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ORIGINAL ARTICLE

Clinicopathological characteristics and prognostic outcomes of bladder urothelial neoplasms in patients under 40 years of age: a multicenter retrospective study

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Abstract

Bladder cancer is rare in patients under 40 years of age, and its clinicopathological behavior in this demographic remains a subject of debate. This study aimed to evaluate the histopathological features and prognosis of bladder tumors in patients under the age of 40. This multicenter retrospective study included bladder transurethral resection, biopsy, and cystectomy samples obtained from patients younger than 40 years of age across 20 centers in Turkiye between 2010 and 2025. Among 1,555 biopsies, 445 patients were diagnosed as urothelial neoplasms. After exclusion of 45 patients lacking hematoxylin and eosin stained slides for re-evaluation, 400 urothelial neoplasms were included in the final cohort. All patients were centrally reviewed by three genitourinary pathologists to establish a consensus diagnosis. Demographic characteristics, clinical presentation, tumor localization, pathological stage, and histological subtypes were analyzed. Follow-up data were available for 206 patients and were used to evaluate clinical outcomes. Statistical analyses were performed using chi-square tests with post-hoc analysis based on adjusted standardized residuals. Low-grade papillary urothelial carcinoma (LGPUC) was the most frequent diagnosis, accounting for 233/400 patients (58.3%), followed by papillary urothelial neoplasm of low malignant potential (PUNLMP) in 55/400 patients (13.8%) and high-grade papillary urothelial carcinoma (HGPUC) in 32/400 patients (8.0%). Overall, 340/400 tumors (85.0%) were non-invasive, whereas 60/400 tumors (15.0%) were invasive. Hematuria was the most common presenting symptom, observed in 197/400 patients (49.3%). Diagnostic revisions after central review were identified in 127/400 patients (31.8%), most commonly involving reclassification between PUNLMP and LGPUC. Age-group analysis demonstrated that urothelial neoplasms occurred most frequently in the 31-40-year age group, which showed a significantly higher proportion of HGPUC and invasive tumors ($p<0.001$). Subtype histology or divergent differentiation was identified in 4/60 invasive tumors (6.7%). Among the 206 patients with available follow-up data, remission was observed in 159/206 patients (77.2%), recurrence in 41/206 (19.9%), progression in 2/206 (1.0%), and death in 4/206 patients (1.9%). Adverse clinical outcomes were largely confined to invasive tumors. Bladder tumors in patients under 40 years of age typically exhibit low-grade, low-stage characteristics with a favorable prognosis. Consistent with the literature, the 31–40 age group appears to be a biological transition zone with increased risks of high-grade and invasive carcinoma. Long-term follow-up remains essential due to the potential for recurrence and progression in specific subtypes.

Keywords Bladder cancer · Early-onset bladder cancer · Urothelial carcinoma · Young patients

Extended author information available on the last page of the article

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Introduction

Bladder cancer is the most common malignancy of the urinary tract. According to the World Health Organization/International Agency for Research on Cancer (WHO/IARC) GLOBOCAN 2022 data, it is the ninth most common cancer worldwide and ranks 13th in cancer-related mortality [1, 2]. Approximately 70–80% of patients present with non-muscle-invasive tumors at initial diagnosis, which have traditionally been managed with transurethral resection [3]. These cancers are more prevalent in men and typically manifest in the sixth and seventh decades of life, reflecting an age-dependent accumulation of carcinogenic exposures and genetic alterations [4–6].

In contrast, the prevalence of bladder cancer in patients under the age of 40 is less than 1% [7, 8]. However, the number of young patients diagnosed with this malignancy is gradually increasing, driven partly by advances in diagnostic technologies and the implementation of early screening protocols. The rarity of the disease in this demographic, combined with the significant implications of follow-up and treatment outcomes on patient management and prognosis, can present a diagnostic challenge and a source of clinical concern for pathologists during histopathological evaluation. While therapeutic strategies and prognostic factors are well-established for the elderly population, reports regarding the clinical behavior and prognosis of urothelial neoplasms in young patients remain contradictory. First of all, a significant methodological consideration in existing literature pertains to the definition of "young" patients. Controversies persist, as researchers have employed various age cut-offs such as 20, 30, 40, or 50 years. However, a growing consensus among oncological experts defines patients under 50 as "young" and those under 40 as "very young" [6]. Moreover, in the literature, whether bladder cancer in young patients indicate more favorable or poorer outcome remains controversial [3, 8–11]. These conflicting opinions, coupled with limited literature, indicate that the complete clinicopathological landscape of urothelial neoplasms in young patients is not yet fully understood [6]. This knowledge gap is attributable to several factors: the rarity of the disease in younger populations, limited single-institution series, varying disease characteristics across different ethnic groups, and the heterogeneity of methodological approaches in published studies [8].

In this multicenter retrospective study, we aimed to analyze the clinicopathological characteristics and prognostic status of urothelial neoplasms in patients under 40 years of age. Our primary objective was to identify the specific types of bladder tumors occurring in patients under the age of 40 and to evaluate the clinical course, histopathological features, and prognosis of these urothelial neoplasms to provide a more comprehensive understanding of the disease in this demographic.

