

First-line treatment patterns among patients with locally advanced or metastatic urothelial cancer (la/mUC): A systematic literature review

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SCOPE

- The objectives of this systematic literature review (SLR) were to comprehensively characterize global treatment patterns, rates of nonreceipt of systemic therapy (NST), rates of attrition across lines of therapy, and factors influencing treatment selection for patients with la/mUC

CONCLUSIONS

- Rates of NST and attrition were high and variable across different regions and did not demonstrate notable improvement over time
- Key prognostic variables, including poor performance status and comorbidities, were associated with NST, but other factors, such as age and female sex, were also noted
- High attrition rates and decreases in overall survival (OS), progression-free survival, and response to treatment with each line of therapy (LOT) suggest that the most effective treatment is needed early in the disease course to provide the best opportunity for durable disease control, delayed time to relapse, and improved survival
- Additional studies are needed to explore the multifactorial treatment selection process to support optimal treatment sequencing in the era of first-line (1L) immunotherapy (IO) maintenance and targeted therapies in later LOTs

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BACKGROUND

- la/mUC is associated with poor prognosis (5-year survival rate <15%) as well as substantial costs and healthcare resource utilization¹⁻³
- Guideline-recommended treatments for la/mUC include 1L platinum-based chemotherapy for eligible patients, followed by avelumab maintenance for patients whose disease has not progressed.⁴ IO is available for PD-L1-positive and platinum-ineligible patients⁵
- Second-line (2L) treatments include IOs, antibody-drug conjugates, fibroblast growth factor receptor inhibitors, and chemotherapeutics, including platinum/taxane-based therapy and vinflunine⁶

- Treatment improves median OS from 9 to 24 months; however, recent studies suggest that a substantial proportion of patients with la/mUC do not receive systemic therapy (ST) either in 1L or subsequent lines of therapy⁷⁻¹²
- Untreated patients (1L or subsequent) have greater healthcare resource utilization and higher costs per-patient per-month than treated patients^{13,14}
- The underutilization of ST has not been comprehensively investigated, and the high attrition rates are not well characterized

