Survival of primary adenocarcinoma of the urinary bladder after radical treatment: National Cancer Institute, 5-years' experience

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Introduction
Primary adenocarcinoma of the urinary bladder (UB) is rare but often aggressive urologic cancer. It represents 0.5–2% of all bladder cancers and affects patients mostly in their sixth decade of life. The incidence is greater in areas where bilharziasis is endemic and is more common in men than women.

Aim of the work
The aim of the study was to review this rare UB malignancy with special emphasis on patients' survival including; disease-free survival (DFS) and overall survival (OS) in relation to different clinical and pathological factors.

Patients and methods
We conducted this retrospective review of 40 patients with primary UB adenocarcinoma who were treated and followed up in the National Cancer Institute, Cairo University between January 2013 and December 2017.

Results
The study included 40 patients with a male to female ratio of 82.5 : 17.5%. The mean age at diagnosis was 61 years. Hematuria was the most common presenting symptom followed by dysuria and frequency. Pathologically, stage III disease, tumor grade II, and adenocarcinoma, not otherwise specified, were the most common findings. Radical cystectomy was done in 82.5% of cases, while anterior pelvic exenteration was done in 17.55% of cases followed in both by different methods of urinary diversions. The median follow-up was 31 months, and the 2-year DFS of all patients was 60.7%. Two-year DFS was significantly affected by tumor grade, disease stage, and lymph node (LN) status (P=0.019, 0.021, 0.001, respectively). Furthermore, 3-year OS of all groups was 57% with a median follow-up of 39.9 month. Tumor grade, disease stage, and LN involvement had an impact on OS. However, the only statistically significant effect is due to LN involvement (P=0.037).

Conclusion
Patients with UB adenocarcinoma commonly present in an advanced disease. DFS and OS are affected by disease stage, tumor grade, and LN involvement. We recommend radical rather than any form of conservative surgery as a primary treatment modality.

Keywords:
adenocarcinoma, survival, urinary bladder

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Introduction

Adenocarcinoma of the urinary bladder (UB) is the third most common histologic type of bladder carcinoma. It accounts for 0.5–2.0% of all bladder tumors [1] with urachal carcinoma representing 0.34–0.7% [2]. In addition, adenocarcinoma of the bladder may also occur in association with schistosomiasis, endometriosis, bladder augmentation, and other irritative conditions of the UB [3]

Adenocarcinoma of the UB is classified according to its origin into three categories: primary, urachal, and metastatic [4]. The pathogenesis of primary nonurachal adenocarcinoma is based on the ability of the urothelium to undergo metaplastic changes. Mostofi and colleagues proposed that the metaplastic potential of the urothelium has two distinct patterns. Progressive invagination of hyperplastic epithelial buds into the lamina propria (von Brunn's nests) leading to the formation of cystitis cystica. Subsequently, metaplasia of the urothelial lining of these cysts to columnar mucin-producing cells results in the production of cystitis glandularis, which is a premalignant lesion [5]. Chronic vesical irritation and infection are the predisposing factors for these changes. This explains

the higher incidence of these tumors among patients with bilharzial cystitis [6].

The WHO 2016 classification of bladder adenocarcinoma is as follows: enteric, mucinous, mixed, and adenocarcinoma, not otherwise specified (NOS) [7].

In most of the patients, primary adenocarcinoma of the bladder presents with hematuria, which may be associated with irritative voiding symptoms and, occasionally, passage of mucus in the urine. In addition, it shows a male predominance, with a male to female ratio of 2.7 : 1 [8]. The prognostic factors for bladder adenocarcinoma outcomes have been reported to include tumor stage, grade, and lymph node (LN) involvement [8]. Recently, it has been identified that tumor locations in the urachus and dome of the bladder were associated with favorable survival and better oncological outcomes, whereas basal location confers poorer outcomes [9].

Patients and methods

Patients and methods :This is a retrospective study of 40 patients with primary adenocarcinoma of the UB who presented and treated at the National Cancer Institute, Cairo University from January 2013 to December 2017 after obtaining IRB approval. All patients signed informed consent. All patients were subjected to radical surgery in the form of radical cystectomy or anterior pelvic exenteration plus pelvic lymphadenectomy. Only patients with final pathology of primary UB adenocarcinoma were included. The pathologic specimens were reviewed by the same pathologist and were subclassified according to the Grignon *et al.* [10] classification. Any specimens with extension to the prostate had to be proven primary UB adenocarcinoma by negative immunohistochemical stain for prostatic specific antigen to be included in the study. Pathologically, primary UB adenocarcinoma was divided into four histological subtypes: (a) enteric (papillary), when the architectural and cytologic features resembled those of the typical colonic adenocarcinoma; (b) mucinous, when the tumor was characterized by single cells or nests of cells floating in lakes of extracellular mucin; (c) signet ring, when the tumor was composed of single signet-ring cells diffusely permeating the tissues; and (d) adenocarcinoma NOS, when the pattern did not fit into any of these previously mentioned categories. Patients and tumor characteristics were reviewed in detail. Different treatment modalities including the type of radical surgery, type of urinary diversion, and adjuvant therapy were thoroughly documented.

All patients were kept under close follow-up that ranged between 21.9 and 40.2 months, with a median of 31.3 months. During follow-up, the patients were examined clinically and evaluated radiologically for any suspicious symptoms or signs of treatment failure. Any local, regional, or distant failure was documented.

Statistical analysis

Comparison between different percentages and frequencies were performed using the standard Student's t test, F test, and χ^2 test. The 5-year disease-free survival (DFS) rates, local control rates, and distant metastasis-free rates were measured using the Kaplan–Meier product limit method. The log-rank test was used for comparison between survival curves. The Cox multivariate analysis was performed to determine the independent prognostic variables that affected the DFS, local control, and distant metastasis-free rates.

