VIGO NORTE INTERNATIONAL GU DEBATES

Estimating risk after nephrectomy
Are we all in the same page?
Are we overtreating?

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DISCLOSURES

Dr. Alonso Gordoa financial interests:

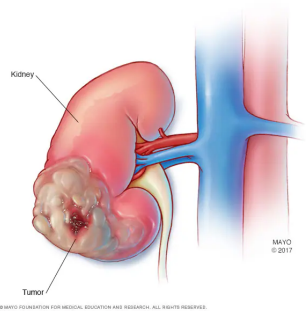
Personal conflicts of interest Scientific consultancy role (speaker and advisory roles) from Lilly, Ipsen, Astellas, Bayer, Johnson & Johnson, Eisai, Novartis, MSD, Recordati, Pfizer, BMS.

Research support Research grants from IPSEN, Johnson & Johnson.

Why does risk estimation after nephrectomy matter?

5-year OS-rate:
Stage I-II is > 80%
Stage III 50-70%

5-year Risk of recurrence:
Stage I = 7%
Stage II = 16%
Stage III = 30% - …60%



Median follow up 49 months (*Adamy et al.*):

83% of recurrences appear within first 5 years after surgery

62-64% of recurrences involve the lung, 9-15% the bone, 6-9% local recurrences

The estimated risk drives some decisions

Surveillance
Adjuvant therapy indication
Trials eligibility

Are good enough the scores we have nowdays?

Adamy A et al. J Urol 2011;185:433-8; Speed JM, et al. Curr Urol Rep. 2017;18:15; Romeo A, et al. Urol Oncol. 2020 Feb;38(2):42.e7-42.e12..

Where do the scores come from — and what for?

1997

TNM 1997

Stage alone is insufficient: grade and performance status add prognostic information

2001

UISS

UCLA · TNM + Fuhrman + ECOG PS · all histologies, M0 and M1.

Goal: overall survival (5 categories)

2002

UISS algorithm

N0M0 vs N+/M1.

Goal: counselling and selecting high-risk **M0** for adjuvant therapy (3 categories)

2002

SSIGN

Mayo · clear cell · stage, size, grade, necrosis.

Goal: cancer-specific death

2003

Leibovich

Mayo · clear cell M0. Goal: metastasis — “a stratification tool for prospective trials”

2017

GRANT

Grade, age, nodes, T stage (1 point each). c-index 0.59–0.61 (ASSURE), 0.63–0.66 (PROSPER)

Goal: A simple score with routine data.

2018

Leibovich update

3,633 pts, 1980–2010 · models per histology · 9 features · c 0.83 (PFS)

Goal: histology-specific prediction

2024

UroPredict

Machine learning · 3,372 pts (UroCCR) · 24 variables · iAUC 0.81, better than GRANT, SSIGN, UISS

Goal: to predict individual disease-free Survival & Very low risk Group to reduce FUP

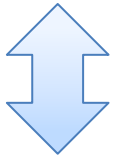
Zisman A, JCO 2001 & 2002 · Frank I, J Urol 2002 · Leibovich BC, Cancer 2003 & Eur Urol 2018 · Buti S, Ann Oncol 2017 & Oncologist 2026 · Correa AF, JCO 2019 · Margue G, npj Precis Oncol 2024 · Marconi L, CGUC 2021

They stratify well… in their own development cohorts

SSIGN Risk Score:
- SSIGN does not define risk groups. A continuous score from 0 to 15 and a table of estimated cancer-specific survival for each score. Scores are grouped only at the extremes.

Leibovich Risk Score:
- TNM, Nuclear Grade, Histologic tumor necrosis.
- Low risk: 0-2; Intermediate risk: 3-5; High risk: ≥ 6

Low risk: 5y-MFS 97.1%
Intermediate: 5y-MFS 73.8%
High risk: 5y-MFS 31.2%



Leibovich adds information to UISS for OS, CSS and DFS ($p \leq .002$); UISS adds nothing to Leibovich

UISS-defined high-risk group:
- pT3N0/x M0, any G, any ECOG PS
- pT any N1-2 M0, any G, any ECOG PS
- pT4N0/x M0, any G, any ECOG PS

Low risk: 5y-DFS 91.1% & 5-y OS 83.8%
Intermediate: 5y-DFS 80.4 % & 5y-OS 71.9%
High risk: 5y-DFS 54.7% & 5y-OS 44.0%

Leibovich BC et al. Cancer 2003;97:1663-71; Zisman A et al. J Clin Oncol 2002;20:4559-66 ; Speed JM et al. Curr Urol Rep 2017;18:15; Tan MH et al. Urology 2010;75:1365-70

