Současné trendy v diagnostických a terapeutických postupech u karcinomu močového měchýře

Gabriel Varga

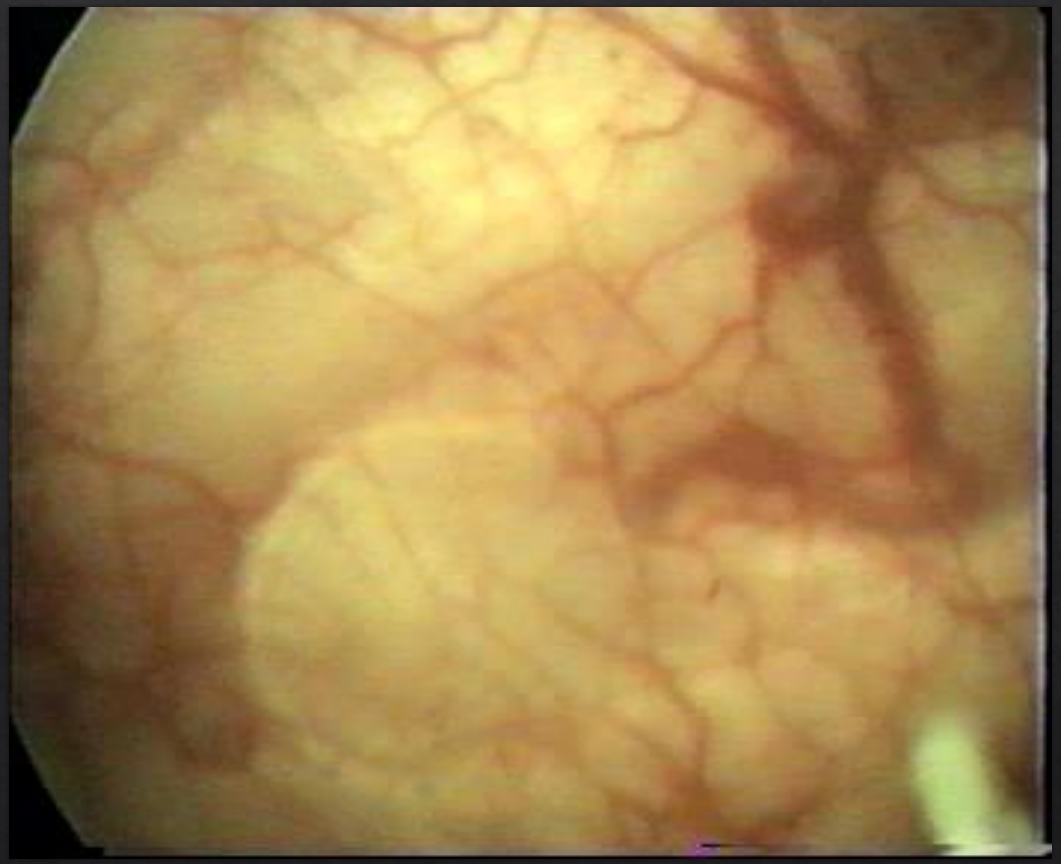
Seminář ČUS, Hotel Continental, Brno

17.9.2020

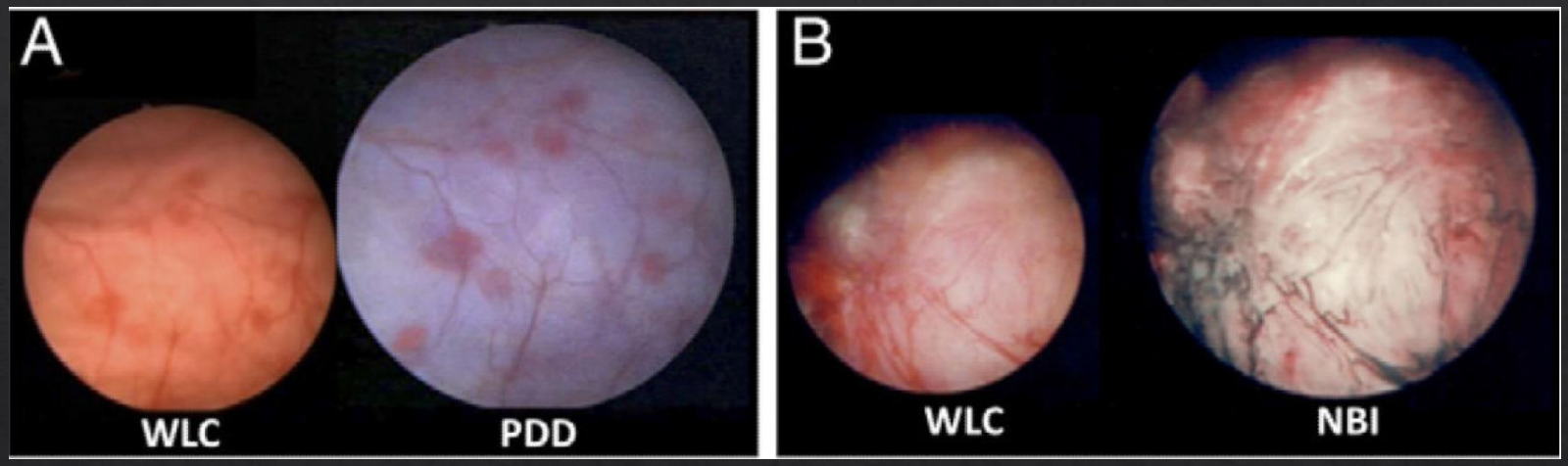
- Anamnéza
- Fyzikální vyšetření
- Laboratoř
- Zobrazovací metody (UZ, CTU,MRI)
- CSK
- TURT
- Cytologie
- Histopatologické vyšetření

- Anamnéza
- Fyzikální vyšetření
- Laboratoř (genetické vyšetření)
- Zobrazovací metody (UZ, CTU,MRI)
- CSK
- TURT
- Cytologie
- Histopatologické vyšetření

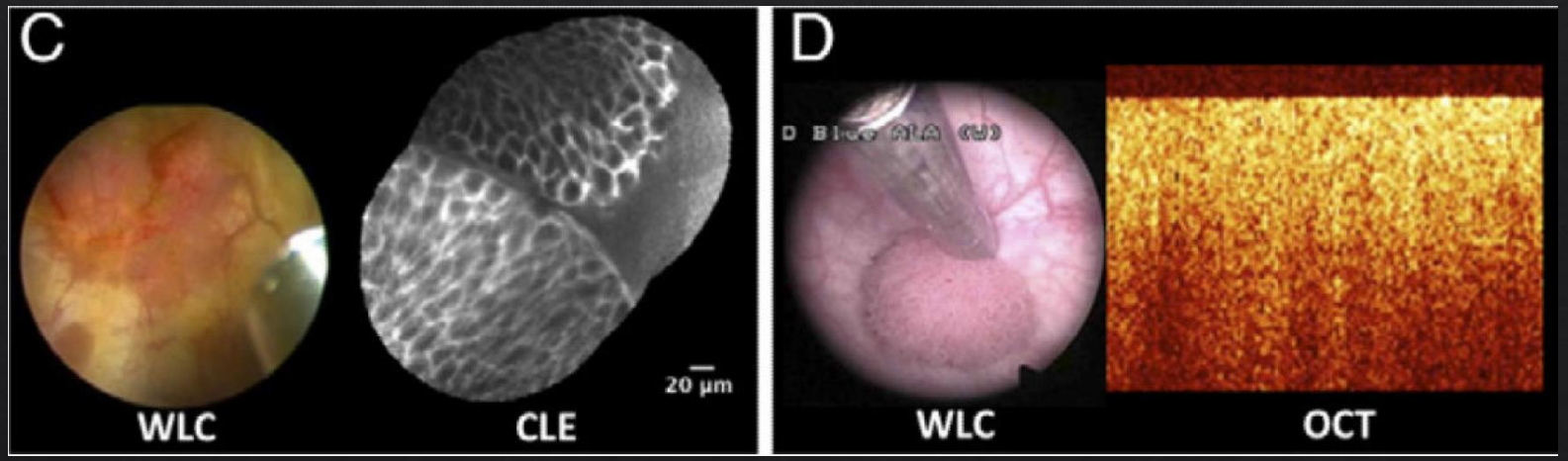
Konvenční CSK



- Makroskopické modality NBI, PDD



- Mikroskopické modality - CLE a OCT,



PDD

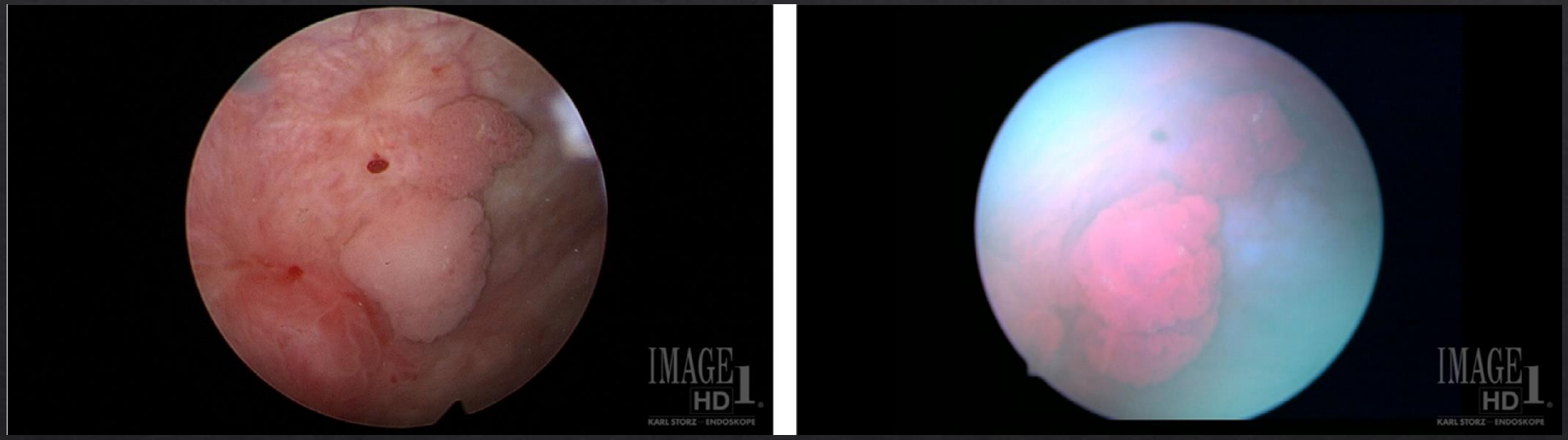
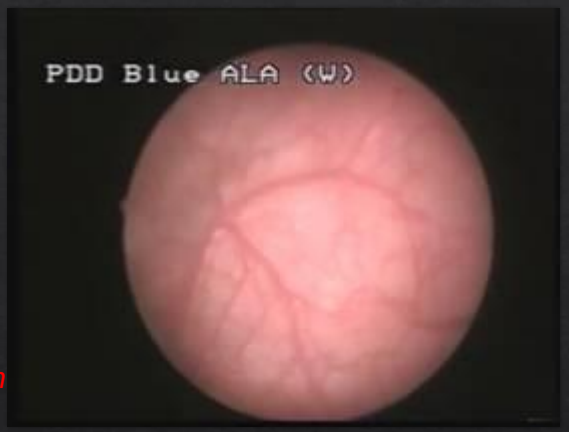


