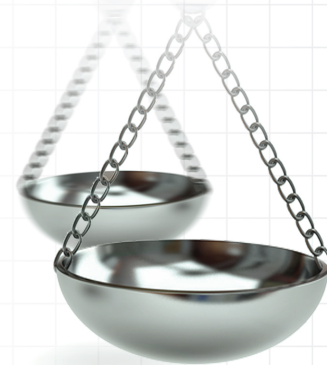




Medical oncology referral and systemic therapy of patients with advanced stage urothelial carcinoma

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Aim: To understand physician visit patterns among patients with stage IV (including nonmetastatic [M0] and metastatic [M1] disease) urothelial carcinoma (UC) and understand factors associated with a timely referral to a medical oncologist and systemic treatment. **Patients & methods:** Retrospective analysis of Surveillance, Epidemiology and End Results-Medicare data. **Results:** First physician encounter was with a urologist (M0: 69%; M1: 53%) or primary care physician (PCP; M0: 19%, M1: 25%) for the majority of patients around UC diagnosis. After the index urologist encounter, most patients had a subsequent medical oncologist visit at a median of 52 days (M0: 69.5 days, M1: 33 days). In an adjusted model, older age, index PCP visit, higher comorbidities and M0 disease were negatively associated with a medical oncologist referral. Among those referred to a medical oncologist, older age, Hispanic or non-Hispanic Black race and not being married were negatively associated with subsequent chemotherapy receipt ($p < 0.05$). **Conclusion:** Many patients with advanced UC encounter multiple specialists during their disease course. Older patients or those with a first UC-related encounter with a PCP are less likely to be referred to medical oncology. Once referred to medical oncology, social determinants, including race and marital status, are relevant predictors of receiving chemotherapy.

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Approximately 75% of patients with urothelial carcinoma (UC) in the USA are diagnosed after the age of 65 years [1,2]. Patients diagnosed with stage IV UC, which includes patients who have locally advanced/unresectable UC that has grown through the bladder wall into the pelvic or abdominal wall without distant metastasis (M0) or those with distant metastasis (M1) [3], may initially be asymptomatic or present to a primary care physician (PCP) or a urologist with loco-regional (e.g., hematuria, dysuria and pelvic pain) and/or systemic/constitutional symptoms. Typically, if deemed clinically warranted, the urologist would then conduct a cystoscopy, obtain a biopsy, obtain appropriate imaging tests and perform a transurethral resection of bladder tumor (either at the initial visit or on a follow-up visit for diagnostic, and potentially therapeutic purposes). The patient may subsequently be referred by the urologist to a medical oncologist to help complete further staging work up and formulate a treatment plan. Although the urologist is generally the gatekeeper in terms of obtaining relevant tumor tissue to help establish pathologic diagnosis, physician-to-physician referral patterns of patients suspected of having UC can vary, which may impact subsequent management.

According to the current National Comprehensive Cancer Network and American Urological Association guidelines, first-line therapy for stage IV M0 patients can include immune checkpoint inhibitors (ICIs), chemoradiation or chemotherapy that may or may not also incorporate cystectomy; upon recurrence, additional systemic ther-

apy, and in select patients, cystectomy or radiation therapy are recommended [4,5]. In patients with M1 disease, guidelines recommend platinum-based chemotherapy and ICIs for first-line therapy and ICIs or chemotherapy as second-line therapies (depending on first-line treatment) [4,5]. Recent studies, however, report that approximately two-thirds of all stage IV bladder cancer patients [6,7] and 55% of those with metastatic UC [8] are not treated with systemic chemotherapy, despite the survival advantage conferred by chemotherapy [6]. Several factors may contribute to whether or not patients go on to receive systemic chemotherapy, including advanced age, poor performance status [9] or potential issues related to timely access/referral to relevant specialists [10].

Having access to a PCP and urologist may play an important role in establishing diagnosis of UC and appropriate referral for treatment. Similarly, since the medical oncologist is the main prescriber of systemic chemotherapy, not having access to a medical oncologist may be a barrier to receiving chemotherapy. One form of this access barrier is the decision point of the urologist or PCP to make the referral to a medical oncologist in the first place; the relative timing of such a referral then would be relevant to receipt of timely systemic therapy. After evaluation, the medical oncologist, together with the patient, would then decide as to whether the patient is an appropriate candidate for chemotherapy. To investigate the impact of these dynamics of patient referrals and evaluations on subsequent systemic treatment of advanced UC, this study was conducted with two objectives in mind: first, to understand the real-world physician visit patterns of patients in the immediate period leading up to *de novo* stage IV UC diagnosis, and their subsequent follow-ups after diagnosis; and second for patients seeing a urologist or/and a PCP around the time UC was suspected, to understand the factors associated with a timely referral to a medical oncologist and identify potential factors associated with institution of systemic chemotherapy. Newer therapies (e.g., immunotherapy, antibody drug–conjugates and targeted agents) are being increasingly incorporated into the management of advanced UC. As a result, using chemotherapy as a model treatment to better understand the dynamics of systemic treatment receipt within the patient–physician journal will become increasingly relevant.

Materials & methods

Database

This was a retrospective analysis using data from the linked Surveillance, Epidemiology and End Results (SEER)-Medicare database and the American Medical Association (AMA) Physician Masterfile. The SEER registry consists of 18 state or regional cancer registries, covering 28% of the US population [11,12], while the Medicare database contains covered healthcare service claims and associated costs for all Medicare beneficiaries from time of eligibility until death [13,14]. The AMA Physician Masterfile contains demographic, education, training, specialty and practice information of physicians in the US and US territories [15].