…but not the same in a prospective trial: validation in ASSURE

1,647 patients · ASSURE

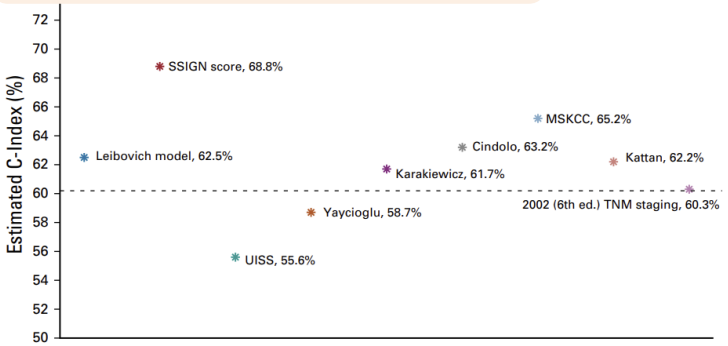
≥pT1b G3–4 or N+ M0

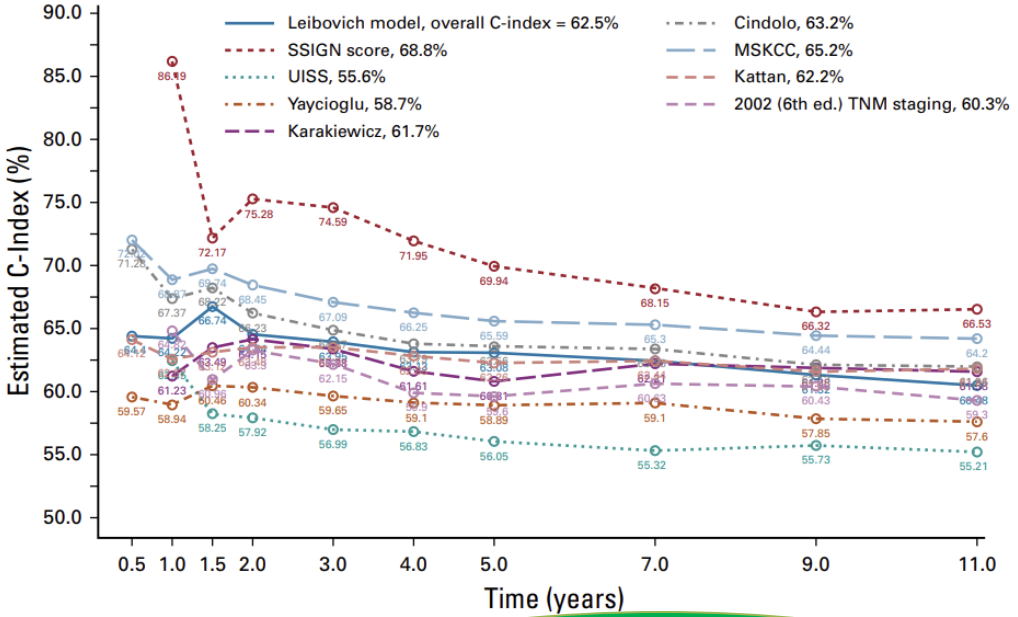
Central pathology review

Median FU 7.85 years

All models fell well below their original c-index

SSIGN 0.69 vs UISS 0.56





Good ranking, not accurate risk.
Discrimination, not for treatment decision.
Population measure, not patient prediction.

Correa AF, et al. J Clin Oncol. 2019 Aug 10;37(23):2062-2071.

KEYNOTE-564 / LITESPARK-022 criteria vs UISS, SSIGN and Leibovich

KN-564 & LITESPARK-022 eligibility

Intermediate–high risk · 86%

pT2 + grade 4 or sarcomatoid, N0 M0
pT3, any grade, N0 M0

High risk · 8%

pT4, any grade, N0 M0
pT any, any grade, N+ M0

M1 NED · 6%

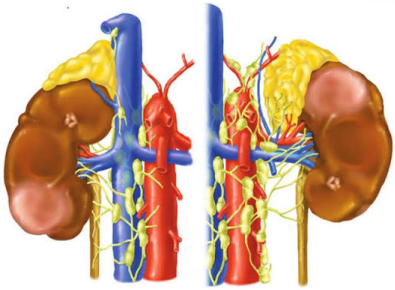
Primary + oligometastases completely resected at, or ≤1/2 years after, nephrectomy

% = distribution in KEYNOTE-564

	KEYNOTE-564 / LITESPARK-022	UISS (N0M0)	SSIGN	Leibovich
TNM edition	AJCC 8th	1997	1997	2002
T stage	✔	✔	✔ pT4 = 0	✔ T1a/T1b
Nodal status	**N+ = high**	N+ → "M" model	+2 (pNx = 0)	+2 (pNx = 0)
Tumour size	—	—	≥5 cm +2	≥10 cm +1
Grade	G4, only in pT2	G1–2 vs 3–4	G3 +1 · G4 +3	G3 +1 · G4 +3
Sarcomatoid	only in pT2	—	—	—
Necrosis	—	—	+2	+1
ECOG PS	—	✔ **0 vs ≥1**	—	—
Resected M1	eligible (M1 NED)	separate model	M1 +4	excluded
Output	Eligible yes / no	Low / Int. / High	Score 0–15, no groups	0–2 / 3–5 / ≥6
Used in	KEYNOTE-564, LITESPARK-022	ASSURE, S-TRAC	PROTECT	SORCE, RAMPART

Choueiri TK et al. NEJM 2021;385:683-94 · Choueiri TK et al. LITESPARK-022, ASCO GU 2026 LBA418 / NEJM 2026 · Zisman A et al. JCO 2002 · Frank I et al. J Urol 2002 · Leibovich BC et al. Cancer 2003 · Correa AF et al. JCO 2019

Lymph node dissection



Mayo Clinic 2017

- 1,797 RN for M0 RCC (1990–2010)
- LND in 34% · pN1 6.2%. Median follow-up 10.6 years
- Propensity score: no ↓ distant metastases, cancer-specific or all-cause mortality
- No benefit even with cN+ or high predicted pN1 risk

Canada 2021

- 2,699 RN for M0 RCC (CKCis)
- LND in 30% · pN1 10.8%
- No improvement in OS, RFS or CSS (4 propensity methods)
- No benefit at increasing pN1 probability. Number of nodes removed not associated with outcome

The same tumour can be “intermediate” or “high risk” if pNx or pN1
Modifies eligibility in trials

