RESEARCH ARTICLE

Demographic and histopathological features of patients with primary bladder cancer without recurrence in two-year follow-up

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Abstract

Objective: To investigate the demographic characteristics associated with bladder cancer recurrence.

Method: The retrospective study was conducted at the Urology Clinic of İzmir Katip Çelebi University Atatürk Training and Research Hospital, Turkiye, and comprised data from 2013 to 2017 related to patients who received intravesical treatment in the early postoperative period and did not show recurrence in at least two years of follow-up. Patients with non-recurrent primary bladder cancer were placed in group A, while patients with recurrent bladder cancer tumours who underwent transurethral bladder tumour resection and received a single dose of intravesical therapy were placed in group B. Demographic and clinical characteristics of all the patients were noted in detail. Data was analysed using SPSS 25.

Results: Of the 118 patients, 67(56.8%) were in group A; 56(83.6%) males and 11(16.4%) females with mean age 63.5±10.3 years. There were 51(43.2%) patients in group B; 44(86.3%) males and 7(13.7%) females with mean age 66.5±10.4 years (p>0.05). The median follow-up time in group A was 24 months (interquartile range: 24-48 months) and it was 24 months (interquartile range: 6-108 months) in group B (p=0.336). There were significant intergroup differences in terms of occupational distributions, living place, exposure to carcinogenic substances, use of plastic ware, six weeks of maintenance intravesical therapy, daily water intake, and coffee consumption (p<0.05).

Conclusion: A number of factors were identified that may have a role in ensuring recurrence-free survival among bladder cancer patients.

Key Words: Bladder cancer, Recurrence, Intravesical drug administration.

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Introduction

Bladder cancer is the seventh most common cancer in men and the 17th most common cancer in women worldwide. In developed countries, the incidence of bladder cancer ranks fourth in men and ninth in women. Due to its high incidence and tendency to recur, bladder cancer poses significant health problems and a significant burden on health expenditure. Invasive disease is present in 20-40% of bladder cancer cases at the time of initial diagnosis, and approximately 25% of these cases have lymph node (LN) metastases during cystectomy.[1] When invasive bladder cancers are not treated, 85% patients die within 2 years. The 10-year disease-free survival (DFS) after cystectomy is 50-66%.[2,3]

Transurethral bladder tumour resection (TUR-MT) is the first step in the treatment of superficial bladder tumours and is considered the gold standard. Bladder cancer is 75-85% non-muscle invasive when first diagnosed[4] However, non-muscle invasive bladder cancers include different groups limited to the mucosa (Ta, Tis [carcinoma in-situ (CIS)]) and submucosa (T1). At the time of diagnosis, 70% of these tumours are Ta, 20% are T1 and 10% are Tis. Approximately 70% of these tumours recur, while 20-30% show progression to a more advanced stage or pathological grade.[5] Although recurrence and progression rates are lower than invasive cancers, these three tumour subtypes show significant differences. Therefore, treatment is performed according to risk groups based on their characteristics and prognostic factors. Approximately 70% of non-muscle invasive bladder tumours without additional treatment after primary TUR-MT recur, while 20-30% show progression to a more advanced stage or pathological grade.[5,6]

The current study was planned to assess demographic and histopathological characteristics associated with bladder cancer recurrence.

Materials and Methods

The retrospective study was conducted at the Urology Clinic of İzmir Katip Çelebi University Atatürk Training and Research Hospital, Turkiye, and comprised data from 2013 to 2017 related to patients who received intravesical

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treatment in the early postoperative period and did not show recurrence in at least two years of follow-up. Patients with non-recurrent primary bladder cancer were placed in group A, while patients with recurrent bladder cancer tumours who underwent TUR-MT and received a single dose of intravesical therapy were placed in group B.

Informed consent had been taken from all patients at the time of treatment. The follow-up interval was three months for most patients, because cystoscopy examination was conducted in the third month for most of the patients. The researchers suggest six-month follow-up interval after initial control cystoscopy, if initial tumour pathology is in the low-risk category, but if it is not in the low-risk category, a 3-month follow-up interval is suggested. Patients who did not complete at least two years of follow-up were excluded. Those who did not undergo intravesical drug administration were also excluded.

Demographic and clinical characteristics of the patients were noted. These included age, gender, occupation, chemical carcinogen exposure, smoking status, TUR-MT pathology, tumour characteristics, use of plastic goods, use of organic agricultural products, psychological status, presence of systemic disease, sleep patterns, dialysis history, canned food consumption, history of additional urological intervention, six-week intravesical treatment, daily fluid intake (water, tea, coffee consumption) and place of residence.

