Effects of Anemia on Overall Survival in Muscle Invasive Bladder Cancer

Aneminin Kas İnvaziv Mesane Kanserinde Genel Sağkalım Üzerine Etkisi

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Abstract

Objective: The aim of this study was to investigate the effect of preoperative anemia on overall survival in patients with muscle-invasive bladder cancer.

Methods: We retrospectively analyzed the medical data of patients with a diagnosis of muscle-invasive bladder cancer who underwent consecutive cystectomy. The patients were divided into two groups as those with and without anemia before the operation. These two groups were compared in terms of age, gender, smoking status, American Society of Anesthesiologists score, the history of neoadjuvant chemotherapy, pathological tumor (pT) stage, pathological node stage, number of lymph nodes removed, positive surgical margin, concomitant carcinoma *in situ* (CIS) presence, lymphovascular invasion, perineural invasion, history of adjuvant chemotherapy, overall survival, recurrence status, urinary diversion type, tumor multiplicity and grade.

Results: A statistically significant difference was found between the groups in terms of overall survival. There was no statistically significant difference between the groups in terms of other variables. Overall survival in group 1 was 61.8 months, and overall survival in group 2 was 32.6 months. Overall survival in all patients was 47.9 months. Five-year overall survival was 54% in group 1 and 20% in group 2.

Conclusion: We detected that the presence of preoperative anemia was associated with poor overall survival rates in patients with muscle-invasive bladder cancer. We consider that preoperative anemia and pT stage are variables that can be used to predict overall survival

Keywords: Anemia, bladder cancer, overall survival

Öz

Amaç: Bu çalışmanın amacı kasa invaziv mesane kanserli hastalarda preoperatif aneminin genel sağkalıma etkisini araştırmaktır.

Yöntem: Kas invaziv mesane kanseri tanısı olan ardışık sistektomi yapılan hastaların tıbbi verilerini geriye dönük olarak inceledik. Hastalar operasyon öncesi anemisi olanlar ve olmayanlar olarak iki gruba ayrıldı. Bu iki grup yaş, cinsiyet, sigara içme durumu, American Society of Anesthesiologists skoru, neoadjuvan kemoterapi öyküsü, patolojik tümör (pT) evresi, patolojik nod evresi, çıkarılan lenf nodu sayısı, cerrahi sınır, eşlik eden karsinoma *in situ* (CIS) varlığı, lenfovasküler invazyon, perinöral invazyon, adjuvan kemoterapi öyküsü, genel sağkalım, nüks durumu, üriner diversiyon tipi, tümör çokluğu ve derecesi açısından karşılaştırıldı.

Öz

Bulgular: Genel sağkalım açısından gruplar arasında istatistiksel olarak anlamlı fark bulundu. Diğer değişkenler açısından gruplar arasında istatistiksel olarak anlamlı fark yoktu. Grup 1'de genel sağkalım 61,8 ay ve grup 2'de genel sağkalım 32,6 ay idi. Tüm hastalarda genel sağkalım 47,9 aydı. Beş yıllık genel sağkalım grup 1'de %54 ve grup 2'de %20 idi.

Sonuç: Kasa invaziv mesane kanserli hastalarda preoperatif anemi varlığının kötü genel sağkalım oranları ile ilişkili olduğunu saptadık. Preoperatif anemi ve pT evresinin genel sağkalımı tahmin etmek için kullanılabilecek değişkenler olduğunu düşünüyoruz.

Anahtar Kelimeler: Anemi, mesane kanseri, genel sağkalım

Introduction

Bladder cancer is one of the most common systemic malignancies in the world. In terms of new cases and death rates, it ranks fourth and eighth, respectively, among all cancers in men[1]. In the European Union, the age-satandardised incidence rate is 20 for men and 4.6 for women[2,3]. At the time of diagnosis, 75% of bladder cancers are superficial bladder cancer, while 25% are muscle-invasive bladder cancer. The age-standardized mortality rate (per 100,000 person/years) in bladder cancer is 3.2 in men and 0.9 in women[4]. The radical cystectomy operation plays a very active role for treating patients with muscle-invasive bladder cancer. Although many factors are accused in the etiology of bladder cancer, the exact cause has not been fully revealed.

