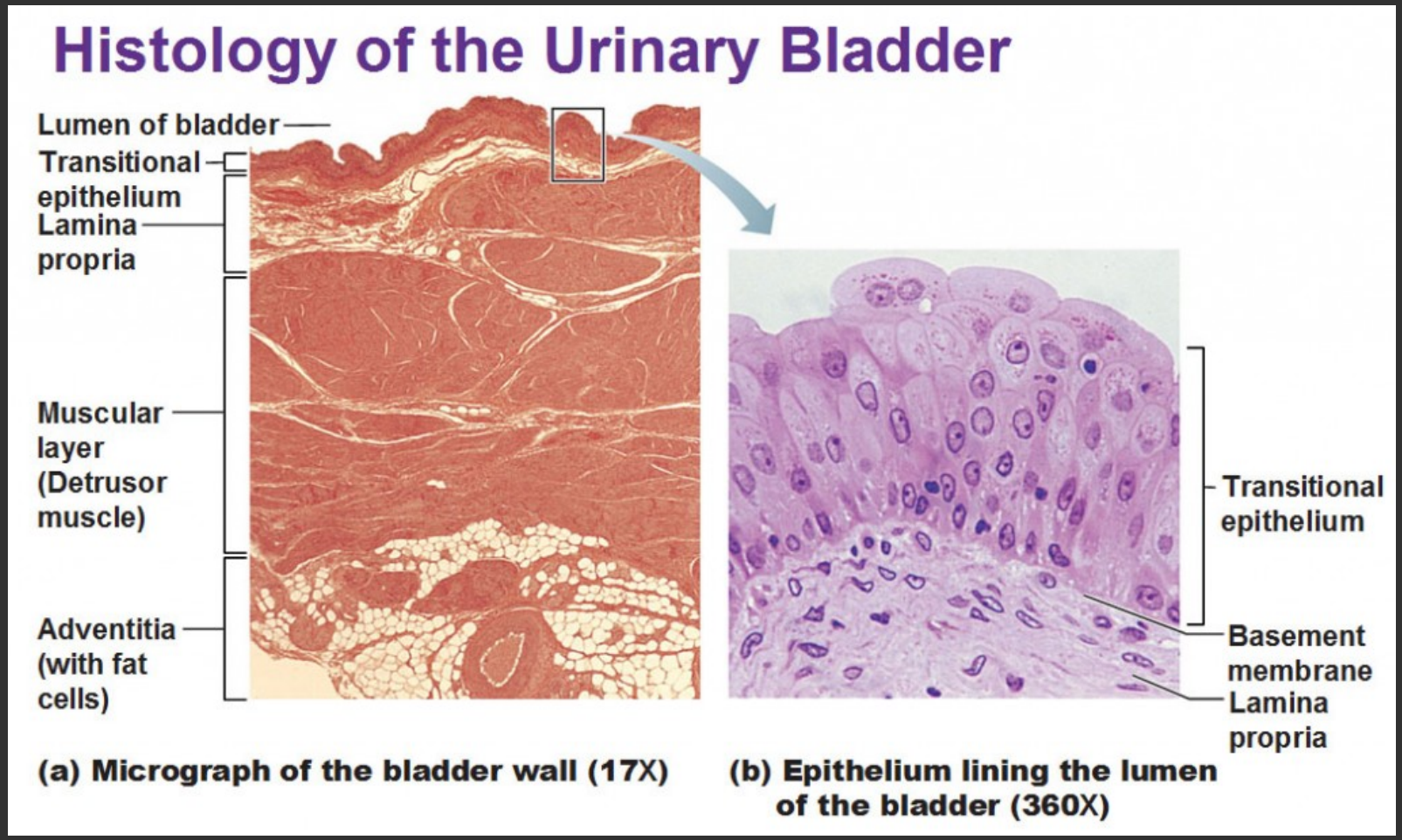
Καρκίνος της ουροδόχου κύστης: Ιστολογικοί υπότυποι και κλινική σημασία

Βασίλειος Τζώρτζης – Αριστοτέλης Μπάμιας

Δεν έχουμε να δηλώσουμε οποιαδήποτε σύγκρουση συμφερόντων

Ουροθήλιο


Histology of the Urinary Bladder
Lumen of bladder
Transitional epithelium
Lamina propria
Muscular layer (Detrusor muscle)
Adventitia (with fat cells)
Transitional epithelium
Basement membrane
Lamina propria
(a) Micrograph of the bladder wall (17X)
(b) Epithelium lining the lumen of the bladder (360X)

Καρκίνος Ουροδόχου Κύστης

- Ουροθηλιακός καρκίνος
  - Μεταβατικό επιθήλιο 90%
    - Αμιγές
    - Μικτό (διάφοροι υπότυποι)

Καρκίνος Ουροδόχου Κύστης

- Μη ουροθηλιακός
  - Πλακώδες επιθήλιο 5%
    - Οφειλόμενο στη σχιστοσωμίαση
    - Μη οφειλόμενο
  - Αδενοκαρκίνωμα 2%
    - Προερχόμενο από τον ουραχό
    - Μη προερχόμενα από το ουραχό
    - Μεταστατικό
  - Σάρκωμα (Μη επιθηλιακός) 2%
    - Υπότυποι
  - Μικροκυτταρικό 1%

Καρκίνος μεταβατικού επιθηλίου: υπότυποι

- Ετερογενής όγκος
- Ικανότητα του ουροθηλίου να διαφοροποιείται
- Ευρεία χρήση ανοσοιστοχημικών τεχνικών
- 13 γνωστοί υπότυποι (WHO)
- Σημασία στην πρόγνωση
- Ποσοστό ανεύρεσης 7%-81%

Διαγνωστικά προβλήματα

- Ποσότητα και ποιότητα του ιστού TUR
- Δεν υπάρχουν διαγνωστικοί κανόνες
- Η ανεύρεση οποιοδήποτε ποσοστού του υπότυπου είναι διαγνωστική!!!!!

- Εξειδικευμένοι παθολογοανατόμοι

Ουρολόγος: υποψία επιθετικότερου τύπου με ανάλογη αντιμετώπιση

Διαγνωστικά προβλήματα

The Impact of Histological Reclassification during Pathology Re-Review—Evidence of a Will Rogers Effect in Bladder Cancer?

Brian J. Linder, Stephen A. Boorjian, John C. Cheville, William R. Sukov, Prabin Thapa, Robert F. Tarrell and Igor Frank*,†

From the Departments of Urology (BJL, SAB, IF), Pathology (JCC, WRS) and Health Sciences Research (PT, RFT), Mayo Clinic, Rochester, Minnesota

	No. Variant UC (%)
Squamous differentiation	122 (30)
Micropapillary	62 (15)
Nested variant	51 (13)
Pure squamous Ca	39 (10)
Small cell Ca	36 (9)
Glandular differentiation	33 (8)
Adenoca	30 (7)
Sarcomatoid	14 (3)
Mixed differentiation	11 (3)
Inverted growth pattern	4 (1)
Plasmacytoid	1 (0.2)

406/1211

Conclusions: Pathological re-review of radical cystectomy specimens identified variant histology in a third of patients. These variants are associated with a high rate of locally advanced disease, which may impact the noted rates of cancer specific and overall survival. Thus, it is critical to be aware of re-review status when interpreting outcomes from historical data sets and stratifying risk.

