7th edition
GLOBAL CONGRESS ON BLADDER CANCER

Update on perioperative systemic therapies for UTUC

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Conflicts of interest

Type of affiliation / financial interest	Name of commercial company
Receipt of grants/research supports	BMS
Receipt of honoraria or consultation fees	Astellas, Astra Zeneca, BMS, Cepheid, Ferring, Ipsen, Janssen, Merck, MSD, Pfizer, Roche
Stock shareholder	-
Other support (please specify):	Allergan, Astellas, Astra Zeneca, Bayer, BMS, Janssen, Merck, MSD, Novartis, Pfizer, Pierre Fabre, Roche

Rationale for perioperative systemic therapy

1. Local & metastatic recurrence rate ~ 40% @ 2 years
2. Deaths are generally not local events → patients die as a result of metastatic disease
3. Local interventions will not deal with micrometastases
4. UC is chemosensitive: multi-agent chemotx can cure some patients with metastatic UC
5. UTUC shares similar biology with MIBC

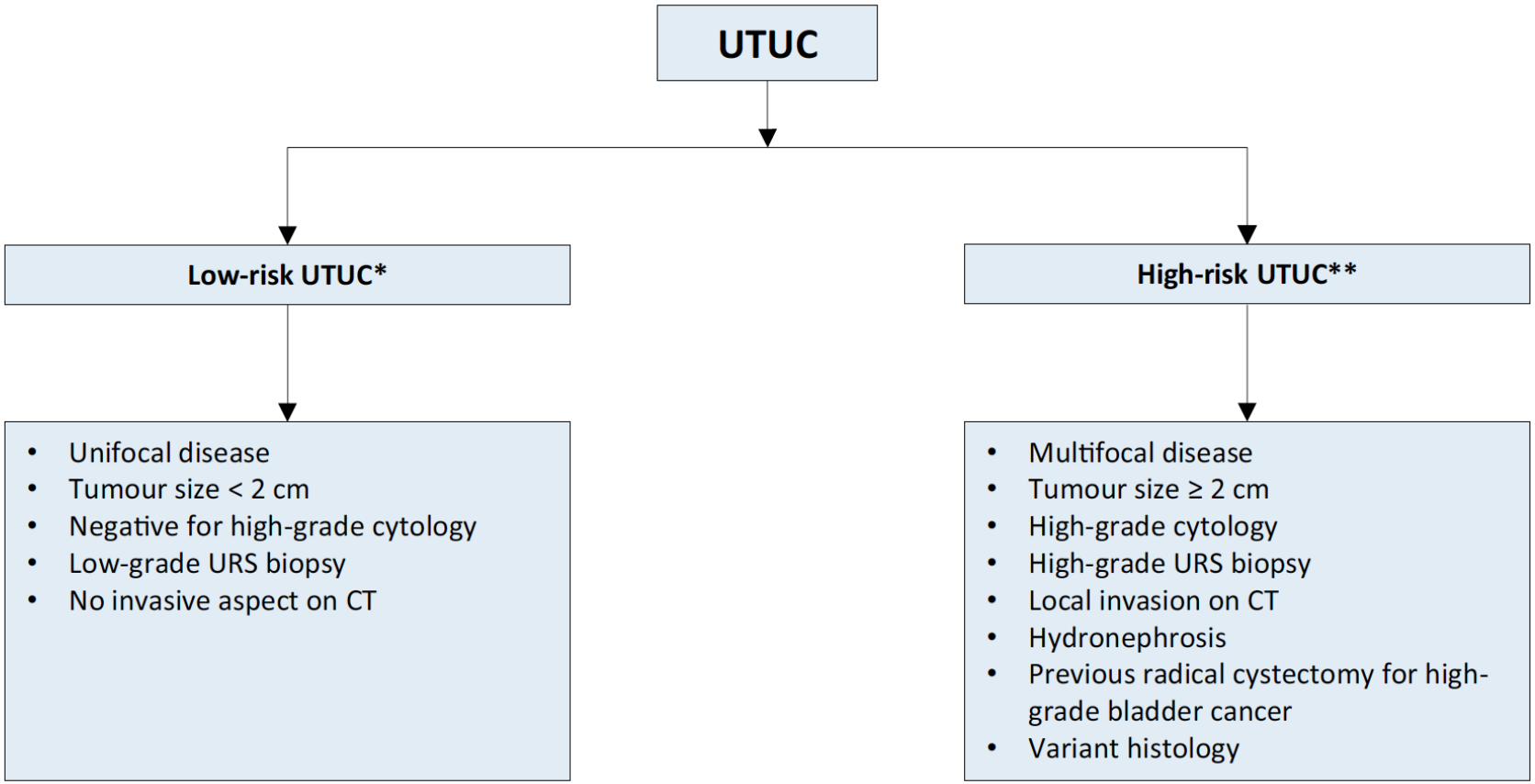
→ systemic therapy could eradicate micrometastatic disease

→ improve cure rates

Which patient might benefit from neoadjuvant systemic therapy?

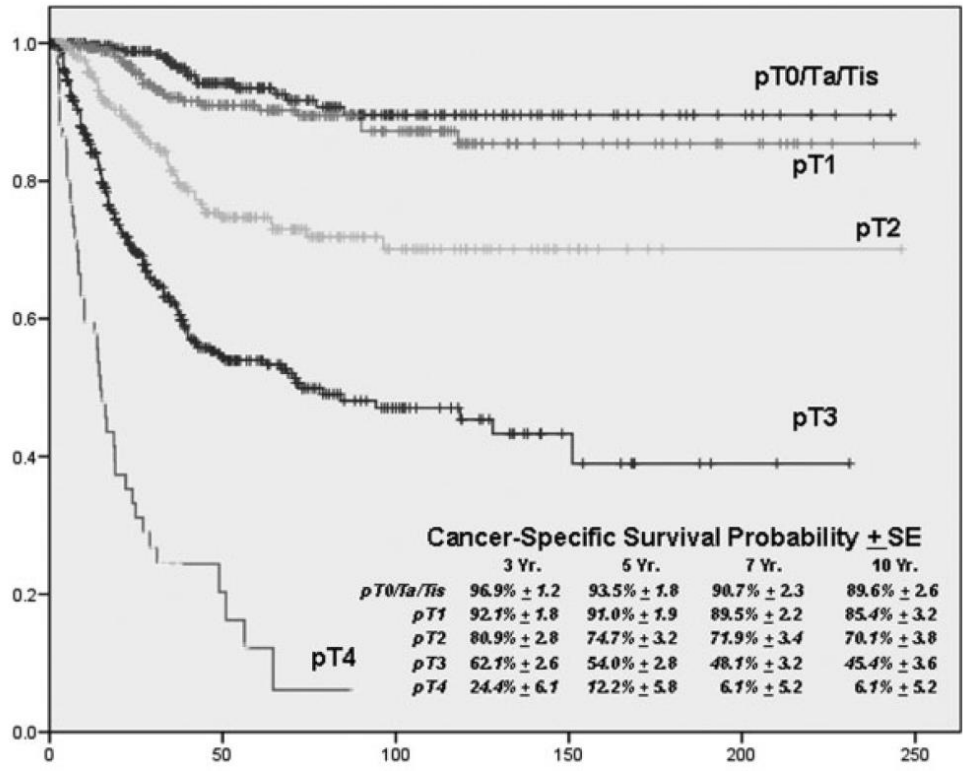
What is the dilemma with UTUC?

Risk stratification of UTUC



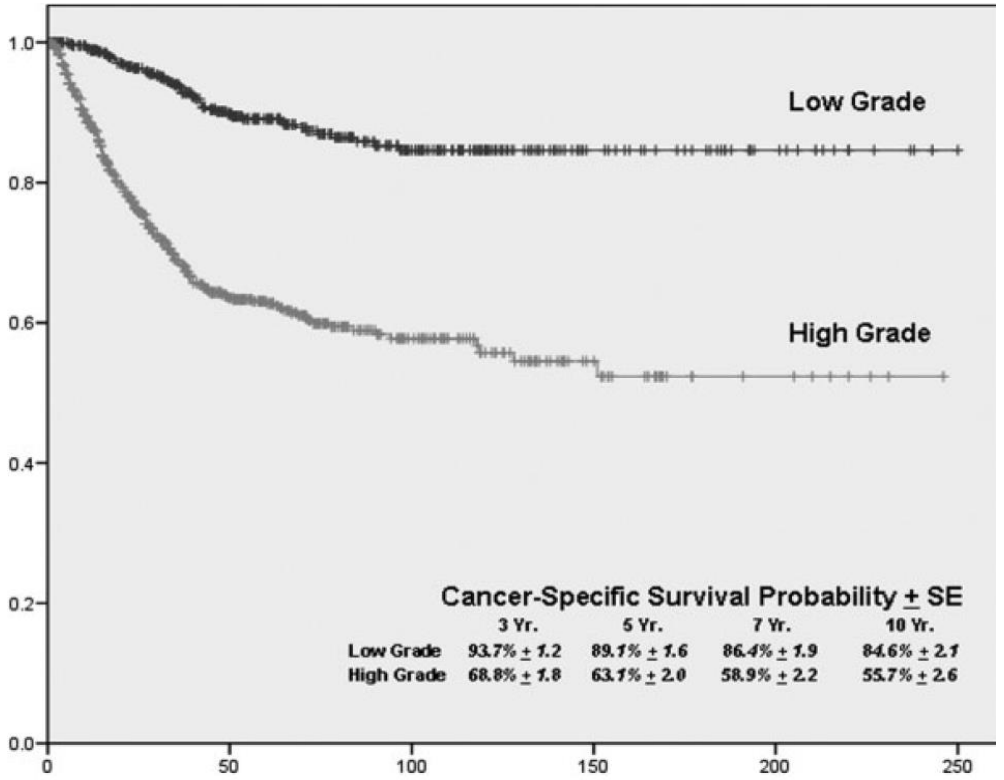
EAU Guidelines (2022)

Cancer specific survival for UTUC



Cancer-Specific Survival Probability ± SE

	3 Yr.	5 Yr.	7 Yr.	10 Yr.
pT0/Ta/Tis	96.9% ± 1.2	93.5% ± 1.8	90.7% ± 2.3	89.6% ± 2.6
pT1	92.1% ± 1.8	91.0% ± 1.9	89.5% ± 2.2	85.4% ± 3.2
pT2	80.9% ± 2.8	74.7% ± 3.2	71.9% ± 3.4	70.1% ± 3.8
pT3	62.1% ± 2.6	54.0% ± 2.8	48.1% ± 3.2	45.4% ± 3.6
pT4	24.4% ± 6.1	12.2% ± 5.8	6.1% ± 5.2	6.1% ± 5.2