Results

The study included 40 patients diagnosed with primary adenocarcinoma of UB treated and followed up at the National Cancer Institute, Cairo University during the period from January 2013 to December 2017. The mean age at diagnosis was 61 years ranging from 35 to 85 years. Male to female ratio was 82.5 : 17.5%. Four (10%) patients were diabetic, seven (17.5%) patients were hypertensive, and 26 (65%) patients were smokers. History of schistosomiasis infestation was noticed in 21 (52.5%) patients, ignored in 12 (30%) patients, and not known in seven (17.5%) patients (Table 1).

The most frequent symptoms were hematuria, dysuria, and others like frequency and urgency [31 (77.5%) patients, 17 (47.5%) patients, and five (12.5%) patients, respectively] (Fig. 1).

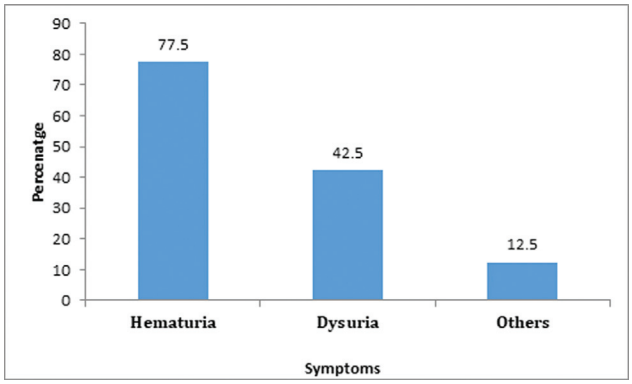
All patients underwent radical surgery and urinary diversion as follows: radical cystectomy and pelvic lymphadenectomy was done in 33 (82.5%) male patients while anterior pelvic exenteration and pelvic lymphadenectomy was done in seven (17.5%) female patients. Different types of urinary diversion were done including ileal loop conduit in 22 (55%) patients, orthotopic neobladder in 10 (25%) patients (ileocecal pouch in six patients and ileal Y-Pouch in four patients). Uretero-cutaneous diversion was done in six (15%) patients, while two (5%) patients underwent Indiana pouch diversion (Fig. 2).

Table 1 Characteristics of the patients

Patient characteristics	*n* (%)
Age (years)	
Mean±SD	61.1±11.6
Range	35–85
Sex [*n* (%)]	
Female	7 (17.5)
Male	33 (82.5)
Residency [*n* (%)]	
Rural	23 (57.5)
Urban	17 (42.5)
Comorbidity [*n* (%)]	
Yes	13 (32.5)
DM	6 (15.0)
HTN	7 (17.5)
Smoking [*n* (%)]	
Yes	26 (65.0)
No	14 (35.0)
Schistosomiasis [*n* (%)]	
Yes	21 (52.5)
No	12 (30.0)
Not known	7 (17.5)
Symptoms [*n* (%)]	
Hematuria	31 (77.5)
Dysuria	17 (42.5)
Others	5 (12.5)

DM, diabetes mellitus; HTN, hypertension.

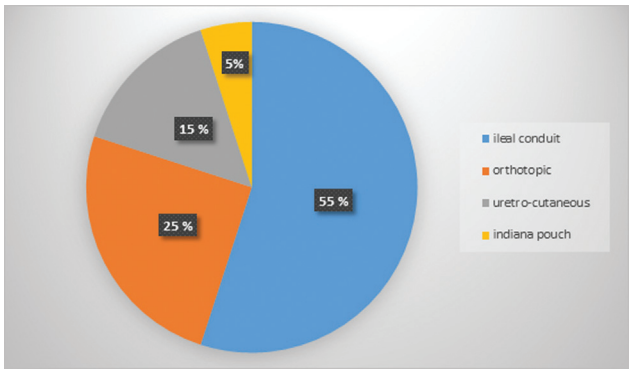
Figure 1



Common presenting symptoms.

Detailed postoperative histopathology showed a predominance of adenocarcinoma NOS followed by adenocarcinoma with signet-ring cell differentiation and then mucinous adenocarcinoma and finally enteric-type adenocarcinoma [21 (52.5%) patients, nine (22.5%) patients, six (15%) patients, four (10%) patients, respectively]. Tumor grade II was found in 21 (52.5%) patients, grade III in 17 (42.5%) patients, and grade I in only two (5%) patients. Pelvic lymphadenectomy showed positive metastatic LNs in 13 (32.5%) patients and negative LNs for metastases in 27 (68.5%) patients. TNM staging system showed 16 (40%) patients stage III, 13 (32.5%) patients stage IV,

Figure 2



Different types of UD. UD, urinary diversion.

Table 2 Postoperative pathologic results

	n (%)
Postoperative pathology	
Adenocarcinoma NOS	21 (52.5)
Adenocarcinoma with signet-ring differentiation	9 (22.5)
Mucinous adenocarcinoma	6 (15)
Adenocarcinoma enteric type	4 (10.0)
Associated	
Bilharzial eggs	8 (20.0)
Cystitis glandularis	2 (5.0)
Grade	
I	2 (5.0)
II	21 (52.5)
III	17 (42.5)
Stage	
I	2 (5.0)
II	9 (22.5)
III	16 (40.0)
IV	13 (32.5)
Lymph nodes	
Negative	27 (67.5)
Positive	13 (32.5)

NOS, not otherwise specified.