Υπότυποι

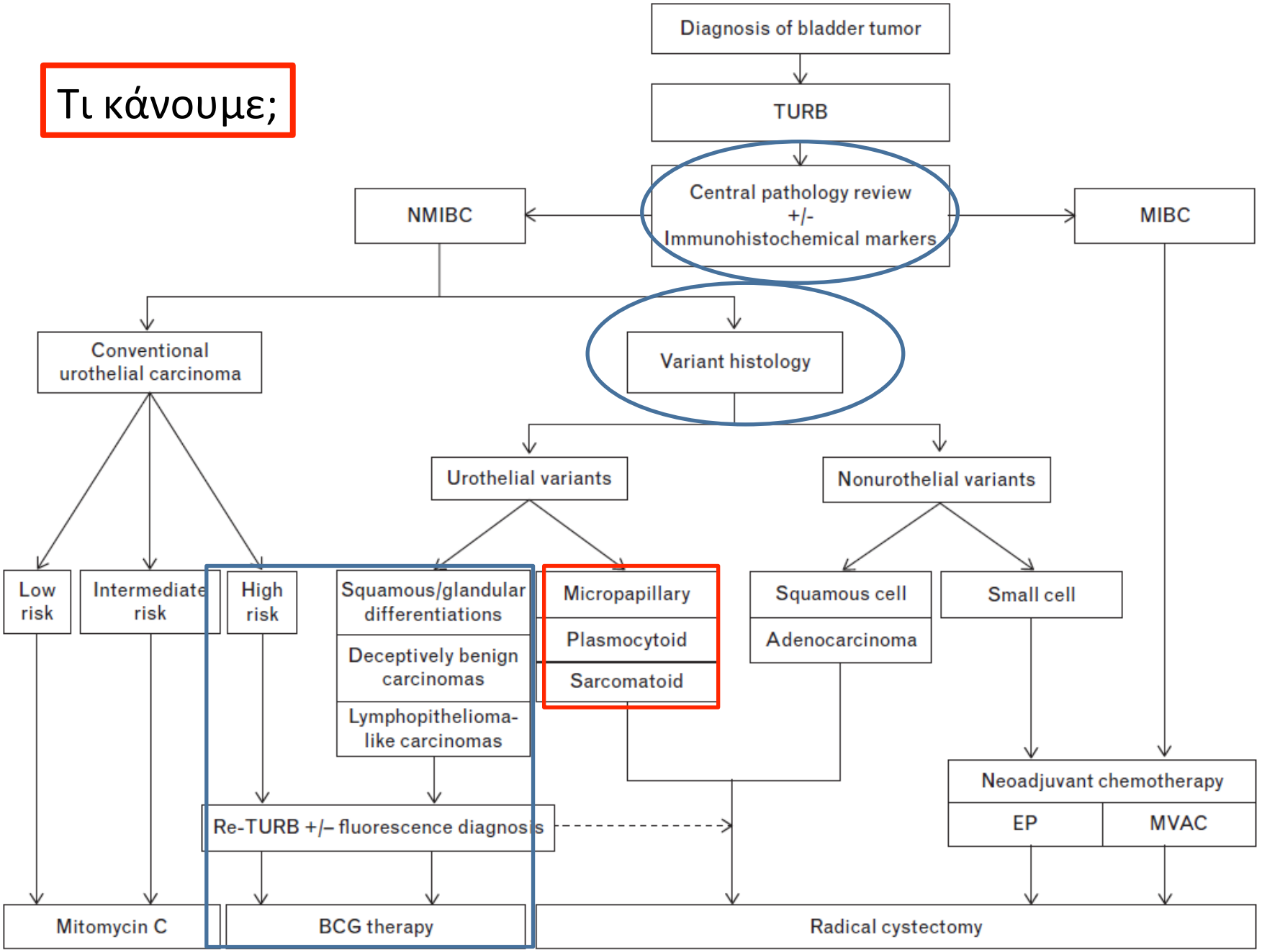
Urothelial variants		Nonurothelial variants
Aggressive variants	**Highly aggressive variants**	
Squamous/glandular differentiation	Micropapillary carcinoma	Squamous cell carcinoma
Deceptively benign carcinomas	Plasmacytoid carcinoma	Adenocarcinoma
Nested carcinoma	Sarcomatoid carcinoma	Neuroendocrine carcinoma
Small tubular carcinoma		Small cell
Microcystic carcinoma		
Inverted papilloma-like growth		
Lymphoepithelioma-like carcinoma		

NMIBC

- Υποσταδιοποίηση: TUR vs Κυστεκτομής 50%

  Abd El-Latif A. J Urol 2013
- PPD ?
- Υποσταδιοποίηση!!!!!
- Συνήθως είναι διηθητικοί

Τι κάνουμε;


Diagnosis of bladder tumor
TURB
Central pathology review
+/-
Immunohistochemical markers
NMIBC
MIBC
Conventional urothelial carcinoma
Variant histology
Urothelial variants
Nonurothelial variants
Low risk
Intermediate risk
High risk
Squamous/glandular differentiations
Deceptively benign carcinomas
Lymphopithelioma-like carcinomas
Micropapillary
Plasmocytoid
Sarcomatoid
Squamous cell
Adenocarcinoma
Small cell
Neoadjuvant chemotherapy
EP
MVAC
Re-TURB +/– fluorescence diagnosis
Mitomycin C
BCG therapy
Radical cystectomy

Impact of histological variants on oncological outcomes of patients with urothelial carcinoma of the bladder treated with radical cystectomy

1984 κυστεκτομές

Evanguelos Xylinas [a,c,k], Michael Rink [a,d,k], Brian D. Robinson [e], Yair Lotan [f], Marek Babjuk [g], Antonin Brisuda [g], David A. Green [a], Luis A. Kluth [a,d], Armin Pycha [h], Yves Fradet [i], Talia Faison [a], Richard K. Lee [a], Pierre I. Karakiewicz [j], Marc Zerbib [c], Douglas S. Scherr [a], Shahrokh F. Shariat [a,b,*]

Histological variant	Number of patients (%)
Pure urothelial carcinoma	1495 (75.4)
Urothelial carcinoma variant	488 (24.6)
Squamous cell differentiation	227 (11.4)
Glandular differentiation	75 (3.8)
Sarcomatoid differentiation	40 (2.0)
Micropapillary differentiation	34 (1.7)
Small cell differentiation	40 (2.0)
Plasmacytoid differentiation	7 (0.4)
Multiple variant differentiation	65 (3.3)

Conclusions: A quarter of UCB patients treated with RC harboured histological UCB variants. Variant UCB histologies were associated with features of biologically aggressive disease. While variant UCB histology was associated with worse outcomes in univariable analyses, this effect did not remain significant in multivariable analyses.