Study population

Medicare patients aged 66 years or older who were newly diagnosed with histologically confirmed stage IV UC from 2004 to 2013 (*International Classification of Diseases for Oncology, Third Edition* [ICD-O-3] codes 8120/3 - 8124/3) and had associated Medicare claims data from 2003 to 2014 were eligible for inclusion. Stage IV UC was defined as: tumor through the bladder wall into the pelvic or abdominal wall but not spread to regional lymph nodes or metastasized to distant sites (T4b/N0/M0); tumor through the bladder wall into nearby organs and regional lymph nodes but not metastasized (any T/N1–3/M0); or disease metastasized to distant lymph nodes or one or more distant organs (e.g., bones, liver or lungs) regardless of whether or not the tumor had grown through the bladder wall into nearby organs or spread to regional lymph nodes (any T/any N/M1) [16]. M0 was defined as a disease that had not spread to distant lymph nodes or distant organs, and M1 was defined as a disease that had spread to distant lymph nodes or one or more distant organs [3].

Exclusion criteria

Patients were excluded if they had a postmortem first diagnosis of UC, an unknown diagnosis month/year, had any other cancer (except nonmelanoma skin cancer) in the 5 years prior to UC diagnosis or lacked continuous enrollment in Medicare Part A and B, or were enrolled in a health maintenance organization in the 12 months prior to diagnosis. Additionally, patients with previous UC diagnosis at earlier stages were excluded to define a truly incident cohort of stage IV patients with UC. Patients were followed until death or end of the study period (31 December 2014).

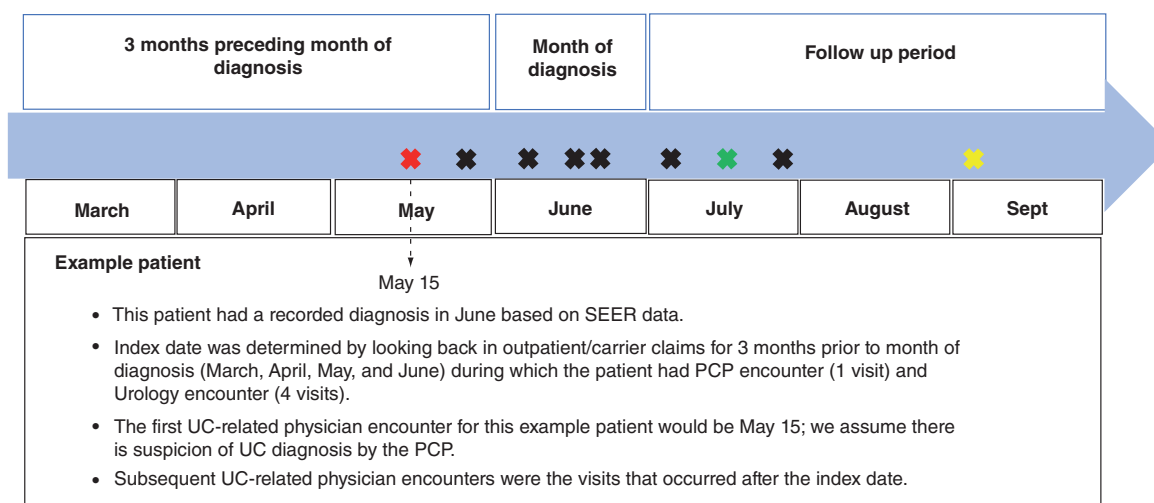


Figure 1. Definition of study index date for a hypothetical patient diagnosed in June. Color of X refers to the specialist (red = PCP, black = urologist, green = medical oncologist, yellow = radiation oncologist). PCP: Primary care physician; SEER: Surveillance, Epidemiology and End Results; UC: Urothelial carcinoma.

Definition of study index date

Patient–physician interactions affecting UC diagnosis and management typically occur a few weeks to months before receiving a confirmed diagnosis and subsequent staging of UC. Therefore, the study examined physician visit patterns from the 3 months prior to the month of stage IV diagnosis and through the ensuing follow-up. During this period, patients' UC-related physician encounters were flagged by the presence of an International Classification of Diseases, Ninth Edition, Clinical Modifications (ICD-9-CM) code 188.9 for malignant neoplasm of bladder on an outpatient setting/carrier claim as well as an available National Provider Identifier/Unique Physician Identification Number record.

The first UC-related physician encounter during the study period described above was defined as the study index date for patients (Figure 1). For 90% of patients, the index date of the first UC-related encounter was the same month in which stage IV UC diagnosis was established, or was the immediate month preceding the month of UC diagnosis. By including physician encounters up to 3 months prior to the diagnosis of UC, we captured the real-world nature of patient–physician encounters that may be related to a suspicion of UC, as well as any subsequent physician referrals and patient flow associated with the management of advanced UC. This approach also addressed some of the limitations inherent within the SEER-Medicare database in that: the dataset does not enable the direct identification of the diagnosing physician; since timing of cancer diagnosis from the SEER registry is available on a month/year basis, this does not completely align with the more refined day/month/year time format of the claims information in the Medicare portion of the linked database (from which we derive the timing of specialist encounters). Subsequent visits were captured only at the times when patients were channeled to a new physician specialist post the index physician visit.

Baseline patient characteristics

Patient demographic characteristics, including age at diagnosis, sex, race/ethnicity, census location and marital status were obtained from the SEER registries. Patient comorbidities that occurred in the 12 months prior to UC diagnosis were extracted from the Medicare claims to calculate the Deyo adaptation of the Charlson Comorbidity Index (CCI) [17]. Performance status was calculated for all patients using a proxy, defined as having a Medicare claim for any of the following in the 12 months prior to UC diagnosis, were the following: wheelchair use, oxygen use, walking aid, hospital bed, hospice, skilled nursing facility or hospitalization.

Index physician characteristics

Physician characteristics were reported only for the index physician (i.e., the first UC-related physician encounter during the study period) to understand those characteristics that could be associated with initial suspicion of UC by M stage. Physician characteristics included age, gender, office location, degree received, training in a US

medical school, years since medical school graduation and physician practice setting. Physician practice settings were classified into solo practice; federal government hospital (e.g., Veterans Administration hospital, hospital affiliated with the Armed Forces and US Public Service); local government hospital (i.e., city, county or state-run facilities); and nongovernment practices (e.g., health maintenance organizations, group practices, two-physician practices, medical schools, locum tenens, nongovernment hospitals or other facilities).

