5th ANNUAL UC COURSE
Emerging personalized therapies for the management of urothelial carcinomas

V CURSO ANUAL DE UC
Terapias personalizadas emergentes en el manejo del carcinoma urotelial

Estratificación del riesgo en cáncer de vejiga no músculo invasivo: *evolucionando de lo antiguo a lo nuevo*

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Hospital Universitario 12 de Octubre

DISCLOSURES	
Research support/PI	Janssen, Pfizer, Taris, BMS, Roche, Seagen, AstraZeneca, Combat Medical, Cepheid, Fidia, Astellas, UroGen
Employee	SERMAS (Servicio Madrileño de Salud)
Consultant	Janssen, Pfizer, Merck, Roche, Taris, Combat Medical, AstraZeneca
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Speaker	Janssen, Nucleix, Pfizer, Merck, BMS, AstraZeneca, Palex, Combat Medical
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Scientific advisory board	AstraZeneca, BMS, Combat Medical, Janssen, Nucleix, Pfizer, Taris, Roche
Manuscript support	Pfizer, Janssen, Combat Medical, AstraZeneca

¿Por qué estratificamos?

PACIENTE 1

Varón 61 años

Hematuria

Tumor vesical único 2 cm

RTU: TaG1BG

Resultados

Probabilidad de progresión después de RTUV sin inducción o mantenimiento de BCG

	BASADO EN OMS 2004/2016 Riesgo Bajo	BASADO EN OMS 1973 Riesgo Bajo
a 1 año	0.06%, 0.01%-0.43%	0.12%, 0.02%-0.82%
a los 5 años	0.93%, 0.49%-1.7%	0.57%, 0.21%-1.5%
a los 10 años	3.7%, 2.3%-5.9%	3.0%, 1.5%-6.3%

Probabilidad de progresión e intervalo de confianza del 95%

PACIENTE 2

Varón 61 años

Hematuria

Tumor vesical único 2 cm

RTU: T1G3AG

Resultados

Probabilidad de progresión después de RTUV sin inducción o mantenimiento de BCG

	BASADO EN OMS 2004/2016 Alto Riesgo	BASADO EN OMS 1973 Alto Riesgo
a 1 año	3.5%, 2.4%-5.2%	3.8%, 2.6%-5.7%
a los 5 años	9.6%, 7.4%-12%	11%, 8.1%-14%
a los 10 años	14%, 11%-18%	14%, 10%-19%

Probabilidad de progresión e intervalo de confianza del 95%

Modelos predictivos	Opiniones de expertos
EORTC	AUA
CUETO	NCCN
EAU 2021	EAU 2020

Table 9 – Risk group stratification.

Risk group stratification	Characteristics
Low-risk tumours	Primary, solitary, TaG1 (PUNLMP, LG[a]), <3 cm, no CIS
Intermediate-risk tumours	All tumours not defined in the two adjacent categories (between the category of low and high risk)
High-risk tumours	Any of the following:
	• T1 tumour
	• G3 (HG[b]) tumour
	• CIS
	• Multiple, recurrent, and large (>3 cm) TaG1G2/LG tumours (all features must be present)[a]
	Subgroup of highest risk tumours:
	T1G3/HG associated with concurrent bladder CIS, multiple and/or large T1G3/HG and/or recurrent T1G3/HG,T1G3/HG with CIS in the prostatic urethra, some forms of variant histology of urothelial carcinoma, lymphovascular invasion

CIS = carcinoma in situ; HG = high grade; LG = low grade; PUNLMP = papillary urothelial neoplasm of low malignant potential.
Substratification of high-risk tumours for clinical purposes is addressed in Table 13.
[a] Low grade is a mixture of G1 and G2.
[b] High grade is a mixture of some G2 and all G3 (see Fig. 4.1 of 2019 NMIBC guidelines).

Table 5 – Weights used to calculate the recurrence and progression scores

Factor	Recurrence	Progression
Number of tumors		
Single	0	0
2 to 7	3	3
≥8	6	3
Tumor size		
<3 cm	0	0
≥3 cm	3	3
Prior recurrence rate		
Primary	0	0
≤1 rec/yr	2	2
>1 rec/yr	4	2
T category		
Ta	0	0
T1	1	4
CIS		
No	0	0
Yes	1	6
Grade		
G1	0	0
G2	1	0
G3	2	5
Total score	0–17	0–23

Table 3. *Factors by weight to calculate recurrence and progression scores using AIC to select most predictive model*

Factor	Recurrence Score	Progression Score
Gender:		
M	0	0
F	3	0
Age:		
Less than 60	0	0
60–70	1	0
Greater than 70	2	2
Recurrent tumor:		
No	0	0
Yes	4	2
No. tumors:		
3 or Less	0	0
Greater than 3	2	1
T category:		
Ta	0	0
T1	0	2
Associated Tis:		
No	0	0
Yes	2	1
Grade:		
G1	0	0
G2	1	2
G3	3	6
Total scores	0–16	0–14

Sylvester, Eur Urol 2006; Fernández-Gómez, J Urol 2009; Babjuk, Eur Urol 2019

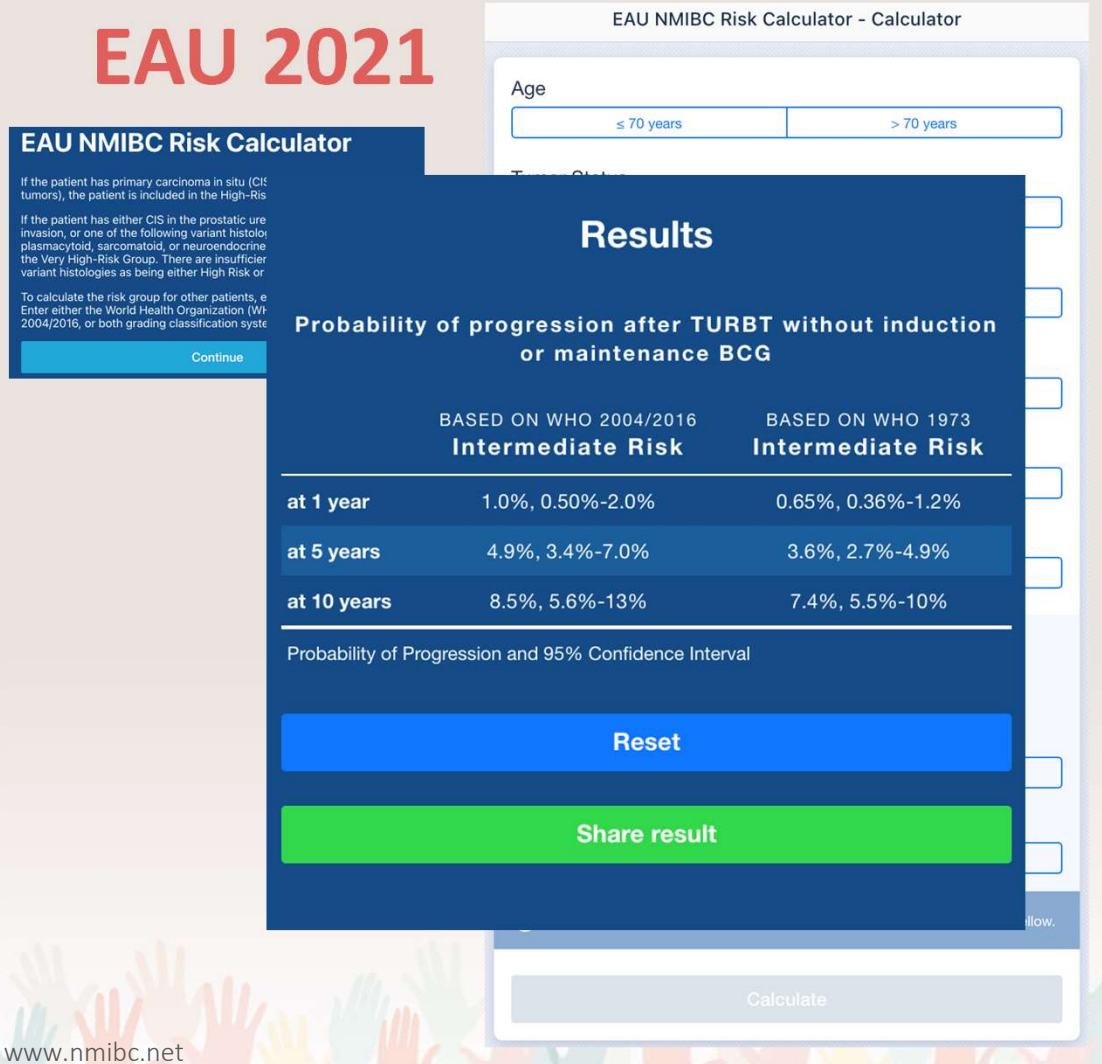
Risk group	
Low Risk	A primary, single, TaT1 LG/G1 tumour < 3 cm in diameter without CIS in a patient ≤ 70 years A primary Ta LG/G1 tumour without CIS with at most ONE of the additional clinical risk factors
Intermediate Risk	Patients without CIS who are not included in either the low-, high-, or very high-risk groups
High Risk	All T1 HG/G3 without CIS, EXCEPT those included in the very high-risk group All CIS patients, EXCEPT those included in the very high-risk group
	Stage, grade with additional clinical risk factors: Ta LG/G2 or T1G1, no CIS with all 3 risk factors Ta HG/G3 or T1 LG, no CIS with at least 2 risk factors T1G2 no CIS with at least 1 risk factor
Very High Risk	**Stage, grade with additional clinical risk factors:** Ta HG/G3 and CIS with all 3 risk factors T1G2 and CIS with at least 2 risk factors T1 HG/G3 and CIS with at least 1 risk factor T1 HG/G3 no CIS with all 3 risk factors

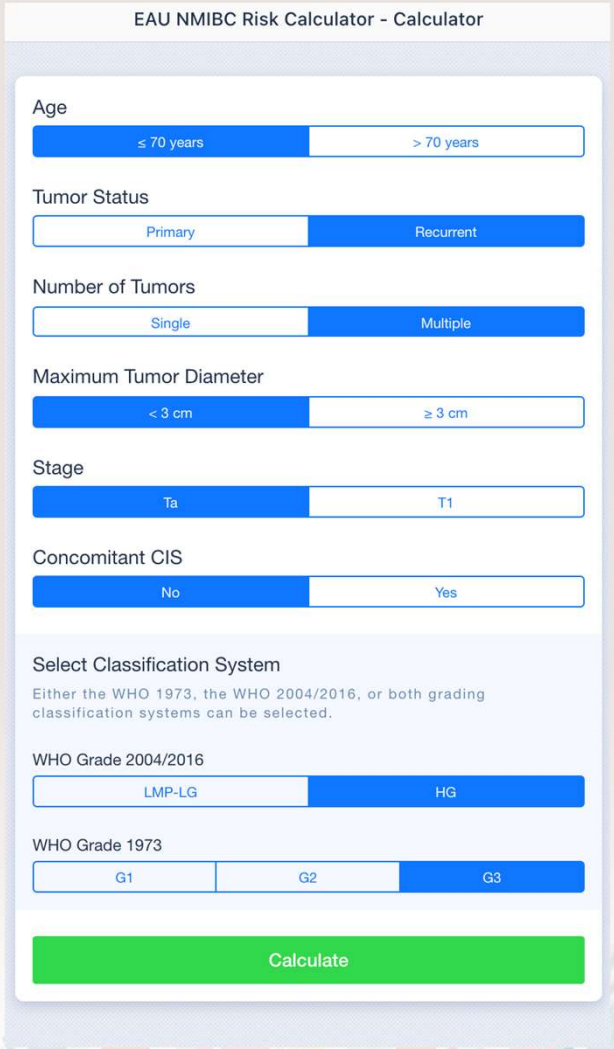
*Additional clinical risk factors are:

- age > 70;
- multiple papillary tumours;
- tumour diameter > 3 cm.

