UROLOGY

Bladder Cancer in Pediatric Population: A Literature Review

Rangga Adhazi Ksatriapraja, Safendra Siregar, Akhmad Mustafa

ABSTRACT

Objectives: **Bladder cancer is extremely rare in children, corresponding to less than 0.4% of all malignancies diagnosed in this population. This study aims to provide a literature review of this extremely rare malignancy.**

Design: **This is a literature review.**

Materials and Methods: **A total of 46 studies were included in this study. We reviewed patients characteristics, epidemiology, risk factors, comorbidities, signs, and symptoms, work up and diagnosis, management, and prognosis in pediatric bladder cancer cases.**

Results: **The most common type of bladder cancer in children are rhabdomyosarcomas or urothelial carcinomas. Painless hematuria, lower urinary tract symptoms (LUTS), and abdominal pain are the most common presenting symptoms. Ultrasonography is the most common diagnostic modality, while, while cystoscopy remains to be the definitive standard. Most patients underwent cystoscopic resection through TURBT. Chemotherapy is usually reserved for invasive carcinomas. The prognosis is generally excellent, but is much less optimistic in invasive carcinomas.**

Discussion: **There is currently no widely-accepted consensus on the diagnosis, staging, treatment, and follow-up for bladder cancer in pediatric population. Clinical approach must be tailored on a case-by-case basis.**

Conclusion: **Further research is required in the diagnosis and treatment of this potentially deadly disease in children.**

KEY WORDS

bladder, cancer, carcinoma, pediatrics, literature review

INTRODUCTION

Bladder cancer is one of the less common malignancies, being the sixth most commonly diagnosed cancer overall. According to the data from GLOBOCAN 2018, the estimated global prevalence of bladder cancer is 500,000 cases in 2018, with an estimated mortality of 200,000 deaths[1]. In Asia, data on the epidemiology of bladder cancer is relatively sparse, and it is estimated that approximately 115,000 new cases were diagnosed in male Asians in 2012, with the highest incidence found in Eastern Asia, but the highest mortality rate in Western Asia[2].

Bladder cancer is usually classified based on the WHO/ISUP 2004 Classification of Tumours of the Urinary System and Male Genital Organs, which was later revised in 2016. Based on the 2016 classification, bladder cancer is classified based on its histopathological characteristics into ten classes, namely urothelial tumors, squamous cell neoplasms, glandular neoplasms, urachal carcinoma, tumors of Mullerian type, neuroendocrine tumors, melanocytic tumors, mesenchymal tumors, hematopoietic and lymphoid tumors of the urothelial tract, and miscellaneous tumors[3]. Mortality due to bladder cancer is relatively low, with an overall death rate of 4.3 per 100,000 men and women per year, and overall survival approaches 77% for all stages combined. Bladder cancer is most commonly diagnosed after 55 years old, with the median age of diagnosis of 73 years old[4]. with the most common signs and symptoms being gross hematuria, dysuria, urinary tract infection, leukocytosis, abdominal pain, constipation, raised inflammatory markers and raised creatinine[5].

In children, malignancies of the bladder are exceedingly rare. It is estimated that the incidence of bladder cancer in the first two decades of life is 0.1-0.4%[6]. Due to its rarity, it is impossible to perform studies with a large number of pediatric cancer patients, and the current body of evidence is dominated by case reports and case series. Moreover, there is no established protocol for the diagnosis, classification, treatment, and follow-up for bladder cancer in the pediatric population and most cases are approached with some modification of adult bladder cancer protocols. Considering the lack of evidence concerning the diagnosis and treatment of bladder cancer in children, we conducted a literature review on the presentation, diagnosis, treatment, and prognosis of bladder cancer in the pediatric population.

PATIENT CHARACTERISTICS AND EPIDEMIOLOGY

Pediatric bladder cancer is an extremely rare occurrence in the clinical setting, with fewer than 1,000 cases reported in modern literature. Although epidemiological data regarding this condition in children is lacking, our review showed that the male predisposition remains accurate in both adults and children. In the reviewed studies, male children are approximately 2-3 times more likely to be diagnosed with bladder cancer compared to females. In our study, the median age of diagnosis

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Department of Urology, Faculty of Medicine, Universitas Padjadjaran, Hasan Sadikin Hospital
Jl. Pasteur no. 38, Bandung, West Java, Indonesia 40161
Correspondence to: Safendra Siregar
(e-mail: safendra_sir@yahoo.co.id)

Table 1: Identified risk factors and comorbidities in case studies of pediatric bladder cancer.