Study outcomes

UC-related physician encounters belonging to the following four specialties were retained: urologist, radiation oncologist, medical oncologist and PCP. Study outcomes included describing the physician visit patterns by specialist type post the index date in other words, time from first specialist visit to a medical oncologist visit. If a PCP refers to a urologist and then the urologist refers to a medical oncologist, the time is measured from the initial PCP visit. In addition, determinants of the time to a medical oncologist visit and chemotherapy receipt after an initial visit to a urologist or PCP was examined. Overall survival by first specialty visit was descriptively examined as an exploratory outcome.

Statistical analysis

Descriptive statistics were used to summarize patient and physician characteristics, physician referral patterns and referral patterns from the index visit to subsequent UC-related physician encounters for M0 and M1 patients. Visual Sankey diagrams outlining physician referrals and associated patient flow were constructed from the index physician encounter through subsequent follow-up. No statistical tests were conducted to compare M0 and M1 patients with respect to patterns and timing of referrals, as M1 patients were expected to have poorer survival and therefore shorter follow-up to make fair comparisons to M0 patients.

Cox proportional hazards model with a backward selection procedure (that included covariates with $p < 0.10$ in the final model) were used to estimate determinants of time to medical oncologist visit after index urologist or PCP visit and time to receiving systemic chemotherapy after index urologist or PCP visit. The covariates that were adjusted in the models included patient clinical characteristics (age, M-stage at diagnosis, Charlson Comorbidity Index (CCI) and performance status at diagnosis), patient demographics (sex, race/ethnicity, marital status, census location, location in an urban vs rural area), receipt of cystectomy and physician characteristics (physician specialty, age, office location and degree received [i.e., MD or DO], US medical school training, years since medical school graduation and practice setting). All analyses were conducted using SAS version 9.4.

Results

Patient characteristics

A total of 2044 stage IV UC patients met inclusion and exclusion criteria ([Supplementary Figure 1](#)). The proportion of patients with M0 (49%; $n = 1007$) or M1 (51%; $n = 1037$) disease at diagnosis was similar. The mean age at UC diagnosis was 77 years; 64% of patients were male and 85% were non-Hispanic whites. ([Table 1](#)). At diagnosis, 71% of patients had a CCI score of 0 or 1 and 25% had a proxy for poor performance status. Patients had a median follow-up of 9 months (interquartile range [IQR]: 4–19 months), which was expectedly shorter for M1 compared with M0 patients (6 [3–13] months vs 14 [7–28] months; $p < 0.001$), likely related to worse survival for M1 patients.

Physician characteristics

The mean age of the index physicians included in the analysis was 50 years; the majority were male (90%) and had a MD degree (96%). Approximately 81% of the index physicians received US medical school training and most practiced in a nongovernment practice (68%). Physicians who suspected UC in M0 patients were more likely to be male and trained in the US compared with M1 patients. No further significant differences in physician characteristics were observed by M stage ([Table 1](#)).

Physician referral patterns

Index specialist visit

The most common index UC-related visit was with a urologist (61%), while those with a PCP (22%), medical oncologist (15%) or radiation oncologist (2%) were less common. More patients who saw index PCP were older than 80 years of age ($p = 0.003$). More patients with CCI score of 3 and greater had an index medical oncologist visit ($p = 0.009$; [Supplementary Table 1](#)). When stratified by M stage, more M0 patients (69%) had index urologist

Table 1. Patient and index physician characteristics by patient M stage at diagnosis.

Characteristic	All (n = 2044)	M0 (n = 1007)	M1 (n = 1037)	p-value
Patient characteristics				
Age at diagnosis, mean (SD), years	76.86 (6.88)	76.21 (6.56)	77.48 (7.13)	<0.001
Age at diagnosis, n (%)				
– 66–70 years	444 (21.7)	238 (23.6)	206 (19.9)	0.013
– 71–75 years	488 (23.9)	254 (25.2)	234 (22.6)	
– 76–80 years	473 (23.1)	231 (22.9)	242 (23.3)	
– 80+ years	639 (31.3)	284 (28.2)	355 (34.2)	
Male, n (%)	1317 (64.4)	661 (65.6)	656 (63.3)	0.261
Race/ethnicity, n (%)				
– Non-Hispanic White	1732 (84.7)	858 (85.2)	874 (84.3)	0.812
– Non-Hispanic Black	143 (7.0)	68 (6.8)	75 (7.2)	
– Hispanic	95 (4.6)	43 (4.3)	52 (5.0)	
– Other	74 (3.6)	38 (3.8)	36 (3.5)	
Marital status at diagnosis, n (%)				
– Single (never married)	173 (8.5)	79 (7.8)	94 (9.1)	<0.001
– Married	1114 (54.5)	597 (59.3)	517 (49.9)	
– Separated/divorced/widowed	692 (33.9)	302 (30.0)	390 (37.6)	
– Unknown	65 (3.2)	29 (2.9)	36 (3.5)	
Census location, n (%)				
– West	868 (42.5)	428 (42.5)	440 (42.4)	0.759
– South	449 (22.0)	219 (21.7)	230 (22.2)	
– Northeast	473 (23.1)	241 (23.9)	232 (22.4)	
– Midwest	254 (12.4)	119 (11.8)	135 (13.0)	
Urban location, n (%)				
– Rural	210 (10.3)	91 (9.0)	119 (11.5)	0.069
– Urban	1834 (89.7)	916 (91.0)	918 (88.5)	
Charlson Comorbidity Index, n (%)				
– 0	957 (46.8)	499 (49.6)	458 (44.2)	<0.001
– 1	494 (24.2)	256 (25.4)	238 (23.0)	
– 2	276 (13.5)	128 (12.7)	148 (14.3)	
– 3+	317 (15.5)	124 (12.3)	193 (18.6)	
Poor performance status, n (%)				
– Yes	509 (24.9)	239 (23.7)	270 (26.0)	0.229
Index physician characteristics				
Age, mean (SD), years	50.51 (10.41)	50.57 (10.42)	50.45 (10.42)	0.875
Male, n (%)	1829 (89.5)	922 (91.6)	907 (87.5)	0.003
Office location, n (%)				
– Northeast	460 (22.5)	238 (23.6)	222 (21.4)	0.472
– North Central	267 (13.1)	123 (12.2)	144 (13.9)	
– South	470 (23.0)	226 (22.4)	244 (23.5)	
– West	847 (41.4)	420 (41.7)	427 (41.2)	
Degree received, n (%)				
– DO	87 (4.3)	34 (3.4)	53 (5.1)	0.052
– MD	1957 (95.7)	973 (96.6)	984 (94.9)	
Trained in US medical school, n (%)	1659 (81.2)	854 (84.8)	805 (77.6)	<0.001
Years since medical school graduation, mean (SD)	23.56 (10.81)	23.76 (10.85)	23.36 (10.77)	0.495