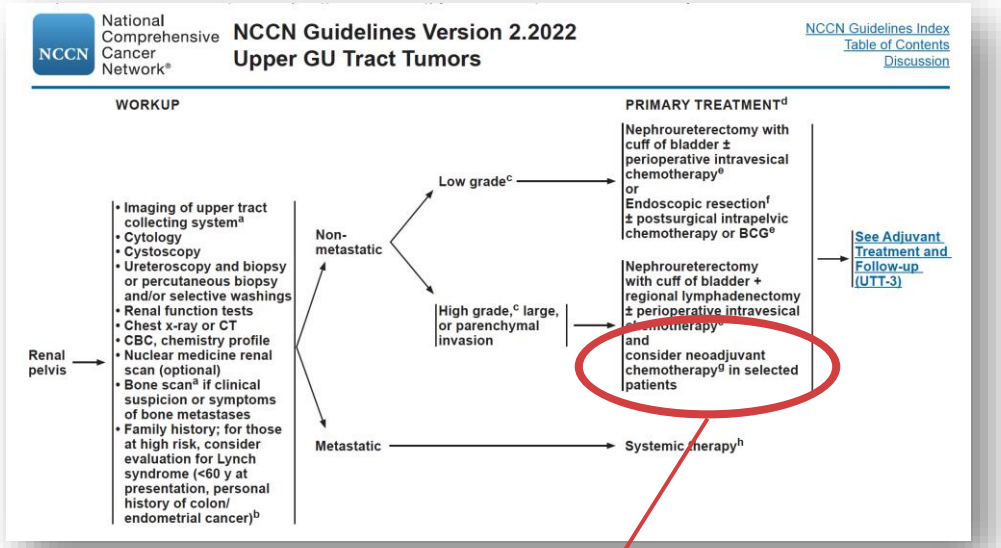


Cancer-Specific Survival Probability ± SE

	3 Yr.	5 Yr.	7 Yr.	10 Yr.
Low Grade	93.7% ± 1.2	89.1% ± 1.6	86.4% ± 1.9	84.6% ± 2.1
High Grade	68.8% ± 1.8	63.1% ± 2.0	58.9% ± 2.2	55.7% ± 2.6

Margulis et al., Cancer (2008)

Neoadjuvant or adjuvant chemotherapy?



consider neoadjuvant chemotherapy[g] in selected patients

Recommendations	Strength rating
Perform radical nephroureterectomy (RNU) in patients with high-risk non-metastatic upper tract urothelial carcinoma (UTUC).	Strong
Perform open RNU in non-organ-confined UTUC.	Weak
Perform a template-based lymphadenectomy in patients with high-risk non-metastatic UTUC.	Strong
Offer post-operative systemic platinum-based chemotherapy to patients with high-risk non-metastatic UTUC.	Strong
Deliver a post-operative bladder instillation of chemotherapy to lower the intravesical recurrence rate.	Strong

7.1.3 ***Peri-operative chemotherapy***

7.1.3.1 *Neoadjuvant chemotherapy*

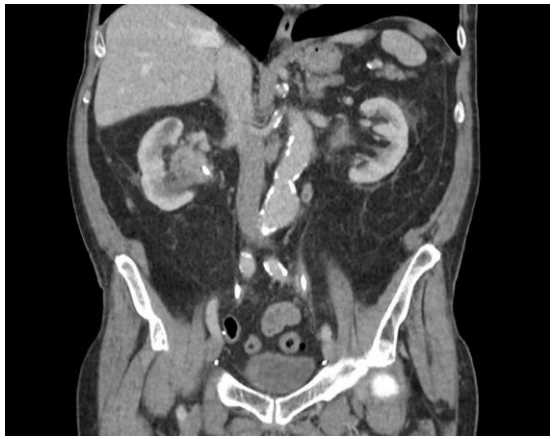
In patients treated prior to losing their renal reserve several retrospective studies evaluating the role of neoadjuvant chemotherapy have shown promising pathological downstaging and complete response rates [164, 237-240]. No RCTs have been published yet but prospective data from a phase II trial showed that the use of neoadjuvant chemotherapy was associated with a 14% pathological complete response rate for high-grade UTUC [241]. In addition, final pathological stage was ≤ ypT1 in more than 60% of included patients with acceptable toxicity profile. In a systematic review and meta-analysis comprising more than 800 patients, neoadjuvant chemotherapy has shown a pathologic partial response of 43% and a downstaging in 33% of patients, and also an OS and CSS survival benefit compared with RNU alone [242]. Furthermore, neoadjuvant chemotherapy has been shown to result in lower disease recurrence and mortality rates compared to RNU alone without compromising the use of definitive surgical treatment [239, 243-245].

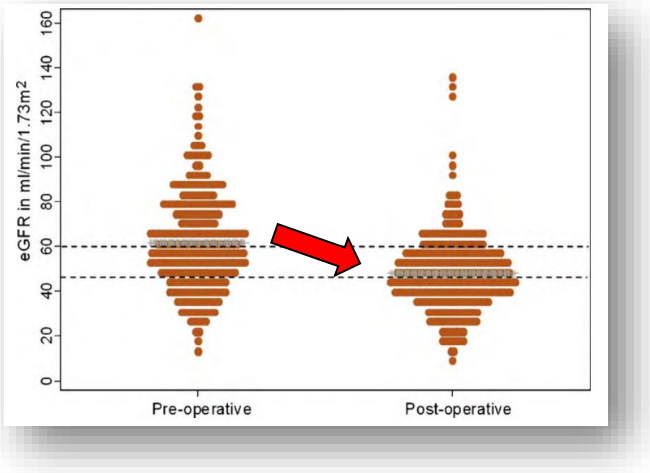
NCCN Guidelines (2022); EAU Guidelines (2022)

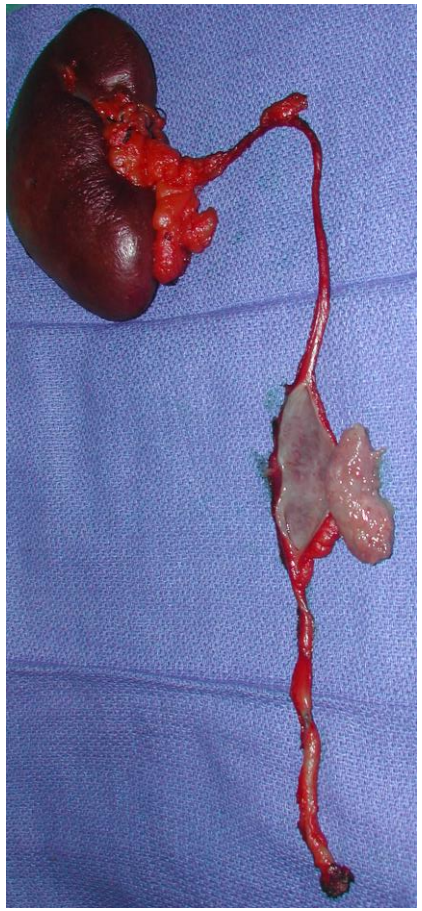
Challenges of perioperative systemic therapy in UTUC

Reduced renal function is common in patients with UTUC

- **40-50%** eligible for **cisplatin-based chemoRx before RNU**
- **but only 20-25% remained eligible after RNU**







Lane et al., Cancer (2010); Xylinas et al., BJUI (2012)

Challenges of perioperative systemic therapy in UTUC

	All patients	High-risk patients*
PRE-OPERATIVELY		
Median eGFR (IQR)	58.8 (55.7-61.1)	58.6 (56.3-60.9)
Eligible for cisplatin-based therapy	359 (49%)	105 (48%)
Ineligible for cisplatin based therapy	379 (51%)	112 (52%)
POST-OPERATIVELY		
Median eGFR (IQR)	46.6 (43.3-49.0)	47.3 (44.8-49.0)
Eligible for cisplatin-based therapy	94 (18%)	34 (21%)
Ineligible for cisplatin based therapy	431 (82%)	126 (79%)

75% of patients who received adjuvant chemotherapy had eGFR <60

Yafi et al., Urol Oncol (2013)

Neoadjuvant systemic therapy for UTUC

What is the evidence?

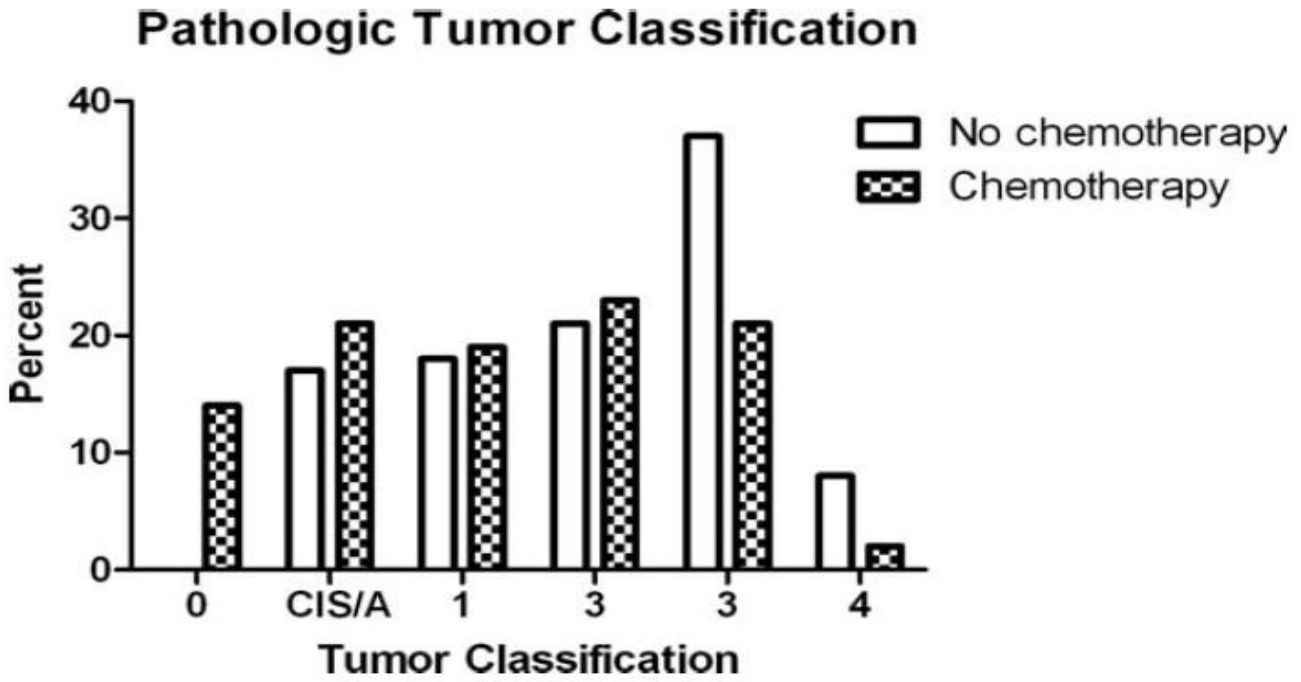
NAC for high-grade UTUC

- N=107 controls
- N=43 neoadjuvant; Bx: HG UTUC

25% **reduction ≥pT2**

42% **reduction ≥ pT3**

14% **CR**



Matin et al., Cancer (2010)