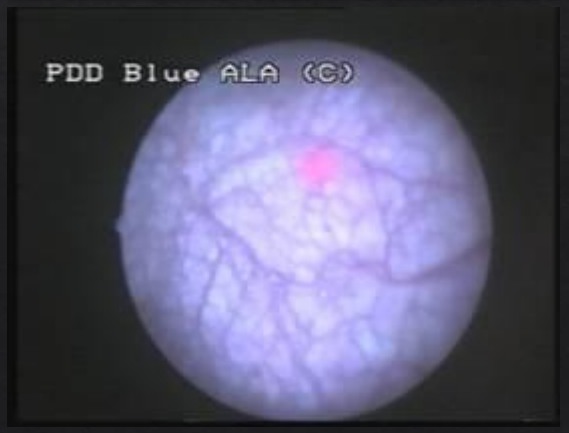
IMAGE1 HD
KARL STORZ – ENDOSKOPE
IMAGE1 HD
KARL STORZ – ENDOSKOPE

PDD

Hungerhuber et al.
875 pacientů
•23,7% pozitivních biopsií u pacientů s negativním nálezem při konvenční CSK.
• 92% senzitivitu pro PDD vs 76% pro kCSK .

Hungerhuber E. et al. (2007) Seven years' experience with 5-aminolevulinic acid in detection of transitional cell carcinoma of the bladder. Urology 69(2):260–264)





- zvýšená detekce nádorových lézí ve všech rizikových skupinách TCC při použití HAL
- absolutní 10% snížení výskytu recidivy v průběhu dvanácti měsíců

Burger, M., *et al.* Photodynamic diagnosis of non-muscle-invasive bladder cancer with hexaminolevulinate cystoscopy: a meta-analysis of detection and recurrence based on raw data. Eur Urol, 2013. 64: 846

PDD zařízení

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

M. Babjuk (Chair), M. Burger (Vice-Chair), E. Compérat, van Rhijn, Zigeuner, D. Cohen, V. Soukup

Take biopsies from abnormal-looking urothelium. Biopsies from normal-looking mucosa (trigone, bladder dome, and right, left, anterior and posterior bladder walls) are recommended when cytology is positive or when high-risk exophytic tumour is expected (non-papillary appearance). If equipment is available, use PDD-guided biopsies.	B
Take biopsy of the prostatic urethra in cases of bladder neck tumour, when bladder CIS is present or suspected, when there is positive cytology without evidence of tumour in the bladder, or when abnormalities of the prostatic urethra are visible. If biopsy is not performed during the initial procedure, it should be completed at the time of the second resection.	C
Take the biopsy from abnormal areas in the prostatic urethra and from the precollicular area (between 5 and 7 o'clock position) using a resection loop. In primary non-muscle-invasive tumours when stromal invasion is not suspected, cold-cup biopsy with forceps can be used.	C
Refer the specimens from different biopsies and resection fractions to the pathologist in separate containers and label them separately.	C
TURB protocol must describe tumour appearance, all steps of the procedure, as well as the extent and completeness of resection.	C
In patients with positive cytology, but negative cystoscopy, exclude a UTUC, CIS in the bladder (random biopsies or PDD-guided biopsies) and tumour in prostatic urethra (prostatic urethra biopsy).	C

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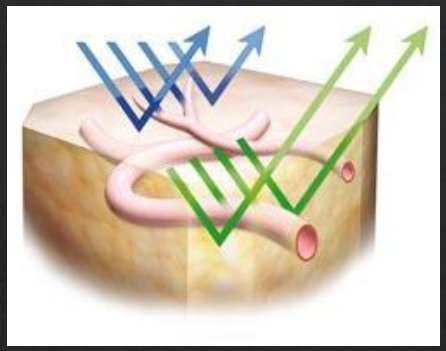
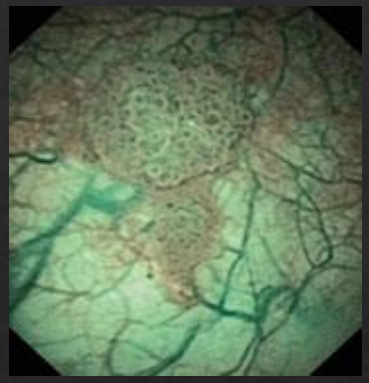
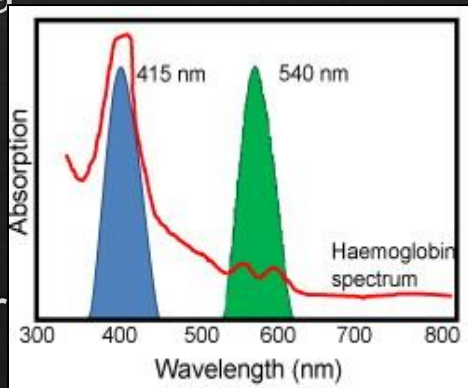
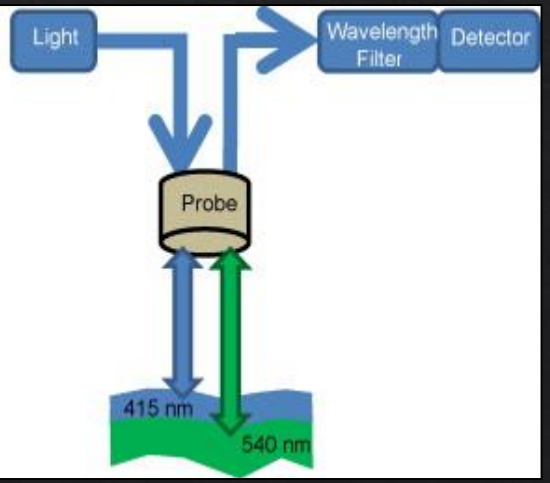
Narrow-band imaging - NBI

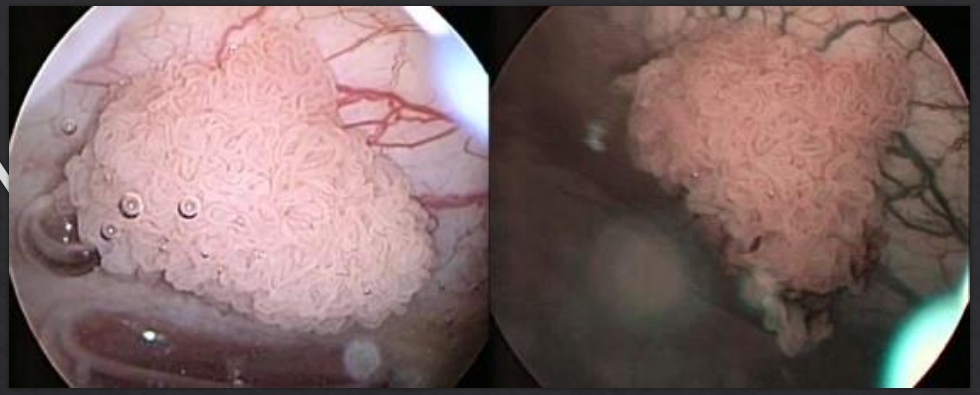
- Zlepšení kontrastu mezi abnormální lézi a normální sliznici měchýře pomocí restrikce světelného optického spektra použitého v průběhu CSK.
- Zúžení světelného spektra filtry, které povolují transmisi světla s vlnovou délkou 415-540nm .
- Absorpce hemoglobinem
- zvyšení viditelnosti kapilár a submukozních krevních cév.





