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Review Article

Mental health implications in bladder cancer patients: A review

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Abstract

Although the majority of bladder cancer literature has been dedicated to optimizing oncological outcomes and focuses on physical prognostic criteria such as nutritional and performance status, emerging data has suggested that both pre- and post-treatment mental health may play as important a role in patient outcomes as physical health. In this review, we summarize the literature regarding the prognostic implications of mental illness on bladder cancer patients and review how both the diagnosis and treatment of bladder cancer can affect mental health across various disease states. Literature review via a modified, nonsystematic analysis was performed from 2000 to 2018 in PubMed, Web of Science, EMBASE, SCOPUS, and OVID. Search terms included "bladder cancer," "non–muscle-invasive bladder cancer," "muscle-invasive bladder cancer," "mental health," "psychological distress," "depression," and "suicide." Articles were limited to English-language, peer-reviewed, original research. A total of 87 publications were reviewed that met our initial inclusion criteria, and 19 relevant publications were incorporated in our review. Eleven studies were prospective and 8 were retrospective. Two articles included non–muscle-invasive bladder cancer patients, 11 included muscle-invasive bladder cancer patients, and 6 incorporated bladder cancer patients across all disease stages. Mental health issues, such as depression and anxiety, often coexist with a diagnosis of bladder cancer with a worse prognosis associated with greater psychological burden. Bladder cancer patients also have an increased risk of suicide especially in older, unmarried, male patients with more advanced disease states. Poor mental health can impact treatment outcomes such as postsurgical complication rates as well as survival-related outcomes similar to physical health. While awareness of the importance of mental health in bladder cancer patients is growing, further studies are needed to assess the role of interventions such as cognitive behavioral therapy or pharmacotherapy in order to optimize treatment.

Keywords: Mental health; Depression; Suicide; Bladder cancer; Urothelial carcinoma

1. Introduction

Bladder cancer is the most common site of malignancy within the urinary tract [1]. It will affect an estimated 81,190 new patients in 2018 in the United States with an estimated 17,240 deaths, accounting for 4.7% of all new cancer diagnoses and 2.8% of all cancer deaths [2]. Bladder cancers are generally classified based upon their depth of invasion into nonmuscle invasive or muscle invasive. Non–muscle-invasive bladder cancer (NMIBC) may be treated with conservative therapies to preserve bladder structure and function such as transurethral resection of bladder tumor (TURBT) plus intravesical agents to prevent recurrence and/or progression such as chemotherapy (i.e., mitomycin C) or Bacillus Calmette Guerin [3]. The current gold standard treatment for muscle-invasive bladder cancer (MIBC), conversely, is radical cystectomy (RC) with pelvic lymphadenectomy and urinary diversion with either an incontinent ileal conduit urostomy, continent cutaneous catheterizable pouch (i.e., Indiana or Florida pouch), or orthotopic neobladder [4].

Although most of the literature in bladder cancer has been dedicated to optimizing oncological outcomes and focusing on physical prognostic criteria such as nutritional and performance status, especially in patients undergoing RC as part of enhanced recovery after surgery protocols, emerging data has suggested that both pre- and post-treatment mental health may play as important a role in patient outcomes as physical health. Patients diagnosed

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with bladder cancer may be more prone to experiencing psychological distress expressed as depression or excessive anxiety, especially in those with a pre-existing mental illness [5]. While the majority of patients are initially diagnosed with NMIBC with a 96% 5-year overall survival (OS) rate, the high risk of recurrence and progression is a constant burden [3]. These patients also require long-term follow-up, which can be physically, emotionally, and economically taxing, especially considering bladder cancer is one of the most expensive malignancies to manage long term [6]. If advised to undergo cystectomy for the treatment of MIBC, patients are then confronted with other stressors such as major surgery, possible loss of sexual and urinary function, and significant physical changes [7]. Pre- and post-treatment psychological distress may manifest as worse outcomes and even suicide if left untreated [8,9].

In this review, we summarize the literature regarding the prognostic implications of mental illness on bladder cancer patients and discuss how both the diagnosis and treatment of this disease can affect mental health over time across various disease states including the risk of suicide.

2. Methods

An assessment of the literature was performed according to a modified, nonsystematic analysis from January 2000 to September 2018. Medical databases that were utilized included: PubMed, Web of Science, EMBASE, SCOPUS, and OVID. The search terms used were “bladder cancer,” “non−muscle-invasive bladder cancer,” “muscle-invasive bladder cancer,” “mental health,” “psychological distress,” “depression,” and “suicide.” Articles were excluded if they were literature reviews, editorials or brief communications, author responses, not written in English, or unrelated to the topic of interest.

Articles assessed were, therefore, limited to English-language, peer-reviewed articles. Preference was given to well-referenced studies, articles in higher impact journals, as well as original research. Quality of life (QOL) articles evaluating physical or functional outcomes (i.e., sexual or urinary function) in bladder cancer or cystectomy patients without measurements of mental health or mental QOL were also excluded. A total of 87 publications were evaluated during the literature search, and 19 relevant publications were incorporated into this review.

3. Results

Of the 19 manuscripts selected for literature review, 11 studies were prospective and 8 were retrospective. Two articles included NMIBC patients, 11 included MIBC patients, and 6 incorporated bladder cancer patients across all disease stages. We have summarized our findings by disease stage as noted below.

