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Clinical-Bladder cancer

Tumor location at trans-urethral resection is predictive of ipsilateral pelvic lymph-nodal metastases in patients undergoing radical cystectomy for bladder cancer

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Abstract

Objective: To assess whether tumor location at diagnostic TURBT is predictive of ipsilateral nodal involvement in patients who underwent radical cystectomy (RC) with lymph-nodes dissection for bladder cancer (BCa).

Materials and methods: All patients who underwent RC for BCa at a single institution between 2014−2023 were assessed. Tumor location at TURBT was defined as right-sided, median-line, left-sided, and diffused. Distribution in the percentage of ipsilateral positive lymph-nodes and number of ipsilateral positive lymph-nodes between tumor locations were assessed with Kruskal-Wallis tests. Linear regressions were fitted to assess whether left or right location, compared to the remaining locations grouped, was associated to the percentage and number of positive ipsilateral lymph-nodes.

Results: 239 patients were included. The number of ipsilateral positive lymph nodes was superior in right-sided tumors when compared to the rest of the bladder (0, I.Q.R. 0−1 vs. 0, I.Q.R. 0−0, $P = 0.047$), as well as the percentage of ipsilateral positive lymph-nodes (0, I.Q.R. 0−14.3 vs. 0, I.Q.R. 0−3.7, $P = 0.042$). The number of ipsilateral positive lymph-nodes in left-sided tumors was superior when compared to the rest of the bladder (0, I.Q.R. 0−1 vs. 0, I.Q.R. 0−0, $P = 0.02$), as well as the percentage (0, I.Q.R. 0−13.7 vs. 0, I.Q.R. 0−0, $P = 0.036$). At linear regression analyses, right- and left-sided tumors were associated with an increased percentage of ipsilateral positive lymph-nodes ($P = 0{,}019$ and $P = 0{,}003$) out of the total ipsilateral lymph-nodes excised.

Conclusions: Lateral wall tumor location at diagnostic TURBT (either right or left side) predicts a higher percentage of ipsilateral positive lymph-nodes s/p RC.

Keywords: TURB; Cystectomy; Pelvic Lymphadenectomy; Bladder Cancer; Lymp-nodal metastasis

1. Introduction

Radical Cystectomy (RC) with pelvic lymph-Nodes dissection (PLND) and urinary diversion is the treatment of choice in T2−T4a, N0M0 muscle-invasive bladder cancer, and in very high-risk nonmuscle invasive bladder cancer (NMIBC), BCG-refractory, BCG-relapsing, and BCG-unresponsive NMIBC [1,2].

Currently, the standard template of PLND during RC includes the excision of lymph-nodes cranially up to the common iliac bifurcation, with the ureter being the medial border, and including the internal iliac, presacral, obturator fossa, and external iliac nodes [3].

Limited, extended, and super-extended PLND have been proposed as alternatives in selected cases; the first includes the nodes from the true pelvis but does not comprise the deep

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obturator lymph-nodes. The second includes all lymph-nodes as the standard one, but its cranial limit is the aortic bifurcation, while the third reaches the inferior mesenteric artery [4,5].

The primary tumor's access to lymphatic and vascular tissue has been suggested as a major contributing factor to the disease spread in loco-regional lymph-nodes: data supporting the correlation between the presence of lymphovascular invasion within the primary tumor and pelvic lymph-nodal involvement is present [6,7].

Moreover, while the diagnostic value of PLND is well established, its therapeutic effect is still debated. While evidence suggests better oncological outcomes in patients treated with PLND, there's no clear evidence on the impact of different PLND templates [8−10].

However, scant and heterogeneous data are available on whether tumor endoluminal location is both prognostically valuable and predictive of lymph-nodal spread [11−15]; indeed, no efforts have been reported on unilaterally modulating the extension of PLND templates based on the tumor's endoluminal location in select cases.

Understanding the relationship between tumor location at the time of its transurethral resection and the respective laterality of lymph-nodal metastases could aid clinicians in risk stratification and surgical planning. Our study aimed to shed some insight into this matter.

