Introduction

Bladder cancer is the ninth most common cancer in the world, and it is the most common cancer of the urinary system. Its incidence varies among countries and among cities in the same country, and it is 70% more in underdeveloped counties than in developed countries (1). Although urothelial carcinomas (UC) constitute a major part of bladder cancer worldwide, squamous cell carcinomas are also frequently observed in African countries, where especially Schistosoma is endemic (2).

Bladder cancer is considered as one of the costliest tumor groups in the world because it progresses chronically and requires a long-term follow-up and treatment in the vast majority of patients. Although the incidence is high in North American and European countries, mortality is higher in countries with a low level of development, resulting in high costs for countries’ health systems (3–5).

Smoking has been reported as the most common etiologic factor, and the incidence of bladder cancer is three to four times more frequent in men than in women worldwide, there has been an increase in the incidence of bladder cancer in women in the recent years due to the increase in cigarette addiction (6).

Bladder cancer is classified according to the histologic grade and invasion status of the patients. Approximately 70% of the cases are limited to the lamina propria and 30% of them show muscle invasion (7). Especially in cases with invasion, apart from classical UC morphology, different histologies are also frequently detected as a result of the fact that the bladder has a high metaplastic exchange capacity and it originates from different embryological structures such as cloaca, allantois, and mesonephric ducts (8–11). While 13 different variants were defined in the 2004 classification of the World Health Organization (WHO), 22 UC variants are accepted today (11, 12). Variants have significant differences in terms of prognosis and treatment approaches among themselves and also cause difficulties in terms of differential diagnosis (7).
In our study, we aimed to investigate the age, stage, histologic grade, and variant distribution of the patients who were diagnosed with UC for the first time between the years 2010 and 2015.

Methods

The list of patients diagnosed with UC through bladder transurethral resection (TUR) biopsy material between 2010 and 2015 was searched in the electronic database of our Medical Pathology Laboratory. The preparations stained with the existing hematoxylin and eosin (H&E) and immunohistochemical marker were taken from the block and slide archive and re-examined. In the study, the first diagnoses of the patients were taken into consideration, and the recurrent cases diagnosed before the year of study (2010), recurrences of the cases, the cases whose paraffin-embedded blocks and slides and sufficient clinical information could not be obtained were excluded from the study. Clinical information about the cases was obtained from the electronic database and patient reports. All cases were diagnosed according to the WHO 2004 classification of urogenital system tumors (13). In the diagnoses of UC variants, the WHO 2004 classification and the variants that were defined in recent years and gained general consensus were taken into consideration (13, 14). The cases in whom biopsy area UC variant was detected at a rate of at least 10% were accepted as the UC variant. The cases in which more than one variant was observed were diagnosed as the variant with the highest percentage. Tumor stage was determined according to the 2010 classification of the American Cancer Society (15).

Table 1. Gender, age, and stage distribution in patients of bladder urothelial carcinoma

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Percentage</th>
<th>Average Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
<td>Total</td>
</tr>
<tr>
<td>Low-grade PTA</td>
<td>246</td>
<td>40</td>
<td>286</td>
</tr>
<tr>
<td>High-grade PTA</td>
<td>63</td>
<td>10</td>
<td>73</td>
</tr>
<tr>
<td>PT1</td>
<td>168</td>
<td>26</td>
<td>194</td>
</tr>
<tr>
<td>PT2</td>
<td>97</td>
<td>12</td>
<td>109</td>
</tr>
<tr>
<td>PT4</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>In Situ</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>UNLMP</td>
<td>10</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>589</td>
<td>90</td>
<td>679</td>
</tr>
</tbody>
</table>

M: male; F: female; UNLMP: urothelial neoplasm of low malignant potential

Statistical Package for Social Sciences version 15.0 (SPSS Inc.; Chicago, IL, USA) for Windows was used for the statistical analysis. Descriptive statistics were given as number and percentage for the categorical variables and as mean, standard deviation, and median for the numerical variables. Student t test was used in the comparisons of two independent groups when the numerical variables provided normal distribution condition, and Mann–Whitney U test was used when they did not. Because the numerical variable provided normal distribution condition, One-way ANOVA test was used in independent multiple group comparisons. Subgroup analyses were examined by Tukey test. In groups, the analysis of the ratios was tested with chi-square. Statistical significance level of alpha was accepted as p<0.05. Verbal approval was received from the cases participating in the study prior to the biopsy.