3.1. NMIBC

The literature is sparse with regards to mental health studies focusing on NMIBC patients. Two prospective, single-cohort, observational studies strictly evaluated patients with noninvasive disease (Table 1). Both articles demonstrated the impact of diagnosis and treatment of NMIBC on mental health based on standardized, externally validated questionnaires, which include the Short-Form 36-item (SF-36) survey that contains 36 questions assessing 8 aspects of physical and mental health including physical functioning, role-physical functioning, bodily pain, general health, vitality, social functioning, role-emotional functioning and mental health, and the Bladder Cancer Index, which measures urinary, bowel, and sexual domains (summary scores range from 0 to 100).

In the first study, Schmidt et al. prospectively analyzed 244 Spanish patients with NMIBC using the SF-36 and the Bladder Cancer Index as surrogate measures of mental QOL [10]. Baseline scores were obtained at the time of diagnosis and at 6- and 12-month follow-up. Mental health in these patients was significantly worse at the time of diagnosis compared to reference norms with a mean SF-36 of 49.7 compared to 53.3 in the general US population. Furthermore, the authors reported an improvement in patient mental health parameters if TURBT was combined with postoperative intravesical therapy to reduce the risk of recurrence compared to TURBT alone. In the second study, Yoshimura et al. prospectively examined the mental impact of sequential TURBTs on 133 patients with NMIBC using the SF-36 [11]. The authors showed that mean SF-36 declined most significantly after the first TURBT but improved with subsequent, repeat procedures. Additionally, role-emotional (role limitations due to emotional problems) and social function domains were at their lowest level after the third TURBT but improved if procedures were repeated 4 or more times. Similar to the first study, use of postoperative intravesical therapy resulted in improved scores in the bodily pain domain during follow-up.

3.2. MIBC

While few studies evaluate mental health exclusively in the NMIBC population, a large amount of literature exists in MIBC with the majority of mental health studies focusing on this disease stage. Relevant studies analyzing mental health in the MIBC population are listed in Table 2.

Several articles assess the impact of diagnosis and treatment of MIBC on mental health. Palapattu et al. prospectively surveyed 74 patients with clinically organ-confined MIBC for psychological distress prior to and 1 month following RC and urinary diversion [5]. Preoperative and postoperative distress scores were determined using the Basic Symptom Inventory-18 (BSI-18), a validated instrument that measures the psychological domains of general distress, anxiety, depression, and somatization. Results were

Table 1
Mental health in non–muscle-invasive bladder cancer

Author	Year	Study design	*n*	Measurement tool	Follow-up	Findings
Schmidt et al. [10]	2015	Prospective cohort	244	SF-36 and BCI	12 months	• Mental health worse in NMIBC patients at diagnosis compared to reference norms • Urinary domain of BCI improved from diagnosis to follow-up while sexual domain worsened • Mental health improved with TURBT and postoperative intravesical therapy (i.e., mitomycin C and BCG) compared to TURBT alone
Yoshimura et al. [11]	2005	Prospective cohort	133	SF-36	N/A	• Mental health declined most significantly after initial TURBT but improved with subsequent procedures • Physical functioning, social functioning, and role-emotional domains only increased after 4 or more TURBTs • Use of intravesical therapy (i.e., mitomycin C and BCG) for prevention of recurrence was associated with improved scores in the bodily pain domain

BCG = Bacillus Calmette Guerin; BCI = Bladder Cancer Index; *n* = number of participants; NMBIC = non–muscle-invasive bladder cancer; SF-36 = Short Form-36; TURBT = transurethral resection of bladder tumor.

Table 2
Mental health in muscle-invasive bladder cancer

Author	Year	Study design	*n*	Measurement tool	Follow-up	Findings
Jazzar et al. [19]	2018	Retrospective	3,709	Clinical diagnosis of psychiatric disorder in SEER-Medicare	1 year	• Patients who underwent RC were at significantly greater risk of having a post-treatment psychiatric illness compared to those who received radiation and/or chemotherapy, which resulted in worse OS and CSS
Sharma et al. [20]	2016	Retrospective	274	SF-12	<6 months preoperatively	• Lower preoperative mental health scores were associated with increased risk of high-grade 30-day complications after RC for MIBC
Mohamed et al. [18]	2014	Prospective cohort	30	Personal interview	72 months	• Patients reported insufficient discussion of urinary diversion options and their side effects, self-care, the recovery process, and medical insurance • During survivorship, unmet needs of patients treated with RC and urinary diversion centered around psychological support (i.e., depression, poor body image, and sexual dysfunction)
Benner et al. [17]	2014	Prospective cohort	33	HADS	6 months	• No significant change in depression, anxiety, fatigue, QOL, spiritual well-being, satisfaction, or family caregiver burden over time
Yang et al. [16]	2013	Prospective cohort	82	SF-36	24 months	• The mental health of RC patients with orthotopic neobladder was more easily restored compared to those with nonorthotopic urinary diversions, reducing their overall recovery time
Asgari et al. [15]	2013	Prospective cohort	149	Author constructed questionnaire (98 items)	2 months	• RC patients with ileal conduits experienced more psychological distress and lower global satisfaction compared to those with continent urinary diversions (i.e., MAINZ pouch and ileal neobladder)