Author	Year	Risk Factors	Comorbidities
Innocenzi *et al*	2019	Active smoking	Eating disorder
Aykan *et al*	2015	Active smoking 1 active smoking patient,	-
Fine *et al*	2005	2 patients with passive smoke inhalation	-
Sheehan *et al*	2015	Active alcohol consumption	12 weeks
Diaz *et al*	2019	BK viremia	Crohn's disease
Aktas *et al*	2019	Passive smoke inhalation	2 years
Peard *et al*	2020	Passive smoke inhalation	18 months
Mau & Leonard	2016	Pulmonary TB, intestinal parasite	Recurrence in 4 patients at 6, 12, 18, and 24 months
Sung & Koyle	2000	Prior cystolithiasis	-
Lerena *et al*	2009	-	1 patient with anorchia and 1 patient with renal hypoplasia
Saleem *et al*	2018	-	Crohn's disease
Ghousheh *et al*	2012	-	Hinman syndrome
Aguiar *et al*	2015	-	Turner syndrome
Di Carlo *et al*	2014	-	1 patient with an abdominal tumor, 1 patient with ovarian teratoma

Table 2: Summary of studies with LUTS, recurrent UTI, abdominal pain, or incidental findings at presentation

Author	Year	Population	Signs and Symptoms
Huang *et al*	2015	4	1 case with dysuria and abdominal pain
Apoznanski *et al*	2015	7	6 cases with hematuria, 1 case with dysuria, 2 cases with abdominal pain
Innocenzi *et al*	2019	2	1 case with hematuria and dysuria, 1 case incidental finding
Ander *et al*	2015	8	7 cases with hematuria, 1 case with urinary retention, 1 case with abdominal pain
Wang *et al*	2014	1	1 case with frequency
Minkowitz *et al*	2016	1	1 case with urinary incontinence, abdominal fullness, and pain
Ghousheh *et al*	2012	1	1 case with recurrent UTI and incomplete emptying of the bladder
Peard *et al*	2020	1	1 case with dysuria, frequency, and urgency
Zribi *et al*	2019	1	1 case with hematuria and dysuria
Davidovics *et al*	2020	2	1 case with hematuria and dysuria, 1 case with recurrent abdominal pain
Fine *et al*	2005	23	Hematuria in 21 cases, 1 case incidental finding, 1 case each of fever, difficulty voiding, and flank pain
Neogi *et al*	2013	1	1 case of hematuria and urinary retention
Karatzas & Vassilios	2019	2	2 cases with dysuria and urgency
Diaz *et al*	2019	1	Incidental finding during MR enteroscopy for the evaluation of Crohn's disease
Saleem *et al*	2018	1	Incidental finding during MR enteroscopy for the evaluation of Crohn's disease

Table 3: Examples of diagnostic modalities used in several studies.

Author	Year	Population	Modality
Kral *et al*	2016	1	Ultrasonography, cystoscopy
Karatzas & Vasillios	2019	2	2 cases undergoing ultrasonography, cystoscopy
Innocenzi *et al*	2019	2	2 cases undergoing ultrasonography, cystoscopy
Korrect *et al*	2011	1	Ultrasonography, cystoscopy
Ucar *et al*	2018	4	4 cases undergoing ultrasonography, cystoscopy
Sheehan *et al*	2015	1	Ultrasonography, abdominal CT
Wang *et al*	2014	1	Abdominal CT, cystoscopy
Ander *et al*	2015	8	8 cases undergoing ultrasonography, cystoscopy, and intravenous pyelography

was approximately 11 years old, although a meta-analysis conducted by Paner, *et al*. showed that the majority of bladder cancer cases were diagnosed at the age of 15-20 years old. The same study also revealed that boys are 5.4 times as likely to be diagnosed with bladder cancer compared to girls[7].

RISK FACTORS AND COMORBIDITIES

Pediatric patients rarely presented with risk factors linked to bladder cancer in adults. Reported risk factors include an active smoking history in one case and a small subset of patients who inhaled smoke passively at home. One case reported active alcohol consumption[8]. Other studies reported several possible risk factors, including previous tuberculosis infection[9], history of cystolithotomy[10], and schistosomiasis, but the relationship between these conditions and bladder cancer in children remains to be proven. A small number of studies reported bladder cancer coincidental with certain genetic syndromes, including Hinman syndrome[11] and Turner syndrome[12]. However, the number of these concurrent conditions is too low to discern a meaningful relationship. In addition, the analyzed studies showed other comorbid conditions in their population, including anorchia, renal aplasia, eating disorder, and Crohn's disease[10,13-17]. Table 1 summarizes the identified risk factors and comorbidities in the literature.