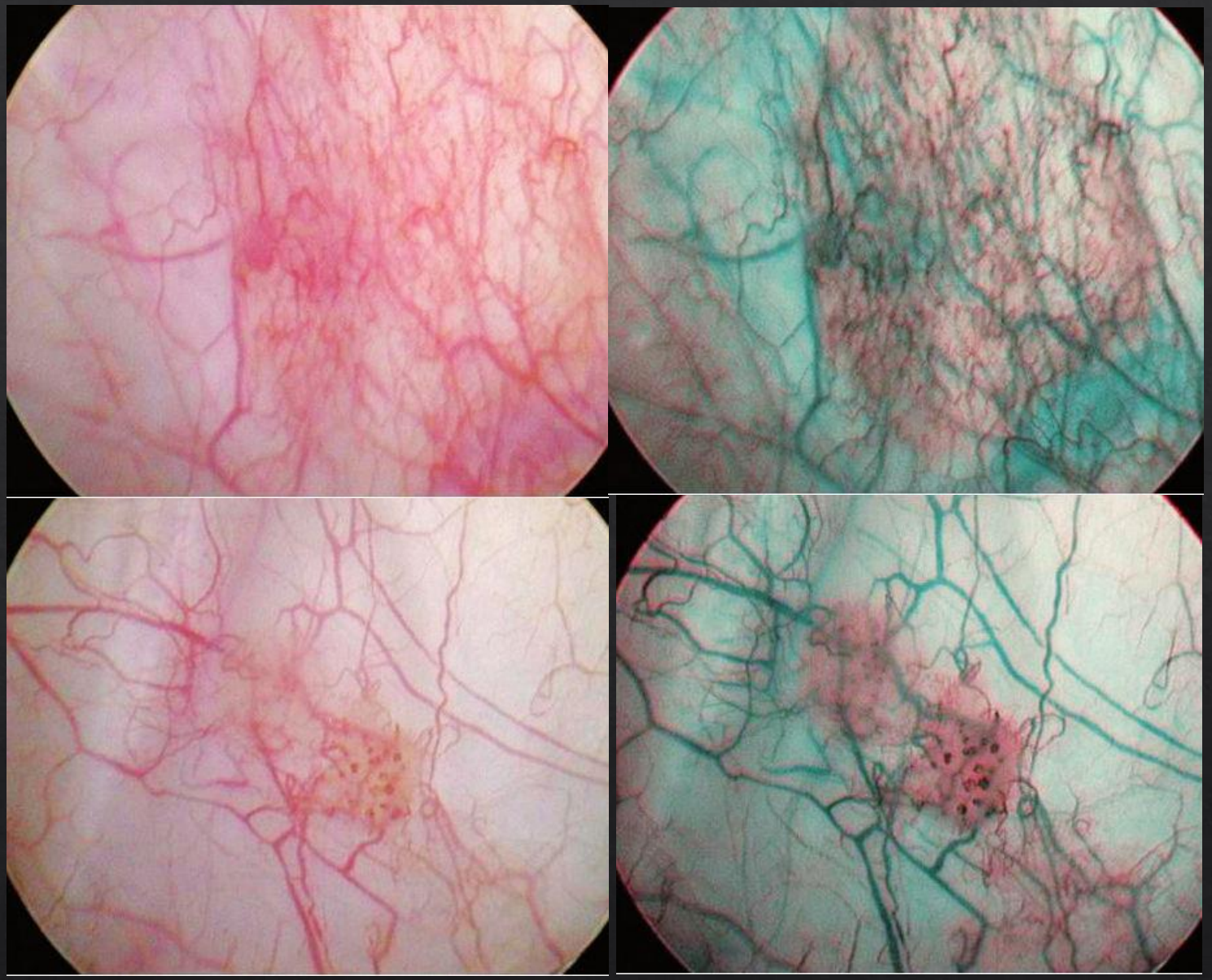






•Uplatnění v GE - metaplasie a prekancerozy žaludku,jícnu, v průběhu kolonoskopie *Machida H, Sano Y, Hamamoto Y, Muto M, Kozu T, Tajiri H, Yoshida S (2004) Narrow-band imaging in the diagnosis of colorectal mucosal lesions: a pilot study. Endoscopy 36(12):1094– 1098).*

•hypervaskularita je nespecifickým nálezem, budou potřebné multicentrické kontrolované studie k potvrzení role NBI v diagnostice prekanceroz a maligních lézi měchýře



Zdroj: Brisuda A., Hrbáček J., Babjuk M. et al. **Využití fotodynamické diagnostiky a úzkopásmového zobrazení v diagnostice a léčbě svalovinu neinfiltrujících nádorů močového měchýře** Ces Urol 2013; 17(2): 79-87.

EUROPEAN UROLOGY 61 (2012) 908–913

available at www.sciencedirect.com
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European Association of Urology

Platinum Priority – Urothelial Cancer

Editorial by Maurizio Brausi on pp. 914-916 of this issue

A Randomized Prospective Trial to Assess the Impact of Transurethral Resection in Narrow Band Imaging Modality on Non–Muscle-Invasive Bladder Cancer Recurrence

Angelo Naselli[a,*], *Carlo Introini*[a], *Luca Timossi*[a], *Bruno Spina*[b], *Vincenzo Fontana*[c], *Riccardo Pezzi*[c], *Francesco Germinale*[d], *Franco Bertolotto*[d], *Paolo Puppo*[a,d]

[a] Department of U... of Anatomy and ...
[c] Department of E... Cancro, Genoa, It...

Conclusions: TUR performed in the NBI modality reduces the recurrence risk of NMIBC by at least 10% at 1 yr.

Article info

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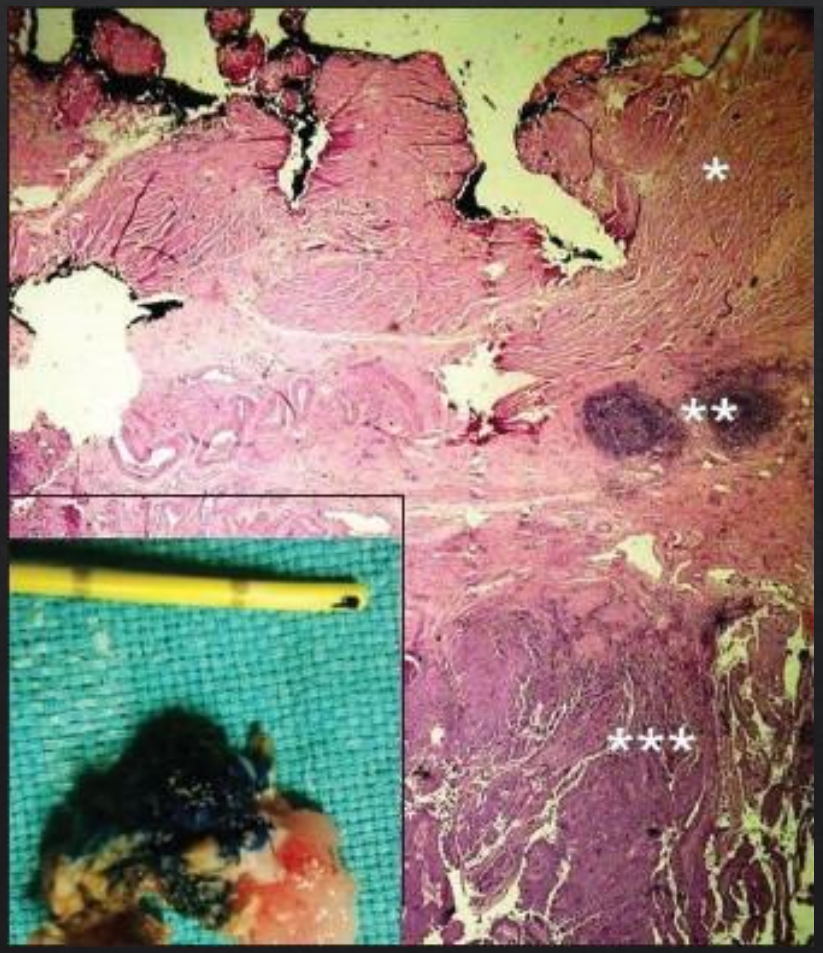
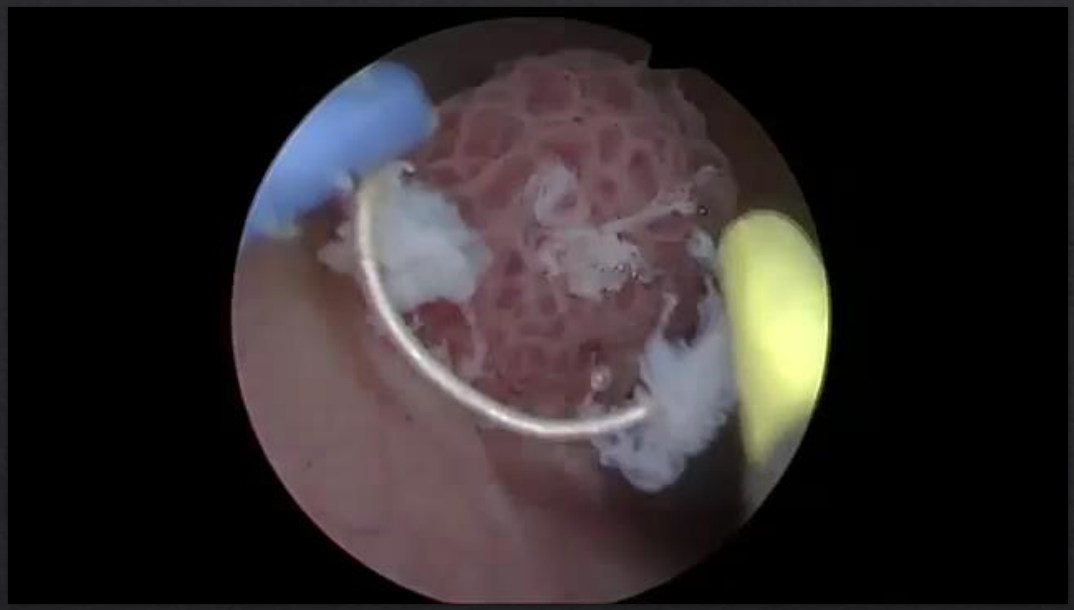
Keywords:
Urinary bladder neoplasms
Cystoscopy
Recurrence
Diagnostic imaging

Abstract

Background: Narrow band imaging (NBI) is an optical enhancement technology that filters white light into two bandwidths of illumination centered on 415 nm (blue) and 540 nm (green). NBI cystoscopy can increase bladder cancer (BCa) visualization and detection at the time of transurethral resection (TUR). NBI may therefore reduce subsequent relapse following TUR.
Objective: Assess the impact of NBI modality on 1-yr non–muscle-invasive BCa (NMIBC) recurrence risk.
Design, setting, and participants: Consecutive patients with overt or suspected BCa were included in a prospective study powered to test a 10% difference in 1-yr recurrence risk in favor of cases submitted to NBI TUR. Excluding patients with muscle-invasive BCa, negative pathologic examination, or without follow-up, the study population was composed of 148 subjects randomized from August 2009 to September 2010 to NBI TUR (76 cases) or white light (WL) TUR (72 cases).
Intervention: TUR was performed in NBI or standard WL modality.
Measurements: The 1-yr recurrence risks in NBI or WL TUR groups were compared using odds ratio (OR) point and interval estimates derived from logistic regression modeling.
Results and limitations: The 1-yr recurrence-risk was 25 of 76 patients (32.9%) in the NBI and 37 of 72 patients (51.4%) in the WL group (OR = 0.62; $p = 0.0141$). Simple and multiple logistic regression analyses provided similar OR points and interval estimates.
Conclusions: TUR performed in the NBI modality reduces the recurrence risk of NMIBC by at least 10% at 1 yr.