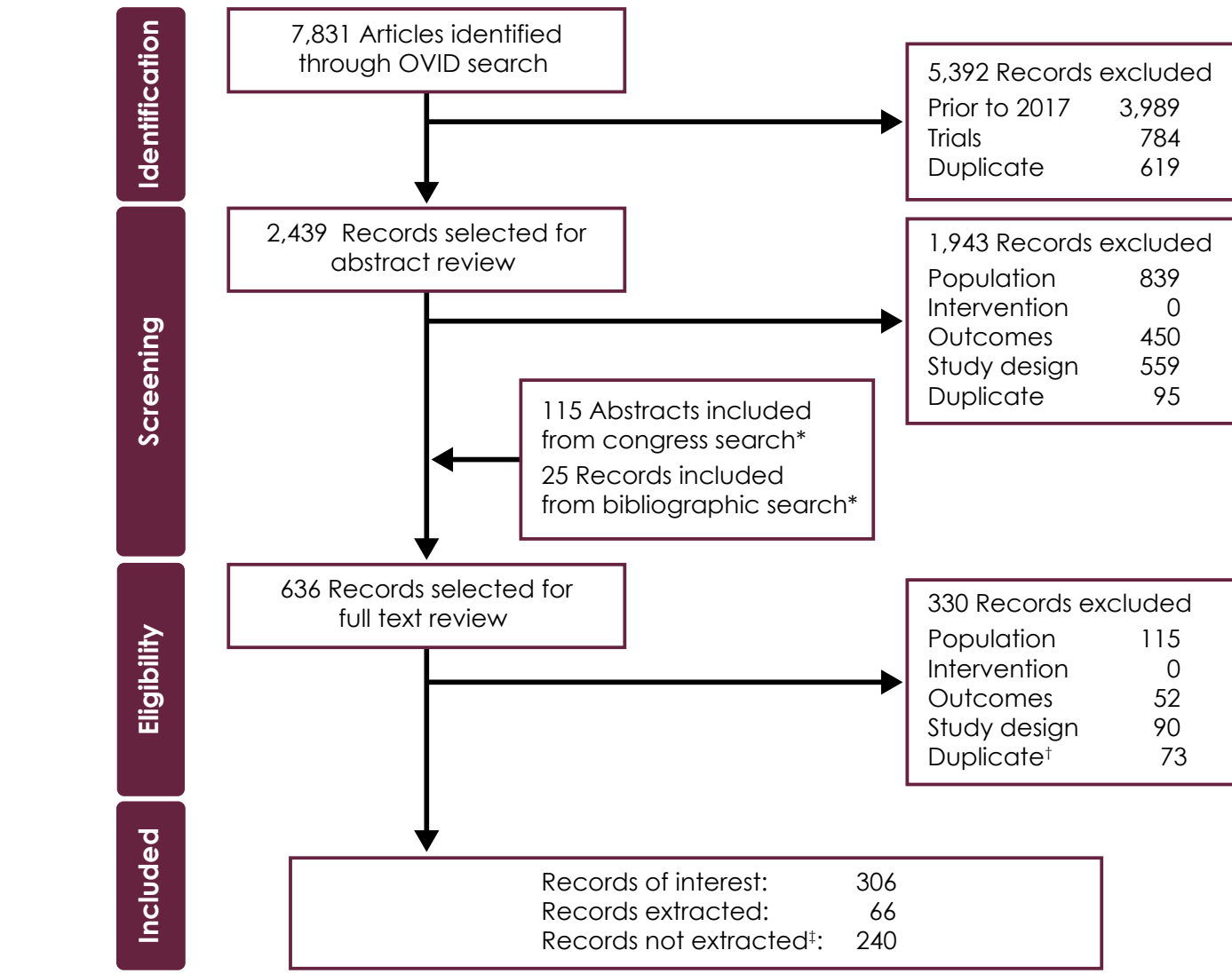
METHODS

- We conducted an SLR of real-world evidence of NST in patients with la/mUC published from 2017 to 2022 (including data from 2015 or later) by searching the Cochrane Library, EconLit, Embase, MEDLINE, and MEDLINE In-Process databases on 25 February 2022
- Relevant conferences were searched for abstracts published in 2017 and later (see Wilke et al¹⁵ for full SLR methodology)
- Fisher exact tests were performed post hoc for categorical variables using MedCalc software if the publication of interest did not include statistical analyses for associations of patient characteristics and NST/attrition

RESULTS

- Of 2,439 publications screened, 66 reported treatment patterns, 1L NST rates, and/or attrition rates (Figure 1)
- Overall, treatment practice generally aligned with clinical guidelines

