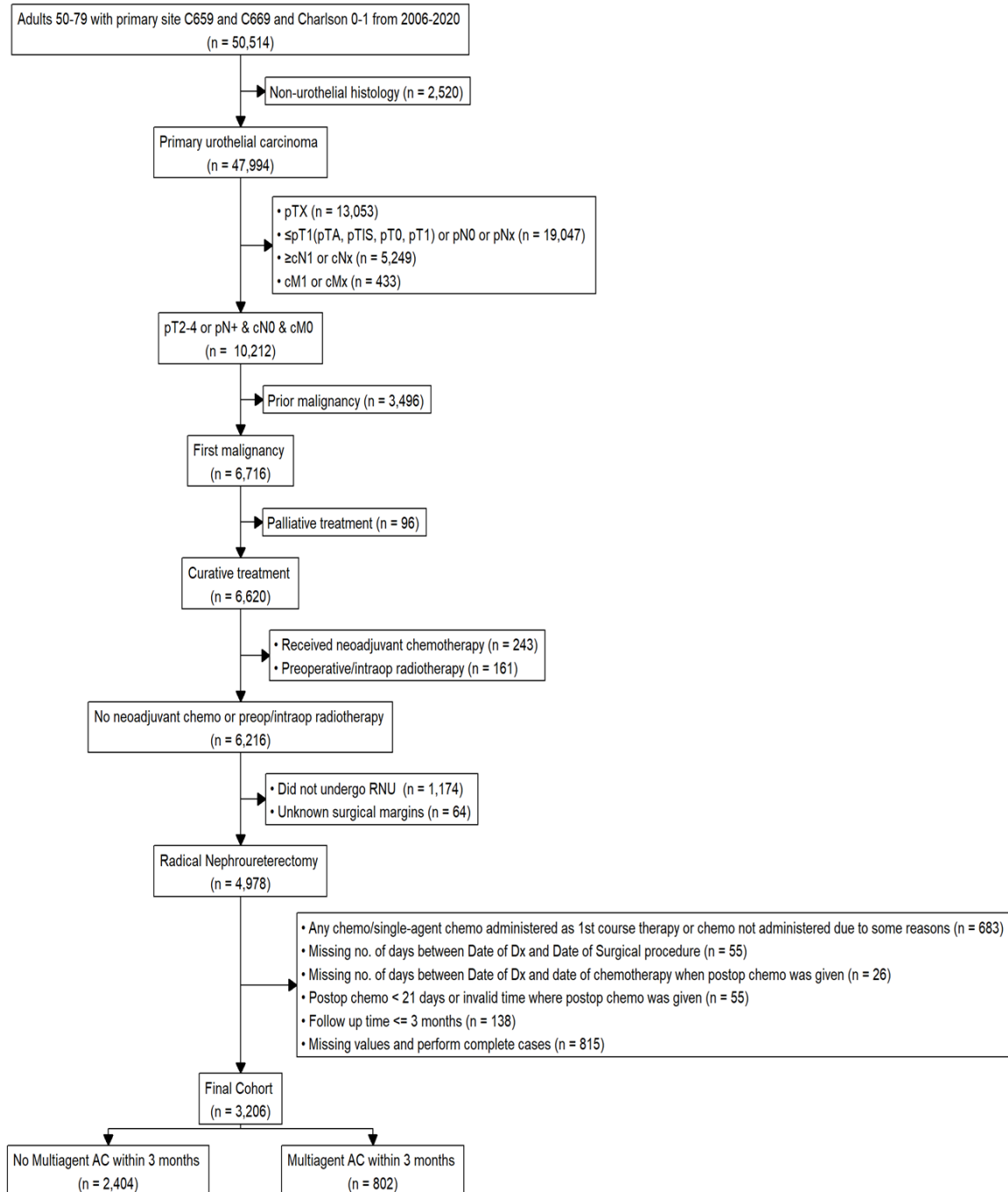


APPENDIX

Supplementary Figure 1. CONSORT flow diagram.



