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Clinical Characteristics, Treatment Delivery, and Cisplatin Eligibility in Korean Patients Initially Diagnosed with Urothelial Carcinoma

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Objectives: The aim of this study was to examine the clinical presentation, treatment delivery, and cisplatin eligibility of Korean patients with urothelial carcinoma (UC) in a real-world setting.

Methods: We performed a retrospective cohort study of patients initially diagnosed with UC from March 2013 to June 2018. Creatinine clearance >60 mL/min and Eastern Cooperative Oncology Group performance status (0–1) were adopted as cisplatin eligibility criteria.

Results: This study included 557 eligible patients. Median age was 71.0 years (range, 33–94 years), and males were dominant (80%). Primary tumor sites were: upper genitourinary tract, 18%; bladder, 81%; and urethra, 0.4%. Initial disease status was non-muscle invasive bladder cancer (313, 56%), diffuse infiltrating non-muscle invasive bladder cancer (19, 3%), cTanyN0 upper tract UC (75, 13%), cT2-4N0 bladder UC (82, 15%), TanyN1-3 UC (36, 7%), or initially metastatic UC (32, 6%). At the time of analysis (June 2019), following treatments were delivered to 134 patients with localized UC: radical operation with or without perioperative treatment (89, 67%), definitive chemoradiation (7, 5%), and palliative surgery or supportive care only (36, 28%). In total, 89 patients had metastatic UC, including those with recurrent disease (n=57), and 34 (38%) of the 89 were eligible for cisplatin.

Conclusion: Clinical presentations in East Asian UC patients were consistent with those of previous studies in other countries, except for a relatively high incidence of upper genitourinary tract. Our results can serve as a benchmark for further advances and future research for treatments of UC in East Asian patients. **(Ewha Med J 2021;44(3):63-69)**

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Key Words
Urothelial carcinoma; Clinical characteristics; Treatment; Cisplatin eligibility; East Asian

Introduction

The clinical presentation of cancer can differ according to race and geographic region [1]. Patterns of treatment delivery also vary according to patient preferences and health system factors [2,3]. Studies of clinical presentations and treatment deliveries of urothelial carcinoma (UC) have examined in Western countries [2–5], while those in East Asian patients are lacking. For example, proportions of primary sites of UC (e.g., upper tract urothelial carcinoma [UTUC] or bladder UC) are known to be differ between East Asian and Western [6], however, they have not been formally reported in East Asian patients. The

treatment approaches and prognoses in perioperative setting differ by primary site of UC [7,8]. Thus, clinical presentations such as primary cancer sites should also be clarified in East Asian UC patients.

In addition, treatment patterns focusing on radical surgery, perioperative chemotherapy, and palliative chemotherapy in real practice have not been identified in East Asia. Studies in other regions have also shown that guideline-recommended treatment for UC is not actually adopted in real practice setting [2,9]. Therefore, further research is needed to clarify whether actual treatments were provided to East Asian patients based on guidelines. Although treatment changes are emerging for UC using immune check-point inhibitors, cisplatin-based chemotherapy is still recommended as a standard chemotherapy regimen in both perioperative and palliative settings [10-13]. Patient groups in whom cisplatin-based chemotherapy can be applied are defined with separate criteria called cisplatin eligibility [14], and the criteria are applied in actual treatment and clinical trials. Therefore, information such as proportion of cisplatin-eligible patients is needed.

In-depth studies on disease presentation, treatment delivery, and cisplatin eligibility can be helpful for developing new therapeutic protocols and guiding future clinical trials, as well as for providing a deeper understanding of currently used treatments. Thus, the aim of this study was to examine real-world clinical presentation, disease status, treatment delivery, and cisplatin eligibility for Korean patients with UC.