Figure 1. PRISMA diagram

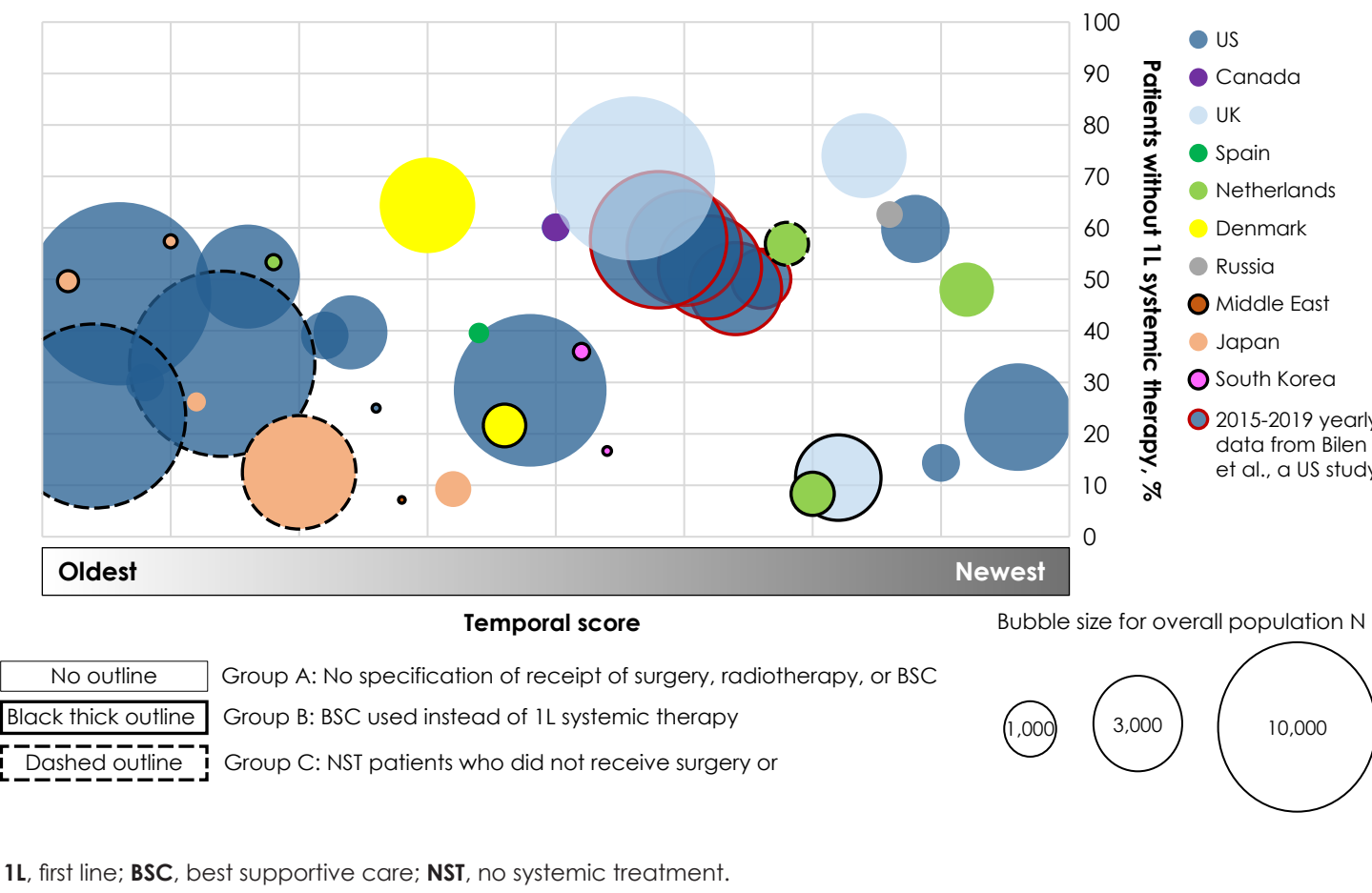


NST, nonreceipt of systemic treatment; **PRISMA**, Preferred Reporting Items for Systematic Reviews and Meta-Analyses. *Includes duplicates with the abstract review. †Includes duplicates between the abstract review and manually added records from congress search and bibliographic search. ‡Records were not extracted unless fulfilling the additional criteria for data extraction: reporting of NST rates and specification of period when data was acquired.