Repeat TURBT, *n* (%)	
No	2696 (79)
Yes	556 (16)
Unknown	149 (4.4)
Initial treatment, *n* (%)	
TURBT alone	1572 (46)
TURBT + chemotherapy	1829 (54)

EAU 2021


EAU NMIBC Risk Calculator
If the patient has primary carcinoma in situ (CIS
tumors), the patient is included in the High-Ris
If the patient has either CIS in the prostatic ure
invasion, or one of the following variant histolo
plasmacytoid, sarcomatoid, or neuroendocrine
the Very High-Risk Group. There are insufficier
variant histologies as being either High Risk or
To calculate the risk group for other patients, e
Enter either the World Health Organization (WH
2004/2016, or both grading classification syste
Continue
Results
Probability of progression after TURBT without induction or maintenance BCG
BASED ON WHO 2004/2016 Intermediate Risk
BASED ON WHO 1973 Intermediate Risk
at 1 year 1.0%, 0.50%-2.0% 0.65%, 0.36%-1.2%
at 5 years 4.9%, 3.4%-7.0% 3.6%, 2.7%-4.9%
at 10 years 8.5%, 5.6%-13% 7.4%, 5.5%-10%
Probability of Progression and 95% Confidence Interval
Reset
Share result
EAU NMIBC Risk Calculator - Calculator
Age
≤ 70 years
> 70 years
Calculate


EAU NMIBC Risk Calculator - Calculator
Age
≤ 70 years
> 70 years
Tumor Status
Primary
Recurrent
Number of Tumors
Single
Multiple
Maximum Tumor Diameter
< 3 cm
≥ 3 cm
Stage
Ta
T1
Concomitant CIS
No
Yes
Select Classification System
Either the WHO 1973, the WHO 2004/2016, or both grading classification systems can be selected.
WHO Grade 2004/2016
LMP-LG
HG
WHO Grade 1973
G1
G2
G3
Calculate

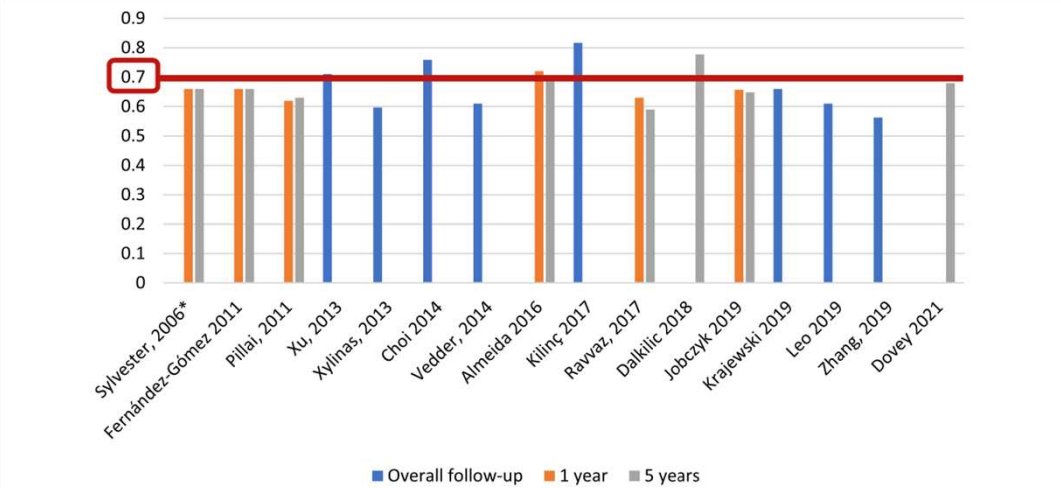


Fig. 3. External validations with c-index for EORTC discrimination of recurrence risk (*refers to the model construction series).

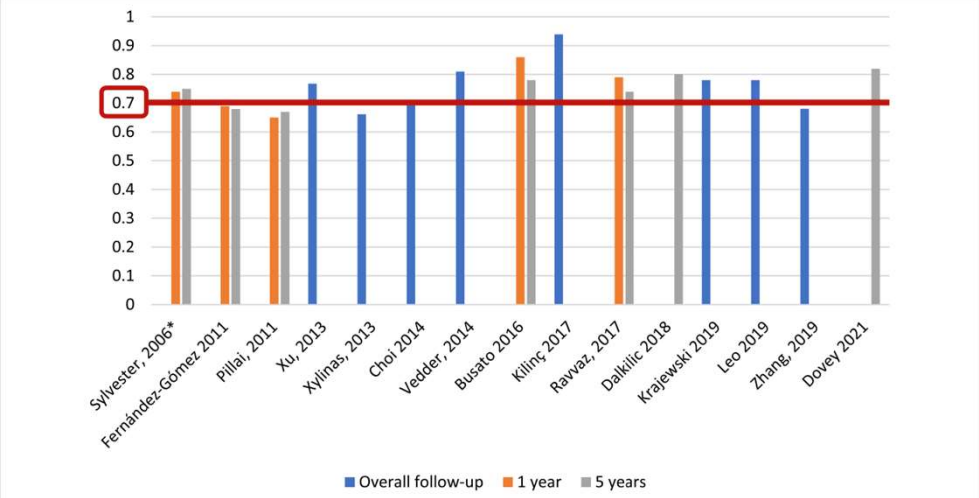


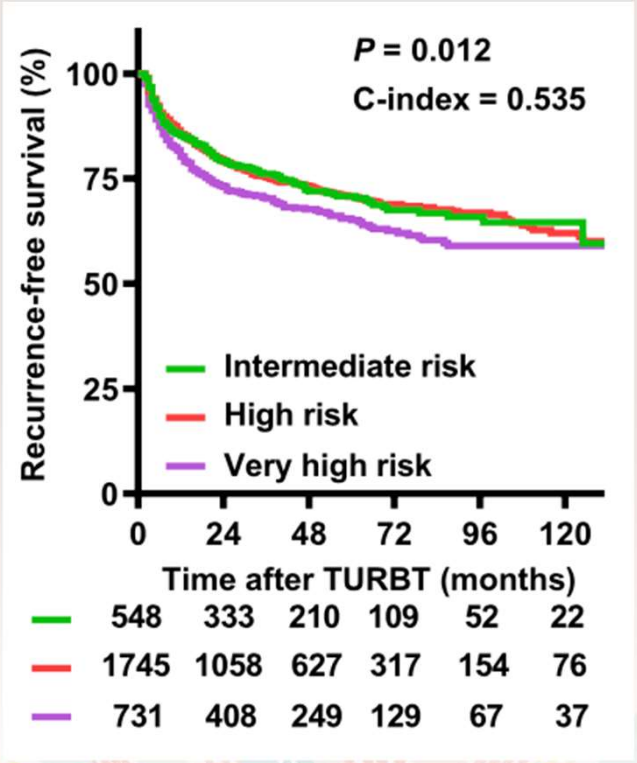
Fig. 5. External validations with c-index for EORTC discrimination of progression risk (*refers to the model construction series).

Las validaciones externas publicadas muestran:
BAJA discriminación **RECURRENCIA**
ACEPTABLE discriminación **PROGRESIÓN**