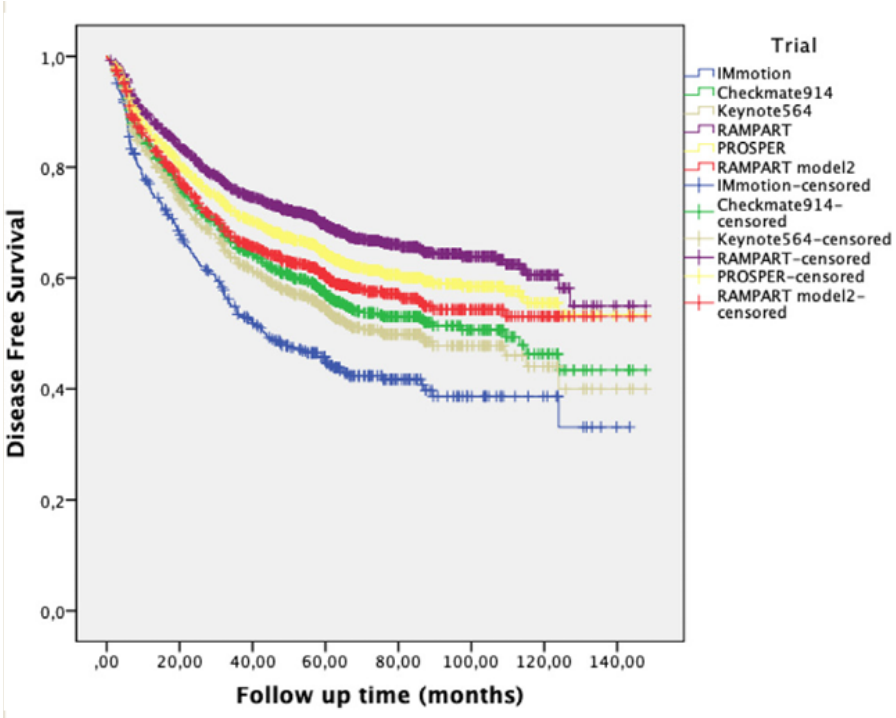
Gershman B et al. Eur Urol 2017;71:560-7; Kokorovic A et al. Urol Oncol 2021;39:371.e17-25; Campi R et al. Eur Urol Oncol 2024;7:323-7

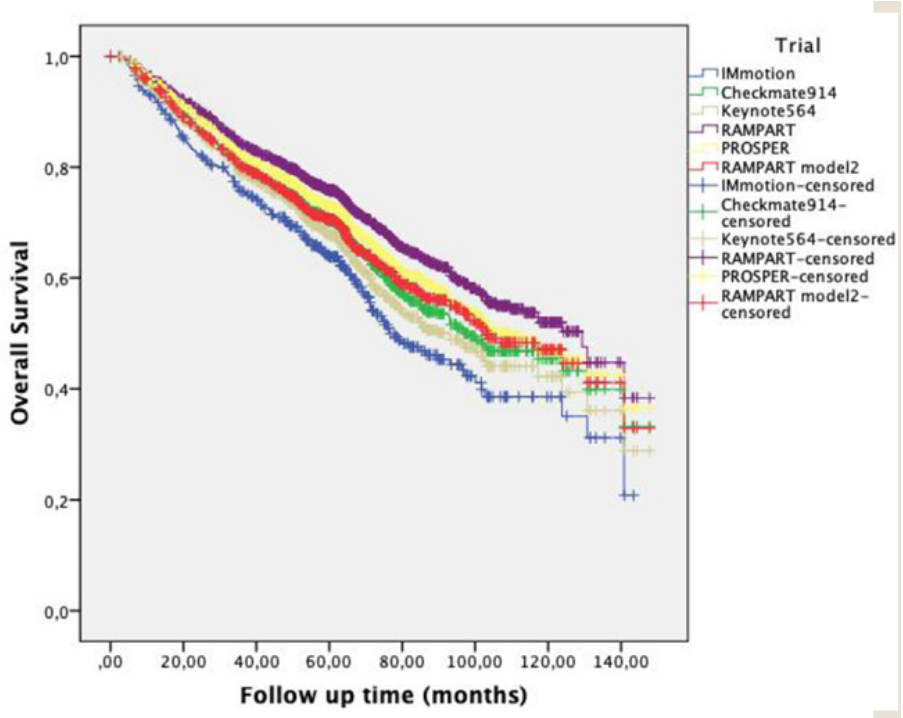
Adjuvant trials have included different eligibility criteria

Trial (n)	Drug	Selection tool	Population
VEGF-TKI / mTOR			
ASSURE (1,943)	Sunitinib / sorafenib	**UISS-based**	≥pT1b G3–4 N0 to pT4 or N+
S-TRAC (615)	Sunitinib	**Modified UISS high risk**	ccRCC · ≥pT3 N0 or N+
PROTECT (1,538)	Pazopanib	**TNM + grade**	ccRCC · pT2 G3–4, pT3–4, N+
SORCE (1,711)	Sorafenib	**Leibovich 3–11**	Any histology · intermediate + high
ATLAS (724)	Axitinib	**TNM stage**	ccRCC (>50%) · ≥pT2 and/or N+, any grade
EVEREST (1,545)	Everolimus (mTOR)	**TNM + grade**	Any histology · pT1b G3–4 to pT4, N+
Immunotherapy			
KEYNOTE-564 (994)	Pembrolizumab	**TNM + grade**	ccRCC · pT2 G4/sarc, pT3, pT4, N+, M1 NED (2y)
IMmotion010 (778)	Atezolizumab	**TNM + grade**	cc/sarc · pT2 G4, pT3a G3–4, pT3b+, N+, M1 NED
CheckMate 914 A (816)	Nivolumab + ipilimumab	**TNM + grade**	ccRCC · pT2a G3–4, pT2b–T4, N+
PROSPER (766)	Periop. nivolumab	**Clinical stage, ≥cT2/N+**	Any histology · ≥cT2 or cN+
RAMPART (1,750)	Durvalumab ± tremelimumab	**Leibovich 3–11**	Any histology · intermediate capped 25%
LITESPARK-022 (1,841)	Pembro + belzutifan vs pembro	**KEYNOTE-564 criteria**	ccRCC · pT2 G4/sarc, pT3, pT4, N+, M1 NED (2y)

