DOI: 10.4081/aiua.2022.3.291

ORIGINAL PAPER

Radical cystectomy for bladder urothelial carcinoma with aggressive variant histology

Vahid Mehrnoush, Logan Brennan, Asmaa Ismail, Ahmed Zakaria, Hazem Elmansy, Walid Shahrour, Owen Prowse, Ahmed Kotb

Urology Department, Northern Ontario School of Medicine, Thunder Bay Regional Health Centre, Ontario, Canada.

Summary

Purpose: *The aim of this study is to report our experience in managing bladder cancer in patients with variant pathology.*

Methods: *Retrospective data collection for all patients managed by radical cystectomy over the last 3 years for a variant pathology was completed. We specifically included micropapillary and nested variants.*

Results: *Ten patients were identified, with eight having micropapillary carcinoma (MPC) and two having nested variants. Nine patients were male. The median age was 75. The two patients with nested variant were 56 and 62 years old, respectively, whereas all patients with MPC were over the age of 70. Upon cystectomy of all micropapillary cases, three patients (37.5%) had positive lymph node invasion and the final pathology was T2 (two patients), T3 (two patients), and T4 (four patients). Barring a grade III complication Clavien-Dindo classification due to wound dehiscence that necessitated secondary surgical closure, there were no specific perioperative complications. Given the urethral invasion, cystourethrectomy was performed on the female patient. Within a median 13-month follow-up, three patients developed local recurrence, including two urethral and one new lateral pelvic mass.*

Conclusions: *Considering the muscle invasive nature of micropapillary and nested bladder cancer, aggressive surgical management should not be postponed. Moreover, due to notable prevalence of concurrent and/or recurrent urethral involvement, initial urethrectomy or early and frequent postoperative urethroscopy should be provided. Patients with variant histology bladder cancer may benefit from early radical cystectomy when compared to bladder sparing protocols and prostate sparing cystectomy treatment options.*

KEY WORDS: *Bladder cancer; Urothelial carcinoma; Variant histology; Radical cystectomy.*

Submitted 30 July 2022; Accepted 20 August 2022

INTRODUCTION

Bladder cancer varies along a wide spectrum of histological variants with urothelial cancer accounting for the vast majority (1, 2). Variant histology accounts for approximately 25% of bladder tumors that can pose distinctive diagnosis and therapy challenges to the overall management of bladder cancer (2). According to the World Health Organization 2016 classification, variant histology of bladder cancer includes urothelial carcinoma with divergent differentiation, such as lymphoepithelioma-like cell variant, sarcomatoid variant, plasmacytoid variant, microcystic variant, micropapillary variant, nested variant, and small cell type (2). Histologic variants are classified primarily based on morphology that is associated with a distinct biological behavior, such as proclivity for local recurrence and metastasis. Moreover there are variations in the clinical course including progression patterns and responses to therapy as well as biologic features in molecular subtypes and DNA alterations (3).

In the past, it was believed that urothelial tumors with divergent differentiation presented at a later stage of diagnosis, and earlier reports indicated a lower survival rate (4). Recent studies show that patients with squamous or glandular urothelial tumors have survival rates comparable to those with pure urothelial tumor (3, 5). In a study by *Sefik et al.* patients with variant histology were observed to have proportionally higher T stage compared to nonvariant urothelial carcinoma; however there were no significant differences for overall survival and cancer-specific survival (6). A recent study by *Pereira et al.* evidenced that although bladder cancers with histological variants are clearly associated with features of more aggressive behavior, they had not any significant impact in survival expectancies (7). Therefore, the clinical impact of tumor with variant histology on the treatment options still remains under a cloud of doubt in that whether the presence of variant histology justifies an aggressive treatment strategy involving early radical cystectomy (8). The final pathology and prognosis of bladder cancer with variant histology differ from that of pure urothelial bladder cancer, and evidence on the response to systemic therapy in these variant histologies is scarce and divergent (9, 10). Current guidelines place urothelial carcinoma with variant histology in the highest risk category, implying that, despite lacking high level of evidence, early radical cystectomy should be considered (11). It is noteworthy, when it comes to management, evidence in some areas is contradictory and inconclusive therefore necessitating further investigation. Our study aims to share our institution experience in treating bladder cancer with variant histology.