Ο ρόλος της χημειοθεραπείας

- Νεοεπικουρική
- Επικουρική

Impact of Histological Variants on Clinical Outcomes of Patients with Upper Urinary Tract Urothelial Carcinoma

From the Weill Medical College of Cornell University, New York-Presbyterian Hospital (MR, BDR, DAG, EKC, CKN, DSS, SFS), New York, New York, University Medical Center Hamburg-Eppendorf (MR, JH, FKC), Hamburg, Germany, University of Montreal (JH, MS, PIK) and McGill University (WK, KS), Montreal, Quebec, Canada, General Hospital of Bolzano (EC, AP), Bolzano, Italy, University of Texas Southwestern Medical Center (VM, WK, YL), Dallas and M.D. Anderson Cancer Center (CCG, GS), Houston, Texas, Penn State Milton S. Hershey Medical Center (JDR), Hershey, Pennsylvania, Hospital Korneuburg (MR) and University of Vienna (AH), Vienna, Austria, University of Rennes (KB, NRL), Rennes, France, and Keio University School of Medicine (EK), Tokyo, Japan

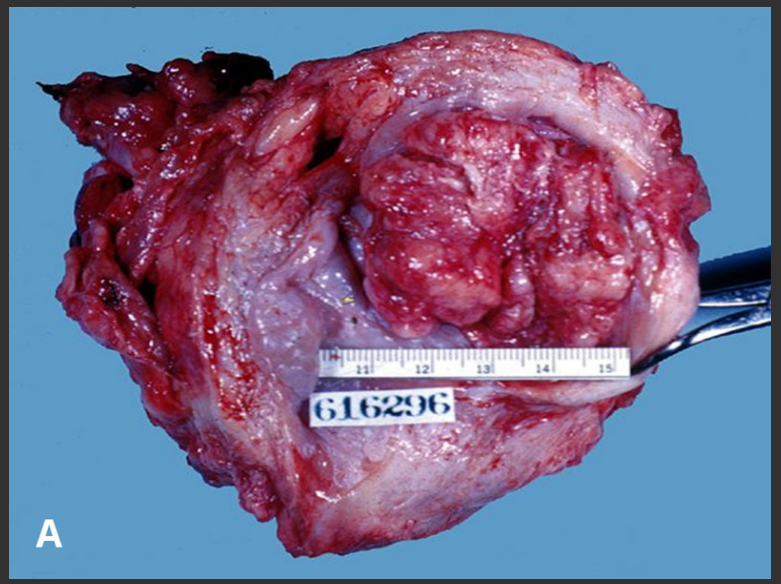
UC histological variants in 1,648 patients with UTUC treated with RNU

UC Histology	No. Pts (%)
Pure	1,250 (75.8)
Variant differentiation:	398 (24.2)
Squamous cell	163 (9.9)
Glandular	66 (4.0)
Sarcomatoid	39 (2.4)
Micropapillary	31 (1.9)
Small cell	32 (1.9)
Plasmacytoid	3 (0.2)
Multiple	64 (3.9)

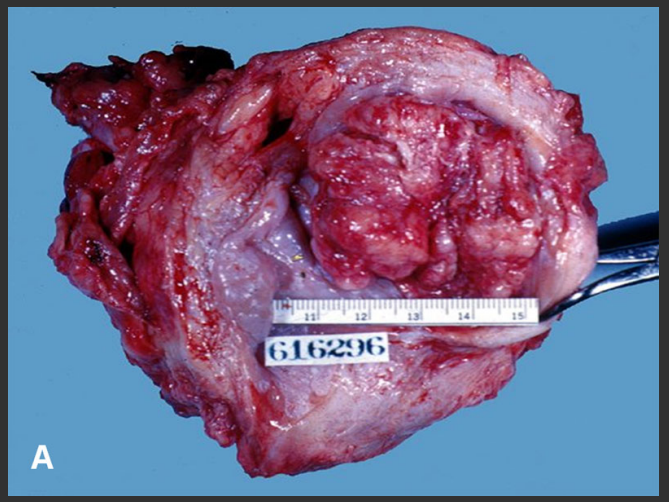
Conclusions: Almost 25% of patients with upper tract urothelial carcinoma treated with radical nephroureterectomy harbored histological variants. Variant histology was associated with features of biologically aggressive upper tract urothelial carcinoma. While variant histology is associated with worse outcomes on univariable analysis but this effect did not remain significant on multivariable analysis.

Πλακώδες επιθήλιο (SCC)

- Σχιστοσωμίαση
  - > 90%
  - Μέση ηλικία εμφάνισης 50 έτη
  - Α:Γ 4-5:1
  - Οζώδης με εξέλκωση
  - Ερεθιστικά συμπτώματα
  - pT3 και pT4 90%
  - LN 15-26%
  - 5ετής επιβίωση 50%



Πλακώδες επιθήλιο (SCC)



- Μη οφειλόμενος σε σχιστοσωμίαση
  - Χρόνια φλεγμονή
  - 10% σε φέροντες Foley ≥10 έτη
  - Μέση ηλικία εμφάνισης 70 έτη
  - Α:Γ 1,3-1,8:1
  - Οζώδης με εξέλκωση και εκτεταμένη νέκρωση
  - pT3 και pT4 > 70%
  - LN 10-25%
  - 5ετής επιβίωση 10%

Πλακώδες επιθήλιο (SCC)

- Θεραπεία
  - Ριζική κυστεκτομή με εκτεταμένο λεμφαδενικό καθαρισμό
  - Σημαντικός παράγοντας επιβίωσης η πύελος
  - + χειρουργικά όρια 8,8% vs τοπική υποτροπή 75% (μικροσκοπική υπολειμματική νόσος)

  - Ακτινοθεραπεία
    - Πρωτόκολλα νέο και επικουρικής ακτινοθεραπείας μετά κυστεκτομή για την μικροσκοπική τοπική νόσο
    - αύξηση επιβίωσης

Ghoneim MA. J Urol 2008
Zaghloul MS. Int J Radiat Oncol Biol Phys 1992

Πλακώδες επιθήλιο (SCC)

- Χημειοθεραπεία

  Neoadjuvant? NO

  Adjuvant? NO

  Advanced

  Squamous carcinomas are generally sensitive to combinations that include a platinum agent with paclitaxel and/ gemcitabine

SCC vs TCC[1]

Table II. *Response rates and survival.*

	TCCs	SCCs	Mixed tumors	*p*-value
Response				
CR, PR	171 (44%)	4 (27%)	14 (34%)	0.210
No response	218 (56%)	11 (73%)	27 (66%)	
Time to progression (months)	7.7 (95% CI 7-8.4)	7.2 (95% CI 2-12)	7.2 (95% CI 3-12)	0.824
Median survival (months)	11.3 (95% CI 10-12.5)	13.6 (95% CI 5.8-21.5)	10.4 (95% CI 4-17)	0.720

CR: complete response; PR: partial response.