Choueiri TK et al. NEJM 2024;390:1359-71 · Pal SK et al. Lancet 2022;400:1103-16 · Motzer RJ et al. Lancet 2023;401:821-32 · Allaf M et al. Ann Oncol 2022;33(s7):LBA67 · Oza B et al. Contemp Clin Trials 2021 (RAMPART design) · RAMPART: ESMO 2025 LBA93 / ASCO 2026 · Zouein J et al. Immunotherapy 2023;15:93-100

Heterogeneous population included in trials (results from the RECUR database)





Marconi L, Sun M, Beisland C, et al. Clin Genitourin Cancer 2021;19:e92-9

One pT4 tumour, but different definitions

57 y-o Male

pT4 N0 M0

Clear cell RCC

8.0 cm

Grade 2

No necrosis

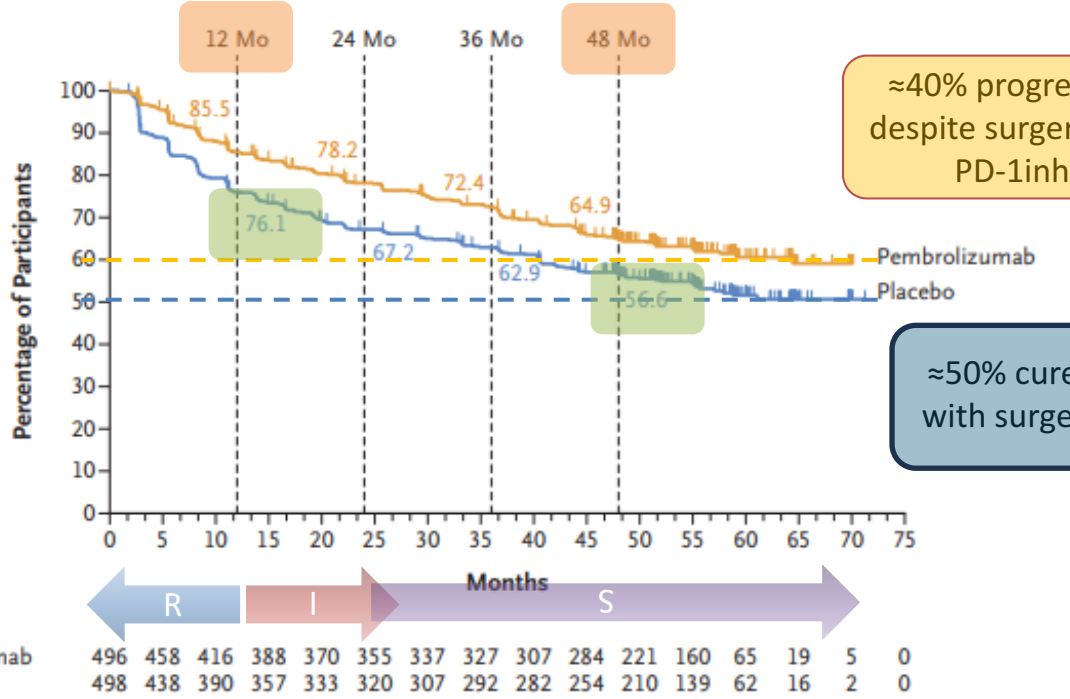
ECOG 0

System	Points for this tumour	Label → expected outcome
SSIGN	pT4 = 0 points; size =2 points	**Score 2 · low category** 5-y CSS 95%
Leibovich	pT4 = 4	**Score 4 · intermediate** 5-y MFS 76%
UISS	categorical: **T4 → high**	**High risk** 5-y DSS 55%
KEYNOTE-564 **LITESPARK-022**	categorical: **pT4 → high**	**High risk** Eligible for adjuvant pembrolizumab (+belzutifan)

Frank I et al. J Urol 2002;168:2395-400 · Leibovich BC et al. Cancer 2003;97:1663-71 · Zisman A et al. J Clin Oncol 2002;20:4559-66 · Choueiri TK et al. NEJM 2021;385:683-94

Are we overtreating? Or undertreating?

mFUP 57.2 months



≈40% progressed despite surgery and PD-1inh

Added benefit from pembrolizumab to surgery

≈50% cured with surgery

Barata P. ASCO GU 2024; Powles T et al. Lancet Oncol 2022;23:1133-44 (DFS by risk, 30-mo update) · Choueiri TK et al. NEJM 2024;390:1359-71 (OS by risk, 57-mo follow-up)