Methods

Study design, demographic and pathological data collection

Bladder specimens obtained via transurethral resection, biopsy, and cystectomy from patients younger than 40 years of age between 2010 and 2025 across 20 centers in Turkiye were included in this study. Clinical data and pathological results were collected. Patients were included if they met the following criteria: (i) age below 40 years at diagnosis, (ii) histopathological diagnosis of a urothelial lesion, and (iii) availability of pathological material for central review. Patients were excluded if they had non-urothelial tumors (such as mesenchymal tumors, metastatic carcinomas, lymphomas, or other rare malignancies), non-neoplastic lesions, or if histological slides were unavailable for re-evaluation.

Representative photomicrographs of patients diagnosed with urothelial lesions from each center were re-evaluated independently by three genitourinary pathologists (DB, BYB, MA). The submitted images were prepared by the local pathology departments from archived original slides. Participating centers were instructed to include all diagnostically relevant areas of the lesion, ranging from low-power architectural views to high-power cytological details, in order to represent the entire specimen. Depending on lesion size and histological complexity, 3 to 15 images were reviewed per case. In a subset of cases, complete slide assessment was additionally possible through whole-slide image sharing or live online slide review. In diagnostically challenging cases or when the submitted material was considered insufficient for confident grading or staging, additional representative images were requested from the contributing center. A consensus diagnosis was reached when at least two of the three experienced uropathologists agreed on the final diagnosis.

Histological type and tumor grade were assessed in accordance with the fifth edition of the WHO Classification of Tumours of the Urinary and Male Genital Systems [12]. The pathological stage was established according to the eighth edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual [13]. For analytical purposes, tumors were also grouped as non-invasive (urothelial papilloma [UP], papillary urothelial neoplasm of low malignant potential [PUNLMP], non-invasive papillary urothelial carcinoma, low-grade [LGPUC], non-invasive papillary urothelial carcinoma, high-grade [HGPUC], dysplasia, and carcinoma in situ [CIS]) and invasive (pT1 and pT2 tumors).

Follow-up data were retrospectively collected from the available clinical records. Follow-up information was available for 206 patients and was used to determine the last recorded clinical status (remission, remission, progression, or exitus). Repeated biopsy sampling during follow-up was documented in 134 of the 400 patients.

For outcome assessment, recurrence was defined as the reappearance of a histologically confirmed urothelial neoplasm after a documented disease-free interval following initial treatment. Progression was defined as an increase in pathological stage (e.g., from non-invasive to invasive disease) or the development of muscle-invasive disease during follow-up. In patients with multiple biopsies, only the initial diagnostic specimen was included in the study, and subsequent biopsies were used solely for the assessment of recurrence and progression.

An age cut-off of 40 years was used to define young-onset bladder tumors, as this threshold balances the rarity and distinct biological behavior of tumors occurring at younger ages with sufficient patient numbers for meaningful analysis. Prognostic outcomes were evaluated only in patients with available follow-up information. Patients lacking follow-up data were excluded from the prognostic outcome analysis.

This study was approved by the Local Institutional Ethics Committee (protocol number: 2025/573, approval date: 18.11.2025) and was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analysis

Statistical analyses were performed using Jamovi software (version 2.6.26). Descriptive statistics for numerical variables were presented as mean ± standard deviation and median (minimum–maximum), while categorical variables were expressed as frequencies and percentages. The distribution of urothelial neoplasm subtypes among four age groups was compared using the chi-square test. A p-value of < 0.05 was considered statistically significant. Following a significant chi-square test, post-hoc analyses were performed using adjusted standardized residuals to identify the cells contributing to the overall association.

Results

Patient characteristics and diagnostic distribution before and after re-evaluation

Figure 1 summarizes the flowchart for case inclusion. Among 1,555 bladder specimens, 47 (3%) were mesenchymal neoplasms (Fig. 2A), 16 (1%) represented secondary involvement of the bladder by carcinomas (Fig. 2B), 10 (0.6%) were non-urothelial carcinomas (3 primary bladder adenocarcinomas, 3 urachal adenocarcinomas (Fig. 2C), 2 neuroendocrine carcinomas (Fig. 2D), 2 squamous cell carcinomas), 3 were paragangliomas, 2 were diffuse large B-cell lymphomas, and 1 was a villous adenoma. Among the mesenchymal neoplasms, rhabdomyosarcoma was the most common (15 of 43; 34.8%). Among tumors showing secondary involvement of the bladder, colorectal carcinomas were the most frequent (9 of 16; 56.2%).

A total of 1032 (66.3%) biopsies resulted in non-neoplastic findings (Fig. 2E F). The remaining 445 patients were diagnosed as urothelial neoplasms; however, 45 patients were excluded because histological slides were unavailable for re-evaluation. Therefore, the final study cohort consisted of 400 (25.7%) patients.

