel I°-II° anno ➢ ogni 4 mesi nel III° anno ➢ ogni 6 mesi nel IV°- V° anno

Le nostre armi….

- **chirurgia (TURBT)**
- **terapie endocavitarie**
  - chemioterapia
  - immunoterapia

T.U.R.B.T.

procedura terapeutica e stadiante



Tecnica endoscopica: *"surgeon skills"*

European Urology

European Urology 41 (2002) 523–531

Variability in the Recurrence Rate at First Follow-up Cystoscopy after TUR in Stage Ta T1 Transitional Cell Carcinoma of the Bladder: A Combined Analysis of Seven EORTC Studies

Maurizio Brausi[a], Laurence Collette[b], Karlheinz Kurth[c], Adrian P. van der Meijden[d], Wim Oosterlinck[e], J.A. Witjes[f], Donald Newling[g], Christian Bouffioux[h], Richard J. Sylvester[b,*]

EORTC Genito-Urinary Tract Cancer Collaborative Group.

Recidiva a 3 mesi:

- tumore singolo: **3** - 20 % *no adj. tr.* / 0-15 % *adj. tr.*
- multiplo (+ adj. tr.): 7 - **46** %

QUALITA' DELLA T.U.R. !!!

re-TUR

- **T1 G3**
  - **TUR: 50 - 80 %** recidiva; **25 - 65** % progressione
  - **TUR + BCG**: **23 - 74** % rec.; **4 - 52** % prog.[1]
- **sottostadiazione della prima TUR**
  - **NO** t. mm. **48** %
  - **SI** t. mm. **14** % [2]
  - errori di refertazione istopatologica: **3.4** % [3]

1. *Barmoshe S and Zlotta AR, Eur Urol 2004; 3: 73*
2. *Herr HW, Urol Oncol 1996; 2: 92*
3. *Ramsay AD. Errors in histopathology reporting: detection and avoidance Histopathology 1999;34:481-490*

re-TUR: indicazioni

Guideline body	Recommendation on suitable reTUR candidates	Level of evidence given	Major differences
EAU (European Association of Urology)	1. Incomplete initial TUR 2. No muscle in specimen with the exception of LG-Ta/GI and primary CIS 3. T1 tumors.	All Grade A (Strong)	*Used as the reference standard*
AUA (American Urological Association)	1. Incomplete initial TUR 2. HG-Ta tumours 3. T1 tumours	1. Grade B (strong) 2. Grade C (moderate) 3. Grade B (strong)	No comment is made that HG-Ta tumours do not need reTUR if muscle is present in the initial TUR
NCCN (National Comprehensive Cancer Network)	1. Incomplete initial TUR 2. No muscle in initial TUR for HG disease 3. Large or multi-focal lesions 4. T1 tumours 5. Select HG-Ta especially if no muscle in initial TUR	All Strong	Include large or multi-focal lesions as a reason to re-resect. Doesn't specifically mention CIS
CUA (Canadian Urology Association)	1. Incomplete initial TUR 2. T1 tumour in absence of muscle 3. Any HG or T1 tumour with benign muscle	1. Grade A 2. Grade A 3. Grade C	Recommend reTUR in T1 or HG-Ta where muscle is present and not malignant.
NICE (Natioanl Institue for Clinical Excellence)	1. All high-risk non-muscle invasive bladder cancer	1. Low	Does not specify whether presence of muscle changes the approach.
ICUD (International Consultation on Bladder Cancer) 2012	1. T1 tumours (regardless of the presence of muscle)	1.Strong	Does not specify whether presence of muscle changes the approach. Does not discuss HG-Ta tumours.

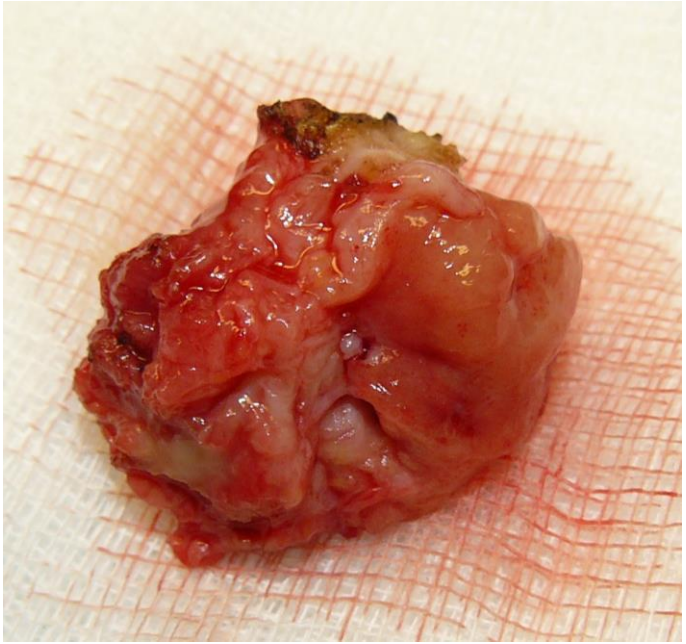
Kwesi Cumberbatch MG et al., Eur Urol 2018

