

Adverse pathological outcomes of patients with de novo muscle invasive bladder cancer in Northern Ontario

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Summary *Objective: This study aimed to investigate the clinical and pathological characteristics of patients with de novo muscle-invasive bladder cancer (MIBC) who underwent radical cystectomy in Northern Ontario.*

Methods: This is a retrospective cross-sectional study of patients with de novo T2 MIBC who underwent radical cystectomy over a 2-year-period in Thunder Bay Regional Health Sciences Centre. Clinical and pathological characteristics of Trans Urethral Resection of Bladder Tumors and cystectomy specimens were analyzed.

Results: Of the 59 patients aged 67 ± 8.8 years, predominated by males (80%), 27.1% were younger than age 60. After surgery, upstaging was noted in 59.3% (T3 in 27.1% and T4 in 32.2%) while node positive was noted in 36% of patients.

Prostate adenocarcinoma was incidentally discovered in 20 (34%) of patients with 50% considered significant (Gleason score ≥ 7). Downstaging was found in those who had neoadjuvant chemotherapy ($p = 0.001$).

Conclusions: The high prevalence of younger ages (less than 60), a high rate of upstaging, the presence of high-grade incidental prostate cancer, and lymph node positives in T2 de novo MIBC in Northern Ontario, warrants further investigation of potential causes and risk factors at individual, public, and population health levels in the region.

KEY WORDS: Bladder cancer; Cystectomy; Northern Ontario.

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INTRODUCTION

According to global cancer statistics, 3% of all new diagnosed cancer and 2.1% of all cancer mortality are due to bladder cancer (1).

Bladder cancer is linked to a number of important risk factors, the most prominent of which are smoking, occupational and environmental exposure to carcinogens, and conditions that cause chronic bladder irritation (2).

Toxins found in the environment, such as aromatic amines like benzidine and 2-naphthylamine, have been linked to up to 27% of bladder cancers (3).

A recent study could identify that patients older than 70-year-old with significant comorbidities have less favourable outcomes (4).

The projected average annual new cases of bladder cancer in 2018-2022 in Ontario has been estimated at 1950 for males and 660 for females (5). With this knowledge, we

sought to provide an overview of de novo T2 muscle invasive bladder cancer of patients who underwent a radical cystectomy in Thunder Bay in order to identify the characteristics of patients with clinically localized muscle invasive bladder carcinoma and to determine their clinical and pathological outcomes.

METHODS

This is a cross-sectional study that retrospectively examined the medical records of 59 patients with documented organ confined de novo T2 muscle invasive bladder cancer confirmed on a diagnostic TURBT who underwent radical cystectomy over a 2 year-period.

Clinical and pathological characteristics of TURBT and cystectomy were retrieved.

The analysis was conducted using IBM SPSS Software (version 19.0, SPSS Inc., Illinois, USA). The continuous data was presented as mean or median with standard deviation and compared using independent t-test while the categorical data was in percentages and compared using the chi-square test.

Statistical significance was defined as $p < 0.05$. A multivariate regression analysis was performed to identify the significant risk factors for upstaging.

RESULTS

The mean age of the patients was 67 ± 8.8 years. Those aged under 60 years old accounted for 27.1% of the sample. Eighty percent of patients were male. Based on final pathological results, upstaging was noted in 59.3% (T3 in 27.1% and T4 in 32.2%).

Thirty-six percent had node-positive disease. Prostate adenocarcinoma was incidentally discovered in 20 (34%) of patients. Significant high-grade prostate cancer was found in 50% of patients. Twenty patients (34%) had their surgery delayed for more than 12 weeks. Overall, 14 patients received neoadjuvant chemotherapy (NAC) (Table 1).

Younger patients (aged ≤ 60 years) had a higher prevalence of pathological upstaging (68.7% vs. 45.8%), as well as a higher chance of positive lymph nodes (37.5% vs. 34.9%), whereas older patients (age > 60) had a higher rate of incidental prostate cancer (34.9% vs. 31.3%). However, these findings were not statistically significant (Table 2).