NAC for high-risk UTUC

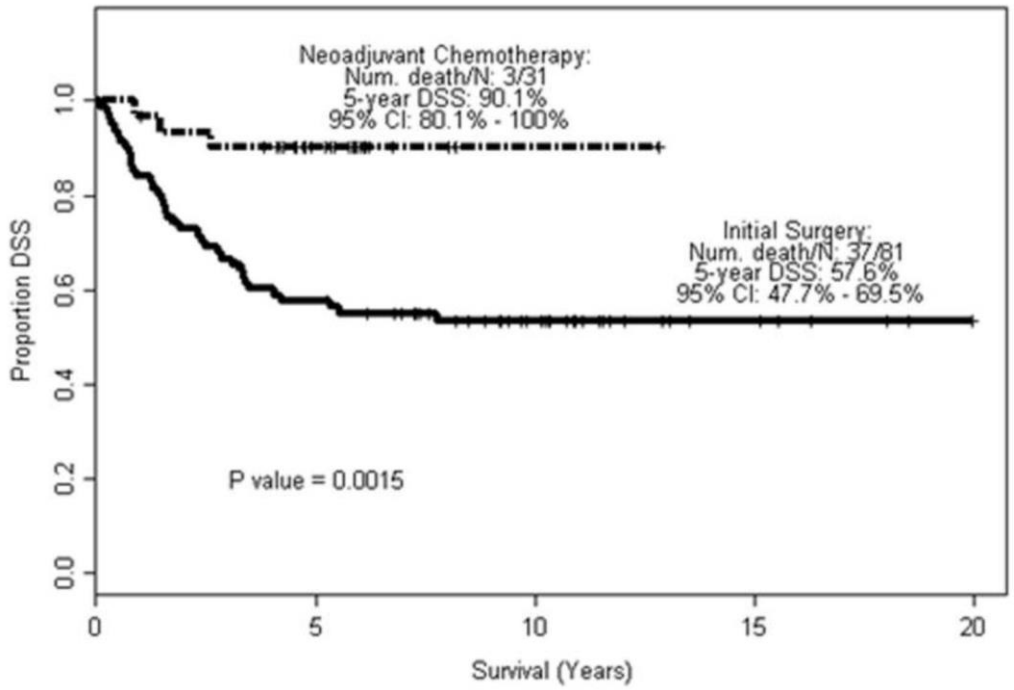
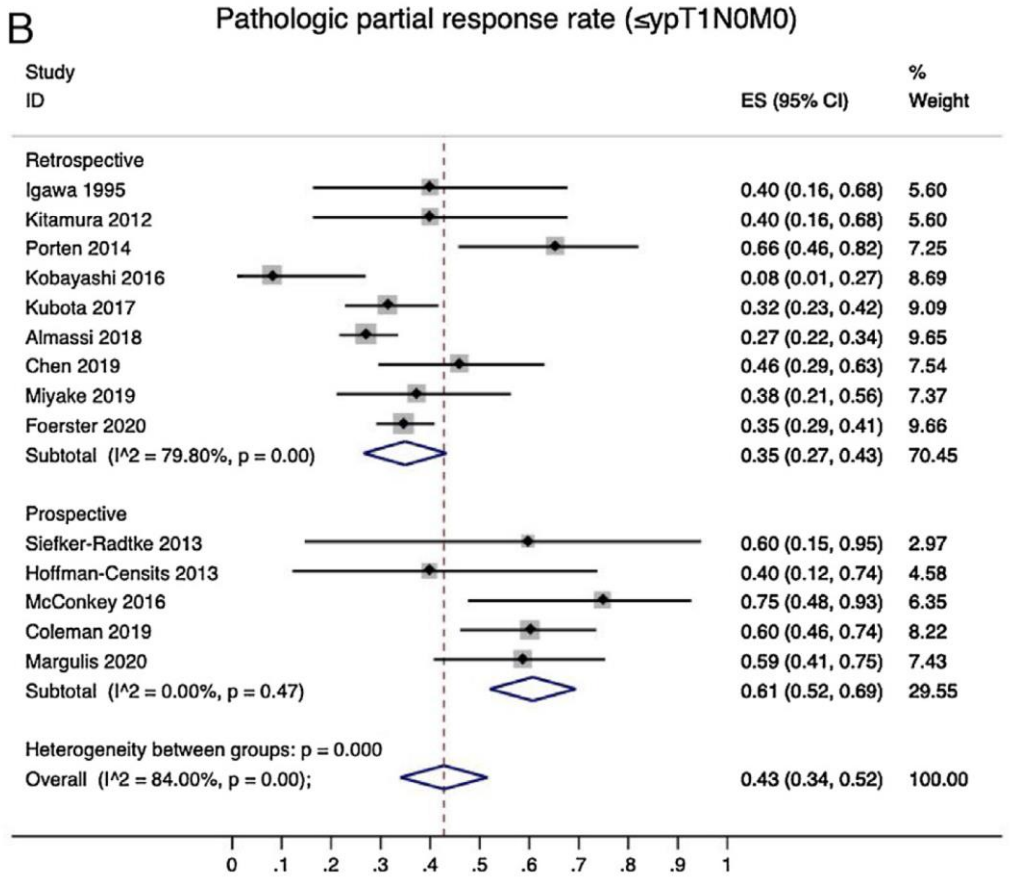


TABLE 3. Multivariate Cox Model for 5-Year Overall Survival and Disease-Specific Survival

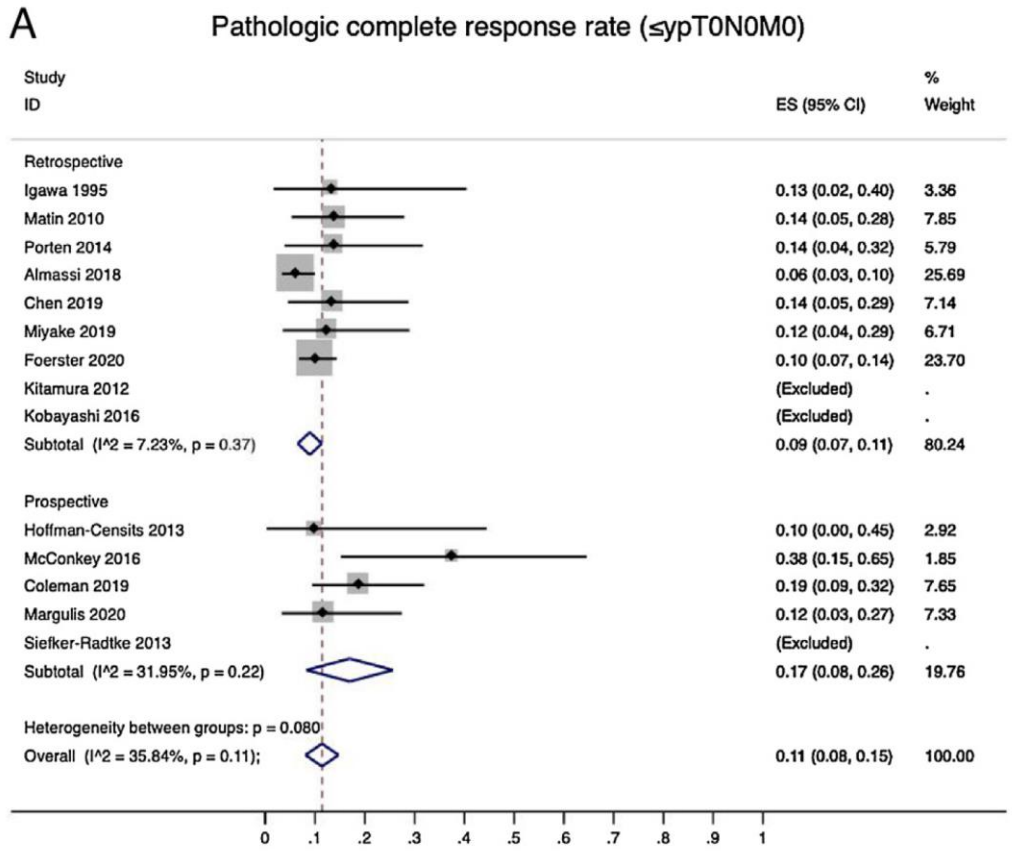
Variable	HR (95% CI)	P^a
Overall survival		
Age	1.02 (0.998-1.05)	.075
Neoadjuvant chemotherapy	0.42 (0.19-0.94)	**.035**
≥8 Lymph nodes removed	0.75 (0.40-1.40)	.370
Sessile tumor architecture	1.16 (0.69-1.96)	.580
Disease-specific survival		
Age	1.01 (0.98-1.04)	.560
Neoadjuvant chemotherapy	0.19 (0.06-0.61)	**.006**
≥8 Lymph nodes removed	0.54 (0.24-1.23)	.140
Sessile tumor architecture	2.77 (1.30-5.89)	**.008**

Porten et al., Cancer (2014)

Pathologic response to NAC in UTUC



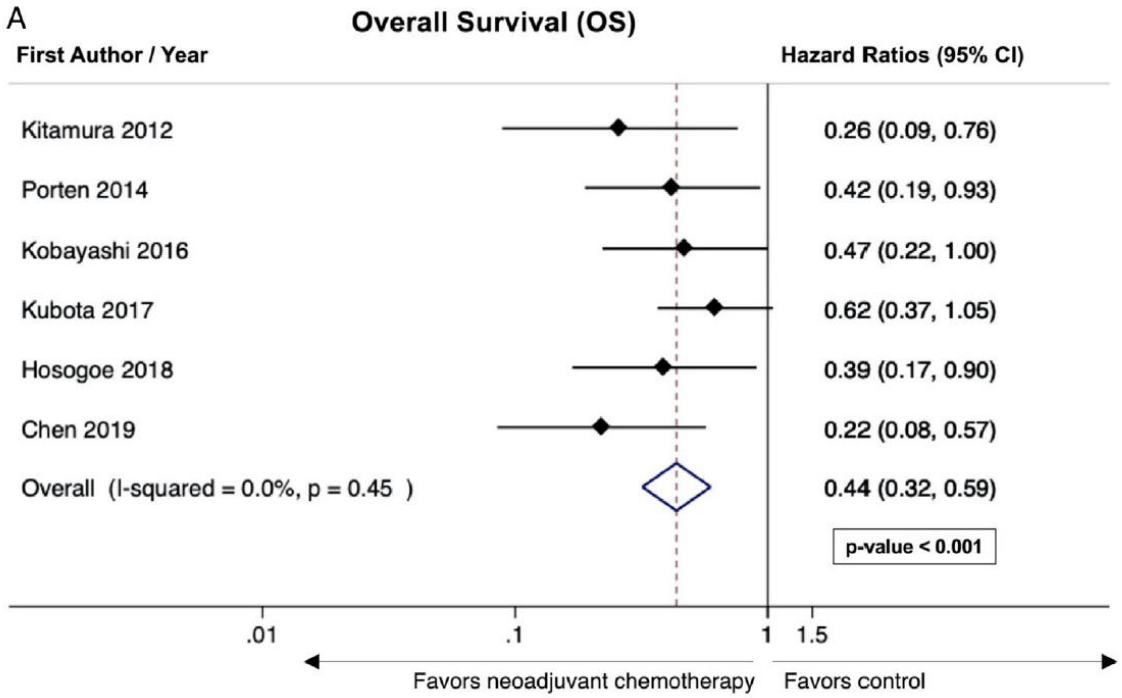
43 %

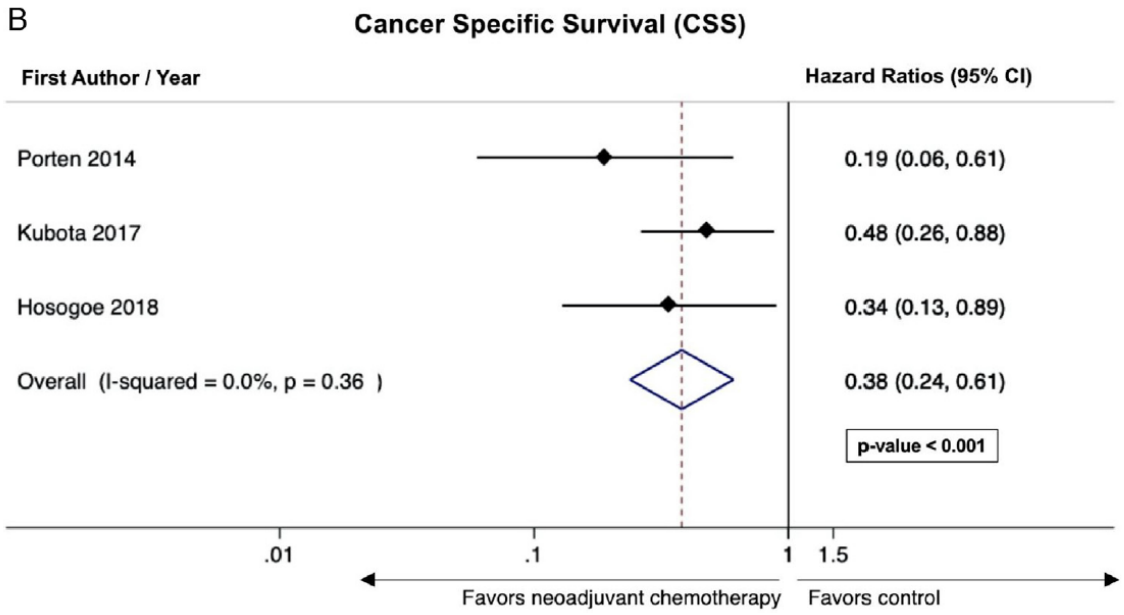


11 %

Leow et al., Eur Urol (2021)