Methods

1. Study design and patients

We performed a retrospective cohort study of patients with UC who were initially diagnosed between June 2013 and June 2018 at Pusan National University Yangsan Hospital. Inclusion criteria were (1) initially diagnosed with UC based on pathologic or clinical confirmation using both imaging and cystoscopic findings; (2) completed staging evaluation with an imaging studies such as chest CT, abdomen-pelvic CT, or bone scan; and (3) followed for more than 3 months with a confirmed treatment plan. Patients were excluded if surveillance was performed at our hospital after the end of treatment at another hospital or if the patient temporarily visited our hospital due to another problem.

2. Staging and taxonomy

The disease status of UC in this study basically followed the staging classification of the American Joint Committee on Cancer 8th edition and categorizes disease according to treatment option (i.e., local treatment, such as transurethral resection and radical surgery, or systemic chemotherapy) into one of the following categories: (1) superficial UC, (2) localized UC, or (3) metastatic UC (Fig. 1). The superficial UC refers to non-muscle invasive bladder cancer (NMIBC), which shows potential curative treatment with transurethral resection without radical surgery. The diffuse infiltrating type of NMIBC, which

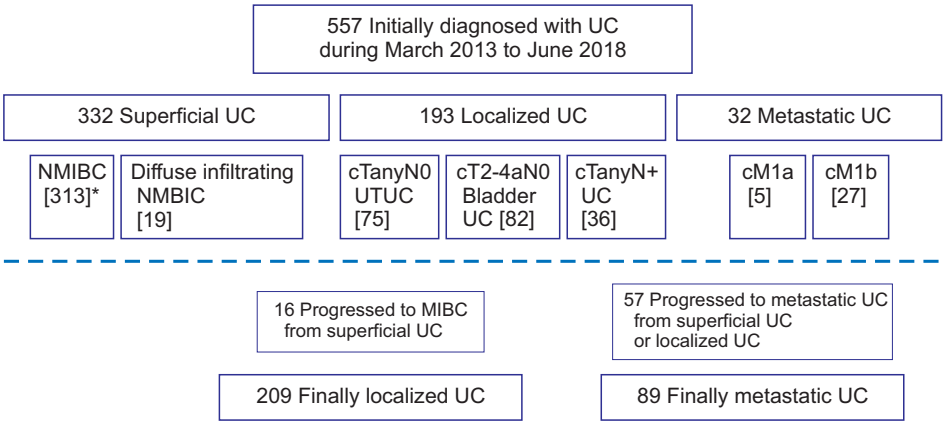

Fig. 1. Toxonomy of urothelial cancer patients according to disease status. The content below the dotted line represents the number of patient experiencing recurrence or progression in superficial or localized urothelial carcinoma (UC) at the time of analysis (June 2019). NIMBC, non-muscle invasive bladder cancer; UTUC, upper tract urothelial carcinoma; MIBC, muscle invasive bladder cancer. *[number] indicates the number of patients receiving the specified category or attending treatment.

tends to be treated with radical surgery, was classified separately. The localized UC corresponds to category that has curative potential using radical surgical treatment with or without perioperative treatment; it was classified into three groups: (1) clinically node-negative UTUC (cTanyN0 UTUC); (2) muscle invasive bladder cancer (MIBC, cT2-4N0); and (3) clinically node positive UC (cTanyN1-3 UC). The metastatic UC was treated with palliative chemotherapy due to low possibility of cure. However, this classification according to treatment options is arbitrary. For UC of bladder lesions, traditional classification such as NMIBC, MIBC, and metastatic bladder cancer are described in the Supplementary Tables 1 and 2.

Patterns of practices such as treatment delivery and cisplatin eligibility for localized UC and metastatic UC were described for patient groups reflecting progression from superficial UC at the time of analysis (June 2019) (Fig. 1, content below the dotted line).