2. Methods

2.1. Patient cohort

From our prospectively-maintained institutional bladder cancer database, we extracted and retrospectively analyzed all patients who underwent RC with bilateral standard PLND − as per institutional protocol − between 2014 and 2023.

Only patients with available data regarding tumor location at TURBT, and lymph-nodal status at final pathology report s/p RC were included in the analysis.

Patients who were clinically node-positive and/or who had metastatic disease at preoperative staging were excluded. Also, patients who underwent neoadjuvant chemotherapy were excluded from the analysis.

Specifically for the purpose of the study, tumor endoluminal location at the last TURBT performed was defined as:

- right-sided, which included disease involving the right bladder wall and/or the right trigone;
- median-line, including disease of the central trigone, the posterior wall, the dome and/or the anterior wall;
- left-sided, with disease involving the left bladder wall and/or the left trigone;
- diffuse, multi-focal disease.

2.2. Lymph node dissection

Lymph node dissection was carried out according to the standard template cited in the introduction. While in some cases, pelvic lymph nodes were excised en-bloc (n=43), in the majority of the patients (n=196), they were individually grouped following a standardized anatomical template, comprising external iliac, internal iliac plus obturator, presacral, Marcille's common iliac, and Cloquet's nodal stations bilaterally. Specimens were immersed in formalin, enumerated, and then examined for cancer infiltration, with staging assigned in accordance with the 2017 version of the TNM system (8th edition).

2.3. Outcome

The primary outcome was to assess whether tumor endoluminal location at TURBT was predictive of ipsilateral pelvic lymph-nodal involvement.

2.4. Covariates

Relevant demographic and tumor-related data were considered to account for the potential effect of confounders. Demographic data included patient age (at the time of surgery), gender, ASA score, and Charlson's comorbidity index. Tumor-related characteristics included endoscopic tumor size (in mm), pT stage, 2016 WHO Grading, histological subtype at TURBT and RC, and number of nodes excised during PLND. The year of surgery was also collected.

2.5. Statistical analysis

Descriptive statistics were used to characterize the study cohort, stratified by tumor location; frequencies and proportions were used for categorical data, while medians, interquartile ranges (IQR), and 5°−95° centiles were used for continuous data. Kruskal-Wallis and chi-square tests were used to compare the statistical significance of differences in the distribution of continuous and categorical variables, respectively, between different endoluminal tumor locations. Distribution in the percentage of ipsilateral positive lymph-nodes and in the number of ipsilateral positive lymph-nodes between different tumor locations was assessed with Kruskal-Wallis. Linear regressions were fitted to assess whether the left or right location, compared to the rest of the locations grouped, was associated with an increased number of ipsilateral positive lymph-nodes and an increased percentage of ipsilateral positive lymph-nodes out of the total number of nodes excised; Beta coefficients and 95%C.I. have been reported.

All statistical tests were performed using SPSS IBM SPSS Statistics version 23.0 (Armonk, NY: IBM Corp.). All tests were two-sided with a significance level set at $P < 0.05$.

3. Results

From a total of 314 patients in the institutional database, 239 patients were included in the analysis after accounting for inclusion/exclusion criteria.

Of these, 64 patients (27%) had a right-sided tumor at TURBT, 84 (35.4%) had a median-line tumor, 69 (29.1%) had a left-side tumor, and 20 (8.4%) had diffuse disease. After TURBT, it was found that 206 (86%) patients were affected by urothelial carcinoma, 12 (5.1%) by urothelial carcinoma with partial squamous differentiation, and 4 (1,7%) by sarcomatoid urothelial carcinoma, with no statistically significant difference between tumor location (Table 1).

The final pathology report of the RC specimens showed that 139 patients (58.2%) had urothelial carcinoma, 34 (14.2%) had urothelial carcinoma with partial squamous differentiation, and 26 (10.9%) showed no residual disease. There was also no statistically significant difference when grouping different tumor locations at TURBT (Table 1).