QUALITA' della TURB

- RECIDIVA & tonaca muscolare nello specimen:
  - ✓ SI: 21,7 %
  - ✓ NO: 44,4 %[1]
- T residuo a TURBT corretta: **9-40** %[2, 3]
- re-TUR & risposta a BCG:
  - ✓ RECIDIVA: 29 vs 57 %
  - ✓ PROGRESSIONE: 7 vs 34 %[4]

1. *Mariappan P et al., Eur Urol 2010; 57:843*
2. *Solsona E et al, J Urol 2000; 164:685*
3. *Babjuk M et al, Eur Urol 2008; 54: 303*
4. *Herr HV, J Urol 2005; 174:2034*

…oltre la reTUR: **TURB *"en bloc"***

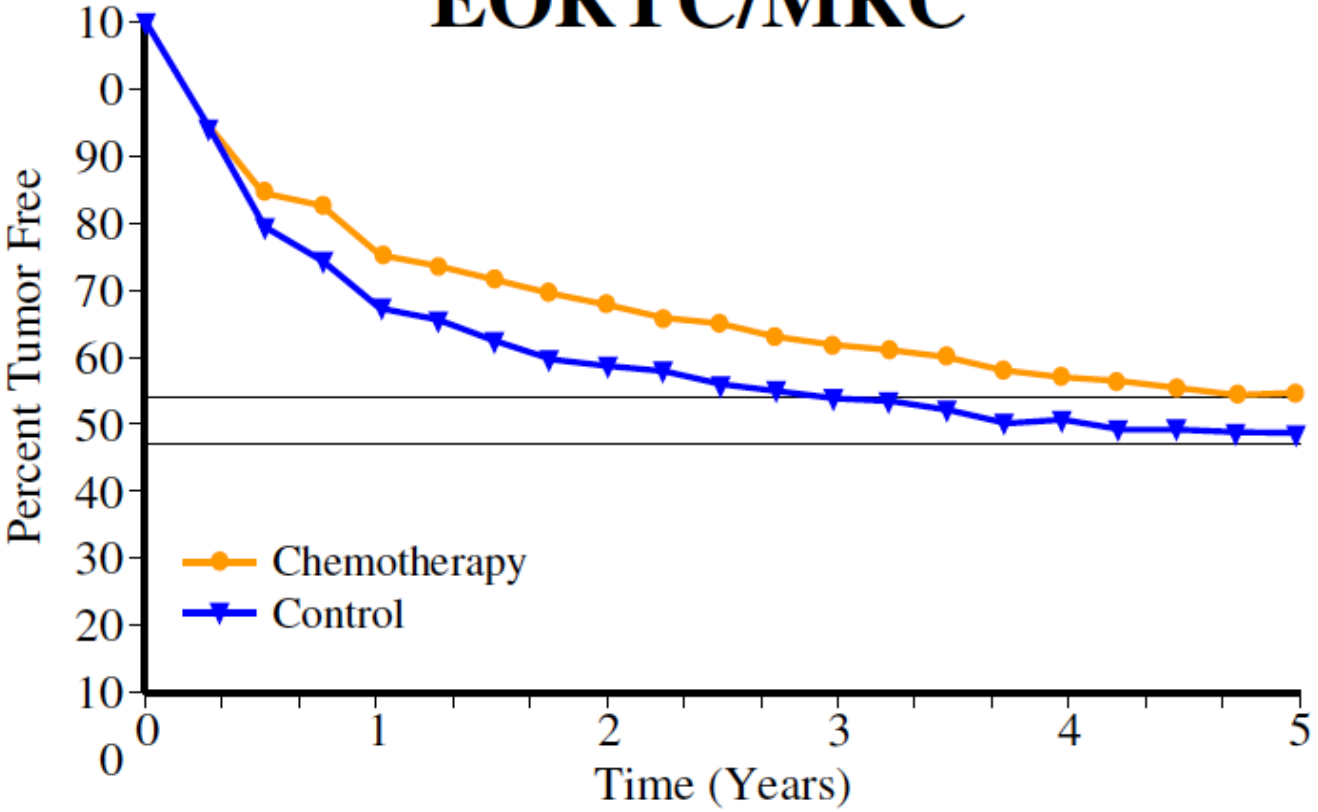


CHEMIOTERAPIA ENDOVESCICALE

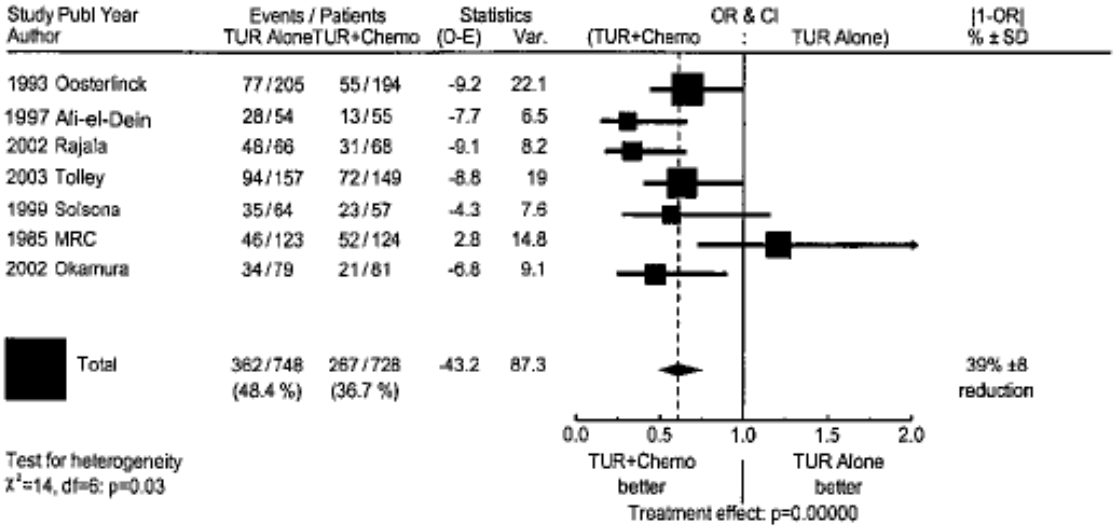
- ↓ RECIDIVA precoce
- efficacia maggiore nel RISCHIO non elevato
- non garantisce protezione a lungo termine
- non previene la PROGRESSIONE
- può essere utilizzata precocemente

5 year Tumor Recurrence Curves With Chemotherapy vs Control

EORTC/MRC



TUR ± CHT



Sylvester RJ et al., J Urol 171, 2186: 2004

EUROPEAN UROLOGY 50 (2006) 225–234

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Recurrence Rate dopo TURBT + CHT: 36-44 %

- Timing delle instillazioni
- ↑ della farmacocinetica
- Nuovi farmaci
- Associazioni di farmaci
- Agenti modulatori
- Tests di chemosensibilità

Mitomicina C

- antibiotico alchilante
- P.M. 334 Daltons →assorbimento sistemico < 1%