Most patients underwent transurethral resection (375 patients, 93.8%). A smaller number of patients required biopsy (15 patients, 3.8%) and cystectomy (10 patients, 2.5%). Upon re-evaluation of specimens from 400 patients by three pathologists, diagnostic revisions were identified in 127 patients (31.8%) (Table 1). The most frequent diagnostic shifts occurred between the PUNLMP and LGPUC categories; among the 65 patients initially diagnosed as PUNLMP (Fig. 3A), 42 (64.6%) were subsequently reclassified as LGPUC. Similarly, a substantial proportion of patients initially diagnosed as UP (Fig. 3B) were reassigned to other diagnostic categories (38/54, 70%), most commonly PUNLMP or LGPUC. Diagnostic changes were also observed in 9 of 24 patients (37.5%) initially diagnosed as HGPUC and in 15 of 71 patients (21.1%) initially diagnosed as invasive papillary urothelial carcinoma (IPUC). Among the latter group, one revision reflected a change in pathological stage rather than diagnostic category, in which a tumor initially interpreted as pT2 (Fig. 3C) was reclassified as pT1 after central review, as the previously interpreted muscularis propria invasion was reassessed as muscularis mucosa involvement.

Notably, 14 tumors initially interpreted as IPUC were reclassified as non-muscle-invasive papillary urothelial carcinomas after central review (Fig. 3D), all of which had been originally staged as pT1.

The median age of the 400 patients with urothelial neoplasms was 34 years (range 3–40, mean 32 ± 7.05). The youngest patient in our cohort was three years old and was diagnosed with papillary urothelial neoplasm of low malignant potential (PUNLMP); however, detailed genetic predisposition data were not available in this retrospective series. The female-to-male ratio was 1:4.2. Urothelial neoplasms were significantly more frequently detected in male patients ($p = 0.009$). Overall, male patients constituted the majority