Treatment patterns in 1L

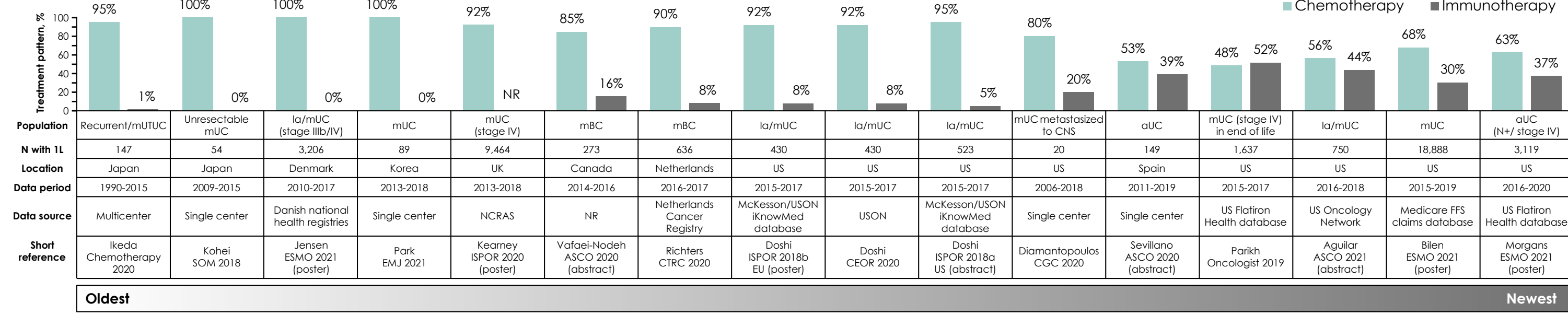
- 29 studies reported NST rates: 8 European-based studies reported NST rates of 40%-74%; 12 US-based studies reported NST rates of 14%-60%; and 9 studies from the rest of the world, including Japan, Canada, and Russia, reported NST rates of 9%-63% (Figure 2)
- Studies varied in reporting of NST data; some provided details about surgery, radiotherapy, or best supportive care, whereas others did not. A detailed breakdown of NST rates by reporting type was provided in Wilke et al¹⁵
- Rates of treatment did not appear to improve considerably over time across included studies
- In studies reporting 1L ST, rates of chemotherapy use ranged from 48%-100%. Rates of 1L IO use were 0%-52% (Figure 3)
- Rates of chemotherapy use declined over time; however, they appeared to rebound in more recent years

Figure 2. NST rates by country over time



1L, first line; **BSC**, best supportive care; **NST**, no systemic treatment.

Figure 3. 1L systemic treatment patterns over time



1L, first line; **aUC**, advanced urothelial cancer; **CNS**, central nervous system; **FPS**, Fraud Prevention Services; **la/mUC**, locally advanced or metastatic urothelial cancer; **mBC**, metastatic bladder cancer; **mUC**, metastatic urothelial cancer; **mUUC**, metastatic upper urinary tract urothelial carcinoma; **N**, node; **NCRAS**, National Cancer Registration and Analysis Service; **NR**, not reported; **USON**, US Oncology Network.

Treatment patterns in 2L or subsequent treatment

- 47 studies reported the rate of 2L or subsequent treatment (Figure 4). Overall, rates of treatment were low and decreased with subsequent LOTs
- Rates of receipt of 2L ST were lower in cisplatin-ineligible vs -eligible patients (37% vs 49%) and in those who received 1L IO vs 1L chemotherapy (31% vs 47%)
 - 2L treatment rates in patients who received cisplatin-based 1L therapy (n=5 subgroups; median, 45%; range, 30%-67%) were slightly higher than those in patients who received carboplatin-based 1L therapy (n=4 subgroups; median, 40%; range, 23%-47%)
 - In patients who received IO as any LOT, 8%-62% (n=19 subgroups; median, 38%) received subsequent therapy
- Attrition rates have not considerably improved in recent years

Factors associated with NST or attrition

- Few studies reported factors associated with NST in 1L or attrition after receipt of 1L therapy
- Reported characteristics associated with NST or attrition included older age and female sex, in addition to poor performance status, poor renal function, and distant metastases (Table)

