The effect of obturator nerve blockade on oncological outcomes of patients with lateral wall localized non-muscle invasive bladder cancer

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Abstract

Objective: To investigate the effect of obturator nerve blockade on oncological outcomes of patients with a diagnosis of lateral wall localized non-muscle invasive bladder cancer. Materials and Methods: One hundred six patients diagnosed with lateral wall localized non-invasive bladder cancer were evaluated between January 2015 and March 2020 in this retrospective, cross-sectional observational study. The patients were divided into two groups: patients receiving only spinal anaesthesia and those receiving spinal anaesthesia combined with ultrasound-guided obturator nerve blockade. Oncological outcomes of the groups were compared statistically. Results: We observed recurrent tumours in 25 patients (45.5%) in Group 1 and 11 patients (21.6%) in Group 2. In addition, we observed tumour progression in eight patients (14.5%) in Group 1 and two patients (3.9%) in Group 2. We observed statistical significance in differences between groups regarding tumour size, recurrence rate, adequate muscle tissue sampling, the ability for complete resection and persistent obturator reflex. The efficacy rate of obturator blockade was 92.1% in Group 2. One-year recurrence-free survival (RFS) was 98.0% and five-year RFS was 23.5% for Group 1, while they were, respectively, 97.4% and 57.2% for Group 2. Conclusion: The obturator reflex is a common and challenging reflex that may cause major complications and result in unintended consequences such as incomplete resection or tumour recurrence with transurethral resection of bladder tumours. In this study, we demonstrated that combining spinal anaesthesia with obturator nerve blockade for lateral wall localized non-muscle invasive bladder cancer may prevent tumour recurrence and reduce perioperative complications.

Introduction

Bladder cancer is the sixth most common cancer in men in the United States (1). Transurethral resection of bladder tumour (TUR-BT) is an initial diagnostic and therapeutic procedure for non-muscle invasive bladder cancer (NMIBC). The most common complications related to tumour resection include minor bleeding and irritative symptoms in the early postoperative period. The major complications, including uncontrolled haematuria and bladder perforation, may occur in approximately 5% of cases (2). The obturator nerve is located near the inferolateral bladder wall, and it arises from the anterior rami of the second, third and fourth lumbar nerves, descends through the psoas major and emerges from the psoas major medial border. The nerve then crosses into the pelvis at the level of the sacroiliac joint. At this point, it courses close to the wall of the bladder (3). TUR-BT of bladder tumours localized close to the lateral side of the bladder may stimulate the obturator nerve and trigger the adductor contraction approximately the rate of 20%, causing

possible inadvertent bladder perforation or an incomplete resection due to hindrance of the tumour resection (4). Spinal anaesthesia combined with obturator nerve blockade in the obturator canal may be effective in preventing adductor spasm (5). Various strategies are recommended to prevent undesirable adductor contractions due to obturator nerve stimulation. For instance, the incidence of obturator nerve stimulation can be reduced by attention to technical strategies, decreasing the intensity of energy, avoiding overdistention of the bladder, and using anaesthetic paralysis or giving general anaesthesia during the resection of lateral wall localized tumours to decrease an obturator reflex response (4,6,7). Meta-analyses comparing bipolar and monopolar TUR-BT have reported no statistically significant differences between bipolar and monopolar TUR-BT in terms of obturator reflex and bladder perforation rates (8,9).

Most of the bladder cancers (70–75%) were NMIBC during the initial diagnosis. Tumour recurrence is more common for NMIBC. Nearly 30% of patients have tumour recurrence within the first 3 months of having TUR-BT, and 50% of patients have a recurrent tumour at the 1-year follow-up (10). The major causes of recurrent tumour have been reported to be residual tumour tissue due to incomplete resection or inability to obtain adequate muscle tissue during TUR-BT (11). The obturator reflex that occurs during the TUR-BT may increase the risk of incomplete resection of the tumour, inability to sample the muscle tissue or tumour dissemination via bladder perforation.