„En-block“ TURT





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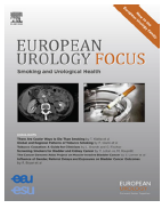

Review – Bladder Cancer

Current Evidence of Transurethral En-bloc Resection of Nonmuscle Invasive Bladder Cancer

Mario W. Kramer[a], *Vincenzo Altieri*[b], *Rodolfo Hurle*[c], *Lukas Lusuardi*[d], *Axel S. Merseburger*[a], *Jens Rassweiler*[e], *Julian P. Struck*[a], *Thomas R.W. Herrmann*[f,*]

Recommendations for transurethral resection of the bladder (TURB) and/or biopsies and pathology report	
Perform *en-block* resection or resection in fractions (exophytic part of the tumour, the underlying bladder wall and the edges of the resection area). The presence of detrusor muscle in the specimen is required in all cases except for TaG1/LG tumours.	B
Perform a second TURB in the following situations: • after (suspicion of) incomplete initial TURB (in the case of any doubt about completeness of a TURB); • if there is no muscle in the specimen after initial resection, with exception of TaLG/G1 tumours and primary CIS; • In T1 tumours.	A
Register the results of a second TURB as it reflects the quality of the initial resection.	A

at improving quality of surgical specimens. Available evidences suggest safety and oncologic equivalence compared with the standard transurethral resection of bladder tumor.

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E-mail address: herrmann.thomas@mh-hannover.de (Thomas R.W. Herrmann).

MIBC –diagnostika

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ARTICLE IN PRESS

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European Association of Urology

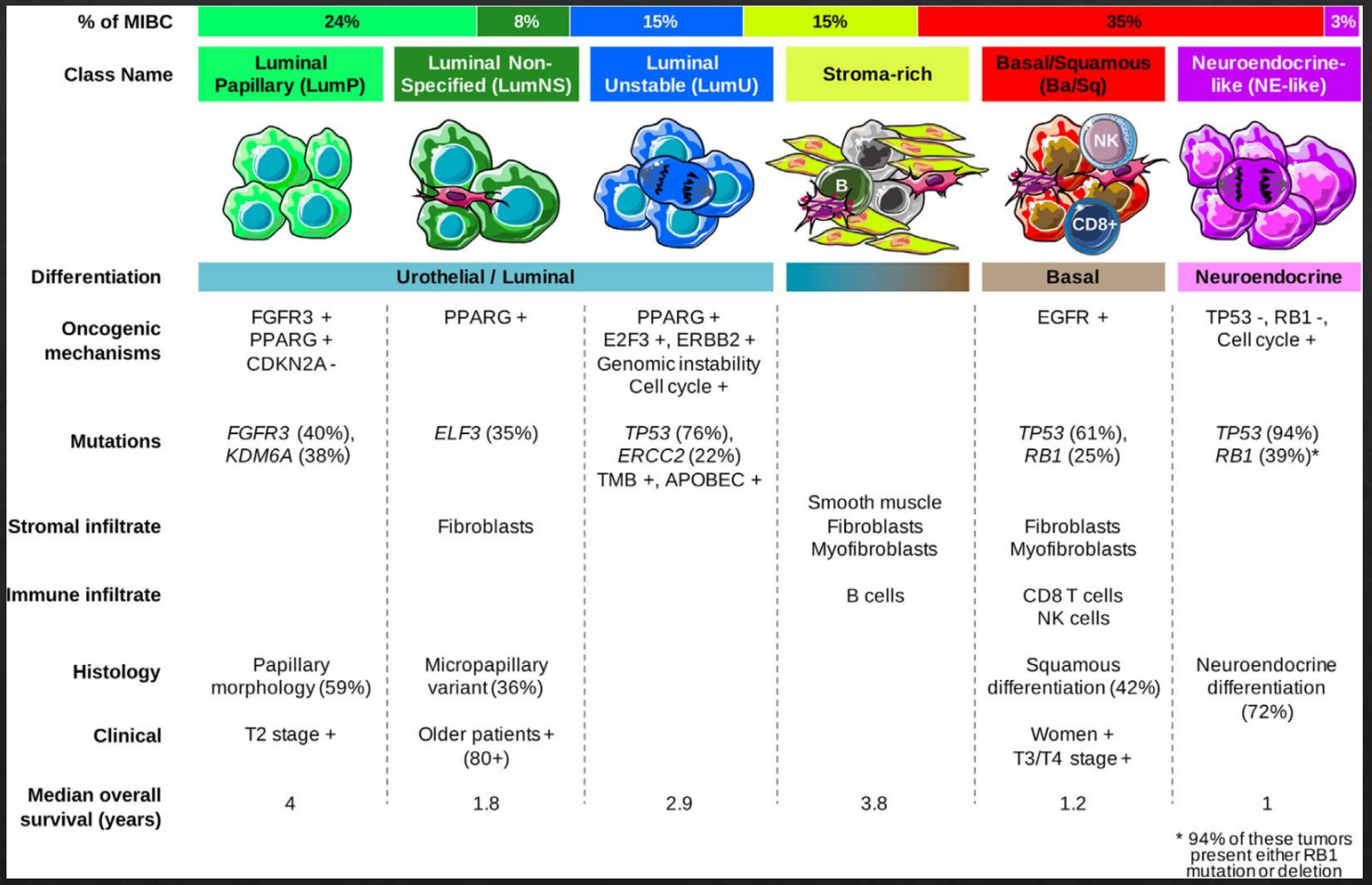
Platinum Priority – Bladder Cancer

Editorial by XXX on pp. x–y of this issue

A Consensus Molecular Classification of Muscle-invasive Bladder Cancer

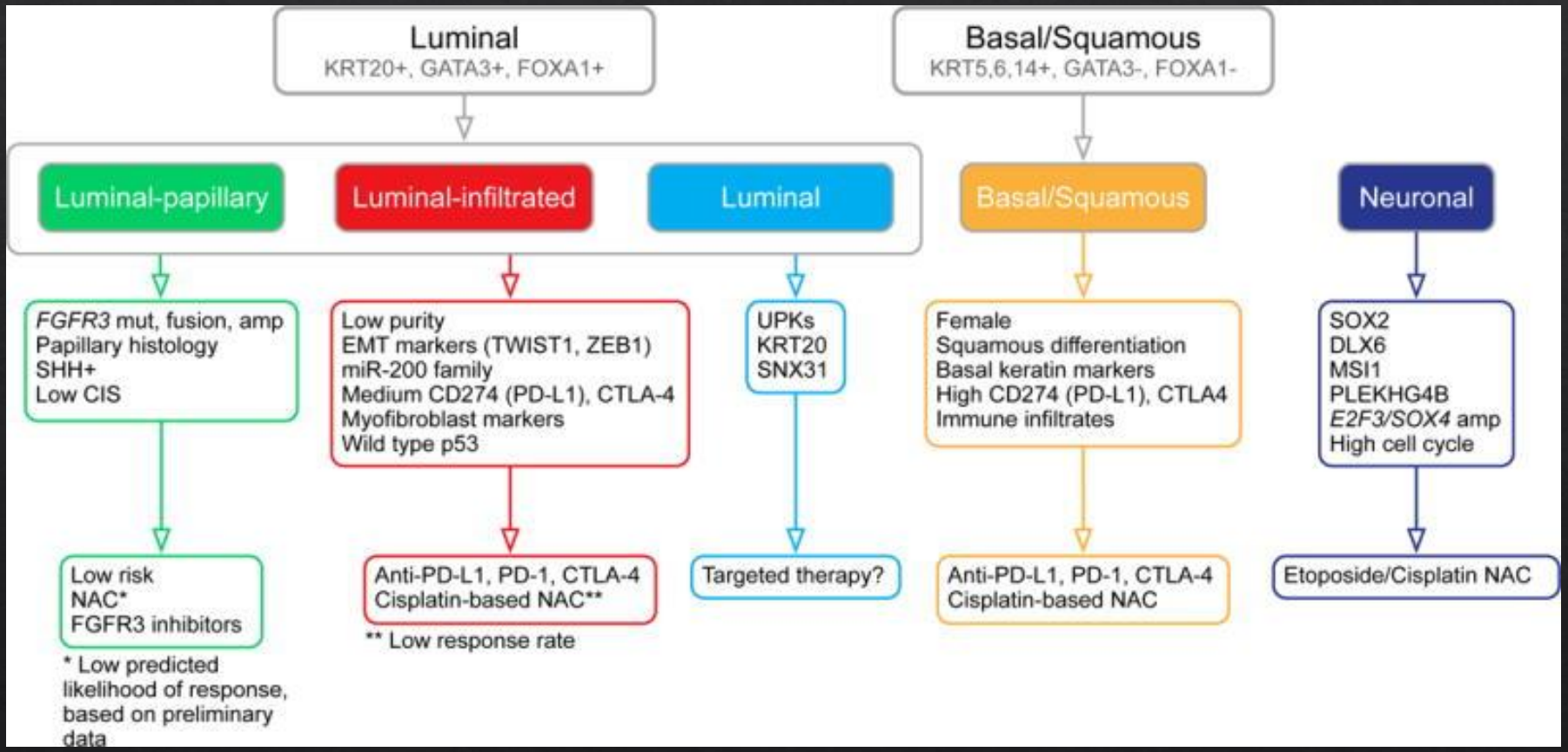
Aurélie Kamoun [a,], Aurélien de Reyniès [a,†], Yves Allory [b,c,†], Gottfrid Sjödahl [d,†], A. Gordon Robertson [e,†], Roland Seiler [f], Katherine A. Hoadley [g], Clarice S. Groeneveld [a,c,h], Hikmat Al-Ahmadie [i], Woonyoung Choi [j], Mauro A.A. Castro [h], Jacqueline Fontugne [b,c], Pontus Eriksson [k], Qianxing Mo [l], Jordan Kardos [g], Alexandre Zlotta [m], Arndt Hartmann [n], Colin P. Dinney [o,p], Joaquim Bellmunt [q], Thomas Powles [r], Núria Malats [s], Keith S. Chan [t], William Y. Kim [u,v], David J. McConkey [j], Peter C. Black [w], Lars Dyrskjøt [x], Mattias Höglund [k], Seth P. Lerner [y], Francisco X. Real [z], François Radvanyi [c], the Bladder Cancer Molecular Taxonomy Group [‡]*