- indicazioni: **RISCHIO INTERMEDIO**
- somministrazione: 40 mg in 50 ml S.F.
  - ESI (Early Single Instillation)
  - Post-TURB (1 volta/settimana)
- dwell time: 1 h
- precauzioni: soggetti con OCU (ritenzione?) e/o IVU
- effetti sistemici
  - rari (< 3%)
  - febbre, malessere, sintomi similinfluenzali, sull' app. emopoietico
- effetti locali (> 30%)
  - frequenti
  - disuria, pollachiuria, stranguria, nicturia, solore sovrapubico
  - → LIDOCAINA 1% in sol. fis.
  - reazioni cutanee (rash, prurito, vescicole)
  - → ATTENZIONE ALLA PREPARAZIONE

Trattamento endocavitario post-TURBT

0022-5347/04/1716-2186/0
THE JOURNAL OF UROLOGY®

Vol. 171, 2186–2190, June 2004
Printed in U.S.A.
DOI: 10.1097/01.ju.0000125486.92260.b2

A SINGLE IMMEDIATE POSTOPERATIVE INSTILLATION OF CHEMOTHERAPY DECREASES THE RISK OF RECURRENCE IN PATIENTS WITH STAGE Ta T1 BLADDER CANCER: A META-ANALYSIS OF PUBLISHED RESULTS OF RANDOMIZED CLINICAL TRIALS

7

RICHARD J. SYLVESTER,* WILLEM OOSTERLINCK AND ADRIAN P. M. VAN DER MEIJDEN

From the European Organization for the Research and Treatment of Cancer Data Center, Brussels, the Universitair Ziekenhuis Gent, Gent, Belgium, and the Jeroen Bosch Hospital, 's-Hertogenbosch, The Netherlands