(*continued*)

Table 2 (***Continued***)

Author	Year	Study design	*n*	Measurement tool	Follow-up	Findings
Palapattu et al. [5]	2004	Prospective cohort	74	BSI-18	1 month	• A large proportion of patients undergoing RC for MIBC experienced psychological distress perioperatively • General distress, depression, and anxiety decreased 1 month after surgery • Worse pathological stage was associated with increased postoperative general distress and anxiety
Palapattu et al. [21]	2004	Prospective cohort	65	BSI-18	Mean: 1.3 years	• Higher preoperative somatic distress scores (≥2) were associated with reduced time to disease progression after RC • No correlation between preoperative depression, anxiety, or general distress and disease progression
Henningsohn et al. [13]	2002	Prospective, case control	101	Author designed questionnaire (137 items)	1 year	• No difference in psychological well-being, high/moderate anxiety, depression, QOL, and level of physical attractiveness after RC and orthotopic neobladder vs. matched controls • Patients with orthotopic neobladders had increased ED, UTIs, distressful bowel symptoms, and urinary leakage but similar incidence of daytime and nighttime urinary frequency
Hara et al. [14]	2002	Retrospective	85	SF-36	45.9 months (neobladder) vs. 130.9 months (ileal conduit)	• No significant difference found between orthotopic neobladder and ileal conduit • Lower scores seen in general health and social functioning compared to US population
Henningsohn et al. [12]	2001	Prospective, case control	251	Author constructed questionnaire (137 items)	10 years	• RC patients had increased UTIs, fecal urgency, fecal leakage, and reduced physical attractiveness long term • Increasing number of long-term symptoms after RC directly correlated with increased risk of anxiety, depression, and low/moderate well-being

BSI-18 = Brief Symptom Inventory-18; CSS = cancer-specific survival; ED = erectile dysfunction; HADS = hospital anxiety and depression scale; MIBC = muscle-invasive bladder cancer; OS = overall survival; RC = radical cystectomy; SEER = Surveillance, Epidemiology, and End Results; SF-12/36 = Short Form-12/36; UTI = urinary tract infection; US = United States.

also stratified with respect to age, sex, marital status, type of surgical reconstruction, and tumor stage. In this study cohort, 45% of patients had preoperative psychological distress, which remained at 34% 1 month after cystectomy. Gender, age, and marital status were not associated with overall prevalence of psychological distress. General distress, depression, and anxiety, however, decreased significantly from preoperative to postoperative assessments, but worsening pathological stage was associated with increased postoperative general distress and anxiety.

Henningsohn et al. also prospectively investigated the effects of chronic symptoms on mental health after RC and urinary diversion [12]. Information was collected through an anonymous postal questionnaire with a control group randomly selected from the general population. Completed questionnaires were returned by 310 controls (71%) and 251 patients (85%) who had undergone RC. Chronic symptoms reported by RC patients included 3-fold increase in urinary tract infections, 5-fold (continent reservoir) and 9-fold (ileal conduit) increase in fecal urgency, 4-fold (continent reservoir), and 6-fold (ileal conduit) increase in fecal leakage, and 5-fold increase in reduced physical attractiveness compared to controls. Subsequently, a low/moderate level of mental well-being was reported in 35% of RC patients who had 0 to 1 long-term symptom, 39% with 2 long-term symptoms, 45% with 3 long-term symptoms, and 66% with 4+ long-term symptoms 2 years after surgery. The total symptom burden was also associated with increased risk of depression and anxiety compared to controls. The authors stressed the importance of reducing adjacent tissue damage during RC to minimize chronic symptoms, which in turn could improve long-term patient mental health. Despite the prevalence of chronic distressful symptoms, 67% of patients would have refused alternative bladder-sparing procedures if they decreased the prospects of survival by even as little as 1%. These same authors also prospectively examined mental QOL, mental well-being, and psychological distress in 101 consecutive, recurrence-

free RC patients after orthotopic bladder substitution with an ileal urethral Kock neobladder compared to a matched control population of 147 patients from the same geographical region [13]. All RC patients had minimum of 1-year follow-up. Information was again collected by means of an anonymous postal questionnaire. Surprisingly, low or moderate psychological well-being (32% vs. 36%), subjective mental QOL (30% vs. 38%), high or moderate anxiety (23% vs. 18%), depression (26% vs. 37%), and level of physical attractiveness were similar in both groups. Patients with orthotopic neobladders who required intermittent self-catheterization, however, had significantly higher anxiety levels than those who could evacuate their neobladders by straining. The authors concluded, therefore, that a less-conservative definition of urinary retention (postvoidal residual >150 to 200 ml) could decrease the number of patients on intermittent self-catheterization, and, in turn, improve long-term mental QOL.