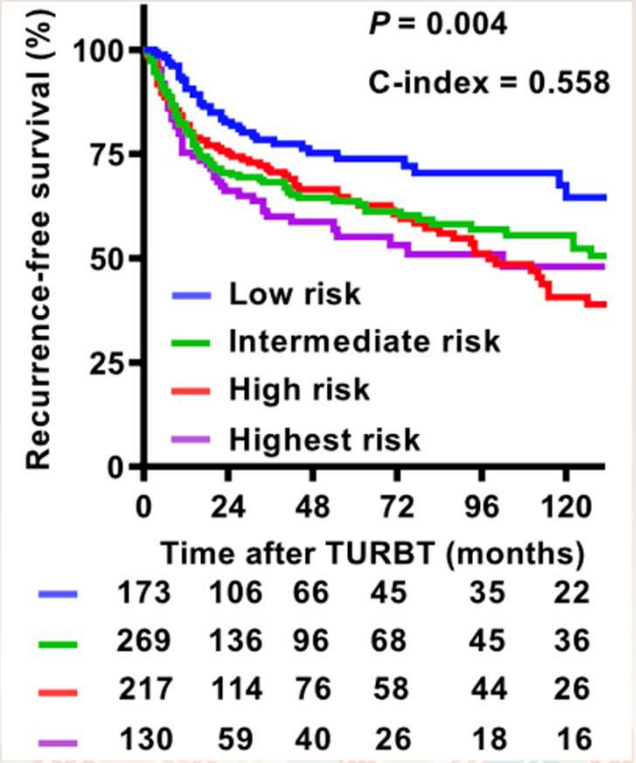
Guerrero-Ramos F, Bladder Cancer 2022

EAU 2021: recurrencia

BCG cohort



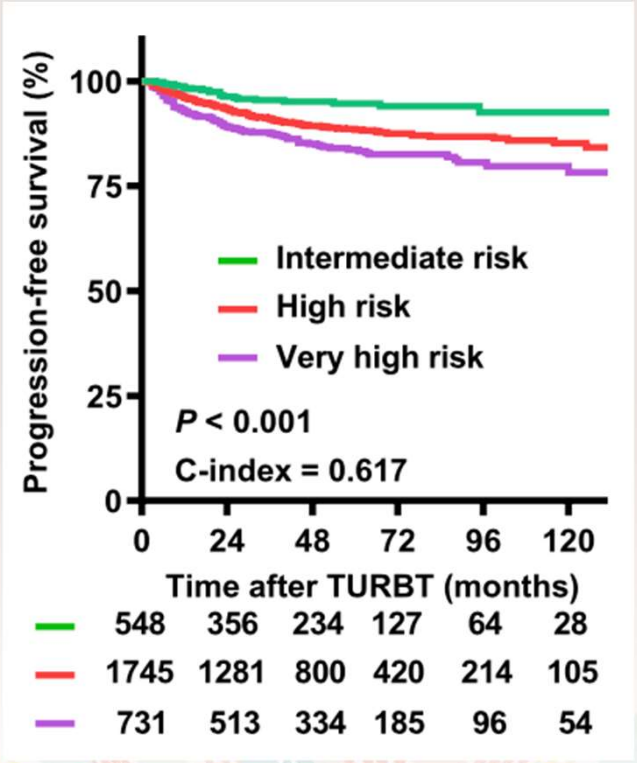
Non-BCG cohort



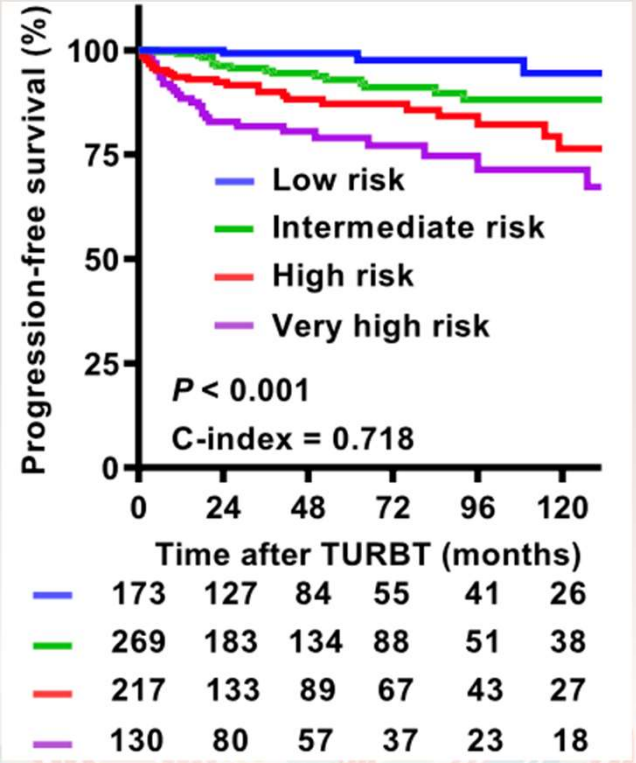
Miyake M, BJUI Compass 2024

EAU 2021: progresión

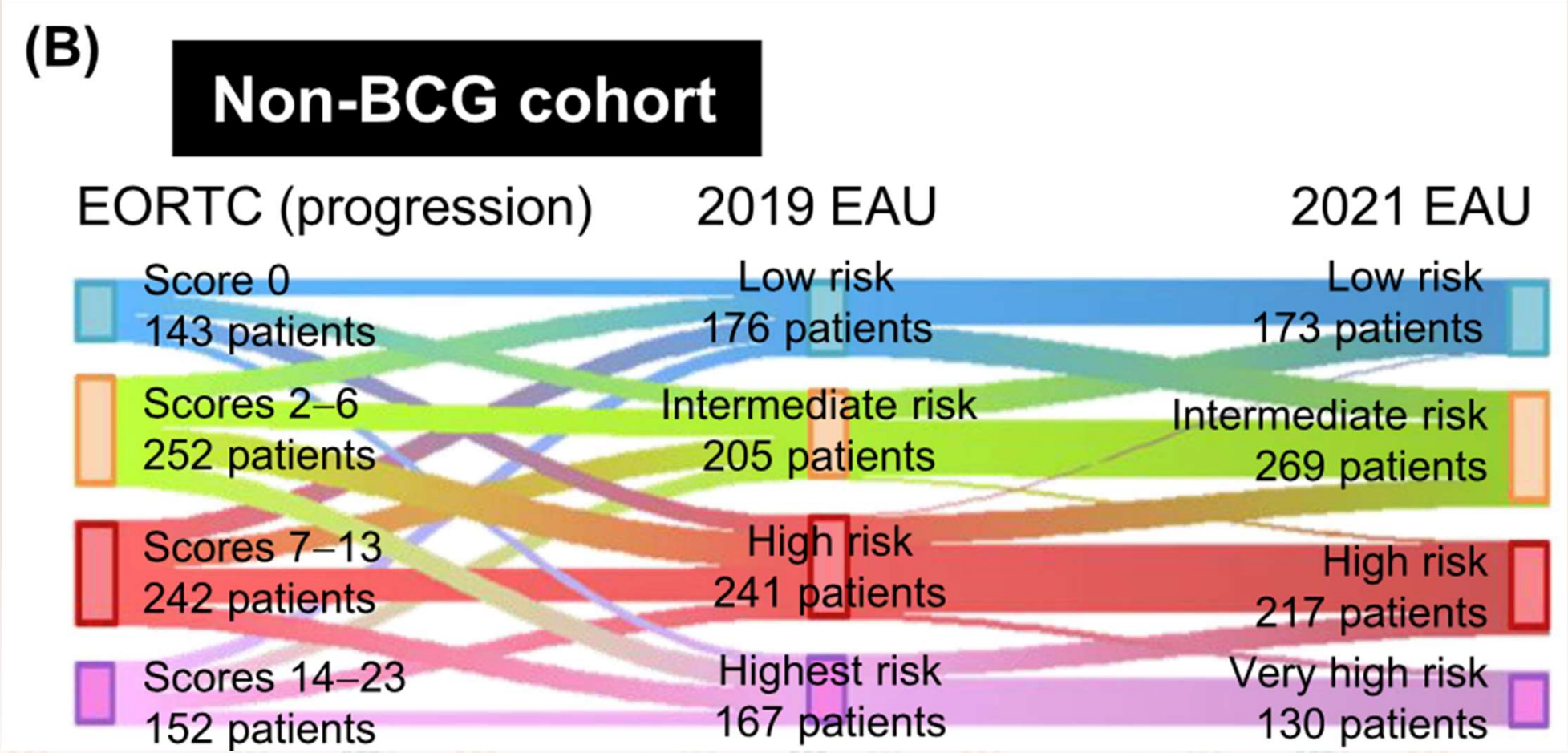
BCG cohort



Non-BCG cohort

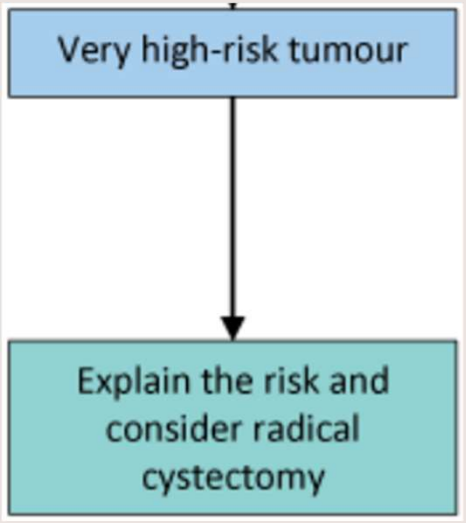


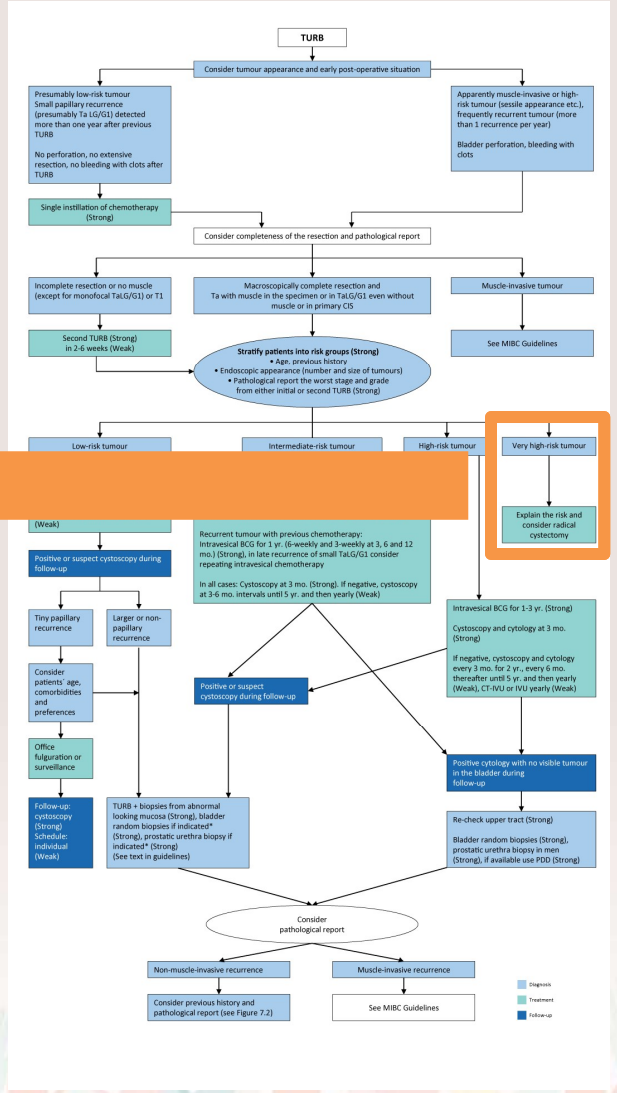
Miyake M, BJUI Compass 2024



Miyake M, BJUI Compass 2024

EAU 2021: very high-risk group





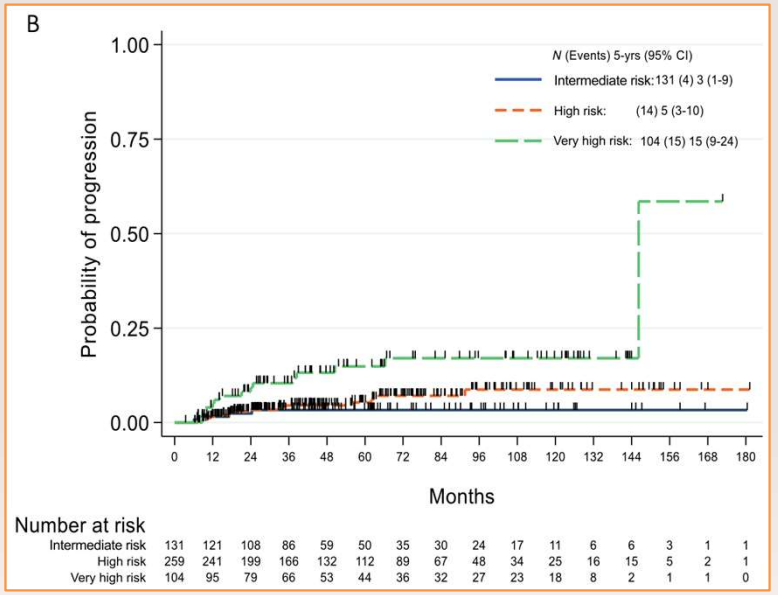
Risk group	Probability of Progression and 95% Confidence Interval (CI)		
	1 Year	5 Years	10 Years
Very High	20% (CI: 12%–32%)	44% (CI: 30%–61%)	59% (CI: 39%–79%)