Are we overtreating? Data from the KN 564 with OS benefit

57%

Of placebo patients disease-free at 4 years

8.3%

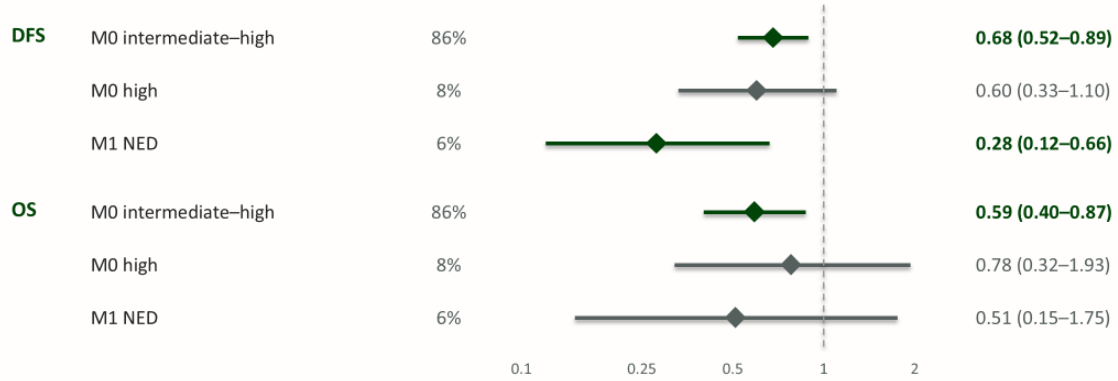
absolute DFS gain at 4 years (64.9% vs 56.6%)

5.2%

absolute OS gain at 4 years (91.2% vs 86.0%)

18.6%

Grade 3-4 Treatment Related Adverse Events



Choueiri TK et al. NEJM 2024;390:1359-71 (48-month DFS 64.9% vs 56.6%; OS 91.2% vs 86.0%) · Rojas PA et al. World J Urol 2025;43:307. NNT derived from 4-year Kaplan–Meier estimates (approximate).

UroPredict calculator ->How to assess the risk of relapse

1 Data

UroCCR registry (France)
23 centres · 2000–2020
3,372 pts · pTany Nany M0
>200 variables

2 Split by centre

Training: 2,241 pts
(10 centres)
Test: 1,131 pts
(13 centres)

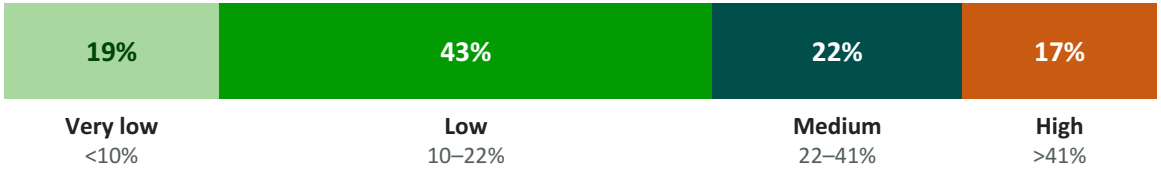
3 Modelling

MICE imputation
Cox-LASSO vs random forest vs gradient boosting
3×10-fold CV → Cox
24 variables

4 Test results

DFS: 480 events (14.2%)
iAUC 0.81 · Brier 0.11
> GRANT, SSIGN, UISS Leibovich-2018 (51%)

Output: web calculator → 4 groups by predicted 5-y recurrence risk (test cohort)



Limitations

geographic external validation (France only); not prospective.

Margue G, et al. NPJ Precis Oncol. 2024 Feb 23;8(1):45.

UroPredict 2 calculator ->How to assess the risk of relapse

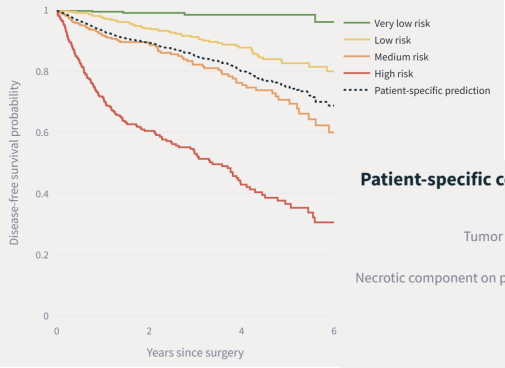
UroCCR
RÉSEAU FRANÇAIS DE RECHERCHE SUR LE CANCER DU REIN

Tumor diameter (cm) 8.0	**Histological subtype** Clear cell	**Age** (years) 57	**Sex** Male	**Fuhrman grade / ISUP** 2
ECOG PS* (1) 0	**Bilateral tumors** No	**pT** (2) pT4	Postoperative complications No	Microvascular emboli on pathology No
pN (3) N0	Necrotic component on pathology No	Symptoms at diagnosis Asympto…	Serum creatinine level* (µmol/L) 56.0	Renal failure at diagnosis (5) No
ASA score* (4) 2	Neutrophils* (10^9/L) 5.00	Lymphocytes* (10^9/L) 0.80	Neutrophils to lymphocyt… 6.25	Surgery type Radical n…
Time from diagnosis to surgery (months) 2.0	Adrenalectomy No	NSS indication (6) Elective	Lymphadenectomy No	Surgical margins Negative