Table 3 Tumor locations within the urinary bladder

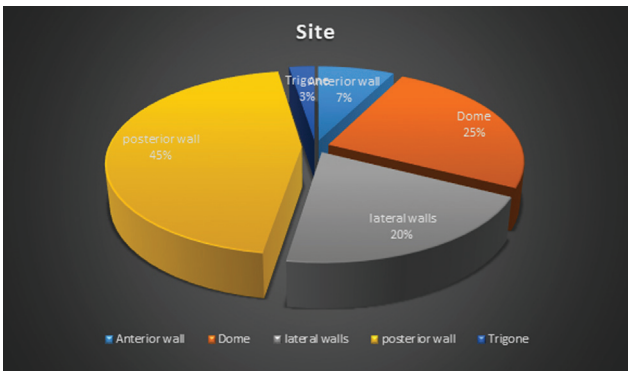
	n (%)
Site	
Anterior wall	3 (7.5)
Dome	10 (25)
Lateral walls	8 (20)
Posterior wall	18 (45)
Trigone	1 (2.5)
Total	40 (100)

nine (22.5%) patients stage II, and two (5%) patients of stage I (Table 2).

Tumor locations within the UB is shown in Table 3 and Fig. 3 where the most common tumor locations were the posterior bladder wall and the dome of the bladder (45.5 and 25%, respectively).

During the follow-up period, treatment failure was detected in 12 (30%) patients and was fractionated as follows: loco-regional recurrence in seven (17.5%) patients including six (15%) patients with iliac and para-aortic nodal recurrence and one (2.5%) patient with intestinal recurrence after ileocecal orthotopic diversion, distant metastasis in three (7.5%) patients in addition to loco-regional recurrence plus distant metastases in two (5%) patients.

Figure 3



Tumor location within UB. UB, urinary bladder.

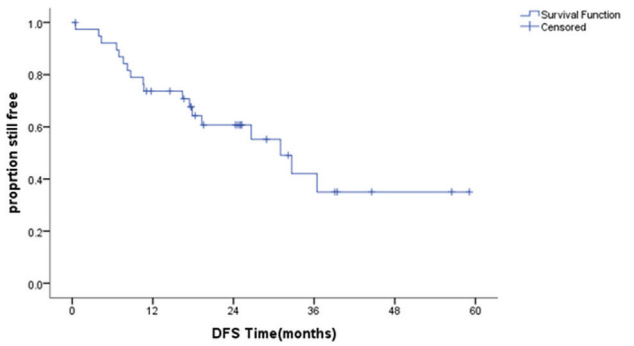
The median follow-up period was 31 months, and the 2-year DFS of all patients was 60.7% (Table 4, Fig. 4). Two-year DFS for tumor grades (I–II) was 85.7%, while it dropped to 28.6% for grade III (P=0.019) (Fig. 5). Two-year DFS for patients with early stages of the disease (I, II) was 100% compared with 48% in late stages (III, IV) with a P value of 0.021. There was also significant difference between both groups (early vs. advanced disease) in 3-year DFS (75 vs. 24%, respectively) (Fig. 6). In regard to the effect of LN metastases on DFS, patients with negative LN

Table 4 Disease-free survival

Factors	*n*	DFS (%)				Median (months)	*P* value
		1 year	2 years	3 years	5 years	95% CI	
All	39	73.3	60.7	35.0	NA	31.3 (21.9–40.2)	NA
Sex							
Male	32	71.9	56.7	33.1	NA	31.0 (0.5–74.6)	0.513
Female	7	83.3	83.3	41.7	NA	26.6 (8.8–44.5)	
Age (years)							
≤62	19	72.2	72.2	45.1	NA	31.0	0.613
>62	20	75.0	51.6	31.0	NA	32.6 (9.8–55.6)	
Comorbidity							
No	27	65.4	54.6	31.2	NA	26.6 (12.5–40.7)	0.232
Yes	12	91.7	73.7	36.7	NA	32.7 (11.5–53.8)	
Smoking							
No	14	84.6	66.6	41.6	NA	31.0 (20.7–41.3)	0.619
Yes	25	68.0	58.2	29.1	NA	32.7 (6.1–29.3)	
Grade							
I–II	22	85.7	85.7	43.5	NA	36.4 (28.8–44.1)	**0.019**
III	17	58.2	28.6	28.6	NA	17.4 (9.0–25.9)	
Stage							
Early (I, II)	10	100	100	75.0	NA	NA	**0.021**
Late (III, IV)	29	65.5	48.0	24.0	NA	19.3 (4.3–34.3)	
Adjuvant							
No	27	73.0	58.8	47.1	NA	32.7	0.704
Yes	12	75.0	65.6	17.5	NA	31.0 (17.5–44.5)	
LN							
Negative	26	84.0	78.8	58.3	NA	NA	**0.001**
Positive	13	53.8	28.8	NA	NA	16.4 (8.3–24.5)	
Pathology							
Adenocarcinoma NOS	21	80.0	80.0	66.7	NA	NA	0.097
Signet ring	9	66.7	41.7	NA	NA	19.3 (14.8–23.7)	
Mucinous	4	50.0	50.0	0	NA	10.6 (0.5–34.2)	
Site							
Lateral	7	85.7	57.1	57.1	NA	NA	0.841
Dome	11	72.2	62.3	46.8	NA	31.0	
Posterior	21	70.0	62.0	25.9	NA	32.7 (15.6–49.6)	

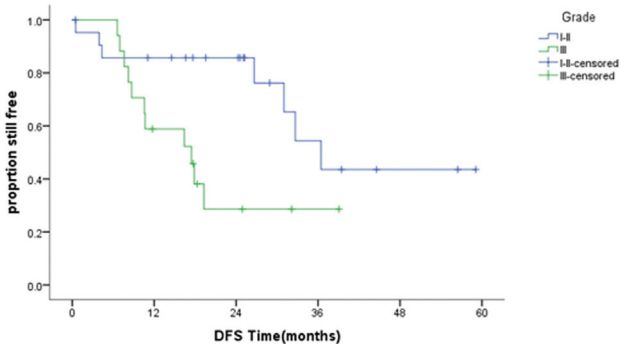
CI, confidence interval' DFS, disease-free survival; LN, lymph node; NOS, not otherwise specified. Bold value means it is clinically significant.