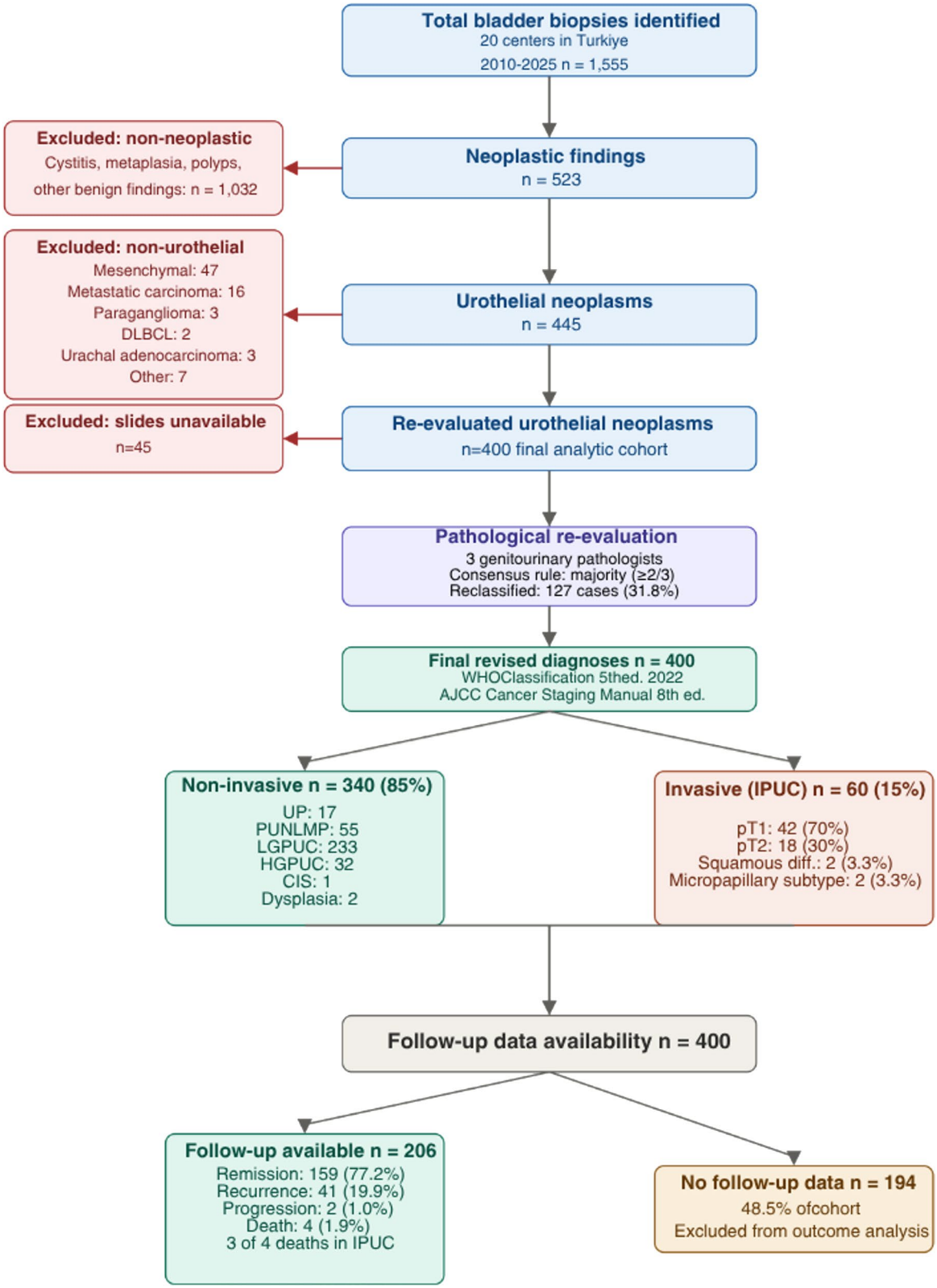


Fig. 1 Flowchart of patient selection and diagnostic re-evaluation

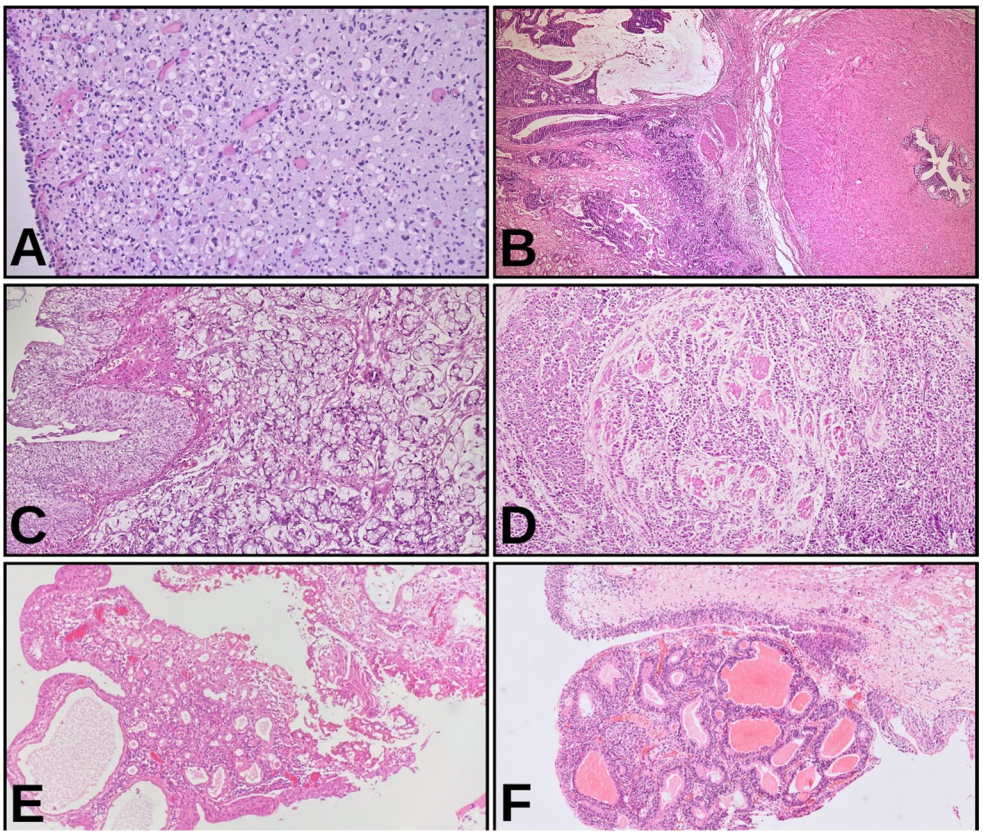


Fig. 2 Representative examples of non-urothelial tumors and benign bladder lesions. (**A**) Rhabdomyosarcoma. (**B**) Secondary involvement of the bladder by colorectal adenocarcinoma. (**C**) Urachal adenocarcinoma. (**D**) Neuroendocrine carcinoma of the bladder.(**E**) Nephrogenic adenoma. (**F**) Polypoid cystitis glandularis

Table 1 Comparison of initial and revised histopathological diagnoses after central review by three genitourinary pathologists

Initial Diagnosis	Revised diagnosis							
	Dysplasia	CIS	UP	PUNLMP	LGPUC	HGPUC	IPUC	Total
Papillary urothelial hyperplasia	0	0	0	2	0	0	0	2
Dysplasia	2	0	0	0	0	0	0	2
IUP	0	1	0	0	0	0	0	1
UP	0	0	16	20	18	0	0	54
PUNLMP	0	0	0	23	42	0	0	65
LGPUC	0	0	1	10	159	10	1	181
HGPUC	0	0	0	0	7	15	2	24
IPUC	0	0	0	0	7	7	57*	71
Total	2	1	17	55	233	32	60	400

* One case initially diagnosed as invasive papillary urothelial carcinoma (IPUC) retained the same diagnostic category after central review but showed a stage revision from pT2 to pT1, as the initially interpreted muscularis propria invasion was re-evaluated as muscularis mucosae involvement.

Abbreviations: *UP* Urothelial papilloma, *IUP* Inverted urothelial papilloma, *PUNLMP* Papillary urothelial neoplasm of low malignant potential, *LGPUC* Low-grade papillary urothelial carcinoma, *HGPUC* High-grade papillary urothelial carcinoma, *IPUC* Invasive papillary urothelial carcinoma, *CIS* Carcinoma in situ

of the cohort, and LGPUC, HGPUC, and IPUC were more frequently observed in males in absolute numbers (Table 2).

Clinical symptoms

The most common presenting symptom was hematuria, observed in 197 patients (49.3%). Other symptoms such as pain (35 patients, 8.8%) and lower urinary tract symptoms (LUTS), including dysuria, pollakiuria, incontinence, nocturnal enuresis, intermittent voiding, and urgency, were less frequent (28 patients, 7.0%). Signs of infection were observed in only 3 patients (0.8%).