EAU 2021: very high-risk group

Presumed EAU21 probability of progression at 10 years in the very high risk group ➔ 59%

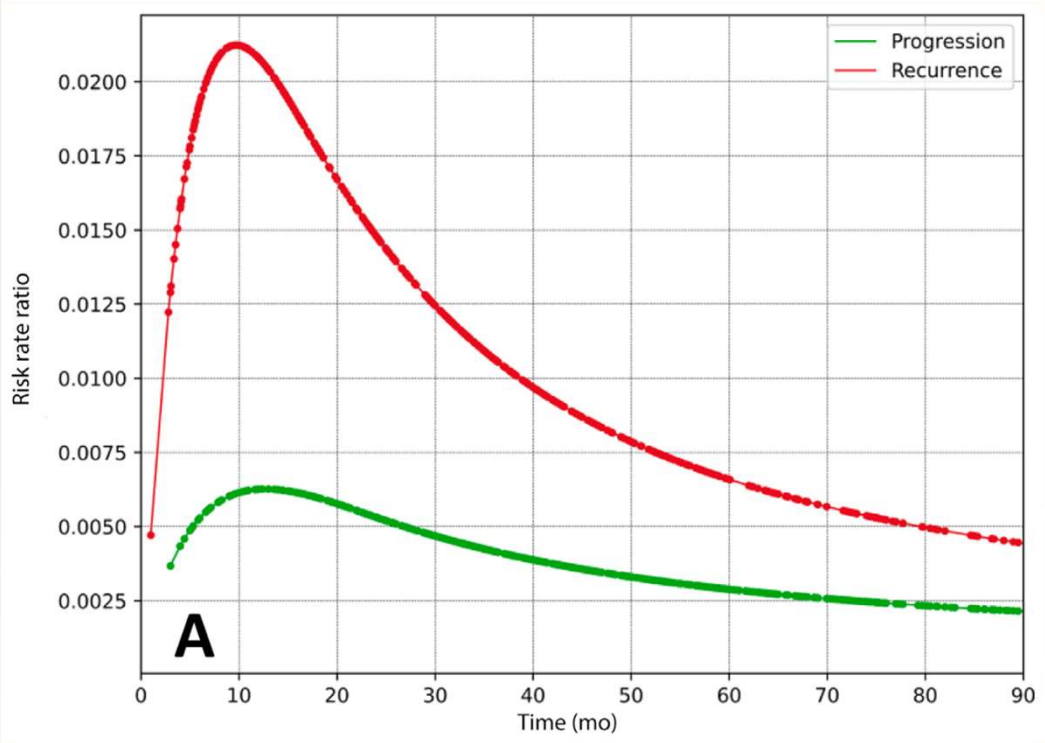
Actual probability of progression at 10 years ➔ 18%

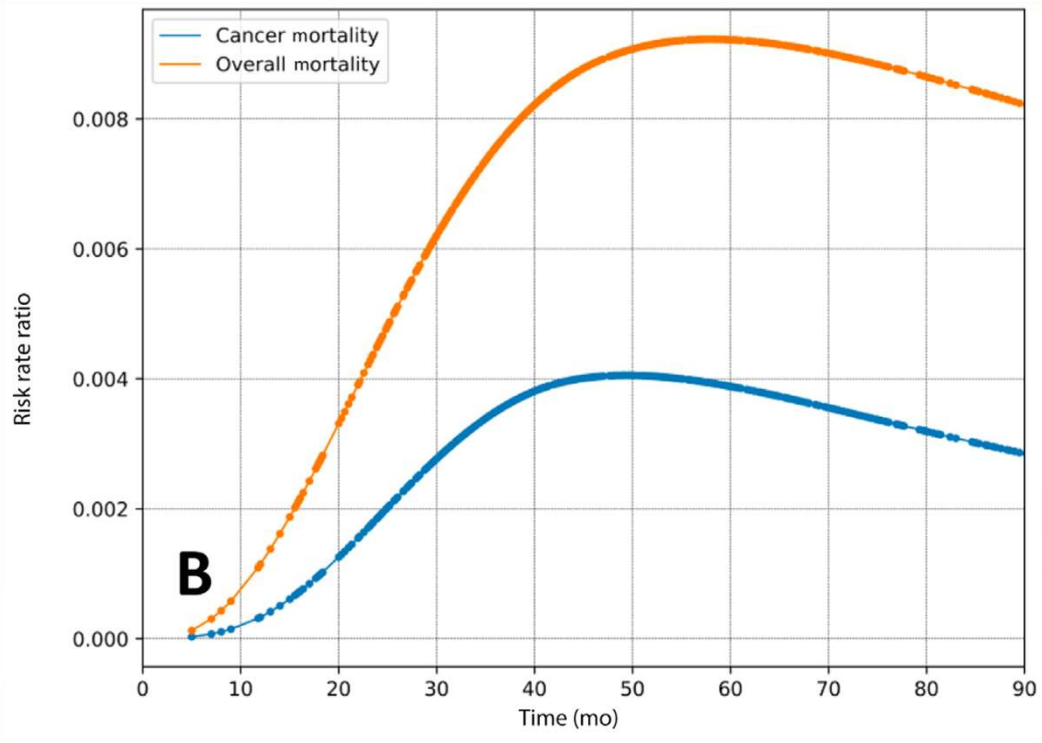
Potential number of patients overtreated with radical cystectomy ➔ 70%