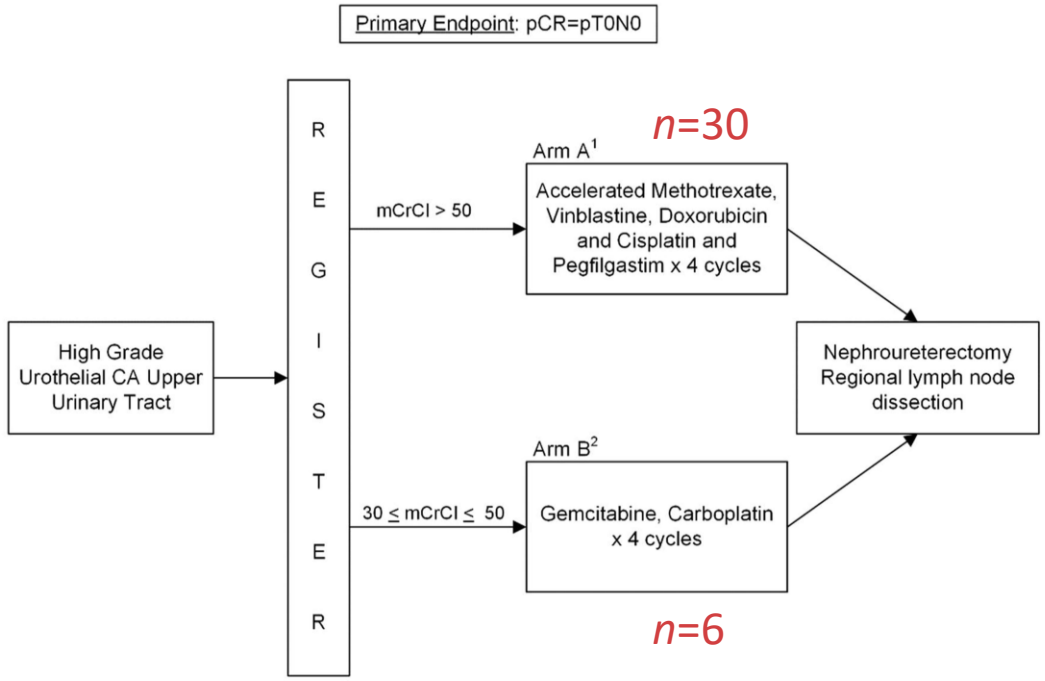
Survival benefit after NAC for UTUC





Leow et al., Eur Urol (2021)

NAC for high grade UTUC (ECOG-ACRIN 8141)



Accrual Goal= 60
30 Patients per arm

1. Regimen repeated every 14 days for 4 cycles.
2. Regimen repeated every 21 days for 4 cycles.

A) aMVAC arm

Clinical stage	Pathologic stage										
	T0N0	T0NX	T1N0	T1NX	T2N0	T3N0	T3NX	TaN0	TaN2	TisN0	Unevaluable
T1N0	-	1	-	-	-	-	-	-	-	1	-
T1N1	-	-	-	-	-	1	-	-	-	-	-
T1NX	-	-	-	-	-	-	1	-	-	-	-
T2N0	1	-	3	-	-	1	-	1	-	1	-
T2NX	-	-	-	-	-	1	-	-	-	-	-
T3N0	-	-	-	-	-	-	1	-	-	1	-
TaN0	1	-	2	-	1	-	-	1*	1	-	-
TaNX	-	-	1	-	-	1	-	-	-	-	-
TXN0	1	-	1	1	-	1	-	1	-	-	-
TXNX	-	-	-	-	-	1	-	-	-	-	1**

B) GCa arm

Clinical stage	Pathologic stage				
	T0N0	T2NX	T3N0	T3N2	TaN0
T1N0	-	1	-	-	-
T2N0	-	-	-	1	-
TaN0	1	-	1	-	2

* One patient in Arm B had R1 disease.

** **Reason unevaluable:** Patient did not have NU

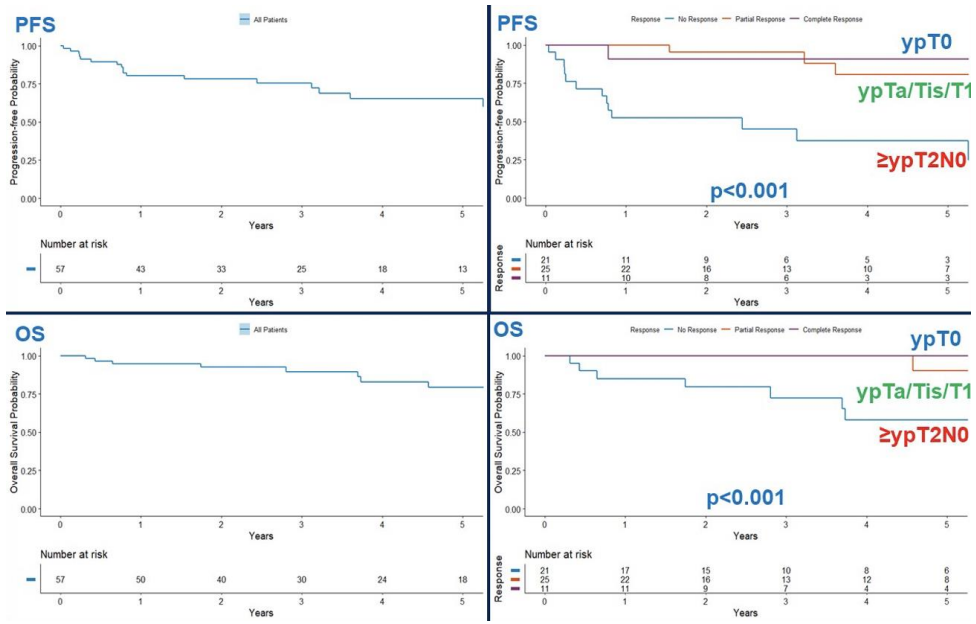
80% completed chemo

pCR 14%

Margulis et al. J Urol (2020)

NAC for high-risk UTUC (single arm phase 2)

- 4 cycles Gem/Cis
- **50/57 (70%) completed all 4 cycles**
- **89% received at least 3 cycles**



Pathologic Response		N = 57
Responders (<ypT2N0)		36 (63%)
	T0	11 (19%)
	Ta	10 (18%)
	Tis	7 (12%)
	T1	8 (14%)
Non-Responders (≥ypT2Nany)		21 (37%)
	T2	5 (9%)
	T3	9 (16%)
	TanyN+	7 (12%)
Progression prior to surgery		0 (0%)

Yip et al., ASCO GU (2022)

Neoadjuvant pembrolizumab for UTUC (PURE-02)

Patient ID	Age (y)	Gender	Smoking status	cT-stage	Maximum tumor diameter (cm)	Hydro-nephrosis	Site of the primary tumor	Tumor biopsy	Urinary cytology (HG)	Baseline GFR[a] (ml/min)	Radiological response (mpMRI)	CT[b]	RNU	Pathological response	Adjuvant CT	Relapse	Survival status	Follow-up (mo)[c]
01	67	M	Former smoker	T2	3.8	Yes	Renal pelvis	No	Yes	61	PR	No	Yes	ypT3N0	No	No	Alive	31
02	63	M	Non smoker	T3	n.e.	No	Renal pelvis + ureter	Yes	No	58	PD	Yes	No	n.a.	Yes	Yes	Alive	15
03	67	M	Active smoker	T2	1	Yes	Renal pelvis	Yes	No	>90	SD	Yes	Yes	ypT1N0	Yes	Yes	Alive	9
04	47	M	Active smoker	T2	4.3	No	Renal pelvis	No	No	>90	SD	No	Yes	ypT2N0	No	No	Alive	7
05	66	M	Former smoker	T2	3	Yes	Ureter	No	Yes	39	SD	No	Yes	ypT2N0	No	Yes	Alive	7
06	63	F	Former smoker	T2	1.4	Yes	Ureter	No	Yes	39	CR	No	No	n.a.	No	No	Alive	6
07	82	M	Non smoker	T3	2.5	No	Ureter	No	No	65	n.a.	No	No	n.a.	No	No	Dead	1
08	72	F	Former smoker	T1	1.4	No	Ureter	Yes	Yes	66	SD	No	Yes	ypT1N0	N/A	N/A	Dead	6
09	71	F	Non smoker	T3	1.7	Yes	Ureter	No	Yes	49	PD	No	Yes	ypT3N2	No	No	Alive	4
10	78	M	Former smoker	T2	2	No	Renal pelvis + ureter	Yes	No	50	SD	No	Yes	ypT3Nx	No	No	Alive	3

Abbreviations: CR = complete response; CT = chemotherapy; HG = high-grade (urothelial carcinoma); mpMRI = multiparametric magnetic resonance imaging; n.a. = not available; n.e. = not evaluable; PD = disease progression; PR = partial response; RNU = radical nephroureterectomy; SD = stable disease; UC = urothelial carcinoma.

ORR 14.3 %

Necchi et al., Urol Oncol (2022)

Adjuvant systemic therapy for UTUC

What is the evidence?