DO: Doctor of Osteopathic Medicine; M0: Nonmetastatic; M1: Metastatic.

Table 1. Patient and index physician characteristics by patient M stage at diagnosis (cont.).

Index physician characteristics				
Practice setting, n (%)				
– Government hospital - federal	23 (1.1%)	12 (1.2%)	11 (1.1%)	0.542
– Government hospital - city/county/state	79 (3.9%)	42 (4.1%)	37 (3.7%)	
– Nongovernment practice	817 (40.0%)	407 (39.3%)	410 (40.6%)	
– Not recorded	922 (45.1%)	462 (45.8%)	460 (44.4%)	
– Solo practice	203 (9.9%)	112 (10.8%)	91 (9.0%)	

DO: Doctor of Osteopathic Medicine; M0: Nonmetastatic; M1: Metastatic.

Table 2. Physician referral patterns by the index specialist with respect to M0 or M1 stage at diagnosis.

Specialist visit	M0 patients(n = 1007)		M1 patients(n = 1037)	
	n (%) of patients	Days to next specialist type, median (Q1–Q3)	n (%) of patients	Days to next specialist type, median (Q1–Q3)
PCP as index specialist (visit 1)	191 (19.0)		255 (24.6)	
Next specialist type (visit 2)				
– None	42 (22.0)	NA	87 (34.1)	NA
– PCP	NA	NA	NA	NA
– Urologist	101 (52.9)	9.0 (3.0–26.0)	92 (36.1)	6.0 (1.0–20.0)
– Medical oncologist	NR	20.0 (7.0–107.0)	NR	14.0 (4.0–34.0)
– Radiation oncologist	NR	7.0 (4.0–46.0)	NR	6.5 (3.0–132.0)
Urologist as index specialist (visit 1)	694 (68.9)		553 (53.3)	
Next specialist type (visit 2)				
– None	68 (9.8)	NA	71 (12.8)	NA
– PCP	297 (42.8)	42.0 (15.0–73.0)	208 (37.6)	27.0 (8.0–59.5)
– Urologist	NA	NA	NA	NA
– Medical oncologist	299 (43.1)	51.0 (17.0–97.0)	236 (42.7)	22.5 (7.5–49.5)
– Radiation oncologist	30 (4.3)	40.5 (14.0–83.0)	38 (6.9)	12.0 (6.0–56.0)
Medical oncologist as index specialist (visit 1)	102 (10.1)		207 (20.0)	
Next specialist type (visit 2)				
– None	29 (28.4)	NA	63 (30.4)	NA
– PCP	24 (23.5)	30.0 (7.5–155.5)	73 (35.3)	24.0 (8.0–80.0)
– Urologist	36 (35.3)	23.0 (5.5–89.0)	43 (20.8)	17.0 (6.0–68.0)
– Medical oncologist	NA	NA	NA	NA
– Radiation oncologist	13 (12.7)	5.0 (3.0–30.0)	28 (13.5)	7.5 (1.0–28.0)

NR: Not reported to be compliant with the data use agreement with the NCI. Minority (2%, n = 20) of patients saw a radiation oncologist at index visit; however, these data are not presented because numbers on the subsequent visits are <11 and thus not compliant with the Data Use Agreement with the NCI.

M0: Nonmetastatic; M1: Metastatic; NA: Not applicable; NR: Not reported; PCP: Primary care physician.

visit compared with M1 patients (53%). However, less M0 patients (19%) had index PCP visit compared with M1 patients (25%). Also, less M0 patients (10%) had index medical oncologist visit compared with M1 patients (20%) (visit 1 in [Figure 2](#)).

Referral to a second specialist

The proportions and median (interquartile range) times between referrals are described in [Table 2](#) & [Figure 2](#). The Sankey diagram visually demonstrates that referrals between specialist types are common for both M0 and M1 patients, as designated by the inflow/outflow bands in [Figure 2](#) from one physician specialty to another. Focusing on the referral patterns from the first (index) visit to the immediate next specialist type (visit 2), patients who had their index specialty visit with a PCP had their most common next visit with a urologist (M0: 52.9%; M1: 36.1%; [Table 2](#)). For those patients who saw a urologist as the index physician, the next specialist type was a medical oncologist (M0: 43.1%; M1: 42.7%). Index medical oncologists seemed to channel patients to the radiation oncologist (M0: 12.7%; M1: 13.5%) almost three-times as often than index PCP or urologists. Of note,

