Research Article

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The influence of anesthesia type on recurrence of the non-muscle invasive bladder tumor according to risk groups: 3 year follow up

Risk gruplarına göre non-muscle invaziv mesane tümörünün nüksüne anestezi türünün etkisi: 3 yıllık takip

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Abstract

Purpose: Many risk factors affecting bladder cancer recurrence, such as genetic and environmental factors, have been previously identified. It has been stated that risk factors that cause immunosuppression play a role in the spread of cancer cells. Anesthetic agent, which is a perioperative factor, may affect the risk of cancer recurrence by disrupting the immune system. The aim of this study was to compare the effect of regional anesthesia (RA) and general anesthesia (GA) on non-muscle invasive bladder cancers (NMIBC) recurrence.

Materials and methods: A total of one hundred seventy-eight patients who underwent transurethral bladder tumor resection (TURBT) for NMIBC and underwent surgery under GA or RA between 2011 and 2016 in the urology departments of Pamukkale University and Uludag University were included in the study. In the first group, 80 patients had RA. In the second group, 98 patients underwent GA during TURBT for NMIBC.

Results: The recurrence time was shorter in the GA group (5.5 months) than in the RA group (11 months) (p=0.015). First-year relapse was higher in the GA group than in the RA group (p=0.048), but there was no difference in third-year relapse between groups (p=0.810). The mean recurrence time was 11 months (95% CI; 9.058-12.942) in the RA group and 5 months (95% CI; 2.090-7.910) in the GA group (p=0.031).

Conclusion: During transurethral resection of the bladder tumor, an increase in the recurrence time was observed in patients with intermediate-risk NMIBC who received RA compared to patients who received GA. RA provided a 7-month benefit in relapse delay.

Keywords: Bladder cancer, bladder tumor, regional anesthesia, general anesthesia.

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Öz

Amaç: Mesane kanseri nüksünü etkileyen genetik ve çevresel faktörler gibi birçok risk faktörü önceden belirlenmiştir. İmmünsüpresyon yaratan risk faktörlerinin, kanser hücrelerinin yayılmasında rol oynadığı belirtilmiştir. Perioperatif bir faktör olan anestezik ajan, bağışıklık sistemini bozarak kanser nüksü riskini etkileyebilir. Bu çalışmanın amacı, bölgesel anestezi (BA) ve genel anestezi (GA) etkilerini özellikle kas invaziv olmayan mesane kanseri (KİOMK) nüksü üzerinde karşılaştırmaktır.

Gereç ve yöntem: Pamukkale Üniversitesi ve Uludağ Üniversitesi Üroloji bölümlerinde 2011-2016 yılları arasında KİOMK için transüretral mesane tümör rezeksiyonu (TURM) geçiren toplamda 178 hasta çalışmaya dahil edildi. Birinci grupta 80 hasta BA aldı. İkinci grupta ise 98 hasta KİOMK için TURM sırasında GA aldı.

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Bulgular: Nüks süresi GA grubunda (5,5 ay) BA grubundan (11 ay) daha kısa idi (p=0,015). İlk yıl nüks, GA grubunda BA grubuna göre daha yüksekti (p=0,048), ancak gruplar arasında üçüncü yıl nüksünde farklılık yoktu (p=0,810). Ortalama nüks süresi BA grubunda 11 ay (%95 CI; 9,058-12,942) ve GA grubunda 5 ay (%95 CI; 2,090-7,910) idi (p=0,031).
Sonuç: Mesane tümörünün transüretral rezeksiyonu sırasında BA alan orta riskli KİOMK hastalarında GA alan hastalara göre nüks süresinde artış gözlendi. BA, nüks gecikmesinde 7 aylık bir fayda sağladı.

Anahtar kelimeler: Mesane kanseri, mesane tümörü, bölgesel anestezi, genel anestezi.

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Introduction

Bladder cancer (BC) is the ninth most common cancer in the world [1]. In total, 70% of bladder cancers are non-muscle invasive bladder cancers (NMIBCs) at the time of diagnosis and are treated with transurethral bladder tumor resection (TURBT) as primary treatment [2]. Many risk factors, such as genetics and environmental determinants, that affect bladder cancer recurrence, have been previously described. However, a limited number of studies focusing on the relation between perioperative factors and NMIBC recurrences were found in the literature [3]. The anesthetic agent, a perioperative factor, may have an influence on the risk of cancer recurrence, which could have a wide-ranging impact on progression by disrupting the balance of cancer immune editing [4].