In addition, there was no statistically significant difference between the four groups when examining the considered covariates (Table 1).

Post RC, 77 patients (32.2%) had pN+ disease. No difference was found when assessing the median number of right and left pelvic lymph-nodes excised, which were 12 (I.Q.R. 8−16, 5°−95° centiles 3−24.2) vs. 10 (I.Q.R. 7−15, 5°−95° centiles 1−21), respectively, $P = 0.28$. Moreover, the median number of positive right and left nodes was 0 (I.Q.R. 0−0, 5°−95° centiles 0−4.1) vs. 0 (I.Q.R. 0−0, 5°−95° centiles 0−4), respectively, with no difference between the groups ($P = 0.4$). Also, there was no difference ($P = 0.37$) between the median percentage of positive right and left lymph-nodes out of the total excised ipsilateral nodes (0, I.Q.R. 0−3.7, 5°−95° centiles 0−50 vs. 0, I.Q.R. 0−0, 5°−95° centiles 0−47.8).

The number of ipsilateral positive nodes in right-sided tumors was superior to that in the rest of the bladder (median 0, I.Q.R. 0−1, 5°−95° centiles 0−10.3 vs. median 0, I.Q.R. 0−0, 5°−95° centiles 0−4, $P = 0.047$), as was the percentage on the right (median 0, I.Q.R. 0−14.3, 5°−95° centiles 0−83 vs. 0, I.Q.R. 0−3.7, 5°−95° centiles 0−41.8, $P = 0.042$).

The number of ipsilateral positive nodes in left-sided tumors was superior to the rest of the bladder (0, I.Q.R. 0−1, 5°−95° centiles 0−7.7 vs. 0, I.Q.R. 0−0, 5°−95° centiles 0−3, $P = 0.02$), as was the percentage on the left (0, I.Q.R. 0−13.7, 5°−95° centiles 0−77.7 vs. 0, I.Q.R. 0−0, 5°−95° centiles 0−30.4, $P = 0.036$).

At linear regression analyses, right-sided tumors were associated with an increased percentage and number of ipsilateral positive nodes compared to the rest of the bladder (respectively $P = 0.019$, Beta 0.18, 95% C.I. 2.4−12.6 vs. 3−8.8 and $P = 0.037$, Beta 0.2, 95% C.I. 1.8−12.3 vs. 1.6−7.3). However, while left-sided tumors were associated with an increased percentage of ipsilateral positive nodes ($P = 0.003$, Beta 0.14, 95% C.I. 0.09−1.2 vs. 0.17−0.7), they were not associated with an increased number of ipsilateral positive nodes ($P = 0.56$).

3.1. Patients with CIS only and Concomitant CIS

Analyzing the subset of patients with CIS only (n=15) and concomitant CIS (n=57) at final pathology, it was found that there was no difference in the prevalence of this histology in different endoluminal locations ($P = 0.4$). In addition, it was found that there was no difference in the distribution of the percentages and number of ipsilateral positive nodes for any location (respectively for the number and percentage on the right $P = 0.09$ and $P = 0.1$, while for the number and percentage on the left respectively $P = 0.6$ and $P = 0.7$).

3.2. Patients without CIS only and without Concomitant CIS

Afterwards, we considered instead the remaining patients after excluding patients with CIS only and concomitant CIS at final pathology (n=167). In this case, the number of ipsilateral positive nodes in right-sided tumors was superior to that in the rest of the bladder (median 0, I.Q.R. 0−1, 5°−95° centiles 0−10.4 vs. median 0, I.Q.R. 0−0, 5°−95° centiles 0−4, $P = 0.05$), as well as the percentage on the right (median 0, I.Q.R. 0−14.3, 5°−95° centiles 0−83 vs. 0, I.Q.R. 0−0, 5°−95° centiles 0−41.8, $P = 0.03$).