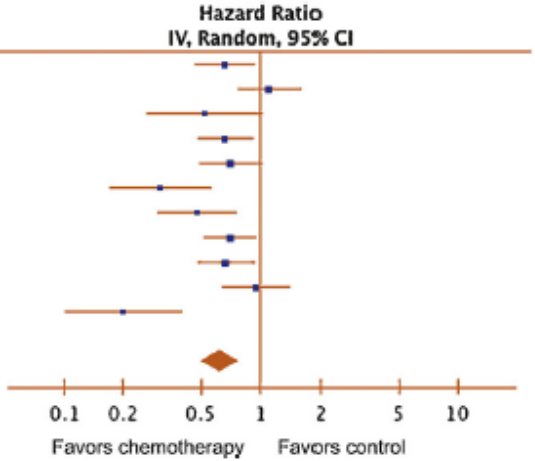
- **TUR + CHT vs. TUR**: ↓ **39** % prob.tà di recidiva con CHT

Immediate Post–Transurethral Resection of Bladder Tumor Intravesical Chemotherapy Prevents Non–Muscle-invasive Bladder Cancer Recurrences: An Updated Meta-analysis on 2548 Patients and Quality-of-Evidence Review

Nathan Perlis [a,b,c,*], *Alexandre R. Zlotta* [a,b,d], *Joseph Beyene* [c,e], *Antonio Finelli* [a,b,f], *Neil E. Fleshner* [a,b,f], *Girish S. Kulkarni* [a,b,g]

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Oosterlinck	-0.4108	0.176	10.3%	0.66 [0.47–0.94]	1993
MRC	0.1044	0.1834	10.1%	1.11 [0.77–1.59]	1994
Fujita	-0.654	0.343	6.0%	0.52 [0.27–1.02]	1994
Tolley	-0.415	0.1632	10.7%	0.66 [0.48–0.91]	1996
Solsona	-0.346	0.1821	10.1%	0.71 [0.50–1.01]	1999
Okamura	-1.17	0.304	6.8%	0.31 [0.17–0.56]	2002
Rajala	-0.742	0.231	8.7%	0.48 [0.30–0.75]	2002
Berrum-Svennung	-0.348	0.1521	11.1%	0.71 [0.52–0.95]	2008
Gudjonsson	-0.4	0.1635	10.7%	0.67 [0.49–0.92]	2009
Bohle	-0.051	0.1979	9.7%	0.95 [0.64–1.40]	2009
De Nunzio	-1.61	0.3504	5.8%	0.20 [0.10–0.40]	2011
Total (95% CI)			**100.0%**	**0.62 [0.50, 0.77]**	

Heterogeneity: $Tau^2 = 0.09$; chi-square = 31.97, df = 10 ($p = 0.0004$); $I^2 = 69\%$
Test for overall effect: Z = 4.29 ($p < 0.0001$)



IMMUNOTERAPIA

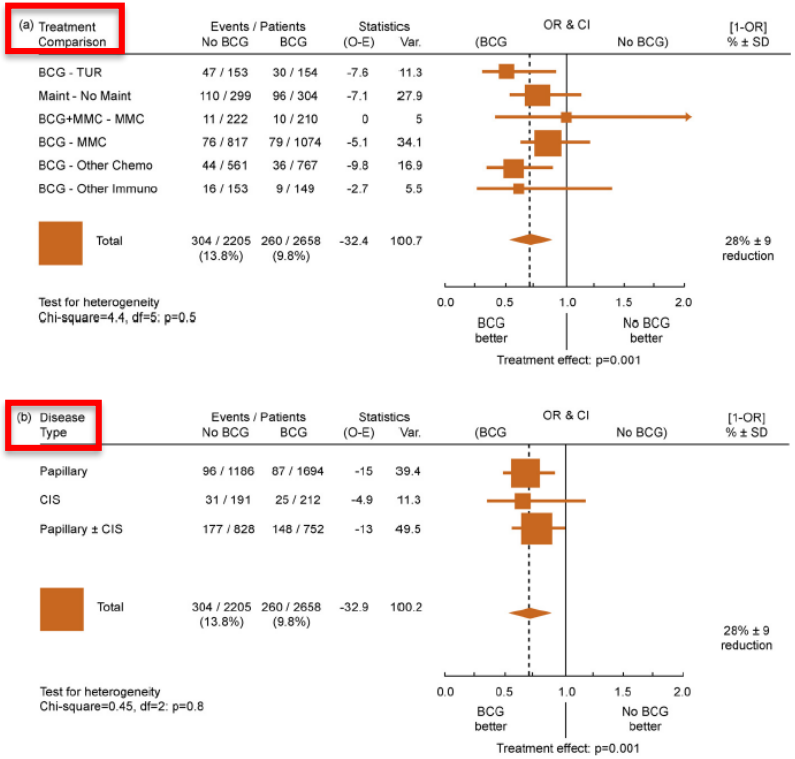
- Bacillo di Calmette-Guerìn (**BCG**)
- Interferone (IFN)

