Original Article

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Survival Outcomes of Treatment Modalities in Patients with Variant Histopathology of Bladder Cancer in First Transurethral Resection of the Bladder

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Abstract

Objective: Diagnoses of variant histopathology (VH) in bladder cancer (BC) are increasing, and although there is a standard treatment algorithm for BC, the guidelines lack a standardized approach for treating VH in BC. We aimed to compare the survival results of the treatment algorithm applied to patients with BC with VH in the first transurethral resection of the bladder (TUR-B) procedure.

Materials and Methods: We retrospectively assessed data on patients with VH of BC in the first TUR-B between January 2000 and January 2021. After the first TUR-B, we determined TUR-B+/- BCG, radical cystectomy (RC), and trimodal therapy (TMT) as the three potential treatments for patients according to the initial plans applied by the clinics.

Results: A total of 289 patients with VH of BC in the first TUR-B were included in the study. Their mean age was 66.7±10.1 years, and most (246, 85.1%) were male. We found that TMT was associated with lower survival, and BCG administration offered no advantage in terms of overall survival (OS) or cancer specific survival (CSS) among patients with non-muscle-invasive bladder cancer (NMIBC). In patients with MIBC, immediate RC provided a significant advantage over other treatment methods in terms of both OS and CSS.

Conclusions: There is still no standard treatment for patients with VH of BC. Patients are less likely to survive TMT than other treatment modalities.

Keywords: Bladder cancer, variant histopathology, transurethral resection of bladder, radical cystectomy, trimodal therapy

Introduction

Bladder cancer (BC) is the seventh most frequently diagnosed cancer in the male population, although it ranks eleventh worldwide when considering both genders; its incidence rates (per 100,000 person/years) are 9.0 for men and 2.2 for women (1). Although 90% of BC is urothelial carcinoma, and mostly pure urothelial carcinoma, several variant histopathology (VH) may arise, some of which are urothelial and others that are non-urothelial (2,3). Currently, the diagnosis of VH in BC is common for transurethral resection of the bladder (TUR-B) or radical cystectomy (RC) specimens (4). Patients are diagnosed with VH when there is >50% of this component in the tumor specimen, and they usually exhibit an aggressive clinical course (5). Over the past decade, VH in BC has become increasingly noted, and several

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studies have been conducted, particularly on patients treated with RC, to evaluate its effect in muscle-invasive BC (MIBC) patients. All of these studies found VH to be associated with poor survival outcomes (6). There are few cases of VH in non-muscle-invasive BC (NMIBC) reported in the literature; however, understanding the role of VH in BC for this patient group is also important so that we can develop effective treatments that prevent cancer progression.

Although the guidelines set out a treatment algorithm for patients with BC, regardless of whether they have NMIBC or MIBC, they do not offer a clear recommendation for BC with VH. This means that urologists follow no specific method when VH is identified in the first TUR-B in BC, instead basing their approach on their expertise and experience. In this context, we compared the survival results of the treatment algorithm when applied to patients with VH identified in the first TUR-B procedure.

Materials and Methods

We retrospectively assessed data on patients with VH of BC identified in the first TUR-B recorded in the BC database of the Urooncology Association of Turkey, involving 11 urology centers, between January 2000 and January 2021.

Patients with pure urothelial carcinoma, urachal carcinoma, or a mesenchymal tumor whose histopathology excluded VH in the first TUR-B (even those who later had VH at the follow-up), whose data could not be obtained, who underwent partial cystectomy, or whose follow-up period was less than 1 year were excluded from the study.

The VH of BC was defined according to the World Health Organization (WHO) classification (3). Several data items-demographic characteristics such as age, gender, body mass index, presence of diabetes, hypertension, glomerular filtration rate, American Society of Anesthesiology score, and Eastern Cooperative Oncology Group performance status score were recorded and analyzed.

After the first TUR-B, we determined TUR-B +/- BCG, immediate RC, and trimodal therapy (TMT) as the three potential treatments according to the initial plans applied by the clinics. Patients who underwent immediate RC with LND within 3 months after the first TUR-B were included in the immediate RC group, whereas those who underwent RC after 3 months of the first TUR-B were grouped based on the first planned treatment. TMT, systemic chemotherapy (CT), radiotherapy (RT), and maximum-applied TUR-B as bladder-sparing therapy were considered.