Anemia is defined as a decrease in erythrocyte mass or blood hemoglobin concentration. Anemia is a common hematological abnormality in cancer patients. The prevalence of preoperative anemia is between 25% and 75% in patients undergoing surgery for cancer[5]. The pathogenesis of preoperative anemia is multifactorial. The main factors affecting the pathogenesis are cancer invasion, chemicals secreted from cancer cells, renal dysfunction and chemotherapy treatment. It has been shown that anemia causes interactions between immune system tumor cells in many cancer patients[6]. Decreased erythrocyte lifespan, increased number of aggressive inflammatory cytokines, a number of erythroid progenitor cells and suppressed bone marrow are effective in this case[6].

It has been shown that preoperative anemia has negative effects on the course of many cancers[7,8]. The number of studies that investigated the effect of preoperative anemia on oncological outcomes of bladder cancer is very few in the literature. The current study investigates the effect of preoperative anemia on overall survival in patients with muscle-invasive bladder cancer.

Materials and Methods

This retrospective study was written in accordance with the 1964 Helsinki Declaration. We retrospectively analyzed the medical data of patients with a diagnosis of muscle-invasive bladder cancer who underwent consecutive cystectomy between the dates of March 2005 and July 2021 in our tertiary referral center hospital. In our study, patients who had cystectomy operation for reasons other than bladder cancer, who had non-transitional cell carcinoma pathology such as adenocarcinoma and squamous cell cancer, who had nephrectomy or nephroureterectomy operations in which other organs were resected together with cystectomy operation, patients who had a salvage cystectomy operation, patients who had blood transfusion in the preoperative period, and patients with missing data were excluded from the study. Additionally, those with chronic diseases such as diabetes, hypertension, hyperlipidemia, kidney disease, bleeding disorder, neurological disease, cardiovascular disease, psychiatric disease, malignancy other than bladder cancer, acute infectious disease, previously undergoing urinary system surgery, patients with a history of radiotherapy treatment, that are thought to affect survival, excluded from the study. Our study included 245 patients who had a cystectomy operation who met the inclusion criteria. The patients were divided into two groups as those with and without anemia before the operation. These two groups were compared in terms of age, gender, smoking status, American Society of Anesthesiologists score, the history of neoadjuvant chemotherapy, pathological tumor (pT) stage, pathological node stage, number of lymph nodes removed, positive surgical margin, concomitant carcinoma *in situ* (CIS) presence, lymphovascular invasion, perineural invasion, history of adjuvant chemotherapy, overall survival, recurrence status, urinary diversion type, tumor multiplicity and grade.

Preoperative anemia was determined as patients with hemoglobin value (Hb) <13 g/dL in men and <12 g/dL in

women, in line with the recommendations of the World Health Organization (WHO). Hemoglobin measurements were made the day before the operation day. Muscle invasive bladder cancer was determined according to the pathology result of transurethral resection bladder tumor operation. All cystectomy operations were performed using the open method. The urinary diversion technique was performed in the form of orthotopic bladder and ureterocutaneous ostomy, mostly with the ileal conduit. A detailed physical examination and abdomino-pelvic tomography (CT) for staging was performed before the cystectomy operation. Bone scintigraphy was requested for patients with suspected bone metastases. None of the patients had metastasis at the time of surgery. Lymph node dissection was performed to the iliac and obturator lymph nodes up to where the ureter crosses the common iliac vessel. TNM staging system was used for clinical staging. All pathological were examined by at least two experienced uropathologists. The 2004 WHO grading system was used for pathological grade. Follow-up after surgery was carried out at certain intervals in line with the recommendations of the guideline.
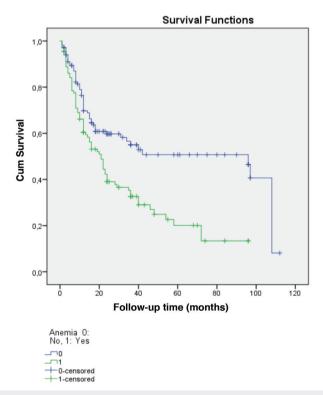
Statistical Analysis