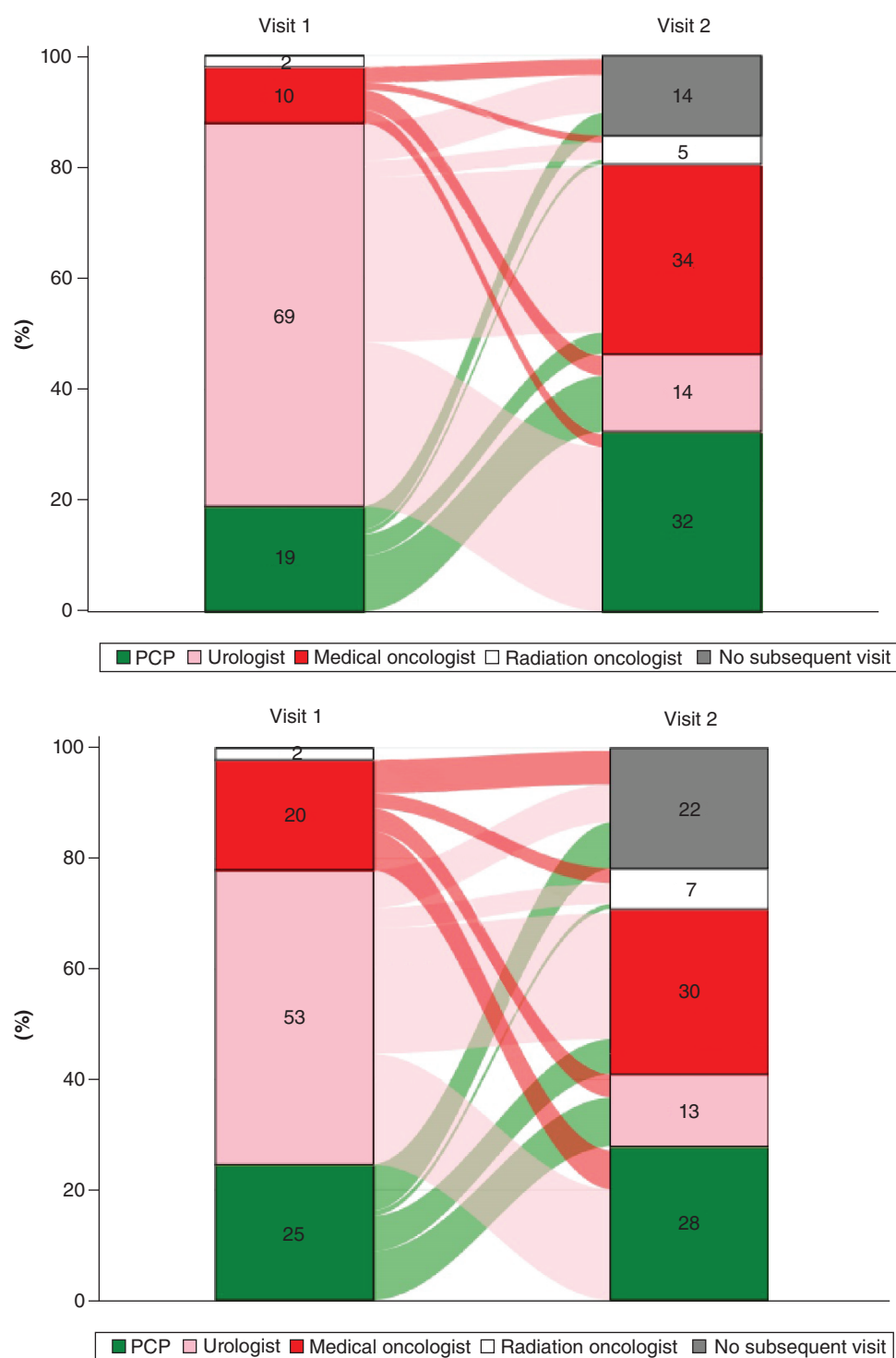


Figure 2. Sankey diagram. Physician referral patterns among nonmetastatic (M0; top panel) and metastatic (M1; bottom panel) patients after index visit. The relative width of the flow between the bars reflect relative distribution of outflow/inflow by specialist type. The outflow from the 2% radiation oncologists have been masked as they represent patient counts of <11 to be compliant with the NCI data use agreement. NCI: National Cancer Institute; PCP: Primary care physician.

Table 3. Referrals to a medical oncologist any time after index visit, by M stage.

Referral patterns to medical oncologist	All	M0 patients	M1 patients
Urologist as index specialist, n	1247	694	553
Any subsequent medical oncologist visit, n (%)	877 (70.3)	512 (73.8)	365 (66.0)
Days from index to first medical oncologist visit			
– Mean (SD)	102.92 (190.57)	114.19 (160.01)	87.11 (225.89)
– Median (Q1–Q3)	52 (20–106)	69.5 (29–126)	33 (14–74)
PCP as index specialist, n	446	191	255
Any subsequent medical oncologist visit, n (%)	226 (50.7)	96 (50.3)	130 (51.0)
Days from index to first medical oncologist visit			
– Mean (SD)	73.5 (183.2)	117.22 (264.1)	41.22 (68.6)
– Median (Q1–Q3)	29 (9–77)	52.0 (16–117.5)	21.5 (6–42)

M0: Nonmetastatic; M1: Metastatic; PCP: Primary care physician; SD: Standard Deviation.

index urologists also had the lowest proportion of not referring patients to any of the other three specialists (M0: 9.8%; M1: 12.8%).

With respect to the median time from the index physician specialist to the next specialist type, the time interval was longest for index urologists (varying between 40 and 51 days to next specialist among M0 and 12–27 days among M1 patients) and relatively short for index PCPs (varying between 7 and 20 days to the next specialist among M0 and 6–14 days among M1 patients; [Table 2](#)).

Subsequent medical oncologist visit

Seventy four percent of M0 patients and 66% of M1 patients had a subsequent medical oncologist visit at any time since index urologist visit. Approximately 50% of M0 and M1 patients had a subsequent medical oncologist visit at any time since index PCP visit. The median time to visiting a medical oncologist was longer for patients who saw an index urologist (52 days) compared with an index PCP (29 days); this trend was similar when stratified by M stage, with M0 patients, as expected, having longer time intervals than M1 patients ([Table 3](#)).