In recent years, risk factors leading to immunosuppression have been described, and these factors play a role in spreading cancer cells. It has been reported that opioids used in RA have less immunosuppression and fewer negative effects on anti-cancer cells [3, 5]. Similar results have been reported for better oncological outcomes of RA in a meta-analysis [6]. However, the impact of anesthesia type on NMIBC recurrence has not been widely evaluated.

The European Organization for Research and Treatment of Cancer's (EORTC) Genito-Urinary Cancer Group developed a scoring system to predict the risks of disease recurrence [7]. The risk groups differ from each other in accordance with oncological behaviors. Analyzing the recurrence according to the EORTC risk group could prevent the effect of risk groups on the anesthesia type. To the best of our knowledge, there is only one study investigating the effect of anesthesia type on NMIBC recurrence rates with regard to EORTC risk groups [8].

In our study, we hypothesized that regional anesthesia (RA) decreased the recurrence of NMIBC compared to general anesthesia (GA) after TURBT. The aim of this study was to compare the effect of RA and GA on the recurrence of NMIBC in different EORTC risk groups.

Materials and methods

Data source and selection criteria

This retrospective study was approved by the Pamukkale University Non-Interventional Clinical Research Ethics Committee. (Board meeting dated 27.11.2018 and numbered 22). Six hundred and twenty-six patients who had undergone TURBT for NMIBC between 2011 and 2016 in the urology department of the Pamukkale University and Uludag University under GA or RA were evaluated. The patients' medical data were obtained from the electronic health record system. Patients operated on BC previously, those with failed RA, incomplete TURBT, those lost to follow-up or with incomplete data, those with benign pathology or patients with clinical stages 3, 4, or pathological stage 2 cancer, and those with synchronous tumors were excluded (Table 1). In total, one hundred and seventy-eight patients were included in the study. In the first group (Group RA), 80 patients had undergone RA. In the second group (Group GA), 98 patients had undergone GA during TURBT for NMIBC.

Table 1. Exclusion criteria

	General anesthesia	Exclusion criteria	Regional anesthesia
Total	360		266
Excluded n	13	Loss on Follow up	9
	9	Failed RA	6
	49	Clinical stage 3, 4	35
	67	Incomplete TURBT	58
	26	Incomplete data	22
	44	Muscle invasive tumor	18
	31	Reoperation	22
	23	Other tumor or surgery	16
Included n	98		80

RA: regional anesthesia, TURBT: transurethral bladder tumor resection

Demographic information including the American Society of Anesthesiologists (ASA), age, sex, tumor characteristics (e.g., tumor number, size, and pathological characteristics), and intravesical Bacillus Calmette-Guérin (BCG) treatment were collected. The EORTC Genito-Urinary Cancers Group risk table was used as risk categorization to stratify into low, intermediate, or high risks to ignore the heterogeneity. Installation of BCG or mitomycin into the urinary bladder was recorded. The cystoscopic evaluation was performed once every three months during the first and second years, and once every six months in the third year unless recurrence developed. All recurrences were histologically verified with cystoscopy.

Anesthesia techniques

All of the enrolled patients had undergone TURBT under GA or RA. The type of anesthesia administered to the patient was determined according to the preference of the anesthesiologist, depending on the clinical condition of the patient. Administration of GA included propofol (2-3 mg/kg) and 0.5 mcg/kg/min remifentanil infusion for induction and rocuronium (0.5-0.6 mg/kg) for muscle relaxation. GA was performed with 50% oxygen, 50% air, and sevoflurane (1-3 vol%). We had no painful procedure; hence, analgesics or opioids were not used intraoperatively. However, 30 mg intravenous ketorolac was administered for postoperative pain when necessary. For RA, spinal anesthesia (SA) was applied, and 10-12 mg of 0.5% heavy bupivacaine was used. The patient was sedated with midazolam (2-5 mg) intravenously.