The patients underwent TUR-MT with either monopolar or plasmacokinetic transurethral resection (TUR) technique. A single intravesical dose of 50mg epirubicin was administered within six hours after the operation. Depending on the TUR-MT pathology, patients were treated with six weeks of intravesical epirubicin 50mg, mitomycin-c 40mg or Bacillus Calmette-Guerin (BCG) 81mg that were administered weekly for six weeks. Patients were followed up postoperatively with cystoscopy. All patients were given a single-dose fosfomycin treatment after cystoscopy.

Data was analysed using SPSS 25. Continuous variables were compared using the student's t-test or Mann–Whitney U test, as appropriate. Categorical variables were compared using the chi-square or Fisher's exact test. P<0.05 was considered statistically significant.

Results

Of the 118 patients, 67(56.8%) were in group A; 56(83.6%) males and 11(16.4%) females with mean age 63.5±10.3 years. There were 51(43.2%) patients in group B; 44(86.3%) males and 7(13.7%) females with mean age 66.5±10.4 years (p>0.05). In group A, 64(95.5%) patients were followed up for three months and 3(4.5%) were followed up for six months. All 51(100%) patients were followed up in the recurrence group for three months (p=0.257). The median follow-up time in group A was 24 months (interquartile range [IQR]: 24-48 months) and it was 24 months (IQR: 6-108 months) in group B (p=0.336). There were significant intergroup differences in terms of occupational distribution, living place, exposure to carcinogenic substances, use of plastic ware, six weeks of maintenance intravesical therapy, daily water intake, and coffee consumption (p<0.05). Smoking status, pathological tumour stage and grade, tumour number, tumour type, tumour type, concomitant systemic disease, dialysis, sleep status, history of urological intervention, patient psychology, chemotherapy/radiotherapy, consumption of organic agricultural products, canned foods, tea consumption were not significantly different

Table-1: Demographic characteristics of the patients (n=118)

	Recurrence		p
	No (n=67)	Yes (n=51)	
Age	63.5±10.3	66.5±10.4	0.121
Gender (n, %)			
Male	56 (83.6%)	44 (86.3%)	0.687
Female	11 (16.4%)	7 (13.7%)	
Occupation (n, %)			
Not working	6 (8.95%)	5 (9.8%)	0.002
Farmer	14 (20.89%)	10 (19.6%)	
Officer	10 (14.92%)	7 (13.7%)	
Worker	7 (10.44%)	21 (41.2%)	
Driver	9 (13.43%)	3 (5.9%)	
Other	21 (31.34%)	5 (9.8%)	
Place of residence (n, %)			
Village	15 (22.4%)	5 (9.8%)	<0.001
County	2 (3%)	15 (29.4%)	
City	50 (74.6%)	31 (60.8%)	

Table-2: History of smoking and carcinogen exposure.

	Recurrence		p
	No (n=67)	Yes (n=51)	
Cigarette use (n, %)			
Non-smoker	5 (7.5%)	11 (21.6%)	0.018
Quit smoking	23 (34.3%)	22 (43.1%)	
Smoker	39 (58.2%)	18 (35.3%)	
Cigarette consumption (pack/year) (Median, Min-Max) (n, %)			
	40 (0-100)	30 (0-120)	0.065
Exposure to carcinogens (n, %)			
No	38 (56.7%)	43 (84.3%)	0.001
Yes	29 (43.3%)	8 (15.7%)	
Use of plastic items (n, %)			
Doesn't use	28 (41.8%)	31 (60.8%)	0.041
Use	39 (58.2%)	20 (39.2%)	

Table-3: Tumour characteristics.