In a retrospective study, Hara et al. compared mental QOL using the SF-36 survey in 48 MIBC patients who underwent RC with orthotopic neobladder (26 with an ileal neobladder and 22 with a colonic neobladder) to 37 patients with an ileal conduit [14]. The authors found no significant difference between the orthotopic neobladder and ileal conduit groups, although both had lower SF-36 scores in general mental health and social functioning compared to the general population. Furthermore, patients with a colonic neobladder had a significantly higher score for role-emotional functioning than those with an ileal neobladder, but the authors believed that patients were generally satisfied with their overall mental QOL regardless of type of urinary diversion. Asgari et al. also prospectively investigated mental QOL in 149 men who underwent RC and urinary diversion (70 ileal conduit, 16 MAINZ pouch, and 63 orthotopic ileal neobladder) for MIBC [15]. Psychological status, social status, sexual life, diversion-related symptoms, and satisfaction with treatment were assessed using an author-constructed questionnaire with assessment performed at 3 months postoperatively. Unlike the Hara et al. study, patients with continent diversion had a more favorable outcome with regards to psychological status, social status, and sexual life compared to patients with ileal conduits. Global satisfaction was also higher in patients with a MAINZ pouch (68.7%) and ileal neobladder (76.2%) compared to those with an ileal conduit (52.8%; $P = 0.002$). Yang et al. also investigated the psychological effect of various surgical methods on RC patients with MIBC [16]. Mental health of 82 patients (54 with orthotopic and 28 with nonorthotopic urinary diversion) were prospectively evaluated with the SF-36 questionnaire 6, 12, and 24 months after surgery. The authors found that the mental health of patients with orthotopic urinary diversion was more easily restored compared to that of patients with nonorthotopic urinary diversion, which they believed helped reduce patients' overall recovery time.

Benner et al. analyzed the natural history of symptom progression and psychological distress in MIBC patients undergoing RC [17]. This prospective study followed 33 patients and family caregivers with validated symptom assessment and satisfaction surveys at baseline, and at 2, 4 and 6 months after surgery. The authors reported no significant change in depression, anxiety, fatigue, mental QOL, spiritual well-being, satisfaction, or family caregiver burden over time. While patients were reassured that their cancer was removed after RC, there was not an improvement in mental symptom burden by 6 months postoperatively. The authors suggested the use of an interdisciplinary team of healthcare professionals (i.e., psychologists, nurses, social workers, etc.), especially in patients with history of depression or anxiety, to improve mental QOL outcomes. In a unique interview-based study by Mohamed et al., the authors met with 30 patients to identify any unmet needs after diagnosis of MIBC and treatment with RC [18]. They found that many patients reported insufficient discussion of certain topics, including urinary diversion options and their side effects, self-care, the recovery process, and medical insurance. Interestingly, patients also reported unmet psychological needs such as depression and anxiety about changes in body image and sexual function, and after 72 months, patients still reported unmet needs surrounding psychological support (i.e., depression, poor body image, and sexual dysfunction) that did not improve over time. The authors emphasized the importance of screening for emotional distress after diagnosis and treatment of MIBC along with making appropriate referrals to prevent depression that may impede recovery.

Other literature in the MIBC population assesses the prognostic implications of mental illness on treatment outcomes. Jazzar et al. retrospectively analyzed patients with MIBC in the Surveillance, Epidemiology, and End Results (SEER)-Medicare database from 2002 to 2011 to assess the impact of psychiatric illnesses diagnosed after treatment on survival outcomes [19]. Of 3,709 patients, 1,870 (50.4%) were diagnosed with a psychiatric disorder after treatment. RC patients were at significantly greater risk of having a post-treatment psychiatric illness compared with those who received chemotherapy and/or radiation (hazard ratio [HR] = 1.19; 95% confidence interval [CI] 1.07–1.31; $P = 0.001$). Patients diagnosed with a post-treatment psychiatric disorder were found to have a worse OS (HR = 2.80; 95% CI 2.47–3.17; $P < 0.001$) and cancer-specific survival (CSS; HR = 2.39; 95% CI 2.05–2.78; $P < 0.001$). The authors concluded that the recognition and treatment of mental illnesses after bladder cancer treatment are of the utmost importance in order to optimize survival outcomes in these patients. Sharma et al. also looked at preoperative patient-reported mental health and its association with high-grade 30-day complications after RC in 274 patients at a single institution [20]. Short Form-12 surveys were utilized for patient self-assessment of health status within 6 months of surgery. Patients that experienced a high-grade 30-day complication after RC and urinary diversion had a lower preoperative median Short Form-12 mental composite score (MCS; 44.8 vs. 49.8; $P =$

0.004). The authors concluded that early recognition of mental illness before treatment could be useful in predicting short-term postoperative outcomes and could represent another variable that may be optimized to reduce treatment-associated complication rates. Finally, Palapattu et al. investigated the association between psychological factors measured preoperatively and bladder cancer progression after RC [21]. The BSI-18 was administered prospectively to 65 patients with clinically localized MIBC before RC. The BSI-18 measures general distress as well as distress in 3 specific domains: (1) depression, (2) anxiety, and (3) somatization (i.e., distress due to somatic symptoms). At mean follow-up of 1.3 years, worse pathologic tumor stage and higher preoperative somatic distress scores were associated with reduced time to disease progression on univariate analysis ($P = 0.038$ and $P = 0.055$, respectively). A somatic distress score of ≥2 was a significant predictor of disease progression during follow-up (HR = 3.31; 95% CI 1.03 −10.60; $P = 0.044$), while BSI-18 scores for depression, anxiety, and general distress were not significantly associated with cancer-related outcomes.