In this study, we aimed to investigate the effect of obturator nerve blockade on oncological outcomes in patients undergoing TUR-BT for lateral wall localized NMIBC.

Materials and Methods

We designed a retrospective cross-sectional observational study that was conducted between January 2015 and March 2020. A total of 315 patients with the diagnosis of NMIBC localized on lateral wall of the bladder were analysed at Izmir Bakircay University Cigli Training and Research Hospital Urology Department and Recep Tayyip Erdogan University Urology Department. Patients with a history of previous TUR-BT, diagnosis of non-urothelial carcinoma, coagulopathy, history of allergic reaction to the local anaesthetic agent, presence of muscle invasive bladder cancer, history of chemotherapy or radiotherapy before TUR-BT, presence of variant histopathology, use of bipolar energy for the resection of bladder tumour, presence of concomitant upper urothelial tract urothelial carcinoma, neuromuscular disease, pregnancy or history of medication affecting the immune system were excluded. Of the initial 315 patients, 209 were excluded from the study, and the remaining 106 patients were included (Fig. 1). After local ethical committee permission was received (local ethical committee number 2020/131), data from the patients with the diagnosis of NMIBC were recorded retrospectively from the hospital patient record system. Patients' demographic characteristics, localization, largest tumour size, histopathological type of tumour, presence of recurrence and/or progression, time to recurrence from initial TUR-BT, presence of muscle tissue in the surgical specimen, inability to complete resection, death from cancer and both perioperative and postoperative complications were recorded for further statistical analyses. All TUR-BT procedures were performed using monopolar energy for the resection of the tumour with a 26 Fr Karl-Storz resectoscope under 30 degree optical vision with adjustment to 120 joules for cutting and 80 joules for coagulation. One surgeon performed the TUR-BT procedure on the patients in group 1 in Recep Tayyip Erdogan University, Urology department and one surgeon performed the TUR-BT procedure on the patients in group 2 in Izmir Bakircay University Cigli Training and Research Hospital, Urology Department. All obturator block decisions were made by the anesthesiologist when the suggestion of surgeon according to the localization of tumor. Spinal anaesthesia was performed in the operating room in a sitting position at the level of the L3–4 or L4–5 intervertebral space with a 25 gauge Quincke needle, and 10–15 mg of 2–3 ml 0.5% hyperbaric bupivacaine was administered through the needle into the subarachnoid space before the patient was repositioned to a supine position. After waiting for 10 min, and when sensorial blockade up to T10 dermatome was observed, a lithotomy position was performed. Additional obturator nerve blockade with ultrasound guidance was performed according to the localization of the tumour. First, the antero-medial side of the femur was demonstrated by

a two-dimensional 38 mm, 6–13 MHz ultrasound probe (Mindray, M7, Biomedical Electronics Co., Shenzhen, China). Afterward, a high-frequency probe was placed proximal to the adductor longus muscle to determine the adductor longus, brevis and magnus muscles. When the obturator nerve was demonstrated between the muscle groups, the position of the nerve was confirmed by setting the current of the stimulator (Braun Stimuplex HNS11, B. Braun, Melsungen, Germany) to 1.5–2 mA and the duration to 0.1 ms. Under ultrasound vision, a 50 mm needle (21 gauge, 50 mm Stimuplex A, B. Braun, Melsungen, Germany) was inserted parallel to the long axis of the probe and guided to the anterior branch of the obturator nerve. After adductor contractions were observed at 0.3–0.5 mA, a maximum of 10 mL 2% lidocaine was injected through the needle. Surgery started after 10 min had passed. During the surgery, patients were monitored with non-invasive blood pressure, pulse, sPO_2 intraoperative electrocardiography.