Upstaging was observed in 30% of patients who had sur-

Table 1.
Characteristics of patients with preoperative T2 transitional cell carcinoma.

Variable	Value
Mean age (years)	67 ± 8.8 (51-88)
Age groups	
≤ 60	16 (27.1%)
> 61	43 (72.9%)
Sex	
Males	47 (80.0%)
Females	12 (20.0%)
Stage	
T0	9 (15.3%)
Ta/T1	6 (10.1%)
T2	9 (15.3%)
T3	16 (27.1%)
T4	19 (32.2%)
Positive Lymph Nods	
No	38 (64.0%)
Yes	21 (36.0%)
Incidental prostate cancer	
No	39 (66.0%)
Yes	20 (34.0%)
Grade of prostate cancer	
3 + 3	10 (50.0%)
3 + 4	8 (40.0%)
4 + 3	2 (10.0%)
Waiting time to surgery (weeks) Mean ± SD	13 ± 8
Wait time (weeks)	
< 6	21 (36.0%)
6- 12	18 (30.0%)
> 12	20 (34.0%)
Neoadjuvant chemotherapy (NAC)	
No	45 (76.0%)
Yes	14 (24.0%)

Table 2.
Comparison of the findings based on age.

Age	< 60 n = 16	> 60 n = 43	P value
Sex			
Males	13 (81.2%)	34 (79.1%)	1.0
Females	3 (18.8%)	9 (20.9%)	
Waiting time to surgery			
< 12	9 (56.2%)	30 (69.8%)	0.3
> 12	7 (43.8%)	13 (30.2%)	
Neoadjuvant chemotherapy (NAC)			
No	11 (68.7%)	34 (79.1%)	0.5
Yes	5 (31.3%)	9 (20.9%)	
Stage			
< T3	5 (31.3%)	19 (44.2%)	0.5
T3/ T4	11 (68.7%)	24 (45.8%)	
Lymph nodes invasion			
Negative	10 (62.5%)	28 (65.1%)	1.0
Positive	6 (37.5%)	15 (34.9%)	
Prostate cancer			
No	11 (68.7%)	28 (65.1%)	1.0
Yes	5 (31.3%)	15 (34.9%)	

gery delayed for more than 12 weeks, whereas upstaging was found in 74.3% of those who had surgery within 12 weeks, which is statistically different (p = 0.001). Not surprisingly, NAC was performed more in the delayed

Table 3.
Comparison of operation waiting time categories against clinical and pathological staging.

Waiting time to surgery	< 12 weeks n = 39	< 12 weeks n = 20	P value
Mean age	68 ± 8	65 ± 9	0.2
Stage			
< T3	10 (25.7%)	14 (70%)	0.001
T3/T4	29 (74.3%)	6 (30%)	
Lymph nodes			
Negative	23 (59%)	15 (75%)	0.2
Positive	16 (41%)	5 (25%)	
Neoadjuvant chemotherapy (NAC)			
Yes	1 (2.6%)	13 (65%)	0.001
No	38 (97.4%)	7 (35%)	

Table 4.
Comparison of patients with or without neoadjuvant chemotherapy (NAC) against clinical and pathological staging.

Neoadjuvant chemotherapy (NAC)	No n = 45	Yes n = 14	P value
Mean age (years)	68 ± 9	64 ± 7	0.1
Stage			
< T3	13 (28.9%)	11 (78.6%)	0.001
T3/T4	32 (71.1%)	3 (21.4%)	
Lymph nodes			
Negative	28 (62.2%)	10 (71.4%)	0.7
Positive	17 (37.8%)	4 (28.6%)	

Table 5.
Multivariate regression analysis for factors associated with upstaging.

	Odds ratio	95% Confident interval Lower limit	Upper limit	P value
Age	-0.23	-0.51	0.04	0.097
Gender	0.04	-0.28	0.36	0.809
Neoadjuvant chemotherapy	-0.38	-0.74	-0.02	0.041*
Waiting time to surgery	-0.08	-0.44	0.28	0.659

* P-value < 0.05 is significant.

group (92.8%) (Table 3). A significant difference in upstaging was found between those who had NAC, 3 (21.4%), and those who did not, 11 (78.6 %) (p = 0.001).