Several lifestyle factors have been linked to bladder cancer in adults, including tobacco smoking[18], exposure to toxins[19], prior history of chemotherapy[20], and schistosomiasis[21]. Due to the limited number of cases, it is unknown whether these risk factors are applicable to the pediatric population. The majority of studies analyzed did not identify any of these risk factors, and other confounding risk factors may contribute to the pathogenesis of bladder cancer in children. In addition, one patient developed bladder cancer after a history of prior rhabdoid tumor treated with multiagent chemotherapy, surgery, and radiotherapy, which may contribute to the occurrence of bladder cancer in this patient[17].

Table 4: Largest identified studies and the most common diagnoses for bladder cancer in children

Author	Year	Population	Diagnoses
Alanee & Shukla	2009	140	PUNLMP (50.7%), rhabdomyosarcoma (36.4%), transitional cell carcinoma (9.3%)
Huppman & Pawel	2011	65	Rhabdomyosarcoma (23%), other non-urothelial neoplasms (25%), urothelial neoplasms (9%)
Fine *et al*	2005	23	2 urothelial papillomas, 10 papillary urothelial neoplasms of low malignant potential (PUNLMPs), 8 low grade and 3 high grade papillary urothelial carcinoma
Di Carlo *et al*	2014	12	1 case of HGPUC and 11 cases of either PUNLMP or LGPUC
Ander *et al*	2015	8	1 case of PUNLMP and 7 cases of LGPUC

Table 5: Summary of treatment approaches for different types of bladder malignancies in children

Diagnosis	Author	Year	N	Treatment	Outcome
PUNLMP	Apoznanski *et al*	2015	7	TURBT with or without intravesical doxorubicin	Local recurrence in 1 case, complete remission in 6 cases
	Fine *et al*	2005	10	TURBT	Complete remission with no recurrence at 4.5 years
LGPUC	Di Carlo *et al*	2014	12	TURBT + intravesical epirubicin or mitomycin	1 recurrence treated with re-TURBT + intravesical mitomycin, 10 complete remission
	Ander *et al*	2015	1	TURBT	Complete remission with no recurrence at 60 months
	Ucar *et al*	2018	4	TURBT or open excision	Complete remission with no recurrence at 2 years
	Peard *et al*	2020	1	TURBT + intravesical BCG	Complete remission with no recurrence
Papilloma	Davidovics *et al*		2	TURBT	Complete remission with no recurrence at 1 & 10 years
	Fine *et al*		2	TURBT	Recurrence in 1 patient at 6, 12, 18, & 24 months
	Marinoni *et al*		2	TURBT	Complete remission with no recurrence at 30 months
HGPUC	Aguiar *et al*	2015	1	TURBT only	Complete remission with no recurrence at 1 year
	Wang *et al*	2016	1	Radical cystectomy with MVAC chemotherapy	Patient death due to progressive disease
	Korrect *et al*	2011	1	Partial cystectomy with intravesical BCG	Complete remission with no recurrence at 1 year
	Neogi *et al*	2013	1	Partial cystectomy with MVAC chemotherapy	Complete remission with no recurrence at 6 months
Rhabdomyosarcoma	Chargari *et al*	2017	100	Partial cystectomy with brachytherapy, chemotherapy	91% overall survival rate and 84% free of recurrence at 5 years
	Nakata *et al*	2017	1	TURBT with VAC chemotherapy	Complete remission with no recurrence at 3 years
	Ahsaini *et al*	2018	1	Chemotherapy with VAC, then radical excision	Complete remission with no recurrence at 2 years

SIGNS AND SYMPTOMS

The majority of pediatric bladder cancer patients presented with gross hematuria as the chief complaint. Hematuria may be accompanied by lower urinary tract symptoms (LUTS) or isolated, in addition to abdominal pain, flank pain, and recurrent UTI. Most cases presented with painless hematuria, although in some cases, microhematuria was found as an incidental finding during urinalysis for evaluation of other conditions. Alongside hematuria, blood clots in urine is also a symptom warranting further evaluation for bladder malignancy. The most common LUTS found in the analyzed studies include dysuria and frequency[11,16,22-32]. Table 2 summarizes studies with less common presentations for pediatric bladder cancer.