Figure 4



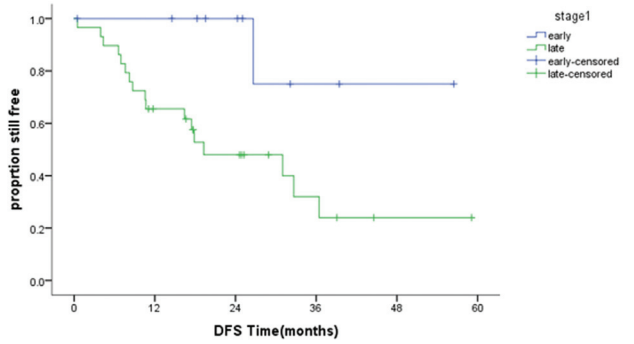
DFS for all patients. DFS, disease-free survival.

Figure 5



DFS in relation to the tumor grade. DFS, disease-free survival.

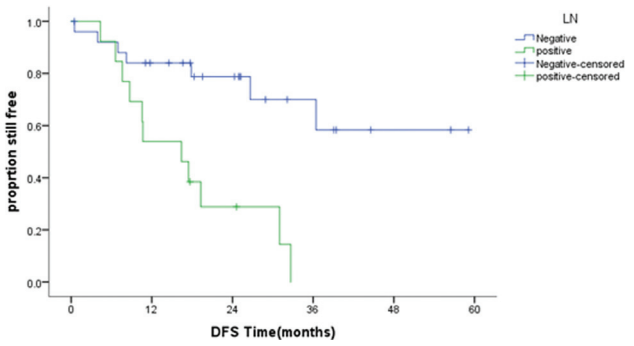
Figure 6



DFS in relation to different disease stages. DFS, disease-free survival.

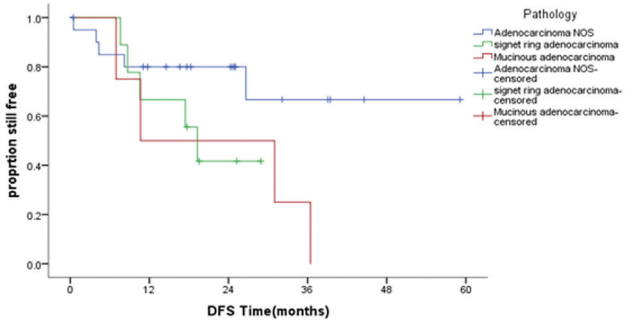
involvement showed a 2-year DFS of 78.8% while in patients with positive LN involvement, 2-year DFS was 28.8% (P=0.001) (Fig. 7). It was found that adenocarcinoma subtype had an impact on DFS, as 2-year DFS for adenocarcinoma NOS was 80%, for mucinous adenocarcinoma was 50%, and for signet-ring adenocarcinoma it was 41.7%. However, these differences were of borderline significance statistically (P=0.09) (Fig. 8). Furthermore, 3-year overall survival (OS) of all groups was 57% with a median follow-up of 39.9 month (Table 5, Fig. 9). Tumor grade, disease stage,

Figure 7



DFS in relation to LN metastases. DFS, disease-free survival; LN, lymph node.

Figure 8



DFS in relation to the subtype of adenocarcinoma. DFS, disease-free survival.

and LN involvement had an impact on OS. However, the only statistically significant value was due to LN involvement (P=0.037) (Figs 10–13). The other factors was of borderline significance mainly due to the small number of cases and the short period of follow-up.

Discussion

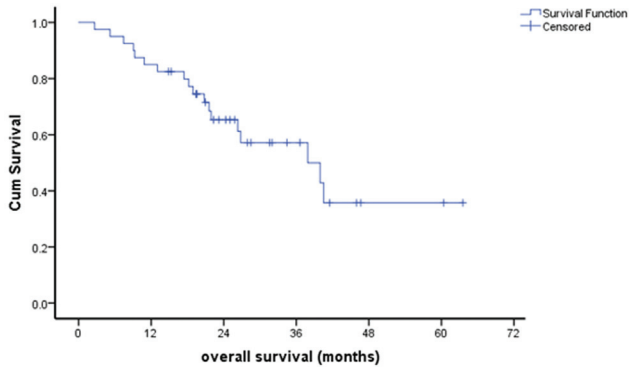
Adenocarcinoma is a rare malignancy of the UB which may arise primarily in the bladder as well as secondarily from a number of other organs. Primary UB adenocarcinoma exhibits several different growth patterns, including enteric, mucinous, signet-ring cell, adenocarcinoma NOS, and mixed patterns. Urachal adenocarcinoma demonstrates similar histologic features but it can be distinguished from bladder adenocarcinoma on careful pathological examination. Noninvasive neoplastic glandular lesions, adenocarcinoma *in situ*, and villous adenoma are frequently associated with bladder adenocarcinoma. Primary UB adenocarcinoma has a poor prognosis largely because it is usually diagnosed at an advanced stage. Urachal adenocarcinoma shares similar histologic features with bladder adenocarcinoma, but it has a more favorable prognosis than bladder