Moreover, the number of ipsilateral positive nodes in left-sided tumors was superior to the rest of the bladder (0, I.Q.R. 0−3, 5°−95° centiles 0−7.8 vs. 0, I.Q.R. 0−0, 5°−95° centiles 0−3, $P = 0.01$), as was the percentage on the left (0, I.Q.R. 0−13.7, 5°−95° centiles 0−76.8 vs. 0, I.Q.R. 0−0, 5°−95° centiles 0−30.2, $P = 0.032$).

At linear regression analyses, both left and right sided tumors were not right-sided tumors were associated with an increased number of ipsilateral positive nodes.

However, both right and left sided tumors were associated with an increased percentage of ipsilateral positive nodes compared to the rest of the bladder (respectively $P = 0.046$, Beta 0.16, 95% C.I. 0.13−12.8 vs. 2.6−8.2 and $P = 0.043$, Beta 0.16, 95% C.I. 0.2−12.4 vs. 1.4−8.2).

4. Discussion

The present institutional analysis found that lateral-wall tumor location at diagnostic TURBT (either on the right or the left side) predicted a higher percentage of ipsilateral positive lymph-nodes s/p RC.

As of today, exploratory studies have been made to determine whether pelvic lymph node dissection (PLND) can be tailored to specific subsets of patients. A research group reported that PLND might be omitted in patients who achieve a complete pathological response following neoadjuvant chemotherapy [16], while another group reported on the feasibility of the use of sentinel node biopsy using the hybrid tracer ICG- 99m Tc-nanocolloid [17]. Moreover, it has been evaluated if a Likert score assessment of lymph node features on contrast-enhanced CT scans could be

Table 1
Patient and operative characteristics according to tumor endoluminal location

