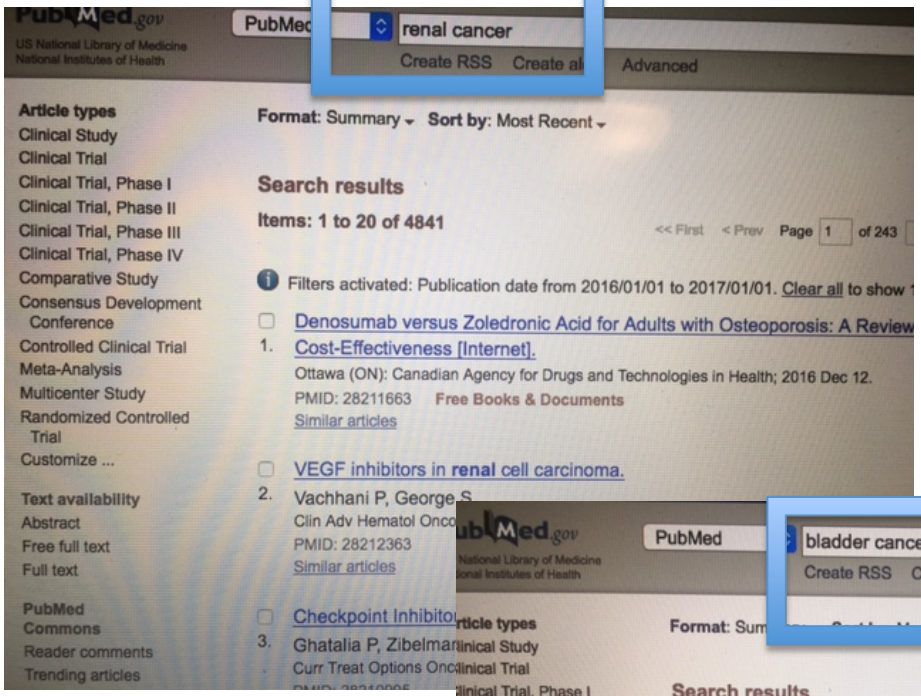
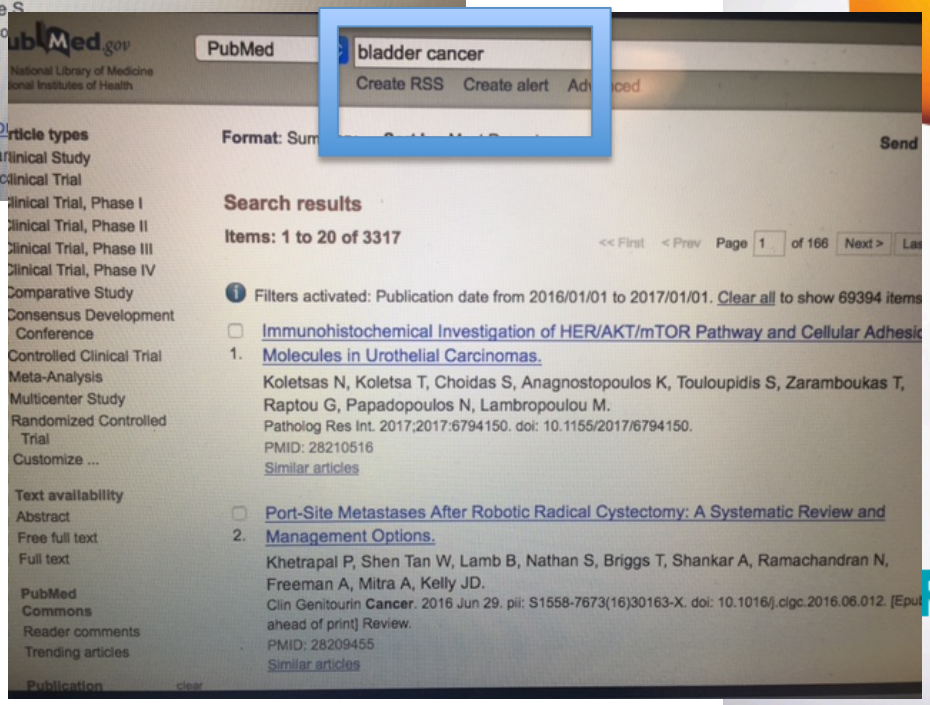
“BEST PAPERS OFF 2016” for Renal cancer & Bladder cancer

ΙΩΑΝΝΗΣ ΒΑΡΚΑΡΑΚΗΣ
ΑΝΑΠΛΗΡΩΤΗΣ ΚΑΘΗΓΗΤΗΣ ΟΥΡΟΛΟΓΙΑΣ
ΕΘΝΙΚΟ & ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ
ΣΙΣΜΑΝΟΓΛΕΙΟ ΝΟΣΟΚΟΜΕΙΟ

Dept. Urology, Athens Medical School, J. Varkarakis

ΔΕΝ ΕΧΩ ΣΥΓΚΡΟΥΣΗ ΣΥΜΦΕΡΟΝΤΩΝ





Dept. Urology, Athens Medical School, J. Varkarakis

Platinum Priority – Kidney Cancer

Editorial by Maria J. Ribal on pp. 91–92 of this issue

Natural History of Renal Angiomyolipoma (AML): Most Patients with Large AMLs >4 cm Can Be Offered Active Surveillance as an Initial Management Strategy

Jaimin R. Bhatt[a,b], Patrick O. Richard[a], Nicole S. Kim[a], Antonio Finelli[a], Karthikeyan Manickavachagam[a], Laura Legere[a], Andrew Evans[c], York Pei[d], Jenna Sykes[e], Kartik Jhaveri[f], Michael A.S. Jewett[a,]*

EAU guidelines recommend **treatment** in:

- large tumors
- women of child-bearing age
- follow-up or access to emergency care is inadequate

A **size threshold for treatment** remains controversial, with previous recommendations suggesting **3–4 cm**.

The 4 cm threshold is **based on a study** by Oesterling et al based on **13 pt**

The true **natural history** may remain **unknown** because **symptomatic cases** are more likely to be identified and **included** in case **series**.

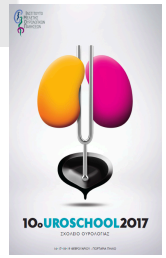
Dept. Urology, Athens Medical School, J. Varkarakis

MATERIALS & METHODS

Radiology record crawler system
(Montage; Montage Healthcare Systems, Philadelphia, USA)

- **2741** patients with renal AML.
- **447** patients with 582 tumors with **>3 abdominal imaging**.
- FU: median **43 mo** (range: 14–144 mo)

Intervention	None	422 (94.4)
	Yes	25 (5.6)
Size of lesion at baseline, cm	≤4	400 (89.5)
	>4	47 (10.5)
Clinical presentation	Incidental	406 (90.8)
	Symptomatic	41 (9.2)



RESULTS

Variable	Category	≤4 cm, *n* (%) (*n* = 400)	>4 cm, *n* (%) (*n* = 47)	Total	*p* value
Age at diagnosis, yr	Median	58.9	52.4	58.1	**0.0057**
	(range)	(18.5–90.3)	(19–89)	(18.5–90.3)	
Gender	Female	319 (79.8)	39 (83)	358 (80.1)	0.7
	Male	81 (20.2)	8 (17)	89 (19.9)	
TSC status	No/unknown	393 (98.2)	37 (78.7)	430 (96.2)	**<0.0001**
	Yes	7 (1.8)	10 (21.3)	17 (3.8)	
Clinical presentation	Incidental	374 (93.4)	32 (68.1)	406 (90.8)	**<0.0001**
	Symptomatic	26 (6.6)	15 (31.9)	41 (9.2)	
Symptom type	Pain	19 (73.1)	10 (66.7)	29 (70.7)	0.73
	Haematuria or bleeding	7 (26.9)	5 (33.3)	12 (29.3)	
Intervention	Yes	7 (1.8)	18 (38)	25 (5.6)	**<0.0001**
	No	393 (98.2)	29 (62)	422 (94.4)	

(**10%**) **Tumors>4cm** more likely

- Younger age
- TSC
- Symptomatic
- intervention

Variable	Estimate	95% CI	*p* value
Baseline estimates:			
≤4 cm†	−0.061	−0.116 to −0.006	0.029
>4 cm	1.921	1.746–2.095	<0.0001
Slope estimates, cm/yr:			
≤4 cm†	0.021	0.015–0.026	<0.0001
>4 cm	0.0017	−0.017 to 0.020	**0.859**

CI = confidence interval.
† Reference group.

No difference in the average growth rate of lesions <4cm vs >4cm

- 91% did not grow or grew slowly (**0.02cm**/y)
- **9%** grew with rate >**0.25cm**/y

Variable	Category	No intervention, *n* (%) (*n* = 422)	Intervention, *n* (%) (*n* = 25)	Total, *n* (%) (*n* = 447)	*p* value
Age at diagnosis, yr	Median	58.1	49	58.1	0.002
	(range)	(18.5–90.3)	(20–66)	(18.5–90.3)	
Gender	Female	336 (79.6)	22 (88)	358 (80.1)	0.44
	Male	86 (20.4)	3 (12)	89 (19.9)	
TSC status	No/not known	411 (97.3)	19 (76)	430 (96.2)	<0.0001
	Yes	11 (2.7)	6 (24)	17 (3.8)	
Clinical presentation	Incidental	394 (93)	12 (48)	406 (90.8)	<0.0001
	Symptomatic	28 (7)	13 (52)	41 (9.2)	
Initial size	≤4 cm	393 (93.1)	7 (28)	400 (89.5)	<0.0001
	>4 cm	29 (6.9)	18 (72)	47 (10.5)	
[illegible]	≤0.25 cm/yr	389 (92)	17 (77)	406 (91.4)	0.03
[illegible]	>0.25 cm/yr	33 (8)	5 (23)	38 (8.6)	

25/447(**5.6%**) had **intervention**

More frequently

- young age
- TSC
- Symptomatic
- >4cm

93% were elective interventions

Dept. Urology, Athens Medical School, J. Varkarakis

RESULTS

SYMPTOMS

In **10%** overall

In 30% if AML>4cm

Most common

hematuria & **pain**

Non TSC **Pain** > hematuria

TSC **Hematuria** > Pain (p=0.16)

Retroperitoneal bleeding

Rare 0.4%

Majority do not have prior Sx

Can happen with RCC as well with same frequency

Intervention 5%

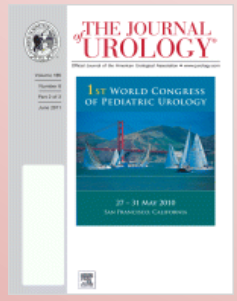
SAE, **RFA**, **mTOR inhibitors**, PNx

TAKE HOME MESSAGE

- Most **sporadic AMLs** are
  - **ASx**
  - do **not grow** or grow **slowly** regardless of initial size.

- Pt with **ASx or mildly Sx AMLs even if >4cm** should be offered initial **AS**

- Pt should be aware of **small risk of progression** especially in fast growing AMLs (**>0.25cm/y**)



Likelihood of Incomplete Kidney Tumor Ablation with Radio Frequency Energy: Degree of Enhancement Matters

Aaron H. Lay, Jeremy Stewart, Noah E. Canvasser, Jeffrey A. Cadeddu* and Jeffrey C. Gahan

From the Department of Urology, University of Texas Southwestern Medical Center, Dallas, Texas

- **Uniform** temperatures **>60C** required my not be reached (**heat sink)**
- **RFA outcomes** associated with
  - Tumor size
  - Clear cell histology

→ Increased failure rates

- **Degree of tumor enhancement**

(change HU from non-contrast to contrast enhanced arterial phase)

→ FAILURE?