Imaging and cystoscopic findings

Radiological and cystoscopic findings were available for 231 patients (57.8%). The most frequent finding in radiological and cystoscopic imaging was a papillary mass (96

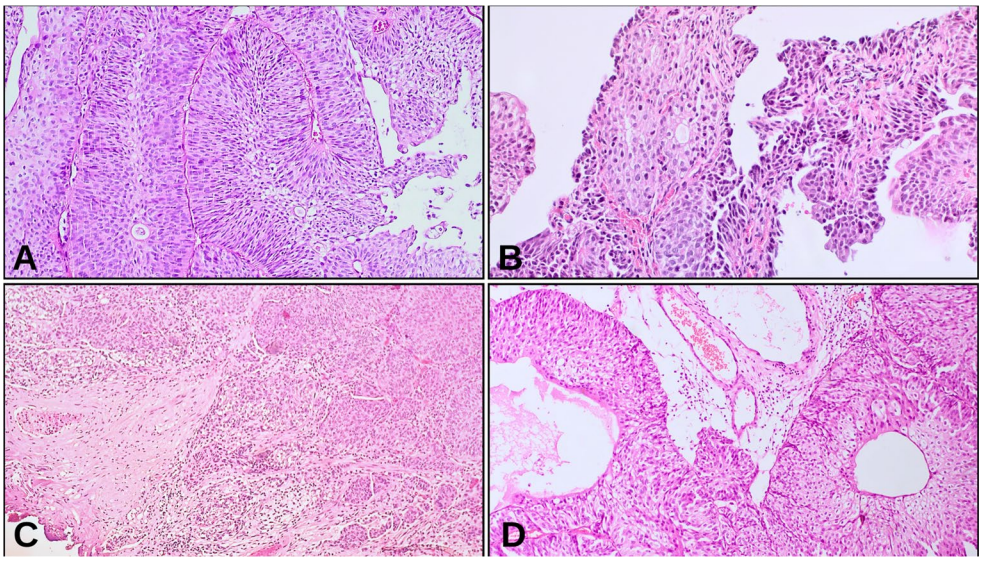


Fig. 3 Diagnostic revisions after central review. (**A**) Papillary urothelial neoplasm of low malignant potential (PUNLMP) reclassified as low-grade papillary urothelial carcinoma (LGPUC). (**B**) Urothelial papilloma (UP) reclassified as LGPUC. (**C**) Tumor initially staged as pT2 reinterpreted as pT1. (**D**) Invasive papillary urothelial carcinoma reclassified as non-invasive papillary urothelial carcinoma (pTa)

Table 2 Distribution of urothelial neoplasm subtypes according to gender

Gender	UP	PUNLMP	LGPUC	HGPUC	IPUC	Dysplasia	CIS	Total
Female (F)	5 (1.3%)	14 (3.5%)	47 (11.8%)	2 (0.5%)	7 (1.8%)	2 (0.5%)	0 (0.0%)	77
Male (M)	12 (3.0%)	41 (10.3%)	186 (46.5%)	30 (7.5%)	53 (13.3%)	0 (0.0%)	1 (0.3%)	323
Total	17 (4.3%)	55 (13.8%)	233 (58.3%)	32 (8.0%)	60 (15.0%)	2 (0.5%)	1 (0.3%)	400

Abbreviations: *UP* Urothelial papilloma, *PUNLMP* Papillary urothelial neoplasm of low malignant potential, *LGPUC* Low-grade papillary urothelial carcinoma, *HGPUC* High-grade papillary urothelial carcinoma, *IPUC* Invasive papillary urothelial carcinoma, *CIS* Carcinoma in situ

patients, 24.0%), followed by solid mass (87 patients, 21.8%), polypoid mass (30 patients, 7.5%), wall thickening (11 patients, 2.8%), contrast enhancement changes (4 patients, 1.3%), and trabeculation (3 patients, 0.8%).

On cystoscopic evaluation, unifocal lesions were more common than multifocal lesions (97 patients, 24.3% vs. 50 patients, 12.5%, respectively). Unifocal lesions frequently exhibited solid and polypoid morphologies (12 patients, 3.0% and 9 patients, 2.3%, respectively), whereas multifocal lesions were predominantly papillary in configuration (14 patients, 3.5%).

Distribution of urothelial neoplasm subtypes and stage

LGPUC ($n=233$, 58.3%; Fig. 4A) was the most frequent diagnosis, followed by PUNLMP ($n=55$, 13.8%; Fig. 4B) and HGPUC ($n=32$, 8.0%; Fig. 4C).

Overall, 340 tumors (85%) were non-invasive and 60 tumors (15%) were invasive. Among the invasive tumors, the majority were staged as pT1 (42/60; 70%), whereas the remaining tumors were classified as pT2 (18/60 tumors; Fig. 4D) (Table 3). When pathological staging was evaluated, 265 tumors were classified as pTa [LGPUC ($n=233$) and HGPUC ($n=32$)], whereas 42 and 18 tumors were staged as pT1 and pT2, respectively [IPUC ($n=60$)]. In the overall cohort, pT1 and pT2 tumors represented 10.5% (42/400) and 4.5% (18/400) of all patients (Table 3). When calculated within the subgroup of 325 papillary urothelial neoplasms for which pathological staging could be assessed [LGPUC ($n=233$), HGPUC ($n=32$), and IPUC ($n=60$)], pTa tumors accounted for 81.5% (265/325), followed by pT1 tumors 12.9% (42/325) and pT2 tumors 5.5% (18/325).