Pathological specimens were evaluated at each institution's pathology department using the tumor node metastasis classification for staging and the 2004 WHO classification for grading.

Overall survival (OS) was defined as freedom from death from any cause. Deaths attributable to BC were coded as cancer-specific death events, and cancer specific survival (CSS) was calculated accordingly. The duration of follow-up was the time from surgery to the date of death or the last date of admission to the outpatient clinic. Patient survival was confirmed by hospital or national health system data.

The ethics committee approval of the study was obtained from the Ethics Committee of the University of Çukurova (decision no: 28, date: 05.03.2021).

Statistical Analysis

Categorical variables are expressed as numbers and percentages, and continuous variables are summarized as means and standard deviations or as medians and minimum-maximum, where appropriate. For univariate analysis, OS and CSS were calculated using the Kaplan-Meier method, and the log-rank test was performed to test the differences between survival curves. Cox proportional hazard regressions were performed to determine significant predictors of OS and CSS. In univariate analysis, variables significant at the $p<0.25$ level were entered into multiple Cox regression analyses (backward procedure, LR method). All analyses were performed using IBM SPSS Statistics version 20.0 software. The statistical level of significance for all tests was considered to be 0.05.

Results

The study included 289 patients with VH of BC identified in the first TUR-B between January 2000 and January 2021. Their mean age was 66.7±10.1 years. Among them, 246 (85.1%) were male and 43 (14.9%) were female. The demographic and clinical characteristics of the study population are summarized in Table 1. In terms of cancer, 34.6% of the patients had NMIBC and 65.4% had MIBC, and 94.8% of the patients had a high grade (HG). The most common variant was squamous differentiation (34.9%), followed by micropapillary differentiation (15.6%). The VH types are summarized in Table 2. Of the patients, 77 (26.6%) received only recurrent TUR-B, 36 (12.5%) received TUR-B + BCG, 146 (50.5%) received immediate RC, and 30 (10.4%) received TMT. RC with LND was later performed in 62 patients who were first treated with TURB +/- BCG, after a mean of 14.96±23.62 months.

The mean follow-up was 30.9±33.3 months, the median OS for all patients was 33.7 months, and the 5-year OS was 37.7%. The results of the survival analyses according to the clinical factors of the 289 patients are shown in Table 3. When we assessed their demographic parameters, we found that neither OS nor CSS significantly differed by gender (p=0.658 and p=0.997, respectively), but OS was shorter in cases where patients were aged ≥65 years (p=0.034). The median OS and CSS were found to be shorter in MIBC cases than in NMIBC cases (p=0.003). Figures 1 and 2 show the corresponding Kaplan-Meier curves. Although the median OS and CSS were shorter in cases with an HG, these differences were not statistically significant (p=0.386 and p=0.653), potentially due to the small number of low grade patients in the study. There was no significant difference between the VH types in terms of OS and CSS (p=0.087 and p=0.557, respectively), but when it came to treatment, the OS and CSS were shorter for those undergoing trimodal treatment (both p=0.001).

The results of the survival analyses performed according to the tumor stage are shown in Tables 4 and 5. Although the treatment method did not affect the OS or CSS of patients with NMIBC, both the median OS and CSS of patients with MIBC

who underwent TMT were shorter than those of the other two methods. In contrast, the median OS and CSS of T2-stage patients who underwent RC were the longest (p=0.022 and p=0.005, respectively).

Potential predictors of OS and CSS were evaluated separately using Cox's proportional hazards model. Multivariate models for NMIBC patients included their age, treatment, and variant type when modeling OS, and their CSS, variant type, and treatment method when modeling CSS. In neither case were significant factors found to have affected OS or CSS. Multivariate models