Variable	Overall	Right side	Central	Left side	Diffuse	*P* value
Age						0.052
Median	71	69.5	71	75	72	
IQR	63−77	64−74.7	63−77	68−80	53−76	
Centiles (5°−95°)	50−85	49−83	52.2−84.7	49−85.4	49.1−88.5	
Gender						0.9
Male	191 (79.9)	53 (82.8)	67 (79.8)	55 (77.5)	16 (80)	
Female	48 (20.1)	11 (20.2)	17 (22.5)	16 (22.5)	4 (20)	
ASA score						0.71
1	4 (1.7)	2 (3.1)	1 (1.2)	0 (0)	1 (5)	
2	135 (56.5)	37 (57.8)	51 (60.7)	39 (54.9)	8 (40)	
3	88 (36.8)	22 (34.4)	28 (33.3)	28 (39.4)	10 (50)	
4	12 (5)	3 (4.7)	4 (4.8)	4 (5.6)	1 (5)	
CCI						0.35
Median	6	6	5	6	6	
IQR	5−7	4−7	5−6	5−7	4−7	
Centiles (5°−95°)	3−9.7	2.6−11.35	3−9.5	3.8−9.1	3−8.5	
Endoscopic tumour size (mm)						0.48
Median	30	30	30	32.5	15	
IQR	15−45	17.5−47.5	16.2−40	42.5	10−80	
Centiles (5°−95°)	10−67.5	10−60	10−70	8.9−61	10−92	
pT at TURBT						0.054
pTa	21 (8.8)	5 (7.8)	8 (9.6)	3 (4.2)	5 (25)	
CIS only	7 (2.9)	1 (1.6)	1 (1.2)	3 (4.2)	2 (10)	
pT1	64 (26.9)	13 (20.3)	23 (27.7)	18 (25.4)	10 (50)	
pT2a	46 (19.3)	14 (21.9)	17 (205)	13 (18.3)	2 (10)	
pT2b	94 (39.5)	29 (45.3)	32 (38.6)	32 (45.1)	1 (5)	
pT3a	4 (1.7)	1 (1.6)	1 (1.2)	2 (2.8)	0 (0)	
pT3b	2 (0.8)	1 (1.6)	1 (1.2)	0 (0)	0 (0)	
pT4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Grading (WHO) at TURBT						0.85
LG	11 (4.8)	2 (3.2)	5 (6.3)	3 (4.4)	1 (5)	
HG	219 (95.2)	61 (96.8)	74 (93.7)	65 (95.6)	19 (95)	
histological subtype both at TURBT						0.51
urothelial Ca	209 (87.4)	53 (82.8)	74 (88.1)	62 (87.3)	20 (100)	
urothelial Ca with partial squamous differentiation	13 (5.4)	7 (10.9)	2 (2.4)	4 (5.6)	0 (0)	
sarcomatoid urothelial Ca	3 (1.3)	0 (0)	1 (1.2)	2 (2.8)	0 (0)	
Other	14 (5,9)	4 (6.3)	7 (8.3)	3 (4.2)	0 (0)	
pT at RC						0.2
pT0	26 (10,9)	4 (6.3)	10 (11.9)	8 (11.3)	4 (20)	
pTa	2 (0.8)	0 (0)	1 (1.2)	0 (0)	1 (5)	
CIS only	15 (6.3)	1 (1.6)	9 (10.7)	4 (5.6)	1 (5)	
pT1	33 (13.8)	8 (12.5)	10 (11.9)	11 (15.5)	4 (20)	
pT2a	18 (7.5)	3. (4.7)	10 (11.9)	3 (4.2)	2 (10)	
pT2b	15 (6.3)	3 (4.7)	7 (8.3)	3 (4.2)	2 (10)	
pT3a	26 (10.9)	8 (12.5)	5 (6)	12 (16.9)	1 (5)	
pT3b	47 (19.7)	20 (31.3)	13 (15.5)	13 (18.3)	1 (5)	
pT4a	42 (17.6)	12 (18.8)	13 (15.5)	14 (19.7)	3 (15)	
pT4b	1 (0.4)	0 (0)	1 (1.2)	0 (0)	0 (0)	
Grading (WHO) at RC						0.9
LG	8 (3.77)	2 (3.0)	2 (2.4)	3 (4.1)	1 (5.6)	
HG	182 (85.8)	49 (74.3)	63 (75.9)	56 (77.8)	14 (77.8)	
missing	57 (10.4)	13 (23.7)	19 (22.9)	12 (16.7)	5 (16.7)	
pN						0.68
pN0	162 (67.8)	40 (62.5)	60 (71.4)	45 (63.4)	17 (85)	
pN1	23 (9.6)	8 (12.5)	8 (9.5)	6 (8.45)	1 (5)	
pN2	37 (15.5)	12 (18.8)	10 (11.9)	14 (19.7)	1 (5)	
pN3	17 (7.1)	4 (6.2)	6 (7.1)	6 (8.45)	1 (5)	
Histological subtype at RC						0.69
Urothelial Ca	139 (58.2)	34 (53.1)	52 (61.9)	41 (57.7)	12 (60)	
Urothelial Ca with partial squamous differentiation	34 (14,2)	16 (25)	8 (9.5)	9 (12.7)	1 (5)	
No residual disease	26 (10,9)	4 (6.3)	10 (11.9)	8 (11.3)	4 (20)	

(*continued*)

Table 1 (***Continued***)

Variable	Overall	Right side	Central	Left side	Diffuse	*P* value
Other	40 (16.7)	10 (15.6)	14 (16.6)	13 (18.3)	3 (15)	
Number of PLN excised at RC						0.73
Median	23	22	22.5	23	27	
IQR	16–31	12–31	17–29.25	16–28	14–37	
Centiles (5°–95°)	6.2–47.6	5–48	7.8–46.6	8.4–48.6	2–42	
Year of surgery						0.92
Median	2017	2017	2017	2017	2017	
IQR	2016–2019	2016–2019	2016–2019	2016–2018	2016–2018	
Centiles (5°–95°)	2014–2022	2015–2022	2015–2022	2014–2022	2015–2023	

employed to assess potential involvement, with preliminary positive results [18].