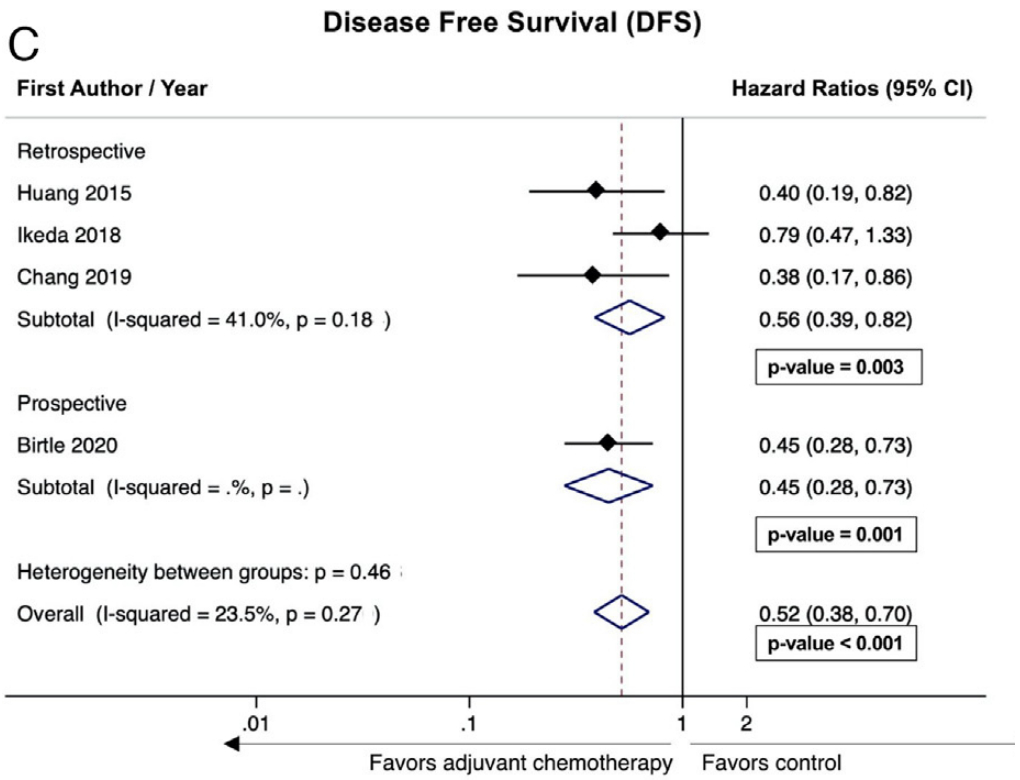
Rationale for adjuvant chemotherapy

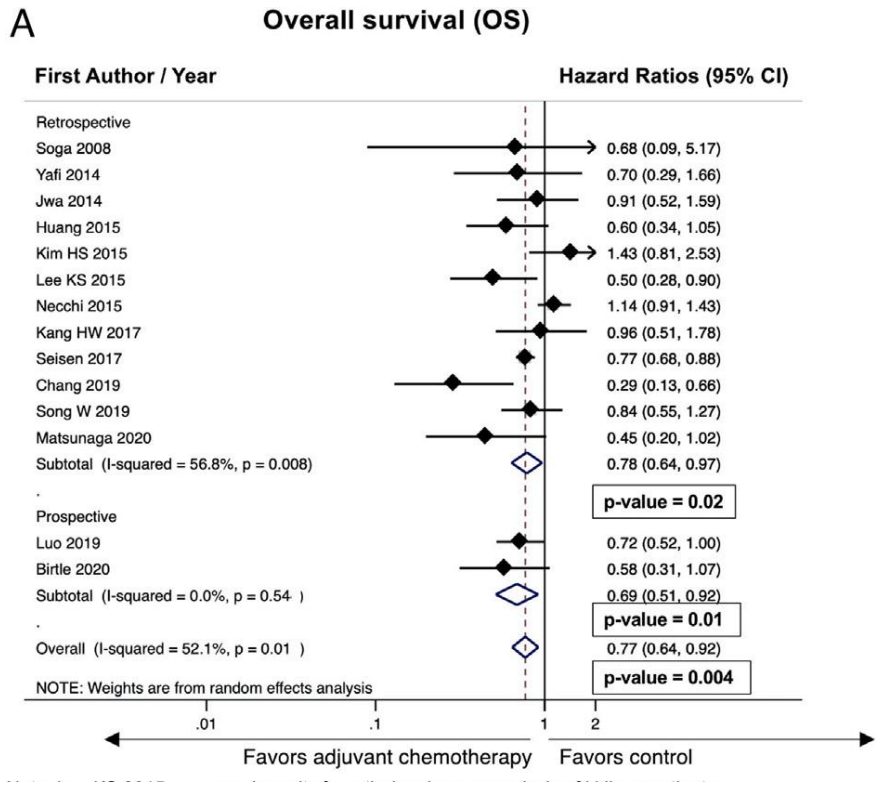
- If the local tumor is the problem→ **deal with it immediately**
- Chemotherapy decisions **based on *true* pathology**
  - specifically in UTUC - suboptimal staging (RNU based on risk grouping)

- **No compromise of local therapy** due to **toxicities**
- **No delay in definitive local therapy**
  - especially for those patients in whom chemotherapy is ineffective

- Successful approach in other malignancies

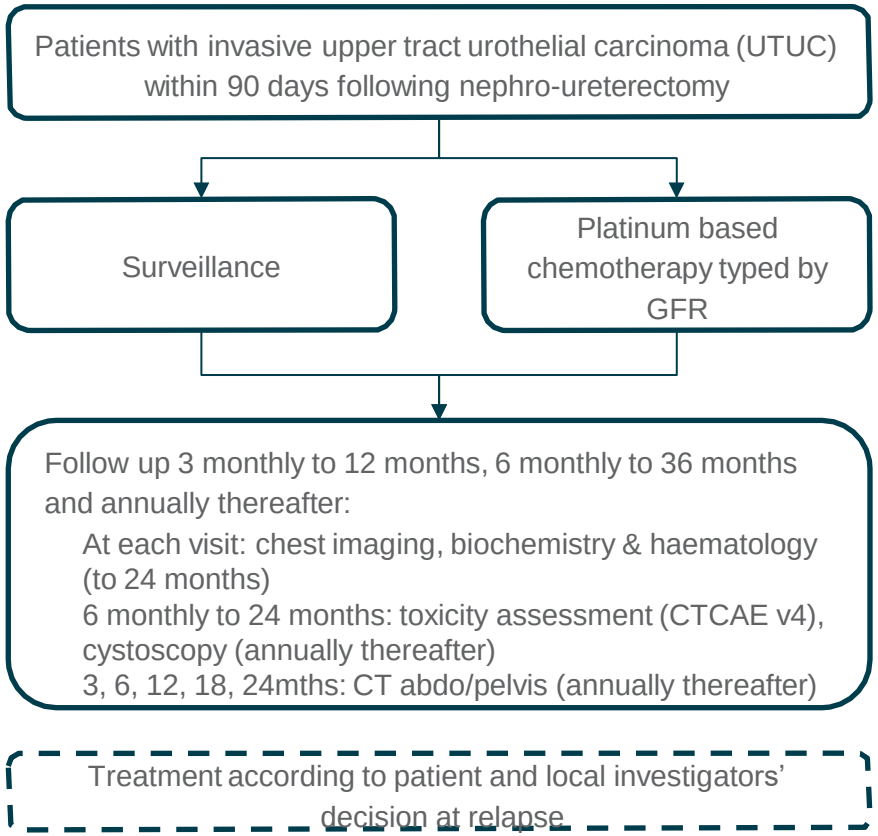
Survival benefit with adjuvant chemotherapy





Leow et al., Eur Urol (2021)

POUT trial design



Inclusion criteria:

- En-bloc radical nephro-ureterectomy
- UTUC **pT2-pT4pN0 M0** or **pTany N1-3 M0** (abnormal nodes resected at surgery)
- Satisfactory haematology profile & liver function tests
- **WHO performance status 0-1**
- Fit to receive chemotherapy within **90 days** following nephro-ureterectomy

Exclusion criteria:

- GFR <30ml/min
- Distant metastases
- Un-resected macroscopic nodal disease
- Concurrent MIBC (concurrent NMIBC acceptable)
- Other malignancy in previous 5 years
- Significant co-morbidities

Birtle et al., ASCO GU (2018)

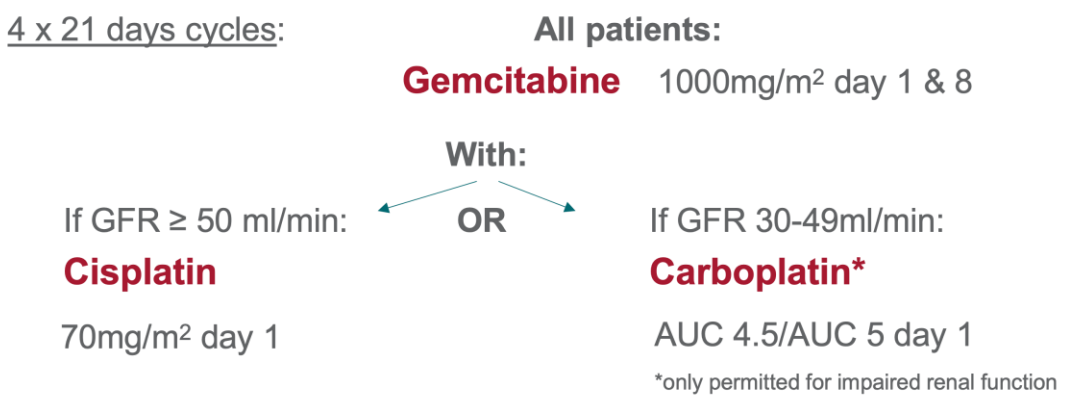
POUT trial design

Primary endpoint:

- **Disease free survival** (DFS)

Secondary endpoints:

- Acute and late toxicity
- Metastasis free survival
- Treatment compliance
- Feasibility of recruitment
- Overall survival
- Incidence of contralateral primary tumours
- Incidence of bladder and second primary tumours
- Quality of life



Birtle et al., ASCO GU (2018)