* *Preoperative*

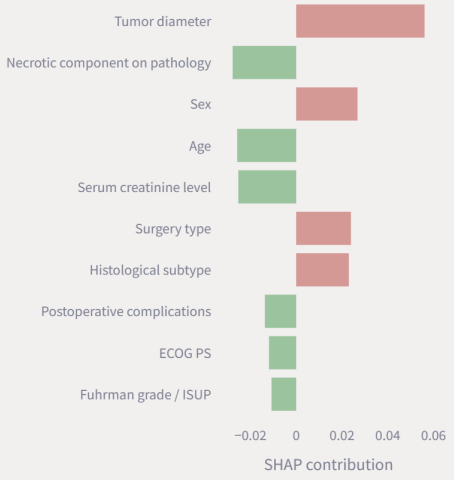
0.25 Medium risk

Patient-specific survival curve compared to pre-defined risk groups



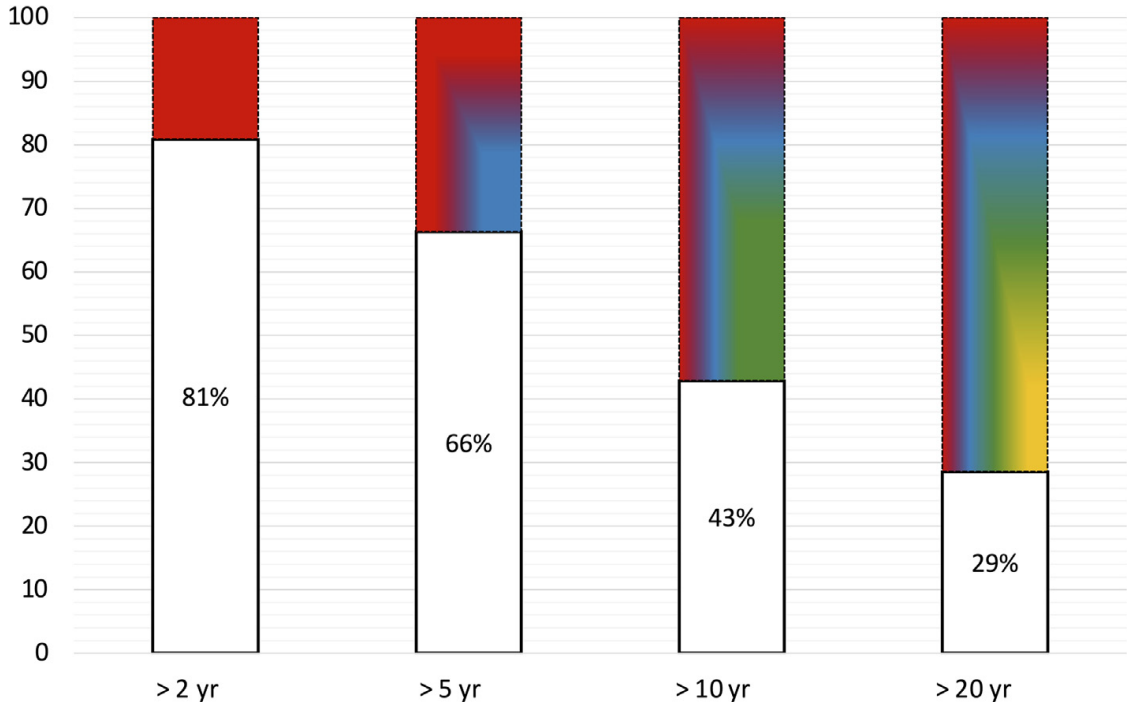
1-y DFS: 0.93
2-y DFS: 0.89
3-y DFS: 0.85
4-y DFS: 0.80
5-y DFS: 0.75

Patient-specific contribution of features



https://uropredict.sophiagenetics.com/?model=uropredict2

Who lives long enough to benefit? Other-cause mortality than of RCC recurrence



1,745 ccRCC → 419 (24%)

met KEYNOTE-564 criteria · 4 European centres, 2015–2021 · 83% pT3N0

Age, Charlson index and stage (Stewart-Merrill model) as part of shared decision-making

Campi R, Pecoraro A, Roussel E, et al. Eur Urol Oncol 2024;7:323-7

Early relapse, early progressors? Or, already metastatic, but tools not enough for M1 detection?

Trial	Arm	N	Events at 12 mo, n (%)	Total DFS events	Approx. % of all events in first 12 mo	Median FU
KEYNOTE-564	Pembrolizumab	496	**≈72 (14.5%)**	174	**≈41%**	57.2 mo
	Placebo	498	**≈119 (23.9%)**	224	**≈53%**	
IMmotion010	Atezolizumab	390	**≈88 (22.6%)**	164	**≈54%**	44.7 mo
	Placebo	388	**≈100 (25.9%)**	168	**≈60%**	
CheckMate 914	Nivolumab + ipilimumab	405	**≈64 (15.8%)**	110	**≈58%**	37.0 mo
	Placebo	411	**≈79 (19.2%)**	118	**≈67%**	

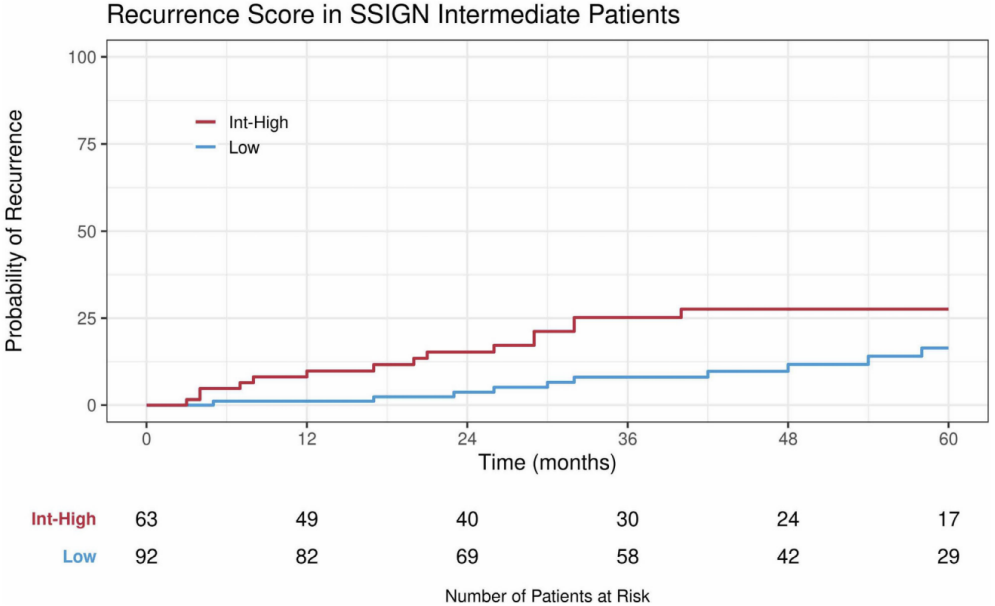
Choueiri TK et al. NEJM 2024;390:1359-71 · Pal SK et al. Lancet 2022;400:1103-16 · Motzer RJ et al. Lancet 2023;401:821-32

Beyond TNM: can biology refine the intermediate-risk group?