3. Treatment and cisplatin eligibility

Radical surgical treatment was defined as radical cystectomy and bilateral pelvic lymph node dissection, or as nephrourectomy (or ureterectomy) and regional lymph node dissection. Pelvic lymph node dissection included external iliac, internal iliac, and obturator lymph nodes. Preoperative chemotherapy was defined as that performed while planning for curative surgery, and postoperative chemotherapy was defined as that applied within 3 months after radical surgery. Perioperative chemotherapy was applied to cisplatin based chemotherapy such as GP (gemcitabine plus cisplatin) or MVAC (methotrexate, vincristine, adriamycin, cisplatin) [10,12]. Cisplatin eligibility was determined as calculated creatinine clearance (CrCl) ≥ 60 mL/min and Eastern Cooperative Oncology Group performance status 0-1.

4. Statistics

We summarized demographics, clinical presentation, perioperative clinical findings, operative details, pathologic information, and laboratory values using descriptive statistics including median, mean, and range. Continuous variables were described by median, and categorical variables were described by absolute numbers and percentages. Excel (Microsoft, Redmond, WA, USA) was used for all data entry and management. This study was approved by the institutional review board of Pusan National University Yangsan Hospital (05-2020-074), which waived the requirement for informed consent due to the retrospective design.

Results

1. Patient characteristics and initial presentation

During the study period, 692 patients were newly diagnosed

Table 1. Patient characteristics

Characteristics	Value
Age (yr)	71 (33-94)
<75	381 (68)
≥75	176 (32)
Sex	
Male	448 (80)
Female	109 (20)
Histology	
Transitional	511 (92)
Mixed	19 (3)
Others (missing data, cytology)	27 (5)
Growth pattern*	
Papillary	153 (35)
Invasive pattern	83 (19)
Mixed pattern	197 (46)
Primary tumor site	
Renal pelvis	41 (7)
Ureter	54 (10)
Bladder	452 (81)
Urethra	2 (0.4)
Bladder plus other site	8 (1.4)
Initial disease status	
Superficial status	332 (60)
Localized status	193 (35)
Metastatic status	32 (6)
Initially symptom†	
Asymptomatic	67 (12)
Gross hematuria	389 (70)
Urination disorder	37 (7)
Abdominal or frank pain	7 (1)
Others	6 (1)

Values are presented as number (range) or number (%).
*Growth patterns was identified in 433 patients.
†Allow duplicate.

as UC, excluding temporary visit patients (n=72) and patients lost to follow-up within 3 months (n=59). A total of 557 patients met the enrollment criteria and was included. The median age of patients was 71.0 years, with 32% being 75 years or older, and the study population was predominantly male (82%). The primary tumor sites were the upper tract (e.g., renal pelvis or ureter) in 17% of the patients and the bladder in 81% of the patients. The most common initial presenting symptom was gross hematuria (70%), and 67 patients (12%) were diagnosed while asymptomatic (Table 1). Initial disease staging was observed for 332 patients of superficial UC (NMIBC, 313 patients; diffuse infiltrating NMIBC, 19 patients), 193 patients of localized UC (cTanyN0 UTUC, 75 patients; cT2-4 bladder UC, 82 patients; TanyN1-3 UC, 36 patients); and 32 patients of initially metastatic UC (Table 2 and Fig. 1, content above the dotted line).

At the time of analysis (June 2019), 209 patients (38%) had localized UC, including 16 relapses of superficial UC, and 89 patients had metastatic UC, including 57 with relapse (17 of superficial UC and 40 of localized UC) (Fig. 1, content below the dotted line).

2. Treatment delivery for localized UC except cTanyN0 UTUC

Actual treatment delivery for 132 localized UC patients indicated for radical surgery and perioperative chemotherapy was: radical surgery with or without perioperative treatment (89, 66%), definitive chemoradiation (7, 5%), palliative operation (9, 7%), or supportive care only (29, 22%) (Table 3). Of the 89