1. Kastritis et al 2006; Anticancer Res 26: 3865-70

SCC vs TCC[1]

Table III. *Univariate and multivariate analysis of factors associated with survival in patients with mixed histology tumors.*

Univariate	*p*-value	Multivariate	*p*-value
ECOG performance status	<0.001	ECOG performance status	0.004
Presence of visceral metastases	0.002	Presence of visceral metastases	0.013
Hemoglobin<10mg%	<0.001	Hemoglobin<10 mg%	0.074
Carboplatin *vs.* Cisplatin-based chemotherapy	0.182		

1. Kastritis et al 2006; Anticancer Res 26: 3865-70

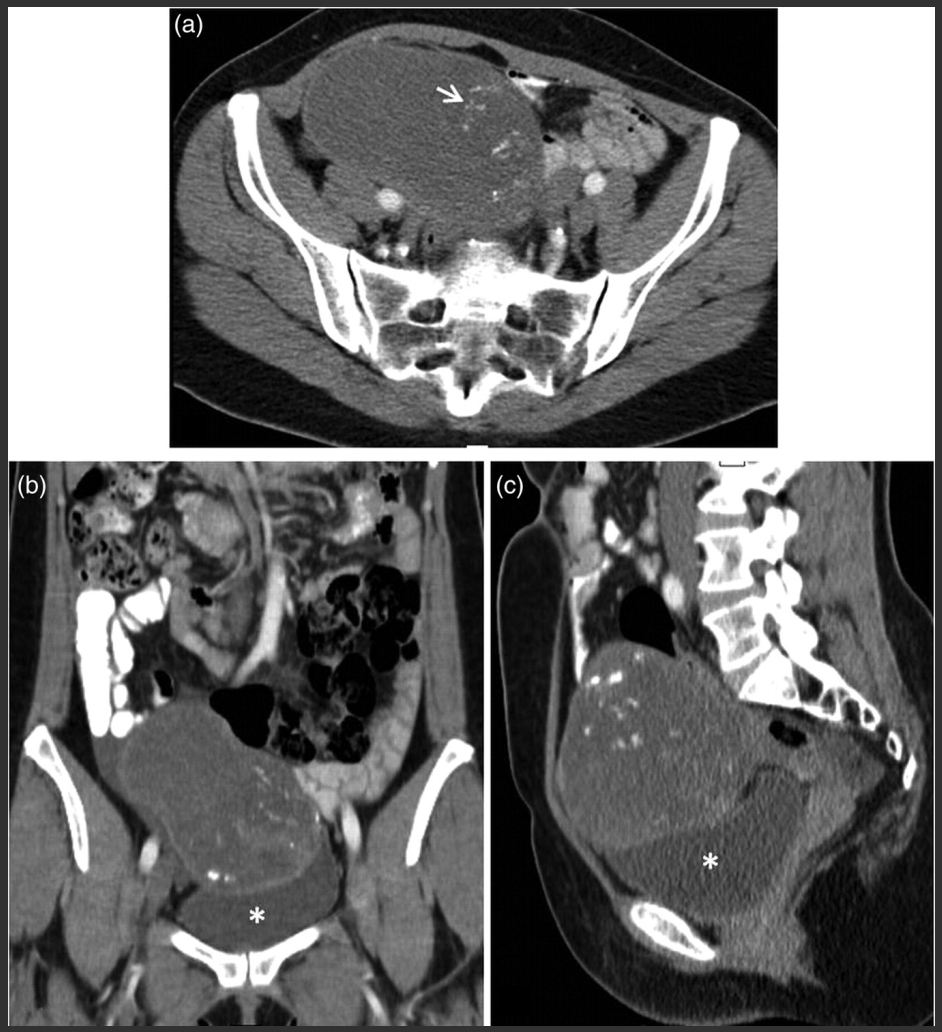
Αδενοκαρκίνωμα

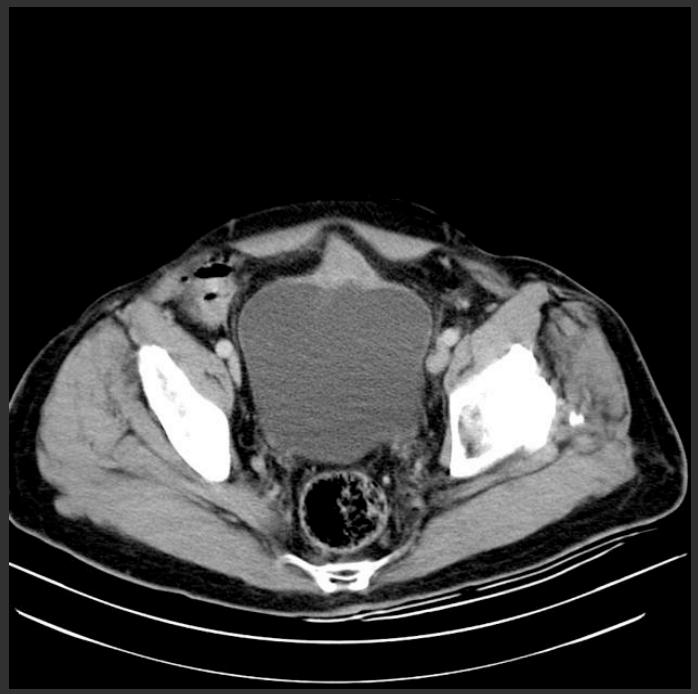
- Ουραχού
  - Συνήθως δεν καταλαμβάνει όλη την κύστη (θόλος)
  - Ανοιχτός ουραχός
  - Αποβολή βλέννης από τα ούρα
  - Ψηλαφητή μάζα υπογαστρίου
  - Νεότεροι ασθενείς
  - Γυναίκες

  - Μερική κυστεκτομή + ουραχός + ομφαλός
  - Ριζική κυστεκτομή
  - 5ετής επιβίωση 49%

Asley R. Cancer 2006

Αδενοκαρκίνωμα Ουραχού





Αδενοκαρκίνωμα

- Πρωτοπαθές – μεταστατικό
- Εκστροφή της κύστης, Σχιστόσωμα, Ενδομητρίωση
- Μεταπλασία – Κυστική κυστίτιδα – Αδενική κυστιτιδα
- Σχεδόν πάντα διηθητικό
- 5ετής επιβίωση 0-31%

- Κυστεκτομή
- Ακτινοθεραπεία
- Χημειοθεραπεία

Αδενοκαρκίνωμα

- Χημειοθεραπεία

  Neoadjuvant? NO

  Adjuvant? NO

  Advanced

    Occasional short-lived responses to combinations used for GI cancers

Σάρκωμα

- Μεσεγχυματικής προέλευσης
  - Λειομυοσάρκωμα 50%
  - Ραβδομυοσάρκωμα 20%
  - Αγγειομυοσάρκωμα
  - Οστεοσάρκωμα
  - Καρκινοσάρκωμα

- Ακτινοβολία πυέλου, κυκλοφωσφαμίδη

- Ριζική κυστεκτομή ± εξεντέρωση
- Αρνητικά χειρουργικά όρια !!!!!!!
- 5ετής επιβίωση 60%