However, the invasion to the lymph nodes was not lower in those who received NAC compared to those who did not (Table 4).

Multivariate regression analysis revealed that NAC was the only factor associated with upstaging, while there was no significant association with other risk factor including age, gender, and waiting time to surgery (Table 5).

The pathology in those who received NAC are approximately 60% less likely to show upstaging (OR = -0.38, CI 95% = -0.74- -0.02) (Table 5).

DISCUSSION

The current case series in Northern Ontario draws attention to the high prevalence of MIBT in patients younger

than 60 years (27.1%), with a high rate of upstaging (68.7%) in this young group of patients.

The findings indicate that approximately 60% of clinically T2 MIBC were T3/T4 at final pathology.

Another highlight is the high rate of clinically significant prostate cancer (50%) in patients with incidental prostate cancer.

In terms of treatment, the findings showed that NAC was underutilized in Northern Ontario (76% did not receive NAC) and that no significant association was found between receiving NAC or delaying surgery and upstaging.

The majority of our patients were male, which was consistent with the literature (80% male vs. 20% female).

Our findings suggest that bladder cancer should not be emphasized in a purely geriatric population in Northern Ontario. The causes of bladder cancer in the younger age group, however, have not been well documented in the literature. According to the findings of a study conducted in *Montreal (Canada)*, natural gas combustion products, aromatic amines, cadmium compounds, photographic products, acrylic fibers, polyethylene, titanium dioxide, and chlorine were found to have weak evidence of being risk factors for bladder cancer.

Occupational exposures such as motor vehicle drivers, particularly among drivers in the motor transport industry, who were more likely to drive full time than drivers in other industries, textile dyers, construction painters, metal machinists and sheet metal workers, and aromatic amines were responsible for 6.5 percent of bladder cancer incidence (6). Another Canadian case control study discovered that miners, metal workers, mechanics, and male hairdressers were more likely to develop bladder cancer. They assumed that exposure to various combustion products and/or oils was a common theme in these occupations (7).

Epidemiological studies in Canada and other countries, including the United States, Italy, and France discovered that carcinogenic chemicals in tap water, such as chloroform and other trihalomethanes, are linked to an increased risk of bladder cancer (8, 9).

Peculiar environmental conditions can also expose this population to risk factors. Northern Ontario is one of the leading mining regions for nickel, copper, uranium, zinc, gold, platinum, and silver. Northern Ontario's economy is built on forestry, transshipment, and manufacturing industries such as textile, steel, pulp, and paper. Moreover, Northern Ontario is the transshipment point of agriculture products across Canada (10).

From the standpoint of public health, the high prevalence of younger age (60 years old) with MIBC in Northern Ontario appears to necessitate a transdisciplinary approach that includes medical, logistical, and municipal sectors to identify the risk factors and implement a multi-level strategy to address this issue.

The findings of our study revealed that a high percentage of patients with clinically T2 MIBC turned into T3/T4 with positive lymph nodes after cystectomy, and that the majority of these patients undergo surgery in less than 12 weeks. According to the pathological results of radical cystectomy, 59.3% of patients were diagnosed at the most advanced stages (T3/T4), and 36% developed node-posi-

tive disease. It is concerning to diagnose patients at such advanced stages.

These findings also emphasize early investigation which leads to earlier diagnosis and intervention with the expectation of a better outcome. In our study; the use of NAC was associated with 60% less likely finding of upstaging on final pathology and so a part of adverse pathological outcomes may be explained by the underutilization of NAC.

In general, delay in cancer diagnosis and treatment is classified into patient delay, health care provider delay, delay in service provider, and finally, treatment delay (11). It has been proposed that differences in socioeconomic status, rural or urban residency, and immigration status can all contribute to disparities in screening, diagnosis staging on presentation, and treatment services (12). Despite enormous efforts to provide equity in health care, the distribution of the population due to the geographic characteristics of Northern Ontario impede some regions from timely access and health monitoring. Moreover, there is only one hospital in all of Northern Ontario that provide urological cancer care.