Lobo N, Eur Urol Oncol 2022

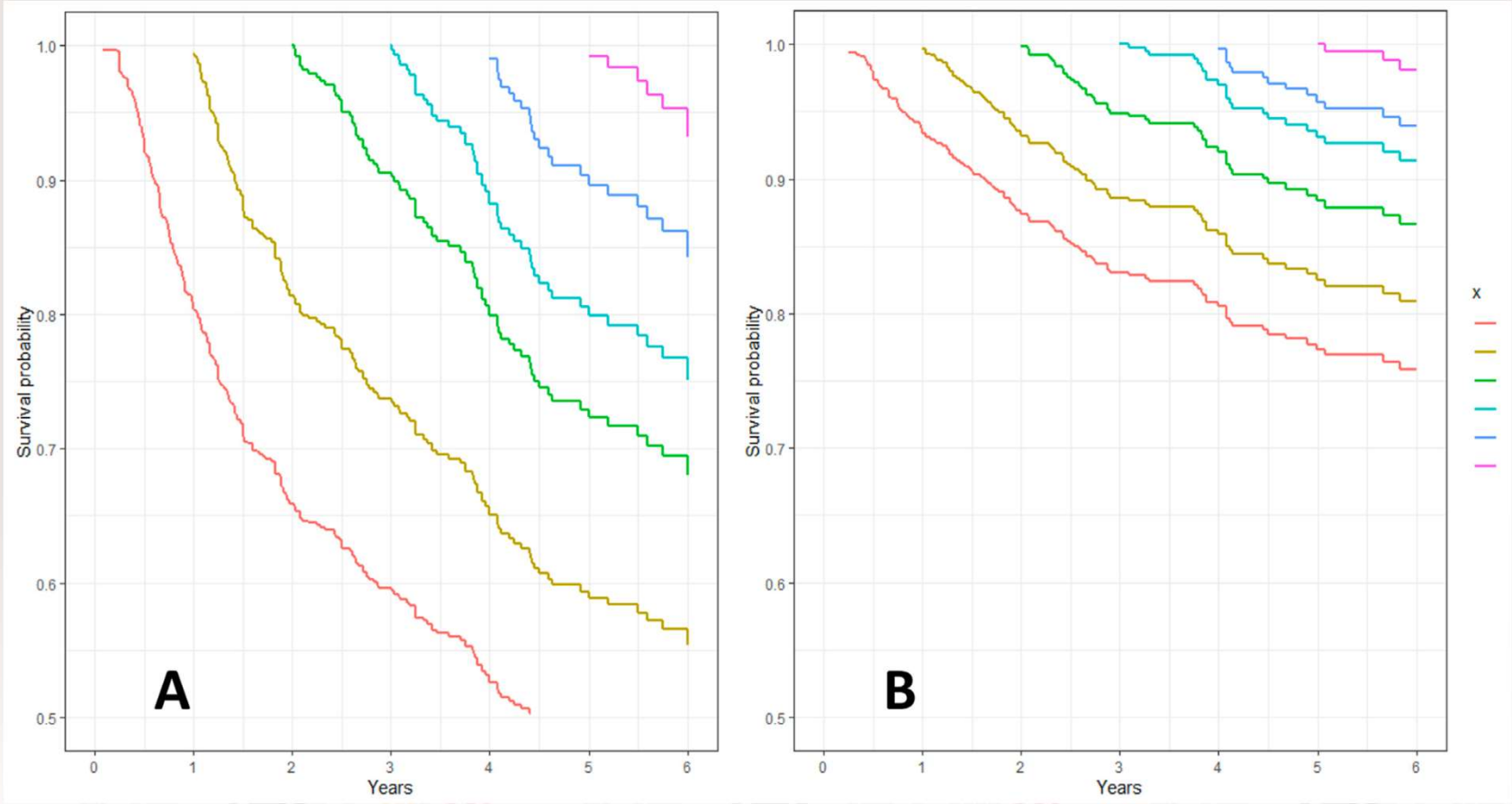
EAU 2021: very high-risk group





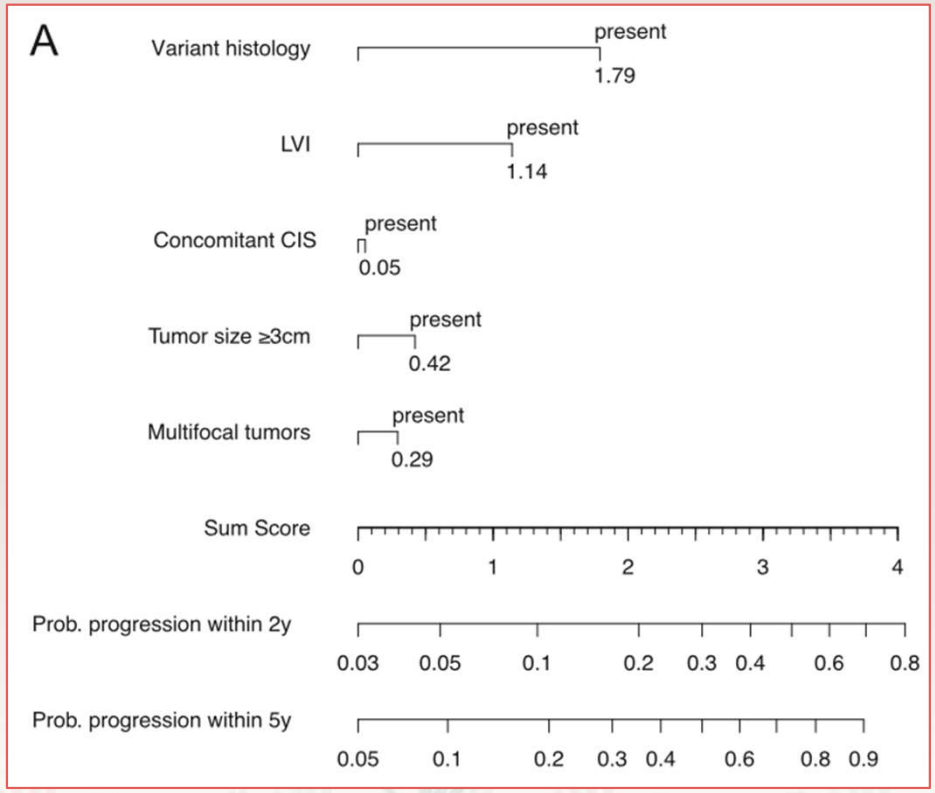
Subiela JD, ..., Guerrero-Ramos F, ..., et al, Eur Urol Oncol 2024

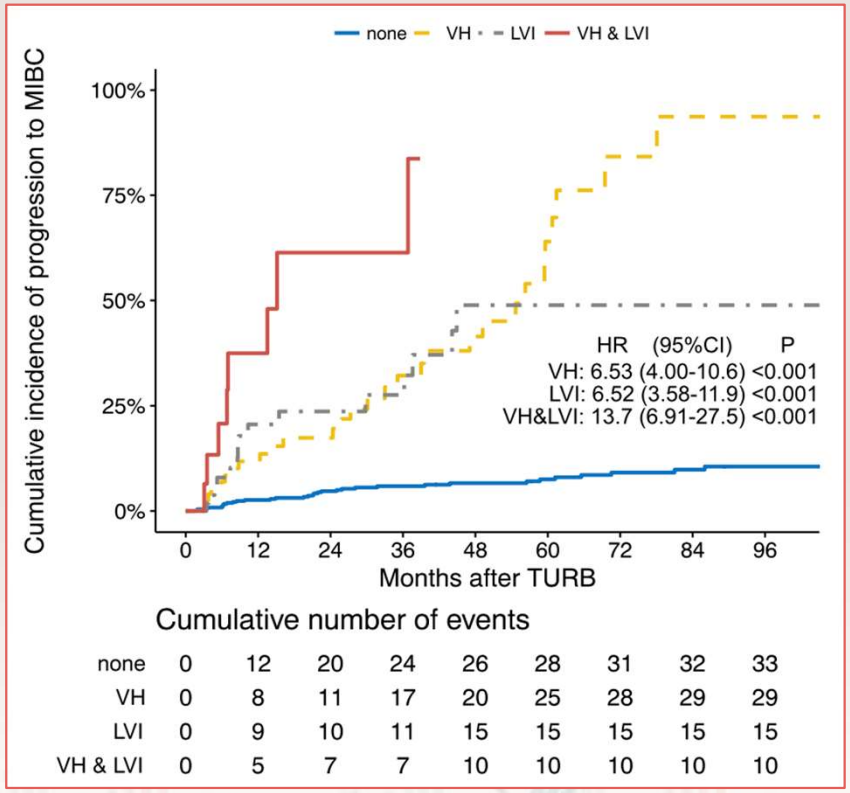
EAU 2021: very high-risk group



Subiela JD, ..., Guerrero-Ramos F, ..., et al, Eur Urol Oncol 2024

Variantes histológicas e invasión linfovascular en T1G3





D'Andrea, Urol Oncol 2018

Subestratificación T1

TABLE 5. Example Methods for Providing Depth of Invasion for T1 Subcategorization

System	Technique	Measure of Invasion	Land or C
T1a/T1b	Histoanatomic	Depth (level)	MM
T1a/T1b/ T1c	Histoanatomic	Depth (level)	MM
T1m/T1e	Micrometric	Depth* or diameter†	0.5
ROL1/ ROL2	Micrometric	Diameter†	1 m
ALLICA	Micrometric	Diameter†	2.3 m

*Initial description measured distance parallel to overlying (n
†Diameter measured in any direction.
‡Optimal cutoff.
ALLICA indicates the aggregate linear length of invasive carci
T1microscopic; VP, vascular plexus.

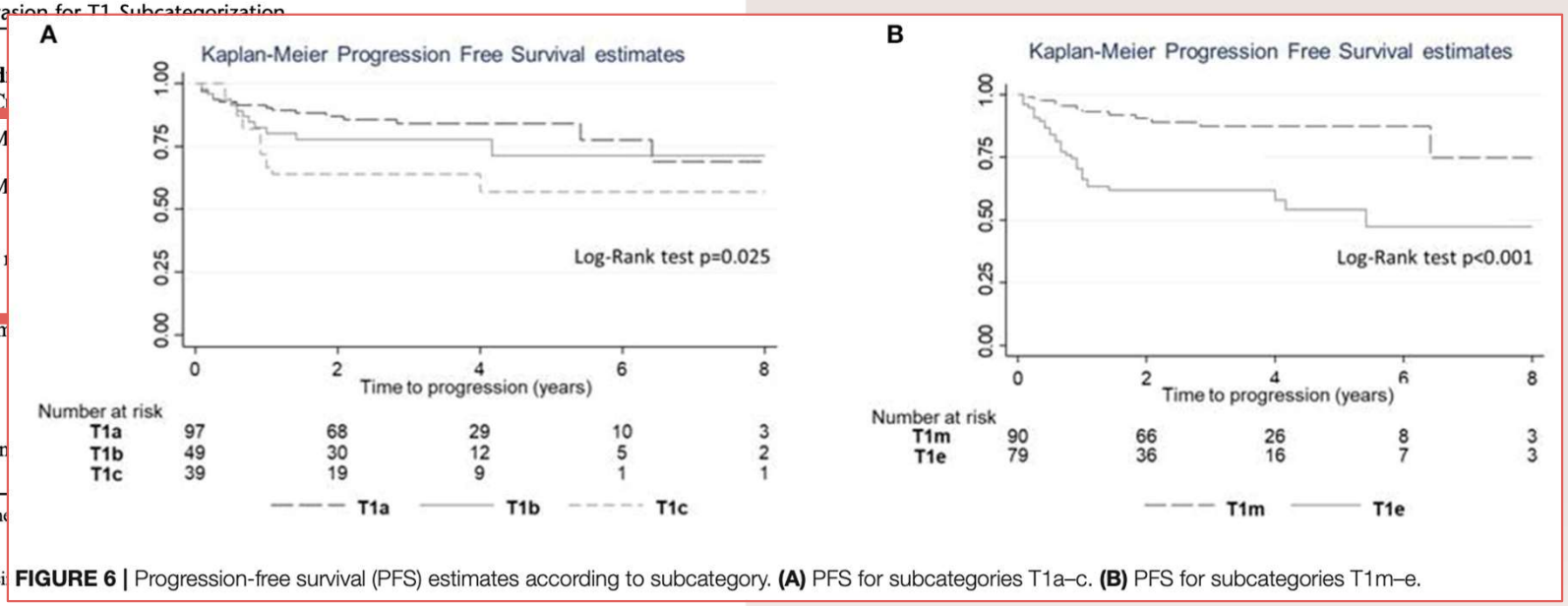
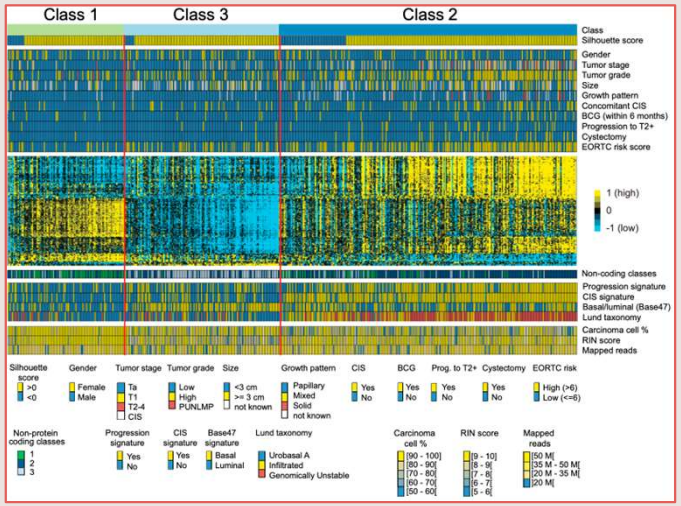
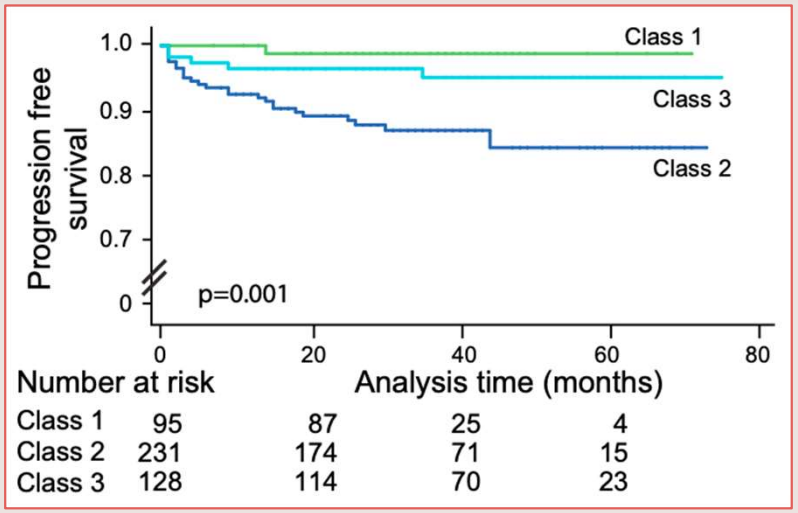