The conformity of the variables to the normal distribution was tested with the Kolmogorov-Smirnov test. The relationship between two categorical variables was investigated using the chi-square test. Two independent means were compared with the Student's t-test or the Mann-Whitney U test. Overall survival was calculated using the Kaplan-Meier log-rank test. Univariate and Multivariate analysis was performed using survival cox regression analysis. The data analysis was performed using Statistical Package for the Social Science (SPSS Inc, Chicago, Illinois, USA) version 24.0 and a p-value of <0.05 was considered statistically significant.

Results

A total of 245 were included in the study. Group 1 was grouped as patients without preoperative anemia and group 2 as patients with preoperative anemia. There were 135 patients in group 1 and 110 patients in group 2. The mean age of the patients in group 1 was 65.1 years, and the mean age of the patients in group 2 was 65.5 years. The mean age of all the patients was 65.3 years. The male:female ratio of the patients included in the study was 90.6:9.3. Clinicopathological features and demographic data of the patients are shown in Table 1. The mean follow-up period of the patients was 25.4 months. There were 75 patients (55.4%) in group 1 with

pT3 and stage 4, and 63 patients (57.2%) in group 2 with pT3 and stage 4. The most preferred diversion technique in cystectomy operation was ileal conduit (93%). Seventy-five (55.5%) of 135 patients in group 1 and 35 (31.8%) of 110 patients in group 2 were alive. A statistically significant difference was found between the groups in terms of overall survival. There was no statistically significant difference between the groups in terms of other variables (Table 1). According to Kaplan-Meier analysis, overall survival in group 1 was 61.8 months, and overall survival in group 2 was 32.6 months. Overall survival in all patients was 47.9 months. The Kaplan-Meier analysis curve is shown in Figure 1. According to this curve, 5-year overall survival was 54% in group 1 and 20% in group 2. In the survival cox multivariate regression analysis, age [hazard ratio (HR): 65,536; p<0.001], presence of preoperative anemia (HR: 2,279, p=0.004) and pT stage (HR: 2,636, p<0.001) were statistically significant with overall survival. A significant correlation was found (Table 2).

Discussion

Figure 1. Kaplan-Meier overall survival curve for patients with and without anemia. Log-rank test was used to compare the curves