In our study, all patients underwent monopolar TUR-BT due to the presence of controversial results regarding bipolar versus monopolar techniques and strong advice to use monopolar TUR-BT in current urology guidelines (12). Patients were divided into two groups according to the anaesthesia used. While only spinal anaesthesia was performed in Group 1, spinal anaesthesia combined with ultrasound-guided obturator nerve blockade according to the localization of the tumour was performed in Group 2. The groups were compared statistically in terms of oncological outcomes. In patients with an incomplete resection, re-TUR-BT was performed 4–6 weeks after the first TUR-BT. The first follow-up was performed with all patients the third month after the initial TUR-BT, and subsequent follow-ups were performed every 3 months up to 2 years, then every 6 months up to 5 years and 1 per year after 5 years. A detailed history, physical examination, cystoscopic examination and urinary cytology were collected at each follow-up (12).

All statistical analyses were conducted using the SPSS Statistics 26.0 (IBM Inc., Armonk, NY, US) software package. Categorical variables were described by frequencies and percentages; continuous variables were described by means and standard deviations. The Kolmogorov–Smirnov test was used to evaluate the normality of the distributions, and the Mann–Whitney U test was used to compare groups and quantitative independent data. The chi-square test was used for qualitative independent data. Spearman's correlation analysis was applied for correlation, and the Kaplan–Meier test was used to calculate survival statistics. A p -value less than 0.05 was chosen as the criterion for statistical significance.

Results

The mean age of the patients was 64.71 ± 11.70 years. The mean follow-up time was 39.75 ± 14.61 months. There were 85 (80.2%) male patients and 21 (19.8%) females. Patients who underwent re-TUR-BT after an initial TUR-BT due to incomplete resection or absence of muscle tissue sampling in the surgical specimens totalled 40 (37.7%). In group 1; while 17 (30.9%) patients underwent Re-TUR-BT, 23 (40.1%) patients underwent Re-TUR-BT in group 2 (p=0.134). In terms of complications, three patients (2.8%) had bladder perforation, six patients (5.7%) had haematuria and 10 patients (9.4%) had cystitis. All patients with bladder perforation were extraperitoneal and managed with catheterization. No patients needed open laparotomy for bladder perforation. No side effects were related to obturator nerve block was observed during the study.

Group 1 including 55 patients (51.9%) underwent TUR-BT with only spinal anaesthesia, and group 2 including 51 patients (48.1%) underwent TUR-BT using spinal anaesthesia combined with ultrasound-guided obturator nerve blockade. In all, the efficacy rate of the obturator nerve blockade was 92.1%. The patients' demographic characteristics that were collected during the first diagnosis are summarized in Table 1. Recurrent tumour was observed in 25 patients (45.5%) in Group 1 and 11 patients (21.6%) in Group 2. In addition, tumour progression was observed in eight patients (14.5%) in Group 1 and two patients (3.9%) in Group 2. For all patients, the 1-year overall recurrence-free survival (RFS) was 99.0%, while the overall 5-year RFS was 49.3%. In Group 1, the 1-year RFS was 98.0% and the 5-year RFS was 23.5%. In Group 2, the 1-year and 5-year RFSs were 97.4% and 57.2%, respectively (Fig. 2). Single-dose adjuvant chemotherapy was administered to 22 patients (40.0%) in Group 1 and 18 patients (35.3%) in Group 2. Adjuvant intravesical immunotherapy was administered to 20 patients (36.4%) in Group 1 and 21 patients (41.2%) in Group 2.