Table 5 Overall survival

Factors	*n*	Overall survival (%)				Median (months)	*P* value
		1 year	2 years	3 years	5 years	95% CI	
All	40	85.0	65.3	57.2	35.7	39.9 (20.2–59.6)	NA
Sex							
Male	33	87.9	64.6	55.4	36.9	37.9 (20.9–54.8)	0.902
Female	7	71.4	71.4	71.4	35.7	39.9 (0.5–90.7)	
Age (years)							
≤62	20	75.0	62.3	62.3	46.7	39.9	0.846
>62	20	90.0	68.9	53.6	26.8	37.9 (21.7–54.1)	
Comorbidity							
No	27	81.5	57.9	52.1	31.3	37.9 (13.2–62.6)	0.362
Yes	13	92.3	76.9	64.1	NA	40.5 (15.1–65.9)	
Smoking							
No	14	85.7	62.3	62.3	41.6	39.9 (1.9–77.9)	0.979
Yes	26	84.6	67.3	55.1	33.0	37.9 (11.7–64.0)	
Grade							
I–II	23	82.6	77.4	77.4	44.3	40.5 (38.9–42.2)	0.070
III	17	88.2	48.3	32.3	NA	21.9 (13.1–30.7)	
Stage							
Early	11	81.8	81.8	81.8	81.8	NA	0.091
Late	29	86.2	58.1	48.4	24.2	26.8 (8.6–45.3)	
Complications							
No	20	100	82.6	73.5	NA	39.9 (35.2–44.7)	0.083
Yes	20	70.0	48.8	41.8	41.8	18.9 (7.1–30.7)	
Adjuvant							
No	28	81.5	60.0	52.5	42.0	40.5 (14.1–66.9)	0.803
Yes	12	92.3	75.5	66.1	NA	37.9 (17.0–58.7)	
LN							
Negative	27	81.5	73.3	73.3	61.1	NA	**0.037**
Positive	13	92.3	51.3	34.2	NA	26.3 (18.5–34.1)	
Pathology							
Adenocarcinoma NOS	21	85.7	73.7	73.7	73.7	NA	0.080
Signet ring	9	100	51.9	NA	NA	NA	
Mucinous	5	60.0	60.0	40.0	NA	26.3 (0.5–59.4)	
Site							
Lateral	7	100	71.4	47.6	NA	26.8	0.841
Dome	11	100	69.3	57.7	28.9	39.9 (19.6–60.3)	
Posterior	22	72.2	61.0	61.0	30.5	37.9 (19.3–56.5)	

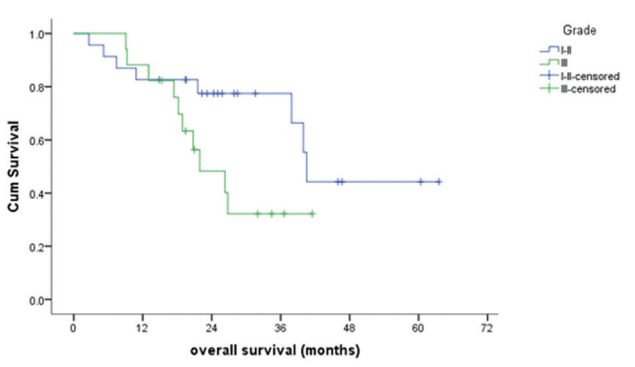
CI, confidence interval; LN, lymph node; NOS, not otherwise specified. Bold value means it is clinically significant.

Figure 9



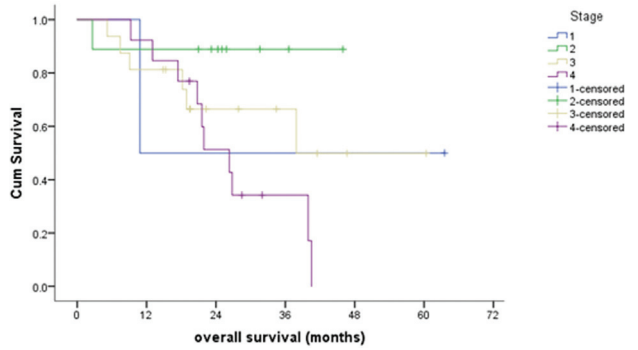
OS of all patients. OS, overall survival.

Figure 10



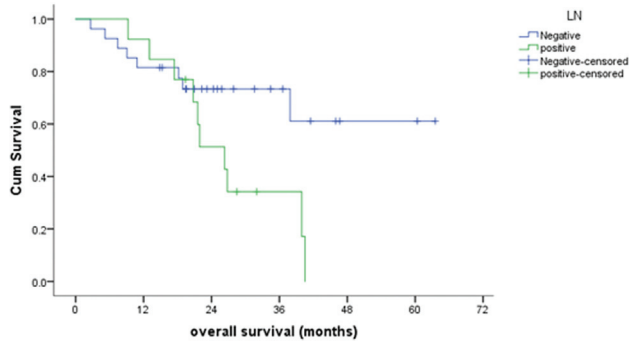
OS in relation to the tumor grade. OS, overall survival.

Figure 11



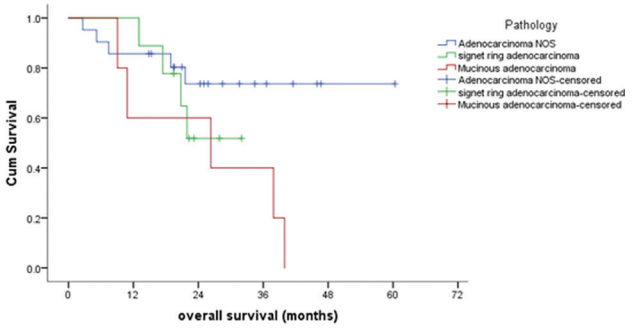
OS in relation to different disease stages. OS, overall survival.

Figure 12



OS in relation to LN metastases. OS, overall survival; LN, lymph node.