Spiess PE. Urol Oncol 2007

Σάρκωμα

Χημειοθεραπεία

Neoadjuvant? NO

Adjuvant? NO

Advanced

Chemoresistant

SMall Cell Carcinoma

Epidemiology

- The first case of primary SCCB was reported in 1981; since then, no more than 1000 cases have been published.
- Extrapulmonary small-cell carcinomas: 2.5%–5.0% of all small-cell carcinomas
- Associated with smoking
- Bladder is the most common site for GU small-cell carcinomas

Small-cell carcinoma of GU tract

TABLE III Published data on small-cell carcinoma of the genitourinary tract

Variable	*Reference*				
	Lo Re et al.[10]	*Holmäng* et al.[17]	*Mangar* et al.[18]	*Choong* et al.[8]	*Current study*
Patients (*n*)	24	25	14	44	58
Tumour site (*n*)					
Urinary bladder	5	25	14	44	35
Prostate	4				17
Kidney	2				
Upper urinary tract					6
Presentation (*n*)					
Limited-stage disease		18	10	39	28
Extensive-stage disease	>50%	7	4	5	24
Unknown					6
Median survival (months)					
Overall	13	7.3		1.7 Years	7.5
Limited-stage disease			21		22
Extensive-stage disease			5		4.1

Small-cell carcinoma GU

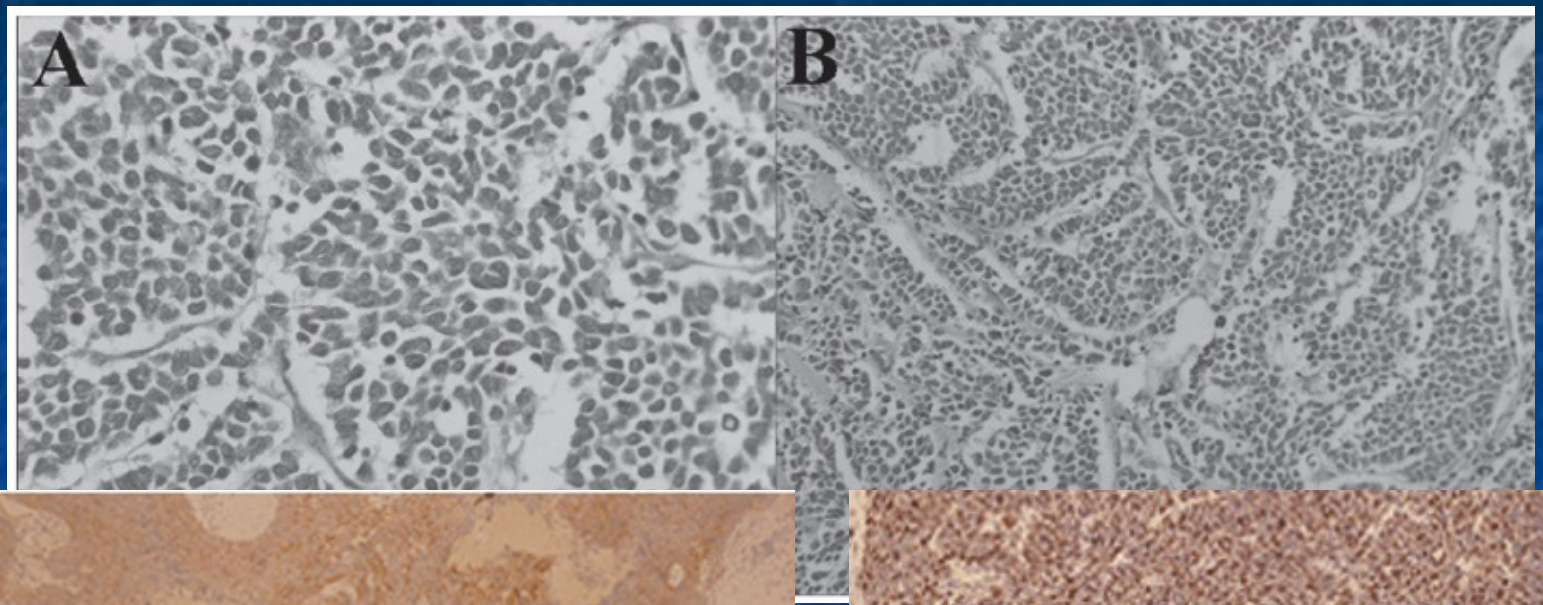
	Transitional	Small-cell bladder	SCLC
Aggressive behaviour	+	+++	+++
Brain mets	+	++	+++
Smoking	+	++	+++
Paraneoplastic sy	+	++	+++