SCOPI PRINCIPALI:

- ↓ RECIDIVA & PROGRESSIONE
- Ritardare la CISTECTOMIA

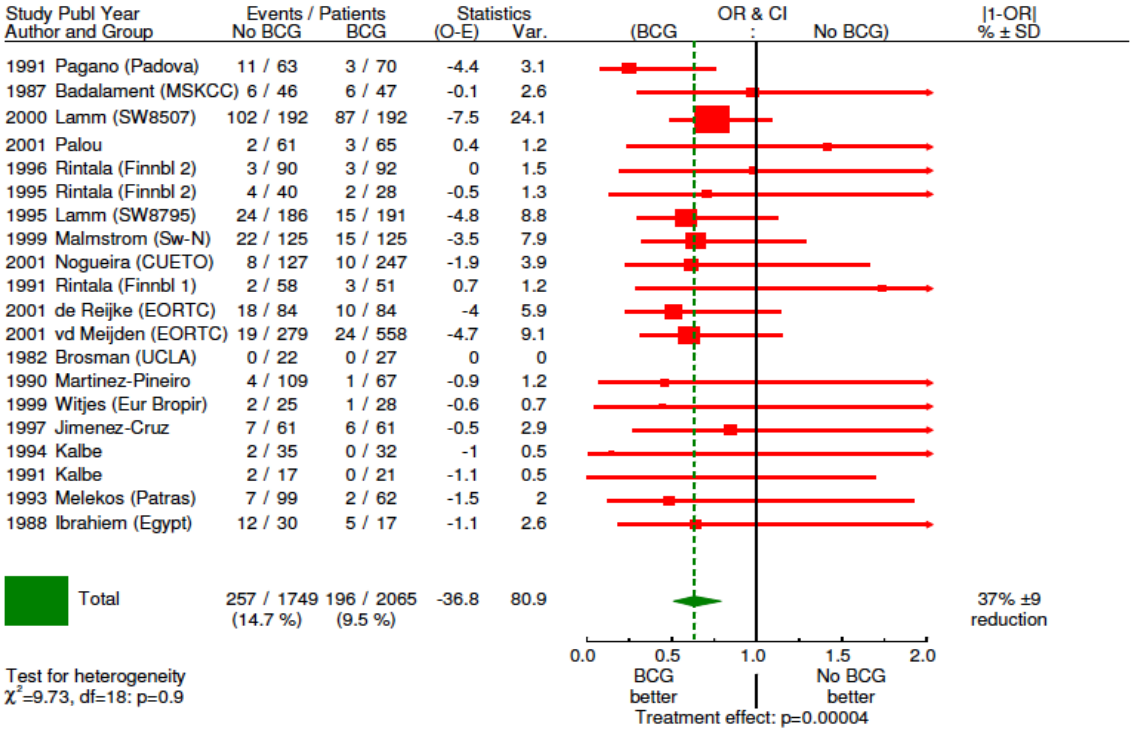
BCG (Bacillo di Calmette-Guerìn)

- ceppo attenuato di Mycobacterium bovis
- primo utilizzo: 1976 (Morales)
- ceppi di utilizzati in clinica: Pasteur, Armand Frappier, Tice, Connaught, Glaxo, Tokio, Dutch, Moreau
- meccanismo d'azione: non è noto, coinvolge meccanismi immunitari e infiammatori
- schema:
  - INDUZIONE: 1/settimana per 6 settimane
  - MANTENIMENTO: 1/settimana per 3 settimane (SWOG: 3-6-12-18-24-30-36 mesi)
- indicazioni:
  - **RISCHIO INTERMEDIO** (specie se recidivo)
  - **ALTO RISCHIO** (TCC papillare e/o **Ca in situ**)