Evaluation by age group showed that urothelial neoplasms occurred most frequently in the 31–40 year age group. In this specific age group, LGPUC (36.3%) and IPUC (13.3%) were the predominant diagnoses (Supplemental Table 1). The occurrence of urothelial carcinoma in patients under the age of ten was extremely rare (3, 0.8%). A statistically significant difference was observed between age groups ($p<0.001$). Post-hoc analysis using adjusted standardized residuals indicated that the higher-than-expected number of HGPUC and IPUC patients in the 31–40 year age group contributed substantially to the observed association. In contrast, the 21–30 age group showed relatively lower IPUC frequencies but higher frequencies of PUNLMP, urothelial papilloma (UP), and dysplasia.

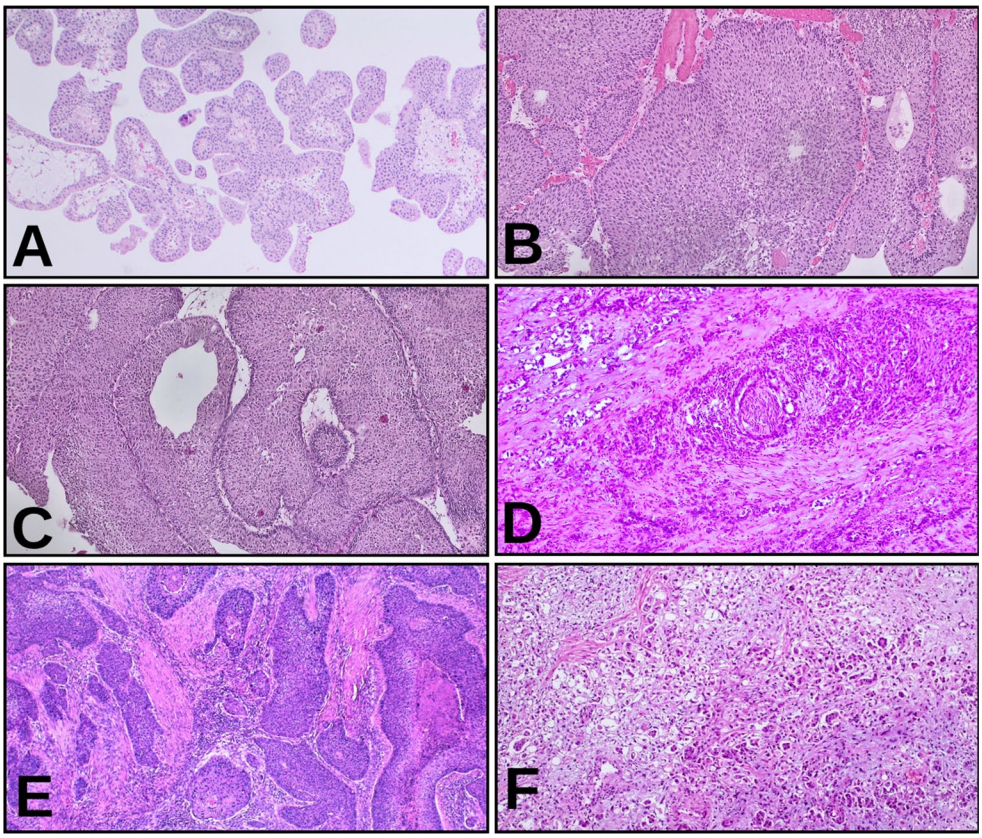


Fig. 4 Histopathological spectrum of urothelial neoplasms in patients younger than 40 years. (**A**) Papillary urothelial neoplasm of low malignant potential (PUNLMP). (**B**) Low-grade papillary urothelial carcinoma (LGPUC). (**C**) High-grade papillary urothelial carcinoma (HGPUC). (**D**) Muscle-invasive urothelial carcinoma (pT2). (**E**) Urothelial carcinoma with squamous differentiation. (**F**) Micropapillary subtype of urothelial carcinoma

Table 3 Distribution of urothelial neoplasms by invasion status and pathological stage

Category	Diagnosis / stage	*n* (%)
Non-invasive tumors		340 (85.0%)
	UP	17 (4.3%)
	PUNLMP	55 (13.8%)
	LGPUC	233 (58.3%)
	HGPUC	32 (8.0%)
	Dysplasia	2 (0.5%)
	CIS	1 (0.3%)
Invasive tumors		60 (15.0%)
	pT1	42 (10.5%)
	pT2	18 (4.5%)
Total		**400 (100%)**

Abbreviations: *UP* Urothelial papilloma, *PUNLMP* Papillary urothelial neoplasm of low malignant potential, *LGPUC* Low-grade papillary urothelial carcinoma, *HGPUC* High-grade papillary urothelial carcinoma, *CIS* Carcinoma in situ, *pT1* Tumor invading the lamina propria, *pT2* Tumor invading the muscularis propria

Divergent differentiation and subtype histology in invasive tumors

Divergent differentiation or subtype histology was identified in 4 of the 60 invasive urothelial carcinomas (6.7%). Two tumors (3.3%; Fig. 4E) showed squamous differentiation, representing divergent differentiation, whereas two tumors (3.3%) exhibited micropapillary subtype (Fig. 4F).