MIBC –diagnostika



Kamoun et al, 2019
European Urology
Volume 77, Issue 4, 420-433

MBIC –diagnostika



Robertson et al, Cell 2017

MBIC –diagnostika

EUROPEAN UROLOGY 76 (2019) 200–206

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

European Association of Urology

Platinum Priority – Bladder Cancer – Editor's Choice

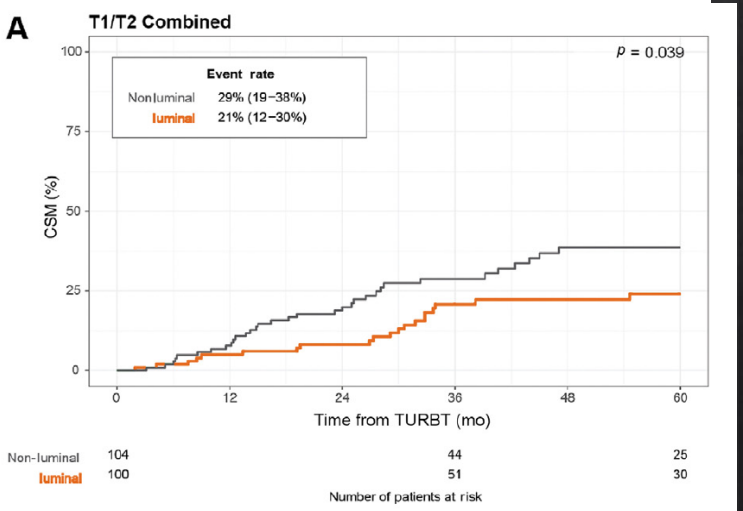
Editorial by Joshua J. Meeks and David J. McConkey on pp. 207–208 of this issue

Molecular Subtyping of Clinically Localized Urothelial Carcinoma Reveals Lower Rates of Pathological Upstaging at Radical Cystectomy Among Luminal Tumors

Yair Lotan [a,], Stephen A. Boorjian [b], Jingbin Zhang [c], Trinity J. Bivalacqua [d], Sima P. Porten [e], Thomas Wheeler [f], Seth P. Lerner [f], Ryan Hutchinson [a], Franto Francis [a], Elai Davicioni [c], Robert S. Svatek [g], Chun-Liang Chen [g], Peter C. Black [h], Ewan A. Gibb [c]*

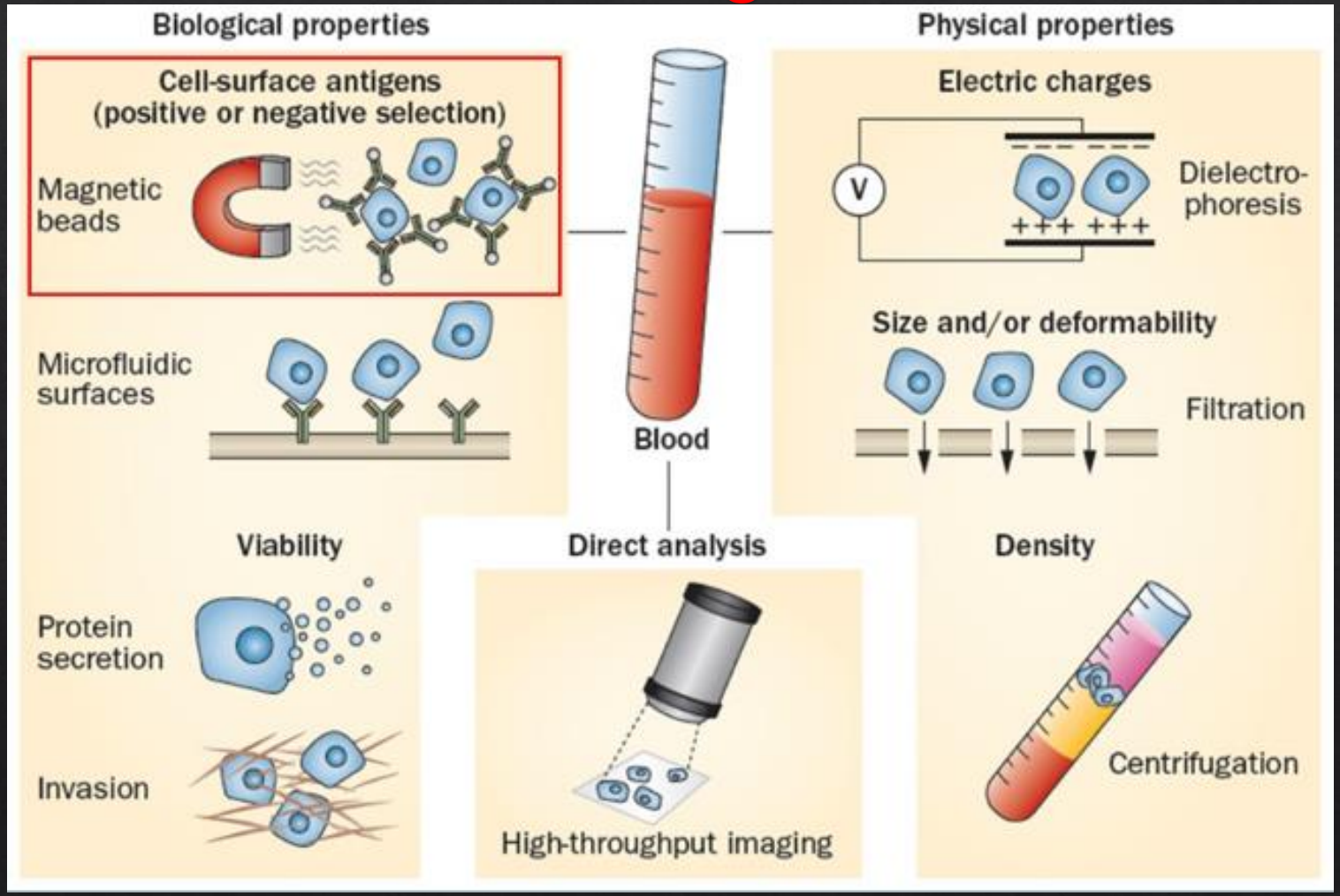
[a] *Department of Urology, University of Texas Southwestern Medical Center, Dallas, TX, USA;* [b] *Mayo Clinic, Rochester, MN, USA;* [c] *GenomeDx Inc, Vancouver, BC, Canada;* [d] *John Hopkins Medical Institute, Baltimore, MD, USA;* [e] *University of California San Francisco, San Francisco, CA, USA;* [f] *Baylor College of Medicine, Houston, TX, USA;* [g] *University of Texas Health San Antonio, San Antonio, TX, USA;* [h] *Vancouver Prostate Centre, University of British Columbia, Vancouver, BC, USA*

Variables	Luminal	Nonluminal	*p* value
Total, *n* (%)	100 (48)	106 (52)	
Upstaging (≥pT3 and/or pTanyN+), *n* (%)			
No	66 (66)	52 (49)	0.02
Yes	34 (34)	54 (51)	
Pathological upstage (pT3–4 only), *n* (%)			
pT0–2	75 (75)	55 (52)	<0.001
pT3–4	24 (24)	50 (47)	
Unavailable	1 (1.0)	1 (0.90)	
Node positive (Tany, N+ only), *n* (%)			
No	79 (79)	78 (74)	0.4
Yes	21 (21)	28 (26)	



- 206 pacientů s MIBC ze 7 center kteří **nedostali** neo CHT
- cT1/2 luminální subtyp → signifikantně nižší míra upstagingu po RACE (34% oproti 51%; p = 0,02)
- luminální → nižší CSM
- data jsou retrospektivní, neověřená a zejména incidence LU+ byla podobná mezi luminálními a neluminálními podtypy (21% oproti 26%; p = 0,4).

MBIC –diagnostika
CTC –circulating tumor cells



MBIC –diagnostika
CTC –circulating tumor cells

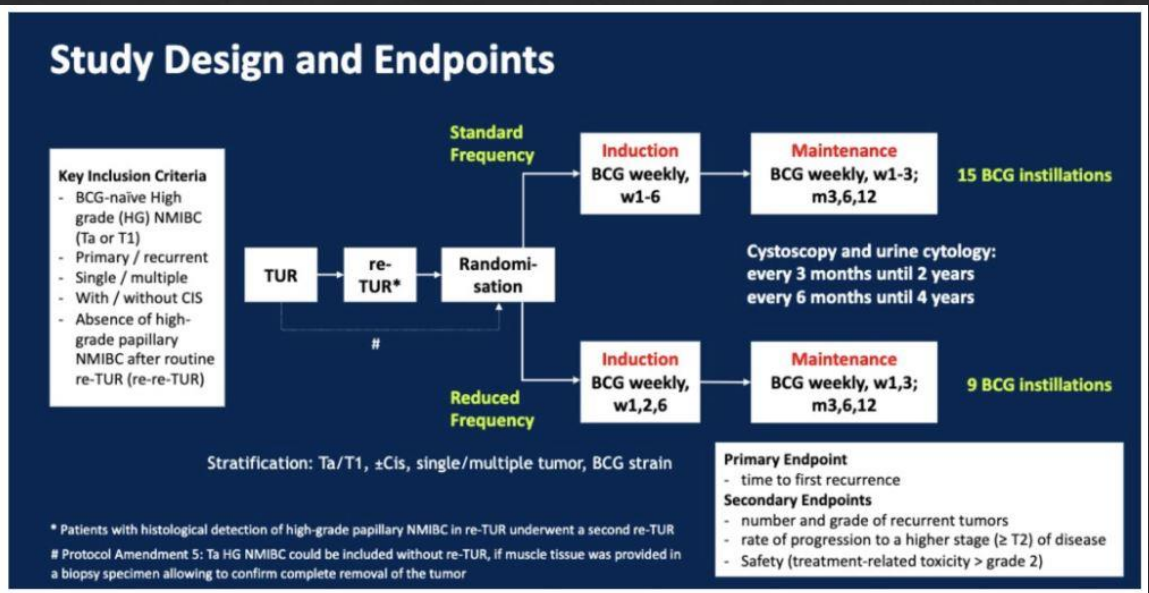
- 30 publikovaných prací o ca m.m.
- výskyt CTC signifikantně koreluje se stádiem nemoci (≤ II vs III, IV), gradingem (I, II vs III), metastázemi a pozitivními regionálními LU.
- detekce CTC signifikantně spojená se špatnou prognózou PFS,CSS
- Detekce CTC je také prognostickým faktorem před RACE .
- pp s detekci CTC měli signifikantně vyšší riziko recidívy a vyšší CSM i OM
- CTC jsou nezávislým prediktorem pro všechny konečné ukazovatele nemoci.