METHODS

A retrospective cohort single center study involving all patients who were treated for bladder cancer with a histological variant admitted to the *Thunder Bay Regional*

No conflict of interest declared.

Health Science Centre. Our patients were treated with either a radical cystectomy or a *transurethral resection of the bladder tumor* (TURBT) alone, or a TURBT combined with adjuvant BCG therapy.

Results

Ten patients (9 male and 1 female) were identified, with eight having micropapillary cancer and two having nested variants. The median age was 75 (56-84). The two patients with the nested variant were 56 and 62 years old, respectively, whereas all patients with *micropapillary cancer* (MPC) were over the age of 70. Of nested variant patients, one patient had a domal T1 tumor and the other had a T2 small trigonal tumor.

Localized cancer was confirmed by staging CT scans. Upon radical cystoprostatectomy, the final pathology for the first patient was pT2N0, while the second patient was pT4aN1. Of the patients with MPC, two were reported to have stage T1 tumors, while six were reported to have stage T2 tumors on TURBT. Stage T4b was found on CT scan in two patients. Despite the instillation of intravesical *bacillus Calmette-Gue'rin* (BCG) induction course, upstaging to T2 was reported in both T1 cases. Upon cystectomy for all micropapillary cases, three patients (37.5%) had positive lymph node invasion and the final pathology came back T2 (two patients), T3 (two patients), and T4 (four patients).

Barring a grade III complication Clavien-Dindo classification due to wound dehiscence that necessitated secondary surgical closure, there were no specific perioperative complications). Given the urethral invasion, the cystourethrectomy was performed on the female patient. Within a median 13-month follow-up, three patients (30%) developed local recurrence, including two urethral and one new lateral pelvic mass.

Table 1 illustrates the clinical characteristics and outcomes to the patients and Figures 1 and 2 represent two cases with micropapillary and nested variant urothelial carcinoma respectively.

Table 1.
Clinical characteristics and outcomes of all cases.

Median age		75 (56- 84)
Sex	Males	9
	Females	1
Histology	Micropapillary	8
	Nested	2
TURBT stage	T1	3
	T2	7
Final T pathology (cystectomy)	T1	0
	T2	3
	T3	2
	T4	5
Final N stage	N0	7
	N1	3
Urethral invasion	No	7
	Present at cystectomy	1
	Early (within 6 months)	2
Local recurrence (within 1 year)	No	7
	Urethra	2
	Pelvic side wall	1

Figure 1.
Abdominal axial CT image showing a large cT4 micropapillary cancer.

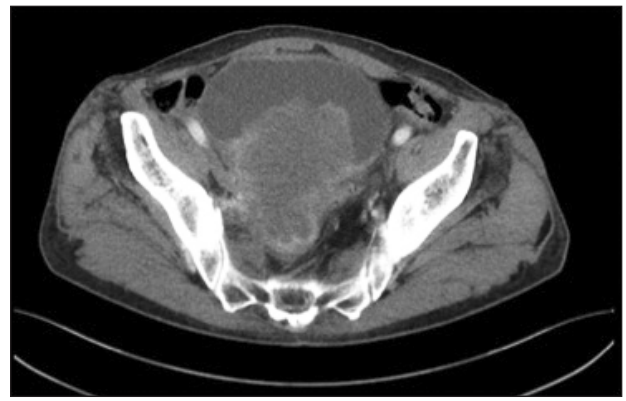
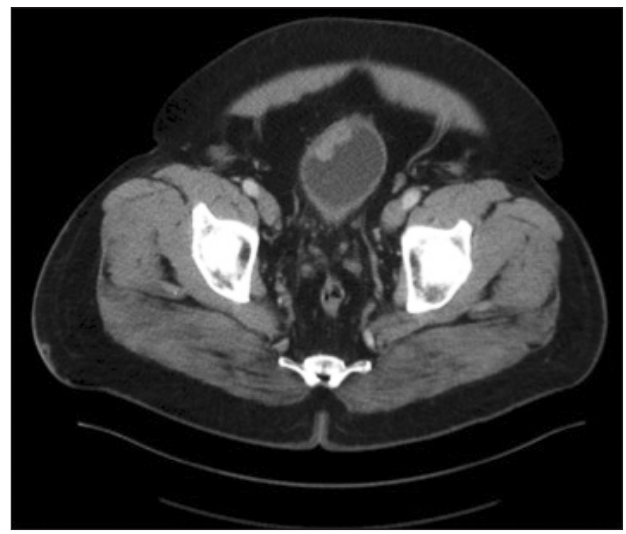


Figure 2.
Abdominal axial CT showing cT1 nested variant.