Table 2. Initial clinical staging according to primary tumor sites

	Bladder (n=452, 81%)		UTUC (n=103, 18%)		Urethra (n=2, 0.4%)	
	Staging	Number (%)	Staging	Number (%)	Staging	Number (%)
Superficial (n=332)		332 (73)	-	-	-	-
	NIMBC	313/332 (94)	-	-	-	-
	Diffuse infiltrating	19/332 (6)	-	-	-	-
Localized (n=193)		104 (23)	-	89 (86)	-	-
	cT2-4N0	82/104 (79)	cTanyN0	75/89 (84)	-	-
	cTanyN1-3	22 (21)	cTanyN1-3	14/89 (16)	-	-
Metastatic (n=32)		16 (4)	-	14 (14)	-	2 (100)
	cM1a	4 (25)	cM1a	1/14 (7)	cM1a	0/2
	cM1b	12 (75)	cM1b	13/14 (93)	cM1b	2/2 (100)

UTUC, upper tract urothelial carcinoma; NMIBC, non-muscle-invasive bladder cancer.

Table 3. Treatment delivery in localized UC who were indicated for radical surgery and perioperative chemotherapy

Characteristics	Total (n=134)	cTanyN+UTUC (n=14)	cT2-4N0 Bladder UC (n=96)	cTanyN+Bladder UC (n=24)
Radical surgery	89 (66)	8 (57)	63 (66)	18 (75)
Radical surgery alone (pT2N0)	23/89 (26)	1/8 (12)	21/63 (33)	1/18 (6)
Radical surgery alone (poor PS or patient's refusal)	32/89 (36)	2/8 (24)	22/63 (35)	8/18 (44)
Radical surgery plus adjuvant chemotherapy	27/89 (30)	4/8 (50)	18/63 (19)	5/18 (28)
Radical surgery plus adjuvant RT	1/89 (1)	0/8 (0)	1/63 (2)	0/18 (0)
Radical surgery plus neoadjuvant chemotherapy	6/89 (7)	1/8 (12)	1/63 (2)	4/18 (22)
Definitive RT or CRT	7 (5)	0 (0)	5 (5)	2 (8)
Palliative surgery	9 (7)	5 (36)	4 (4)	0 (0)
Supportive care only	29 (22)	1 (7)	24 (25)	4 (17)

Values are presented as number (%).
UC, urothelial carcinoma; UTUC, upper tract urothelial carcinoma; PS, performance status; RT, radiation therapy; CRT, chemoradiation therapy.

Table 4. First-line palliative treatment delivery in metastatic urothelial carcinoma

Characteristics	Total (n=89)	Cisplatin eligible (n=34, 38%)	Cisplatin ineligible (n=55, 62%)
Palliative chemotherapy	49 (55.7)	29 (85)	20 (36)
GP	33/49 (67)	24/29 (83)	9/20 (45)
MVAC	5/49 (10)	3/29 (10)	2/20 (10)
GCb	7/49 (14)	2/29 (7)	5/20 (25)
Gemcitabine alone	4/49 (8)	0/29 (0)	4/20 (20)
Metastasectomy	2 (2.2)	2 (6)	0 (0)
Palliative surgery	2 (2.3)	0 (0)	2 (4)
Supportive care only	30 (34.1)	0 (0)	30 (55)
Others	6 (6.8)	3 (9)	3 (5)

Values are presented as number (%).
GP, gemcitabine plus cisplatin; MVAC, methotraxate, vinblastine, adriamycin, cisplatin; GCb, gemcitabine plus carboplatin.

patients treated with radical surgery, 34 received perioperative treatment (chemotherapy, 33 patients; radiation therapy, one patient), 23 patients did not receive perioperative chemotherapy at the discretion of the clinician due to pathologic staging of pT2N0; and 32 patients did not receive treatment due to poor performance status or patient refusal despite T3–4 or lymph node–positive pathologic staging. Neoadjuvant chemotherapy was administered to only to six (7%) of the 89 patients who were targets of neoadjuvant chemotherapy.