MATERIALS & METHODS

RESULTS

- **158** patients RFA ablation
- **Biopsy** confirmed RCC in **81%**

- **7% incomplete ablation**

- **93%** (99 pt) **RCC successful ablation**

Table 4. *Incomplete ablation rates*

	Incomplete Ablation Rate (%)	p Value
Size (cm):		
Less than 3	5.4	0.266
3 or Greater	12.0	
NS:		
Less than 6	8.9	0.411
6 or Greater	4.7	
HU change:		
Less than 60	0	0.005
60 or Greater	14.6	
Cell type:		
Clear cell	5.7	0.697
Nonclear cell	7.8	

Sample?

Table 5. *Multivariate logistic regression analysis of tumor factors predicting incomplete ablation*

Tumor Variable	OR for Incomplete Ablation (95% CI)	p Value
Size	1.06 (0.94–1.17)	
Reference: less than 3 cm		0.341
Enhancement change	1.14 (1.04–1.24)	
Reference: less than 60 HU		0.003
NS	0.96 (0.86–1.06)	
Reference: less than 6		0.470
Cell type	0.99 (0.89–1.10)	
Reference: nonclear cell		0.972

RESULTS

5-year DFS

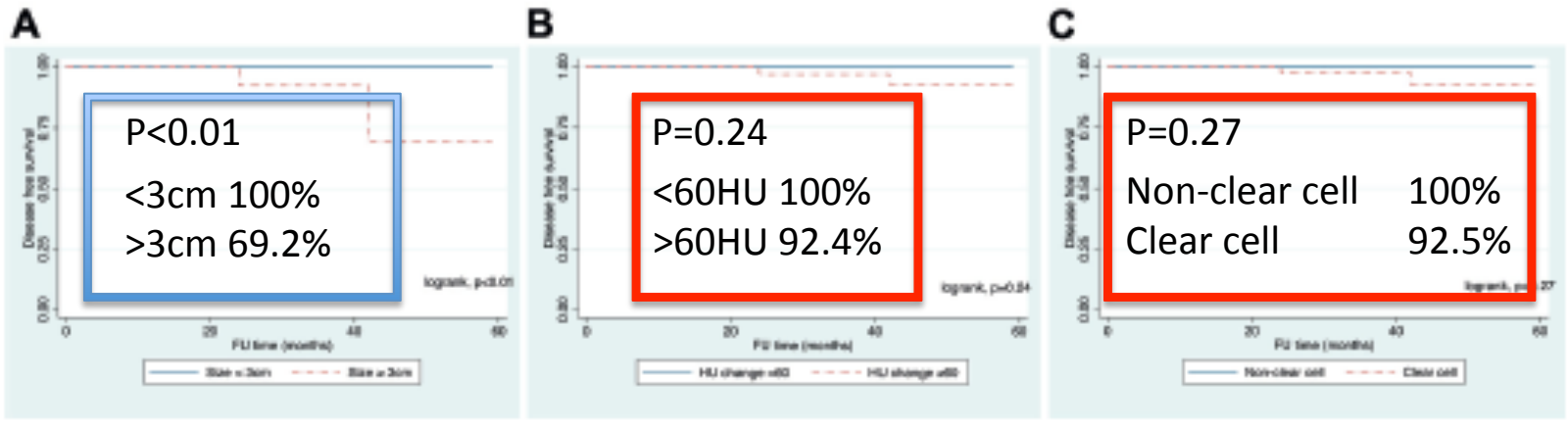


Figure 2. Kaplan-Meier survival curve for DFS stratified by size (*A*), HU change (*B*) and cell type (*C*). *FU*, followup.

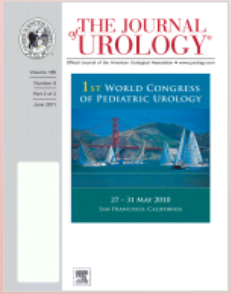
- Disease recurrence **5.4%** (5 pt)
- Median follow up **30 mo**

STUDY LIMITATIONS

- **Retrospective** study.
- **Limited number** of pt.
- **Standard protocol** for contrast use in CT was used
  - **some variation** is expected:
    - ***Degree of enhancement*** *within the tumor depends on*
      - ***timing***
      - ***amount of contrast*** *used*
    - ***Part of tumor measured***
      - ***tumors are heterogeneous*** *and degree of enhancement can vary.*

TAKE HOME MESSAGE

- Tumors with contrast **enhancement >60HU** have **higher incomplete ablation** after **RFA**
- Contrast enhancement **cannot** predict **DFS**
- **Tumor size** >3cm remains a significant risk **factor** for DFS



Positive Surgical Margins Increase Risk of Recurrence after Partial Nephrectomy for High Risk Renal Tumors

Paras H. Shah,* Daniel M. Moreira, Zhamshid Okhunov, Vinay R. Patel, Sameer Chopra, Aria A. Razmaria, Manaf Alom, Arvin K. George, Oksana Yaskiv, Michael J. Schwartz, Mihir Desai, Manish A. Vira, Lee Richstone, Jaime Landman, Arieh L. Shalhav, Inderbir Gill and Louis R. Kavoussi

Heterogeneous behavior of RCC **lesions**

- Low grade & stage → indolent course
- High grade & stage → risk of growth and systemic spread

Residual tumor in the context of PSM **mimics the primary lesion**

Lack of consensus for **clinical relevance of a PSM after PNx**

- **Variability in pathological** characteristics in various studies
- Contemporary studies **lack the statistical power**
  - **High risk** patients with and without PSM
  - **PSM** in high and low risk patients

MATERIALS & METHODS

A retrospective multi-institutional review

- **1240** pt PNx (O/L/R)

- Median **FU 33mo**
- **+sm 7.8%** (97)
  - 2/3 in Low risk pt (71%)
  - **1/3 in High risk** pt (29%)
- **Recurrence 5.6%** (69)
- Median time **19mo**

Table 1. *Baseline patient and disease characteristics*

	Overall		PSM		NSM		p Value
No. pts (%)	1,240	(100)	97	(8)	1,143	(92)	–
Mean pt age (SD)	59.1	(11.9)	59.7	(11.5)	59.0	(11.9)	0.57
No. gender (%):							0.82
M	832	(67)	64	(66)	768	(67)	
F	408	(33)	33	(34)	375	(33)	
Mean cm tumor size (SD)	3.2	(1.7)	3.3	(1.8)	3.2	(1.6)	0.64
No. Fuhrman grade (%):							0.29
I	184	(15)	12	(12)	172	(15)	
II	743	(60)	60	(62)	683	(60)	
III	290	(23)	21	(22)	269	(24)	
IV	23	(2)	4	(4)	19	(2)	
No. tumor histology (%):							0.56
Clear cell	851	(69)	69	(71)	782	(69)	
Papillary	321	(26)	21	(22)	300	(26)	
Chromophobe	50	(4)	5	(5)	45	(4)	
Other	18	(1)	2	(2)	16	(1)	
No. tumor stage (%):							0.16
pT1	1,145	(92)	86	(89)	1,059	(93)	
pT2	32	(3)	2	(2)	30	(3)	
pT3a	63	(5)	9	(9)	54	(5)	
No. tumor focality (%):							0.61
						8)	
						2)	
							0.95
						1)	
						7)	
Bilat	25	(2)	1	(1)	24	(2)	

PSM was unrelated to
tumor size, stage, grade, histology, focality (all p > 0.05).

Dept. Urology, Athens Medical School, J. Varkarakis

univariable

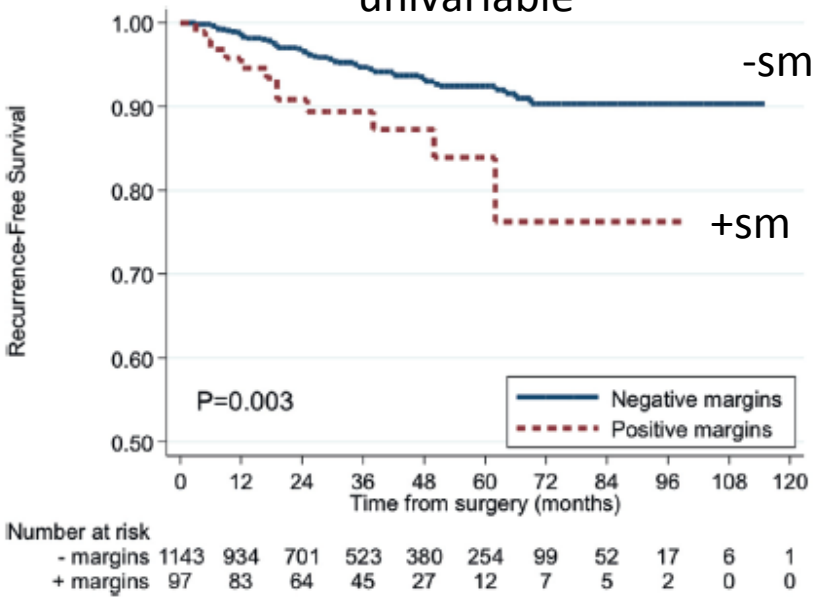


Figure 1. RFS by margin status

RESULTS

Table 2. *Sites of disease recurrence*

	No. PSMs	No. NSMs
Local 61%	8	34
Distant: 39%		
Lungs	2	9
Retroperitoneal lymph nodes	3	5
Bones	1	3
Adrenal	1	2
Liver	1	2
Omentum	0	1
Peritoneum	1	1
Gallbladder	0	1

- A **+margin** was associated with an **increased risk of relapse** on multivariable analysis (HR 2.08, 95% CI 1.09e 3.97, p. 0.03) **but not with site of recurrence**.

increased risk of **local** as well as **metastatic** relapse.