Discussion

The current study is a report on our experience in treating bladder cancer with aggressive variant histology. *Micropapillary urothelial carcinoma* (MPC) was a male-predominant variant found in our patients. MPC has received the most attention of the variant histologies in recent years and may be more familiar to many pathologists than other variants (8). Clinically, it is an aggressive variant that typically manifests at an advanced stage and accounts for 2-5% of urothelial carcinomas (8) which have a poor prognosis (12). The fast progression of non-muscle invasive micropapillary urothelial carcinoma to muscle invasive or metastatic bladder carcinoma is concerning and is a well demonstrated concern in our cases (13).

MPC is tightly linked to lymph vascular invasion and lymph node metastasis, in that pT1 bladder cancer with micropapillary variant is frequently upstaged to more advanced stages during investigation and treatment (12).

As a result, the *European Association of Urology-European Society* of *Medical Oncology Guidelines Committees* recently agreed that T1 high-grade bladder urothelial carcinoma with micropapillary histology should be treated with immediate radical cystectomy and lymphadenectomy (11). Therefore, in such cases, most centers consider early radical cystectomy to be the standard of care; however, there have been reports of reasonable outcomes in series in which bladder preservation therapies were used in highly selected patients with a relatively small micropapillary component (14). Although there is still limited evidence on the preferred treatment option, reports show no statistically significant differences in overall survival between groups that received neoadjuvant chemotherapy plus early radical cystectomy *vs.* radical cystectomy alone in muscle-invasive micropapillary urothelial carcinoma (15, 16). On the other hand, evidence is lacking on the added benefit of neoadjuvant chemotherapy to the treatment of the bladder cancers with variant histology (17).

A study on patients with muscle-invasive urothelial carcinoma with variant histology comparing neoadjuvant chemotherapy plus radical cystectomy *vs.* early radical cystectomy only showed an improvement in overall survival and a lower rate of non-organ-confined disease at the time of radical cystectomy in patients with neuroendocrine tumor neoadjuvant chemotherapy. Neoadjuvant chemotherapy reduced the rate of non-organ-confined disease but had no effect on overall survival in bladder tumors with micropapillary differentiation, sarcomatoid differentiation, or adenocarcinoma (9). Evidence also recommended that muscle-invasive bladder urothelial carcinoma with micropapillary or plasmacytoid differentiation, as well as squamous or glandular differentiation, should be treated with neoadjuvant chemotherapy followed by radical cystectomy and concomitant lymphadenectomy (11).

The role of adjuvant radiotherapy for muscle-invasive urothelial carcinoma and variant histologies is controversial. Some evidence recommends that adjuvant radiotherapy (with or without radiosensitizing chemotherapy) is a standard treatment for patients with muscle-invasive urothelial carcinoma with variant histology (11, 18). Other evidence states that it is prudent to consider adjuvant radiotherapy to improve local control. This is particularly important in cases with positive margins like patients with urothelial carcinoma with squamous and/or glandular differentiation who are more likely to have pT3-T4 tumors, pelvic lymph node involvement, and local or distant metastasis-related to increased mortality when compared to those with pure urothelial carcinoma (19-21).

It has been reported that the response rate to intravesical BCG administration for micropapillary variant is poor (11, 22).

In a study of 72 patients with MPC, 40 received primary intravesical BCG and 26 received early radical cystectomy. The BCG group were more inclined to recurrence, progression, and lymph node metastasis at a 75%, 45%, and 35% rate, respectively 22. While certain patients with T1 MPC may respond to intravesical BCG, patients who undergo early radical cystectomy have improved survival outcome (22). In our center, we tried a BCG induction course for patients with T1, but due to T2 progression, they eventually underwent radical cystectomy.