Predictors of time from index urologist or PCP visit to first medical oncologist visit

Since patients with UC most often see a urologist or a PCP at initial presentation, predictors of time to seeing a medical oncologist were assessed among patients with an index urologist or PCP visit. In a multivariate Cox regression model, patients whose index specialty visit was with a PCP (hazard ratio [HR]: 0.82 [0.74, 0.97]), were aged 80 years or older (HR: 0.71 [0.60, 0.84]), had CCI score of 3 or greater (HR: 0.78 [0.64, 0.95]), were recipients of cystectomy (HR: 0.80 [0.69, 0.91]) or whose index visit was in a ‘solo practice’ setting (HR: 0.74 [0.60, 0.92]) had lower relative likelihood of seeing a medical oncologist at any time after their index visit compared with the respective reference groups. Overall, M1 patients had a higher relative likelihood of seeing a medical oncologist compared with M0 patients (HR: 1.17 [1.00, 1.36], $p = 0.048$; [Figure 3](#)).

Predictors of time from index urologist or PCP visit to chemotherapy receipt among patients with subsequent medical oncologist visit

With respect to the predictors of time to systemic chemotherapy receipt post-index urologist or PCP visit and who had subsequent medical oncologist visit, cystectomy recipients (0.63 [0.53, 0.75]), non-Hispanic Black (0.69 [0.49, 0.97]), Hispanic (0.57 [0.38, 0.86]), separated/divorced/widowed (0.79 [0.66, 0.94]) or older patients (gradient of 0.70 [0.58, 0.85], 0.59 [0.48, 0.73] and 0.38 [0.30, 0.47] within the different categories of increasing age) had a significantly lower relative likelihood of receiving a systemic line of chemotherapy ([Figure 4](#)). Patients whose physicians were in the Southern US had a 27% lower relative likelihood of receiving a systemic line of chemotherapy compared with patients whose providers were in the West (0.73 [0.59, 0.90]). M stage and whether the patient’s index visit was with a PCP or a urologist did not significantly affect whether the patient received a systemic line of chemotherapy. Stratifying the analysis by M stage confirmed that the initial specialist seen does not have an impact on whether patients receive systemic chemotherapy (had they also seen a subsequent medical oncologist), while some of the characteristics mentioned above were no longer statistically significant. This likely was due to the now smaller sample size in each group ([Supplementary Figure 2](#)).

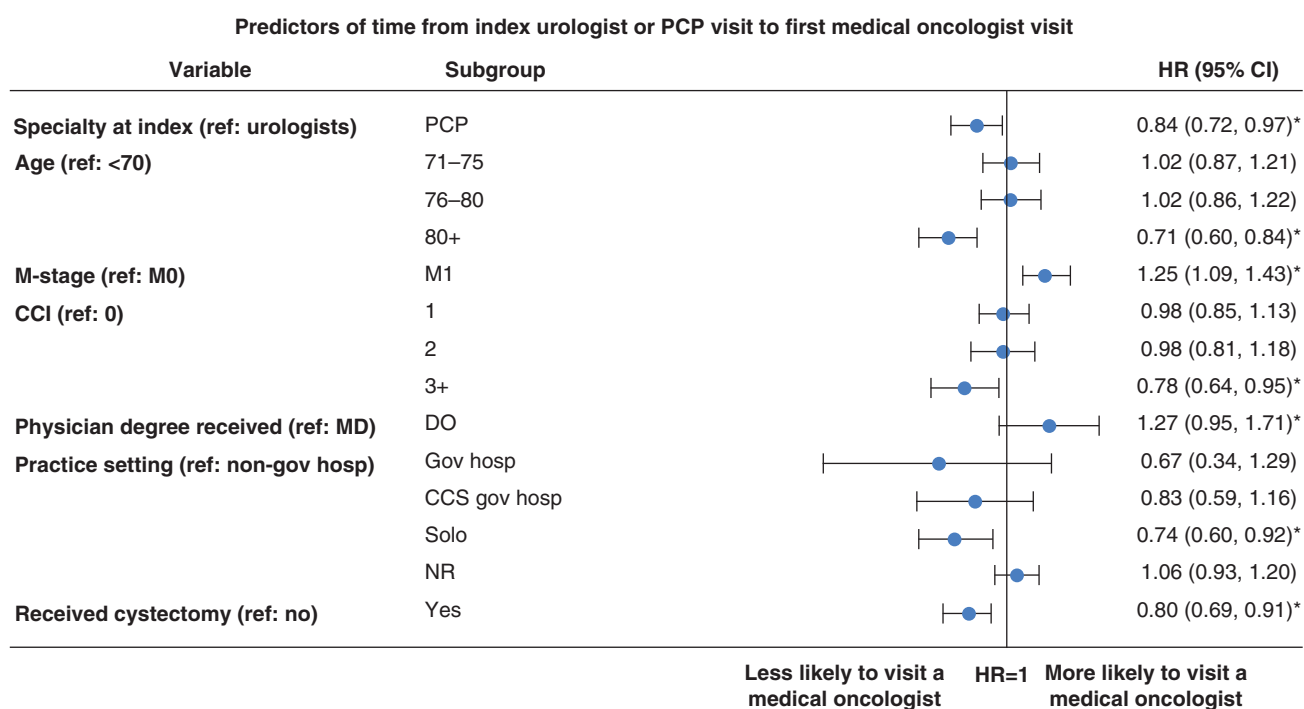


Figure 3. Multivariate Cox model of determinants of time to medical oncologist visit after index urologist visit.

* $p < 0.05$.

CCI: Charlson Comorbidity Index; CCS: City/county/state; Gov: Government; HR: Hazard ratio; Hosp: Hospital; M0: Nonmetastatic; M1: Metastatic; NR: Not reported; PCP: Primary care physician; Ref: Reference; US: United States.