RESULTS

Subgroups in which PSM was a predictor of recurrence

Group	HR (95%CI)	N	Events
pT1	1.31 (0.52-3.31)	1145	51
pT2-3a	5.92 (2.28-15.36)	95	18
Clear cell	2.53 (1.27-5.04)	851	55
Non-clear cell	2 (0.45-8.95)	389	14
Grade 1-2	1.37 (0.48-3.87)	927	36
Grade 3-4	4.61 (2.08-10.24)	313	33
All comers	2.49 (1.33-4.64)	1240	69

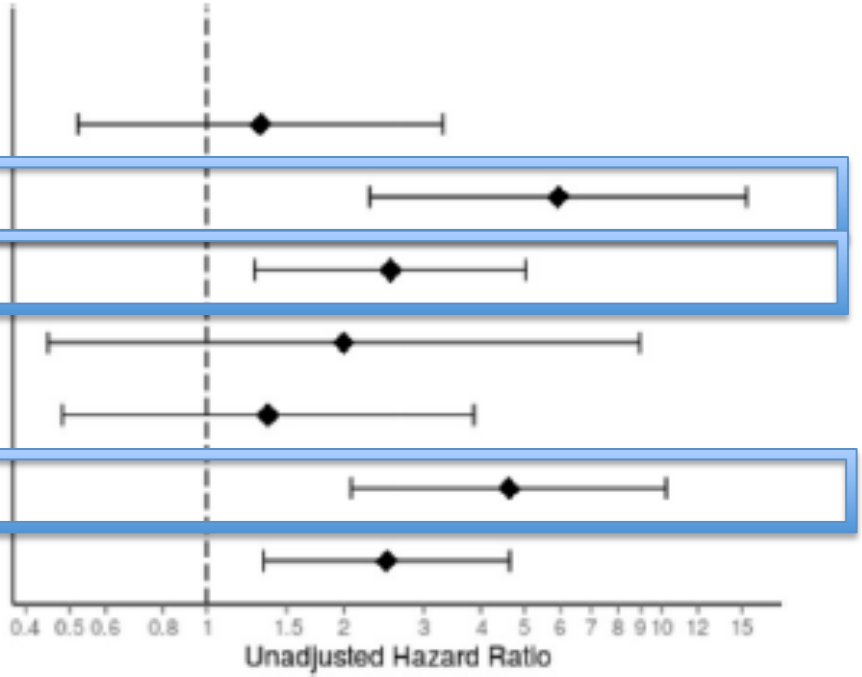
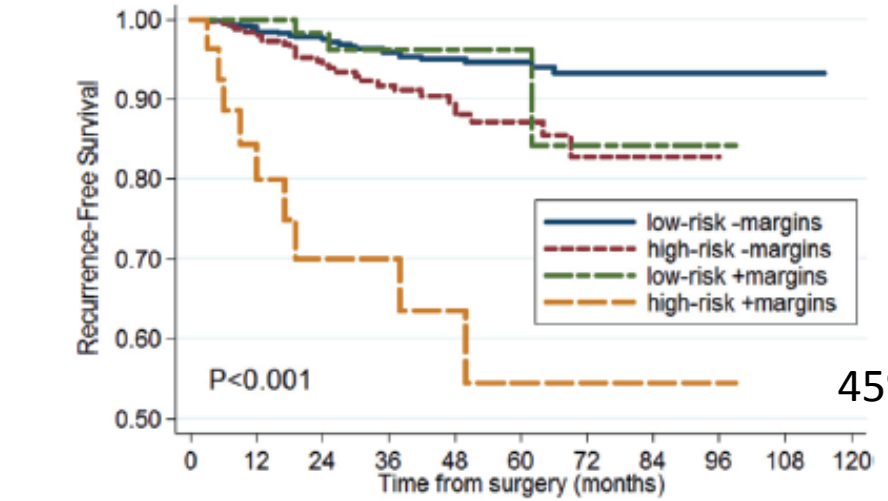


Figure 2. Association of PSM with recurrence by subgroups

Median time to recurrence was **19 months** for high risk cases.

RESULTS



Number at risk

LR-NSM	801	658	485	369	268	185	75	41	15	6	1
HR-NSM	342	276	216	154	112	69	24	11	2	0	0
LR-PSM	69	63	50	34	20	9	5	3	1	0	0
HR-PSM	28	20	14	11	7	3	2	2	1	0	0

Figure 3. RFS by margin status and risk group. Low risk (*LR*)—pT1 and Fuhrman grade I-II. High risk (*HR*)—pT2-3 or Fuhrman grade III-IV.

45% in 5 years

- a **positive surgical margin** was significantly associated with **a higher risk of recurrence** in cases considered **high risk** (p < **0.001**) **but not low risk** (p. **0.647**).

STUDY LIMITATIONS

- **Retrospective** nature
- **Heterogeneity**
  - Surgical technique
  - Pt selection
  - Follow up
- **Incomplete information**
  - Nephrometry score
  - **Intraoperative biopsy**
  - **Management of intraoperative biopsy**
  - **Depth and magnitude of PSM**
- Not powered for analysis of **recurrence location**

TAKE HOME MESSAGE

- **PSM associated** with **local and metastatic** tumor **recurrence** after PN
- This relationship observed **specifically** for **tumors with high risk features**
- **RFS** was **similar** among **low risk** features **regardless of margin** status
- In complex **cT2** maybe **RNx better ?**

Kidney Cancer

Prediction of Pulmonary Metastasis in Renal Cell Carcinoma Patients with Indeterminate Pulmonary Nodules

Mehrad Adibi[a], Patrick A. Kenney[a], Arun Z. Thomas[a], Leonardo D. Borregales[a], Graciela M. Nogueras-González[b], Xuemei Wang[b], Catherine E. Devine[c], Jose A. Karam[a], Christopher G. Wood[a,]*

[a]Department of Urology, University of Texas MD Anderson Cancer Center, Houston, TX, USA; [b]Department of Biostatistics, University of Texas MD Anderson Cancer Center, Houston, TX, USA; [c]Department of Radiology, University of Texas MD Anderson Cancer Center, Houston, TX, USA

- Most common site of **metastasis** in pt with RCC is the **lung** (45-75%)
- **Indeterminate pulmonary nodules** (**IPN**): 1mm-2cm round pulmonary opacity that may **be benign or malignant**
- Determine **predictors of progression of an IPN to pulmonary metastasis** in pt with localized or locally advanced RCC treated with nephrectomy.

Table 1 – Patients characteristics

	All patients		Pulmonary metastasis development				p value
			No		Yes		
Age at surgery							0.7
N	251		179		72		
Median (IQR)	64.1 (54.1–71.3)		64.3 (53.9–71.5)		63.9 (54.3–69.8)		
BMI							0.5
N	251		179		72		
Median (IQR)	28.8 (25.3–38.8)		28.9 (25.4–33.0)		28.7 (24.7–32.4)		
Largest tumor diameter (cm)							<0.001
N	251		179		72		
Median (IQR)	8.0 (5.2–10.4)		7.3 (4.6–9.5)		9.5 (7.0–11.2)		
Creatinine							0.002
N	250		179		71		
Median (IQR)	1.1(0.9–1.3)		1 (0.9–1.2)		1.2 (1.0–1.4)		
Albumin							0.5
N	187		136		51		
Median (IQR)	4.2 (4.0–4.5)		4.2 (4.0–4.5)		4.3 (3.8–4.6)		
LDH							0.08
N	223		158		65		
Median (IQR)	456.0 (389–553)		471.5 (399–557)		426 (377–508)		
Hemoglobin							0.002
N	249		179		70		
Median (IQR)	13.3 (12.1–14.2)		13.4 (12.7–14.5)		12.9 (11.4–13.9)		
Calcium							0.2
N	198		143		55		
Median (IQR)	9.4 (9.1–9.7)		9.4 (9.1–9.8)		9.5 (9.2–9.7)		
	N	%	*N*	%	*N*	%	
Sexr							0.06
Male	159	63	107	59	52	72	
Female	92	37	72	41	20	28	
Race							0.9
White	202	81	144	80	58	81	
Other	49	19	35	20	14	19	
ASA							0.14
2	61	24	48	27	13	18	
>2	190	76	131	73	59	82	
Smoker							0.8
No	106	42	75	42	31	43	
Yes	145	58	104	58	41	57	
ECOG							0.002
0	76	30	65	36	11	15	
1	165	66	106	59	59	82	
>1	10	4	8	5	2	3	
Charlson score (not age-adjusted)							0.08
0–2	118		92	51	26	36	
3–5	114		73	41	41	57	
≥6	19		14	8	5	7	
Symptomatic presentation							<0.001
No	112	45	93	52	19	26	
Yes	139	55	86	48	53	74	
Respiratory symptoms							0.002
	233	93	172	96	61	85	
	18	7	7	4	11	15	

American Society of Anesthesiologists; IQR = interquartile range; LDH = lactate dehydrogenase.

MATERIALS & METHODS

- **251 pt** with **IPM** in prop CT
- FU at least **3years**
  - (Q3-6mt CT or CXR)

- **IPM <2cm**
- Considered **Pulmonary M when**
  - Increase of size
  - Increase of number
  - Histological diagnosis

RESULTS

IPN developed in **M+** **29%** (FU 35.3mo)
IPN **not** develop in M+ **71%** (FU 38mo)

Dept. Urology, Athens Medical School, J. Varkarakis

RESULTS

Table 2 – Pathological characteristics

	All patients		Pulmonary metastasis development				p value
			No		Yes		
	N	%	N	%	N	%	
Pathologic T stage							<0.001
pT1/T2	95	38	86	48	9	13	
pT3/ T4	156	62	93	52	63	87	
Pathologic N stage							<0.001
p N0	112	45	68	38	44	61	
p N1	13	5	6	3	7	10	
p Nx	126	50	105	59	21	29	
Fuhrman grade							<0.001
G1-G2	65	26	62	36	3	4	
G3-G4	181	74	112	64	69	96	
Histology							0.03
Clear-cell	201	80	137	77	64	89	
Non clear-cell	50	20	42	23	8	11	
LVI							0.003
No	220	88	164	92	56	78	
Yes	31	12	15	8	16	22	
Sarcomatoid							<0.001
No	235	94	174	97.2	61	85	
Yes	16	6	5	2.8	11	15	
Venous tumor thrombus							<0.001
None	154	61	128	72	26	36	
Renal vein	48	19	33	18	15	21	
IVC below diaphragm	44	18	17	9	27	38	
IVC above diaphragm	5	2	1	1	4	5	
Fat invasion							<0.001
No	108	43	95	53	13	18	
Yes	143	57	84	47	59	82	

IVC = intravenous cholangiogram; LVI = lymphovascular invasion.

T

N

G

LVI

Sarc

IVC

pT3a

RESULTS

Table 3 – Radiologic characteristics on chest computed tomography

	All patients		Pulmonary metastasis development				p value
			No		Yes		
Number of nodules on CT							<0.001
N	250		178		72		
Median (IQR)	3.0 (2–6)		3 (2–5)		4 (3–7)		
Size of nodules on CT (mm)							<0.001
N	250		178		72		
Median (IQR)	4.0 (3–6)		4 (3–5)		5 (3–7)		
D from chest CT to surgery							0.4
N	250		178		72		
Median (IQR)	18.0 (8–29)		18 (8–29)		15 (7.5–27)		
Days from CXR to surgery							0.7
N	227		160		67		
Median (IQR)	15.0 (8–26)		15 (7.5–26)		17 (8–26)		
	N	%	*N*	%	*N*	%	
Preoperative CXR							0.4
No	24	10	19	11	5	7	
Yes	227	90	160	89	67	93	
Metastasis at same location as largest Pulmonary nodule							0.5
No	37	51	2	100	35	49	
Yes	36	49	0	0	36	51	
Location of largest nodule							0.6
LLL	48	19	37	21	11	14	
LUL	51	21	34	19	17	24	
RLL	58	23	38	21	20	28	
RML	28	11	21	12	7	10	
RUL	65	26	48	27	17	24	
Nodule calcification							0.6
No	150	60	105	59	45	63	
Yes	100	40	73	41	27	37	
Pleural effusion							0.5
No	239	96	171	96	68	94	
Yes	11	4	7	4	4	6	

C = computed tomography; XR = chest X-ray; IQR = interquartile range.