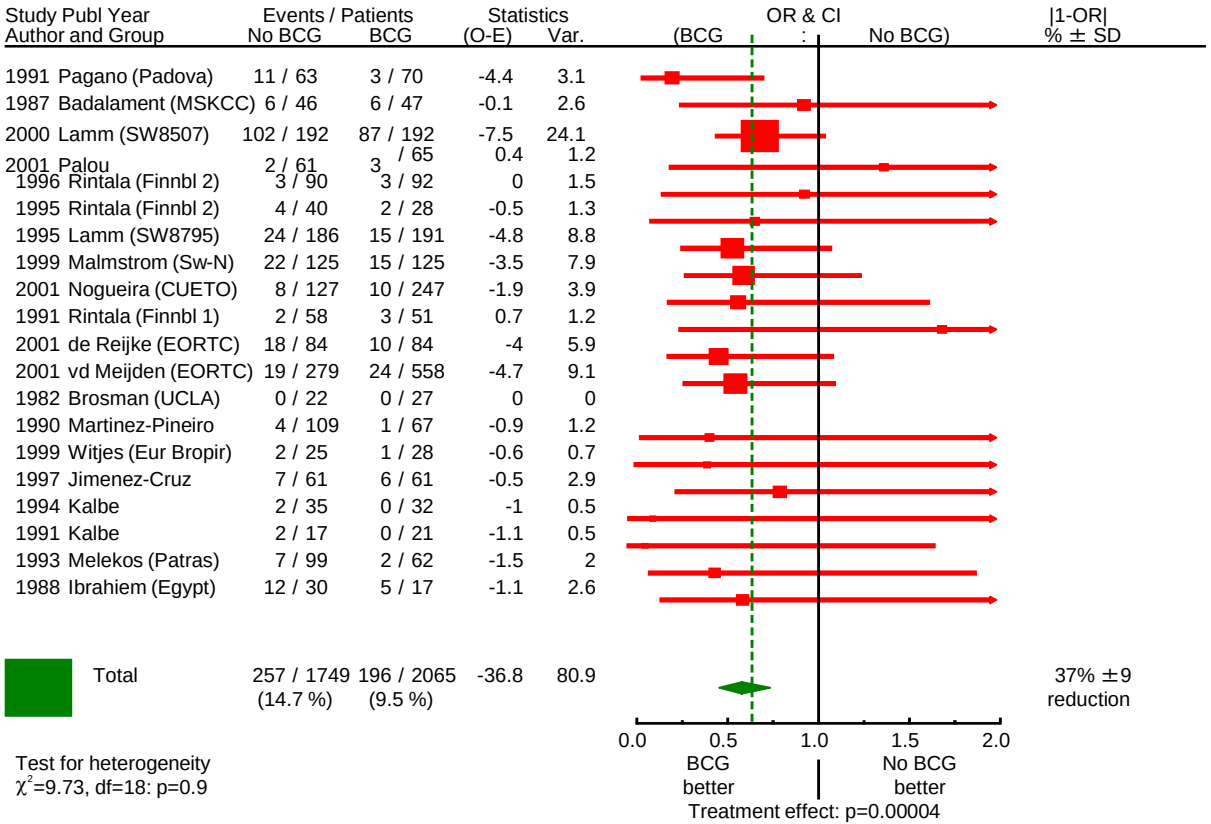


Persad M et al., Eur Urol 2008; suppl 7:637

BCG


Study Publ Year
Author and Group
Events / Patients
No BCG
BCG
Statistics
(O-E)
Var.
OR & CI
(BCG : No BCG)
|1-OR|
% ± SD
1991 Pagano (Padova) 11 / 63 3 / 70 -4.4 3.1
1987 Badalament (MSKCC) 6 / 46 6 / 47 -0.1 2.6
2000 Lamm (SW8507) 102 / 192 87 / 192 -7.5 24.1
2001 Palou 2 / 61 3 / 65 0.4 1.2
1996 Rintala (Finnbl 2) 3 / 90 3 / 92 0 1.5
1995 Rintala (Finnbl 2) 4 / 40 2 / 28 -0.5 1.3
1995 Lamm (SW8795) 24 / 186 15 / 191 -4.8 8.8
1999 Malmstrom (Sw-N) 22 / 125 15 / 125 -3.5 7.9
2001 Nogueira (CUETO) 8 / 127 10 / 247 -1.9 3.9
1991 Rintala (Finnbl 1) 2 / 58 3 / 51 0.7 1.2
2001 de Reijke (EORTC) 18 / 84 10 / 84 -4 5.9
2001 vd Meijden (EORTC) 19 / 279 24 / 558 -4.7 9.1
1982 Brosman (UCLA) 0 / 22 0 / 27 0 0
1990 Martinez-Pineiro 4 / 109 1 / 67 -0.9 1.2
1999 Witjes (Eur Bropir) 2 / 25 1 / 28 -0.6 0.7
1997 Jimenez-Cruz 7 / 61 6 / 61 -0.5 2.9
1994 Kalbe 2 / 35 0 / 32 -1 0.5
1991 Kalbe 2 / 17 0 / 21 -1.1 0.5
1993 Melekos (Patras) 7 / 99 2 / 62 -1.5 2
1988 Ibrahiem (Egypt) 12 / 30 5 / 17 -1.1 2.6
Total
257 / 1749 (14.7 %)
196 / 2065 (9.5 %)
-36.8
80.9
37% ±9 reduction
0.0
0.5
1.0
1.5
2.0
BCG better
No BCG better
Test for heterogeneity
χ²=9.73, df=18: p=0.9
Treatment effect: p=0.00004