	Recurrence		p
	No (n=67)	Yes (n=51)	
Stage (n, %)			
TA	41 (61.2%)	32 (62.7%)	0.864
T1	26 (38.8%)	19 (37.3%)	
Grade (n, %)			
G1	23 (34.32%)	19 (37.3%)	0.205
G2	11 (16.41%)	2 (3.9%)	
G2A	13 (19.40%)	8 (15.7%)	
G2B	10 (14.92%)	10 (19.6%)	
G3	10 (14.92%)	12 (23.5%)	
Number of focal points (n, %)			
Single	46 (68.7%)	32 (62.7%)	0.502
Multiple	21 (31.3%)	19 (37.3%)	
Localisation (n, %)			
Opposite wall	7 (10.4%)	9 (17.6%)	0.435
Dome	3 (4.5%)	1 (2%)	
Around the right orifice	12 (17.9%)	12 (23.5%)	
Right side wall	20 (29.9%)	14 (27.5%)	
Around the left orifice	14 (20.9%)	7 (13.7%)	
Left side wall	11 (16.4%)	6 (11.8%)	
Neck	0 (0%)	2 (3.9%)	
Size (Median, Min-Max) (n, %)3 (1-7)		3 (1-7)	0.936
Tumour type (n, %)			
Papillary	62 (92.5%)	41 (80.4%)	0.041
Solid	4 (6%)	10 (19.6%)	
Solidopapillary	1 (1.5%)	0 (0%)	

Table-4: Treatment characteristics.

	Recurrence		p
	No (n=67)	Yes (n=51)	
6-week maintenance (n, %)			
No maintenance	2 (3%)	14 (27.5%)	<0.001
BCG	12 (17.9%)	22 (43.1%)	
Epirubicin	29 (43.3%)	6 (11.8%)	
Mitomycin	24 (35.8%)	9 (17.6%)	
Follow-up interval (n, %)			
3 months	64 (95.5%)	51 (100%)	0.257
6 months	3 (4.5%)	0 (0%)	
Follow-up period (month) (Median, Min-Max)	24 (24-48)	24 (6-108)	0.366

BCG: Bacillus Calmette-Guerin.

Table-5: Other characteristics.

	Recurrence		p
	No (n=67)	Yes (n=51)	
Systemic disease (n, %)			
None	30 (44.8%)	30 (58.8%)	0.556
DM	7 (10.4%)	6 (11.8%)	
HTN	17 (25.4%)	8 (15.7%)	
DM+HTN	9 (13.4%)	5 (9.8%)	

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Other	4 (6%)	2 (3.9%)	
Dialysis (n, %)			
No	66 (98.5%)	50 (98%)	>0.999
Yes	1 (1.5%)	1 (2%)	
KT/RT (n, %)			
No	66 (98.5%)	47 (92.2%)	0.164
Yes	1 (1.5%)	4 (7.8%)	
Other urologic interventions (n, %)			
No	50 (74.6%)	44 (86.3%)	0.119
Yes	17 (25.4%)	7 (13.7%)	
Patient psychology (n, %)			
Negative	12 (17.9%)	5 (9.8%)	0.214
Positive	55 (82.1%)	46 (90.2%)	
Regular sleep (n, %)			
No	12 (17.9%)	12 (23.5%)	0.453
Yes	55 (82.1%)	39 (76.5%)	

DM: Diabetes mellitus, HTN: Hypertension, KT: , RT: .

Table-6: Dietary habits.

	Recurrence		p
	No (n=67)	Yes (n=51)	
Consumption of organic agricultural products (n, %)			
Not paying attention	12 (17.9%)	16 (31.4%)	0.089
Paying attention	55 (82.1%)	35 (68.6%)	
Consumption of canned food (n, %)			
Not consuming	52 (77.6%)	38 (74.5%)	0.695
Consuming	15 (22.4%)	13 (25.5%)	
Water (glass/day) (Median, Min-Max) (n, %)	5 (2-20%)	8 (2-20%)	0.004
Tea (glass/day) (Median, Min-Max) (n, %)	5 (0-20%)	5 (0-15%)	0.468
Coffee (n, %)			
Does not drink / Occasionally	63 (94.0%)	25 (49%)	<0.001
1-2 cups/day	4 (6.0%)	26 (51%)	

Table-7: Recurrence pathology.

Recurrence pT	n (%)
CIS	4 (8.2%)
TA	36 (73.5%)
T1	7 (14.3%)
T2	2 (4.1%)
Recurrence Grade (n, %)	
CIS	4 (8.2%)
G1	28 (57.1%)
G2	1 (2%)
G2A	3 (6.1%)
G2B	4 (8.2%)
G3	9 (18.4%)

CIS: Carcinoma in-situ.

between the groups (Tables 1-7).