3.3. NMIBC and MIBC

Several studies that evaluate mental health in bladder cancer across all disease stages are summarized in Table 3. Smith et al. used data from SEER linked with Medicare Health Outcomes Survey data to identify changes in mental health-related QOL in bladder cancer patients and controls [22]. Of the 535 patients identified with bladder cancer, 458 had NMIBC and 77 had MIBC with 2,770 control subjects. After diagnosis, patients with bladder cancer experienced significant declines in mental and social QOL relative to controls, which were more pronounced in MIBC patients. While there was no significant difference in mental health or role-emotional scores between bladder cancer patients and controls, social functioning scores were significantly worse in bladder cancer patients over time. Patients who underwent RC for MIBC had significant declines in several mental health domains, including role emotion, vitality, and social functioning scores compared to patients treated more conservatively. The authors also found that in the RC group, a history of depression was a strong predictor of decline in both the mental and physical component of health-related QOL. A cross-sectional study by Fung et al. looked at the impact of bladder cancer diagnosis (NMIBC and MIBC) on 1,476 patients 65 years or older in the SEER-Medicare Health Outcomes Survey linkage database between 1998 and 2007 [23]. A total of 1,234 patients (83.6%) had NMIBC at initial diagnosis. The difference in mean MCS based on the SF-36 survey before and after bladder cancer diagnosis was −1.4, which was significantly different ($P < 0.01$). This difference, however, normalized and was no longer significant after 5 years. Mean MCS also did not differ significantly between NMIBC and MIBC patients pre- and postdiagnosis.

In another cross-sectional study, Singer et al. compared the mental QOL of 812 patients with bladder cancer (NMIBC and MIBC) to 2,037 people in the general US population using the European Organization for Research and Treatment of Cancer QLQ-C30 questionnaire [24]. There were 210 patients (25.9%) diagnosed with NMIBC in this study. The authors reported that patients with both NMIBC and MIBC had decreased emotional functioning, social functioning, role functioning, and increased fatigue when compared with the general US population. Radiation was associated with more pain, dyspnea, constipation, appetite loss, and decreased social functioning, chemotherapy was associated with more dyspnea, and RC was associated with more fatigue, appetite loss, and decreased role functioning when compared to controls. Male patients ≥70 years of age with an ileal conduit experienced more sleep and emotional problems. Mental QOL, however, in both NMIBC and MIBC patients improved over time ($P < 0.01$). After adjusting for the effects of age, gender, treatment, and time after surgery, there were also no differences in mental QOL between NMIBC and MIBC groups.

Li and Wang explored the association of psychological stress with depressive and anxiety symptoms in Chinese patients diagnosed with bladder cancer [25]. In a cross-sectional study of 327 bladder cancer patients (not differentiated between NMIBC and MIBC), the Center for Epidemiologic Studies-Depression Scale (CES-D), Zung Self-Rating Anxiety Scale, Resilience Scale-14, and Perceived Stress Scale-10 questionnaires were administered from July 2013 to July 2014. The prevalence of depressive and anxiety symptoms was 78.0% and 71.3%, respectively, in bladder cancer patients. Psychological stress was shown to be positively related to increased depressive and anxiety symptoms, but patients with higher education had decreased prevalence of depression. Furthermore, resilience, which refers to an interactive dynamic construct, a positive coping style, and a positive personality trait, was found to be inversely related to depression and anxiety. The authors recommend that programs used to enhance patient resilience should be incorporated into treatment strategies for bladder cancer. Draeger et al. used 2 patient-reported validated questionnaires (Distress Thermometer and Hornheider Screening Instrument) to assess the stress level in 301 bladder cancer patients undergoing treatment and the need for psychosocial support [26]. The mean stress level across all bladder cancer patients was 4.6 with 28% expressing a need for psychosocial support. In patients with progressive disease, significantly higher stress scores (5.4) were seen as well as a higher need of psychosocial care (41%).

Lastly, Lin et al. studied the association of depressive symptoms and telomere length to mortality and recurrence/progression in 464 patients with bladder cancer (234 NMIBC and 202 MIBC/metastatic) [27]. The authors used the CES-D and the Structured Clinical Interview for DSM-IV Disorder scale to assess current depressive symptoms and lifetime major depressive disorder, respectively, and