The time of the first recurrence was noted. The rates of recurrence during the 1st, 2nd, and 3rd years were compared.

Statistical methods

SPSS version 22 (IBM Corp, Armonk, NY, USA) was used to perform all statistical analyses. The Shapiro-Wilk test was used to assess the normality of the continuous variables. The normally distributed continuous variables were analyzed using the Student's t-test, and the non-normally distributed continuous variables were analyzed using the Mann-Whitney U-test. The nominal data were assessed by the chi-square test. The Kaplan–Meier analysis was used to estimate the recurrence curves after TURBT. The log-rank test was performed to provide a statistical comparison between the groups. A p value of <0.05 was considered statistically significant.

Results

The median age of the patients was 72.5 years in the RA group and 70 years in the GA group. The mean follow-up time was 36.7 (±4.23) months in the RA group and 37.15 (±5.97) months in the GA group (p=0.56). The clinical demographic characteristics of the groups are presented in Table 2. No differences were observed in any parameters between the groups except for tumor stage. Tumor stage T1 was more prevalent in the GA group than in the RA group (42.9% vs. 22.5%, respectively; p=0.004). Hospital stays and operation times were similar between the groups. No patient received blood transfusions during the perioperative period.

Table 2. The clinical and demographic characteristics of the groups

		Group RA n=80	Group GA n=98	*p* value
Age (years) Median (min- max)		72.5 (38-93)	70.0 (32-87)	0.179♦
BMI (kg/m²) (Mean±SD)		27.03±3.73	27.67±5.65	0.383◊
Hospital stay (days) (Mean±SD)		4.34±0.65	4.48±0.63	0.143◊
Operation time (minutes) (Mean±SD)		52.25±8.42	54.78±9.87	0.067◊
ASA physical status	ASA 1 n (%)	16 (20)	10 (10.2)	0.109¥
	ASA 2 n (%)	53 (66.3)	78 (79.6)	
	ASA 3 n (%)	11 (13.8)	10 (10.2)	
Gender	Female n (%)	7 (8.8)	14 (14.3)	0.255¥
	Male n (%)	73 (91.2)	84 (85.7)	
Smoking	No n (%)	47 (59.5)	62 (63.3)	0.608¥
	Yes n (%)	32 (40.5)	36 (36.7)	
Alcohol use	No n (%)	78 (97.5)	96 (98.0)	1.000#
	Yes n (%)	2 (2.5)	2 (2.0)	
Diabetes mellitus comorbidity	No n (%)	65 (81.2)	75 (76.5)	0.445¥
	Yes n (%)	15 (18.8)	23 (23.5)	
Hypertension comorbidity	No n (%)	32 (40.0)	51 (52.0)	0.109¥
	Yes n (%)	48 (60.0)	47 (48.0)	
Heart disease comorbidity	No n (%)	45 (56.3)	62 (63.3)	0.342¥
	Yes n (%)	35 (43.7)	36 (36.7)	
Tumor size	<3 cm n (%)	32 (40.0)	48 (49.0)	0.148¥
	>3 cm n (%)	48 (60.0)	50 (51.0)	
Tumor number	Single n (%)	38 (47.5)	59 (60.2)	0.062¥
	Multiple n (%)	42 (52.5)	39 (38.8)	
Tumor grade	Low grade n (%)	55 (68.8)	64 (65.3)	0.373¥
	High grade n (%)	25 (31.3)	34 (34.7)	
Tumor stage	Ta n (%)	62 (77.5)	56 (57.1)	0.004*¥
	T1 n (%)	18 (22.5)	42 (42.9)	
Post-operative early Mitomycin-C application	No n (%)	65 (81.2)	85 (86.7)	0.317¥
	Yes n (%)	15 (18.8)	13 (13.3)	
Risk category	Low-risk tumours n (%)	10 (12.5)	22 (22.5)	0.161¥
	Intermediate-risk tumours n (%)	13 (13.7)	16 (16.3)	
	High-risk tumours n (%)	59 (73.8)	60 (61.2)	
Carcinoma in situ	No n (%)	72 (90.0)	94 (95.9)	0.117¥
	Yes n (%)	8 (10.0)	4 (4.1)	

♦ Mann-Whitney U test, ◊ Student t test, ¥ Chi-square test, # Fisher's exact test, *: p<0.05 statistically significant
ASA: American Society of Anesthesiologists, GA: general anesthesia, RA: regional anesthesia

The recurrence time was shorter in the GA group (5.5 months) than in the RA group (11 months) (p=0.015). While the recurrence rate in the first year was higher in the GA group compared to the RA group (p=0.048), there was no difference in the third-year recurrence rate between the groups (p=0.810) (Table 3).