Discussion

Many factors play a role in the aetiology of bladder cancer. In a study in which the socioeconomic status was analysed by dividing it into five classes, from very poor to rich, it was shown that bladder cancer increased with increasing social class, even when male/female and race/ethnicity effects were taken into account.[6,7]

In the United States, an increase of approximately 40% in the incidence of bladder cancer has been observed in the last 15 years. This increase has been explained by exposure to carcinogens.[8,9] Carcinogen exposure was not detected in 38(56.7%) of the non-relapse cases and 43(84.3%) of the relapse cases in the current study. Substances such as tobacco, ether, varnish, lacquer, shoe polish, gasoline and diesel oil were considered chemical carcinogens to which the patients were exposed due to their occupations. Considering that carcinogen exposure is one of the most important causes of bladder tumour aetiology, the reason for the low carcinogen exposure in the non-relapse group may be related to the insufficient number of patients in the study.

Smoking is the most important risk factor for bladder cancer. Studies have shown that smoking increased the risk of bladder cancer 3-4 times.[10,11] A direct pathophysiological relationship has been shown between smoking and bladder cancer. Cigarettes contain aromatic amines known to cause bladder cancer, such as beta (β)-naphthylamine and polycyclic aromatic hydrocarbons. These substances are excreted through the kidney and have a carcinogenic effect on the urinary system. In Turkiye, 52% of bladder cancers in men in İzmir and 40% in Turkiye were found to be related to smoking .[11] In the current study, 62(92.5%) patients in the non-relapse group and 40(78.4%) in the relapse group were smokers, or had smoked at some point in their lives. This finding was statistically significant. The lower rate of smoking in the relapse group was probably due to the insufficient number of patients in the study.

Occupation was the first and second most important risk factor. It is estimated that occupational exposures play a role in 5-25% of all bladder cancers.[12] Although not directly related to the risk of bladder cancer, β-naphthylamine, 4-aminobiphenyl, and benzidine exposures are special agents to which especially textile dye workers and workers in the tire industry are exposed. The incidence of bladder cancer in Western communities has decreased due to a ban on these specific chemicals in workplaces, and strict controls in this regard.[13] However, candidate chemicals, such as orthotoluidine, important in bladder carcinogenesis, are still used in the paint, tire, chemical and pesticide industries. Although the exact source has not been determined, 4-aminobiphenyl is commonly found in the environment.[14] In the current study, 4(5.9%) patients in the non-relapse group and 7(13.7%) in the relapse group were in the risky occupational group.

The association between coffee and bladder cancer risk has been frequently investigated. Although there is a weak positive association, the results are inconsistent.[15] Most of these inconsistencies are because factors, such as smoking with coffee, have not been well investigated. Frequent smoking of cigarettes with coffee may lead to an apparent association with bladder cancer. Even if caffeine increases the risk of bladder cancer, this risk is too small to be demonstrated by epidemiological studies.[6] Among the patients included in the study, 63(94%) in the non-relapse group did not drink coffee, while 4(6%) drank coffee. In the relapse group, 25 (49%) did not drink coffee, and 26(51%) drank coffee. This can be considered a significant factor in recurrence.

Radiotherapy is a known risk factor for bladder cancer. Kaldor et al. investigated the risk of bladder cancer formation in the follow-up of a group of patients who had previously undergone radiotherapy for ovarian cancer, and showed that the risk of bladder tumour increased in patients who received radiotherapy or chemotherapy (thiotepa and melphalan) compared to patients treated with surgery alone.[16] In the current study, only 1(1.5%) patient in the non-relapse group had a history of radiotherapy, whereas 4(7.8%) patients in the relapse group had a history of radiotherapy. This finding may not have been significant due to insufficient number of patients.

The effects of dietary factors on bladder cancer have also been examined. Fruits and vegetables (especially citrus fruits, apples, strawberries, tomatoes, and carrots) contain important components that play a role in detoxifying carcinogenic substances. Therefore, they prevent deoxyribonucleic acid (DNA) damage and oxidative damage. De Stefani et al. found that tea, coffee and sugar increased the risk of bladder cancer by about three times, whereas there was no such risk in a diet containing fresh vegetables and fruits.[17] Narii et al. showed that the total intake of vegetables and fruits did not reduce the risk of bladder cancer, but the risk decreased with the information about high-fibre vegetables.[18] In the current study, 55(82.1%) patients in the non-relapse group and 35(68.6%) in the relapse group paid attention to consuming organic agricultural products. The fact that this was not statistically significant may be because of a small study sample. Nevertheless, proportional data

suggest that nutrition may be one of the important factors in preventing the recurrence of bladder cancer.