Table 4 – Univariable and multivariable analysis for lung metastasis-free survival

	Univariable analysis			Multivariable analysis		
	HR	95% CI for HR	*p* value	HR	95% CI for HR	*p* value
Largest tumor diameter (cm)	1.12	(1.06–1.18)	<0.001	1.01	(0.94–1.09)	0.8
Number of nodules on CT	1.15	(1.08–1.23)	<0.001	1.11	(1.03–1.19)	0.004
Size of nodules on CT (mm)	1.27	(1.16–1.39)	<0.001	1.17	(1.05–1.30)	0.006
Smoker						
No	Ref			Ref		
Yes	1.01	(0.64–1.62)	0.9	0.82	(0.50–1.35)	0.4
Charlson score (not age-adjusted)						
0–2	Ref					
3-5	1.80	(1.10–2.95)	0.02			
≥6	1.67	(0.64–4.36)	0.3			
ECOG						
0	Ref					
1	3.04	(1.59–5.79)	0.001			
>1	1.94	(0.43–8.81)	0.4			
T stage						
T1/T2	Ref					
T3/T4	5.45	(2.71–10.98)	<0.001			
N stage						
N0	Ref			Ref		
N1	2.21	(0.99–4.96)	0.053	1.38	(0.60–3.21)	0.5
Nx	0.35	(0.21–0.58)	<0.001	0.57	(0.32–1.02)	0.057
Fuhrman grade						
G1–G2	Ref			Ref		
G3–G4	9.71	(3.06–30.85)	<0.001	4.88	(1.48–16.10)	0.009
Histology						
Clear-cell	Ref					
Non clear-cell	0.49	(0.23–1.01)	0.054			
LVI						
No	Ref					
Yes	3.09	(1.77–5.40)	<0.001			
Sarcomatoid						
No	Ref			Ref		
Yes	4.59	(2.28–8.30)	<0.001	2.23	(1.06–4.70)	0.03
Venous tumor thrombus						
None	Ref	(1.02–3.65)	0.043	Ref	(0.49–1.92)	0.9
Renal vein	1.93	(3.48–10.37)	<0.001	0.97	(1.17–4.15)	0.01
IVC below diaphragm	6.01	(3.23–27.17)	<0.001	2.20	(0.68–8.53)	0.2
IVC above diaphragm	9.37	(1.02–3.65)	0.043	2.40	(0.49–1.92)	0.9
Fat invasion						
No	Ref					
Yes	4.59	(2.51–8.39)	<0.001	2.05	1.01–4.14	0.046
Location of largest nodule						
LLL	Ref					
[illegible]	1.53	(0.71–3.26)	0.3			
[illegible]	1.53	(0.73–3.19)	0.3			
[illegible]	1.10	(0.43–2.85)	0.8			
[illegible]	1.21	(0.57–2.59)	0.6			
[illegible]fusion						
[illegible]	Ref					
[illegible]	1.29	(0.47–3.54)	0.6			

RESULTS

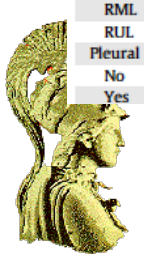
LMFS
@ 3y 71%
@5y 65%

Table 5 – Univariable and multivariable analysis for disease-specific survival

	Univariable analysis			Multivariable analysis		
	HR	95% CI for HR	*p* value	HR	95% CI for HR	*p* value
Largest tumor diameter (cm)	1.15	(1.07–1.25)	<0.001	1.03	(0.90–1.16)	0.7
Number of nodules on CT	1.17	(1.08–1.26)	<0.001	1.09	(0.99–1.19)	0.07
Size of nodules on CT (mm)	1.27	(1.13–1.43)	<0.001	1.14	(0.99–1.32)	0.07
Smoker						
No	Ref			Ref		
Yes	1.47	(0.75–2.87)	0.3	1.37	(0.67–2.81)	0.4
Charlson score (not age–adjusted)						
0–2	Ref					
3–5	2.08	(1.03–4.20)	0.04			
≥6	4.05	(1.29–12.71)	0.02			
ECOG						
0	Ref					
1	5.90	(1.81–19.28)	0.003			
>1	13.58	(2.70–68.21)	0.002			
T stage						
T1/T2	Ref					
T3/T4	24.69	(3.39–180.06)	0.002			
N stage						
N0	Ref			Ref		
N1	2.87	(1.08–7.63)	0.03	1.98	(0.67–5.88)	0.2
Nx	0.48	(0.23–0.97)	0.04	1.23	(0.56–2.69)	0.6
Fuhrman grade						
G1–G2	Ref			Ref		
G3–G4	12.84	(1.76–93.61)	0.01	4.53	(0.59–34.84)	0.15
Histology						
Clear–cell	Ref					
Non clear–cell	1.19	(0.54–2.59)	0.7			
LVI						
No	Ref					
Yes	5.69	(2.97–10.92)	<0.001			
Sarcomatoid						
No	Ref			Ref		
Yes	2.08	(0.74–5.88)	0.16	0.76	(0.24–2.46)	0.6
Venous tumor thrombus						
None	Ref			Ref		
Renal vein	1.48	(0.56–3.96)	0.4	0.56	(0.20–1.54)	0.3
IVC below diaphragm	6.30	(3.00–13.21)	<0.001	1.65	(0.71–3.86)	0.2
IVC above diaphragm	9.29	(2.60–33.23)	0.001	2.71	(0.60–12.15)	0.2
Fat invasion						
None	Ref			Ref		
Yes	32.14	(4.41–234.45)	0.001	19.14	(2.46–148.91)	0.005
Location of largest nodule						
LLL	Ref					
LUL	1.15	(0.51–2.63)	0.7			
RLL	0.53	(0.20–1.38)	0.2			
RML	0.32	(0.07–1.47)	0.14			
RUL	0.44	(0.16–1.21)	0.11			
Pleural effusion						
No	Ref					
Yes	2.39	(0.85–6.75)	0.09			

RESULTS

DSS
@3y 86%
@5y 79%



Dept. Urology, Athens Medical School, J. Varkarakis

Nomogram for LMFS

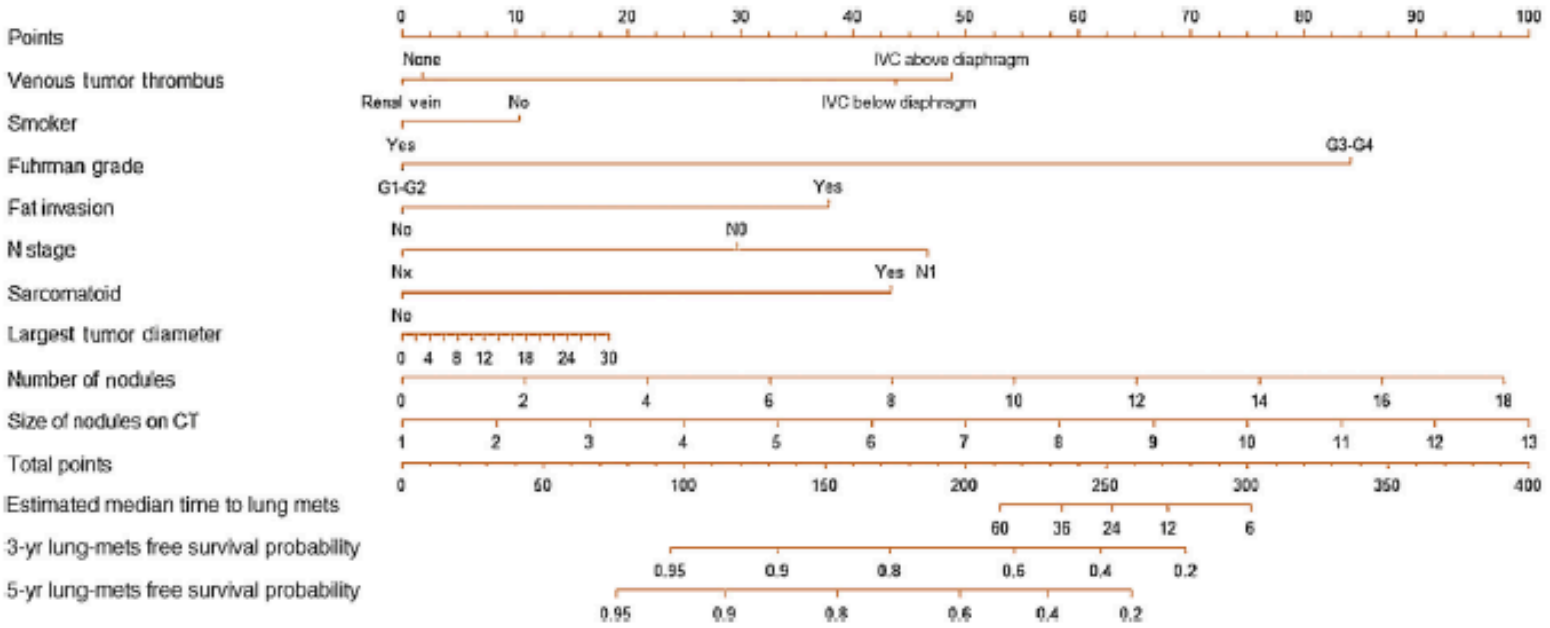


Fig. 1 – Nomogram for lung metastasis-free survival at 3 yr and 5 yr, as well as the median lung metastasis-free survival based on the fitted Cox model. CT = computed tomography; IVC = intravenous cholangiogram.

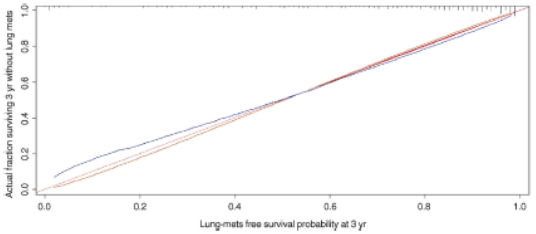


Fig. 2 – Calibration of the nomogram.

Calibration plot of the **predicted probability** of LMFS @ 3y **vs actual** % of pt who survived 3y without LM

Dept. Urology, Athens Medical School, J. Varkarakis

STUDY LIMITATIONS

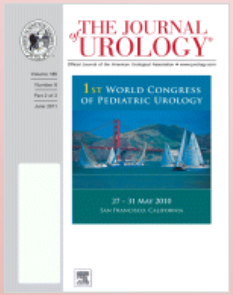
- Retrospective study
- Single institution
- Selection bias
- **NOT standard** preoperative and postoperative **imaging strategy**
- **Heterogeneous treatment strategy** after diagnosis of pulmonary M may change **DSS**

TAKE HOME MESSAGE

IPN have a higher probability of becoming M+ in pt with

- high T stage
- high N stage
- high Grade
- thrombi
- Presence of fat invasion
- Presence of LVI
- **Presence of more and larger nodules in preop CT**

Although this knowledge will **not change clinical management** **Better risk stratification** will change **FU timing** and influence **adjuvant** TX strategies.



Resection of the Intramural Portion of the Distal Ureter during Transurethral Resection of Bladder Tumors: Predictive Factors for Secondary Stenosis and Development of Upper Urinary Tract Recurrence

Oscar Rodriguez Faba,* J. M. Gaya, Alberto Breda, Pablo Juarez del Dago, Francesca Pisano, Daniel Salas and Juan Palou

From the Department of Urology, Fundació Puigvert, Barcelona, Spain

- Tumor in the **IMPDU** is **unusual** (finding of tumor in UO during TURBT)
- Complete TURBT (wide **resection of the UO)**
- Potentially higher risk of
  - **Ureteral scarring/stricture**
  - **UTUC recurrence** (reflux?)
- **Predictive factors** for development of
  - **Ureteral scarring/stricture**
  - **UTUC recurrence** (reflux?)