Discussion

Prior literature has documented the benefits of multidisciplinary management of UC patients, which is associated with improvement in informed and collaborative decision making and possibly earlier initiation of definitive treatments [17–19]. Using the linked SEER-Medicare dataset, we provide a detailed analysis that fills knowledge gaps related to patients with newly diagnosed advanced UC in terms of physician visits, patient referrals and treatment. In this study, we used chemotherapy as the ‘anchor’ to gauge receipt of systemic treatment for the aggregate stage IV UC patient population as well as the M0 and M1 subpopulations that together define stage IV disease. Our aim is to provide more granular information about these aspects of UC management than are generally reported, particularly since such an analysis may help provide a model to further study and understand UC management and outcomes as the treatment landscape continues to evolve with the advent of other systemic therapies beyond the traditional chemotherapy which remains an important backbone of treating advanced UC.

This study found that referral among physician specialties was common, consistent with reported literature [18–20]. An important aspect of the study was to not only look at the urologist but also the relatively understudied specialist, the PCP, within the context of their potential ‘gatekeeper’ role as they may relate to UC. Interestingly, patients who presented to a PCP initially were more likely to be older, have higher comorbidities and poor performance status compared with those presenting to a urologist, suggesting that PCPs may be interacting with the sicker UC population at the index visit (Supplementary Table 1). Although physician referrals varied by the index physician, the role of the PCP in the management of UC patients was prominent. Remarkably, 29% of patients with an index PCP visit were not referred to another specialist, and 50% never saw a medical oncologist over their disease course, which is surprising given that PCPs generally do not provide UC-directed care. Among the patients with index PCP visits who were referred out, the referrals tended to occur rapidly and were predominantly channeled to a urologist, with only a minority of such patients being directly referred to a medical oncologist.

Our descriptive and adjusted models show that urologists were more likely, compared with PCPs, to refer UC patients to a medical oncologist. Interestingly, the median time to visiting a medical oncologist is longer for patients

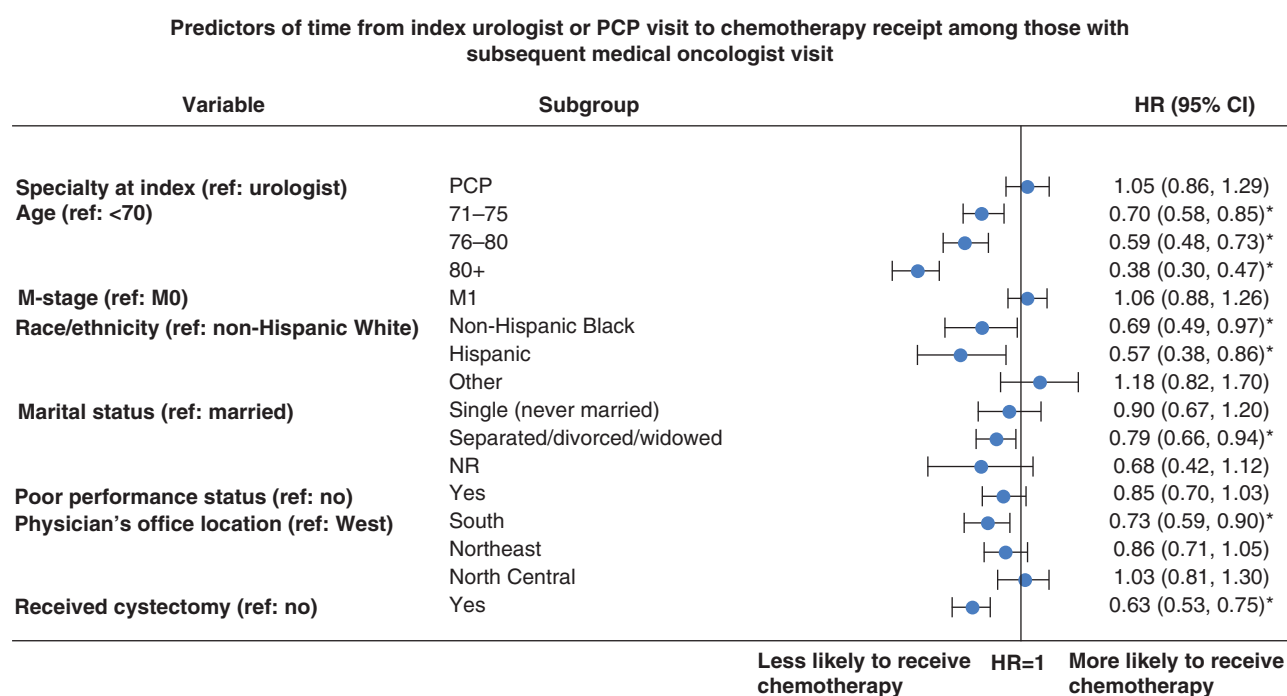


Figure 4. Multivariate Cox model of determinants for time to chemotherapy receipt after index urologist visit.

* $p < 0.05$.

HR: Hazard ratio; NR: Not reported; PCP: Primary care physician; Ref: Reference.

who see an index urologist (52 days) compared with an index PCP (29 days). Seventy percent of the referrals to the medical oncologist stemmed from the urologist, highlighting the prominent role of the latter in channeling patients to systemic treatment. In exploratory descriptive analyses of overall survival by first specialty visits, patients who were initially managed by a urologist had the highest median survival while those initially seen by a PCP had the lowest survival; this trend was observed for both M0 and M1 patients (Supplementary Figure 3). Our results for stage IV UC also mirror findings of a study of muscle invasive bladder cancer, which found that more than 80% of medical oncologists had their patients referred from a urologist, with very few receiving referrals from PCPs or radiation oncologists [21], underscoring the gatekeeper role of the urologist in mediating patient flow and receipt of systemic therapy in both advanced UC and earlier stages of UC. Despite their key role in UC management, our analysis revealed that 30% of stage IV UC patients with index urologist visit did not get any subsequent medical oncologist referral during their entire disease course. However, this is still a lower proportion of patients not being referred out compared with those who had index PCP visit where 50% never had a medical oncology follow-up. Our model also shows that patients had lower relative likelihood of being referred to medical oncology if they were M0, aged 80 years or older, had more comorbidities or underwent cystectomy. It has been shown previously that patients who are older and have comorbidities are less likely to be suitable for chemotherapy [8,22], and hence not referred as quickly to medical oncology. Patients undergoing cystectomy may also be less likely to be referred to medical oncology as they could be receiving peri-operative and postoperative care through the urologist [23].