Maintenance immunotherapy could be completed in 14 patients (25.5%) in Group 1 and 10 patients (19.6%) in Group 2. While no death due to bladder cancer was observed in our study, one patient died due to acute myocardial infarction. Oncological outcomes of the groups are summarized in Table 2. Statistical significance was observed in differences between the groups in terms of tumour size, recurrence rate, adequate muscle tissue sampling, ability to complete resection and persistent obturator reflex. In the Spearman's correlation analysis, we observed a positive correlation between obturator nerve blockade and tumour size, adequate muscle tissue sampling and ability to complete resection. There were also negative correlations between obturator nerve blockade and tumour recurrence and persistent obturator reflex (Table 3). On multivariate analysis after age, gender, presence of muscle tissue on the surgical specimen, presence of complete or incomplete resection, tumor size, tumor number, pathological T stage, tumor grade and obturator blockade were adjusted as a confounding factors for tumor recurrence and progression, while gender (p:0.011, OR:4.12, 95% CI: 1,37-12,35) and obturator nerve blockade (p:0.049, OR:0.35, 95% CI:0.12-0.99) were independent risk factor for tumor recurrence, gender and obturator nerve blockade were not independent risk factor in terms of tumor progression.

Discussion

In this study, we investigated the effects of an obturator nerve blockade on oncological outcomes in patients who underwent TUR-BT. The results revealed that ultrasound-guided obturator nerve blockade combined with spinal anaesthesia was associated with lower rates of tumour recurrence, better rates of RFS, tumour size, adequate muscle tissue and complete resection. Ultrasound-guided obturator nerve blockade combined with spinal anaesthesia had a positive correlation with tumour size, adequate muscle tissue sampling and complete resection rates and a negative correlation with tumour recurrence and persistent obturator reflex.

TUR-BT is the gold standard method for both the initial diagnosis and treatment of patients with NMIBC. The frequency of severe adductor muscle contractions during the transurethral resection of laterally located bladder tumours has been stated to be approximately 20% (13). Major complications such as bladder perforation and excessive haemorrhage, incomplete resection of tumour and inadequate sampling of muscle tissue in the surgical specimens may occur during resection due to adductor muscle contractions via stimulation of the obturator nerve (14). In order to prevent this undesirable adductor reflex, obturator nerve blockade with ultrasound guidance has been recommended in several studies (6, 15, 16). First, Labat described the obturator nerve blockade with nerve stimulator in 1922 (17). Afterwards, Wassef described the inter-adductor approach (18), Khorammi described the transvesical approach using a nerve stimulator (2), Choquet studied the inguinal approach to block the obturator nerve (19), and several studies compared sonographic demonstrations of obturator nerve-to-nerve stimulation methods (20). In a recent study, Smith reported a combined ultrasound and nerve stimulator approach (21). Despite all of these techniques effectively blocking the obturator nerve, undesirable adductor muscle spasms may still occur during TUR-BT even when an obturator nerve block is performed correctly due to variations in the obturator nerve's ramifications (22). The efficacy rate of obturator nerve blockade is between 84% and 96%, according to several studies (23, 24). In our study, we performed a combination of ultrasound guidance and nerve stimulator to block the obturator nerve, and our efficacy rate was 92.1%, meaning it was as effective as the rates reported in other studies.

Although an obturator nerve blockade is an intervention that reassures the surgeon during surgery and reduces the rate of peroperative complications, its contribution to oncological outcomes is not yet clear. Erbay showed that patients with lateral wall localized NMIBC who underwent spinal anaesthesia combined with obturator nerve blockade had longer RFS than patients who received only spinal anaesthesia (25). Additionally, rates of complete resection and the presence of muscle tissue in the surgical specimen were higher in patients who received an obturator nerve blockade combined with spinal anaesthesia (25). Tekgul reported that patients with lateral wall localized bladder tumour had a prolonged time to recurrence than patients without an obturator nerve blockade. They reported that bladder perforation was reported in two patients without obturator nerve block, whereas none of the patients who did not undergo obturator nerve

block developed bladder perforation. Authors also reported that they did not observe tumor progression during the study (16). We observed a significantly increased RFS in patients who received an obturator nerve blockade, but we did not find any significant difference in prolonged time to recurrence. Similar to Tekgül's study, while we observed bladder perforation in three patients without obturator nerve block, we did not observe perforation in any of the patients who underwent obturator nerve block. Authors also did not observe tumor progression in their study in three years period. In our study, although we observed tumor progression in 8 (14.5%) patients in group 1 and 2 (3.9%) patients in groups 2, that result was insignificant statistically.