Results

Between 2010 and 2015, 1355 bladder TUR biopsies of 1081 patients were examined. A total of 676 cases most of whom were recurrent cases were excluded from the study and 679 cases were found to meet the study criteria. Age, gender, stage, and grades of the cases are shown in Table 1.

Of the cases, 589 were male (86.7%) and 90 were female (13.3%), and the mean age was 64.2±11.4 y and 66.0±15.0 y, respectively. The youngest age was 16 y and the oldest age was 92 y. There was no statistically significant difference in the mean age of male and female patients (p=0.079).

Of the cases, 298 (43.8%) had low-grade (LG) carcinomas and 381 (56.2%) of them had high-grade (HG) carcinomas. The mean age of those with LG carcinomas was found statistically significantly lower than the mean age of those with HG carcinomas (p<0.001).

When the mean age of the cases was examined according to the stages, it was found as 62.8±12.4 in pTa cases, as 66.7±11.3 in pT1 cases, as 66.1±10.3 in pT2 cases, and as 61.3±20.2 in in situ carcinomas. The mean age of PTA group was statistically significantly lower than pT1 group (p<0.001).

When bladder UC cases were examined in terms of the WHO 2004 UC classification and newly identified variants, a UC variant was detected in 153 cases (22.5%), who constituted at least 10% of the biopsy area. In our study, 15 different UC variants were detected, including squamous, glandular, small cell, micropapillary, sarcomatoid, lymphoepitheliomale-like, nested, large nested, large-cell neuroendocrine, pleomorphic, trophoblastic, plasmacytoid, rhabdoid, chordoid, and undifferentiated. The age, gender, stage, and rates of the cases are shown in Table 2. While the most frequent variants were squamous cell and micropapillary, large cell undifferentiated, giant cell, osteoclast-rich giant cell, clear cell, pleomorphic giant cell, acinar/tubular type, and microcystic variant UC cases were not observed.

Statistical analysis showed no significant difference in the mean age of patients with invasive bladder carcinoma with and without variant (p=0.954).
Table 2. Percentage of bladder urothelial carcinoma variants in age, stage, and all urothelial carcinomas according to genders

<table>
<thead>
<tr>
<th>Urothelial Carcinoma Variants</th>
<th>F</th>
<th>M</th>
<th>General %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous</td>
<td>7</td>
<td>40</td>
<td>6.92%</td>
</tr>
<tr>
<td>Glandular</td>
<td>1</td>
<td>12</td>
<td>1.91%</td>
</tr>
<tr>
<td>Small Cell</td>
<td>1</td>
<td>5</td>
<td>0.88%</td>
</tr>
<tr>
<td>Micropapillary</td>
<td>4</td>
<td>19</td>
<td>3.38%</td>
</tr>
<tr>
<td>Sarcomatoid</td>
<td>-</td>
<td>5</td>
<td>0.73%</td>
</tr>
<tr>
<td>Lymphoepithelioma-like</td>
<td>1</td>
<td>2</td>
<td>0.44%</td>
</tr>
<tr>
<td>Nested</td>
<td>3</td>
<td>15</td>
<td>2.65%</td>
</tr>
<tr>
<td>Large Nested</td>
<td>3</td>
<td>11</td>
<td>2.06%</td>
</tr>
<tr>
<td>Large Cell NED</td>
<td>-</td>
<td>2</td>
<td>0.29%</td>
</tr>
<tr>
<td>Pleomorphic</td>
<td>1</td>
<td>10</td>
<td>1.62%</td>
</tr>
<tr>
<td>Trophoblastic</td>
<td>-</td>
<td>1</td>
<td>0.14%</td>
</tr>
<tr>
<td>Plasmacytoid</td>
<td>-</td>
<td>2</td>
<td>0.29%</td>
</tr>
<tr>
<td>Rhabdoid</td>
<td>-</td>
<td>2</td>
<td>0.29%</td>
</tr>
<tr>
<td>Chordoid</td>
<td>-</td>
<td>3</td>
<td>0.44%</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>-</td>
<td>3</td>
<td>0.44%</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>132</td>
<td>66.6</td>
</tr>
</tbody>
</table>