However, no criteria have ever been identified to predict exclusively ipsilateral lymph-nodal metastasis. The largest reported cohort focusing on this matter is the one by May et al. on the PROMETRICS 2011 database[11]: during this study, data regarding 678 patients were recorded, but only 148 node-positive patients were considered in the final analysis: it was established that although there is an association between intravesical tumor location and the laterality of lymph-nodal metastasis in bladder cancer, this finding does not support an individualized approach to limiting the extent of PLND during RC.

Small sample sizes, different inclusion criteria, and conflicting results have limited other reports. Svatek et al. [12] found that there was a higher likelihood of lymph-nodal metastases among the 86 node-positive patients out of the 545 who underwent RC for both muscle-invasive and non-muscle-invasive diseases when the tumor was located at the trigone (OR 1.83, $P = 0.017$). Additionally, the authors observed a higher risk of cancer-specific mortality (HR 1.68, $P = 0.015$) with this tumor location.

In addition, Bruins et al. reported on 637 patients who underwent RC for NMIBC. While they discussed in depth the relationship between positive lymph nodes and tumor characteristics, they did not focus on tumor endoluminal location [19].

In the setting of a study investigating the impact of tumor location at TURBT, Wedel et al. [13] analyzed 50 patients who underwent RC and were diagnosed with nodal metastases. The occurrence of nodal metastases varied based on the location of the tumor. The authors noted a significantly elevated rate of nodal metastases among patients with tumors confined to the lateral walls of the bladder and among those patients who had tumors with any involvement of the lateral walls. Furthermore, the authors observed the strongest correlation with nodal metastases in patients with tumors exclusively affecting the lateral walls.

In this setting, we designed our study not to analyze the trigone as a whole entity but to divide it into parts based on the closest lymphovascular bundle and include it as a single region subject to the same drainage. Meanwhile, we isolated the center of the bladder to prevent it from acting as a confounder due to its equidistance to the lymphovascular bundles.

Likely due to an appropriate, albeit arbitrary, regionalization of the bladder, our cohort exhibited exceptional homogeneity among tumor endoluminal location groups. To the extent that none of the considered covariates (Table 1) showed a statistically significant difference. This suggests that the tumor endoluminal location is not associated with any other tumor characteristic or clinical parameter.

We decided not to include in our cohort patients who underwent neoadjuvant chemotherapy in order to avoid any potential effect on lymph node involvement rates that might bias the data. [16,20,21]

Therefore, at univariate analysis, it was possible to observe a statistically significant association between tumors located on either the right or left side of the bladder and both a higher percentage of ipsilateral positive nodes out of the total number of ipsilateral nodes excised, as well as the number of ipsilateral positive nodes, regardless of the total ipsilateral nodes excised.

Furthermore, to verify if tumor location was indeed predictive of ipsilateral node-positivity, linear regression analyses were fitted. It was observed, as originally hypothesized, that tumor location was predictive of tumor spread to the ipsilateral nodes. We found that both right and left tumor endoluminal locations predicted a higher percentage of ipsilateral positive nodes out of the total number of ipsilateral nodes excised (respectively $P = 0.019$ and $P = 0.037$).

Moreover, the right tumor endoluminal location predicted the presence of ipsilateral positive nodes, regardless of the total number of ipsilateral nodes removed ($P = 0.003$). However, this was not observed for left-sided tumors, probably due to insufficient events ($P = 0.56$).

Ultimately, due to the aforementioned lack of statistical difference in the covariates, a multivariable linear regression was not fitted (Fig. 1).