Supplementary Table 1. Mini protocol for the POUT trial and hypothetical target trial to be emulated		
Protocol component	POUT Trial [REF] ¹⁴	Hypothetical Target Trial (NCDB)
Eligibility criteria	Inclusion: Patients aged ≥ 16 with pT2-4 pNany or pTany pN1–3 M0 UTUC, after en-bloc RNU w/ resection of all radiographically or macroscopically abnormal lymph nodes (formal ext LND not mandated). Predominantly transitional cell carcinoma histology, fit to receive adjuvant chemotherapy within 90 days surgery. Adequate hematological function adequate renal function (eGFR ≥ 30 mL/min). Exclusion: Residual LN's on post-operative imaging	Inclusion: Patients age 50-79 pT2-4 pNany or pTany pN+ & M0 UTUC, after RNU from 2006-2020, Charlson 0-1.
Treatment strategies	AC (one of 2 regimens below) started within 14 days of randomization after surgery versus observation (no AC) Regimens: Gem/Cisplatin 21 day cycle, or Gem/Carboplatin (if eGFR ≥ 30 mL/min and < 50 mL/min)	Multiagent chemotherapy (AC) within 3 months of RC versus observation (no AC within 3 months)
Assignment procedures	Un-blinded random assignment to treatments	Un-blinded random assignment to treatments
Followup period	Starts at randomization; ends on date of last available data in observational dataset or at the occurrence of outcome event, loss to follow-up, or death (whichever is earlier)	Starts at randomization; ends on date of last available data in observational dataset or at the occurrence of outcome event, loss to follow-up, or death (whichever is earlier)
Outcomes	Disease-free survival (time from randomization to first recurrence in tumor bed, first metastasis, or death from any cause), Overall survival	Overall survival
Causal contrasts	Causal effect comparing point (non-time-varying) treatments within a grace period	Causal effect comparing point (non-time-varying) treatments within a grace period
Analysis plan	Analyze patients “as randomized”; compare overall survival and disease-free survival using the Kaplan-Meier method. Estimate absolute and relative measures of treatment effects.	Analyze patients as treated; compare overall survival using the Kaplan-Meier method with inverse-probability of treatment weighting; estimate the hazard ratio comparing treatment groups with Cox proportional hazards regression with inverse probability of treatment weighting.

Supplementary Table 2. Preoperative characteristics after sIPW re-weighting

Characteristic	Treatment		SMD ¹
	No multiagent AC within 3 months (2423)	Multiagent AC within 3 months (769) ¹	
Age, years	69 (62, 74)	69 (62, 73)	0.018
Gender			0.021
Male	1,417 (59)	442 (58)	
Female	1,006 (41)	327 (42)	
Charlson index			0.004
0	1,806 (75)	572 (74)	
1	618 (25)	197 (26)	
Year of diagnosis			0.099
2006	47 (2)	14 (2)	
2007	64 (3)	19 (2)	
2008	118 (5)	35 (5)	
2009	133 (6)	37 (5)	
2010	180 (7)	54 (7)	
2011	173 (7)	60 (8)	
2012	190 (8)	72 (9)	
2013	190 (8)	57 (7)	
2014	220 (9)	63 (8)	
2015	205 (8)	68 (9)	
2016	194 (8)	54 (7)	
2017	175 (7)	55 (7)	
2018	172 (7)	54 (7)	
2019	205 (8)	75 (10)	
2020	156 (6)	54 (7)	
Race			0.029
White	2210 (91)	707 (92)	
Black	123 (5)	37 (5)	
Others	90 (4)	25 (3)	
Hispanic			0.004
No	2335 (96)	740 (96)	
Yes	89 (4)	29 (4)	
Insurance status			0.051
Not insured	41 (2)	15 (2)	
Private/managed care	756 (31)	241 (31)	
Medicaid	85 (4)	21 (3)	
Medicare	1513 (62)	484 (63)	
VA/military	30 (1)	9 (1)	
Geographic location			0.034
Northeast	564 (23)	172 (22)	
South/Southeast	852 (35)	280 (36)	