1 Tissue transcriptomics

16-gene recurrence score · TCGA, 428 ccRCC

- **SSIGN intermediate split:** 3-y recurrence 8.0% (RS low) vs 25.2% (RS high)
- **AUC at 3 y:** SSIGN 0.69 → RS 0.74 → combined 0.78



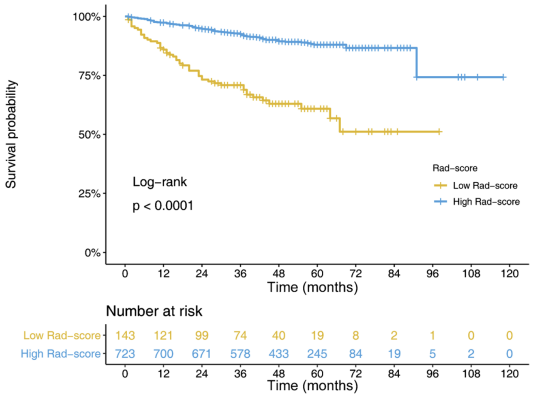
Patel N et al. Cancer Med 2023;12:6437-44 · Yang G et al. Eur J Nucl Med Mol Imaging 2022;49:2949-59 · Rini BI, Albiges L, et al. Ann Oncol 2025;36:1525

Beyond TNM: can biology refine the risk groups?

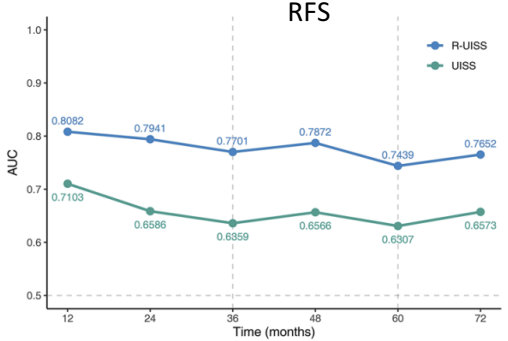
2 **CT radiomics**

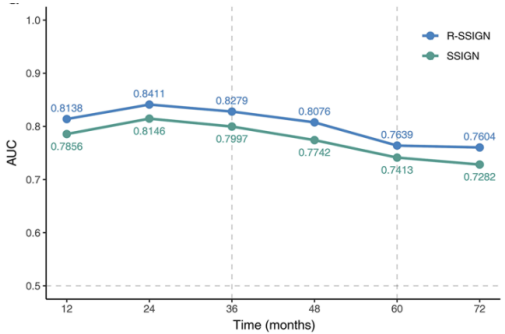
Tumour heterogeneity · 866 ccRCC, 12 centres

- **Independent predictor of RFS** (HR 4.44)
- **c-index:** UISS 0.64 → 0.74 · SSIGN 0.76 → 0.78



Time-AUC and decision curve analysis (DCA) of the combined nomograms in the prediction of RFS





Patel N et al. Cancer Med 2023;12:6437-44 · Yang G et al. Eur J Nucl Med Mol Imaging 2022;49:2949-59 · Rini BI, Albiges L, et al. Ann Oncol 2025;36:1525

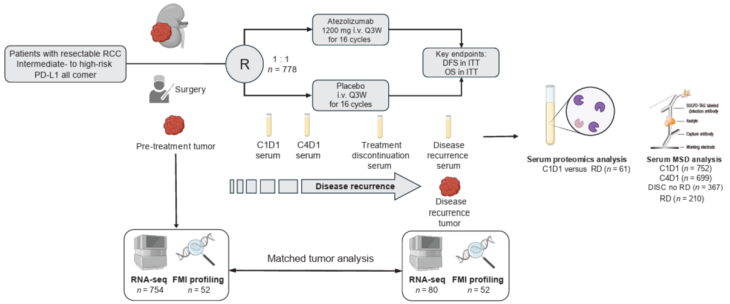
Beyond TNM: can biology refine the risk groups?

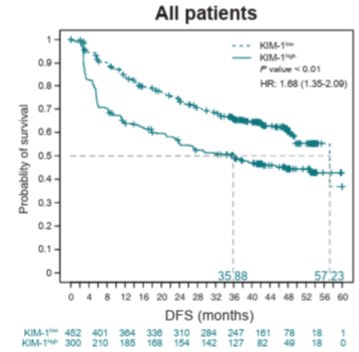
3 **KIM-1**

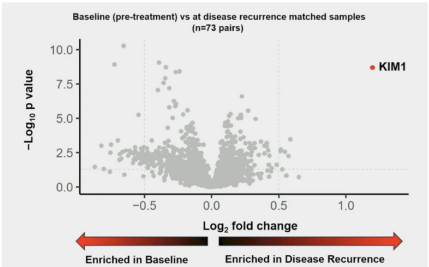
IMmotion010 post-hoc · 752 serum samples