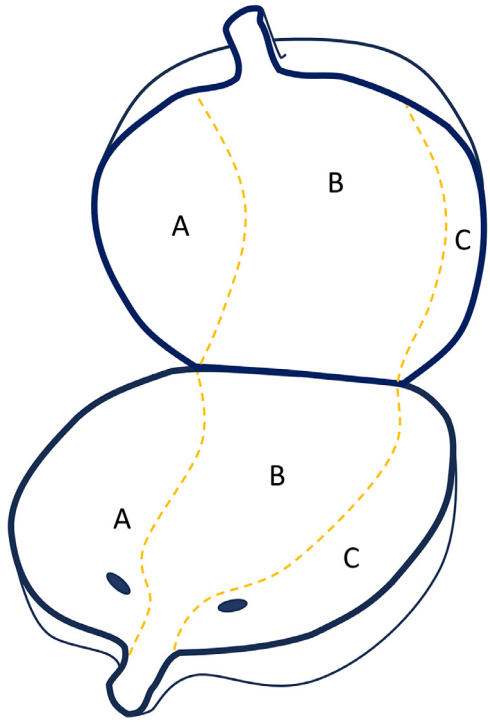

Fig. 1. Scheme showing tumor endoluminal localization. (**A**) Right side: including right bladder wall and/or right trigone. (**B**) Central: including disease in central trigone, posterior wall, cupola and/or anterior wall. (**C**) Left side: including left bladder wall and/or left trigone.

Afterward, we focused on patients with CIS only and concomitant CIS at final pathology to account for different lymphovascular drainage patterns that characterize this population [22]. In this subset, we did not find any association between tumor location and lymph node involvement.

Therefore, we analyzed the remaining population and found that, indeed, statistically significant associations between tumors located on either the right or left side of the bladder and both a higher percentage of ipsilateral positive nodes out of the total number of ipsilateral nodes excised and the number of ipsilateral positive nodes, regardless of the total ipsilateral nodes excised, was present. In this case, also, linear regression analyses were fitted and found to be statically significant for the percentage of positive ipsilateral lymph nodes but not for their number. This is probably due, in the author's opinion, to a reduced number of patients in this subset (n=167).

While our study provided some insight and confirmation into a sparsely investigated matter, it is hampered both by a cohort not sufficiently large enough to allow further in-depth analyses and by its single-center nature, which might skew the data.

However, it could be the first hypothesis-generating experience suggesting that limiting PLND ipsilaterally to a sided tumor—either on the right or the left bladder wall—might be worth more extensive investigation.

Whether this will allow us to evaluate the hypothesis of a unilateral PLND versus an intensified PLND on the tumor-carrying side is unknown and beyond the scope of the present study.

We emphasize that although our focus was not specifically on a surgical approach to RC with PLND, the median number of excised lymph nodes was 22 (I.Q.R. 16−31), which we believe to constitute an adequate control for the scopes of the present study.

Conclusions

In patients undergoing RC with PLND, lateral tumor location at TURBT - either right- or left-sided - is predictive of a higher percentage of ipsilateral positive nodes at final pathology after RC. This is a hypothesis-generating study. Further research is needed in the field.

Declaration of competing interest

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CRediT authorship contribution statement

Francesco Cianflone: Writing − original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Giovanni Mazzucato:** Visualization, Validation, Data curation. **Emanuele Rubilotta:** Visualization, Validation, Resources. **Rossella Orlando:** Visualization, Validation, Data curation. **Nicola De Maria:** Visualization, Validation, Data curation. **Michele Boldini:** Visualization, Validation, Data curation. **Francesca Fumanelli:** Visualization, Validation, Data curation. **Francesca Montanaro:** Visualization, Validation, Data curation. **Greta Pettenuzzo:** Visualization, Validation, Data curation. **Luca Roggero:** Visualization, Validation, Data curation. **Alessandra Gozzo:** Visualization, Validation, Data curation. **Alberto Bianchi:** Visualization, Validation, Data curation. **Alessandro Veccia:** Visualization, Validation, Resources, Methodology, Data curation. **Riccardo Giuseppe Bertolo:** Writing − review & editing, Validation, Supervision, Project administration, Methodology. **Maria Angela Cerruto:** Visualization, Validation, Supervision. **Alessandro Antonelli:** Writing − review & editing, Visualization, Validation, Supervision, Resources, Project administration, Methodology.

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