M: male; F: female; NED: neuroendocrine differentiation

Figure 1. Bladder urothelial carcinoma, squamous variant (H&E 200x)

Figure 2. Bladder urothelial carcinoma, glandular variant (H&E 200x)

Figure 3. Bladder urothelial carcinoma, micropapillary variant (H&E 200x)

Figure 4. Bladder urothelial carcinoma, nested variant (H&E 200x)
When the variant detection rates were statistically examined in all pT1 and pT2 cases, the variant detection rate of pT2 patients was significantly higher than pT1 patients (p<0.001).

**Discussion**

Bladder cancer is the ninth most frequent cancer in the world, and 430,000 new cases were diagnosed in 2012 (4). The incidence is 70% less in underdeveloped countries than in developed countries, and it is the fourth most common cancer in males and tenth most common cancer in females (3). While squamous cell carcinoma is more frequently seen due to endemic schistosomiasis in North Africa, UC is seen at about 95% in Western countries (2, 4, 16).

In our country, bladder cancers are the third most common cancer with a rate of 7.9% after respiratory system cancers (23.3%) and prostate carcinomas (12.9%). The incidence that was 12.4/100.000 in 2002 increased rapidly to 20.7 in 2010. This increase may be because the exposure to cigarette smoking and to carcinogenic materials increased and because national cancer statistics may have been better kept. In women, bladder cancers have been observed among the most commonly detected 10 cancers (17).

Bladder cancer is three to four times more common in men than in women worldwide. However, in Mediterranean countries such as Spain, Italy, and Turkey, this ratio reaches up to 6-fold (18). In our study, of the 679 patients, 86.7% were male and 13.3% were female; thus, bladder carcinoma was detected 6.5 times more in men than in women.

The average age of diagnosis in bladder carcinomas is 67 years and bladder cancers are also found in young adults and, more rarely, in children (2, 6, 8). In our study, the mean age of the males was 64.2±11.4 y, and the average age of the females was 64.0±15.9 y. Despite the fact that men were diagnosed about 2 years earlier than women in our study, this difference was not found statistically significant (p=0.079).

When we evaluated the cases as high and low grade, 298 (43.8%) of them were diagnosed with LG and 381 (56.2%) were diagnosed with HG. While the mean age of diagnosis of the cases with LG was 62.3±11.8 y, it was found as 66.1±11.0 y in those with HG. When statistically examined, the mean age of those with LG was significantly lower than those with HG (p <0.01).

When assessed according to the stage, the age of diagnosis in UCs with pTa was 62.8±12.4 y, 66.7±11.3 y in UCs with pT1, 66.1±10.3 y in UCs with pT2, and 61.3±20.2 y in in situ UCs. The age of diagnosis of pTa (non-invasive) patients was statistically significantly lower than that of pT1 and pT2 patients. There may be many reasons why the age of diagnosis is different between invasive (pT1 and pT2) and non-invasive (pTa) tumors and LG and HG tumors. The most important reason is that pTa (large part is constituted by the UC with LG) and pT1-2 with HG develop from different pathways in terms of tumorigenesis (10, 19–24). A second reason may be that approximately 5%–10% of the UCs with LG progress to the LG lesions in their recurrences over the years. Similarly, the fact that the age of diagnosis of the in situ UC patients (61.3±20.2 y) is about 5 years earlier than the age of diagnosis of the pT1 (66.7±11.3) and pT2 (66.1±10.3) patients supports that in situ carcinoma patients show progression to invasive carcinomas over time.