MATERIALS & METHODS

- Retrospective analysis: 2,317 TURBT pt
- **112 pt** with tumors of the **IMPDU**
- Complete TURBT with wide **resection of UO**
- **Double-J catheter** for 15d:
  - extensive **resection of the trigone**
  - **macroscopic tumor remaining** in the distal ureter
- All cases **BCG**
- FU
  - **U/S 1 mo** after.
  - If hydro noted **CTU**
  - **CTU @ 3 mt and Q6mt**
- Stricture if intervention needed

Dept. Urology, Athens Medical School, J. Varkarakis

RESULTS

- **4.83%** (112pt) resection of **UO**
  - Ta in 64% of cases
  - T1 in 27.7%
  - CIS in 17%
- **31% Double-J catheter** (36 pt)
- **Double J** did not influence
  - **ureteral stenosis**
  - **recurrent UTUC**
- Distal ureteral **stenosis in 11.6%** at a median of **47 days**
- **UTUC developed in 15.2%** (22mt FU)
  - **Distal** ureter in 65.4%
  - Invasive or high grade 59%-NUx

RESULTS

Recurrent Tumor association with Ureteral Stenosis and **UTUC**

- 42% were recurrent
- SS differences between **primary and recurrent tumors** with respect to the incidence of:
  - ✓ symptoms at diagnosis (60% vs 26%, p <0.001),
  - ✓ **development of ureteral stenosis** (4.6% vs **21.3%**, p . 0.007)
  - ✓ **incidence of UTUC** (4.6% vs **29.8%**, p <0.001).

Treatment of 13 patients with ureteral stenosis:

- de-obstructive **TURBT** in 6 (**46%**),
- ureteral **reimplantation** in 5 (**38%**)
- **balloon** dilation in 2 (**15%**)

RESULTS

Backward stepwise univariate and multivariate Cox regression models of ureteral stenosis and recurrent UTUC

	Ureteral Stenosis				Recurrent UTUC			
	Crude HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value	Crude HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
Age	0.957 (0.916–1.001)	0.055	–	–			–	–
Sex								
Female (referent)	1		–	–	1		–	–
Male	0.741 (0.198–3.519)	0.741	–		0.523 (0.163–1.682)	0.001		
Associated bladder CIS:			–	–			–	–
No (referent)	1				1			
Yes	1.756 (0.490–6.288)	0.387			6.000 (1.996–11.034)	0.001		
IMPDU stage:							–	–
Ta, Tis (referent)	1		1		1			
T1	6.870 (1.997–11.641)	0.002	8.525 (1.257–15.252)	0.005	4.922 (1.664–7.732)	0.004		
IMPDU 2004 grade:			–	–			–	–
Low (referent)	1				1			
High	1.191 (0.373–3.809)	0.469			10.000 (2.159–26.250)	0.003		
Associated IMPDU CIS:			–	–				
No (referent)	1				1		1	
Yes	5.670 (1.646–10.528)	0.006			7.501 (5.825–9.250)	0.001	6.850 (4.202–8.253)	0.006
Treatment:	–	–	–	–			–	–
Mitomycin (referent)					1			
BCG					2.464 (0.525–11.596)	0.300		

	UO stenosis		UTUC	
	univariate	multivariate	univariate	multivariate
Recurrent tumors	0.013	0.025	0.001	0.003
Tumor Size>1.5cm	0.001	0.023	0.017	
T1 bladder & IMDU	0.002	0.005	0.001	0.001
Cis IMDU	0.006		0.001	0.006

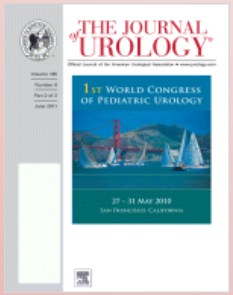
Dept. Urology, Athens Medical School, J. Varkarakis

STUDY LIMITATIONS

- **Retrospective** study
- **Small number** of pt with **stenosis & UTUC** recurrence
- Stent placement only when **extended resection** – *selection bias*
- **Not able to evaluate vesicoureteral reflux** and therefore not possible to associate recurrent UTUC with reflux or primary multifocal disease

TAKE HOME MESSAGE

- **Tumor at the UO** occurs with at **4.8%** of TURBTs
- After **complete Resection of the UO** after a mean FU 56mo:
  - **Stenosis** occurred at **11.6%**
  - **UTUC** occurred **15.2%**
- On **multivariate** analysis
  - Tumor **size >1.5cm** and **T1** stage were factors for **stenosis**
  - **T1** in the bladder and **CIS i**n the IMPDU were factors **for UTUC recurrence**
- **Double J stent** did **not influence** the occurrence or not of **stenosis**



The Timing of Radical Cystectomy for bacillus Calmette-Guérin Failure: Comparison of Outcomes and Risk Factors for Prognosis

Christopher R. Haas,* LaMont J. Barlow, Gina M. Badalato, G. Joel DeCastro, Mitchell C. Benson and James M. McKiernan

From the Herbert Irving Cancer Center and Department of Urology, College of Physicians and Surgeons, Columbia University, New York, New York

- **Immediate RC** is considered the **gold standard** after BCG failure
- **Salvage IVT** in patients who want to maintain their bladder
- **Early RC** after **BCG fails** vs. **delayed RC** after **salvage IVT fails**

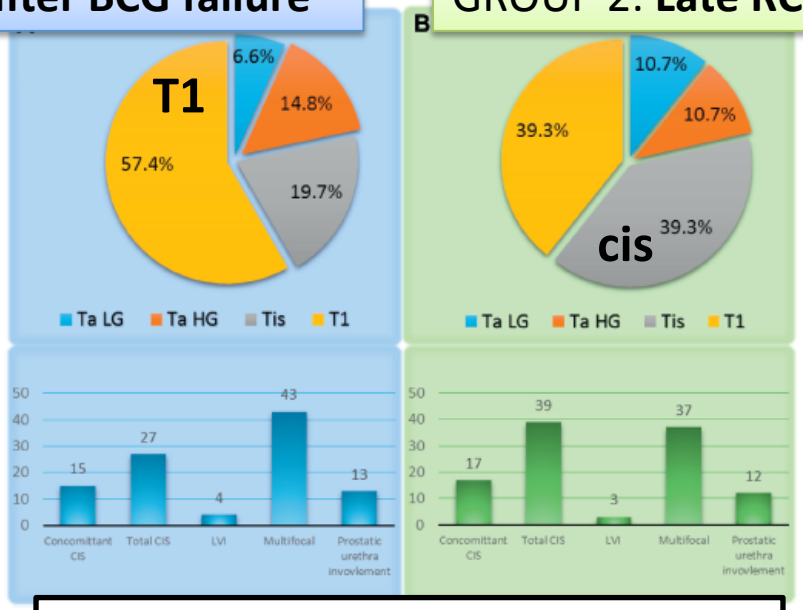
MATERIALS & METHODS

GROUP 1: **Early RCx after BCG failure**

61 pt

GROUP 2: **Late RCx after salvage IVT**

56 pt



Path report of last TURB before RCB

Dept. Urology, Athens Medical School, J. Varkarakis

10o UROSCHOOL 2017

RESULTS

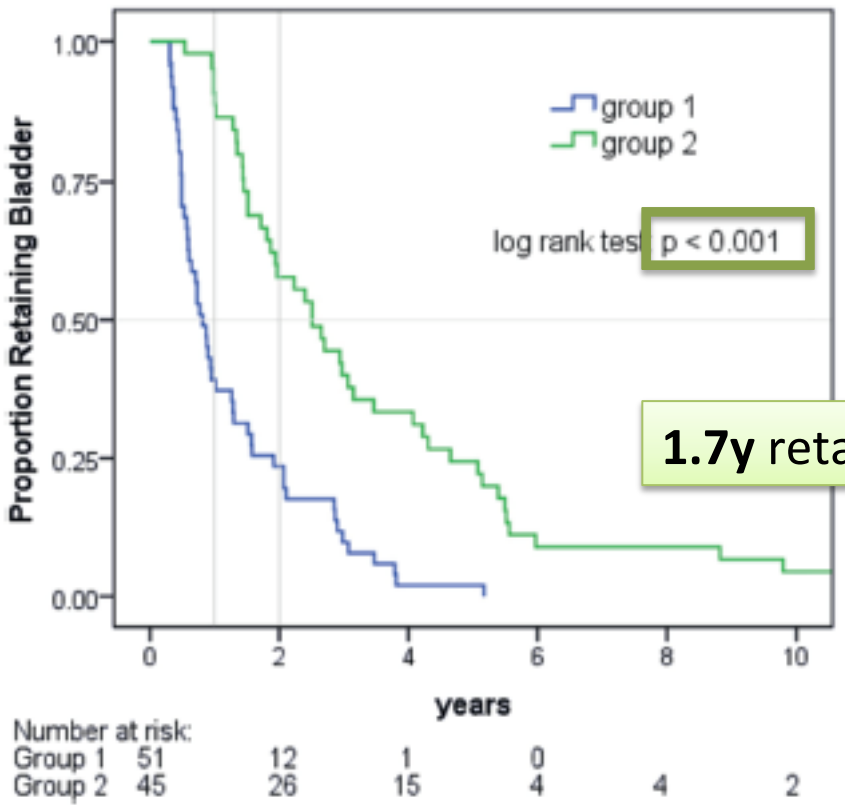


Figure 2. Kaplan-Meier curves of bladder retention in groups 1 and 2.

Median **time** from diagnosis prompting for **BCG to RCx**

- 0.81years in group A
- 2.51 years in group B

1.7y retained their bladder **more** in group B

Group B **Underestimated**

37 pt NOT included

Did not require RCx after salvage IVT (for 5.7years)

RESULTS

Table 1. *Final pathology results at RC and cohort followup characteristics after RC*

	No. Group 1 (%)	No. Group 2 (%)	Total No. (%)
Overall	61	56	117
Stage:			
T0	7 (11)	2 (4)	9 (7.7)
Ta	10 (16)	10 (18)	20 (17.1)
Tis	15 (25)	26 (46)	41 (35.0)
T1	16 (28)	7 (13)	23 (19.7)
T2 or greater:	13 (21)	11 (20)	24 (20.5)
T2	5 (8)	4 (7)	[illegible]
T3	5 (8)	4 (7)	9 (7.7)
T4a	3 (5)	3 (5)	6 (5.1)
Lymph node status:			
Any	8 (13)	4 (7)	12 (10.3)
Nx	3 (5)	7 (13)	10 (8.5)
N0	50 (82)	45 (80)	95 (81.2)
N1	3 (5)	0 (0)	3 (2.6)
N2	5 (8)	3 (5)	8 (7.7)
N3	0	1 (2)	1 (0.09)
Present:			
CIS	45 (74)	51 (91)	96 (82.1)
LVI	10 (16)	11 (20)	21 (17.9)
Post-RC followup:			
Urinary tract urothelial cell Ca recurrence	7 (11)	11 (20)	18 (15.4)
Urothelial cell Ca metastasis	13 (21)	12 (21)	25 (21.3)
Local +/or metastatic recurrence	15 (24)	17 (30)	32 (27.3)
Alive	33 (54)	26 (46)	59 (50.4)
Dead of disease	13 (21)	12 (21)	25 (21.4)
Dead of other cause	15 (25)	18 (32)	33 (28.2)

Predictors of **upstaging**

Table 2. *Univariate and multivariate logistic regression analysis of up-staging to muscle invasion or greater on final pathology evaluation*