3. Treatment delivery and cisplatin eligibility of patients with metastatic UC

Among 89 patients with metastatic disease, 34 (38%) had cisplatin eligibility. Of the cisplatin eligible patients, 29 (85%) received first-line palliative chemotherapy, 27 patients (79%) were treated with a cisplatin-based chemotherapy regimen. Of the 55 (62%) cisplatin-ineligible patients, 20 (36%) received palliative chemotherapy, and 11 (20%) were treated with a cisplatin-based chemotherapy regimen despite having cisplatin ineligible status (Table 4).

Discussion

This study presented information on clinical presentations, cisplatin eligibility, and actual treatment delivery based on a large Korean papulation with UC. In line with previous results from other countries, the primary initial disease status was superficial UC (60%), with metastatic UC patients being relatively rare (6%). Patients older than 75 years of age accounted for 32% of the study population, and cisplatin eligibility among patients with metastatic UC was 38%. While, our results were different from those of previous reports in that the proportion of UTUC was relatively higher (17%), and neoadjuvant chemotherapy was given to only 8% of potential candidates. Our study has strengths in two aspects: it is the first report on clinical characteristics of UC patients in East Asian, and it is based on robust dataset from real practice, unlikely population-based databases that mostly lack of available information [2,4].

Regarding the primary site of UC, our data showed that the proportion of Korean UC patients with UTUC was relatively high, up to 17% including superficial UC, compared to data from Western populations. We also identified 36% of metastatic UC patients (33/89) and 43% of localized UC patients (89/209) to have UTUC. Although the cause of this unexpected finding has not been clarified, it might be due to genetic and environmental differences between East Asian and Western populations. The UTUC is known to be different from bladder UC in diagnostic method, surgical treatment, and prognosis [7,8,15], and clinical trials tend to be conducted separately [16]. Considering the relatively high proportion of UTUC and insufficient scientific evidence, our study suggests that Korean physicians should pay more attention to UTUC, and further clinical trials are needed.

In this study, the application rate of neoadjuvant chemotherapy was only 7%, different from the international treatment guidelines for UC. This phenomenon is similar to Western data, which report that only 12% of patients with bladder cancer received neoadjuvant chemotherapy [17]. Considering mount-

ing evidence showing the beneficial role of neoadjuvant chemotherapy in survival [18] and the negative impact of surgical treatment on the availability of perioperative chemotherapy [19,20], neoadjuvant chemotherapy should be applied more actively. However, the wide gap between scientific evidence and real practice is probably due to clinicians' intuitive concern for the toxicity of cisplatin-based chemotherapy or the habitual delay of surgical treatment. Thus, to create a favorable atmosphere for providing neoadjuvant chemotherapy to UC patients, additional prospective clinical trials are needed to focus on safety and feasibility as well as efficacy.

Palliative chemotherapy was delivered to 56% of patients, in particular 88% of cisplatin-eligible patients. The proportion of metastatic UC patients treated with the standard cisplatin-based chemotherapy was 77%, which is a relatively high proportion compared to 30% to 50% observed in Western populations [21]. This result might be explained by our study analyzing patients between 2013 and 2018, when multiagent chemotherapy such as GP or MVAC were commonly used in combination with antiemetics and granulocyte-colony stimulating factor. A prior study showed that the use of chemotherapy has been increasing since the late 2000s [2]. On the other hand, other study reported that cisplatin-based chemotherapy was used in 45% of cisplatin-ineligible patients, but not used in 18% of cisplatin-eligible patients [5]. Our data showed similar findings, with 20% of cisplatin-ineligible patients treated with cisplatin-based chemotherapy. Although the eligibility criteria for cisplatin proposed by Galsky et al. [14] is widely used, they cannot fully reflect actual application of cisplatin in real practice. Considering the development of supportive care for chemotherapy-related adverse events, it is necessary to consider modified or updated criteria for cisplatin eligibility, especially in aspects of renal function or comprehensive geriatric assessment including patient comorbidities.