This results in a long waiting list, making timely access to equitable care more difficult for the population.

Further research is also needed to investigate and identify the factors associated with bladder cancer patients' delayed diagnosis and late-stage presentation in Northern Ontario.

According to our findings, prostate cancer, which is the third leading cause of cancer death in Canadian males (5), was discovered incidentally (34%) during a cystectomy, which is consistent with literature reported 23-54% (13, 14). However, 50% of our patients had significant prostate cancer (Gleason score ≥ 7 out of 10), which is notably higher than literature. *Djaladat et al.* studied 1964 patients with primary transitional cell carcinoma of the bladder who underwent radical cystectomy.

Thirty six percent of the patients ($n = 559$) had incidental prostate cancer with the Gleason scores ≤ 6 for 458 (82%) patients (14).

Another study by *Mazzucchelli et al.* found that the majority (81.3%) of incidentally detected prostate cancers by radical cystoprostatectomy had a Gleason score of 4 or less (15). *Hiros et al.* reported 68% of incidental prostate cancer were low grade (Gleason scores less than 6) and 32% were high grade (16).

One study found that overall survival for patients with incidental prostate cancer was lower than for patients without (28.1 ± 27.5 month vs 45.5 ± 35 month). Given the significant impact on overall survival, they highlighted the importance of paying closer attention to this concurrent pathology (13).

Therefore, given the high prevalence of high grade prostate cancer in our population, it may be practical to assign a greater importance to performing prostate cancer screening during bladder cancer work-up, regardless of the patients' age. Furthermore, additional workup such as MRI to rule out prostate cancer is required if a patient chooses trimodal therapy.

Radical cystectomy is the standard treatment for patients with MIBC (17). However, the time of performing cystectomy is controversial. Some literature has shown that cys-

tectomy after 12 weeks is not associated with an unfavorable outcome (18, 19) while a population-based study and the *European Association of Urology* have recommended to not delay cystectomy for more than 3 months due to the increasing risk of progression and mortality (20). Based on *Canadian Urological Association guideline*, the optimal timing of radical cystectomy where NAC has not been administered is within six weeks of TURBT (21). According to our findings, upstaging was observed in 29 (74.3%) and 6 (30%) of patients who had surgery < 12 weeks and > 12 weeks, respectively. The lower likelihood of upstaging in > 12 week surgery waiting time can be interpreted that the delay in surgery for the sake of receiving NAC does not negatively affect the staging and progression. In our study, a lower upstaging rate was found in those who had NAC compared to those who did not (21.4% vs 71.1%). However, NAC did not significantly decrease the invasion to lymph nodes.

The advantages of NAC in patients with MIBC have been reported in literature. NAC is recommended to improve the outcome of radical cystectomy which is the gold standard of treatment in MIBC with a 5-year survival of about 50% (22). Accordingly, it seems that the rate of perioperative NAC in Ontario, Canada follows an increasing trend from 19% in 2009 to 27% in 2013 (23). However, the rate of perioperative NAC in our study was only 23.7%. Despite the survival benefit, practicing NAC has been underutilized in Northern Ontario. The finding of this study may prompt urologists and medical oncologists to incorporate NAC more frequently in their practice. Due to the lack of clinical outcomes, our findings cannot be interpreted as supporting or opposing the controversial opinions on surgery before or after 12 weeks. However, the findings suggest that the surgical delay of more than 12 weeks due to the NAC may not negatively impact the pathological outcomes.

The interpretation of the current study's results may be limited by the small sample size. Furthermore, including only one center negatively affects the external validity of the results while having a positive impact on improving the internal validity of the study.

We can conclude that the high rate of pathological upstaging detected in more than half of the patients undergoing radical cystectomy in this study warrants performing multidisciplinary quality improvements including pathology, medical and radiation oncology, and urology. Moreover, the high prevalence of younger ages (aged less than 60), upstaging, lymph positive in T2 de novo MIBC, call for further investigation of possible causes of delay and potential risk factors for bladder tumors at individual, public, and population health levels in Northern Ontario.

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