	Univariable			Multivariable		
	OR (95% CI)		p Value	OR (95% CI)		p Value
Binary variables						
Group 2	0.82	(0.37–2.22)	0.823	3.02	(0.74–12.32)	0.124
Female gender	1.25	(0.46–3.40)	0.658	—		—
Initial:						
T1	2.44	(0.88–6.7)	0.084	—		—
CIS	4.23	(1.89–13.89)	0.017	—		—
T1 after 1st BCG	4.89	(1.55–15.42)	0.007	—		—
Ever:						
Ta low grade/ multifocal	0		0.998	—		—
Concomitant CIS	2.48	(0.94–6.54)	0.066	—		—
LVI	22.75	(4.42–117)	<0.001	20.9	(3.53–124.1)	0.001
Prostatic urethra	1.39	(0.55–3.56)	0.489	—		—
Up-staged to T1	1.93	(0.70–5.27)	0.203	—		—
Continuous variables						
Age	1.05	(0.99–1.11)	0.128	1.09	(1.02–1.17)	0.015
Yrs from 1st BCG-RC	0.86	(0.65–1.14)	0.291	—		—
No. IVTs	0.82	(0.56–1.19)	0.294	—		—
% TUR:						
T1	1.02	(1.01–1.04)	0.003	1.040	(1.02–1.07)	0.001
CIS	1.01	(0.99–1.03)	0.203	1.026	(1.00–1.05)	0.034
Multifocal	0.99	(0.98–1.01)	0.335	—		—

- LVI most strongly predicted muscle invasion
- **8 /10** pt with at least 1 TUR specimen with LVI **progressed** to pT2 or greater at RC

RESULTS

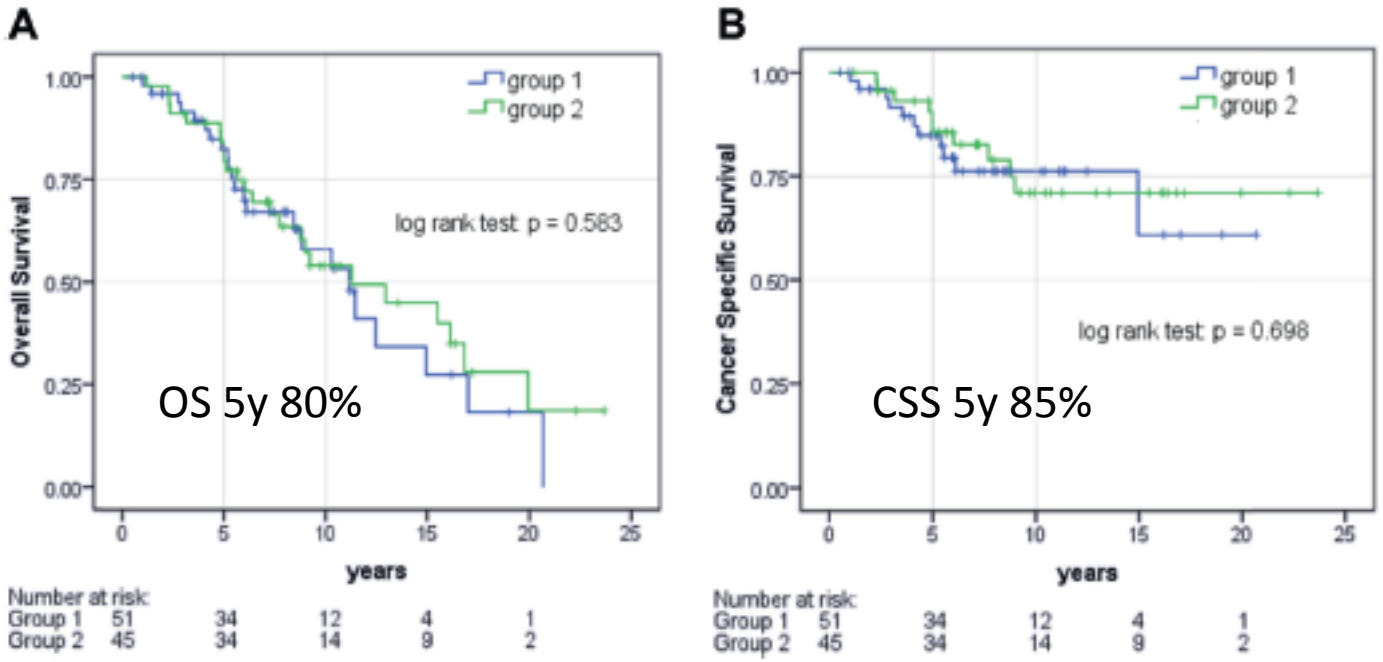


Figure 3. Kaplan-Meier analysis of OS (*A*) and CSS (*B*) in groups 1 and 2 with time from first diagnosis prompting BCG induction

Median FU after RCx

- Group A 4.68y
- Group B 5.14y

After RC bladder cancer **recurred** in 32 patients,

- 15 in group 1
- 17 in group 2.

Dept. Urology, Athens Medical School, J. Varkarakis

RESULTS

Significant predictors of death

Table 3. *Univariate and multivariate Cox regression analysis of OS and CSS*

	Univariate		Multivariate OS		Multivariate CSS	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Binary:						
Group 2	1.26 (0.75–2.12)	0.379	1.08 (0.60–1.92)	0.808	0.87 (0.36–2.09)	0.758
Female gender	0.62 (0.32–1.24)	0.117	—	—	—	—
Initial T1	0.70 (0.37–1.33)	0.277	—	—	—	—
T1 after 1st BCG	1.27 (0.75–2.16)	0.369	—	—	—	—
Ta low grade/multifocal ever	1.12 (0.57–2.24)	0.735	—	—	—	—
Concomitant CIS ever	1.33 (0.78–2.25)	0.297	—	—	—	—
Up-staged to cT1 after IVT	1.77 (0.96–3.21)	0.061	1.88 (1.01–3.50)	0.045	2.64 (1.09–6.39)	0.032
LVI ever	2.01 (0.94–4.31)	0.071	2.58 (1.14–5.84)	0.023	8.26 (3.11–21.9)	<0.001
Prostatic urethra ever	1.69 (0.99–2.87)	0.055	1.95 (1.07–3.54)	0.029	4.29 (1.78–10.3)	0.001
Continuous:						
Age	1.05 (1.01–1.08)	0.007	1.03 (0.99–1.07)	0.119	1.00 (0.96–1.04)	0.962
Yrs from 1st BCG-RC	1.00 (0.90–1.13)	0.919	—	—		
No. IVTs	1.04 (0.85–1.26)	0.723	—	—		
% TUR T1	1.00 (0.99–1.01)	0.685	—	—		
% TUR CIS	1.01 (0.99–1.02)	0.113	—	—		

TAKE HOME MESSAGE

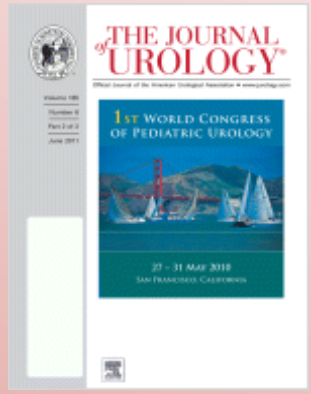
Patients that select to defer RCx and do further IVT after they fail BCG, have **similar OS and CSS while keeping** their **bladder** for **longer.**

Risk factors of poor prognosis in **this population** include

- repetitive instances of **cT1 and CIS**,
- upstaging to cT1
- **prostatic urethra** involvement.
- **LVI** on any TUR specimen (very poor prognosticator)

(8/10 pt had MIBC at RC & 7/10 died of BC)

2 or more of these risk factors should prompt serious consideration of **abandoning further IVT** in favor of RC.



A Retrospective Analysis of the Effect on Survival of Time from Diagnosis to Neoadjuvant Chemotherapy to Cystectomy for Muscle Invasive Bladder Cancer

Jong Chul Park,* Nilay M. Gandhi,* Michael A. Carducci,* Mario A. Eisenberger,* Alexander S. Baras,* George J. Netto,* Jen-Jane Liu,* Charles G. Drake,* Mark P. Schoenberg,† Trinity J. Bivalacqua* and Noah M. Hahn*,‡

From the Departments of Oncology (JCP, MAC, MAE, CGD, NMH), Urology (NMG, MAC, MAE, JJL, CGD, TJB, NMH), Pathology (ASB, GJN) and Immunology (CGD), Johns Hopkins University Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland, and Department of Urology, Montefiore Medical Center and Albert Einstein College of Medicine, New York, New York (MPS)

- **Delay of RCx >12 weeks** from diagnosis is associated with **inferior survival (higher pT3-4, pN+)**

- Determine the **effect on survival** of the **timing of radical cystectomy** from the diagnosis of MIBC in patients who **received NAC**

MATERIALS & METHODS

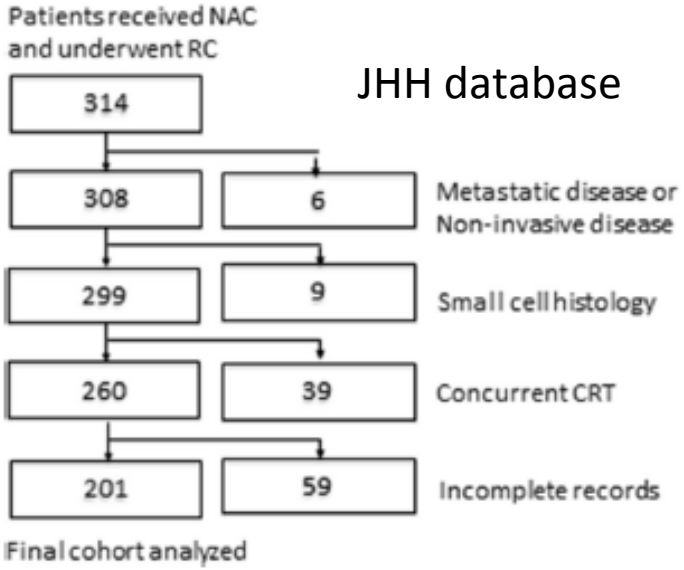


Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram shows study cohort of 201 patients who received NAC and underwent RC for MIBC. *CRT*, chemoradiation therapy.

CX + NAC 1996-2014

Patient Population

Patient charts for

1) **pretreatment characteristics** (demographics, clinical stage, histology and previous IVT)

2) **intervals** between diagnosis of MIBC and the initiation of NAC and RCx;

3) **Post-treatment** and **treatment** clinical and pathological characteristics.

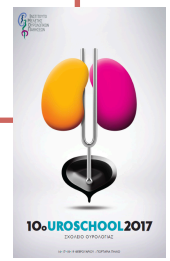
Study End Points

Complete pathological response after NAC
(no tumor)

Partial pathological response after NAC
(no MIBC)

Pathological **response rate**
(%of patients with CR & PR)

Overall survival



RESULTS

Table 1. *Treatment related and posttreatment characteristics*

	No. (%)
Cisplatin based NAC:	
MVAC	10 (5.0)
GC	168 (83.5)
Other*	6 (3.0)
Noncisplatin based NAC	17 (8.5)
No. NAC cycles:	
Less than 3	114 (56.7)
3 or Greater	87 (43.3)
Pathological T stage:	
Complete response (ypT0)	44 (21.9)
Noninvasive disease (ypTa,Tis,T1)	62 (30.8)
Invasive disease:	
ypT2	23 (11.4)
yp3/4	77 (38.3)
Pathological N stage:	
ypN0	160 (79.6)
ypN≥1	41 (20.4)

*Carboplatin/paclitaxel, carboplatin/gemcitabine, cisplatin/gemcitabine/paclitaxel, cisplatin/paclitaxel, ifosfamide.