The present study has several limitations. First, it was based on a single-institution cohort, so generalization of our results to general Korean patients needs cautious interpretation. However, our study used a relatively large sample consisting of initially diagnosed UC patients, and the robust dataset with detailed assessments. Second, the categorization for disease was somewhat arbitrary, unlike the general treatment guidelines for UC. The classification categories were adopted to organize all types of UC, including both UTUC and bladder UC, according to the actual treatment application. Patient with bladder UC with clinically lymph node involvement (cN+) showed effectiveness in curative combined-modality therapy of cystectomy and perioperative chemotherapy compared to palliative chemotherapy [22,23]. The regional lymph node-positive bladder cancer was previously classified as stage IV in the American Joint Committee on Cancer 7th edition but was changed to stage IIIB in the revised 8th edition in 2018. Third, only performance status and CrCl were used in the cisplatin eligibility evaluations because other components such as hearing impairment and neuropathy could not be determined due to the innate limitations of a retrospective study. However, considering that 90% of cisplatin ineligibility evaluations were determined by Eastern Cooperative Oncology Group performance status and CrCl in prior studies [5,11], our findings could be acceptable in real practice.

Our study showed the first real practice-based clinical data for East Asian populations with UC. Clinical presentations in these patients were consistent with those of previous studies in other countries, except for a relatively high incidence of the upper genitourinary tract. Our results could be useful for determining treatment options for UC patients and can serve as a benchmark for further advances and clinical trials for treatments of East Asian patients with UC.

Supplementary Materials

Supplementary Tables are available from: https://doi.org/10.12771/emj.2021.44.3.63.

Supplementary Table 1. Patient characteristics of bladder cancer

Supplementary Table 2. Treatment delivery in bladder ca who were indicated for radical surgery and perioperative chemotherapy

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Supplementary Table 1. Patient characteristics of bladder cancer

Characteristics	Total (n=452)	Superficial (n=332, 73%)	MIBC (n=82, 18%)	Metastatic (n=38, 8%)
Age (yr)	69.5 (33–94)	68.0 (34–94)	72.5 (33–89)	73.0 (48–87)
<75	317 (70)	239 (72)	54 (66)	24 (63)
≥75	135 (30)	93 (28)	28 (34)	14 (37)
Sex				
Male	378 (84)	281 (85)	64 (78)	33 (87)
Female	74 (16)	51 (15)	18 (22)	5 (13)
Histology				
Transitional	414 (92)	313 (94)	68 (83)	33 (87)
Mixed	22 (5)	5 (2)	14 (17)	3 (8)
Others (missing data, cytology)	16 (3)	14 (4)	0 (0)	2 (5)
Growth pattern*				
Papillary	151 (33)	136 (41)	3 (4)	2 (5)
Invasive pattern	84 (19)	27 (8)	29 (35)	10 (26)
Mixed pattern	198 (48)	91 (27)	42 (51)	15 (39)
Initially symptom†				
Asymptomatic	56 (12)	53 (16)	2 (2)	1 (2)
Gross hematuria	323 (71)	233 (70)	62 (76)	28 (74)
Urination disorder	33 (7)	19 (6)	10 (12)	4 (11)
Abdominal or frank pain	6 (1)	4 (1)	1 (1)	1 (2)

Values are presented as number (range) or number (%).
MIBC, muscle-invasive bladder cancer.
*Growth patterns was identified in 433 patients.
†Allow duplicate.

Supplementary Table 2. Treatment delivery in bladder ca who were indicated for radical surgery and perioperative chemotherapy

Characteristics	Total (n=120)
Radical surgery	81 (68)
Radical surgery alone (pT2N0)	22 (27)
Radical surgery alone (poor PS or patient's refusal)	30 (37)
Radical surgery plus adjuvant chemotherapy	23 (28)
Radical surgery plus adjuvant RT	1 (1)
Radical surgery plus neoadjuvant chemotherapy	5 (6)
Definitive RT or CRT	7 (6)
Palliative surgery	4 (3)
Supportive care only	28 (23)

Values are presented as number (%).
PS, performance status; RT, radiation therapy; CRT, chemoradiation therapy.