The Rate of Neoadjuvant Chemotherapy Use in Muscle Invasive Bladder Cancer and The Approach of Urologists in Turkey

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Purpose: To investigate the proportion of neoadjuvant chemotherapy (NAC) use in patients with muscle invasive bladder cancer before radical cystectomy and the approach of urologists to this subject.

Materials and Methods: We invited 242 urologists during the 12th International Urooncology Congress in Turkey to answer a self-administered questionnaire. The questionnaire included questions related to radical cystectomy, lymph node dissection and neoadjuvant chemotherapy that had been performed in patients with muscle invasive bladder cancer by the urologist.

Results: The median number of radical cystectomy operations was 20 per year. 122 (50.5 %) of 242 urologists had used neoadjuvant chemotherapy for the treatment of muscle invasive bladder cancer before radical cystectomy. The mean rate of neoadjuvant chemotherapy use by these urologists (n=122) was 28.46 %. The most common reasons for not using neoadjuvant chemotherapy by urologists in Turkey were as follows: (i) neoadjuvant chemotherapy might lead to a decrease in the cure rate of radical cystectomy due to delayed surgery (ii) complication rate of radical cystectomy might be elevated and the surgery might be complicated by NAC use.

Conclusion: Although the European Association of Urology (EAU) guidelines panel on muscle invasive bladder cancer recommends using NAC in T2-T4a bladder, the rate of neoadjuvant chemotherapy use was still found to be low in our country because urologists have concerns about adverse effects NAC on radical cystectomy.

Keywords: bladder cancer; chemotherapy; neoadjuvant treatment

INTRODUCTION

Bladder cancer (BC) is a worldwide problem, as being the fourth most common cancer in men and the eighth one in women and 80% of all BC patients are males [(1)]. Worldwide estimates suggest that approximately 330,000 cases are diagnosed with BC each year, and 123,000 patients will die due to this cancer[(2)]. The most common histological types of BCs are transitional cell or urothelial carcinoma, constituting 90% of all BCs and 30% of these casesmare muscle invasive bladder cancer (MIBC) at the time of initial diagnosis. Radical cystectomy (RC) and pelvic lymph node dissection are considered to be the gold standard treatment for MIBC [(3)]. Although this treatment may be curative, a large proportion of the patients will harbor micrometastatic disease, contributing to recurrence rates of up to 40% at 5 years[(4)]. An early study of Southwest Oncology Group demonstrated that radiotherapy before RC did not change the results[(5)]. Therefore systemic chemotherapy has been investigated as a treatment option in both neoadjuvant and adjuvant settings since the 1980s. Although the data supporting adjuvant chemotherapy are insufficient, neoadjuvant chemotherapy (NAC) that includes cisplatin-based combination therapy is recommended for MIBC by the guidelines for muscle invasive and metastatic bladder cancer of the European Association of Urology[(6)]. Although according to the American National Cancer Database records, only 1.2 % of patients with MIBC received neoadjuvant chemotherapy between 1998 and 2003[(7)], this rate was reported as 12 % by Feifer et al. in 2011[(8)]. Despite the recommendation of NAC use in MIBC and the outcomes of randomized trials, the rate of patients receiving NAC has increased only quite a little[(6)]. The aim of the present study was to investigate the rate of NAC use in patients with MIBC before radical cystectomy and the approach of urologists to this subject in Turkey.

MATERIALS AND METHODS

Three hundred and ten urologists, who participated in 12th International Urooncology Congress (total number of participants was about 750) between 18th and 22nd of November 2015 in Antalya-Turkey, filled out a self-administered questionnaire. Two hundred and forty two of the 310 participants who were working in Turkey were enrolled in the study. 68 urologists were excluded from the study either because they did not perform radical cystectomy in their clinics or did not completely fill in the questionnaire form. The study questionnaire was developed by the study team and consisted of three parts as follows:[(1)] socio-demographic data;[(2)] five questions about how the urologists performed radical cystectomy procedure in their clinics;[(3)] four questions about their preference for NAC use for the treatment of MIBC. If they

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Table 1. Demographic data of urologists in the study

Age (years)	N	%
20-30	38	15.7
31-40	66	27.2
41-50	76	31.5
51-60	45	18.6
> 60	17	7.0
Degree		
Urology specialists	55	22.7
Assistant Professor	32	13.2
Associated Professor	68	28.1
Professor	87	36.0
Institution		
University	153	63.2
Training and research hospital	68	28.1
Private hospital	21	8.7

answered that they did not choose to give NAC then they were asked why they did not prefer to use it. Statistical analysis was performed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA). The demographic data and responses to the questions were statistically evaluated. The participants were divided into two groups according to whether they used NAC or not and into three groups according to their responses (yes, no or I do not know) to the question "Do medical oncologists recommend NAC in your hospital?" The groups were statistically compared by using the Chi-square test. Statistical significance was considered at $P < .05$.