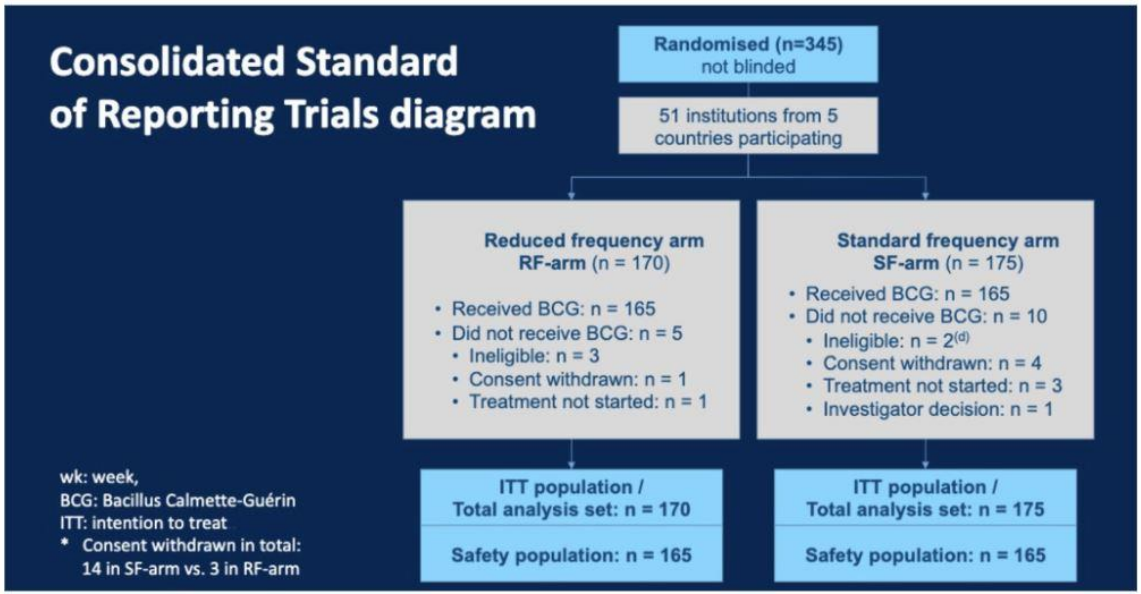
Zhang Z, Fan W, Deng Q, et al. The prognostic and diagnostic value of circulating tumor cells in bladder cancer and upper tract urothelial carcinoma: A meta-analysis of 30 published studies. *Oncotarget* 2017 Jun 16;8(35):59527-59538.

LÉČBA NMIBC

NMIBC - léčba

NIMBUS





NMIBC - léčba

NIMBUS

Patient outcomes

		RF-arm (n=170)	SF-arm (n=175)	Total (n=345)
End of study, n (%)	Yes	69 (40.6)	52 (29.7)	121 (35.1)
	No	101 (59.4)	123 (70.3)	224 (64.9)
Recurrence, n (%)		46 (27.1)	21 (12.0)	67 (19.4)
Progression to ≥ T2, n (%)*		1 (0.6)	6 (3.4)	7 (2.0)
Distant metastases, n (%)		0 (0.0)	1 (0.6)	1 (0.3)
Survival Status, n (%)	Alive	163 (95.9)	172 (98.3)	335 (97.1)
	Dead	7 (4.1)#	3 (1.7)##	10 (2.9)
AEs, n		670	1469	2139
No. of patients with AEs, n (%)		113/165§ (68.5)	136/165§ (82.4)	249/330§ (75.5)

* at first recurrence

\# none related to study drug: 1x autoimmune encephalitis or paraneoplastic syndrome, 1x pulmonary embolism, 1x sepsis, 5x other reasons

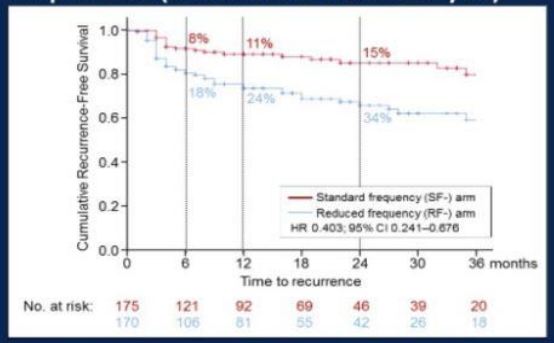
none related to study drug: 1x acute cardiac death, 2x other reasons

§ of patients treated at least once with BCG

Kaplan Meier Survival Analysis - Time to Recurrence

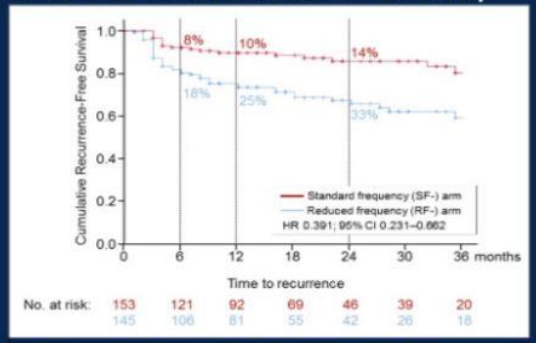
(time between randomization and date of first recurrence or last follow-up)

All patients (intention to treat analysis)



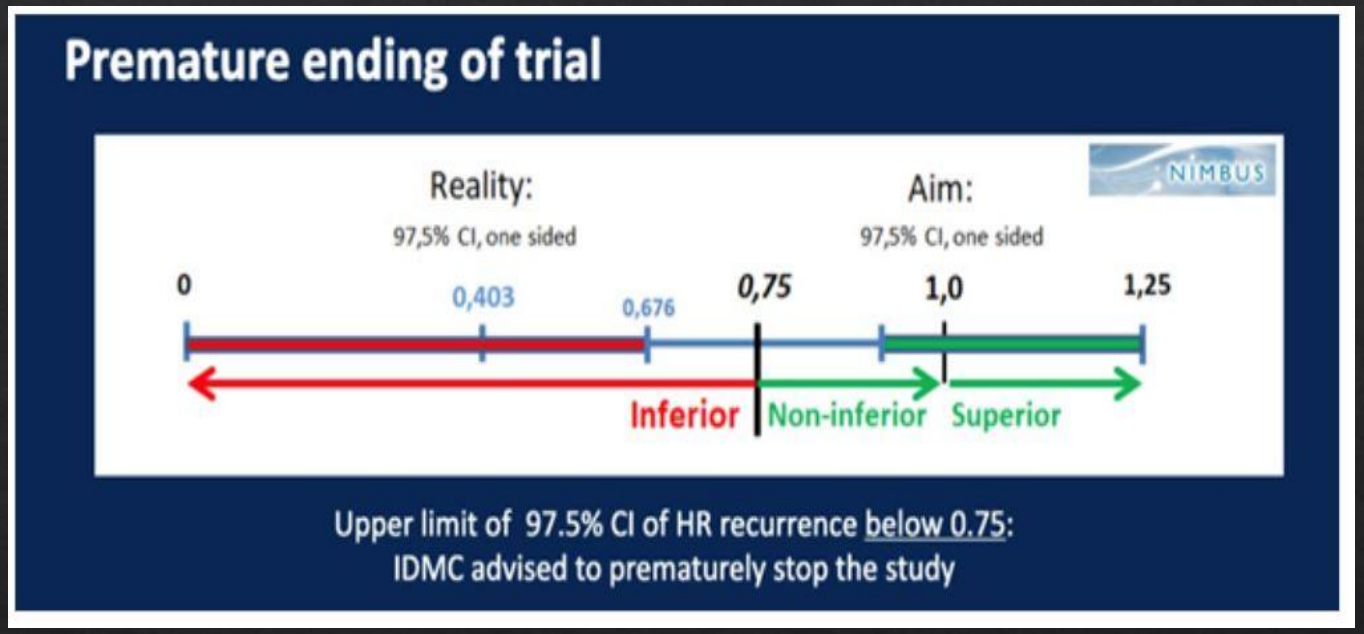
HR 0.403 (97.5% CI: 0.241 – **0.676**)

Patients observed for at least 6 months since their randomisation in the study



HR 0.391 (97.5% CI: 0.231 – **0.662**)

NMIBC - léčba
NIMBUS



NMIBC - léčba

KEYNOTE 057

KEYNOTE-057 Phase 2 Trial of Pembrolizumab for Patients With High-Risk Non–Muscle-Invasive Bladder Cancer Unresponsive to Bacillus Calmette-Guérin: Updated Interim Results

A. V. Balar[1]; G. S. Kulkarni[2]; E. Uchio[3]; J. L. Boormans[4]; L. Mourey[5]; L. Krieger[6]; E. A. Singer[7]; D. Bajorin[8]; A. Kamat[9]; P. Grivas[10]; H. K. Seo[11]; H. Nishiyama[12]; B. Konety[13]; K. Nam[14]; E. Kapadia[14]; T. Frenkl[14]; R. de Wit[4]

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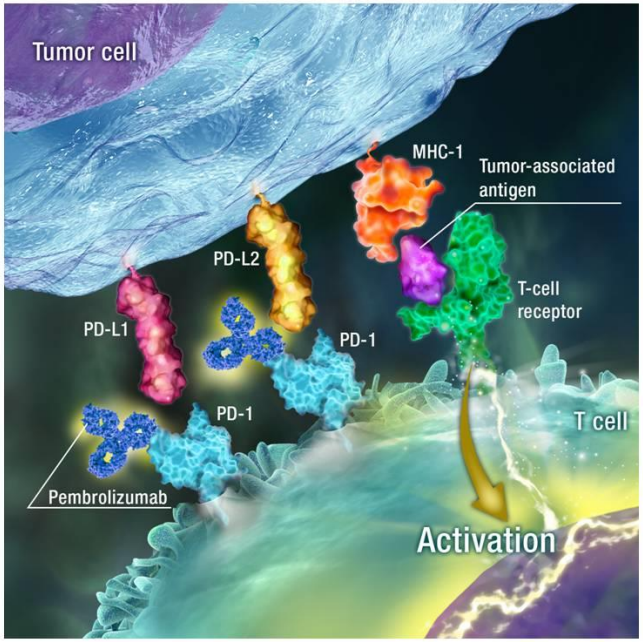
NMIBC and the PD-1/PD-L1 Pathway

- Programmed death-1 (PD-1) pathway activation has been implicated in BCG resistance[1]
- Pembrolizumab, a PD-1 inhibitor, has shown significant and durable antitumor activity in metastatic urothelial carcinoma[2,3]
  - Overall survival benefit versus chemotherapy in platinum-refractory disease[3]
- Little is known about anti–PD-1 monotherapy for NMIBC



1. Fukumoto K et al. *Ann Surg Oncol.* 2018;25:2484-2491. 2. Balar AV et al. *Lancet Oncol.* 2017;18:1483-1492. 3. Bellmunt J et al. *N Engl J Med.* 2017;376:1015-1026.