Table 1. Demographical and clinical characteristics

	n=289
Age (years)	66.7±10.1
	68.0 (29.0-92.0)
Gender, n (%)	
Male	246 (85.1)
Female	43 (14.9)
BMI kg/m^2	25.8±4.3
	25.3 (15.9-39.1)
Smoking n (%)	222 (76.8)
Diabetes mellitus, n (%)	67 (23.2)
Hypertension, n (%)	110 (38.1)
ECOG, n (%)	
<3	164 (56.7)
≥3	8 (2.8)
Missing information	117 (40.5)
ASA, n (%)	
<3	103 (35.6)
≥3	53 (18.3)
Missing information	133 (46.0)
eGFR	88.7±12.9
	89.5 (13.6-124.7)
Histology, n (%)	
Ta	14 (4.8)
T1	86 (29.8)
T2	189 (65.4)
Grading, n (%)	
Low grade	15 (5.2)
High grade	274 (94.8)
Carcinoma *in situ*, n (%)	57 (19.7)
Treatment method, n (%)	
TUR-B +/- BCG	113 (39.1)
Radical cystectomy	146 (50.5)
Trimodal therapy	30 (10.4)
Neoadjuvant chemotherapy, n (%)	27 (9.3)

Unless otherwise expressed, data are expressed as mean ± standard deviation, median (minimum-maximum), BMI: Body mass index, ECOG: Eastern Cooperative Oncology Group, ASA: American Society of Anesthesiology, eGFR: Estimated glomerular filtration rate, TUR-B: Transurethral resection of bladder, BCG: Bacillus Calmette-Guerin

Table 2. Variant histopathology

Subgroups	**n (%)**
Squamous differentiation	101 (34.9)
Micropapillary	45 (15.6)
Nested	38 (13.1)
Sarcomatoid differentiation	30 (10.4)
Glandular differentiation	27 (9.3)
Small cell	10 (3.4)
Plasmacytoid	18 (6.2)
Trophoblastic	8 (2.8)
Microcystic	9 (3.1)
Lymphoepithelioma-like	3 (1)

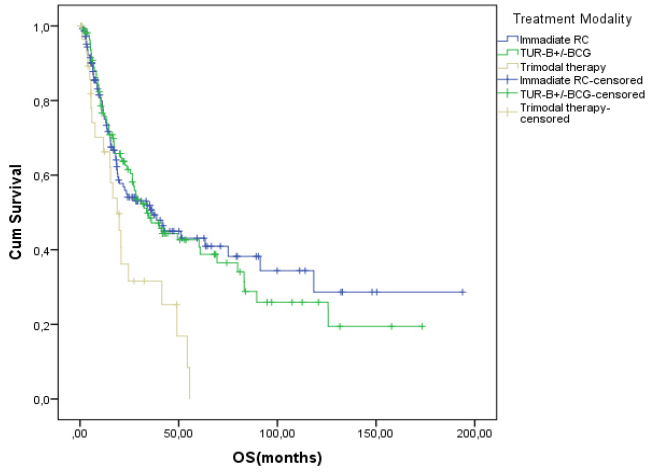

Figure 1. Kaplan-Meier plots of overall survival according to treatment modality

BCG: Bacillus Calmette-Guerin, RC: Radical cystectomy, TUR-B: Transurethral resection of bladder, OS: Overall survival

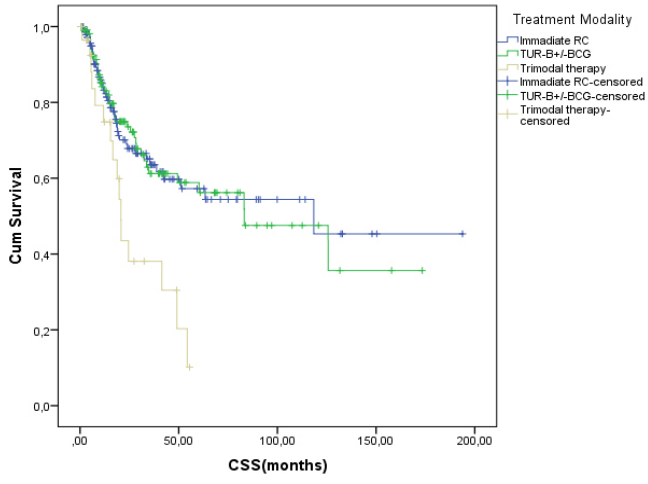

Figure 2. Kaplan-Meier plots of CSS according to the treatment modality

BCG: Bacillus Calmette-Guerin, RC: Radical cystectomy, TUR-B: Transurethral resection of bladder, CSS: Cancer specific survival

for T2-stage patients then included their age, diabetes mellitus, variant type, and treatment method when modeling their OS, and their age, variant type, and treatment method when modeling their CSS. Having undergone TMT was associated with a significantly higher risk of death and cancer-specific death than immediate RC treatment [hazard ratio (HR) =2.22, 95% confidence interval (CI): 1.23-4.01, p=0.008 vs. HR=2.87, 95% CI: 1.49-5.54, p=0.002]; no other factor was associated with OS or CSS in T2-stage patients.