The median recurrence time was 11 months (95% CI; 9.058-12.942) in the RA group and 5 months (95% CI; 2.090-7.910) in the GA group (p=0.031).

The results regarding the effect of the EORTC risk category on recurrence were as follows: an earlier recurrence time was observed in high-risk tumors than in low- and intermediate-risk tumors (p=0.010 and p=0.002, respectively). There was no difference between low-risk and intermediate-risk tumors (p=0.460).

The recurrence times according to the risk categories are displayed in Table 4. There was a significant difference between the groups regarding recurrence times, regardless of the risk category (p=0.008). The recurrence times according to the risk categories of the groups are given in Table 5. The recurrence times were similar in low-risk tumors (p=0.489). The recurrence time was significantly longer in the RA group than in the GA group for intermediate-risk tumors (17 and 10 months, respectively; p=0.028). The recurrence time was longer in the RA group than in the GA group for high-risk tumors (9 and 4 months, respectively; p=0.057).

Table 3. Recurrence properties of groups

		Group SA (Spinal Anesthesia) n=80	**Group GA (General Anesthesia) n=98**	***p* value**
Recurrence time (months) Median (Min.- Max.)		11.0 (1-36)	5.5 (1-36)	0.015*♦
1th Year Recurrence	No n (%)	36 (45.0)	30 (30.6)	0.048*¥
	Yes n (%)	44 (55.0)	68 (69.4)	
3th Year Recurrence	No n (%)	13 (36.1)	10 (33.3)	0.810¥
	Yes n (%)	23 (63.9)	20 (66.7)	

♦ Mann-Whitney U test, ¥ Chi-square test, *: p<0.05 statistically significant

Tablo 4. Recurrence properties of risk group stratification

Risk group stratification	**Median time (months)**	**95% Confidence Interval**	
		Lower Bound	**Upper Bound**
Low-risk tumours	13.0	8.574	17.426
Intermediate-risk tumours	12.0	9.819	14.181
High-risk tumours	5.0	3.666	6.334

♦ The Kaplan–Meier analysis

Tablo 5. Recurrence times according to the risk categories of the groups

Risk group stratification		Median time (months)	95% Confidence Interval		*p* value
			Lower Bound	Upper Bound	
Low-risk tumours	Group RA	14.0	10.901	17.099	0.489
	Group GA	9.0	0.956	17.044	
Intermediate-risk tumours	Group RA	17.0	16.740	30.351	0.028*
	Group GA	10.0	8.055	11.945	
High-risk tumours	Group RA	9.0	4.489	13.511	0.057
	Group GA	4.0	2.741	5.259	

♦ The log-rank test ,RA: regional anesthesia, GA: general anesthesia, *: $p<0.05$ statistically significant

Discussion

In the current study, we investigated the relationship between the anesthesia type and NMIBC postoperative recurrence. We found that the recurrence time was longer in the RA group than in the GA group. Many mechanisms have been defined to explain the potential benefit of RA on tumor recurrence. It was reported that RA decreased factor-1 production, resulting in reduced cancer cell proliferation; however, volatile anesthetic agents induced factor-1 production [9]. Wada et al. [10] stated that epidural anesthesia increased the phagocytic function of monocytes during total hip arthroplasty surgery; however, GA decreased this function. Ahlers et al. [11] reported that RA reduced stress and decreased immunosuppression by activating the hypothalamic-pituitary-adrenal system, which reduced the activities of NK cells, T cells, and macrophages. In accordance with the mentioned studies, a recent in vitro study showed that lidocaine and ropivacaine used for RA inhibited the proliferation of gastric cancer cells [12].