BCG
Progressione di malattia
(Mantenimento)



BJUI
BJU International

Trial

Increased accuracy of a novel mRNA-based urine test for bladder cancer surveillance

Renate Pichler*, Josef Fritz†, Gennadi Tulchiner*, Gerald Klinglmair*, Afschin Soleiman‡, Wolfgang Horninger*, Helmut Klocker*§ and Isabel Heidegger*

*Department of Urology, Medical University Innsbruck, Innsbruck, Austria, †Department of Medical Statistics, Informatics and Health Economics, Medical University Innsbruck, Innsbruck, Austria, ‡Clinical Pathology and Cytodiagnostics, Tyrolean State Hospitals Ltd, Innsbruck, Austria, and §Urological Laboratory and Division of Experimental Urology, Innsbruck, Austria

In this study, we report for the first time that the Xpert BC Monitor, a new mRNA-based urine test, outperforms cytology with regard to sensitivity and NPV, even in low-grade and pTa tumours, with no reduction of specificity.

BJU Int 2018; **121**: 29–37

BJUI
BJU International
Trial

Increased accuracy of a novel mRNA-based urine test for bladder cancer surveillance

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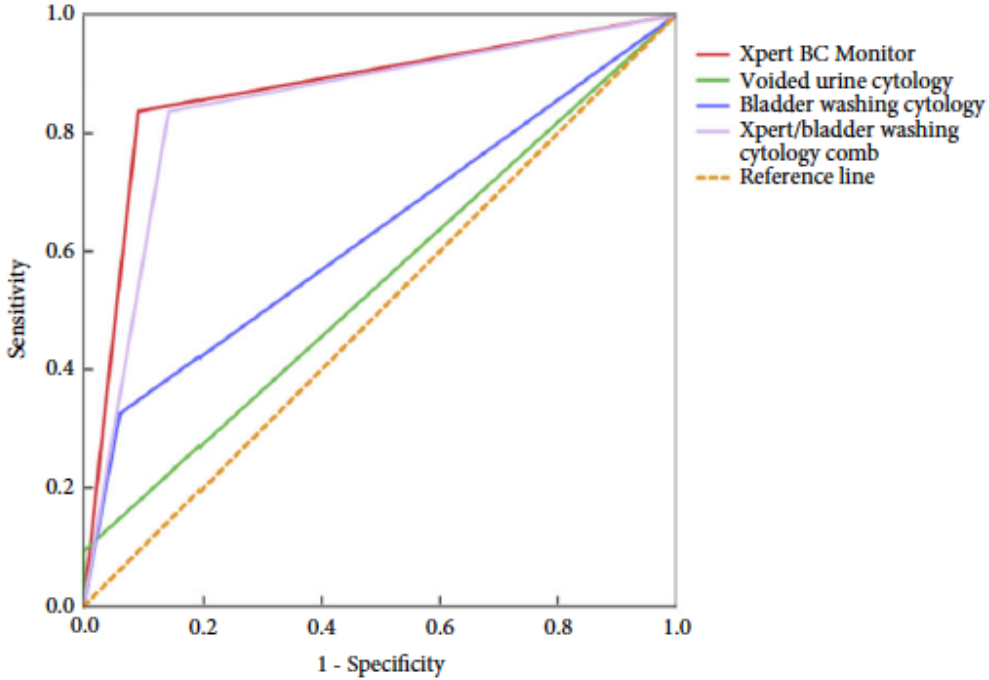
*Department of Urology, Medical University Innsbruck, Innsbruck, Austria, †Department of Medical Statistics, Informatics and Health Economics, Medical University Innsbruck, Innsbruck, Austria, ‡Clinical Pathology and Cytodiagnostics, Tyrolean State Hospitals Ltd, Innsbruck, Austria, and §Urological Laboratory and Division of Experimental Urology, Innsbruck, Austria