Table 3
Mental health in non−muscle-invasive and muscle-invasive bladder cancer

Author	Year	Study design	*n*	Measurement tool	Follow-up	Findings
Smith et al. [22]	2018	Retrospective case control	535	SF-36 (MHOS)	12 months	• Bladder cancer patients experienced significant declines in physical, mental, and social QOL compared to controls • RC patients had lower role emotion, vitality, and social functioning scores with a history of depression predicting a greater decline over time of mental health domains
Li and Wang [25]	2016	Retrospective	327	CES-D, SAS, RS-14, and PSS-10	N/A	• Depression and anxiety was seen in 78.0% and 71.3% of Chinese bladder cancer patients • Patients with higher education had decreased prevalence of depression • Psychological stress was positively related to depressive and anxiety symptoms, while resilience was negatively related to these symptoms
Lin et al. [27]	2015	Prospective cohort	464	CES-D and SCID	Mean: 21.6 months	• Patients with depressive symptoms had almost 2-fold increased risk of mortality compared to patients without depressive symptoms • Patients with both depressive symptoms and lifetime history of MDD had almost 5-fold increased risk of mortality compared to patients with neither condition • Patients with depressive symptoms and shorter telomere length had almost 4-fold increased risk of mortality compared to patients without depressive symptoms and longer telomere length • Patients with depressive symptoms, lifetime history of MDD, and shorter telomere length had reduced disease-free survival time
Fung et al. [23]	2014	Retrospective case control	1,476	SF-36 (MHOS)	Median: 5.4 years	• MCS after bladder cancer diagnosis differed significantly from that before diagnosis, but this normalized after 5 years • MCS was not significantly different between NMIBC and MIBC patients pre- and postdiagnosis
Draeger et al. [26]	2018	Retrospective	301	DT and Hornheider Screening Instrument	N/A	• Mean stress level in bladder cancer patients was 4.6 with 28% needing psychosocial support • Patient with progressive disease had higher stress scores and higher need for psychosocial support
Singer et al. [24]	2013	Retrospective case control	823	EORTC QLQ-C30	30−40 days after treatment	• Bladder cancer patients had decreased emotional functioning, social functioning, role functioning, and increased fatigue when compared to the general US population • QOL improved over time, and there were no differences between NMIBC and MIBC patients

CES-D = Center for Epidemiologic Studies-Depression Scale; DT = Distress Thermometer; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; MCS = mental composite score; MDD = major depressive disorder; MHOS = Medicare Health Outcomes Survey; MIBC = muscle-invasive bladder cancer; NMIBC = non−muscle-invasive bladder cancer; PSS-10 = Perceived Stress Scale-10; QOL = quality of life; RC = radical cystectomy; RS-14 = Resilience Scale-14; SAS = Zung Self-Rating Anxiety Scale; SCID = Structured Clinical Interview for DSM-IV; SF-36 = Short Form-36.

telomere length was assessed from peripheral blood lymphocytes by quantitative polymerase chain reaction. The authors determined that patients with depressive symptoms (CES-D ≥16) had a 1.83-fold (95% CI 1.08−3.08; P = 0.024) increased risk of mortality compared to patients without depressive symptoms (CES-D <16) as well as a shorter disease-free survival time. Additionally, patients with both depressive symptoms and lifetime history of major depressive disorder were at 4.88-fold (95% CI 1.40 −16.99; P = 0.013) increased risk of mortality compared to patients with neither condition. On univariate analysis, 1 unit increase in telomere length was associated with a significantly reduced risk of bladder cancer-associated death (HR = 0.39; 95% CI 0.20−0.78; P = 0.007), and median survival time was significantly reduced in patients with shorter vs. longer telomere lengths (58.26 months vs. >200

months; $P = 0.013$). When adjusting for age, gender, ethnicity, smoking status, tumor stage, grade, and treatment in the multivariate model, however, the associated between telomere length and CSS did not reach statistical significance. Finally, patients with depressive symptoms and shorter telomere length exhibited a 4-fold increased risk of mortality (HR 3.96 [95% CI 1.86–8.41]; $P = 0.0003$) and significantly shorter disease-free survival time vs. patients without depressive symptoms and longer telomere length.

3.4. Bladder cancer and suicide

Patients with cancer in the United States have nearly twice the incidence of suicide compared to the general population based on registry data from SEER [28]. Standardized mortality ratios (SMRs) were highest in the first 5 years after diagnosis with cancer [28]. Suicide in patients with genitourinary (GU) malignancies poses a public health dilemma, especially among men, the elderly, and those with aggressive disease [29]. Literature reporting on the impact of bladder cancer on patient suicide is shown in Table 4.

Klaassen et al. used the SEER database from 1988 to 2010 and identified 2,268 suicides among 1,239,522 individuals with GU malignancies [29]. Bladder cancer was found to have the highest SMR at 2.71 (95% CI 2.02–3.62) compared to prostate and kidney cancer with male gender, increasing age, and metastatic disease associated with higher odds of suicide (odds ratio [OR] 6.63, 1.03, and 5.43, respectively). The highest incidence of suicide was noted within the first 5 years after diagnosis (SMR = 3.05; 95% CI 2.26–3.96). African American and married bladder cancer patients were less likely to commit suicide (OR 0.46 and 0.61, respectively). Interestingly, bladder cancer patients were the only group found to have a higher SMR for those who received surgical intervention compared with those who did not (cystectomy SMR = 3.54 [95% CI 2.70–4.54] vs. no cystectomy SMR = 2.66 [95% CI 1.95–3.54]). Of the 439 suicides among patients with bladder cancer, the strongest predictors of suicide were male vs. female gender (OR 6.63) and distant vs. localized disease (OR 5.43). In another retrospective review of SEER between 1973 and 2013 by Klaassen et al., patients with urothelial carcinoma of the bladder were identified and analyzed to determine trends regarding patient suicide [9]. Of 333,679 patients diagnosed with bladder cancer, 794 patients (0.24%) died of suicide. Patients were found to be at increased risk of suicide if they were diagnosed between 1973 and 1983 (HR 2.22), unmarried (HR 1.74), white race (HR 2.22), male (HR 6.91), had regional disease (HR 2.49), lived in the southeastern United States (HR 2.43), and had not undergone RC (HR 1.42). Older age (>70 years) was also associated with suicide, whereas younger age was protective. Furthermore, patients with no RC (OR 0.45), older age (OR 0.32), unmarried status (OR 0.65), and regional disease (OR 0.19) were associated with decreased odds of suicidal death >36 months after diagnosis. Finally, de Lima et al. found that the prevalence of suicide in the bladder cancer population was second