Figure 13



OS in relation to the subtype of adenocarcinoma. OS, overall survival.

adenocarcinoma, partly due to the relatively young age of patients with urachal adenocarcinoma. Worldwide, UB adenocarcinoma is the third most common histologic type (0.5–2% of all bladder cancers). However, the incidence is reported to be higher up to 10% in regions where schistosomiasis is endemic. Patients are usually in the their sixth and seventh decades of life at the time of diagnosis with male predominance [11–13]. The reported incidence of primary UB adenocarcinoma in the National Cancer Institute, Cairo is 3.8% of all UB cancers. Zheng and colleagues reported that adenocarcinoma, like squamous cell carcinoma, appears to occur at a younger age than urothelial carcinoma (UC). Indeed the mean ages for men and women were, respectively, 54.3 and 54.2 years, significantly younger than the mean ages we reported for UC that were 61.3 and 60.2 year, respectively [14]. Similarly, Lughezzani *et al.* [15] reported a younger age at diagnosis in a sureillance epidemiology and end results (SEER)-based series of 306 adenocarcinoma cases compared with nearly 12 000 UC, but did not report sex-specific age differences. In one of the largest studies of 192 patients with primary adenocarcinoma of UB, Zaghloul *et al.* [16] reported a mean age of 51 years with less male predominance (male to female ratio of 2.25 : 1) in addition to approximately one-third of the patients who had LN metastases at the time of presentation. These reports did not concur with our results where the mean age of our patients was 61 years with male predominance (male to female ratio is 4.7 : 1). However, they were similar in terms of regional LNs metastases where in our series; 13 (32.5%) the patients were found to have pelvic LN metastases while in 27 (67.5%) patients, the LNs were free of metastases. In their work, Rogers *et al.* [17] found that most of the patients were at an advanced stage at the time of diagnosis due to late presentation. Even in our study, early disease stages (I and II) were found only in 11 (27.5%) patients while advanced stages (III and IV) were found in 29 (72.5%) patients.

Although the pathogenesis of UB adenocarcinoma is not yet entirely understood, several risk factors have been described. Most notably, almost 90% of bladder tumors in patients with exstrophy of the bladder are adenocarcinoma [18]. Other possible risk factors include chronic irritation, obstruction, cystocele, and endometriosis [19]. Cystitis glandularis and intestinal metaplasia, on the other hand, are often found adjacent to bladder adenocarcinoma, but recent studies have shown that cystitis glandularis and intestinal metaplasia are not associated with an increased risk of adenocarcinoma [20]. Between 2006 and 2014, in a large multicenter case–control study in Egypt to address the risk factors associated with UB cancer, Amr *et al.* [21] found that smoking, schistosomiasis, and urinary tract infection were significantly associated with adenocarcinoma of the UB in both men and women. Similarly in our study, smoking was highly prevalent among men (79% of male patients) but not present in female patients. History of schistosomiasis was also documented in more than 50% of patients where bilharzial eggs were found in 20% of pathology specimens. This explains why male sex, smoking, and

schistosomiasis were the highest risk factors for primary UB adenocarcinoma in our study. The symptoms of adenocarcinoma do not differ from other kinds of bladder tumors. In our series, hematuria was the most frequent presenting symptom (77.5%). Irritative symptoms including irritability, frequency, urgency, and dysuria were less common. In a population-based study from Wright *et al.* [2] including 151 patients with urachal adenocarcinomas and 1374 patients with primary bladder adenocarcinomas, the mucinous/colloid pattern was detected in 48% of urachal adenocarcinomas. But in our analysis, the mucinous type represented the third most common special type of adenocarcinomas (15%). In Wright and colleagues' work, the second most common pattern was the adenocarcinoma NOS type (39%), which in our analysis accounted for the most dominant type (52.5%). However, in their analysis, the enteric type was not explicitly mentioned, which comprised 5% in our study. Additionally, they described the signet-ring cell type and the mixed type in 7% each contrary to our results in which adenocarcinoma with signet ring differentiation and mucinous adenocarcinoma comprised 22.5 and 15% of cases, respectively. The difference in the distribution of adenocarcinoma subtypes in our study and the other studies may be due to the differentiation between urachal and nonurachal adenocarcinoma in the other's studies but not in our study. The prognostic value of these histopathologic features, however, remains to be established while a more favorable clinical course for urachal adenocarcinomas as compared with primary bladder adenocarcinomas was found [2]. Additionally, the presence of high tumor grade and adenocarcinoma of signet-ring cell morphology were identified to be of unfavorable prognostic value in some [10,22–25] but not all series [26]. In our study, detailed pathologic data showed the tumor grade II to be the most common (52.5%) and grade I is the rarest (5%), adenocarcinoma. NOS was reported in more than 50% of cases followed by adenocarcinoma with signet-ring differentiation and mucinous adenocarcinoma (22.5 and 15%, respectively). To the best of our knowledge, the identification of urachal from nonurachal adenocarcinoma is a clinicopathologic problem and there is still no agreed diagnostic criteria. An important question here: Is it necessary to separate adenocarcinoma into urachal and nonurachal types? Most authors agree that both of these tumors probably have, in most instances, the same pathogenesis. It remains unclear whether the survival of patients with urachal adenocarcinoma differs from that of patients with nonurachal adenocarcinoma. Dandekar *et al.* [27] found the difference between the two was not significant. Wright *et al.* [28] found that urachal cancer had a significantly better prognosis than nonurachal cancer, while Mostofi *et al.* [5] found that urachal adenocarcinomas were associated with a significantly worse prognosis. In the current study, although the tumor location was determined accurately within the UB, we did not differentiate between urachal and non-urachal UB adenocarcinoma in terms of prognosis or survival. The majority of patients with primary bladder adenocarcinoma have a muscle-invasive disease, and these patients are usually treated with radical cystectomy and pelvic LN dissection [29–31]. Primary radiation therapy may be considered for some patients who are not appropriate cystectomy candidates. The efficacy of which in comparison to surgery is unclear due to the limited experience with this rare disease. The traditional cisplatin-based chemotherapy regimens [i.e. MVAC (Methotrxate–Vinbalstine, Doxorubicin , Cisplatin)] that are used effectively for UC appear to have little impact on adenocarcinoma. In our institute, there is no role for any chemotherapy in the treatment of patients with UB adenocarcinoma even in recurrent or metastatic cases. In regard to radiotherapy, it was given as an adjuvant treatment after surgery in certain cases as indicated but not as a primary therapy. Many surgical treatment strategies for treatment of UB adenocarcinoma are available including transurethral resection, partial cystectomy, and radical cystectomy. We believe that transurethral resection is not sufficient for muscle invasive bladder cancer. However, it is agreed that partial cystectomy with removal of the urachal tract and umbilectomy is the treatment of choice for tumors localized to the dome [32]. We are in favor of radical surgery. Nevertheless, the treatment selected reflected the local extent as well as the disease stage, so in our study, all patients underwent radical cystectomy and pelvic LN dissection followed by different types of urinary diversions (22 patients with ileal loop conduit, 10 patients with orthotopic neobladder, six patients with uretero-cutaneous, and one patient with Indian pouch diversion). Khaled and colleagues established bladder prognostic index for bilharzial-related invasive bladder cancer [squamous cell carcinoma (SCC) and adenocarcinoma] and they found that disease stage, tumor grade, and nodal involvement were the only significant factors with impact on survival (P=0.008, 0.051, 0.004, respectively). These three prognostic indexes were used to design a model to predict an individual patient's risk factor for recurrence [33]. Adenocarcinoma of the bladder is believed to be associated with a poor prognosis in most studies; however, recent observations indicate that bladder