Discussion

Diagnoses of VH in BC are increasing nowadays, and although there is a standard treatment algorithm for BC, the guidelines lack a standardized approach for treating VH in BC. In this context, we compared the survival results of treatment methods applied to patients from 11 urology centers diagnosed with VH of BC in the first TUR-B procedure. We found that TMT was associated with lower survival, and BCG administration offered no advantage in terms of OS or CSS among patients with NMIBC. In patients with MIBC, immediate RC provided a significant advantage over other treatment methods in terms of both OS and CSS.

Three-quarters of patients with newly diagnosed BC have NMIBC, which is associated with recurrence in 60-80% and progression in 10-30% (7-9). The standard initial therapy is complete tumor removal via transurethral resection. Based on the risks of recurrence and progression, the European guidelines (determined by the European Organization for Cancer Research and Treatment scoring system) strongly recommend adding BCG to transurethral resection for patients with NMIBC intermediate- and high-risk tumors (10).

When NMIBC is accompanied by VH, a more aggressive disease occurs, and the progression rate is approximately 40% (11). There is no clear treatment algorithm for such patients. Previous studies have presented conflicting data on the use of BCG in NMIBC with VH (11-14). Shapur et al. (12) compared

Table 3. Results of survival analyses based on clinical and prognostic factors

	OS			CSS		
	Total N/N of events	**OS (months) mean/median**	**p-value**	**Total N/N of events**	**CSS (months) mean/median**	**p-value**
Age						
<65	122/60	84.6/41.6	0.034	120/40	113.6/-	0.169
≥65	167/93	49.5/26.5		166/58	70.2/60.3	
Gender						
Male	246/132	67.6/30.9	0.658	245/84	97.6/83.1	0.997
Female	43/21	60.1/38.8		41/14	75.5/63.4	
Variant type						
Nested	38/19	72.5/42.3	0.087	36/15	82.5/63.4	0.557
Squamous	101/50	66.2/41.5		101/31	92.5/-	
Sarcomatous	30/20	60.7/14.38		30/13	96.9/23.5	
Glandular	27/10	77.9/60.9		26/7	98.9/118.4	
Micropapillary	45/30	33.1/21.0		45/16	49.3/34.8	
Others	48/24	55.5/35.4		48/16	74.4/49.1	
Tumor stage						
Ta+T1	100/41	82.8/83.1	0.003	99/23	112.6/118.4	0.003
T2	189/112	59.1/23.7		187/75	84.9/42.3	
Tumor grade						
LG	15/7	82.6/83.1	0.386	15/5	104.6/83.1	0.653
HG	274/146	68.9/30.9		271/93	97.2/63.4	
Carcinoma *in situ*						
No	232/120	73.3/33.7	0.437	231/74	105.1/83.2	0.118
Yes	57/33	50.3/33.7		55/24	64.7/38.8	
Treatment modality						
TUR-B+/-BCG	113/63	65.3/33.7	0.011	110/38	93.4/83.2	0.005
Immediate RC	146/69	79.1/36.7		146/44	108.6/118.4	
Trimodal therapy	30/21	24.5/18.8		30/16	28.1/30.7	
Total	289/153	69.1/33.7		286/98	98.3/83.1	

OS: Overall survival, CSS: Cancer specific survival, LG: Low grade, HG: High grade, TUR-B: Transurethral resection of bladder, BCG: Bacillus Calmette-Guerin, RC: Radical cystectomy

data from 22 patients with VH of NMIBC who received BCG immunotherapy with data from 144 patients with HG urothelial carcinoma. They concluded that patients with VH of NMIBC could be treated with intravesical immunotherapy if the tumor was non-bulky (>4 cm), and although progression was more common, their life expectancy was similar to that of patients with HG urothelial carcinoma (12). However, in some variant subgroups (small-cell carcinoma, pure sarcomatoid, plasmacytoid, and micropapillary), intravesical treatments such as BCG immunotherapy are ineffective and, therefore, not recommended (11-13). Suh et al. (14) retrospectively evaluated the results of BCG instillation and RC (group 1) versus observation alone (group 2) in patients with high-risk NMIBC squamous or glandular variants. Both the 5-year OS and CSS rates in the BCG instillation and RC groups reflected a survival advantage over the observation group. They concluded that intravesical BCG and RC led to increased survival in high-risk patients diagnosed with NMIBC with squamous or glandular histological variants (14).