- **201 pt** NAC + RCx
- @Dx extravesical Dx (**35%**)
  - T3 28%
  - T4 7%
  - LND 9%
- 29% had **variant histologies** (squamous/ adenomatous/ micropapillary /sarcomatoid)

RESULTS

Table 1. *Treatment related and posttreatment characteristics*

	No. (%)
Cisplatin based NAC:	
MVAC	10 (5.0)
GC	168 (83.5)
Other*	6 (3.0)
Noncisplatin based NAC	17 (8.5)
No. NAC cycles:	
Less than 3	114 (56.7)
3 or Greater	87 (43.3)
Pathological T stage:	
Complete response (ypT0)	44 (21.9)
Noninvasive disease (ypTa,Tis,T1)	62 (30.8)
Invasive disease:	
ypT2	23 (11.4)
yp3/4	77 (38.3)
Pathological N stage:	
ypN0	160 (79.6)
ypN≥1	41 (20.4)

*Carboplatin/paclitaxel, carboplatin/gemcitabine, cisplatin/gemcitabine/paclitaxel, cisplatin/paclitaxel, ifosfamide.

At cystectomy

- **22% complete pathological response** (T0)
- **29% partial** pathological response (Tis/T1)
- **51% pathological response rate**

- Median **OS 43.2 mo**

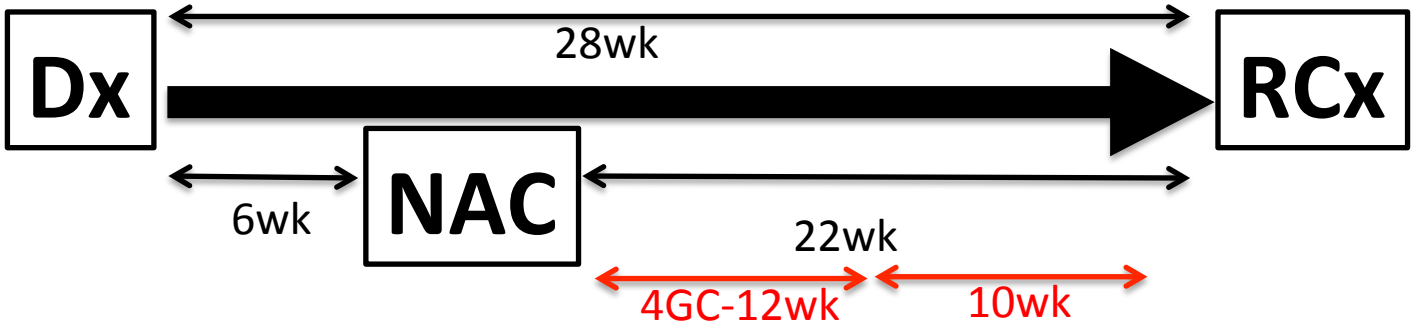
Better OS

- **age < 62** years (p . 0.034)
- **pure urothelial** histology (p . 0.001)

Worse OS

- **< 3 cycles NAC**
- **extravesical /N+** disease (p . 0.001).

RESULTS



Association of OS and Treatment Intervals

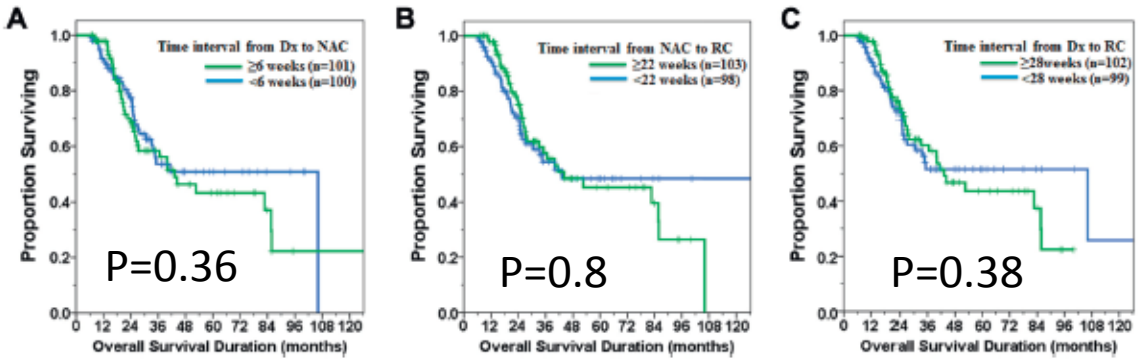


Figure 2. Kaplan-Meier estimated OS for each treatment interval. Timing of NAC initiation from diagnosis (*A*), RC from NAC initiation (*B*) or from diagnosis (*C*) was not associated with statistically significant difference in OS. Dx, diagnosis date from TURBT. *NAC*, initiation date of NAC. *RC*, date of RC.

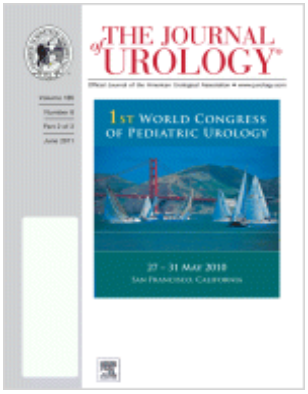
None of the treatment intervals was significantly associated with OS

STUDY LIMITATIONS

- Retrospective
- Inherent **selection bias**
  (Young/caucasian pt)
- Small sample
- GC predominantly used in this study (safety profile)
- Short FU
- Pt treated with NAC who had **progression or toxicity** were **not captured** in this database

TAKE HOME MESSAGES

- There was a **51% pathological response rate (22% CR, 29% PR)**
- **NO association** between **OS** and **time between** MIBC **diagnosis and cystectomy** in patients with MIBC receiving NAC.
- **Less than 3 cycles of NAC** and **extravesical** and or **pN+** Dx is associated with **worse OS**.
- However **delays in treatment** should **not** be **legitimized** based on this study.
- In **patients not receiving NAC**, **prompt surgical** intervention remains the standard of care.



Randomized Controlled Study of the Efficacy, Safety and Quality of Life with Low Dose bacillus Calmette-Guérin Instillation Therapy for Nonmuscle Invasive Bladder Cancer

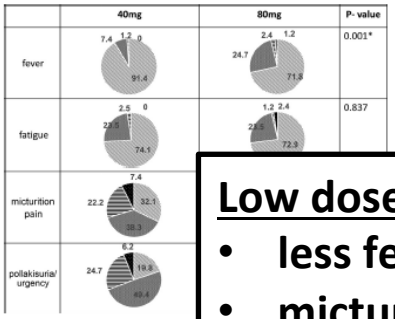
Akira Yokomizo,* Yusuke Kanimoto, Takehiko Okamura, Seiichiro Ozono,† Hirofumi Koga, Masatsugu Iwamura, Hiroshi Tanaka, Satoru Takahashi, Tomoyasu Tsushima, Hiro-omi Kanayama, Hideyuki Akaza, Nobuo Shinohara, Soichi Mugiya, Koichiro Nomata, Tsuyoshi Nakamura and Seiji Naito*,‡

166 T1 HG randomised

- **Low dose 40mg**
- 8wk
- **Standard dose 80mg**

Complete response rates

low dose	**79%**
standard dose	**85%**



Low dose

- **less fever (p = 0.001)**
- **micturition pain (p = 0.047)**
- **higher quality of life scores.**

No differences

- **recurrence,**
- **Progression**
- **Overall survival**

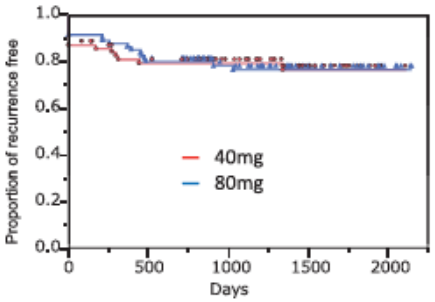
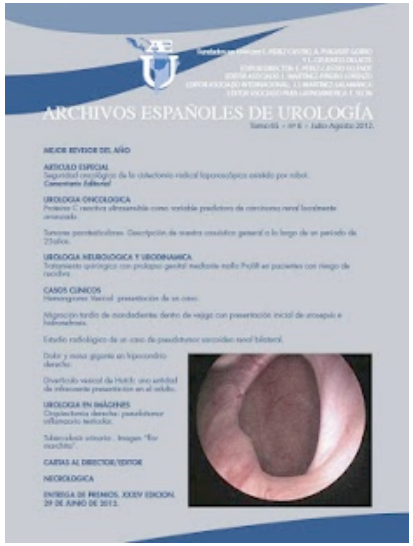


Figure 3. Recurrence-free survival curves after first instillation of BCG. No significant difference in recurrence-free survival between groups (log rank test p = 0.938).

Dept. Urology, Athens Medical School, J. Varkarakis



Comparing the short-term outcomes and complications of monopolar and bipolar transurethral resection of non-muscle invasive bladder cancers: a prospective, randomized, controlled study.

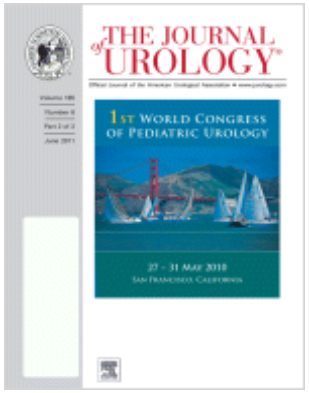
Bolat D[1], Gunlusoy B[1], Degirmenci T[1], Ceylan Y[1], Polat S[1], Aydin E[1], Aydogdu O[1], Kozacioglu Z[1].

Bipolar TURBT had significantly **lower obturator jerk** and bladder **perforation** than monopolar. B- TURBT is a reasonable treatment modality in patients with NMIBC.

Dept. Urology, Athens Medical School, J. Varkarakis

Ευχαριστώ

Dept. Urology, Athens Medical School, J. Varkarakis



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

Kamran Zargar-Shoshtari, Homayoun Zargar, Yair Lotan, Jay B. Shah, Bas W. van Rhijn, Siamak Daneshmand, Philippe E. Spiess and Peter C. Black*

From the Department of Genitourinary Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida (KZ-S, PES), Vancouver Prostate Centre, Vancouver, British Columbia, Canada (HZ, PCB), Department of Urology, University of Texas Southwestern Medical Center, Dallas (YL), Department of Urology, MD Anderson Cancer Center, Houston, Texas (JBS), Department of Urology, The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands (BWvR), and USC/Norris Comprehensive Cancer Center, Institute of Urology, University of Southern California, Los Angeles, California (SD)

- **5% improvement in OS with NAC included only 4% with cN1-3** disease.
- Thus, NAC results may **not necessarily extend to cN1-3**.
- **Clinical** outcomes in pt with BCa & **cN1-3** treated **with induction chemotherapy** followed by **radical cystectomy** are **limited.**
- In this study we assess **pathological and survival outcomes**

PATIENTS & METHODS

- **Multi-institutional** retrospective analysis (19 centers)
- Patients with **cT1-4aN1-N3** urothelial carcinoma who received **NAC followed by RCB**.