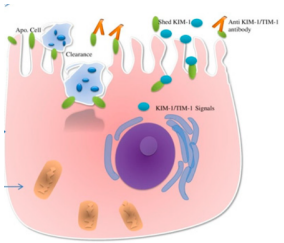
- **Prognostic:** KIM-1 high → worse DFS (HR 1.68)
- **Predictive:** atezolizumab benefit if KIM-1 high (HR 0.72 vs 1.20)

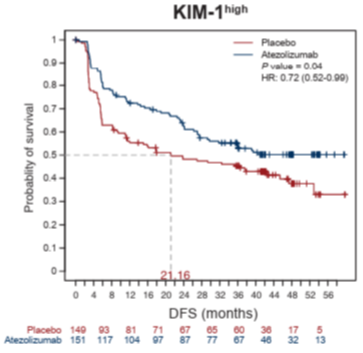
PART 2. Association of circulating KIM-1 with DFS outcomes (N=300 vs N=452)

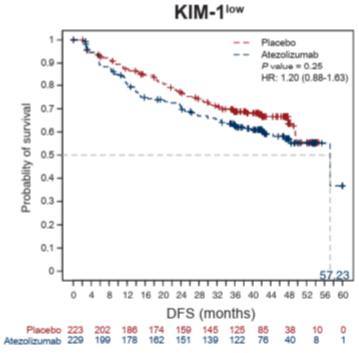












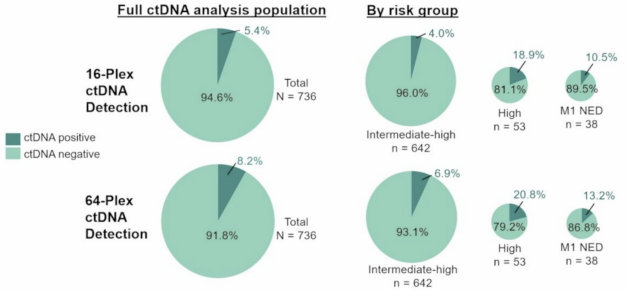
PART 1 (N=73 Baseline vs Disease recurrence)

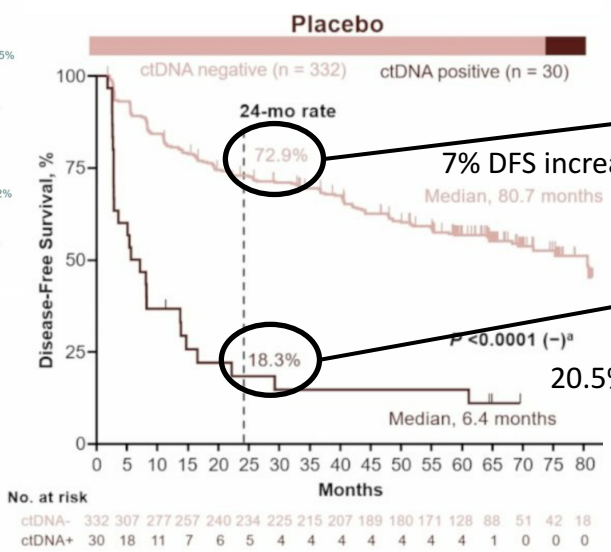
Patel N et al. Cancer Med 2023;12:6437-44 · Yang G et al. Eur J Nucl Med Mol Imaging 2022;49:2949-59 · Rini BI, Albiges L, et al. Ann Oncol 2025;36:1525

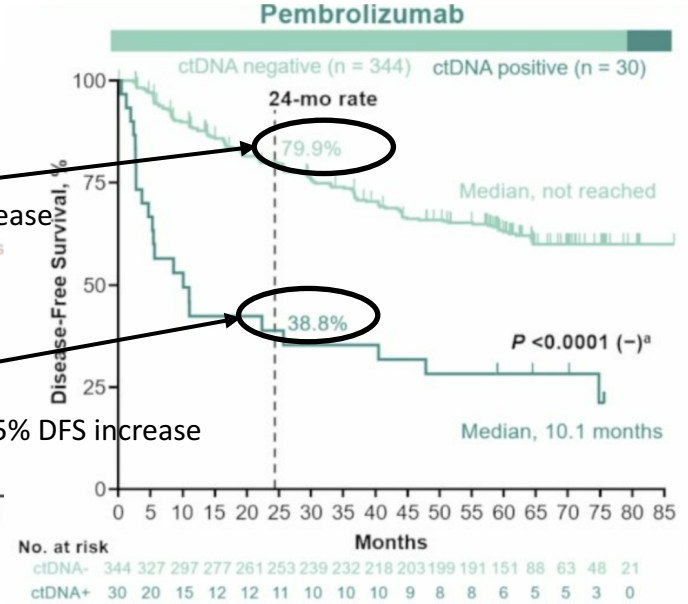
Beyond TNM: can biology refine the risk groups?

4 **ctDNA**

Keynote 564 – post hoc analysis







7% DFS increase

20.5% DFS increase

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Take-home messages

- Classic scores (UISS, SSIGN, Leibovich) were built on 1970–2000 cohorts to describe prognosis; prospective c-index 0.56–0.69, barely above TNM (0.60). Uropredict2 offers a contemporary calculator of individual patient risk.
- Positive trials (KEYNOTE-564, LITESPARK-022) select by TNM + grade, not by these previous scores. Eligibility ≠ Prognostic scale.
- ≈ 50% of patients are free of disease at 4 years FUP, but also, 30-40% of patients will progress irrespective of adjuvant treatment.
- Novel markers: Transcriptomics, radiomics, KIM1,…?
- We are still looking for the best deffinition of “high risk” patients & the prediction of response.