POUT statistical design

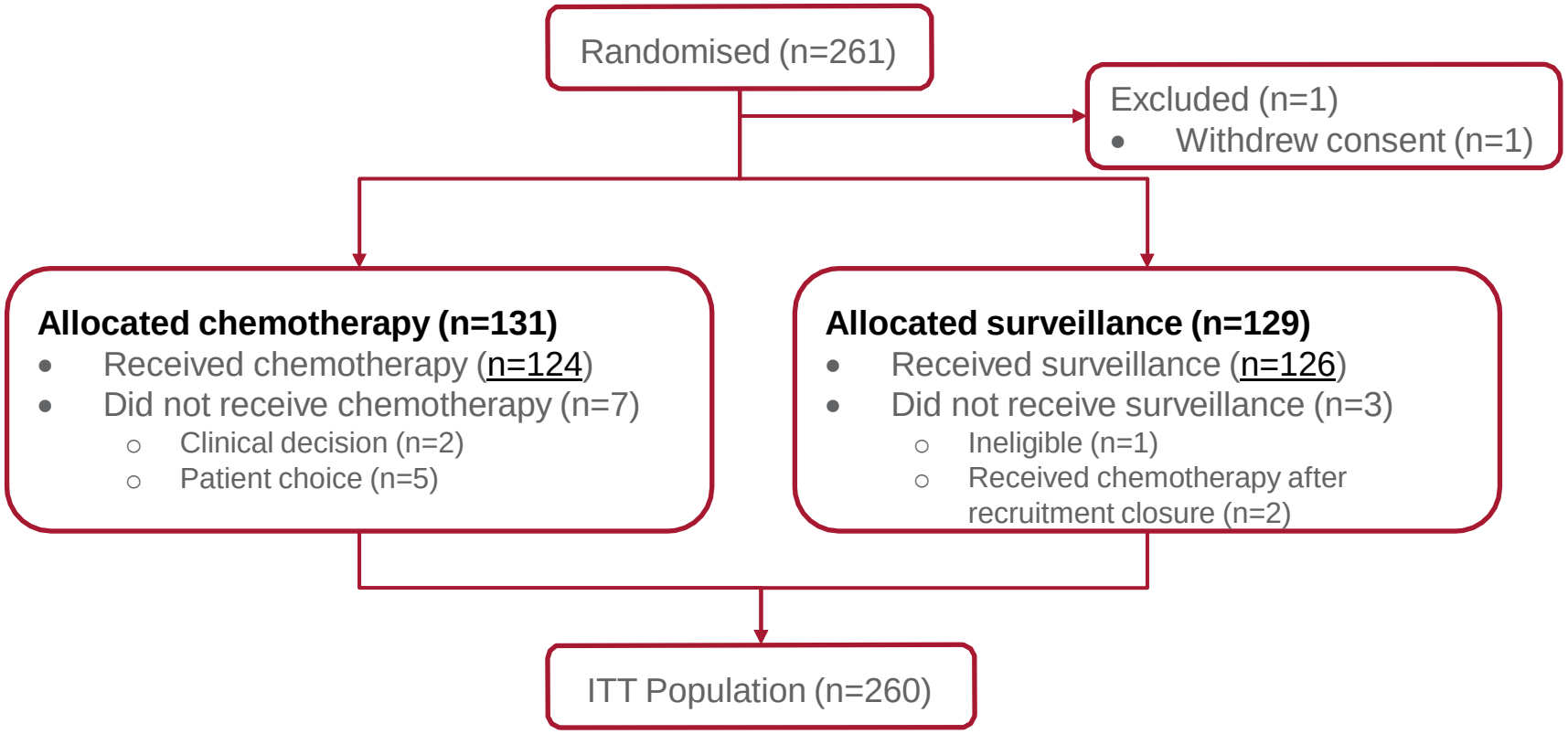
- 3 year DFS in the control arm assumed to be 40%
- Trial powered to detect a 15% improvement in 3 year DFS (HR=0.65)

- **Planned sample size – 338 patients**; 172 events required for 80% power, 2- sided 5% significance level

- Monitoring of safety and efficacy by an Independent Data Monitoring Committee (IDMC), with defined Peto-Haybittle stopping rule ($p<0.001$) for efficacy and inefficacy
- Analysis by **intention to treat** except where stated

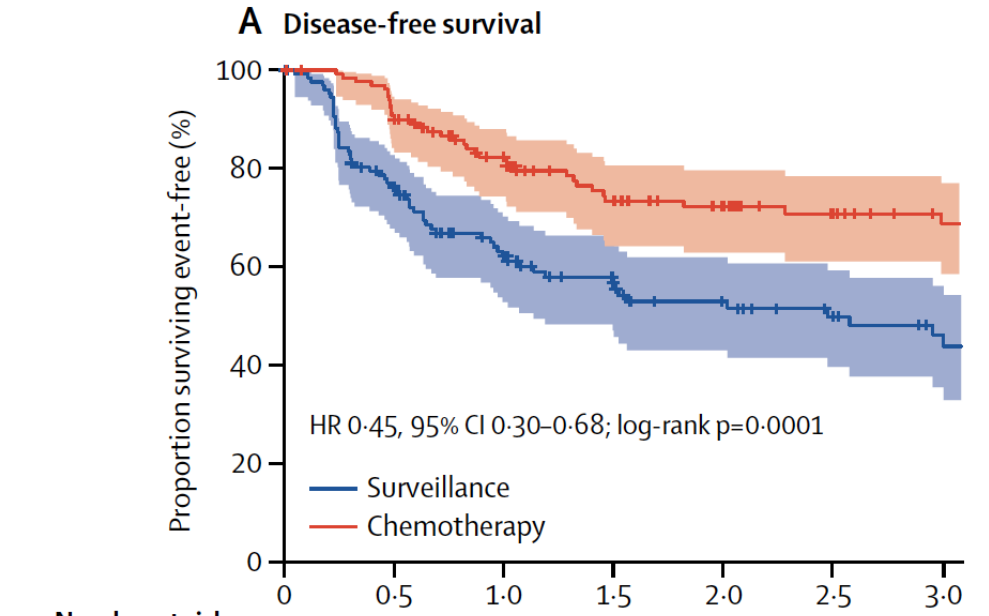
Birtle et al., ASCO GU (2018)

POUT consort diagram

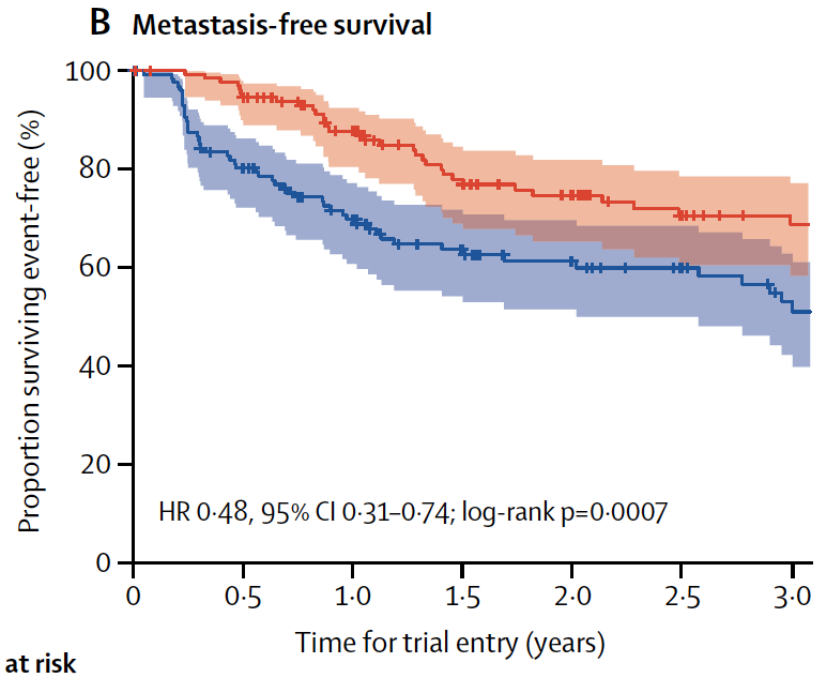


Birtle et al., ASCO GU (2018)

Adjuvant platin-based chemotherapy for UTUC (POUT)



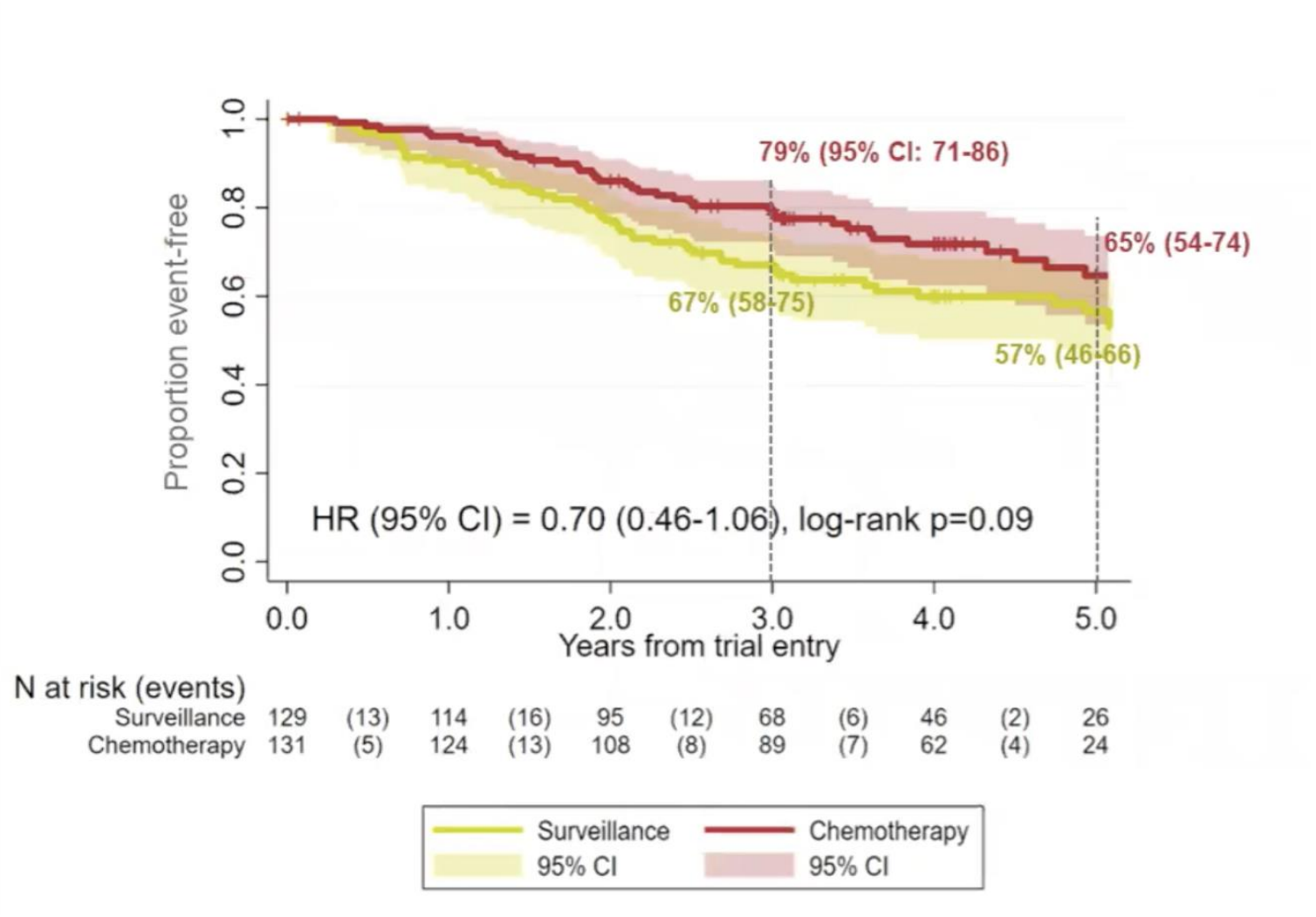
Number at risk (number censored)							
Surveillance	129 (7)	92 (14)	62 (9)	48 (8)	37 (5)	30 (4)	24 (··)
Chemotherapy	131 (4)	114 (14)	91 (10)	72 (11)	60 (14)	45 (9)	36 (··)



Number at risk (number censored)							
Surveillance	129 (6)	98 (13)	73 (9)	58 (10)	46 (7)	38 (4)	30 (··)
Chemotherapy	131 (4)	120 (14)	98 (10)	78 (10)	65 (14)	48 (8)	40(··)