Diagnostic test method	AUC (95% CI)	*P*
Xpert BC Monitor	0.872 (0.800-0.945)	<0.001***
Voided urine cytology	0.547 (0.440-0.653)	0.381
Bladder washing cytology	0.632 (0.525-0.739)	0.013*
Xpert/bladder washing cytology combined	0.846 (0.771-0.922)	<0.001***

SWOG MVAC Trial

- Chemo regimen

Methotrexate 30mg/m2 D1, D15, D22

Vinblastine 3mg/m2 D2, D15, D22

Doxorubicin 30mg/m2 D2

Cisplatin 70mg/m2 D2

- Median survival 77 months in the chemo arm vs 46 months in the surgery alone arm
- 38% had complete pathologic response

GC vs MVAC

Efficacy/ Response

Response rates

	GC	MVAC
Overall Response*	**49%**	**46%**
Complete	**12%**	**12%**
Partial	**37%**	**34%**
Stable	**33%**	**33%**

Median duration of overall response

Gemcitabine plus Cisplatin	**9.6 months (8.0-11.9)**
MVAC	**11.0 months (9.4-13.2)**

* **Response rates independently reviewed**

Von der Maase, 2015

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma

J. Bellmunt, R. de Wit, D.J. Vaughn, Y. Fradet, J.-L. Lee, L. Fong, N.J. Vogelzang, M.A. Climent, D.P. Petrylak, T.K. Choueiri, A. Necchi, W. Gerritsen, H. Gurney, D.I. Quinn, S. Culine, C.N. Sternberg, Y. Mai, C.H. Poehlein, R.F. Perini, and D.F. Bajorin, for the KEYNOTE-045 Investigators*

CONCLUSIONS

Pembrolizumab was associated with significantly longer overall survival (by approximately 3 months) and with a lower rate of treatment-related adverse events than chemotherapy as second-line therapy for platinum-refractory advanced urothelial carcinoma. (Funded by Merck; KEYNOTE-045 ClinicalTrials.gov number, NCT02256436.)

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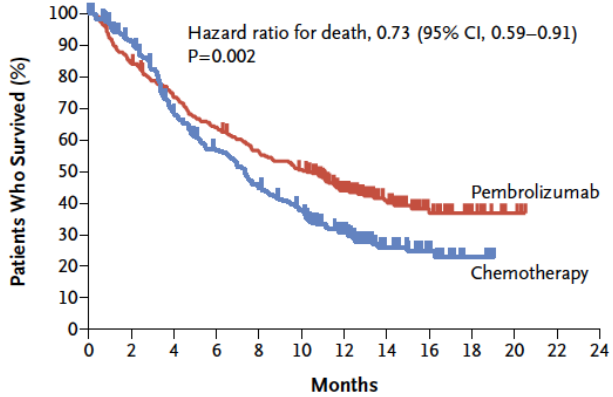
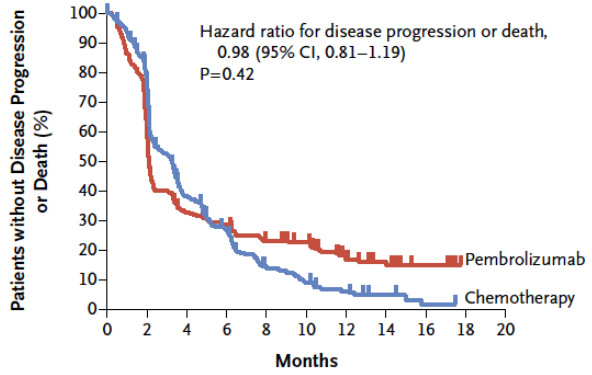
Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma

A **Overall Survival**



No. at Risk												
Pembrolizumab	270	226	194	169	147	131	87	54	27	13	4	0	0
Chemotherapy	272	232	171	138	109	89	55	27	14	3	0	0	0

B **Progression-free Survival**



No. at Risk											
Pembrolizumab	270	165	85	73	56	51	23	16	7	0	0
Chemotherapy	272	188	85	56	27	17	10	5	1	0	0

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CONCLUSIONI

- BC è patologia con diverse caratteristiche
- La stadiazione iniziale con TURB è fondamentale
- La terapia adiuvante delle forme nonmioinvasive è vantaggiosa
- Mancano ancora validi INDICATORI di PROGRESSIONE
- Nelle forme mioinvasive la terapia elettiva è la CISTECTOMIA, quando possibile preceduta dalla CHEMIOTERAPIA NEOADIUVANTE
- Stanno comparendo terapie di II LINEA nelle FORME AVANZATE