Nested variant urothelial carcinoma is more common in men over the age of 60, which is similar to the occurrence of classic urothelial carcinoma; however, it has been reported in patients ranging in age from 42 to 90 years (23). In our findings, the nested variant, in contrast to MPC, were found in younger cases. The nested variant, according to the 2016 WHO classification, includes urothelial carcinoma with small tubules and microcysts (24). It is distinguished by disorderly proliferation of confluent nests with minimal cell atypia (25) which is frequently mistaken for benign cytology that leads to a delay in the definitive diagnosis. Nested urothelial carcinomas typically manifest as advanced disease and may be associated with a poor prognosis when compared to pure urothelial carcinoma (26). It has similar characteristics and clinical outcomes to classical urothelial carcinoma, with little to no difference in recurrence or survival rate when treated with radical cystectomy in either non muscle invasive or muscle invasive bladder cancer (25). Data from two matched cohorts revealed that patients with nested variants had similar oncological outcomes after radical cystectomy compared to pure urothelial carcinoma (27, 28). Although lacking consensus due to a lack of evidence, it is recommended that T1 high-grade bladder urothelial carcinoma with nested variants confirmed (after complete TURBT and/or re-TURBT) should be treated with immediate radical cystectomy and concomitant lymph node dissection (11).

The treatment of bladder cancer including transurethral surgery, intravesical chemotherapy and immunotherapy, radical cystectomy, systemic combination chemotherapy, and, in some cases, radiation therapy has evolved over time to the point where clinical risk markers are now employed to make the best decision for patients. As a result, variant histology can serve as a risk stratification factor that can contribute to improved clinical decision making (17).

Conclusions

Aggressive surgical treatment for patients with micropapillary and nested muscle invasive bladder cancer should not be postponed. A large proportion of these patients have urethral involvement.

Thus, an initial urethrectomy or early and frequent postoperative urethroscopy should be included in the treatment and management of variant histology bladder cancers. For bladder cancer with variant histology, bladder sparing protocols and prostate sparing cystectomy may not be the best treatment options.

Key messages

1. Urothelial variant bladder cancer is always upstaged on radical cystectomy.
2. Radical cystectomy for T1 variant histology should be offered rather than surveillance.
3. Urethrectomy may be considered at time of radical cystectomy.
4. Urothelial variant histology was a male predominant finding in our series.

References

1. *Chalasani V, Chin JL, Izawa JI. Histologic variants of urothelial bladder cancer and nonurothelial histology in bladder cancer. Can Urol Assoc J. 2009; 3(6 Suppl 4):193-198.*

2. *Humphrey PA, Moch H, Cubilla AL, et al. The 2016 WHO Classification of tumours of the urinary system and male genital organs-part B: prostate and bladder tumours. Eur Urol. 2016; 70:106-119.*

3. *Burger M, Kamat AM, McConkey D. Does variant histology change management of non-muscle-invasive bladder cancer? Eur Urol Oncol. 2021; 4:510-514.*

4. *Shapur NK, Katz R, Pode D, et al. Is radical cystectomy mandatory in every patient with variant histology of bladder cancer. Rare Tumors. 2011; 3:e22.*

5. *Barata PC, Rini BI. Treatment of renal cell carcinoma: Current status and future directions. CA Cancer J Clin. 2017; 67:507-524.*

6. *Sefik E, Celik S, Basmaci I, et al. Effect of variant histology presence and squamous differentiation on oncological results and patient's survival after radical cystectomy. Arch Ital Urol Androl. 2018; 90:172-175.*

7. *Pereira JN, Reis JD, Braga I, et al. Variant histologies of urothelial carcinoma: Does it change the survival outcomes in patients managed with radical cystectomy? Arch Ital Urol Androl. 2022; 94:138-143.*

8. *Black AJ, Black PC. Variant histology in bladder cancer: diagnostic and clinical implications. Transl Cancer Res. 2020; 9:6565-6575.*

9. *Vetterlein MW, Wankowicz SAM, Seisen T, et al. Neoadjuvant chemotherapy prior to radical cystectomy for muscle-invasive bladder cancer with variant histology. Cancer. 2017; 123:4346-4355.*

10. *Choi W, Porten S, Kim S, et al. Identification of distinct basal and luminal subtypes of muscle-invasive bladder cancer with different sensitivities to frontline chemotherapy. Cancer Cell. 2014; 25:152-165.*