Table 1. Characteristic of patients in groups				
Variables	Group 1 (without anemia) (n=135)	Group 2 (with anemia) (n=110)	Total (n=245)	p-value
Age (years) (SD)	65.1 (9)	65.5 (9.6)	65.3 (9.3)	0.718
Gender (n, %)				
Male	121 (89.6)	101 (91.8)	222 (90.6)	0.561
Female	14 (10.3)	9 (8.1)	23 (9.3)	
Smoking (n, %)				
No	60 (44.4)	43 (39)	103 (42)	0.401
Yes	75 (55.5)	67 (60.9)	142 (57.9)	
ASA score (n, %)				
1	18 (13.3)	18 (16.3)	36 (14.6)	
2	74 (54.8)	56 (50.9)	130 (53)	0.673
3	42 (31.1)	35 (31.8)	77 (31.4)	
4	1 (0.7)	1 (0.9)	2 (0.8)	
Neoadjuvant chemotherapy (n, %)				
No	127 (94)	104 (94.5)	231 (94.2)	0.875
Yes	8 (5.9)	6 (5.4)	14 (5.7)	
pT stage (n, %)				
pT1	18 (13.3)	12 (10.9)	30 (12.2)	
pT2	42 (31.1)	35 (31.8)	77 (31.4)	0.856
pT3	49 (36.2)	44 (40)	93 (37.9)	
pT4	26 (19.2)	19 (17.2)	45 (18.3)	
pN stage (n, %)				
pN0	96 (71.1)	74 (67.2)	170 (69.3)	
pN1	24 (17.7)	17 (15.4)	41 (16.7)	0.220
pN2	15 (11.1)	17 (15.4)	32 (13)	
pN3	0 (0)	2 (1.8)	2 (0.8)	
Lymph nodes removed (n) (SD)	13.6 (7.4)	12.9 (7.1)	13.3 (7.3)	0.435
Positive surgical margin (n, %)				
Negative	121 (89.6)	93 (84.5)	214 (87.3)	0.236
Positive	14 (10.3)	17 (15.4)	31 (12.6)	
Concomitant CIS (n, %)				
No	64 (47.4)	53 (48.1)	117 (47.7)	0.973
Yes	71 (52.5)	57 (51.8)	128 (52.2)	
Lymphovascular invasion (n, %)				
No	64 (47.4)	53 (48.1)	117 (47.7)	0.904
Yes	71 (52.5)	57 (51.8)	128 (52.2)	
Perineural invasion (n, %)				
No	77 (57)	53 (48.1)	130 (53)	0.135
Yes	58 (42.9)	57 (51.8)	114 (46.5)	
Adjuvant chemotherapy (n, %)				
No	106 (78.5)	85 (77.2)	191 (77.9)	0.816
Yes	29 (21.4)	25 (22.7)	54 (22)	

Table 1. contiuned				
Variables	Group 1 (without anemia) (n=135)	Group 2 (with anemia) (n=110)	Total (n=245)	p-value
Overall survival (n, %)				
Alive	75 (55.5)	35 (31.8)	110 (44.8)	<0.001
Death	60 (44.4)	75 (68.1)	135 (55.1)	
Follow-up time, months (n) (SD)	28 (29)	22.3 (21.2)	25.4 (25.9)	0.085
Recurrence (n, %)				
None	104 (77)	75 (68.1)	179 (73)	0.229
Local	11 (8.1)	14 (12.7)	25 (10.2)	
Metastatic	20 (14.8)	21 (19)	41 (16.7)	
Type of urinary diversion (n, %)				
Ileal	127 (94)	101 (91.8)	228 (93)	0.395
Orthotopic	2 (1.4)	1 (0.9)	3 (1.2)	
Ureterocutaneostomy	6 (4.4)	8 (7.2)	14 (5.7)	
Multiplicity (n, %)				
Single	62 (45.9)	53 (48.1)	115 (46.9)	0.675
Multiple	73 (54)	57 (51.8)	130 (53)	
Grade (n, %)				
High	130 (96.2)	105 (95.4)	235 (95.9)	0.335
Low	5 (3.7)	5 (4.5)	10 (4)	
ASA: American Society of Anesthesiologists, pT: Pathological tumor, pN: Pathological node, CIS: Carcinoma *in situ*, OS: Overall survival, SD: Standard deviation				

Table 2. Multivariate analyses of variables		
Variables	Multivariate analysis	
	HR (95% CI)	p-value
Age	65.536 (63.01-63.8)	<0.001
Smoking	0.609 (0.876-1.753)	0.543
Anemia	2.279 (1.087-3.629)	0.004
pT stage	2.636 (1.027-1.506)	<0.001
pN stage	0.518 (1.316-1.984)	0.368
Positive surgical margin	1.67 (0.98-1.94)	0.143
Concomittant CIS	0.231 (0.045-0.734)	0.934
Lymphovascular invasion	1.231 (1.002-2.150)	0.105
Lymphovascular invasion	0.98 (0.76-1.09)	0.465
Grade	0.56 (0.23-0.96)	0.219
Lymph nodes removed	0.790 (0.672-0.808)	0.427
pT: Pathological tumor, pN: Pathological node, HR: Hazard ratio, CI: Confidence interval, CIS: Carcinoma *in situ*		