- Lymph **node** status based on imaging criteria
- Chemotherapy regimens:
  - MVAC
  - GC
  - "other" (not cisplatin)

- End points
  - **pathological response** rates
    - **complete** (**pT0N0**)
    - **partial** (**pT1N0** or less)
  - **overall survival**.
  - **factors** predicting outcomes

Dept. Urology, Athens Medical School, J. Varkarakis

RESULTS

Number of patients

- **304**/1618 (19%) had cN1-3
- **248**/304 (82%) had pN0-3

Chemo regimens

- GC 43%
- MVAC 42%
- Other 15%

(median 4 cycles)

Pathological Complete and Partial Response

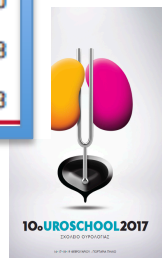
- pCR (**pT0N0**) **14.5%**
- pPR (**pT1N0 or less**) **27%**

(pCR was only seen in patients with cN1-N2).

Table 1. *Logistic regression analysis of clinical and pathological predictors of pN0, complete and partial response to induction chemotherapy*

		pN0		pCR		pPR	
Variables in Equation	Category	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
Gender:					0.14	0.61 (0.30–1.23)	0.17
Age:					0.40	1.45 (0.81–2.59)	0.21
Clinical T stage:					0.34	1.02 (0.57–1.83)	0.96
Clinical node st					0.69	0.78 (0.43–1.40)	0.40
No. chemothera					0.27	1.90 (0.93–3.86)	0.08
Chemotherapy r					0.93	0.56 (0.22–1.44)	0.23

- On multivariable analysis **none of the selected variables** were **independent predictors** of pCR or pPR
- *pCR & pPR was similar with all chemo regimens*



RESULTS

Table 2. *Median months overall survival (IQR) according to nodal status*

	Clinical Node Status		
	cN1	cN2-3	cN1-3
Median pathological node status (IQR):			
pN0	71 (24–not reached)	84 (23–177)	84 (23–177)
pN1-3	13 (4–34)	16 (6–39)	14 (5–35)
pNx	24 (13–64)	11 (4–17)	13 (7–43)
p Value:			
pN0 vs pN1-3	<0.001	0.001	<0.001
pN0 vs pNx	0.07	<0.001	<0.001
pN1-3 vs pNx	0.06	0.24	0.69

OS improved in cN2-3 cases that became **pN0** vs those remained pN+.

Pathological Nodal Response.

pCNR (pN0) **48%**

- 56% of cN1
- 39% of cN2
- 39% of cN3

(p.0.03)

*Of **pT0** bladder status patients **38%** were found to have positive lymph nodes (**pT0N+**)*

RESULTS

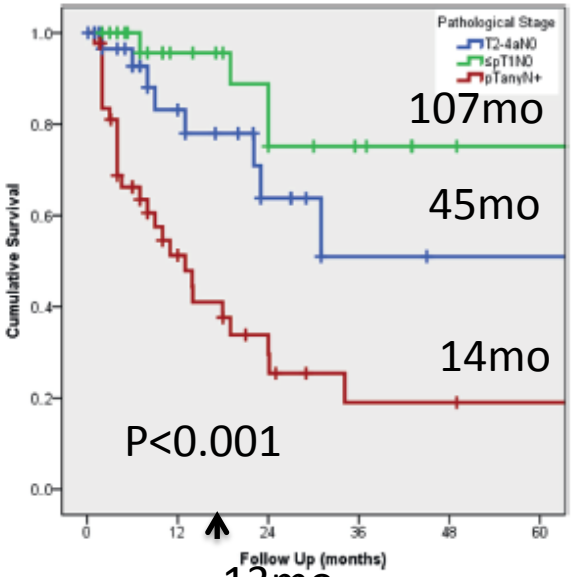


Figure 1. KM plot for OS and pathological response

Median OS for the entire cohort was **23 mo**

55% local **recurrence or M+** disease (151 pt)

Overall **50% pt died** during FU (median of 10 mo)
88% of them died of **bladder cancer**

- 28% with pT0
- 23% with pN0
- 18% with pCR

Table 3. *OS and pathological response*

Pathological Stage	No.	OS (IQR)	Mean (95% CI)
pT0N0	36	84 (1—not reached)	93 (54—94)
pT<2N0	66	NR (1—not reached)	107 (76—138)
pT≥2N0	53	45 (16—177)	83 (49—118)
pT0N1-3	22	16 7—not reached)	35 (16—54)
pT<2N1-3	33	16 4—not reached)	32 (17—47)
pT≥2N1-3	96	13 (5—34)	48 (24—72)

RESULTS

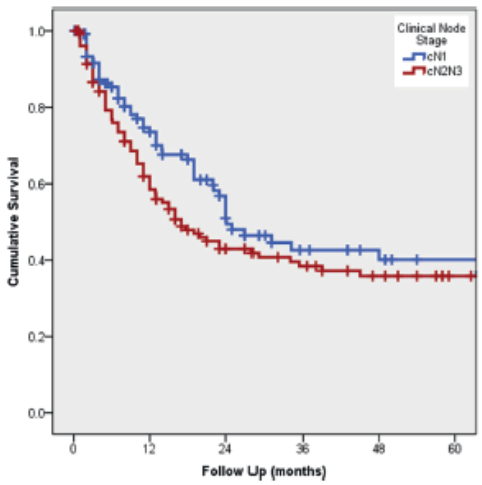


Figure 2. KM plot for OS and clinical nodal stage

OS longer for cN1 vs cN2-3 **but** NSS (**p=0.23**)
Remained NSS after controlling for age, gender , T stage (p=0.11)
At the **cutoff point of 15 lymph nodes** removed OS was **p=0.01**

Table 4. *Cox proportional hazard model for predicting death from any cause*

Variables in Equation	Compared Categories	HR (95% CI)	p Value
Gender:	M		
	F	1.57 (0.98–2.51)	0.06
Age:	Less than 65		
	65 or Greater	1.03 (0.69–1.55)	0.88
Pathological T stage:	Less than pT2		
	pT2 or greater	0.76 (0.46–1.26)	0.29
Pathological margin:	Neg		
	Pos	2.96 (1.72–5.09)	<0.001
No. pos nodes:	Zero	Reference	
	Single	2.56 (1.47–4.47)	0.001
	2 or Greater	3.26 (1.98–5.36)	<0.001
No. nodes removed:	Less than 15		
	15 or Greater	0.55 (0.36–0.86)	0.01
No. chemotherapy cycles:	1–3		
	4 or Greater	1.17 (0.72–1.90)	0.54
Chemotherapy regimen:	MVAC/GC		
	Other	1.88 (1.06–3.34)	0.03

Overall 205 cases included in analysis.

OS associated with

- pCR of nodes (**pN0**)
- **Number of nodes** removed
- **(-)sm**
- **Cisplatin** Tx (MVAC vs GC same)

RESULTS

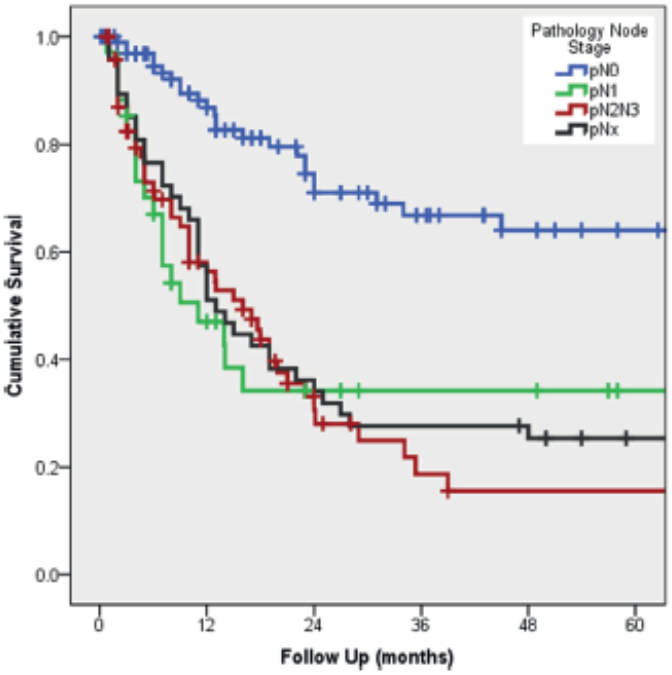


Figure 3. KM plot for OS and pathological nodal response

Patients with Unknown Pathological Nodal status

Median survival similar

- to the pN+ cohort
- worse than the pN0

STUDY LIMITATIONS

- Retrospective study
- No standardization of chemotherapy (dose, data on toxicity, morbidity and mortality)
- Selection bias in the choice of chemotherapy regimens.
- Some Pt with cN1-3 not proceed to RC (selection bias-favorable subset of cN1-3pt)
- Not centralized radiological and pathological review
- Not always biopsy confirmation of nodal involvement
- Risk factors not included
  - performance status
  - medical comorbidities,
  - Hydronephrosis
  - Cardiovascular status
  - Renal function

TAKE HOME MESSAGES

- **Induction chemotherapy** in **N+** patients associated with a clinically **significant pathological response**.
- **Complete** pathological **nodal** response **can be achieved**, even in patients with cN2-3 disease, and this corresponds to **improved survival**.
  - **48% of cN1-3 cases** converted to **pN0**
  - **down staging to pT0** occurred in **24%** of cases
  - **38% of pT0 had +N**
  - **pCR (pT0No) <u>only</u> 14.5%**

In patients with cN1-3 disease the **best outcomes** are seen in those

- Receiving **cisplatin** based chemo

  Same GC and MVAC
- Have **negative margins**
- **Complete nodal response** at RC.

Dept. Urology, Athens Medical School, J. Varkarakis

Eur Urol. 2016 Jan;69(1):60-9. doi: 10.1016/j.eururo.2015.06.045. Epub 2015 Jul 23.

EORTC Nomograms and Risk Groups for Predicting Recurrence, Progression, and Disease-specific and Overall Survival in Non-Muscle-invasive Stage Ta-T1 Urothelial Bladder Cancer Patients Treated with 1-3 Years of Maintenance Bacillus Calmette-Guérin.

Cambier S[1], Sylvester RJ[2], Collette L[1], Gontero P[3], Brausi MA[4], van Andel G[5], Kirkels WJ[6], Silva FC[7], Oosterlinck W[8], Prescott S[9], Kirkali Z[10], Powell PH[11], de Reijke TM[12], Turkeri L[13], Collette S[1], Oddens J[14].

Data for 1812 patients were merged from two European Organization for Research and Treatment of Cancer randomized phase 3 trials in intermediate- and high-risk NMIBC.

With a median follow-up of 7.4 yr, 762 patients recurred; 173 progressed; and 520 died, 83 due to bladder cancer (BCa). Statistically significant prognostic factors identified by multivariable analyses were prior recurrence rate and number of tumors for recurrence, and tumor stage and grade for progression and death due to BCa. T1G3 patients do poorly, with 1- and 5-yr disease-progression rates of 11.4% and 19.8%, respectively, and 1- and 5-yr disease-specific death rates of 4.8% and 11.3%. Limitations include lack of repeat transurethral resection in high-risk patients and exclusion of patients with carcinoma in situ.

NMIBC patients treated with 1-3 yr of maintenance BCG have a heterogeneous prognosis. Patients at high risk of recurrence and/or progression do poorly on currently recommended maintenance schedules. Alternative treatments are urgently required.