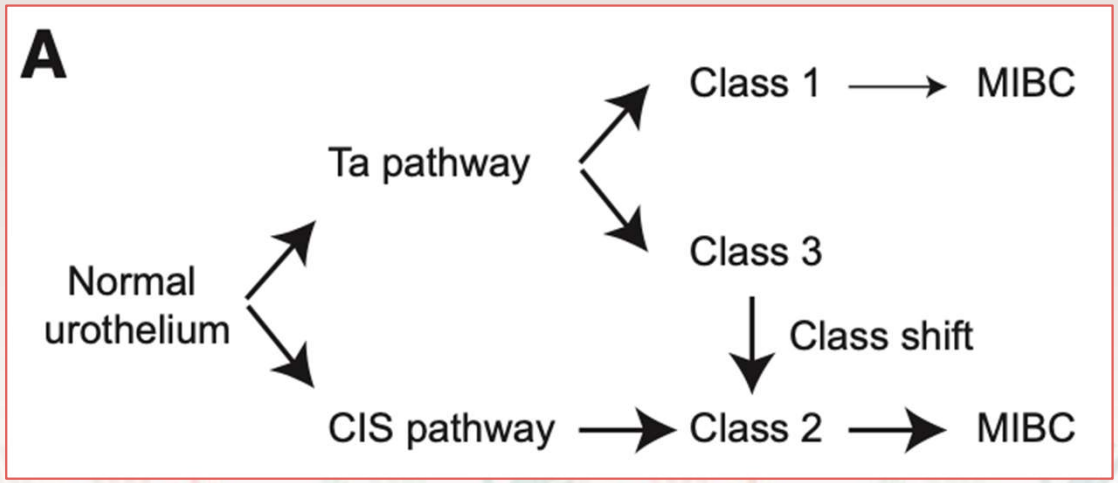
FIGURE 6 | Progression-free survival (PFS) estimates according to subcategory. **(A)** PFS for subcategories T1a–c. **(B)** PFS for subcategories T1m–e.

- T1a/b/c técnicamente posible en el 40-100% de las RTUv con T1
- Técnicas micrométricas factibles en > 99% de las RTUv con T1

Compérat E, Adv Anat Pathol 2021; Asimakopuolos, Front Surg 2021



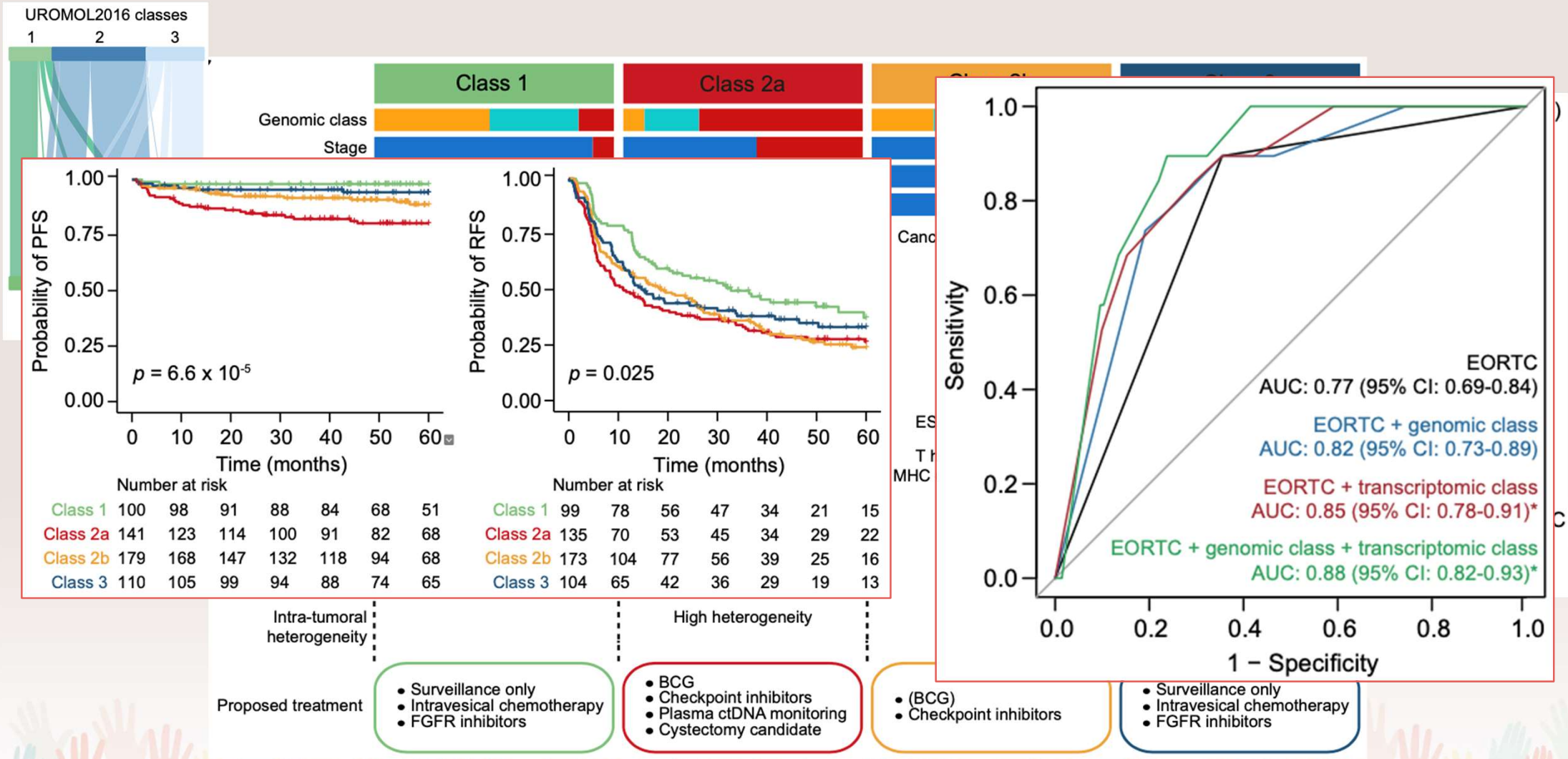




B

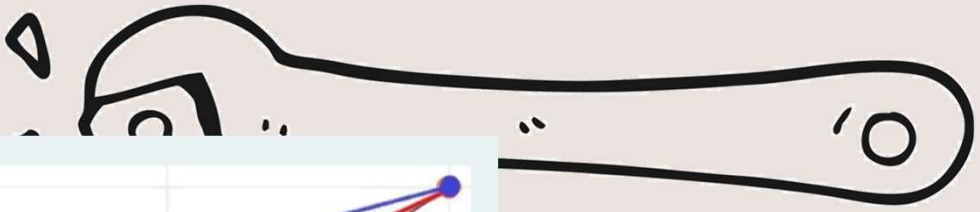
	Luminal-like Differentiation	Basal-like	EMT TF activity	CSC activity	Cell cycle activity	Molecular signature	Mutations
Class 1	UPKs PPARG GRHL3 BAMBI SPINK1			SHH RPSA ALDH1A3 ITGA6	*Early:* CCND1 ID1 RBL2		*FGFR3*
Class 3	GATA3	KRT5 KRT14 KRT15 CD44		ITGA6		BASE47+	*FGFR3* RNA-editing signature
Class 2	UPKs PPARG KRT20 GRHL3 BAMBI SPINK1	KRT14	SOX9 TWIST1 FOXF1 ZEB1 ZEB2 GATA6	PROM1 ALDH1A1 ALDH1A2 ALDH1A3 NES THY	*Late:* CDC20 CDC25A CDKs PLK1	CIS+ Prog.+	*TP53* *ERCC2* APOBEC mutation signature

Hedegaard, Cancer Cell 2016



Lindskrog, Nat Commun 2021

¿Y estratificar antes de la RTU?