Looking at patient–physician flow patterns and chemotherapy receipt, certain demographic characteristics emerge that predict for the likelihood of receiving systemic therapy. Consistent with prior studies, older patients have a lower relative likelihood of seeing a medical oncologist or receiving chemotherapy post urologist visit, perhaps in part due to potential comorbidities/relative performance status [6,8,24,25]. Further, being Hispanic, non-Hispanic black, widowed/separated/divorced/never married or being treated by a physician in the Southern US are predictors of lower relative likelihood of receiving chemotherapy. The role of race in the context of delay in chemotherapy receipt or less likelihood of receiving multimodal therapy, or not receiving chemotherapy altogether, as well as poorer survival outcomes, have been well documented by others [26–29]. Better social support, as reflected by marital

status, has been shown to lead to greater relative likelihood of UC treatment and overall survival, particularly among males [27,28]. The role of geography also needs further clarification but may reflect physician availability and proximity to treatment centers, keeping in mind that the Southern US houses some of the most socioeconomically deprived counties in the country [26,30,31]. Outlining the referral patterns could be helpful in informing patients, payers and specialists as it provides an understanding around the patient journey, characteristics and the time it takes for a stage IV patient to be referred to medical oncology and to receive systemic chemotherapy. Our analysis suggests that we should educate on the importance of timely referral from PCP/Urologist to medical oncology for timely receipt of systemic chemotherapy.

Strengths of the study include the fact that the SEER-Medicare database is a large nationally representative database that provides relevant longitudinal information on patients. Since the median age at diagnosis for all (not only Medicare) patients with UC is about 73 years, the SEER-Medicare dataset captures most of the UC patients. Further, the availability of tumor, nodes and metastases (TNM) staging within SEER allows for analyzing advanced stage UC patient data, which would not be possible with claims data alone. Finally, linking outpatient and carrier files to the AMA Physician Masterfile allowed us to identify the specialties and demographics of the treating physicians. The integration of these three data sources provide robust insights into patient and provider demographics and treatment patterns.

Our study also has some inherent limitations. As referral patterns were captured over the duration of study follow-up from the time of the index visit, some patients with poor prognosis and shorter overall survival may not have enough time to enable referrals to different specialists. Similarly, patients diagnosed in the last year of the data cut may be administratively censored in other words, they may have seen specialists, but we were not able to capture such data since the most updated data available would be too close to their diagnosis. Further, UC patients may see specialists beyond those identified in this analysis (e.g., physician assistants, oncology nurses, nutrition specialists, pathologists and others). Clinical characteristics, including M stage, CCI score and performance status were measured only at diagnosis, and therefore disease improvement or progression during follow-up that could possibly affect patient treatment or referral patterns was not captured. Although the data used for this analysis was from 2003 through 2014, which precedes the recent integration of ICIs and other newer therapies in advanced UC, our study provides a relevant benchmark to further assess patient–physician dynamics in the context of emerging therapies, keeping in mind that up to very recently, chemotherapy has been the mainstay of systemic management of UC [32,33].

Conclusion

This is one of the few studies to look at physician specialty visits and referral patterns, as well as the determinants of time to medical oncologist visit and chemotherapy receipt among patients diagnosed with incident stage IV UC, including the M0 and M1 subpopulations that define stage IV disease. Future studies should continue to explore which configurations of multispecialists result in the most coordinated, timely and optimal care and improved survival for these patients, particularly as some of the newer therapies become increasingly available for the UC patient. Although younger age, good performance status, social support and race/ethnicity were important determinants of time to seeing a medical oncologist or receiving chemotherapy, it will be relevant in future work to monitor whether the newer therapies can help bridge some of the gaps observed in the management and outcomes of advanced UC patients.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/cer-2020-0093

Author contributions

A Aly, MF Botteman, Y Doleh and R Shenolikar conceptualized the research question and study design. MF Botteman was responsible for data acquisition. A Hussain was the lead clinician reviewing methods and results.

A Aly and C Johnson were responsible for data analysis and C Johnson drafted a first version of the manuscript. All authors reviewed and approved the final version of the manuscript. The authors on this manuscript have no other relevant financial or other relationships to disclose.

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A Aly was an employee of Pharmerit International during the conduct of this study and is currently an employee of AstraZeneca (200 Orchard Ridge Drive, Gaithersburg, MD 20878).

Financial & competing interests disclosure

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Ethical conduct of research

This retrospective longitudinal analysis used de-identified data from SEER-Medicare database, and was granted Institutional Review Board exemption. All results were reported per the data use agreement with the National Cancer Institute.

Summary points

- Among stage IV urothelial carcinoma (UC) patients, most of initial encounters related to a suspicion of UC are with a urologist (M0: 69%; M1: 53%) followed by a primary care physician (PCP) (M0: 19%; M1: 25%).
- The median time to visiting a medical oncologist is longer for patients who see an index urologist (52 days) compared with an index PCP (29 days).
- The descriptive and adjusted models show that urologists are more likely, compared with PCPs, to refer UC patients to a medical oncologist.
- Patients whose initial encounter related to a suspicion of UC specialty visit is with a PCP, are 80 years of age or older, have Charlson Comorbidity Index score of 3 or greater, have M0 disease, undergo cystectomy or whose index visit is with a 'solo practitioner' have lower relative likelihood of being referred to a medical oncologist.
- Patients who are of Hispanic ethnicity or non-Hispanic Black race/ethnicity, are separated/divorced/widowed, are older, have Charlson Comorbidity Index score of 3 or greater, undergo cystectomy or are being treated by a physician in the Southern part of the United States have lower relative likelihood of receiving chemotherapy once they see a medical oncologist.
- This study fills knowledge gaps related to physician specialty visits and referral patterns among patients with stage IV UC as well as the effect of referral patterns on chemotherapy receipt.

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