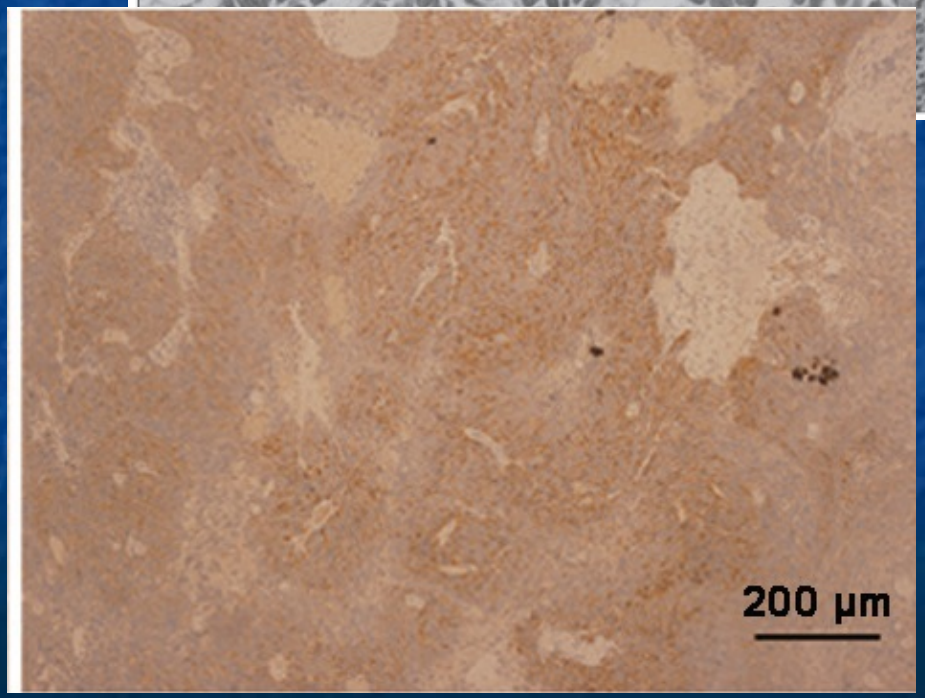
Manifestations

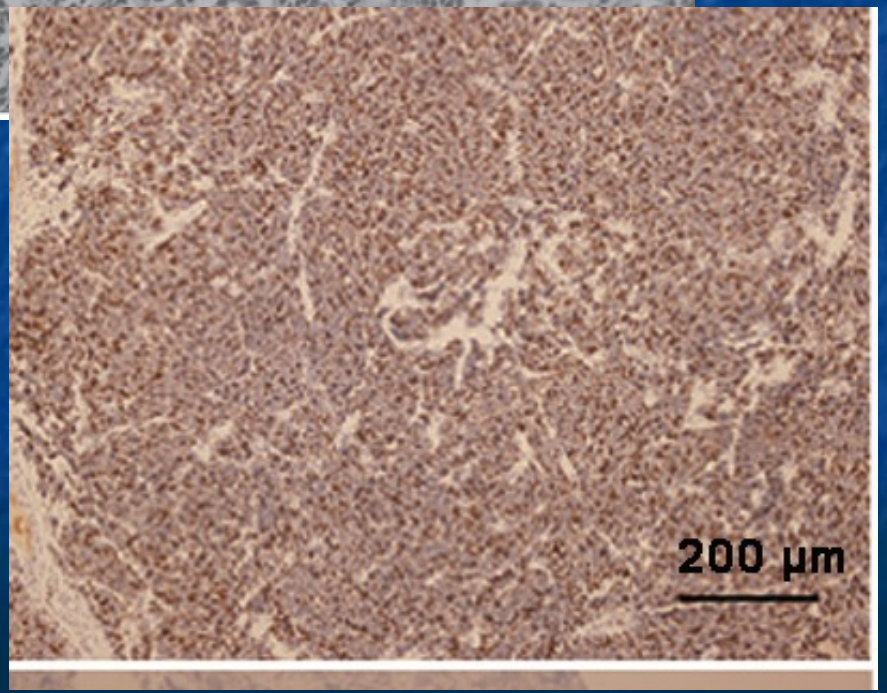
- Hematuria: 62% of patients[1]
- Paraneoplastic syndrome: hypercalcemia, SIADH, Cushing's Sy, Lambert-Eaton sy
- >50% LS

1. Pervez et al. Curr Oncol, 2013; 20, pp. 258-264

PATHOLOGY







Pathological diagnosis

Recommendation:

Pathology should be reviewed at a tertiary centre if there is a suspicion of a small cell component. Percentage of small cell component, as well as other histological features of the tumour, should be reported. ***Level 4 Grade C***

Immunohistochemistry should be attempted to demonstrate neuroendocrine differentiation, but more importantly to rule out other possible neoplasms, specifically lymphoma. This panel should include the following: CD56, synaptophysin, CD45, low molecular weight cytokeratin (CAM5.2 or CK8/18). In cases where neuroendocrine differentiation cannot be demonstrated and where lymphoma has been ruled out, additional markers could be performed and include, but are not limited to, CK7, CK20 and TTF-1. ***Level 4 Grade C***

Μικροκυτταρικό καρκίνωμα

- Πλήρης σταδιοποίηση με τη διάγνωση
  - CT ΑΟΚ, Θώρακος, Εγκεφάλου, Scan οστών

Staging[1]

- LIMITED STAGE

A primary tumour confined to the bladder with or without regional lymph node which:

a. Can be resected or
b. Can be encompassed within a tolerable radiation port

- EXTENSIVE STAGE

All others

- ***TNM?***

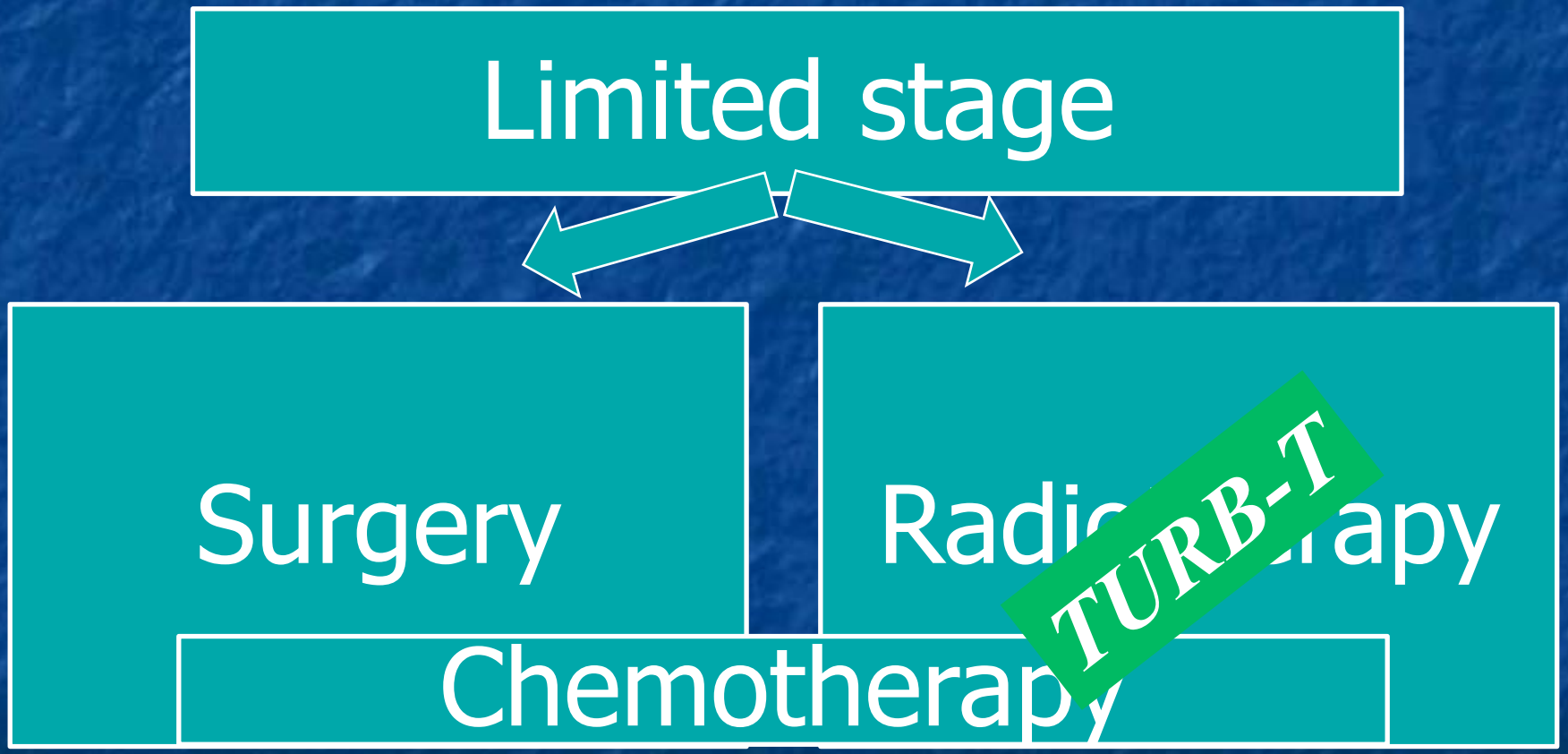
1. Pervez et al. Curr Oncol, 2013; 20, pp. 258-264