11. *Horwich A, Babjuk M, Bellmunt J, et al. EAU–ESMO consensus statements on the management of advanced and variant bladder cancer—an international collaborative multi-stakeholder effort: under the auspices of the EAU and ESMO Guidelines Committees. Ann Oncol. 2019; 30:1697-1727.*

12. *Compérat E, Roupret M, Yaxley J, et al. Micropapillary urothelial carcinoma of the urinary bladder: a clinicopathological analysis of 72 cases. Pathology. 2010; 42:650-654.*

13. *Ramos P, Pereira P, Dinis P, Pacheco-Figueiredo L. Bladder cancer variant histologies: epidemiology, diagnosis, treatment and prognosis. In Ed F. Ziglioli Modern approach to diagnosis and treatment of bladder cancer. IntechOpen 2021.*

14. *Berg S, D'Andrea D, Vetterlein MW, et al. Impact of adjuvant chemotherapy in patients with adverse features and variant histology at radical cystectomy for muscle-invasive carcinoma of the bladder: Does histologic subtype matter? Cancer. 2019; 125:1449-1458.*

15. *Lobo N, Shariat SF, Guo CC, et al. What is the significance of variant histology in urothelial carcinoma? Eur Urol Focus. 2020; 6:653-663.*

16. *Sui W, Matulay JT, James MB, et al. Micropapillary bladder cancer: insights from the National Cancer Database. Bladder Cancer. 2016; 2:415-423.*

17. *Black PC, Brown GA, Dinney CPN. The impact of variant histology on the outcome of bladder cancer treated with curative intent. Urol Oncol. 2009; 27:3-7.*

18. *Chua KLM, Kusumawidjaja G, Murgic J, Chua MLK. Adjuvant treatment following radical cystectomy for muscle-invasive urothelial carcinoma and variant histologies: Is there a role for radiotherapy? ESMO open. 2016; 1:e000123.*

19. *Honma I, Masumori N, Sato E, et al. Local recurrence after radical cystectomy for invasive bladder cancer: an analysis of predictive factors. Urology. 2004; 64:744-748.*

20. *Zaghloul MS, Awwad HK, Akoush HH, et al. Postoperative radiotherapy of carcinoma in bilharzial bladder: improved disease free survival through improving local control. Int J Radiat Oncol Biol Phys. 1992; 23:511-517.*

21. *Lewis GD, Haque W, Verma V, et al. The role of adjuvant radiation therapy in locally advanced bladder cancer. Bladder Cancer. 2018; 4:205-213.*

22. *Willis DL, Fernandez MI, Dickstein RJ, et al. Clinical outcomes of cT1 micropapillary bladder cancer. J Urol. 2015; 193:1129-1134.*

23. *Venyo AK. Nested variant of urothelial carcinoma. Adv Urol. 2014; 2014:192720.*

24. *Warrick JI. Clinical significance of histologic variants of bladder cancer. J Natl Compr Canc Netw. 2017; 15:1268-1274.*

25. *Aron M. Variant histology in bladder cancer-current understanding of pathologic subtypes. Curr Urol Rep. 2019; 20:80.*

26. *Lopez-Beltran A, Henriques V, Montironi R, et al. Variants and new entities of bladder cancer. Histopathology. 2019; 74:77-96.*

27. *Beltran AL, Cheng L, Montironi R, et al. Clinicopathological characteristics and outcome of nested carcinoma of the urinary bladder. Virchows Arch. 2014; 465:199-205.*

28. *Linder BJ, Frank I, Cheville JC, et al. Outcomes following radical cystectomy for nested variant of urothelial carcinoma: a matched cohort analysis. J Urol. 2013; 189:1670-1675.*

Correspondence

Vahid Mehrnoush, MD
vahidmehrnoush7@gmail.com

Logan Brennan
lobrennan@nosm.ca

Asmaa Ismail
asmaaismail0782@gmail.com

Ahmed Zakaria
aszakaria81@yahoo.com

Hazem Elmansy
hazemuro100@yahoo.com

Walid Shahrour
walid.shahrour@gmail.com

Owen Prowse
owen.prowse@tbh.net

Ahmed Kotb (Corresponding Author)
drahmedfali@gmail.com

Urology Department, Northern Ontario School of Medicine, Thunder Bay Regional Health Centre, Ontario, Canada