adenocarcinoma might have the same natural history as transitional cell carcinoma. Survival analysis in the Netherlands Cancer Registry showed that the survival of patients with muscle-invasive bladder adenocarcinoma is similar to the survival of patients with muscle-invasive UC [34]. Ghoneim *et al.* [8] also found no statistically significant differences between bladder adenocarcinoma and UC in terms of mortality. In our study, the median follow-up period was 31 months. DFS for all patients is shown in Table 4 and Fig. 4. Among the different clinicopathologic factors, the most effective with a significant *P* value were the LN status (P=0.001), tumor grade (P=0.019), and the pathologic stage (P=0.021). We also found that adenocarcinoma tumor subtype had an impact on DFS as the 2-year DFS for adenocarcinoma NOS, mucinous adenocarcinoma, and signet adenocarcinoma was 80, 50, and 41.7%, respectively. However, these differences were of borderline significance statistically (P=0.09). (Figs 5–8). In the current study, a 3-year OS of all groups was 57% with a median follow-up of 39.9 months (Table 5 and Fig. 9). Adenocarcinoma subtype, tumor grade, disease stage, and LN involvement had an impact on OS but the only factor that had a statistically significant value was the LN involvement (P=0.037) (Figs 10–13). The other factors was of borderline significance mainly due to the small number of cases and short period of follow-up. In our survival analysis, due to the small number of cases and short follow-up period, the impact of these different histological subtypes on DFS or OS was of borderline significance (P=0.097 and 0.080, respectively).

Conclusion

Primary adenocarcinoma of the UB is rare but often aggressive urologic cancer. It represents 0.5–2% of all bladder cancers and affects patients mostly in their sixth decade of life. The incidence is greater in areas where bilharziasis is endemic and is more common in men than women. Patients with UB adenocarcinoma commonly present in an advanced disease which in fact lead to poor prognosis. DFS and OS are affected by disease stage, tumor grade, and LN involvement. Radical surgery is the primary treatment of choice and the standard of care is followed by adjuvant radiation therapy if indicated.

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Conflicts of interest

There are no conflicts of interest.

References

1 Abol-Enein H, Kava BR, Carmack AJK. Nonurothelial cancer of the bladder. Urology 2007; 69:93–104.

2 Wright JL, Porter MP, Li CI, Lange PH, Lin DW. Differences in survival among patients with urachal and nonurachal adenocarcinomas of the bladder. Cancer 2006; 107:721–728.

3 Dahm P, Gschwend JE. Malignant non-urothelial neoplasms of the urinary bladder: a review. Eur Urol 2003; 44:672–681.

4 Khan R, Ibrahim H, Tulpule S, Iroka N. Bladder cancer in a young patient: undiscovered risk factors. Oncol Lett 2016; 11:3202–3204.

5 Mostofi FK, Thomson RV, Dean AL Jr. Mucous adenocarcinoma of the urinary bladder. Cancer 1955; 8:741–758.

6 El-Mekresh MM, El-Baz MA, Abol-Enein H, Ghoneim MA. Primary adenocarcinoma of the urinary bladder: a report of 185 cases. Br J Urol 1998; 82:206–212.

7 Humphrey PA, Moch H, Cubilla AL, Ulbright TM, Reu-ter VE, *et al.* The 2016 WHO classifiatin of tumors of the urinary system and male genital organs—part B: prostate and bladder tumors. Eur Urol 2016; 70:106–119.

8 Ghoneim MA, Abdel-Lati M, el-Mekresh M, Abol-Ene-in H, Mosbah A, *et al.* Radical cystectomy for carcinoma of the bladder: 2,720 consecutie cases 5 years later. J Urol 2008; 180:121–127.