Among the muscle-invasive tumors (pT2, $n=18$), three patients demonstrated either divergent differentiation or subtype histology (16.7%). The remaining patient showing these features was classified as pT1 high-grade urothelial carcinoma.

Localization characteristics

Based on available localization data, the left lateral wall was the most frequently involved site across most diagnostic groups, whereas anterior wall involvement was relatively uncommon (Supplemental Table 2).

Prognosis

Follow-up data were available for 206 of the 400 patients (51.5%), whereas the remaining 194 patients (48.5%) lacked follow-up information and were therefore excluded from outcome analysis. Repeated biopsy sampling during follow-up was documented in 134 of the 400 patients. Among patients with available follow-up, remission was observed in 159 patients (77.2%), recurrence in 41 patients (19.9%), death in 4 patients (1.9%), and disease progression in 2 patients (1.0%) (Supplemental Table 3). Recurrence was most frequently observed in patients diagnosed with LGPUC and IPUC, whereas mortality was rare and

primarily limited to invasive tumors. Among the four deaths, three patients (75%) occurred in patients with IPUC. All four deaths were cancer-specific and occurred in patients with clinically progressive disease. In one patient, extensive cauterization artifacts in the biopsy specimen initially prevented reliable assessment of stromal invasion, leading to an initial interpretation of LGPUC; subsequent evaluation revealed invasive disease. Overall, among the invasive tumors, three deaths and two progression events were recorded.

Prognosis according to age groups

Prognostic outcomes varied across age groups, with younger patients generally demonstrating more favorable outcomes. Notably, recurrence, progression, and mortality were observed exclusively in patients older than 20 years. In the 1–10 and 11–20 age groups, all patients achieved remission. In the 21–30 age group ($n=52$), remission was observed in 42 patients (80.8%), recurrence in 9 patients (17.3%), and death in 1 patient (1.9%). In the 31–40 age group ($n=139$), remission occurred in 102 patients (73.4%), recurrence in 32 patients (23.0%), death in 3 patients (2.2%), and progression in 2 patients (1.4%). Due to the very low number of progression and death events, reliable statistical comparison of prognostic outcomes between age groups was not feasible. Overall, these findings indicate that urothelial neoplasms diagnosed at younger ages are predominantly low-grade lesions with favorable clinical outcomes, while adverse events are largely confined to invasive tumors.

Discussion

This study evaluates one of the largest cohorts of younger patients with urinary bladder neoplasms and may serve as a reference cohort for bladder cancer in this age group. Previous studies have shown that urothelial carcinoma diagnosed during the first two decades of life accounts for approximately 0.1–0.4% of all bladder cancer patients, whereas this rate increases to about 1.0–2.4% in patients younger than 40 years of age [14, 15]. Urothelial tumors occurring in the first decade of life are exceedingly rare and, although genetic susceptibility has occasionally been suggested, most reported cases appear to arise sporadically. In another retrospective analysis, patients under 40 years constituted only 4.86% of all bladder cancer patients [6]. The scarcity of prospective cohorts for these rare tumors limits clinical experience and complicates the development of early diagnostic and therapeutic strategies.

Diagnosis may also be challenging in young patients because symptoms can mimic benign conditions such as urinary tract infection, urolithiasis, or nephropathy [7]. Therefore, a high index of clinical suspicion is required in young patients presenting with hematuria or irritative urinary symptoms. Macroscopic hematuria is the most frequent presenting symptom in young patients and has been reported in approximately 78.5% of patients in the literature [8, 15, 16], similar to our cohort. Lower urinary tract symptoms such as dysuria and urinary frequency, as well as pelvic pain, are reported less frequently in the literature and were also observed at relatively low rates in our study [14]. Ultrasonography and cystoscopy are the first-line diagnostic tools in the evaluation of suspected bladder tumors; however, reluctance of younger patients to undergo cystoscopy may contribute to diagnostic delays [7]. In previously published studies, the majority of tumors in patients younger than 40 years are reported to be smaller than 3 cm and predominantly unifocal (approximately 88.2%) [10, 14]. Consistent with the literature, unifocal lesions were also more frequently observed than multifocal lesions in our series.

One of the notable findings of our study was the substantial proportion of patients who were diagnostically reclassified following expert pathological review (31.8%), which represents a clinically meaningful rate of diagnostic discordance. Consistent with previous reports, discrepancies were particularly observed in the classification of papillary lesions with low-grade or minimal atypia. In particular, the distinction between PUNLMP and low-grade papillary urothelial carcinoma remains inherently challenging due to overlapping architectural and cytological features, subjective interpretation of atypia, and the absence of well-defined quantitative thresholds. These findings highlight the diagnostic challenges associated with distinguishing between urothelial papilloma, PUNLMP, and low-grade papillary urothelial carcinoma in routine practice. Several studies have also reported that the PUNLMP category represents one of the least reproducible diagnostic entities in urothelial pathology [17–19]. Therefore, our findings further support the critical role of expert genitourinary pathology review in improving diagnostic accuracy and ensuring appropriate clinical management. Although the overall diagnostic revision rate was 31.8%, clinically significant reclassification affecting tumor invasiveness or stage was identified in 18 patients (4.5% of the cohort), including 2 cases reclassified from HGPUC to IPUC, 1 case from LGPUC to IPUC, 14 cases from IPUC to non-invasive carcinoma (pTa), and 1 case with stage revision from pT2 to pT1. In addition, the reclassification of a subset of tumors initially diagnosed as invasive papillary urothelial carcinoma as non-invasive carcinoma following re-evaluation indicates that the assessment of lamina propria invasion may represent another area prone to diagnostic variability.