Survival

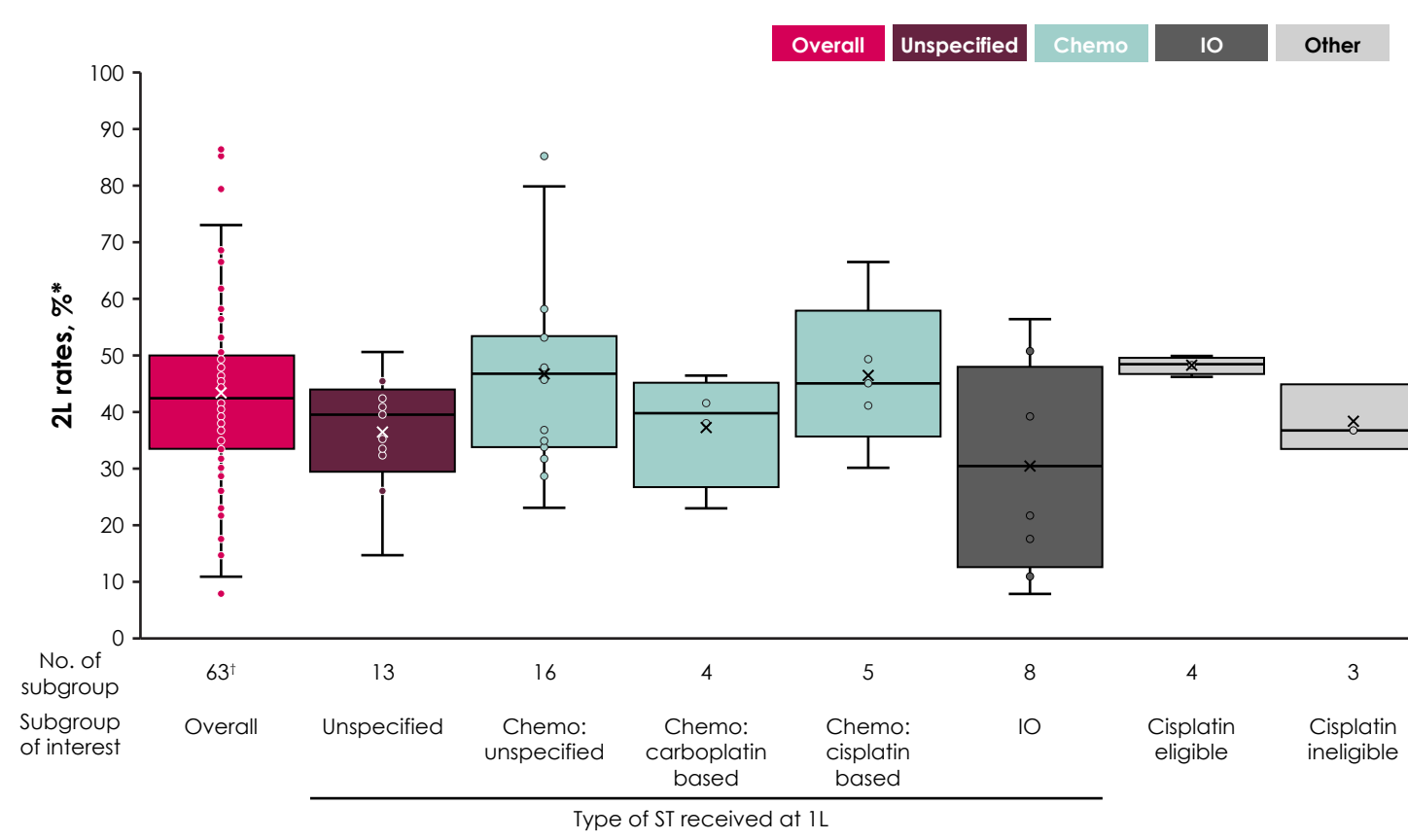
- In the 8 studies reporting survival, the median OS was 2.0-6.9 months with NST and 9.2-34.5 months with ST (see Wilke et al¹⁵ for full data)