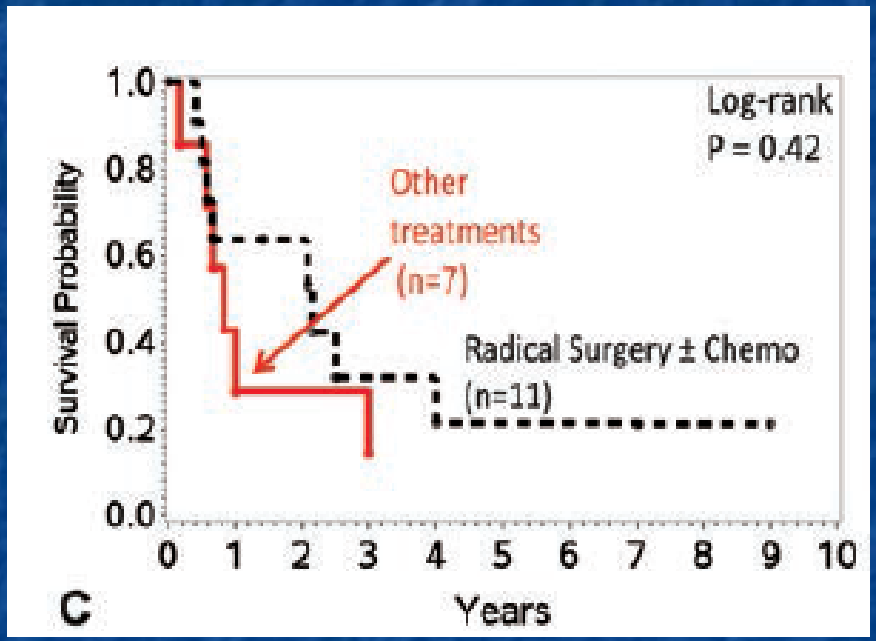
Treatment guidelines

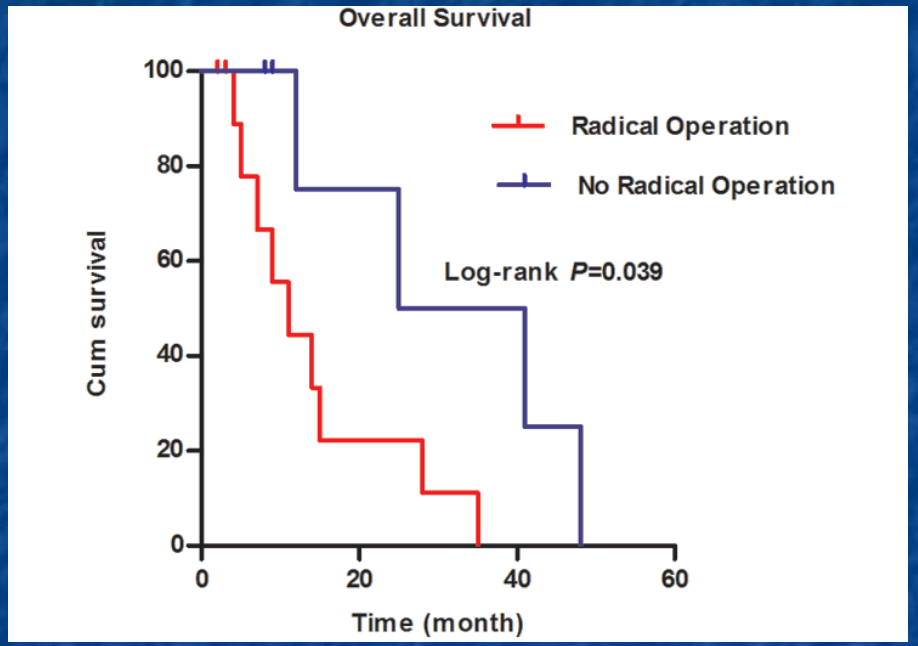
- NCCN

Management of small cell carcinoma of the bladder: Consensus guidelines from the Canadian Association of Genitourinary Medical Oncologists (CAGMO)

Treatment




Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
0 1 2 3 4 5 6 7 8 9 10
Years
Log-rank
P = 0.42
Other
treatments
(n=7)
Radical Surgery ± Chemo
(n=11)
C


Overall Survival
Cum survival
100
80
60
40
20
0
0 20 40 60
Time (month)
Radical Operation
No Radical Operation
Log-rank P=0.039

Treatment

Extensive stage

Chemotherapy

Table 2. Outcomes of neuroendocrine bladder cancer based on histology and therapy.

Variable	1-yr OS, %	3-yr OS, %	5-yr OS, %	Median OS	Log-rank P-value
Histology					
Pure	43 (10-73)	21 (1-58)	21 (1-58)	8 months	0.96
Mixed	54 (23-78)	27 (6-54)	14 (1-42)	25 months	
Therapy					
Radical surgery± chemo	64 (30-84)	32 (8-60)	21 (3-49)	26 months	0.42
Other treatment	28 (4-61)	14 (1-46)	14 (1-46)	10 months	

OS, overall survival.

Αντιμετώπιση

Disease	Optimal Treatment	Grade of Recommendation
Squamous cell carcinoma	Radical cystectomy	B
Primary adenocarcinoma	Radical cystectomy	B
Urachal adenocarcinoma	En bloc excision of urachus and umbilicus with partial cystectomy	B
Metastatic adenocarcinoma involving the bladder	Complete resection of involved portion of the bladder; partial cystectomy with negative margins or radical cystectomy	B
Small cell carcinoma	Local treatment and chemotherapy	B
Bladder sarcoma	Radical cystectomy	C
Carcinosarcoma, sarcomatoid tumors	Multimodality therapy	C
Paraganglioma and pheochromocytoma	Partial cystectomy with pelvic lymph node dissection; perioperative adrenergic blockade	C
Pseudotumor	Transurethral resection or partial cystectomy	C
Melanoma, primary, of bladder	Radical cystectomy	C
Lymphoma, primary	Local irradiation	C