We retrospectively evaluated the preoperative Hb levels of muscle invasive bladder cancer patients. We determined that the patients with preoperative anemia have worse overall survival compared with the patients without anemia. The variables to predicting overall survival after cystectomy, were the presence of preoperative anemia and pT stage.

In their meta-analysis of 3815 patients, including 12 studies, Luo et al.[9], found that preoperative anemia was associated with poor progression free survival and overall survival the patients with urothelial carcinoma. The pathway between anemia and cancer-related death is not been fully enlightened. Anemia causes hypoxia in cancer tissues and leads to the modification of hypoxia-induced genes such as VEGF, p53, HIF 1. These modifications lead to chronic inflammation, progression of the disease and cancer-related death[10,11]. Additionally, studies have shown that increased VEGF level induces angiogenesis and *p53* gene activation suppresses apoptosis in the hypoxic microenvironment of tumor cells of patients with preoperative anemia[12]. Cancer related anemia is caused by many factors such as functional

iron deficiency, involvement of bone marrow by the tumor cells, erythropoietin deficiency due to renal dysfunction. Increased inflammatory cytokine overexpression in cancer patients suppresses erythroid progenitor cells and contributes the development of preoperative anemia in cancer patients[9,13].

Cystectomy is the gold-standard therapy in patients with muscle-invasive bladder tumor. Morgan et al.[14] detected a statistically significant relationship between preoperative blood transfusion rates and post-cystectomy mortality in their study with 777 patients with an average follow-up of 25 months. In a multicenter study involving 684 patients, it was concluded that the presence of preoperative anemia in patients who underwent radical cystectomy was associated with poor oncologic outcomes[15]. In a meta-analysis including 17 studies, Xia and Guzzo[16] reported that the presence of anemia before cystectomy was associated with earlier recurrence and shorter survival in bladder cancer patients. In our study, we compared the survival of patients with muscle-invasive bladder cancer with and without anemia before cystectomy. Consistent with the literature, we showed that patients with anemia had lower overall survival rates than those without anemia. It has been demonstrated that preoperative anemia is associated with poor clinical outcomes in cardiac and non-cardiac surgeries. In their retrospective study involving 500,000 patients, Saager et al.[17] reported that preoperative anemia was a predictor of postoperative mortality. Similarly, Wu et al.[18] found that the presence of preoperative anemia in patients over 65 years of age, was associated with 30-day postoperative mortality and cardiac events.

Pagano et al.[19] reported the 5-year overall survival as 31% in patients with pT3 stage and 21% in patients with pT4 stage. In our study, pT stage is associated with survival in consistent with the literature.

Study Limitations

Our study has some limitations as being a single-centered retrospective study and the small number of patients. The patients had preoperative hematuria, but the degree of hematuria and anemia are not clarified. Another limitation is that the postoperative complications are not evaluated.

Conclusion

In our study, we detected that the presence of preoperative anemia was associated with poor overall survival rates in patients with muscle-invasive bladder cancer. We consider

that preoperative anemia and pT stage are variables that can be used to predict overall survival. The results of our study are compatible with the literature. Multicenter, prospective studies with larger patient series are needed to clarify this issue.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital Ethics Committee (decision no: 20201/10-26, date: 15.10.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.E.Y., Design: E.E.Y., Data Collection or Processing: E.E.Y., M.C.K., Analysis or Interpretation: E.E.Y., M.Z.K., Critical Revision: E.E.Y., S.D.S., Statistical Analysis: U.M., M.Y.Y., M.Y., Supervision: Y.Ö.İ.

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

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