Table. Factors associated with NST and attrition

Type of undertreatment	NST						1L chemo → 2L attrition	1L IO → 2L attrition	2L IO → 3L attrition
Reference	Parikh et al, 2019	Ikeda et al, 2020	Geynisman et al, 2021	Bilen et al, 2021	Reesink et al, 2020	Richters et al, 2020	Flannery et al, 2019	Gómez de Llaño Liza et al, 2020	Gómez de Llaño Liza et al, 2020
Geographic location	US	Japan	US	US	Netherlands	Netherlands	US	European countries	European countries
Study period	2015-2017	1990-2015	2011-2020	2015-2019	2008-2016	2016-2017	2010-2016	2013-2017	2013-2017
Statistics	Reported	Reported	Post hoc	Post hoc	Post hoc	Post hoc	Reported	Reported	Reported
Older age	Age <65 vs ≥65 years p<0.005	Median age p<0.05	Age <65 vs ≥65 years p<0.05	–	Age <70 vs ≥70 years p<0.001	Age <60 vs ≥60 years p<0.001	Median age p<0.005	Median age NR	Median age NR
Poor ECOG PS	ECOG PS 0/1 vs ≥2 p<0.05	–	ECOG PS 0/1 vs ≥2 NR	–	–	ECOG PS 0/1 vs ≥2 p<0.001	ECOG PS 0/1 vs ≥2 p<0.005	–	–
Poor renal function	–	eGFR change rate: normal vs moderate vs severe NR	–	–	eGFR ≤30 vs >30 mL/min; ≤60 vs >60 mL/min p<0.05	eGFR ≤30 vs >30 mL/min; ≤60 vs >60 mL/min p<0.001	CrCl <60 vs ≥60 mL/min p<0.005	–	–
Metastatic disease	–	–	–	–	M0 vs M1 p<0.05	Lymph nodes only vs spread outside lymph nodes p<0.001	–	Lymph nodes only vs spread outside lymph nodes NR	Lymph nodes only vs spread outside lymph nodes p<0.05
Comorbidities	–	–	–	Comorbidities vs no comorbidities p<0.001	–	No. of comorbidities: 1/2 vs ≥2 p<0.05	–	–	–
Non-White race	White vs non-White NR	–	White vs non-White p<0.05	White vs non-White p<0.001	–	–	White vs Black vs other* NR	–	–
Sex	Male vs female NR	Male vs female NR	Male vs female NR	Male vs female p<0.001	Male vs female NR	Male vs female NR	Male vs female p<0.005	Male vs female NR	Male vs female NR
Primary organ being bladder	–	–	Bladder vs nonbladder p<0.001	–	–	–	–	Bladder vs nonbladder NR	Bladder vs nonbladder NR
Higher stage at initial diagnosis	–	T stage <pT3 vs ≥pT3 NR	–	–	–	–	0 vs I vs II vs III vs IV NR	0-III vs IV p<0.05	0-III vs IV NS
No. of metastatic sites	–	–	–	–	–	–	1 vs ≥2 NR	0 vs ≥1 NR	1 vs ≥1 p<0.05