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

European Society for Medical Oncology

BIOLOGY

Comprehensive molecular characterisation of urothelial bladder carcinoma

The Genome Atlas Research Network

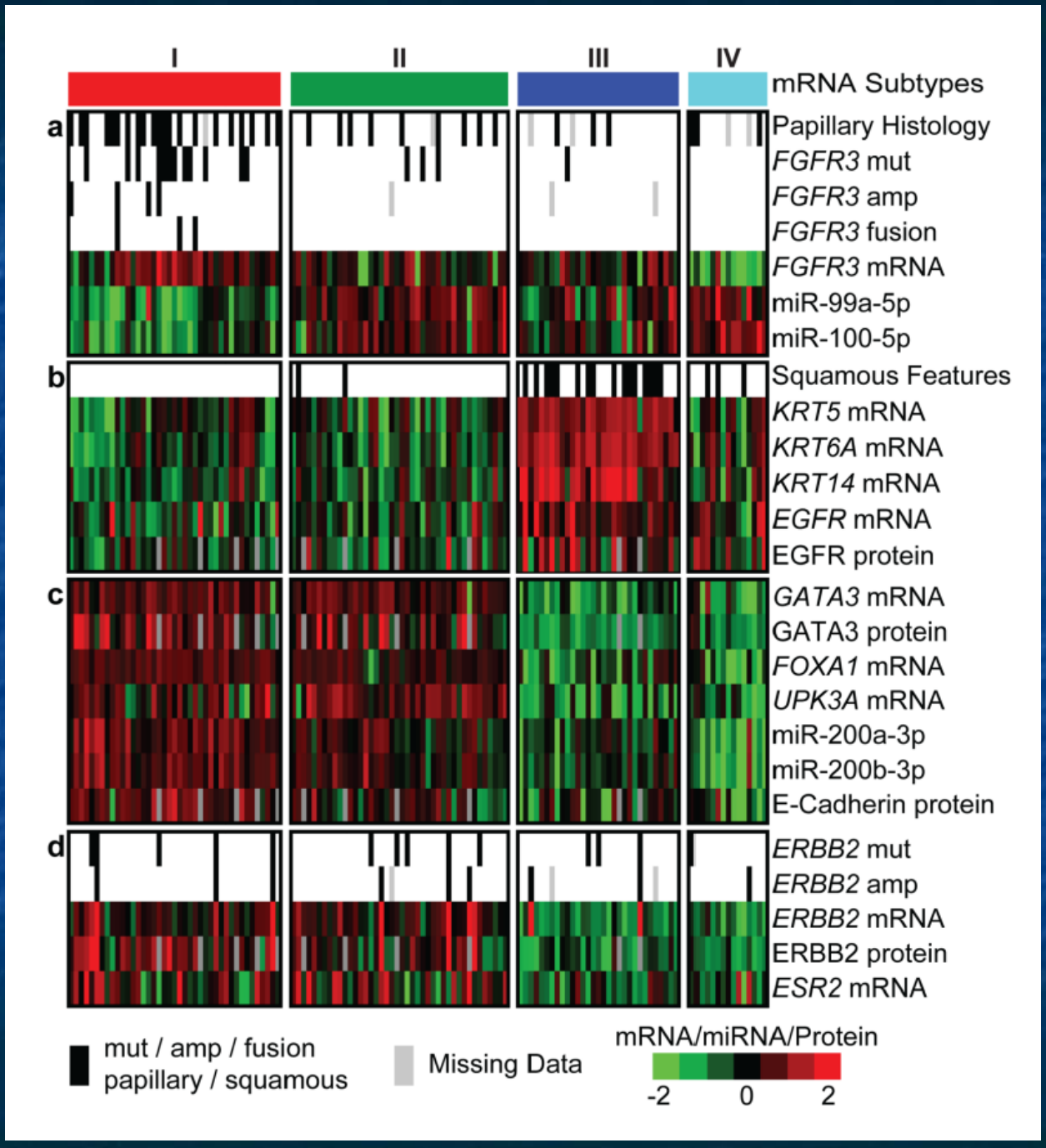
Nature 2014; 507:315-322

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
European Society for Medical Oncology

Comprehensive molecular characterisation of urothelial carcinoma

- Identification of alterations in 69% of the tumours amenable to therapeutic target
  - 42% targets in **PI3K/AKT/mTOR pathway**
    - Mutations *PIK3CA* → **17%** potentially R to PI3K inhibitors
    - Mutations/ deletions *TSC1* or *TSC2* → **9%** potentially R to mTOR inhibitors
    - Overexpression *AKT3* → **10%** potentially R to AKT inhibitors
  - 45% targets (including *ERBB2*) in **RTK/MAPK pathway**
    - Mutations/amplifications *ERBB2*→ **9%** potentially R to *ERBB2* kinase inhibitors/Ab
- Recurrent in-frame activating ***FGFR3-TACC3* fusions** / ↑ ***FGFR3*** expression
    - Enriched in tumours with papillary morphology
    - Activating events of FGFR3 → **17%** potentially R to *FGFR* inhibitors
- Expression/ integration of several **viruses** (including CMV and HPV16) associated with gene inactivation (<10% cases)
- **Chromatin regulatory genes** frequently mutated:
  - *76% inactivated mutations in one or more genes. 41% alterations in at least 2 genes*
  - *≥20% mutations/CNA:* **Methyltransferases:** *MML2 /MLL3 and* **Demethylases:** *KDM6A / KDM6B*

PI3K: phosphatidylinositol-3-OH kinase; AKT: protein kinase B; mTOR: mechanistic target of rapamycin; R: responsive; RTK: receptor tyrosine kinase; MAPK: mitogen-activated protein kinase; Ab: antibody



Cluster I : papillary like

Elevated FGFR3 expression and positive for FGFR3-TACC3 fusions

Cluster I-II

Elevated HER2 (*ERBB2*), ESR2, GATA3 and FOXA1 expression

Cluster III: basal/ squamous-like

KRT14, KRT5, KRT6 and EGFR expression
Stem-cell like expression features

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

European Society for Medical Oncology

BIOLOGY

Identification of distinct basal and luminal subtypes of muscle-invasive bladder cancer with different sensitivities to frontline chemotherapy

Choi W, Porten S, Kim S, Willis D, Plimack ER, Hoffman-Censits J, Roth B, Cheng T, Tran M, Lee IL, Melquist J, Bondaruk J, Majewski T, Zhang S, Pretzsch S, Baggerly K, Siefker-Radtke A, Czerniak B, Dinney CP, McConkey DJ

Cancer Cell. 2014 Feb 10;25(2):152-65

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
European Society for Medical Oncology

Molecular Subtypes of MIBCs

- **Subtypes**:
  - **Basal MIBCs:**
    - Shared biomarkers with basal breast cancers: CD44, KRT5, KRT6, KRT14 and CDH3
    - Characterised by p63 activation, squamous differentiation and more aggressive disease at presentation
  - **Luminal MIBCs:**
    - Contained signature biomarkers for luminal: CD24, FOXA1, GATA3, ERBB2, ERBB3, XBP1 and KRT20
    - Features of PPARγ and oestrogen receptor transcription
    - Enriched with activating *FGFR3* mutations
  - **p53-like MIBCs:**
    - Resistant to MVAC chemotherapy
    - All chemoresistant tumours adopt a p53-like phenotype after therapy

MIBCs: muscle-invasive bladder cancers; PPAR: peroxisome proliferator activator receptor

HER2 as a target in invasive urothelial carcinoma

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Table 2. Frequency of IHC 3+, FISH amplification, and aCGH gain.

	Spanish, *N* (%)	Greek, *N* (%)
FISH		
Normal	57 (80)	90 (96)
Amplified	14 (20)	4 (4)
IHC		
Negative (scored 0, 1+, 2+)	69 (78)	89 (96)
Positive (scored 3+)	19 (22)	4 (4)
aCGH		
Negative	80 (85)	
Positive	14 (15)