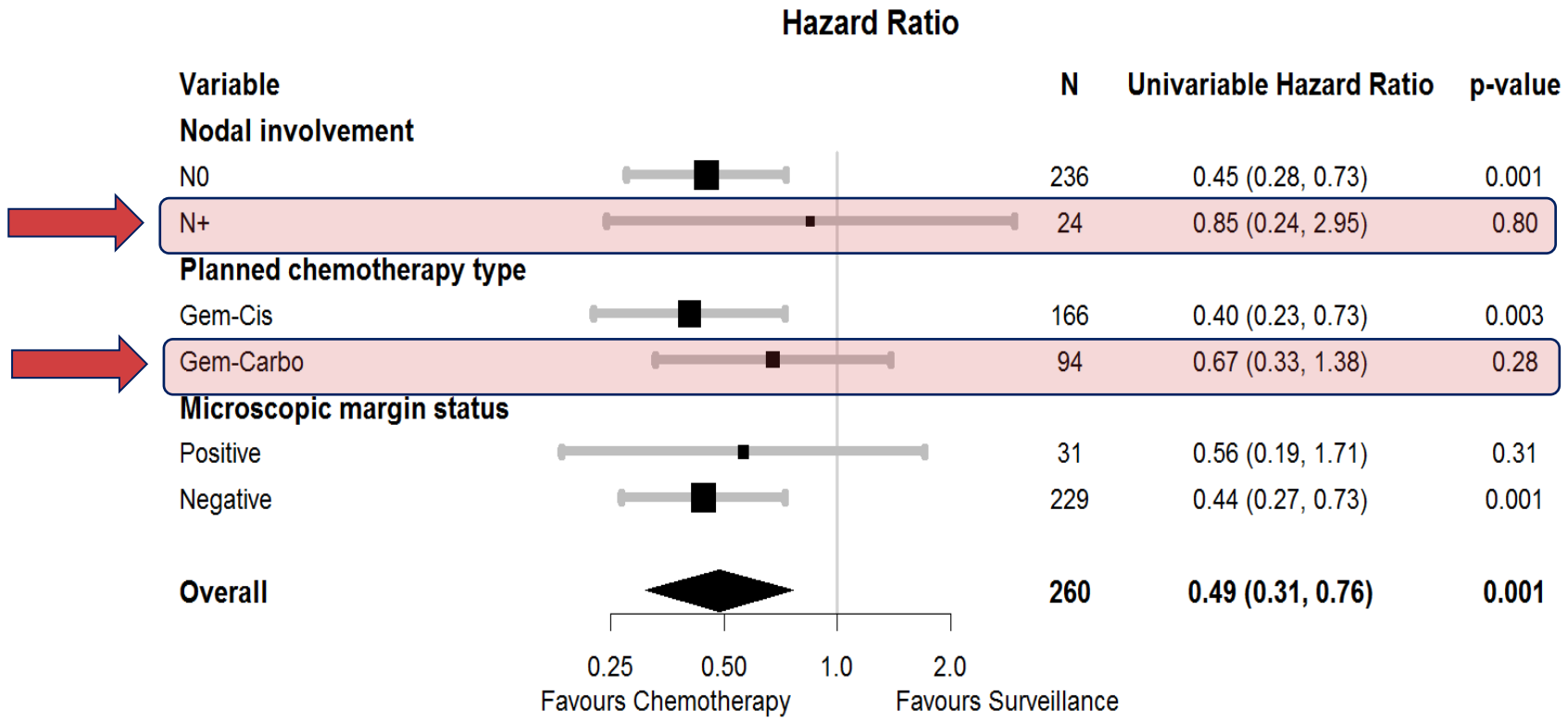
Birtle et al., Lancet (2020)

Overall survival (POUT)



Birtle et al., ASCO GU (2021)

Adjuvant platin-based chemotherapy for UTUC (POUT)



Birtle et al., ASCO GU (2018)

CheckMate 274

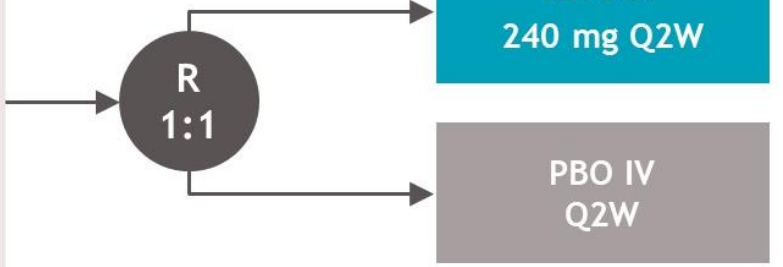
N = 709

Key inclusion criteria

- Patients with ypT2-ypT4a or ypN+ MIUC who had neoadjuvant cisplatin chemotherapy
- Patients with pT3-pT4a or pN+ MIUC without prior neoadjuvant cisplatin chemotherapy and not eligible/refuse adjuvant cisplatin chemotherapy
- Radical surgery within the past 120 days
- Disease-free status within 4 weeks of dosing

Stratification factors

- PD-L1 status (<1% vs ≥ 1%)[a]
- Prior neoadjuvant cisplatin-based chemotherapy
- Nodal status



Treat for up to 1 year of adjuvant therapy

Minimum follow-up, 5.9 months
Median follow-up in ITT population, 20.9 months (NIVO) and 19.5 months (PBO)

Primary endpoints: DFS in ITT population and DFS in all randomized patients with tumor PD-L1 ≥ 1%
Secondary endpoints: NUTRFS, DSS, and OS[b]
Exploratory endpoints included: DMFS, safety, HRQoL

Bajorin et al., NEJM (2021) and updated data

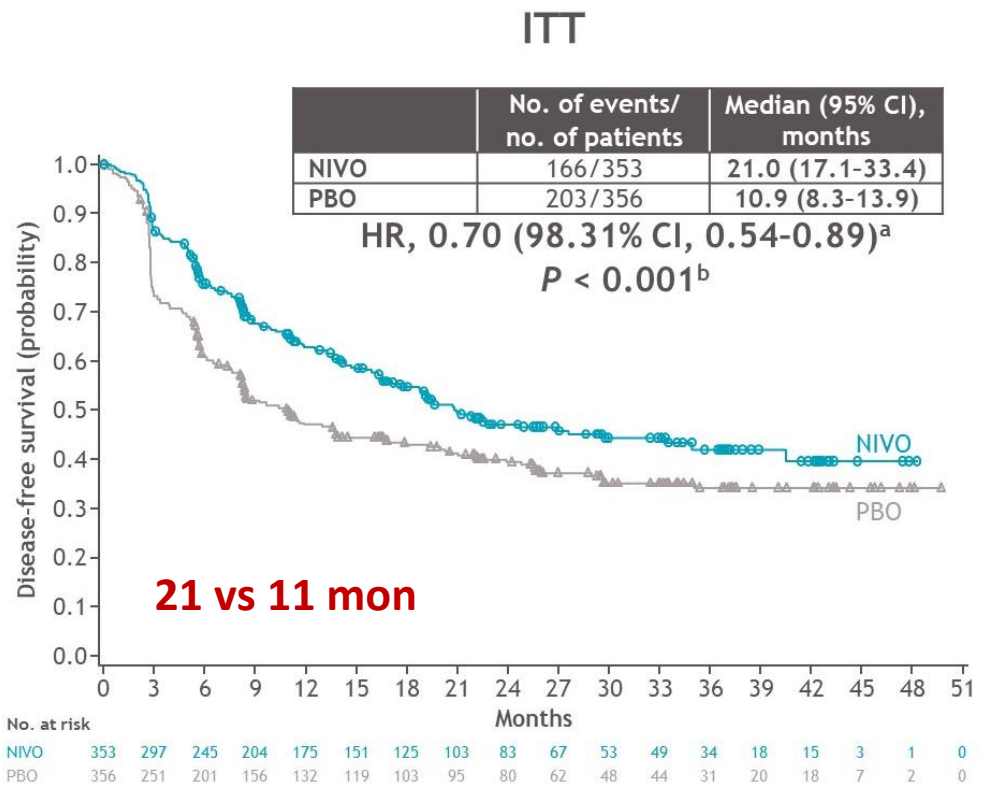
CheckMate 274

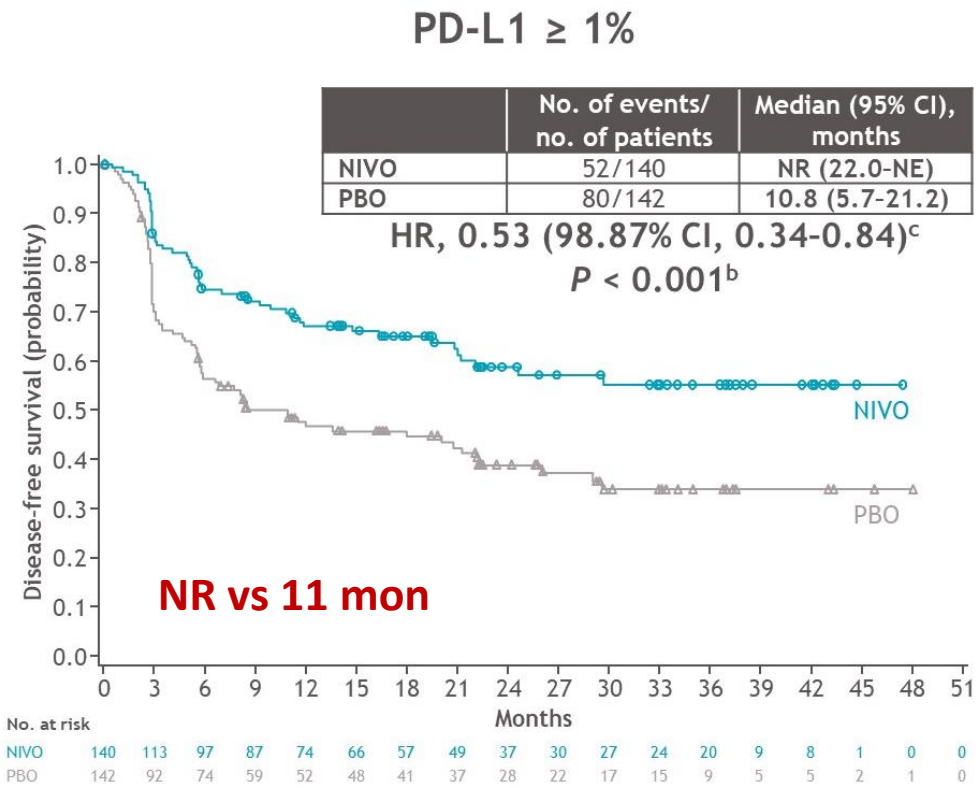
Tumor origin at initial diagnosis — no. (%)		
Urinary bladder	279 (79.0)	281 (78.9)
Renal pelvis	44 (12.5)	52 (14.6)
Ureter	30 (8.5)	23 (6.5)

20% of patients with UTUC

Bajorin et al., NEJM (2021) and updated data

Adjuvant nivolumab for UTUC (CheckMate 274)