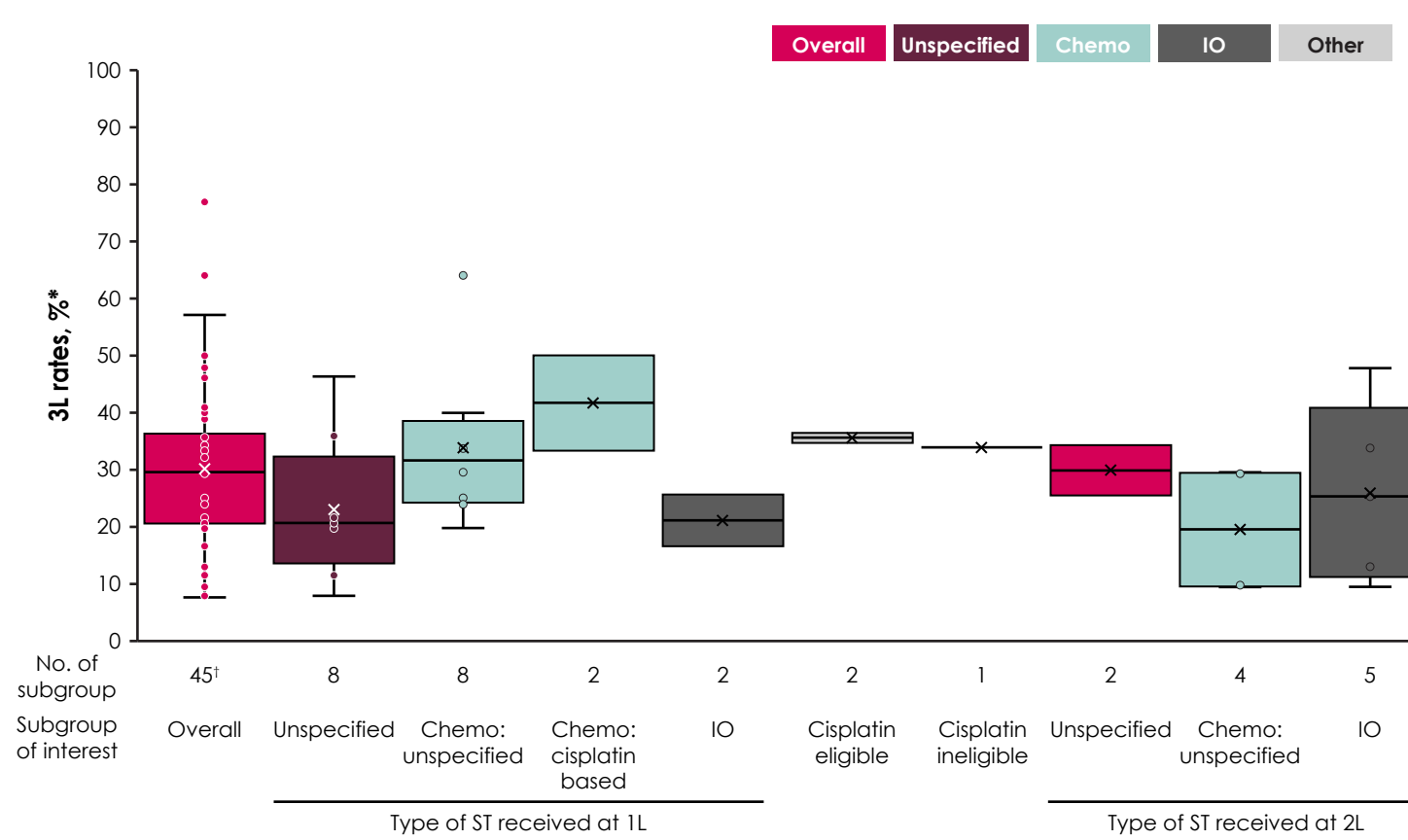
1L, first line; 2L, second line; 3L, third line; **chemo**, chemotherapy; **CrCl**, creatinine clearance; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **eGFR**, estimated glomerular filtration rate; **IO**, immunotherapy; **NR**, not reported; **NST**, nonreceipt of systemic treatment; *Asian, American Indian, Alaska native.

Figure 4A. Rates of 2L treatment



1L, first line; 2L, second line; **chemo**, chemotherapy; **IO**, immunotherapy; **ST**, systemic treatment. *2L rates were calculated as a percentage of patients who received 1L therapy as the denominator. †The number of subgroups does not add up as not all subgroups of interest are presented in this figure.

Figure 4B. Rates of 3L treatment



1L, first line; 2L, second line; 3L, third line; **chemo**, chemotherapy; **IO**, immunotherapy; **ST**, systemic treatment. *3L rates were calculated as a percentage of patients who received 2L therapy as the denominator. †The number of subgroups does not add up as not all subgroups of interest are presented in this figure.

Strengths

- To our knowledge, this is the first SLR to evaluate real-world treatment patterns, focusing on NST and attrition across LOT in la/mUC
- This study used a comprehensive search strategy that included a broad geographical reach, several languages, and relatively recent data sources (2017-2022)
- While results were mainly qualitative, quantitative analysis was performed when possible

Limitations

- Only real-world data were identified from studies published in the literature, and our search strategy did not involve specific database or registry searches
- A number of studies identified in this review were congress abstracts, which had limited information on study methods
- Several data gaps were identified, including a paucity of data in 2L and subsequent LOT, limiting our interpretation and ability to perform quantitative analyses
- Patient decision and physician factors were not included as reasons for nontreatment and attrition