RESULTS

Two hundred and forty two of the 310 participants were enrolled in the study. 68 urologists (21.9%) were excluded from the study either because they did not perform radical cystectomy in their clinics or did not completely fill in the questionnaire form. The demographic data of urologists in this study is presented in **Table 1**. The median number of radical cystectomy operations was 20 (2-200) per year. All the participants performed lymph node dissection during radical cystoprostatectomy. The rate of lymph node dissection during radical cystectomy was 100 %. The mean rate of extended lymph node dissection was 65.05 ± 3.64 (0-100). 122 of 242 urologists performed NAC before radical cystectomy for the treatment of MIBC. The mean rate of NAC use was 28.46 % ± 24.39 % (5-100%). 120 urologists, who did not use NAC were asked, why they did not use NAC. The distribution of responses to this question is summarized in **Table 2**. The responses to two questions about their urooncologic council and medical oncologists' approach in their hospital are summarized in **Table 3**. Logistic regression was used to assess the effect of potentially relevant factors on the NAC use. We found that the participants who worked with medical oncologist that recommended NAC used NAC 3.24 (2.19 - 4.79) times more than other participants.

DISCUSSION

The risk of recurrence following RC for the treatment of MIBC is high and correlates with pathologic staging[9]. Although RC is gold standard, it provides 5-year survival only in approximately 50 % of patients[6]. Despite this gold standard treatment, patients with MIBC face a 50% chance of recurrence[10]. Some authors suggested that the predominant cause of this high recurrence rate was occult micro-metastases present at the time of RC[1]. NAC has been investigated for last three decades for their effect in MIBC. There are many advantages of NAC for the patients with MIBC, including: (1) chemotherapy is delivered at the earliest time-point and allows for earlier exposure of micro-metastatic cells to chemotherapeutic agents;[2] we can determine the chemosensitivity of tumor cells in vivo; and[3] patient compliance and tolerability are better before RC than after it[6]. The most recent meta-analysis with updated results from 11 randomized trials (n = 3005) detected a significant survival benefit associated with platinum based combination chemotherapy for the treatment of MIBC before RC[11]. The results of this meta-analysis showed a 5 % absolute improvement in survival at 5 years. Similarly, the Nordic combined trial showed an 8 % absolute improvement

Table 2. Responses to the question "why not do you use neoadjuvant chemotherapy before radical cystectomy for the treatment of muscle invasive bladder cancer".

No	Responses to the question	N	%
1	It may decrease the chance of cure because of delayed RC	21	17.5
2	It may complicate RC and increase the complications of surgery	21	17.5
3	Adjuvant chemotherapy is more effective than neoadjuvant	12	10
4	I do not believe in the effectiveness of neoadjuvant chemotherapy	7	5.8
5	1+2	35	29.2
6	1+3	5	4.1
7	1+4	5	4.1
8	Others	14	11.8
Total		120	100

Abbreviation: RC, Radical cystectomy

Table 3. The comparison of the responses to the two questions about their urooncologic council and aspect of medical oncologists in their hospital.

		Do you use neoadjuvant chemotherapy?			
		N (%)			***P* value**
		Yes	No	Total	
Does an urooncology council regularly meet in your hospital? N (%)	Yes	91 (74.5)	79 (64.7)	170 (70.2)	
	No	31 (25.5)	41 (35.3)	72 (29.8)	0.51
	Total	122 (100)	120 (100)	242 (100)	
Do medical oncologists recommend neoadjuvant chemotherapy before radical cystectomy in your hospital? N (%)	Yes	104 (85.2)	42 (34.4)	146 (60.4)	< 0.001
	No	3 (2.4)	45 (36.8)	48 (19.8)	
	I do not know1	5 (12.4)	33 (28.8)	48 (19,8)	
	Total	122 (100)	120 (100)	242 (100)	