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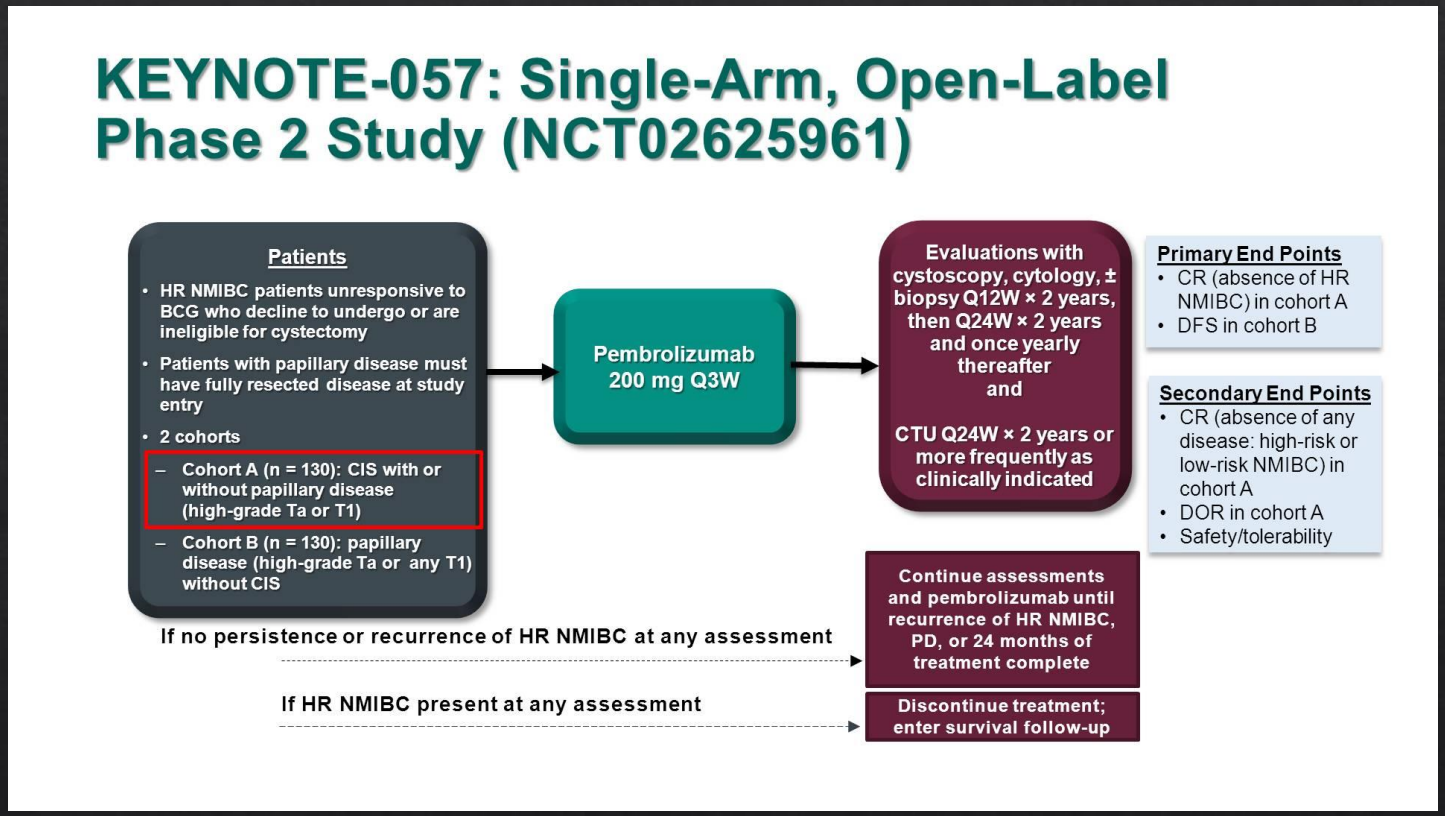

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Overall Response Rate at Month 3[a]

Response	Total Population (N = 102)		
	n	%	95% CI
CR	**41**	**40.2**	**30.6-50.4**
Non-CR	57	55.9	45.7-65.7
Persistent[b]	41	40.2	30.6-50.4
Recurrent[c]	6	5.9	2.2-12.4
NMIBC stage progression[d]	9	8.8	4.1-16.1
Non-bladder malignancy[e]	1	1.0	0.0-5.3
Progression to T2	0	0	NA-NA
Nonevaluable[f]	4	3.9	1.1-9.7

[a]Summary of overall responses of HR NMIBC per central assessment at month 3 in all patients who received ≥1 dose of trial treatment, had baseline evaluations, and also had ≥1 postbaseline disease assessment. [b]Defined as patients with CIS at baseline who at month 3 also had CIS ± papillary tumor. [c]Defined as pathologically confirmed appearance of papillary tumor (high-grade Ta or T1) without CIS at month 3.[d]Increase in stage from CIS and/or high-grade Ta at baseline to T1 disease. [e]Defined as presence of lesions suspicious for locally advanced or metastatic bladder cancer on imaging. Patient developed new liver lesions, as seen on imaging, and was later found to have a second primary malignancy of pancreatic cancer. Subsequent review of the baseline scan showed subtle findings that, in retrospect, could be attributed to pancreatic cancer. [f]Patients whose protocol-specified efficacy assessments were missing or who discontinued from the trial for reasons other than progressive disease were considered not evaluable for efficacy.
Database cutoff: September 14, 2018.

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Conclusions

- In this updated interim analysis of 102 patients from an ongoing study, pembrolizumab continued to show encouraging antitumor activity in patients with HR BCG-unresponsive CIS (with or without papillary disease) who declined to undergo or were ineligible for cystectomy and who had limited alternative treatment options
  - 40.2% CR rate at month 3; median duration of CR, 12.7 months (0.0+ to 20.5+ months)
- No patients with recurrent HR NMIBC experienced progression to muscle-invasive or metastatic bladder cancer while on study therapy
- Pembrolizumab AE profile is consistent with that of previous studies
- A phase 3 study to evaluate efficacy and safety of pembrolizumab plus BCG in HR NMIBC that is persistent/recurrent after BCG induction is currently open to enrollment (KEYNOTE-676, ClinicalTrials.gov identifier, NCT03711032)

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World Journal of Urology
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ORIGINAL ARTICLE

Check for updates

Impact of time to second transurethral resection on oncological outcomes of patients with high-grade T1 bladder cancer treated with intravesical Bacillus Calmette–Guerin

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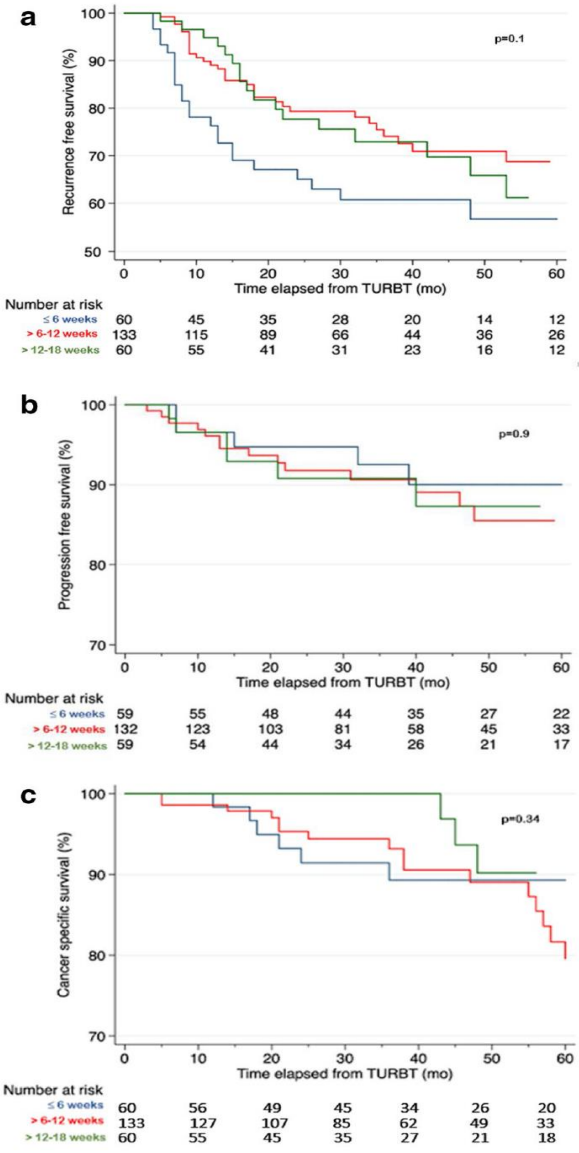
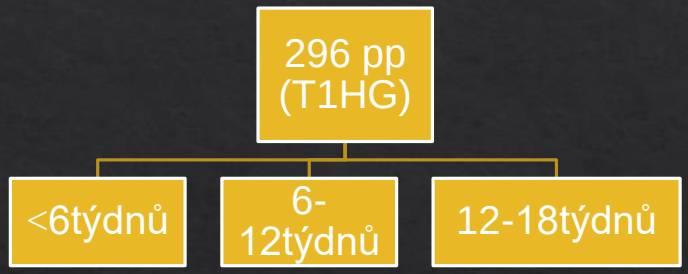


Fig. 1 Kaplan–Meier plots showing recurrence-free survival (**a**), progression-free survival (**b**) and cancer specific survival (**c**) according to time to Re-TUR (group A: ≤ 6 weeks; group B: > 6–12 weeks; group C: > 12–18 weeks)