Table 4
Bladder cancer and suicide

Author	Year	Study design	*n*	Measurement tool	Follow-up	Findings
Klaassen et al. [29]	2015	Retrospective	439	SMR	N/A	• Bladder cancer was found to have the highest SMR for patient suicide compared to prostate and kidney cancer with the highest incidence noted within the first 5 years after diagnosis • Bladder cancer patients were the only group found to have a higher SMR for those who received surgical intervention compared with those who did not • The strongest predictors of suicide in bladder cancer patients were male gender and distant disease
Klaassen et al. [9]	2018	Retrospective	794	Death from suicide	N/A	• Bladder cancer patients were found to be at increased risk of suicide if they were diagnosed between 1973 and 1983, older age (>70 years), unmarried, white race, male, had regional disease, lived in the southeastern US, and had not undergone RC • Bladder cancer patients with no RC, older age, unmarried status, and regional disease were at reduced odds of suicidal death >36 months after diagnosis
de Lima and Tobias-Machado [8]	2017	Retrospective	N/A	Death from suicide	N/A	• Among patients with GU malignancies, the prevalence of suicide in bladder cancer was second only to prostate cancer • Bladder cancer patients who did not undergo surgery, with comorbid conditions, and with metastases had the highest risk of suicide

GU = genitourinary; RC = radical cystectomy; SMR = standardized mortality ratio; US = United States.

only to prostate cancer in their study cohort of patients with GU malignancies [8]. The authors reported that GU cancer patients with metastasis had a 2.85- to 5.43-fold increased risk of suicide, and when compared to other GU malignancies, bladder cancer had the highest rate of suicide postoperatively. Contrary to the Klaaseen et al. studies, the highest risk of suicide was in bladder cancer patients who did not undergo surgery, and comorbid conditions were also associated with higher rates of suicide in patients with bladder cancer.

4. Discussion

The interest in mental health of bladder cancer patients is becoming increasingly popular as it becomes a significant prognostic indicator of patient outcomes. The literature on this topic is also growing as studies continue to demonstrate the relationship between bladder cancer and subsequent development of mental health disorders. These mental health issues, including depression and anxiety, are quick to appear after diagnosis and treatment [24]. Studies by Fung et al. and Singer et al., however, have shown improvement in mental QOL over time regardless of urinary diversion type with normalization of mean MCS 5 years after treatment for MIBC when compared with age-matched controls [23,24]. Asgari et al. also reported that the mental health of patients with orthotopic urinary diversion was more easily restored compared to that of patients with nonorthotopic urinary diversion, and Henningsohn et al. reported no difference in psychological well-being, subjective mental QOL, anxiety, or depression levels in Kock neobladder patients after 1-year follow-up compared to controls from the general population [13,15]. Conversely, Smith et al. showed that most physical, mental, and social health-related QOL domains remained low over 1 year after diagnosis of bladder cancer [22]. While some studies describe a return to baseline mental health over time, long-term studies of lasting psychological changes have yet to be investigated in this patient population to date [11–13,16,18,24].

There is inconclusive data regarding mental health differences in bladder cancer patients across age, gender, race, and disease stage [22–25]. Bladder cancer is a disease of the elderly and more common in men, and it is suggested that both older age and male gender are risk factors for emotional and psychological distress as well as worse mental QOL after diagnosis and treatment, especially in patients with pre-existing depression and/or anxiety [26]. Other studies have not shown any gender disparity in comorbid mental health conditions in cancer patients [30]. Racial disparities in mental QOL in the bladder cancer population are also largely unknown and understudied although could represent an area of future investigation. Finally, although there is a trend toward more significant mental health burden in patients with a worse cancer prognosis [5,22], several studies did not successfully show any differences in mental health between NMIBC and MIBC patients [22–24]. Palapattu et al. and Draeger et al. did demonstrate higher preoperative somatic distress scores, stress levels, and need for psychosocial support in patients with disease progression, but further studies are necessary to corroborate these findings [21,26].

With regards to different treatment modalities for MIBC (surgery vs. chemotherapy/radiation vs. trimodal bladder-preserving therapy), some authors have described differences based on single-cohort, prospective studies with limited follow-up demonstrating worse mental health with increased symptom burden and worsened lifestyle after RC and urinary diversion, such as requirements to begin intermittent catheterization [12,13,21]. Henningsohn et al. reported that chronic symptom burden after RC and urinary diversion in bladder cancer patients was associated with increased risk of depression and anxiety compared to controls, and Jazzar et al. showed that RC patients were at significantly greater risk of having a post-treatment psychiatric illness compared with those who received chemotherapy and/or radiation in a cohort of over 3,500 MIBC patients from SEER-Medicare [12,19]. There are, however, no conclusive trials to date comparing mental QOL across treatment modalities for MIBC with a standardized control group, although it could be suggested that surgical or treatment options that enable patients to make minimal lifestyle changes reduce ostomies, or catheterization requirements would be less harmful to the patient's psychological state [13–16].