The presence of detrusor muscle tissue in the specimen provides accurate pathologic staging that allows the determination of an adequate follow-up protocol and potential adjuvant treatment according to tumour grade and invasiveness. Additionally, a complete resection of all tumour tissues significantly reduces the risk of NMIBC recurrence and progression. Understaging of NMIBCs at first resection due to failure of the presence of detrusor muscle in the resected specimen is reported in up to 49% of patients, compared with 14% for patients with adequate muscle tissue sampling (26, 27). In our study, we found lower inadequate muscle tissue sampling and higher detrusor muscle complete resection rates in the obturator nerve blockade group.

After an incomplete resection, the recurrence rate is 15%–61% in Ta and T1 tumours in the first year (12). The presence of residual tumour tissue after a TUR-BT procedure increases the recurrence rates and decreases the RFS. One study investigating the presence of residual tumour in the marginal resection after a complete TUR-BT of Ta/T1 transitional urinary bladder cancer reported that 26% of patients had residual tumour tissue after a complete resection of Ta/T1 bladder tumours (28). This possibility particularly increases in undesirable conditions such as obturator reflex during the resection of tumours located in the lateral wall of the bladder, and our results were similar. In our study, RFS was longer in patients who underwent spinal anaesthesia combined with obturator nerve blockade, and no patients had tumour progression. Moreover, we observed that patients who received an obturator nerve blockade had a higher pathological T stage according to TNM classification and decreased recurrence rates as compared with patients who did not receive an obturator nerve blockade.

Another challenging complication due to adductor spasm from stimulation of the obturator nerve during resection is bladder perforation. Several studies have reported bladder perforation due to obturator reflex in ranges between 0.9% and 5% (29, 30). Extravesical dissemination of the tumour may occur due to bladder perforation (31). In our study, only three patients (2.8%) had extraperitoneal bladder perforation, and they were treated with only a urinary catheter. All these three patients underwent TUR-BT with only spinal anaesthesia. Open laparotomy was not required in any of the patients with bladder perforation, and no pelvic mass was observed at follow-ups due to extravesical tumour dissemination. Although perioperative complication rates were not statistically significant, consider that difference between groups in terms of perioperative complication rates were clinically significant.

This study has some limitations. First, due to the retrospective design of the study, randomization could not be included. Second, the study population was small, and we may not have reached statistical significance in terms of some variables such as time to recurrence, tumor progression, and perioperative complication rates due to population size.

Conclusion

This study revealed that patients with NMIBC localized on lateral wall of the bladder who received an obturator nerve blockade combined with spinal anaesthesia had a significantly increased RFS, increased rate of complete resection and adequate detrusor muscle sampling. Although we could not observe statistically significant difference in terms of perioperative complication rates, patients underwent obturator nerve blockade combined with spinal anaesthesia had lower clinically significant peroperative complication rates. The

obturator nerve blockade combined with spinal anaesthesia also contributes to the correct staging of patients with lateral wall localized NMIBC, which plays a critical role in their subsequent treatment.

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Author Contributions

Conseption; MOH, HE, Performance of Working; ED, AC, OE, Analyse of Data; MOH, Writing the article;MOH, HE, SK, HA.

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Figure Legends

Fig. 1 The clinical course of the study.

Fig. 2 Group Kaplan–Meier curves in terms of recurrence-free survival.

Tables and legends

Table 1 Patients' demographic characteristics at initial diagnosis according to the groups.