Angiogenesis plays an essential role in tumor growth and metastasis [13]. Angiogenic factors are found in NMIBC [14]. Several researchers have agreed that the use of opioids increases pro-angiogenic effects [3, 15-17]. GA induces angiogenesis, mitogenesis, and metastasis in tumors, and opioid analgesics also reduce the response of the immune system [9].

In the literature, conflicting results have been reported on the influence of the anesthesia type on urological cancer recurrence, and most of these studies have evaluated prostate cancer. However, a limited number of studies have investigated the relationship between anesthesia type and bladder cancer recurrence. A meta-analysis on the effect of anesthesia type on prostate cancer outcomes reported no differences between GA and combined RA and GA with regard to biochemical recurrence-free survival or progression-free survival with a median follow-up of 3.2 to 16.2 years [18]. However, the mortality rate was decreased by 19% in patients receiving RA combined with GA, significantly improving overall survival [16]. Doiron et al. [19] reported no differences in the effect of neuroaxial analgesia (single dose intrathecal opioid) on muscle-invasive bladder cancer. However, these studies compared GA with GA combined with RA, which is different from the current study.

In their retrospective study, Jang et al. [20] found no detectable differences in recurrence rates after five years of follow-up between patients who had undergone TURBT under RA and GA, but they reported significant partial correlations between an increased 5-year survival and RA. However, the number of patients receiving GA was far fewer than those receiving RA in that study. On the contrary, in the present study, RA reduced the recurrence of patients with NMIBC compared to GA. Likewise, Choi et al. [21] showed that RA was associated with a lower incidence of recurrence and a longer time (approximately 6 months) to recurrence with a median follow-up of 35 months compared to GA in patients who had undergone TURBT. Different from those studies, we additionally evaluated recurrence according to the EORTC risk group.

The EORTC Genito-Urinary Cancer Group developed a scoring system to predict the risks of disease recurrence and progression based on the number of tumors, tumor diameter, prior recurrence rate, pathology characteristics including stage, concurrent CIS, and grade [7]. The treatment and follow-up protocols are based on the prognosis of patients with NMIBC [22].

NMIBC is classified as low-, intermediate-, and high-risk according to the EORTC classification. We analyzed the patients according to the EORTC classification, as the risk groups differ from each other in accordance with recurrence rate, progression, and oncological behavior. In this way, we could prevent the influence of the differences in the risk groups on recurrence.

In the present study, subgroup analysis revealed that RA reduced cancer recurrence in the intermediate-risk group, but there was no benefit of RA on recurrence in the low-risk group. However, in the high-risk group, RA had a 5-month recurrence benefit over GA (p=0.056). It should be kept in mind that several factors, such as the oncological characteristics of high-risk NMIBC, are dissimilar to those of intermediate- and low-risk NMIBC. High-risk NMIBC has different oncogenic features, and circulating tumor cells are defined in some high-risk patients [23, 24]. In our study, these factors may have limited the effect of RA on the recurrence of high-risk NMIBC. On the contrary, Koumpan et al. [8] stated that GA was associated with a higher incidence of recurrence and an earlier time to recurrence compared to RA in patients with NMIBC who had undergone TURBT. They also reported that RA significantly reduced the rate of recurrence in the high-risk patient group [24]. The different results noted between that study and ours may relate to the variations between the high-risk patients included in the studies.

This study had some limitations. This study includes retrospective data taken from two centers. However, a standard data sheet was used for data extraction to minimize the scope for bias. The number of patients with high-risk NMIBC was higher in the GA group than in the RA group, which was another limitation of this study. To prevent the influence of the differences in the risk groups on recurrence, we compared the anesthesia groups according to EORTC risk groups. Biological and environmental factors can affect cancer progression. It is also important whether patients smoke or not during their follow-up. Despite these limitations, the present findings serve as a recommendation for clinicians when choosing the type of anesthesia during TURBT for NMIBC.

Further prospective multicenter studies are needed to compare the effects of different types of anesthesia on cancer recurrence after TURBT with a larger sample size.

In conclusion, during transurethral resection of the bladder tumor, an increased recurrence time was observed in patients with intermediate-risk NMIBC who received RA compared to those who received GA. RA provided a 7-month benefit in delaying relapse.

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