in survival at 5 years and 11 % in the cT3 disease[3]. The largest randomized trial with a median follow–up of 8 years confirmed these results. This trial showed that NAC (cisplatinum, metotrexate and vinblastine) increased the 10 years survival rate from 30% to 36%[12]. Despite these benefits of platinum based NAC, most urologists still do not use it before surgery[8]. Actually use of NAC has been rising in the last decades globally, but it still remains underutilized. In a retrospective study, Krabbe LA et al. reported that the usage of cisplatin-based NAC increased from 17% to 35% between 2008 and 2012[13]. In a larger data set from National Cancer Database in USA, it was reported that use of NAC in MIBC increased from 13% in 2007 to 21% in 2010[14]. In our study, the mean rate of NAC administration by urologists was found to be 28.4%. This result is higher than the rates reported in the older studies[7,8], but it is similar to some contemporary series[13,14]. We do not have any historical data for use of NAC in our county. Therefore we could not compare our result with any historical Turkish series. In this study we found a good rate for NAC in MIBC but this rate is still low. The two most common reasons that urologists claim for not using NAC are as follows: (i) it may decrease the chance of cure because of delayed RC and (ii) it may complicate RC and increase the complications of surgery. 72.4% of the urologists participating in this study chose one of these two responses to the question "Why don't you use NAC ? ". In fact, the results of the combined Nordic trial responded to the concern of urologists regarding the adverse effect of NAC on RC[3]. The results showed that NAC did not have any major influence on the percentage of performable RC. The cystectomy frequency in all patients allocated to the NAC arm was 86% and in the control arm was 87%. Three studies that investigated the effect of NAC on perioperative mortality and morbidity were published in 2014[15-17]. The findings of these studies showed that NAC was not associated with an increase in perioperative complications or death. The other most common concern of urologists in our study was that it might decrease the chance of cure because of delayed RC. European Association of Urology guidelines on muscle-invasive and metastatic bladder cancer reported a significant survival benefit of NAC for the treatment of MIBC and recommend it for T2-4a, N0M0 bladder cancer. Delayed RC may influence only patients, who are not sensitive to chemotherapy. However, there are no studies, which show that delayed RC due to NAC, can have a negative impact on survival[6]. Therefore, the fears of urologists, who did not use NAC before RC are unwarranted in fact. The main problem regarding the use of NAC is actually risk of overtreatment. However, none of the urologists in our study mentioned this as a concern for not using NAC. Bimanual palpation, computerized tomography and magnetic resonance imaging are often used for diagnosis of bladder cancer. Clinical staging using these modalities may result in both over and under-staging and lead to a staging accuracy of only 70%[18,19]. Thus, overtreatment or undertreatment is possible for some cases. In the present study, we also assessed the effects of medical oncologists and regular meetings of multidisciplinary urooncologic council on the preference of urologists with regard to NAC use. There was no significant relationship between the preferences of urologists and regular meetings of multidisciplinary urooncologic council, on the other hand there was a significant relationship between the preference of urologists and the recommendation of medical oncologists (**Table 3**). The recommendations of medical oncologists that worked in the same hospital with urologists who preferred to use NAC and who did not, were 85.2% and 34.4%, respectively ($P < .001$). Also the results of logistic regression indicated that the NAC use frequency of participants who worked with medical oncologist who recommended NAC was 3.24 (2.19 - 4.79) fold higher than those who did not. This result shows that recommendation of medical oncologists plays an important role in the preference of urologists regarding NAC. A limitation of our study was that the rate of NAC use was only determined according to the written statement of urologists. If this rate was calculated with data obtained from hospital archives, the results could be more reliable.

CONCLUSIONS

The findings of our study shows that the rate of NAC use before RC in our country was low despite the strong recommendations of urology guidelines. The reasons for the reluctance to use NAC are found to be concerns about: A) the fear that NAC may decrease the chance of cure due to delayed RC and B) increase in surgical mortality and morbidity. There are many evidences showing that NAC does not lead to these situations in the literature. We suggest that it should be emphasized that these concerns about NAC are un-

warranted and the recommendations of the current guidelines by urology associations should be reminded in congresses or via internet. In addition, we recommend that urologists and medical oncologists should be working in collaboration for the treatment of MIBC.

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