	Group 1 $n = 55$	**Group 2** $n = 51$	p**-Value**
Age, *mean ± standard deviation (SD), years*	66.02±10.56	63.29±12.78	0.354
Gender, *n, %*			0.132
Male	41 (74.5%)	44 (83.3%)	
Female	14 (25.5%)	7 (13.7%)	
Diabetes mellitus, *n, %*			0.113
Present	42 (76.4%)	45(88.2%)	
Absent	13 (23.6%)	6 (11.8%)	
Hypertension, *n, %*			0.922
Present	34(61.8%)	32 (62.7%)	
Absent	21 (38.2%)	19 (37.3%)	
Tumour localization, *n, %*			0.646
Left	31(56.4%)	31(60.8%)	
Right	24 (43.6%)	10 (39.2%)	

Table 2 Comparison of group oncological outcomes.

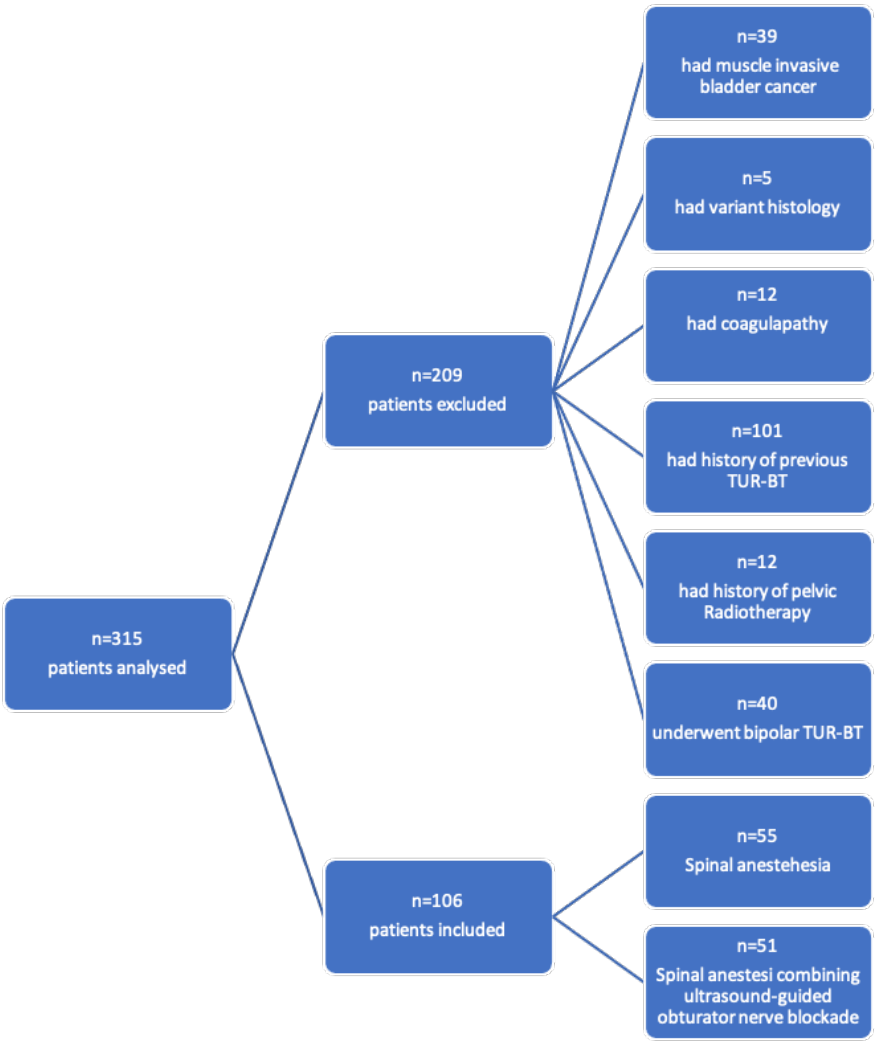
	Group 1 $n = 55$	**Group 2** $n = 51$	p**-Value**
Tumour size, *mean ± standard deviation (SD), mm*	2.90 ± 1.43	3.55 ± 1.37	**0.030**
T stage, *n, %*			0.131
Ta	41 (74.5%)	31 (60.8%)	
T1	14 (25.5%)	20 (39.2%)	
Grade, *n, %*			0.057
Low grade	40 (72.7%)	28 (54.9%)	