VH increases BC risk even if it is not muscle-invasive; therefore, early, aggressive intervention using RC is often recommended for patients with VH (15). In a study by Dursun et al. (16)

Table 4. Results of Ta+T1 patients Cox proportional-hazards regression analysis of the effect of potential prognostic factors on OS and CSS

	Total N/N of events	OS (months) mean/median	p-value	Total N/N of events	CSS (months) mean/median	p-value
Ta+T1						
BCG						
No	65/29	76.5/60.9	0.104	65/18	97.5/118.4	0.043
Yes	34/11	79.7/69.4		33/4	114.1/-	
Treatment modality						
TUR-B+/-BCG	57/23	90.7/83.1	0.088	56/13	121.4/-	0.254
Immediate RC	32/11	78.6/118.4		32/6	95.6/118.4	
Trimodal therapy	11/7	30.7/41.5		11/4	36.8/41.5	
Variant type						
Nested	16/6	104.9/83.2	0.112	15/4	119.9/-	0.471
Squamous	36/16	59.8/14.7		36/8	84.3/-	
Sarcomatous	9/5	48.0/2.4		9/4	60.9/-	
Glandular	10/2	89.7/-		10/1	118.4/118.4	
Micropapillary	15/9	43.2/14.3		15/3	63.8/-	
Others	14/3	116.8/-		14/3	116.8/-	

OS: Overall survival, CSS: Cancer specific survival, BCG: Bacillus Calmette-Guerin, RC: Radical cystectomy, TUR-B: Transurethral resection of bladder

Table 5. Results of T2 Patients Cox proportional hazards regression analysis of the effect of potential prognostic factors on OS and CSS

	Total N/N of events	OS (months) mean/median	p-value	Total N/N of events	CSS (months) mean/median	p-value
T2						
BCG						
No	180/109	58.0/22.9	0.397	179/73	84.8/38.8	0.731
Yes	6/3	55.6/41.3		5/2	60.4/60.3	
Treatment modality						
TUR-B +/- BCG	56/40	40.5/26.5	0.022	54/25	58.1/32.4	0.005
Immediate RC	114/58	75.7/33.7		114/38	106.5/63.4	
Trimodal therapy	19/14	20.6/18.8		19/12	22.7/19.8	
Variant type						
Nested	22/13	31.5/19.4	0.353	21/11	33.5/19.4	0.440
Squamous	65/34	62.9/33.7		65/23	84.2/60.3	
Sarcomatous	21/15	53.6/15.5		21/9	97.5/23.5	
Glandular	17/8	76.1/36.1		16/6	91.1/-	
Micropapillary	30/21	28.4/20.5		30/13	38.2/30.9	
Others	34/21	38.9/27.6		34/13	54.9/49.1	

OS: Overall survival, CSS: Cancer specific survival, BCG: Bacillus Calmette-Guerin, RC: Radical cystectomy, TUR-B: Transurethral resection of bladder

comparing the results of bladder preservation therapy and RC OS for NMIBC patients, based on a total sample of 8920, the researchers concluded that RC led to a better OS for sarcomatoid, squamous, glandular, and neuroendocrine variants compared with bladder preservation therapy, but this result was not observed in patients with micropapillary VH. In a further study of 119 patients with T1 HG micropapillary BC, the authors evaluated survival outcomes after immediate RC versus conservative management with BCG and found that CSM and OM did not differ significantly between the two groups (17). Using the Surveillance Epidemiology, and End Results database, Deuker et al. (18) evaluated CSS in VH of BC patients treated with or without RC and found that RC was performed in 7.4-10% of VH of BC patients vs. 5.1% of HG urothelial BC patients. They revealed that RC was associated with higher CSS rates than other treatments in T1 VH of BC patients, whereas no differences were recorded for adenocarcinoma or other VH of BC types. Therefore, they concluded that RC, for stage T1N0M0 VH of BC, appears to provide a protective effect with respect to squamous or neuroendocrine carcinoma, thereby improving the patients' CSS, but not in adenocarcinoma or other VH of BC types (18). In our study, most of our NMIBC patients were HGs. Although intravesical BCG was administered to 34 patients with NMIBC, we did not observe a positive effect on survival. While immediate RC produced similar OS and CSS rates to TUR-B +/ BCG, TMT led to worse survival results than the other two treatments. The difference we found was not statistically significant, but it may become meaningful when a greater number of patients are studied.