One of the most important results of the study is that the rate (42.12%) of non-invasive UC with LG has been found to be low compared to the literature. The reason for this may be that the UC grading may show differences among pathologists (25), that most tumors show a mixed degree (high+low grade), and that a very detailed examination can detect the HG components accompanying LG lesions.
When invasive carcinomas were examined in reference to the WHO 2004 UC classification and newly identified variants; UC (22.5%) variant was detected in a total of 153 patients, who constituted at least 10% of the biopsy area. It is seen that this rate is slightly lower compared with 25% to 40% in the literature. We think that this difference may be due to the lack of precise data in different studies on how much the minimum variant area required for the variant diagnosis should be and due to the distribution differences in the stages of the cases in different studies. It may also be a characteristic of the UC cases in our country. Because this is the study that has been made with the largest series of patients in our country.

In our study, while squamous differentiation was observed most commonly, which is consistent with the literature, micropapillary and nested variants follow this. The rate of large nested (2.06%) cases is higher than the literature.

Urothelial epithelium originates from different embryological structures such as cloaca, allantois, and mesonephric duct during embryological development (8–11). We think that originating from different structures can lead to high metaplastic change capacity and variants. The variants can cause diagnostic difficulties because they show very different differentiation besides the classical UC morphology, and they are very important as prognostic markers.

All of the cases in whom variant was observed in our study were invasive and had high grade. In the statistical examination, the rate of variant incidence was higher in pT2 patients than in pT1 patients (p<0.01). Increasing rates of variant incidence as the tumor stage progresses may indicate different differentiation capacities of invasive tumors; it also shows that the invasion capacity of variant-containing tumors may be higher. The fact that the lesions containing variant have a worse prognosis than the conventional UCs and the fact that cystectomy and chemoradiotherapy regimens are recommended to be applied together even in the early stages by many authors (2–29) show the importance of recognizing these cases.

Different pathways, which were also supported by animal experiments, were described for LG and HG lesions in the development of UCs. HG lesions are quite different from LG lesions and they are histologically and molecularly heterogeneous (10). Because of this heterogeneity, there are difficulties in target treatment, but new treatment possibilities are also investigated in some cases. In recent studies, the overexpression of Human Epidermal Receptor Protein-2 was detected in conventional UC and micropapillary variants, and it was reported that they could be candidates for target treatment (30).

**Conclusion**

In the reporting of bladder TUR biopsy materials, the grade should be given together with the percentage of variant area if present in the tumor, in addition to stage, angiolymphatic invasion, and the like parameters. In some variants such as small cell, lymphoepithelioma-like, and micropapillary, treatment approaches and prognosis may be different, and metastatic lesions that may develop in cases may be with pure variant morphology. Variants should be reported in pathology reports both to affect the treatment and follow-up modalities and to avoid diagnostic difficulties of the metastatic lesions, which may develop during follow-up.

While 13 variants were defined in 2004 WHO classification, there are now 22 accepted variants. It is quite difficult to say that all of these described variants are very different from each other and it reduces the repeatability of the diagnoses. Because some histologic and prognostic features of some variants are similar, we think it would be better to group many variants under mutual names. For example, “large cell undifferentiated carcinoma,” “osteoclast-rich undifferentiated carcinoma,” “pleomorphic giant cell carcinoma,” and “undifferentiated carcinoma” cases can be grouped under the name of “undifferentiated carcinoma,” and “nested variant,” “tubular/acinar variant,” “microcystic variant,” and the subtypes of “glandular differentiation” can be grouped under the name of “glandular variant.” Similar examples can be increased. Because of this histological heterogeneity in the UCs, it appears that there will be new variants and nomenclatures in every WHO classification.

**Ethics Committee Approval:** Since our study was retrospective and the slide and blocks of urothelial carcinoma cases in our archive were used, no ethics committee was applied.

**Informed Consent:** Verbal informed consent was obtained from patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

**Author contributions:** - K.B., O.O.; Analysis and/or Interpretation - O.O., K.B.; Literature Search - O.O., K.B.; Data Collection and/or Processing - K.B., O.O.; Writing - O.O., K.B.; Critical Reviews - K.B.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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