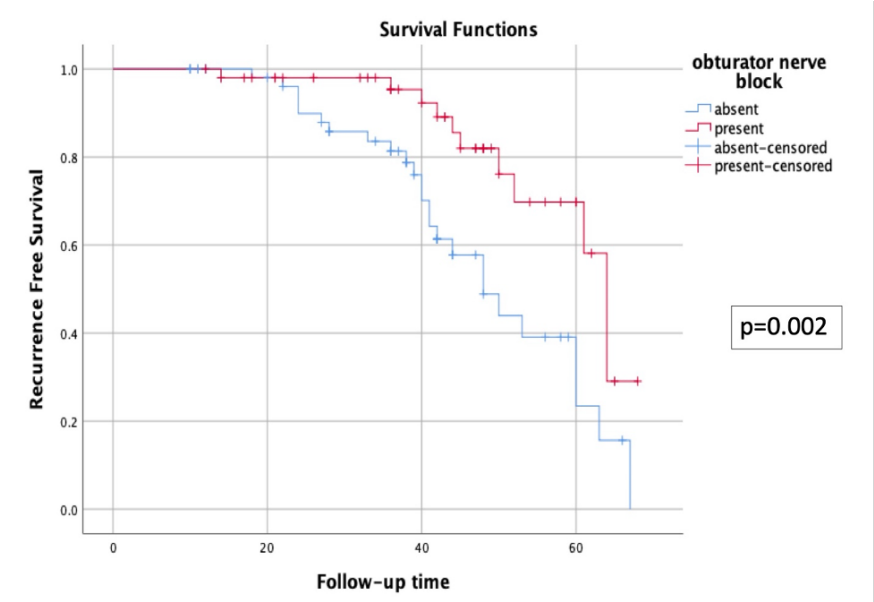
	Group 1 $n = 55$	**Group 2** $n = 51$	p**-Value**
High grade	15 (27.3%)	23 (45.1%)	
Muscle tissue sampling			**0.010**
Absent	15 (27.3%)	4 (7.8%)	
Present	40 (70.2%)	47 (92.2%)	
Resection			**0.021**
Incomplete	10 (18.2%)	2 (3.9%)	
Complete	45 (81.8%)	49 (96.1%)	
Obturator reflex			**0.003**
Absent	38 (69.1%)	47 (92.2%)	
Present	17 (30.9%)	4 (7.8%)	
Recurrence, *n, %*			**0.010**
Absent	30 (54.5%)	40 (78.4%)	
Present	25 (45.5%)	11 (21.6%)	
Progression, *n, %*			0.106
Absent	47 (85.5%)	49 (96.1%)	
Present	8 (14.5%)	2 (3.9%)	
Time to recurrence, *mean ± SD, month*	4.44 ± 6.02	7.76 ± 15.66	0.097
Complication, *n, %*			0.117
Haematuria	5 (9.1%)	1 (2.0%)	
Cystitis	5 (9.1%)	5 (9.8%)	
Bladder perforation	3 (5.5%)	0	

Table 3 Correlation coefficients of study parameters (Spearman's correlation).

	Obturator nerve blockade	**Presence of muscle tissue**	**Complete resection**	**Tu**
Obturator nerve blockade	1			
Presence of muscle tissue	**0.253****	1		
Complete resection	**0.225***	**0.532****	1	
Tumour size	**0.208***	0.089	0.056	1
Recurrence	**-0.252****	-0.132	-0.058	0.0
Progression	-0.182	-0.102	-0.088	-0.
Time to recurrence	-0.162	-0.055	-0.015	0.0
Complication	-0.153	0.032	-0.049	0.0

Values in bold are statistically significantly different. $*p < 0.05$, $**p < 0.01$





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