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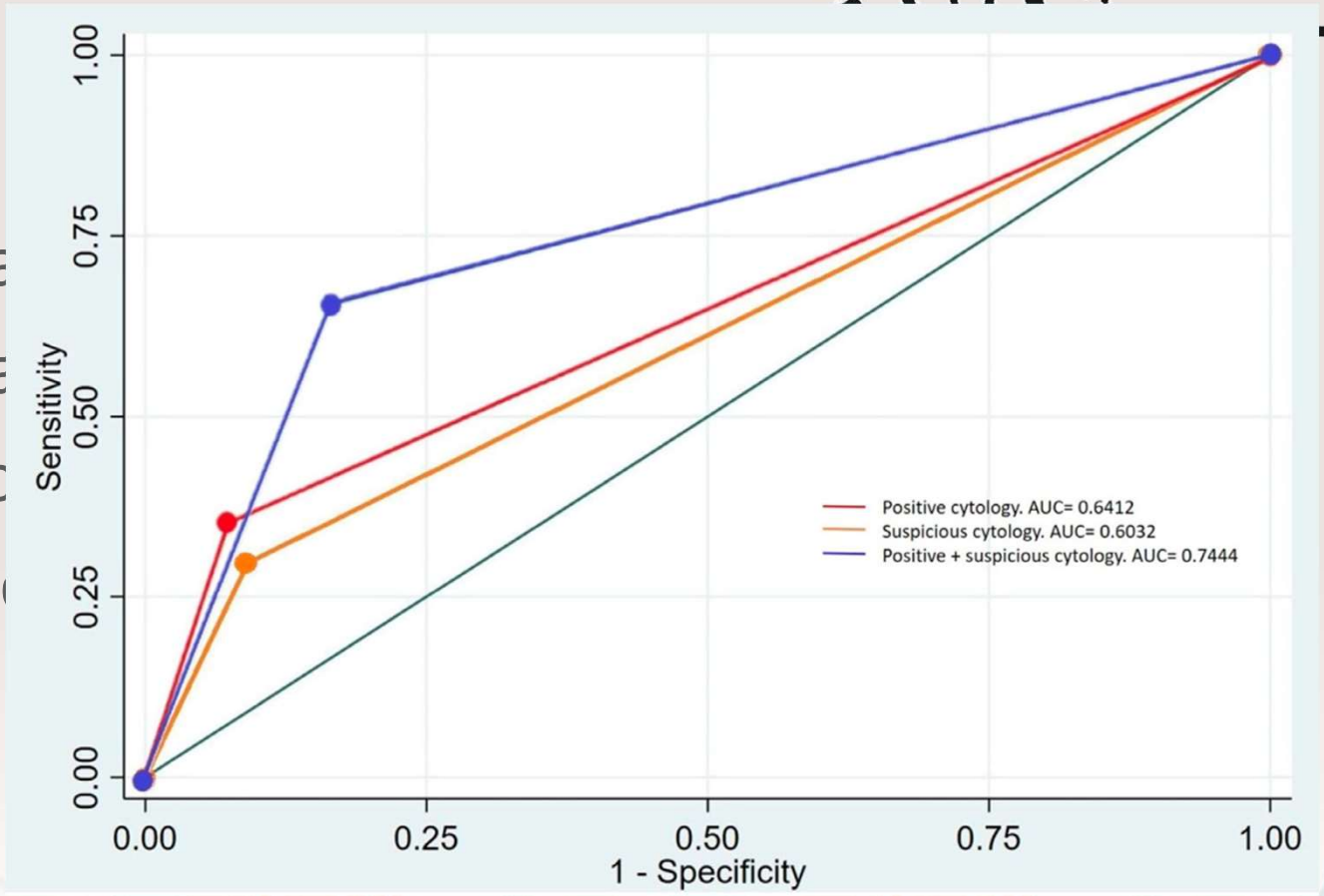
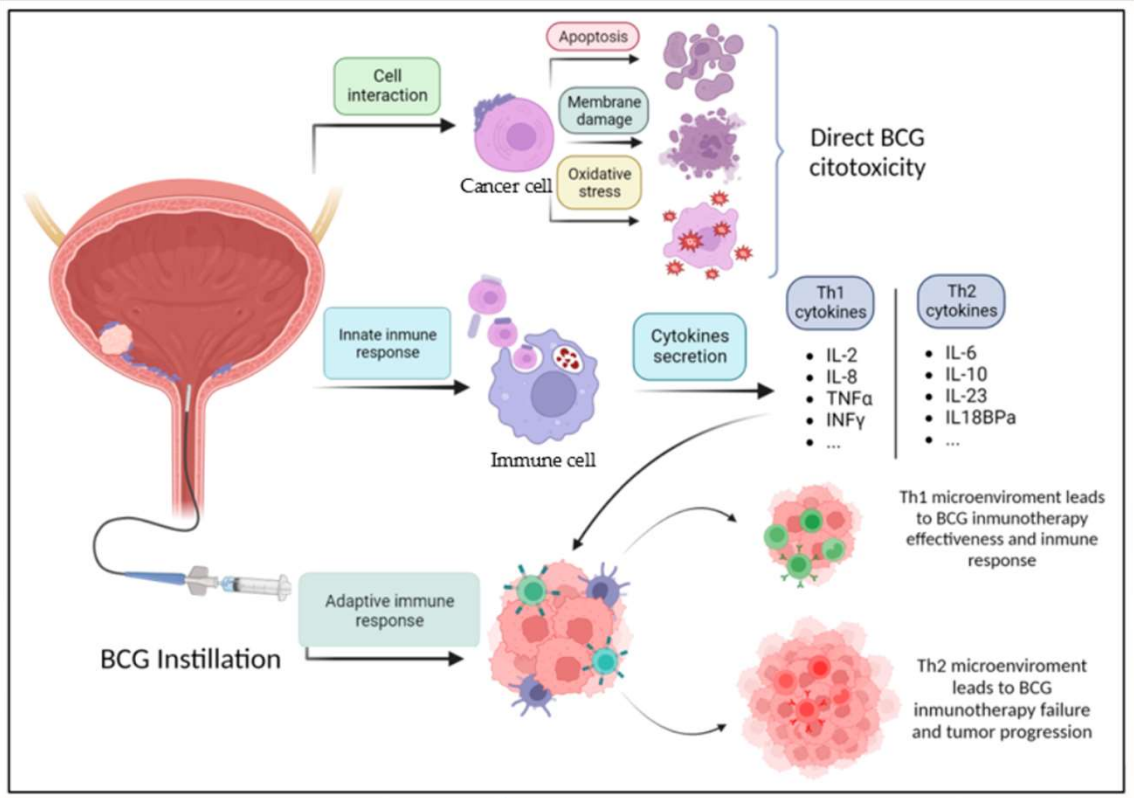


Gómez del Cañizo C, ..., Guerrero-Ramos F, Urol Oncol 2024, IN PRESS

¿Y estratificar según respuesta a BCG?



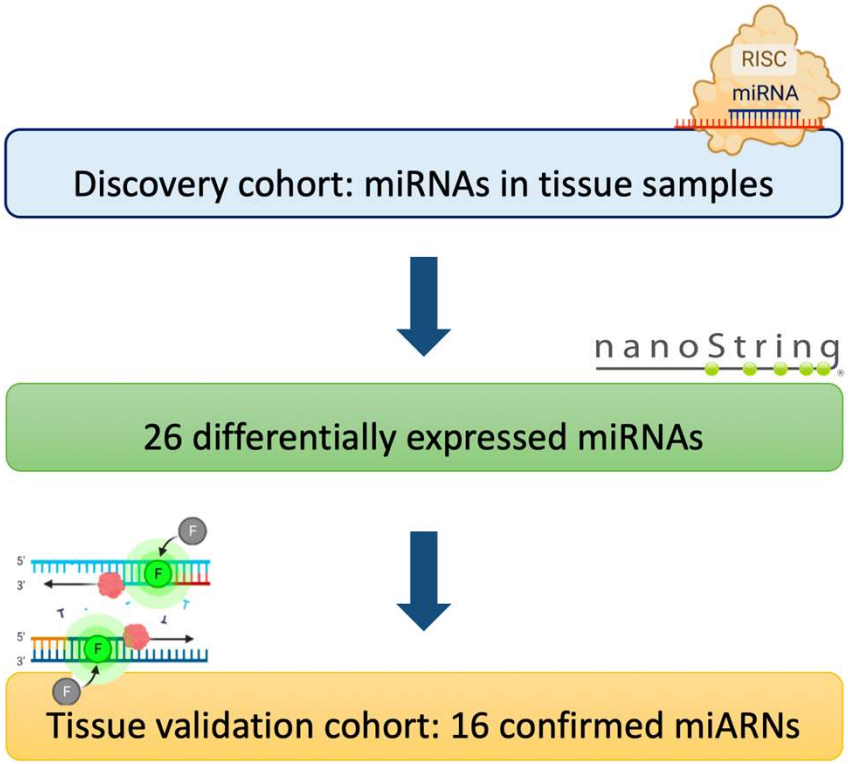
cancers
MDPI
Review

Immune Predictors of Response after Bacillus *Calmette–Guérin* Treatment in Non-Muscle-Invasive Bladder Cancer

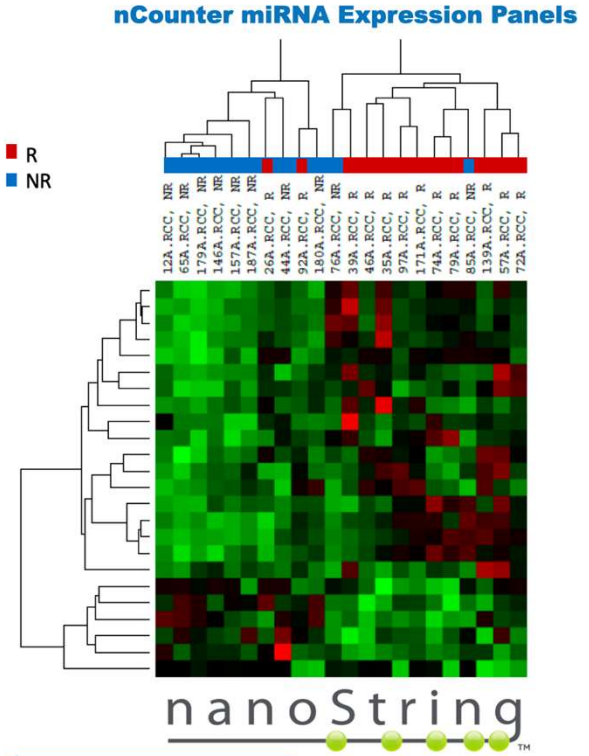
Marta Rodríguez-Izquierdo [1,*], Carmen G. Del Cañizo [1], Carolina Rubio [2,3,4], Ignacio A. Reina [2,3,4], Mario Hernández Arroyo [1], Alfredo Rodríguez Antolín [1], Marta Dueñas Porto [2,3,4] and Félix Guerrero-Ramos [1,4,5]

Rodríguez-Izquierdo M, …, Guerrero-Ramos F, Cancers 2023

¿Y estratificar según respuesta a BCG?



National patent (ES2856232)
PCT/ES2021/070204

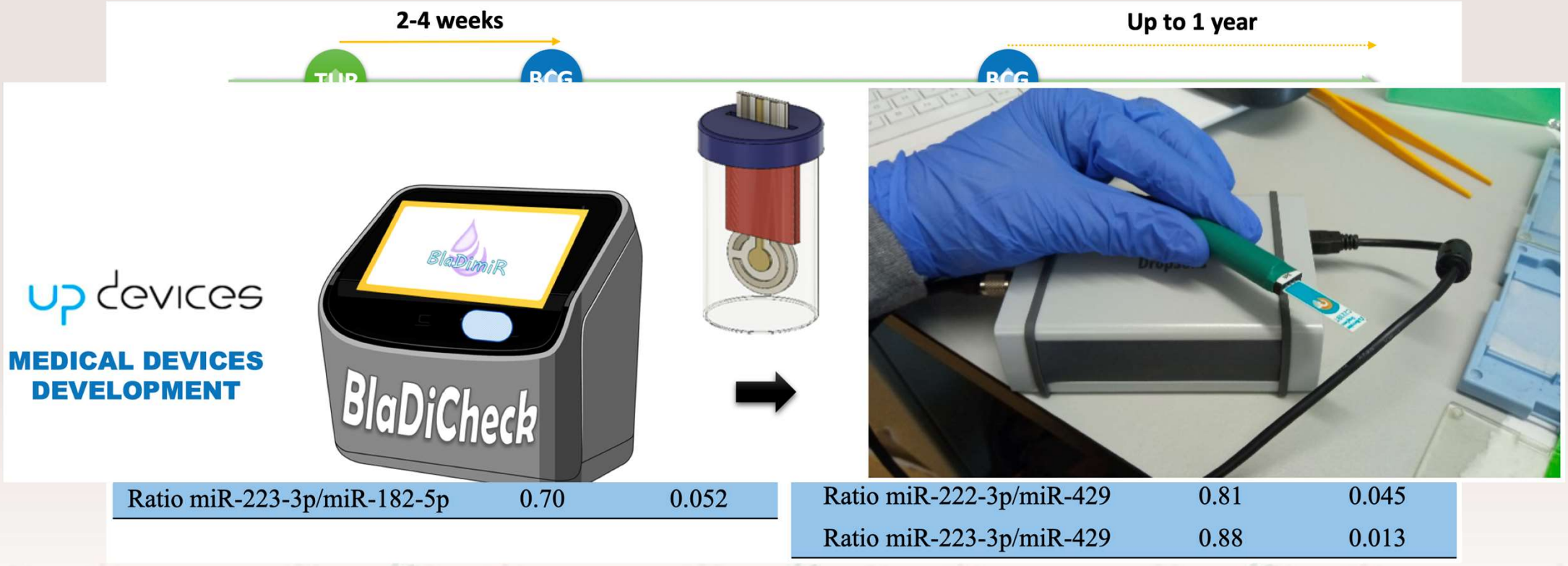


Responders (R; n=25)

Non responders (NR; n=14)

Dueñas M, Guerrero-Ramos F, UNPUBLISHED DATA

¿Y estratificar según respuesta a BCG?