Nearly 30% of new BC diagnoses are MIBC, including cancer in stages T2-T4 (19). MIBC treatment is based on multidisciplinary collaboration involving surgical, RT, and medical oncology teams (20). RC with lymph node dissection, with or without neoadjuvant treatment, has become accepted as the standard treatment approach in MIBC. With an overall complication rate of 27-64%, RC is an aggressive surgical procedure associated with high perioperative mortality, and the 5-year OS of patients who have undergone RC remains below 60% (21,22). Many patients are unsuitable for surgery; therefore, bladder-sparing strategies are performed as their treatment instead (20). Bladder-sparing chemoradiotherapy avoids the morbidity and mortality of radical surgery and allows for the preservation of the natural bladder, which is why it is preferred by some patients (23). However, RC with LND, with or without neoadjuvant CT, remains the primary treatment for patients with VH of BC presenting with localized MIBC (24). In a meta-analysis study of VH by Mori et al. (22) that evaluated the prognoses of BC patients undergoing RC, VH was associated with worse cancer-specific, overall, and relapse-free survival rates. Subgroup analyses demonstrated that micropapillary, plasmacytoid, and small-cell VH were associated with worse OS (22).

To date, there have been no randomized prospective studies on the strongest treatment method to choose for patients with variant MIBC. Krasnow et al. (25), in a study in which they administered TMT to 303 patients, 66 of whom had a variant, found 5- and 10-year disease specific survival rates of 75% and 67%, respectively, in papillary urothelial BC, versus 64% and 64% in VH of BC. The 5- and 10-year OS rates, meanwhile, were 61% and 42% in papillary urothelial BC versus 52% and 42% in the VH of BC. They concluded that the VH of BC responded to TMT, and there was no significant difference in oncological results compared with papillary urothelial BC (25). In a study using the National Cancer Database, Janopaul-Naylor et al. (23) reported the results of different treatments applied to patients with VH of MIBC, with TMT applied to 356 patients and RC applied to 2093 patients. They found that in a multivariate analysis, there was a trend toward worse OS with TMT compared with surgery (HR 1.15, 95% CI 1.00-1.33, p=0.052). Although there was a trend toward better OS with TMT in the first year of follow-up, there was worse OS with TMT after 1 year (23). In our study, we found that patients with MIBC who underwent TMT had worse survival rates than those who underwent immediate RC. We conclude that immediate RC should be recommended if applicable to these patients.

Study Limitations

We must note that our study had some limitations. One of the most important aspects was its retrospective and multicenter nature. Although the number of patients was high overall, there were not enough for specific subgroups. We also failed to perform survival analyses for the VH subgroups.

Conclusion

Although VH is one of the most important factors affecting survival in BC, urological centers still lack a standard treatment approach for affected patients, to be applied regardless of whether they have NMIBC or MIBC. Currently, the survival outcome of TMT is worse than those of other treatment modalities, which is concerning and calls for immediate research efforts to address this issue. Accordingly, prospective, randomized, multicenter studies on this subject are urgently needed.

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Ethics

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Informed Consent: Retrospective study.

Authorship Contributions

Concept: V.İ., M.D., Design: V.İ., M.D., Data Collection or Processing: V.İ., M.D., B.A., M.A., G.A., S.Ç., B.Ar., H.Ş., S.B., Analysis or Interpretation: V.İ., M.D., B.A., M.A., G.A., S.Ç., B.Ar., S.B., Literature Search: V.İ., M.D., Writing: V.İ., M.D., B.A., M.A., G.A., S.Ç., B.Ar., H.Ş., S.B.

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