After re-evaluation, the vast majority of tumors in our cohort were classified as non-invasive. In our series, LGPUC represented the most common diagnosis, accounting for 58.3% of patients. The frequency of HGPUC was lower and accounted for 8% of patients. These findings are consistent with previous reports indicating that low-grade and non-invasive tumors constitute the majority of bladder tumors in younger patients. The prevalence of PUNLMP in patients younger than 40 years has been reported as approximately 28.6%, with its frequency decreasing with increasing age [10]. In a meta-analysis evaluating patients younger than 21 years, 76% of tumors were classified as PUNLMP or LGPUC, whereas high-grade tumors were identified in only 9% of patients and muscle-invasive disease in approximately 5% [15]. In our cohort, urothelial carcinoma subtypes or divergent differentiation were identified in a small subset of invasive tumors, suggesting that aggressive tumor biology cannot be completely excluded in this age group.

Although most tumors in young patients are non-invasive, the presence of high-grade or invasive tumors indicates that aggressive disease can still occur, albeit rarely. Several studies have suggested that urothelial tumors arising in younger patients may exhibit a lower mutational burden and reduced genomic instability compared with tumors in older individuals, which may partly explain their generally favorable clinical behavior [10, 14, 15]. In our cohort, urothelial carcinoma subtypes or divergent differentiation were identified in a small subset of invasive tumors, suggesting that aggressive tumor biology cannot be completely excluded in this age group. In the study by Tatar et al., pT1 tumors were reported in 9.5% to 19.6% of younger patients, whereas pT2 tumors ranged from 1.2% to 18.6%, depending on the analyzed age subgroup [6]. Similarly, in our study, 10.5% of tumors were staged as pT1 and 4.5% as pT2. Other studies have also reported that pT1 tumors occur more frequently than pT2 tumors in younger patients [20–22]. Furthermore, some studies have suggested that tumor behavior may become more aggressive with increasing age, particularly in the 30–40 year age range [3, 14]. While some studies have reported no progression in patients younger than 40 years, progression rates ranging from 0% to 21.4% have been described in others. The risk of progression is primarily associated with high tumor grade, advanced stage, and larger tumor size [7, 10, 14]. A gradual increase in tumor grade and stage with increasing age has also been described [6]. Although overall survival rates are generally favorable in young patients, the possibility of recurrence or progression necessitates careful and long-term follow-up [10, 14].

Our study has several limitations. The retrospective design and potential variations in data collection protocols among participating centers may introduce bias. In addition, differences in follow-up duration and surveillance protocols across centers may have influenced the assessment of clinical outcomes. In some patients, representative pathological image sets rather than complete slide sets were available for re-evaluation. Although participating centers were instructed to submit images covering all diagnostically relevant areas, additional images were requested when necessary, and consensus review was performed by three experienced genitourinary pathologists, this may still have introduced case-selection bias or limited evaluation of focal findings in selected cases. However, this approach enabled centralized expert review of a large multicenter national cohort that would otherwise have been difficult to assemble. A further limitation is the relatively high proportion of patients (48.5%) without available follow-up data, which may influence the interpretation of recurrence, progression, and mortality rates. Moreover, the relatively low number of progression and mortality events limited the ability to perform robust statistical comparisons of prognostic outcomes between subgroups. In addition, in one fatal patient initially diagnosed as LGPUC, extensive cautery artifacts limited accurate evaluation of stromal invasion and may have masked a more advanced stage of disease. Although central review was performed by experienced genitourinary pathologists, formal interobserver agreement analysis was not conducted, which may be considered an additional limitation. These limitations restrict the ability to establish definitive clinical recommendations. Therefore, prospective multicenter studies are needed to validate and expand upon these findings.

In conclusion, urothelial neoplasms of the bladder in patients younger than 40 years are characterized predominantly by low-grade, low-stage tumors and generally favorable clinical outcomes. However, the relatively higher frequency of high-grade and invasive tumors in the 31–40 year age group suggests that this age range may represent a transitional biological phase. Male predominance, the predominance of hematuria as the most common presenting symptom, and the overall dominance of low-grade tumors in young patients were consistent with previously published studies. Nevertheless, the potential for aggressive tumor behavior in higher-stage and higher-grade tumors should not be underestimated. Prospective multicenter studies are necessary to better define age-specific disease behavior and to develop evidence-based management strategies for bladder tumors occurring in patients younger than 40 years.

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Data availability All data generated or analyzed during this study were included in this published article.

Declarations

Ethical approval The study protocol was approved by the Ethical Committee of Non-invasive Clinical Research of Kocaeli University (GOKAEK-2025/573).

Competing interests The authors declare that they have no competing interests.

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