There is growing evidence demonstrating a clear increased risk of suicide amongst bladder cancer patients, which has one of the highest incidence when compared against other GU cancers [8,29]. Predictors of suicide include older age, being unmarried, male gender, and metastatic disease [29]. While some studies have shown varying suicide rates based on different treatment modalities with increased risk in the RC population, the evidence is still conflicting [9]. While suicide rates are difficult to determine in large populations, there is a general trend suggesting that malignancies that impact mental QOL are associated with higher rates of suicide [28,29]. Bladder cancer, for example, can have varying impact on QOL depending on the intervention from minimal (cystoscopic surveillance with TURBT) to drastic (RC and urinary diversion associated with urostomy or intermittent catheterization). One main limitation on studying suicide in bladder cancer patients is that risk factors for both have a large amount of overlap (i.e., elderly, male, smokers, medical comorbidities, etc.), but this may compound suicide risk in this population. It is also important for physicians to note that the highest rates of suicide come shortly after the diagnosis of cancer. Many of the findings in relation to suicide and bladder cancer are similar to those of general mental health as suicide is highly correlated to one's mental well-being. While details regarding the association of bladder cancer and suicide have not been fully investigated, current information demonstrates

the potentially devastating effects of mental health changes in this cohort.

One area of investigation of particular interest to practitioners is the impact of mental health on overall patient mortality and disease prognosis. In this review, several articles demonstrated the negative effect of mental health symptoms on CSS and OS from bladder cancer [19–21,27]. Furthermore, 1 study showed that poor mental health can be predictive of short-term, high-grade postoperative complications after RC [20]. These findings clearly demonstrate the need for physicians to address this issue in their patients not only to improve QOL, but also to improve outcomes from the disease and minimize side effects from treatment. It has also been well described in the general cancer patient population that mental health changes, such as depression and anxiety, lead to poor follow-up, decreased medication and treatment adherence, and worsening patient understanding of their disease [31]. These changes could explain or at least partially explain its impact on survival in the bladder cancer population in addition to the increased suicidal ideation.

While mental health disorders may impact the outcome and prognosis of bladder cancer patients, there are currently few studies describing possible interventions to prevent or treat this problem. During our literature review, we found minimal evidence on specific treatments or preventative strategies. Many authors highlighted the importance of physicians to be aware of mental health changes in bladder cancer patients, but few recommended specific interventions [31,32]. In the general cancer population, cognitive behavioral therapy and other nonpharmacological interventions have preliminary data showing positive outcomes in treating psychological changes following a cancer diagnosis, but the efficacy of these techniques on cancer prognosis is inconclusive [32–36]. The use of pharmacotherapy in the treatment of symptoms such as depression, delirium, and anxiety in cancer patients has been shown to be useful and is recommended in a multidisciplinary fashion to not only provide mental support but also social support during treatment [35]. Furthermore, treatment of cancer-related psychological disorders with cognitive behavioral therapy and pharmacotherapy is seen in the geriatric population, although there are concerns with polypharmacy, treatment adherence, and attitudes or stigma associated with psychological disorders [36]. Research will continue to progress as we further understand the complex interaction between mental health and survival-related outcomes, specifically after a cancer diagnosis has been made.

Another promising area of future research is prehabilitation programs. These programs focus on preoperative and perioperative interventions, such as physical therapy, counseling, and addressing modifiable risk factors to reduce morbidity and mortality associated with surgery [37–40]. Several authors have demonstrated the success of prehabilitation programs in reducing postoperative complications, shortening hospital stays, and reducing overall morbidity associated with certain operations such as RC and urinary diversion for bladder cancer [37–39]. Unfortunately, there is minimal inclusion of mental health in these protocols [40]. As enhanced recovery after surgery protocols continue to be adopted in the treatment of bladder cancer patients nationwide, inclusion of a mental health branch with cognitive behavioral therapy, psychological counseling, and possible pharmacotherapy is necessary to further optimize cancer-related outcomes.

Limitations do exist with the data reviewed. Many different mechanisms were used to diagnose mental health changes in bladder cancer patients, including chart reviews and numerous patient surveys. Due to this heterogeneity, it is difficult to compile uniform data for large-scale analysis. Confounders for mental health are also numerous and often unaccounted for in most studies as mental health is a complex interconnection of social factors, physical factors, emotional factors, and overall health. Despite these drawbacks, future research focusing on mental health during the diagnosis and treatment of bladder cancer will continue to push the field forward and further enhance care in this group.

5. Conclusions

Mental health and bladder cancer have significant effects on one another. Mental health changes are apparent in many patients soon after they are diagnosed with bladder cancer. These psychological factors have been shown to independently worsen patient morbidity and mortality rates. The incidence of suicide is also greater in this population. Unfortunately, there have been few studies regarding preventative or treatment interventions. We recommend practitioners to be conscious of mental health changes in their patients with bladder cancer with the goal of intervening before patients undergo irreversible damage to their overall outlook.

Conflicts of interest

The authors declare that they have nothing to disclose.

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