Studies have shown that a single dose of chemotherapy administered in the early postoperative period after TUR-MT can reduce recurrences by 50%, and that no additional treatment options are required in low-risk patients.[19] In the current study, all patients received intravesical treatment in the early postoperative period, and the results suggested that postoperative single-dose intravesical treatment may be effective in preventing recurrence. A meta-analysis of seven randomised trials evaluating intravesical chemotherapy in the early postoperative period found that single-dose chemotherapy reduced the risk of recurrence by 39%. Although the risk reduction occurred in patients with both single and multiple tumours, recurrence was found to be 35.8% in patients with single tumours and 65.2% in patients with multiple tumours.[20]

In patients with superficial bladder tumours, immunotherapeutic or chemotherapeutic agents can be administered into the bladder with a urethral catheter to prevent recurrence and progression and to avoid the morbidity of systemic treatments. It is effective in preventing recurrence and progression as well as in the treatment of diffuse superficial tumours for which resection is impossible.[21,22] In the current study, only 2(3%) patients in the non-recurrent group and 14(27.5%) in the recurrent group did not receive intravesical six-week maintenance therapy. This finding was statistically significant, showing the importance of intravesical treatment in preventing recurrence. In 2006, the European Organisation for Research and Treatment of Cancer (EORTC), Genito-Urinary Cancer Group (GUCG) developed a scoring system and risk tables based on the six most significant clinical and pathological parameters in order to determine separate long and short-term risks for recurrence and progression. There were 2,596 patients diagnosed with Ta and T1 bladder cancer who were randomised into seven separate EORTC-GUCG study arms, and patients with only CIS were excluded. Of the randomised patients, 78% received intravesical chemotherapy. However, no patient received secondary TUR or maintenance BCG treatment. The scoring system was based on tumour number, size, previous recurrence rate, T stage, presence of concomitant CIS and tumour grade, and total scores were calculated separately for recurrence and progression. The pathological stage of the patients in the non-recurrent group included in the study was Ta 41(61.2%) and T1 26(38.8%). Tumour grades were G1 in 23(34.3%) patients, G2 in 11 (16.4%), G2A in 13(19.4%), G2B in 10(14.9%) and G3 in 10(14.9%) patients. In the recurrent group, 32(62.7%) patients were Ta and 19(37.3%) were T1. Tumour grades were G1 in 19(37.3%) patients, G2 in 2(3.9%), G2A in 8(15.7%), G2B in 10(19.6%) and G3 in 12(23.5%) patients. In the current study, patients who did not recur were mostly patients with Ta pathology and low-grade. A total of 46(68.7%) patients in the non-recurrent group had a single focal tumour. In the recurrent group, 32(62.7%) patients had a single focal tumour.

Tumour size (≥3cm) has been defined as one of the risk factors for recurrence.[23] In the current study, the mean tumour size was 3cm in both groups. This may be related to the insufficient number of patients in the study.

In a study investigating the effect of tumour localisation on recurrence, it was reported that tumours localised around the ureteral orifice were predictive of recurrence .[24] In the current study, tumours were found around the orifice in 26(39%) patients in the non-recurrent group and 19 (37.3%) patients in the recurrent group. The observation of tumours outside the orifice in the majority of patients is supported by literature, which indicates that the lateral and posterior walls are the most frequent sites for primary bladder tumours.[25,26] Chronic renal failure has been reported to be a poor prognosis for tumour recurrence and progression.[27] In the current study, the finding of chronic renal failure in only one patient in the non-recurrent group and in one patient in the recurrent group seems to be inconsistent with the existing literature.[27]

Boorjian et al. showed that radiotherapy in prostate cancer treatment increased the risk of bladder cancer.[28] In the current study, one patient in the non-relapse group and four patients in the relapse group had a history of radiotherapy, which supports the literature. The fact that this finding was not statistically significant may be related to the small number of patients in the current study.

In the current study, 28(41.8%) patients in the non-relapse group and 31(60.8%) in the relapse group did not use plastic items. This criterion was statistically significant.

The current study has limitations of having a small sample size. Also, some lifestyle data, such as the amount of daily liquid intake, and sleeping pattern, was self-reported by the patients. Large-scale, prospective, randomised controlled trials are recommended.

Conclusion

A number of factors were identified as having a role in the non-recurrence of bladder cancer. Molecular, genetic as well as environmental factors may also play a role. On this

topic, a large number of patients and prospective and randomized controlled trials are needed.

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EU, YY, YA & SNG: Concept, design, data acquisition, analysis, interpretation, drafting, revision, final approval and agreement to be accountable for all aspects of the work.