Střední doba sledování 49,3m

LÉČBA MIBC

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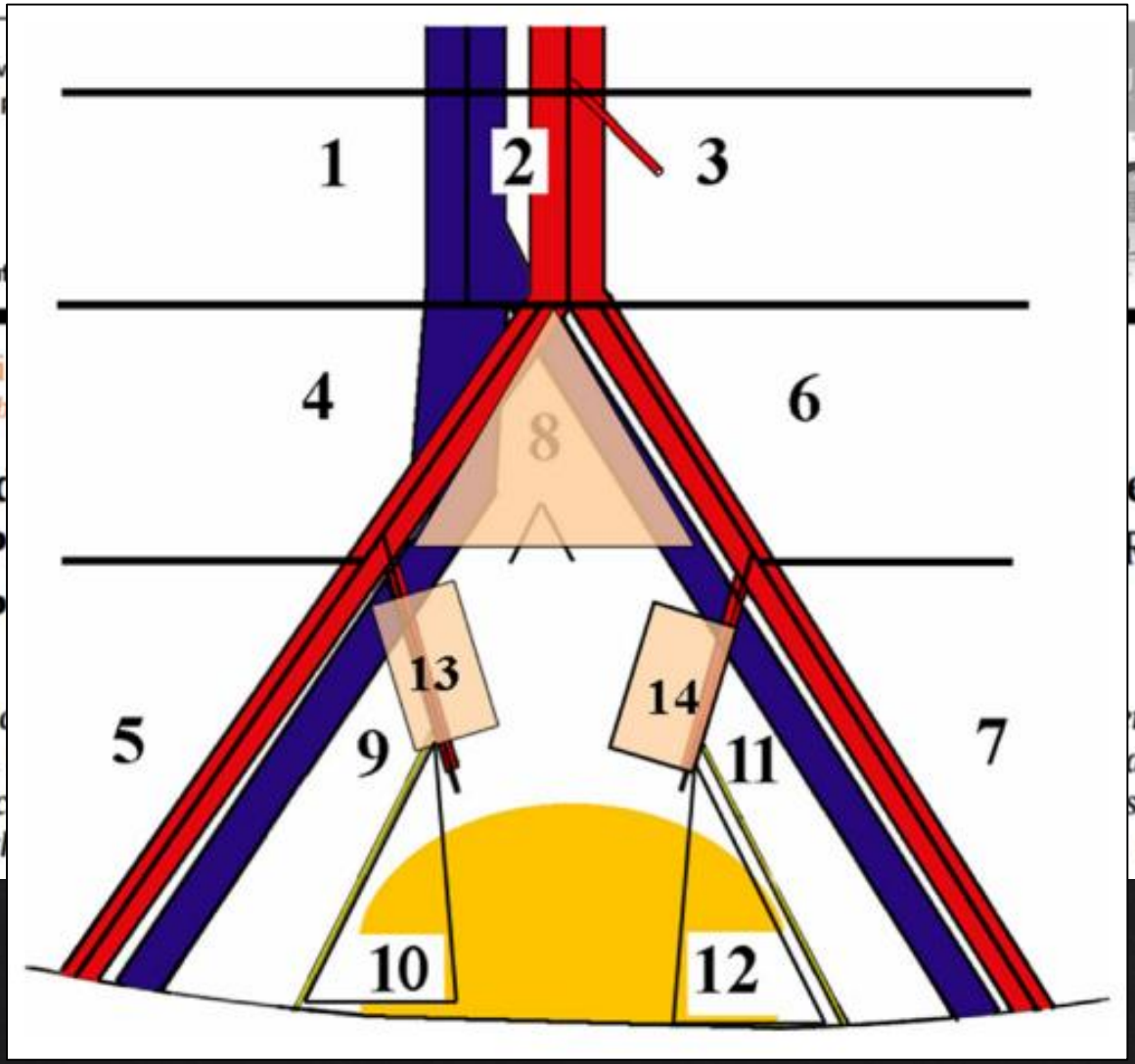

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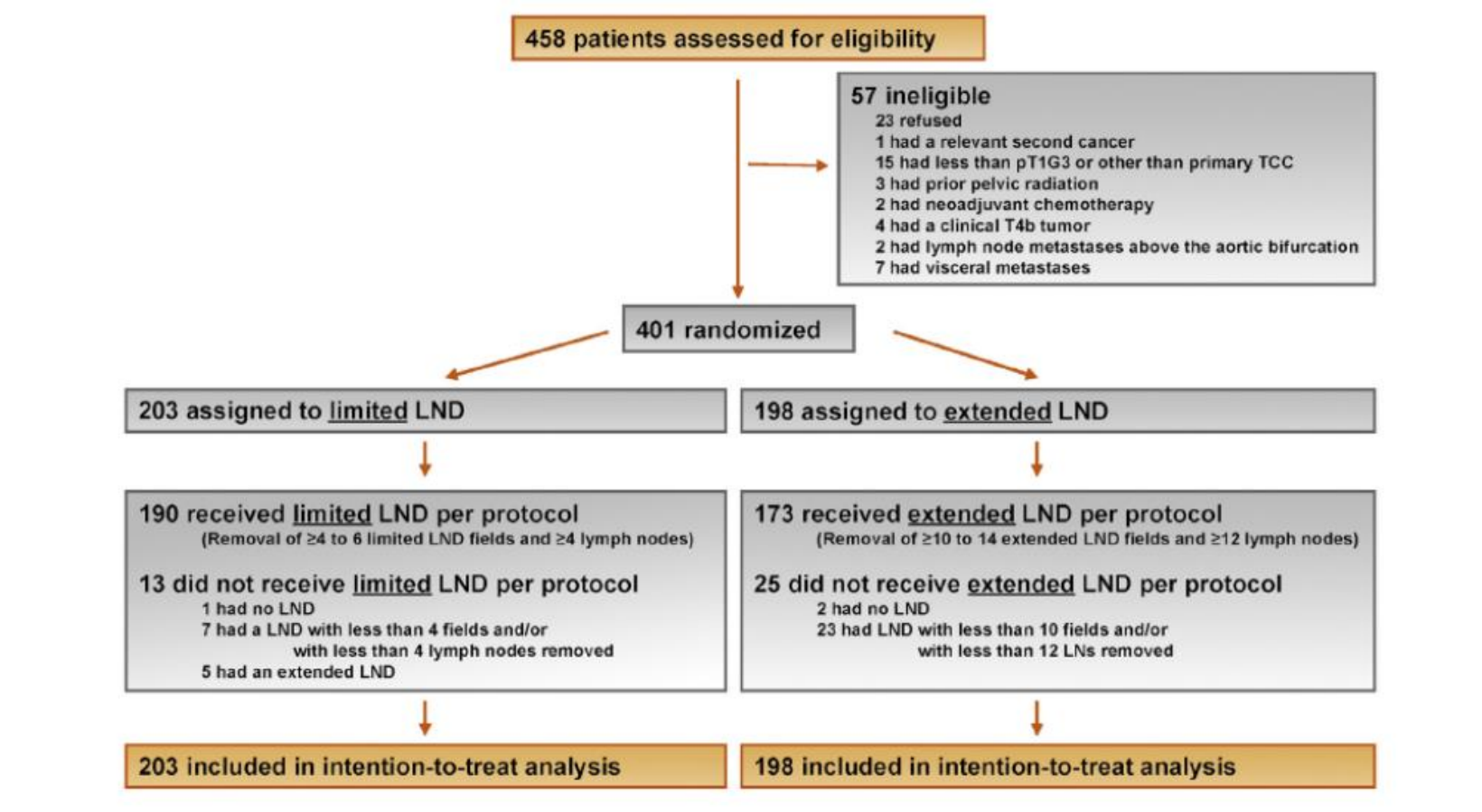
458 patients assessed for eligibility
57 ineligible
23 refused
1 had a relevant second cancer
15 had less than pT1G3 or other than primary TCC
3 had prior pelvic radiation
2 had neoadjuvant chemotherapy
4 had a clinical T4b tumor
2 had lymph node metastases above the aortic bifurcation
7 had visceral metastases
401 randomized
203 assigned to limited LND
198 assigned to extended LND
190 received limited LND per protocol
(Removal of ≥4 to 6 limited LND fields and ≥4 lymph nodes)
13 did not receive limited LND per protocol
1 had no LND
7 had a LND with less than 4 fields and/or
with less than 4 lymph nodes removed
5 had an extended LND
173 received extended LND per protocol
(Removal of ≥10 to 14 extended LND fields and ≥12 lymph nodes)
25 did not receive extended LND per protocol
2 had no LND
23 had LND with less than 10 fields and/or
with less than 12 LNs removed
203 included in intention-to-treat analysis
198 included in intention-to-treat analysis

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European Association of Urology

Platinum Priority – Bladder Cancer – Editor's Choice
Editorial by Seth P. Lerner and Robert S. Svatek on pp. 612–614 of this issue

Extended Versus Limited Lymph Node Dissection in Bladder Cancer Patients Undergoing Radical Cystectomy: Survival Results from a Prospective, Randomized Trial

Jürgen E. Gschwend[a,i,], Matthias M. Heck[a,i], Jan Lehmann[b], Herbert Rübben[c], Peter Albers[d], Johannes M. Wolff[e], Detlef Frohneberg[f], Patrick de Geeter[g], Axel Heidenreich[h], Tilman Kälble[i], Michael Stöckle[j], Thomas Schnöller[k], Arnulf Stenzl[l], Markus Müller[m], Michael Truss[n], Stephan Roth[o], Uwe-Bernd Liehr[p], Joachim Leißner[q], Thomas Bregenzer[b], Margitta Retz[a]*

- 5 leté přežívaní bez relapsu 59% PLND x 64% ePLND
- v rameni ePLND signifikantně vyšší míra výskytu lymfokély(8,6% oproti 3,4%; p = 0,04).
- probíhá rozsáhlá studie (SWOG S-1011), která by se k této otázce měla definitívně vyjádřit.

„Take home message“
Diagnostika

- CTC lze předoperačně detekovat u 20-30% pp
- CTC pozitivita je asociována s vyšším stadiem nemoci
- Přítomnost CTC u pp s MIBC předpovídá špatnou prognózu
- Molekulární analýza CTC buněk v budoucnosti představuje slibnější trend než prognostické biomarkery

„Take home message“
Léčba

Subtypizace nádoru je způsob, jak popsat MIBC, včetně diferenciace/nediferenciace epitelu, stromy a imunitních buněk v nádoru; představuje cestu kategorizace nádoru do klinických studií

Rozšířená PLND se zatím nejeví účinnější ve srovnání s klasickou PLND

- Děkuji za pozornost!