Supplementary Table 2. Preoperative characteristics after sIPW re-weighting

Characteristic	Treatment		SMD ¹
	No multiagent AC within 3 months (2423)	Multiagent AC within 3 months (769) ¹	
Midwest	610 (25)	188 (24)	
West	398 (16)	130 (17)	
Facility type			0.048
Community cancer program	177 (7)	65 (9)	
Comprehensive community cancer program	959 (40)	308 (40)	
Academic/research program	853 (35)	261 (34)	
Integrated network cancer program	434 (18)	135 (18)	
Distance from hospital	10.90 (4.92, 27.62)	11.20 (4.80, 24.99)	0.066
Rurality			0.021
Metropolitan	1,999 (83)	636 (83)	
Urban	375 (16)	120 (16)	
Rural	49 (2)	14 (2)	
Income level (quartiles)*			0.036
Q1	355 (15)	113 (15)	
Q2	534 (22)	159 (21)	
Q3	621 (26)	197 (26)	
Q4	914 (38)	300 (39)	
Education level (quartiles)*			0.050
Q1	384 (16)	131 (17)	
Q2	636 (26)	205 (27)	
Q3	753 (31)	223 (29)	
Q4	650 (27)	210 (27)	
pT stage			0.083
≤pT2	715 (30)	199 (26)	
pT3	1572 (65)	524 (68)	
pT4	136 (6)	46 (6)	
pN stage			0.021
pNX	1737 (72)	558 (73)	
pN0	544 (23)	168 (22)	
pN+	142 (6)	43 (6)	
Tumor site			0.027
Renal pelvis	1645 (68)	532 (69)	
Ureter	779 (32)	237 (31)	
Surgical margins			0.006
Negative	2190 (90)	694 (90)	
Positive	233 (10)	76 (10)	
Tumor grade			0.091

Supplementary Table 2. Preoperative characteristics after sIPW re-weighting

Characteristic	Treatment		SMD ¹
	No multiagent AC within 3 months (2423)	Multiagent AC within 3 months (769) ¹	
Grade 1–2	231 (10)	55 (7)	
Grade 3–4	1,964 (81)	634 (83)	
Unknown	229 (9)	80 (10)	
LN removed	0 (0, 1)	0 (0, 1)	0.028
Annual average hospital RNU volume	22.40 (11.60, 37.99)	21.22 (10.80, 36.87)	0.035

*Quartile cutoffs for education level and income varied according to ear of data. ¹Median (IQR); n (%).

²SMD: standardized mean difference.

Supplementary Table 3. Proportion of missing data for each covariate included in the analysis

		Adjuvant chemotherapy	
Characteristic	Total Missing n (%)	No multiagent AC within 3 months Missing n (%)	Multiagent AC within 3 months Missing n (%)
Age, years	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gender	0 (0.0%)	0 (0.0%)	0 (0.0%)
Charlson index	0 (0.0%)	0 (0.0%)	0 (0.0%)
Year of diagnosis	0 (0.0%)	0 (0.0%)	0 (0.0%)
Race	37 (0.9%)	29 (1.0%)	8 (0.8%)
Hispanic	123 (3.1%)	96 (3.2%)	27 (2.6%)
Insurance status	38 (0.9%)	29 (1.0%)	9 (0.9%)
Geographic location	0 (0.0%)	0 (0.0%)	0 (0.0%)
Facility type	499 (12%)	354 (12%)	145 (14%)
Rurality	144 (3.6%)	114 (3.8%)	30 (2.9%)
Income	528 (13%)	376 (13%)	152 (15%)
Education level	520 (13%)	370 (12%)	150 (15%)
pT stage	0 (0.0%)	0 (0.0%)	0 (0.0%)
pN stage	18 (0.4%)	11 (0.4%)	7 (0.7%)
Tumor site	0 (0.0%)	0 (0.0%)	0 (0.0%)
Surgical margins	0 (0.0%)	0 (0.0%)	0 (0.0%)
Tumor grde	4 (<0.1%)	3 (0.1%)	1 (<0.1%)
Annual hospital cystectomy volume	0 (0.0%)	0 (0.0%)	0 (0.0%)
LN removed	0 (0.0%)	0 (0.0%)	0 (0.0%)
LN positive	2888 (72%)	2236 (75%)	652 (64%)

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