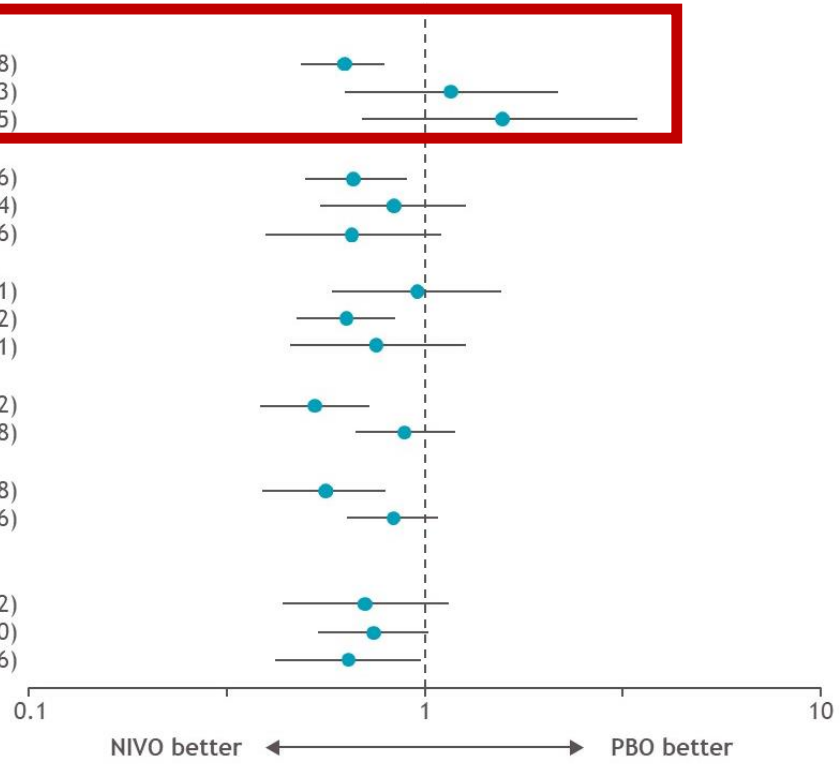




Bajorin et al., NEJM (2021) and updated data

Adjuvant nivolumab for UTUC (CheckMate 274)

Subgroup	Nivolumab	Placebo	HR (95% CI)
	no. of events/ no. of patients		
Initial tumor origin			
Urinary bladder	126/279	165/281	0.62 (0.49-0.78)
Renal pelvis	23/44	25/52	1.16 (0.63-2.13)
Ureter	17/30	13/23	1.55 (0.70-3.45)
Pathologic lymph node status			
N+	95/167	115/168	0.65 (0.49-0.86)
N0/x with < 10 nodes removed	44/94	50/99	0.82 (0.54-1.24)
N0 with ≥ 10 nodes removed	27/91	37/88	0.64 (0.39-1.06)
Pathologic status			
pT0-2	36/80	40/86	0.93 (0.58-1.51)
pT3	94/206	119/204	0.62 (0.47-0.82)
pT4a	34/57	40/62	0.74 (0.45-1.21)
Prior neoadjuvant cisplatin			
Yes	69/153	99/155	0.53 (0.39-0.72)
No	97/200	104/201	0.89 (0.67-1.18)
Baseline PD-L1 expression			
≥ 1%	52/139	78/141	0.55 (0.39-0.78)
< 1%	113/210	120/209	0.82 (0.63-1.06)
Time from IUC surgery to randomization, days			
> 30-60	43/79	39/70	0.70 (0.43-1.12)
> 60-90	76/165	93/177	0.73 (0.53-1.00)
> 90-120	45/103	62/95	0.64 (0.42-0.96)

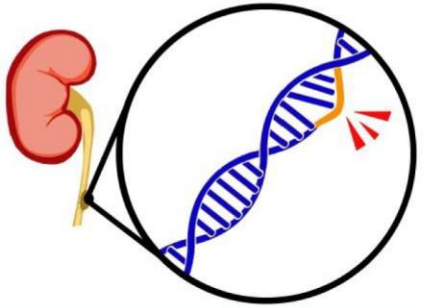


Bajorin et al., NEJM (2021) and updated data

Molecular characteristics of UTUC

Potential drugable targets

Molecular characterization of UTUC

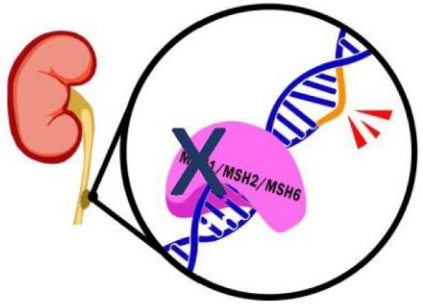


sporadic (80-90%)

LG
- *FGFR3* mut (>90%) [10]
- RTK/RAS alteration [12]

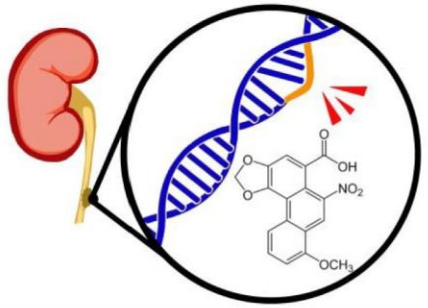
HG
- *TP53/MDM2* mut ↑ [11, 16]
- Genomic instability ↑ [11, 16]
- *FGFR3* mut (31%) [10, 12, 17]

LG+HG
- Chromatin mod. Mut [10]
- APOBEC profile [16-18]



LS-associated (10-20%)

- Germ-line mutation in mismatch-repair gene
- Similar mutational landscape to sporadic [21]
- Overall mut load ↑ [21]
- MSI score ↑ [21]
- Presence of *FGFR3 R248C* [21]

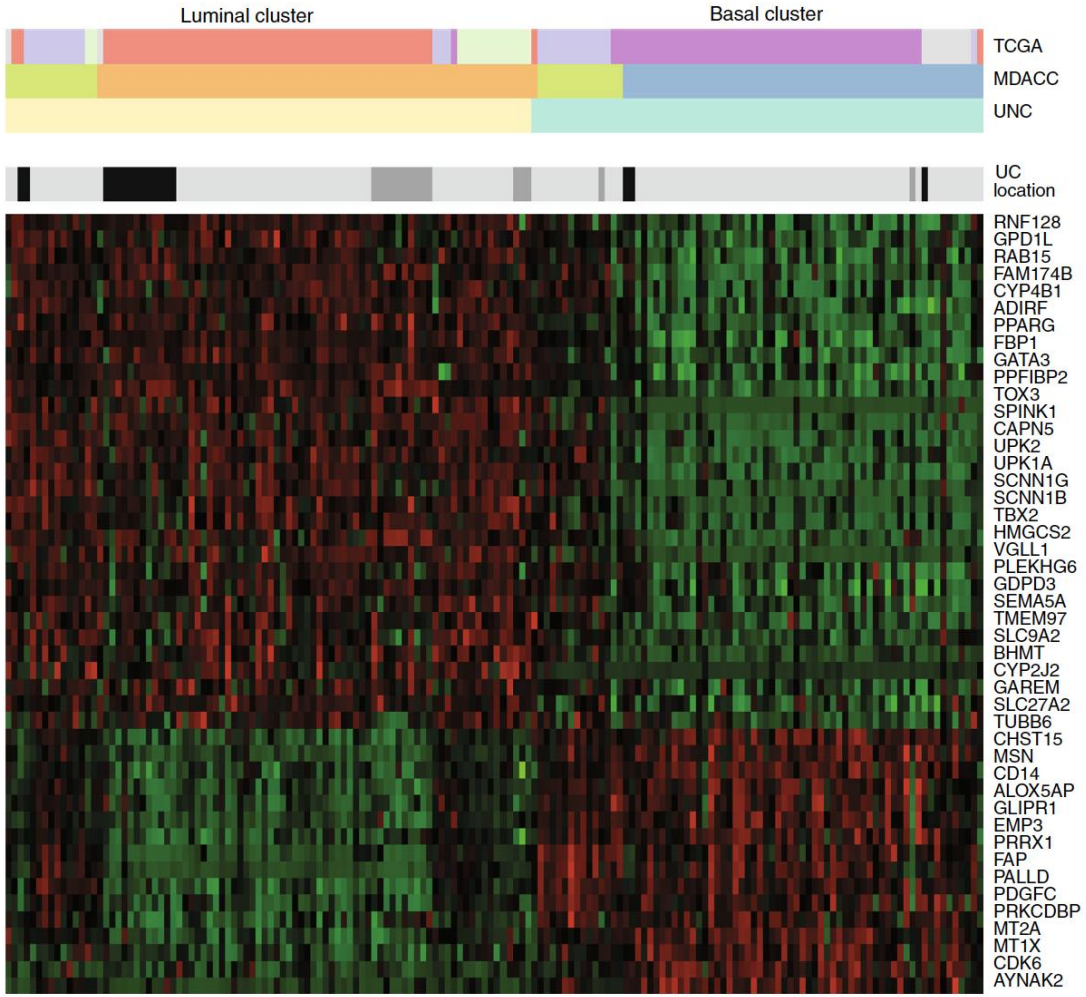


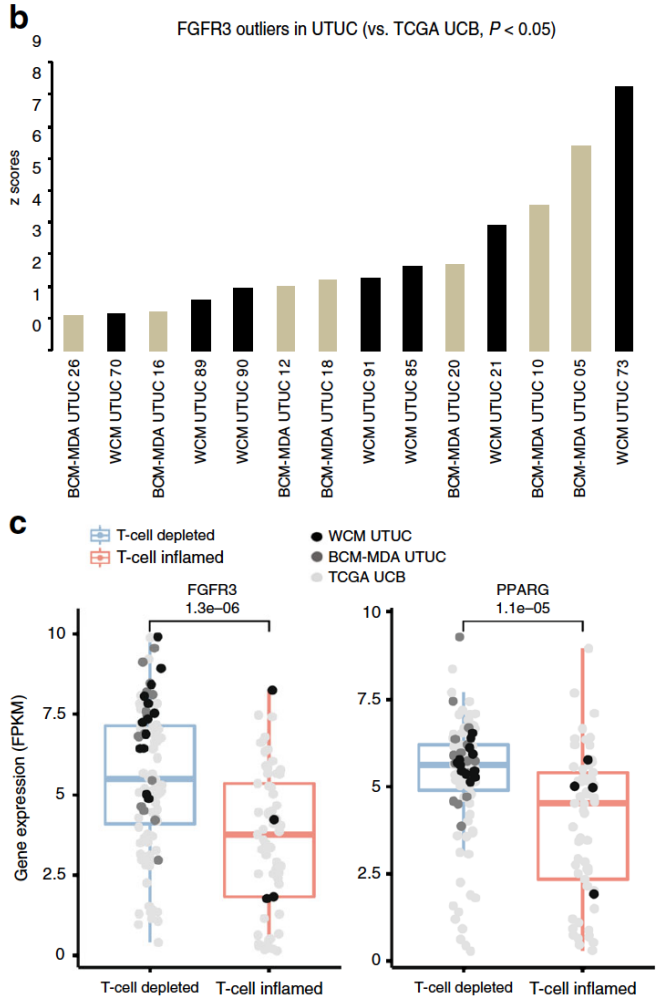
AA-associated (endemic/exposure)

- A > T transversions [32-34]
- Overall mut load ↑ [32]
- APOBEC profile [34]
- Mutations at non-transcribed strand [32]
- Rare FGFR3 mutations [32-34]

Hassler et al., Eur Urol (2020)

Molecular characterization of UTUC





Robinson et al., Nature (2019)

Conclusions

- Adjuvant platin-based chemotherapy remains standard for high-risk UTUC
  - *based on the evidence*
- Neoadjuvant cisplatin-based chemotherapy seems to be benefitial
  - *based on the experience*
  - small phase 2 trials
  - challenge to get level 1 evidence in rare diseases
- Adjuvant CPI (nivolumab) needs further evaluation
- Molecular characteristics of UTUC offer several targetable alterations