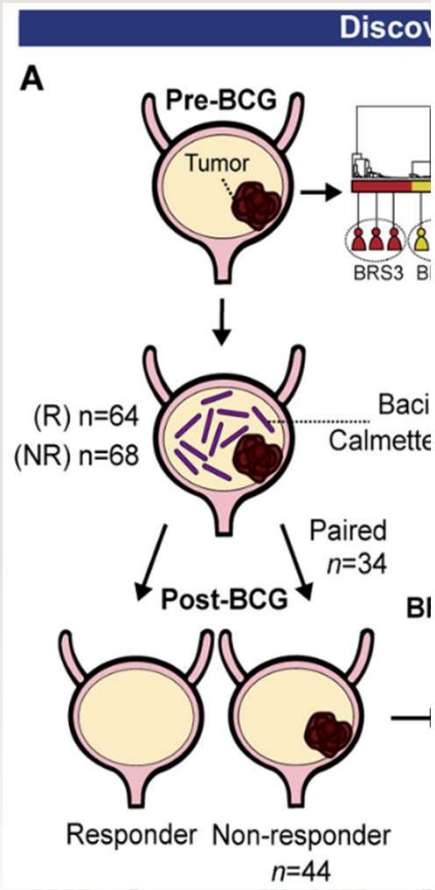


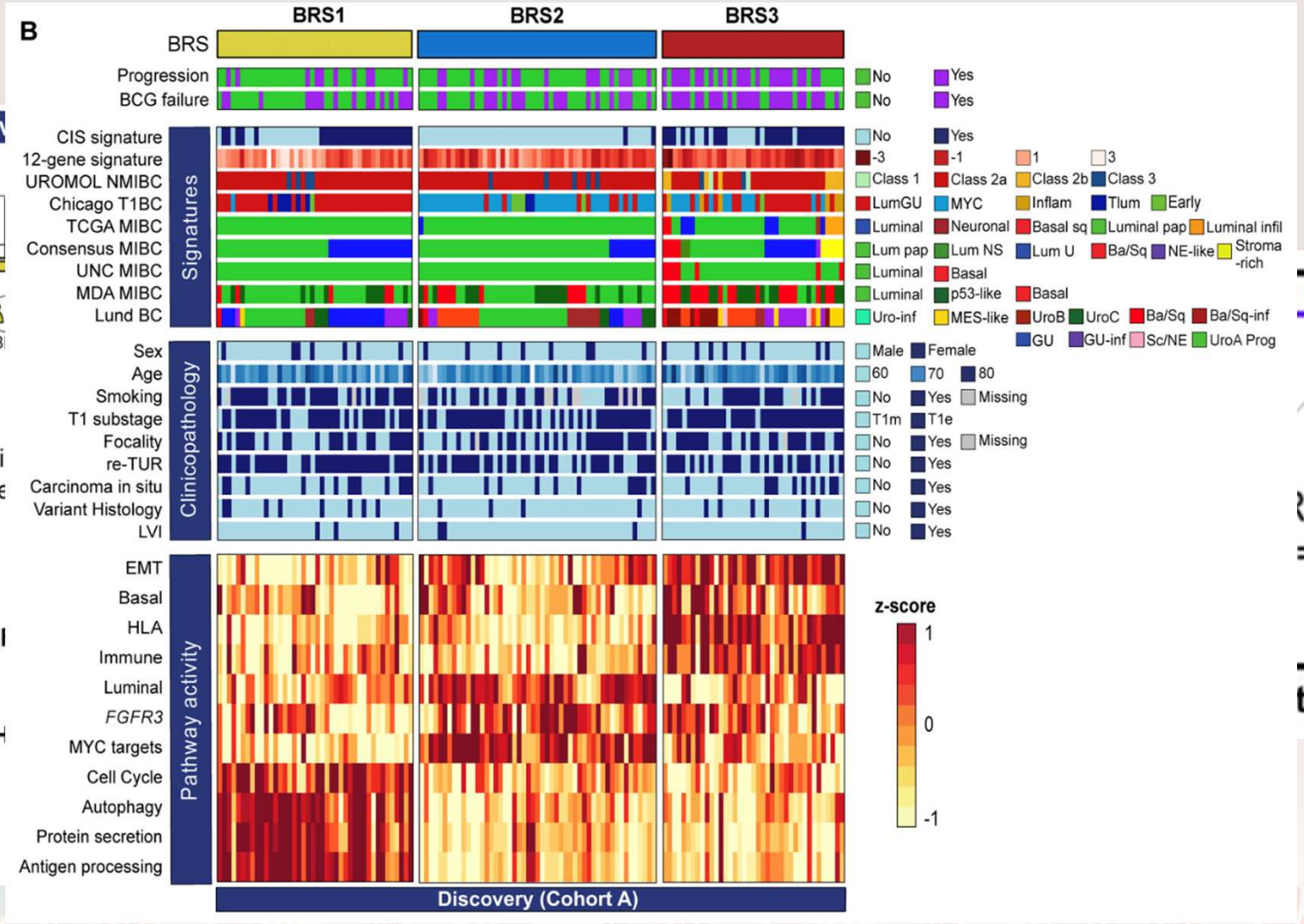
Ratio miR-223-3p/miR-182-5p	0.70	0.052

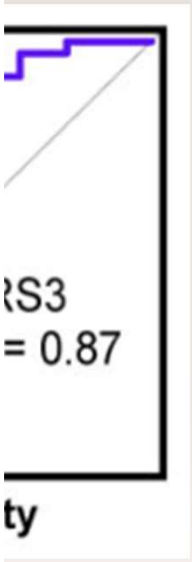
Ratio miR-222-3p/miR-429	0.81	0.045
Ratio miR-223-3p/miR-429	0.88	0.013

Dueñas M, Guerrero-Ramos F, UNPUBLISHED DATA

¿Y estratificar



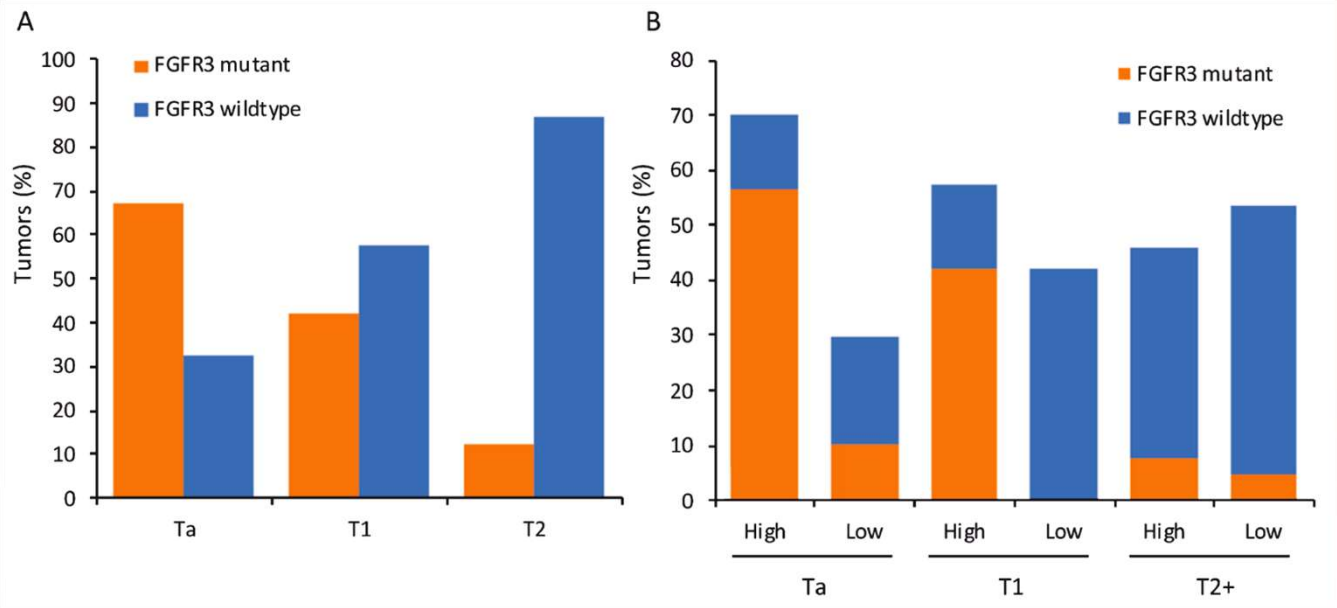




Jong FC, Sci Transl Med 2023

¿Y la "medicina personalizada" en NMIBC…?

- Sasanlimab
- Durvalumab
- Atezolizumab
- Nivolumab
- Pembrolizumab
- Enfortumab vedotin
- Nadofaragene firadenovec
- N-803
- Erdafitinib
- …



Knowles, World J Urol 2007

Reflexiones finales

- Importantes limitaciones en los grupos de riesgo actuales
- Futuro: integración de factores clínico-patológicos con firmas moleculares (asistido por inteligencia artificial)
- Limitaciones en clasificaciones moleculares (escasa evidencia, heterogeneidad en las técnicas, ausencia de validación clínica, aplicabilidad real)
- Impacto de los nuevos tratamientos en las diferentes clasificaciones (pronóstico)
- Predicción del riesgo → Predicción de la respuesta → MEDICINA PERSONALIZADA
- ABORDAJE MULTIDISCIPLINAR

5th ANNUAL UC COURSE
Emerging personalized therapies for the management of urothelial carcinomas

V CURSO ANUAL DE UC
Terapias personalizadas emergentes en el manejo del carcinoma urotelial

GRACIAS

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