9 Dutt R, Abdelhalim A, Marti JW, Vernez SL, Faltas B, Lotan Y, Youssef R. Effect of tumor location on survival in urinary bladder adenocarcinoma: a population-based analysis. Urol Oncol Semin Orig Investi 2016; 34:531.

10 Grignon DJ, Ro JY, Ayala AG, Johnson DE, Ordonez NG. Primary adenocarcinoma of the urinary bladder: a clinicopathologic analysis of 72 cases. Cancer 1991; 67:2165–2172.

11 Wang HL, Lu DW, Yerian LM, Alsikafi N, Steinberg G, Hart J, Yang XJ. Immunohistochemical distinction between primary adenocarcinoma of the bladder and secondary colorectal adenocarcinoma. Am J Surg Pathol 2001; 25:1380–1387.

12 Wilson TG, Pritchett TR, Lieskovsky G, Warner NE, Skinner DG. Primary adenocarcinoma of bladder. Urology 1991; 38:223–226.

13 Grignon DJ, Ro JY, Ayala AG, Johnson DE, Ordóñez NG. Primary adenocarcinoma of the urinary bladder. A clinicopathologic analysis of 72 cases. Cancer 1991; 67:2165–2172.

14 Zheng YL, Amr S, Saleh DA, Dash C, Ezzat S, Mikhail NN, Gouda I, *et al.* Urinary bladder cancer risk factors in Egypt: a multicenter case-control study. Cancer Epidemiol Biomarkers Prev 2012; 21: 537–546.

15 Lughezzani G, Sun M, Jeldres C, Alasker A, Budaus L, Shariat SF, *et al.* Adenocarcinoma versus urothelial carcinoma of the urinary bladder: comparison between pathologic stage at radical cystectomy and cancer-specific mortality. Urology 2010; 75:376–381.

16 Zaghloul MS, Nouh A, Nazmy M, Ramzy S, Zaghloul AS, Sedira MA, Khalil E. Long-term results of primary adenocarcinoma of the urinary bladder: a report on 192 patients. Urol Oncol 2006; 24:13–20.

17 Rogers CG, Palapattu GS, Shariat SF, Karakiewicz PI, Bastian PJ, Lotan Y, *et al.* Clinical outcomes following radical cystectomy for primary nontransitional cell carcinoma of the bladder compared to transitional cell carcinoma of the bladder. J Urol 2006; 175:2048–2053.

18 Epstein JI, Amin MB, Reuter VE. Glandular lesions. In Epstein JI, Amin MB, Reuter VE, eds. Biopsy interpretation of the bladder. 2nd ed. Philadelphia, PA: Lippincott Williams; 2010. 180–213

19 Eble J, Sauter G, Epstein JI, Sesterhenn IA. Pathology and genetics of tumours of the urinary system and male genital organs. Lyon, France: IARC Press 2004.

20 Smith AK, Hansel DE, Jones JS. Role of cystitis cystica et glandularis and intestinal metaplasia in development of bladder carcinoma. Urology 2008; 71:915–918.

21 Amr S, Loffredo CA, McClain KM, Kallakury B, Zheng YL. Adenocarcinoma of the urinary bladder in Egypt: potential risk factors. World J Nephrol Urol 2015; 4:227–231.

22 Pinthus JH, Haddad R, Trachtenberg J, Holoway E, Bowler J, Herzenberg AM. Population based survival data on urachal tumors. J Urol 2006; 175:2042–2047.

23 Nakanishi K, Kawai T, Suzuki M, CTorikata C. Prognostic factors in urachal adenocarcinoma. A study in 41 specimens of DNA status, proliferating cell-nuclear antigen immunostaining, and argyrophilic nucleolar-organizerregion counts. Hum Pathol 1996; 27:240–247.

24 Santucci RA, True LD, Lange PH. Ispartialcystectomy the treatment of choice for mucinous adenocarcinoma of the urachus?. Urology 1997; 49:536–540.

25 Thomas AA, Stephenson AJ, Campbell SC, Jones JS, Hansel DE. Clinicopathologic features and utility of immunohistochemical markers in signet-ring cell adenocarcinoma of the bladder. Hum Pathol 2009; 40:108–116.

26 Siefker-Radtke AO, Gee J, Shen YU, We S, Daliani D, Millikan RE, Pisters LL. Multimodality management of urachal carcinoma: the M. D. Anderson Cancer Center experience. J Urol 2003; 169:1295–1298.

27 Dandekar NP, Dalal AV, Tongaonkar HB, Kamat MR. Adenocarcinoma of bladder. Eur J Surg Oncol 1997; 23:157–160.

28 Wright JL, Porter MP, Li CI, Paul , Daniel W. Differences in survival among patients with urachal and nonurachal adenocarcinomas of the bladder. Cancer 2006; 107:721–728.

29 Shah JB, McConkey DJ, Dinney CP. New strategies in muscle-invasive bladder cancer: on the road to personalized medicine. Clin Cancer Res 2011; 17:2608–2612.

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

31 Porten SP, Willis D, Kamat AM. Variant histology: role in management and prognosis of nonmuscle invasive bladder cancer. Curr Opin Urol 2014; 24:517–523.

32 Johnson DE, Hodge GB, Abdul-Karim FW, Ayala AG. Urachal carcinoma. Urology 1985; 26:218–221.

33 Khaled H, El-Hattab O, Moneim DA, Kassim HA, Morsi A, Sherif G, *et al.* A prognostic index (bladder prognostic index) for bilharzial-related invasive bladder cancer. Urol Oncol 2005; 23:254–260.

34 Ploeg M, Aben KK, Hulsbergen-van de K aa CA, Mark P, Johannes A, Lambertus A. Clinical epidemiology of nonurothelial bladder cancer: analysis of The Netherlands Cancer Registry. J Urol 2010; 183:915–920.