The presentation of bladder cancer in pediatric patients are similar to adults as well, with gross hematuria, with or without pain, being the most common chief complaint in the reviewed studies. In adults, hematuria is often accompanied by blood clots in the urine, while in the analyzed studies, blood clots were reported only in one patient. Recurring urinary tract infections are a known risk factor for bladder cancer[33], and in children, recurring UTI requires a careful investigation for other concurrent conditions. Physical examination rarely yields any useful findings. In addition, several studies reported patients presenting with lower urinary tract symptoms (LUTS), including dysuria, frequency, hesitancy, and urgency[11,25,32]; and less frequently, abdominal or flank pain[23,24]. In addition, two studies reported bladder neoplasms as incidental findings during an MR enteroscopy for the evaluation of Crohn's Disease[13,14]. Due to its rarity, diagnosis of bladder cancer in children with gross hematuria is frequently delayed, with up to 26% delayed by over 1 year after first presentation[7].

WORKUP AND DIAGNOSIS

Bladder ultrasonography is generally the first-line diagnostic method for bladder cancer in children, due to its safety and relatively high

Table 6: Studies utilizing chemotherapy as a treatment for bladder malignancies

Author	Year	Diagnosis	Treatment	Outcome
Ghousheh *et al*	2012	Invasive transitional cell carcinoma	6 cycles of gemcitabine + cisplatin with radiotherapy	Patient death due to metastatic disease
Aykan *et al*	2015	Grade 3 transitional cell carcinoma	28-day regimen of gemcitabine + cisplatin + paclitaxel with radiotherapy	Patient death due to metastatic disease
Ordonez-Tanchiva *et al*	2020	Myoepithelial Carcinoma	6 courses of ifosfamide + cisplatin + etoposide with radiotherapy, followed by partial cystectomy	Complete remission with no recurrence
Lezama-del Valle *et al*	2004	HGPUC with atypical sarcomatoid	Methotrexate + vinblastine + doxorubicin + cisplatin followed by radical cystectomy	Tumor recurrence and progression after chemotherapy resulting in patient death
Neogi	2013	HGPUC	Partial cystectomy followed by 3 cycles of methotrexate + vinblastine + doxorubicin + cisplatin	Remission with no recurrence at 6 months follow-up
Wang *et al*	2014	HGPUC with sarcomatoid differentiation	Radical cystectomy followed by 4 cycles of vinblastine + doxorubicin + cisplatin	Disease progression despite chemotherapy resulting in patient death

Table 7: Summary of studies using intravesical therapy for bladder cancer

Author	Year	Diagnosis	Treatment	Outcome
Korrect *et al*	2011	HGPUC	TURBT with intravesical BCG	Remission with no recurrence at 12 months
Sheehan *et al*	2015	LGPUC	TURBT with intravesical mitomycin C	Remission with no recurrence at 6 months
Huang *et al*	2015	LGPUC	TURBT with Intravesical hydroxycamptothecine	Remission with no recurrence at 24 months
Apoznanski *et al*	2015	PUNLMP	TURBT with intravesical doxorubicin	Remission with no recurrence at 8 years
Peard *et al*	2020	Recurrent LGPUC	TURBT with 2 courses of intravesical BCG	Remission after twice recurrence

Table 8: Studies reporting disease recurrence or patient death.

Author	Year	Recurrence	Death
Wang *et al*	2014	No	Death 6 months after surgery due to metastatic disease
Aykan *et al*	2015	No	Death within 1 year of diagnosis due to bone metastasis
Ghousheh *et al*	2012	No	Death due to metastatic disease
Lezama-del Valle *et al*	2004	12 weeks	Death 9 months after diagnosis due to myelosuppression and infection
Di Carlo *et al*	2014	1 year	-
Apoznanski *et al*	2015	2 years	-
Peard *et al*	2020	18 months	-
Fine *et al*	2005	Recurrence in 4 patients at 6, 12, 18, and 24 months-	

accuracy. A high index of suspicion for bladder tumor in ultrasonography warrants a confirmatory examination with CT-scan or MRI. In addition, cystoscopy remains the definitive diagnostic tool for bladder cancer in children and also provides a therapeutic approach through TURBT. A study also used intravenous urography (IVU) as an adjunct diagnostic examination[24]. Several studies also reported bladder masses discovered as incidental findings during evaluation for other conditions, either through sonography, CT-scan, or MRI[13,14,25]. Immunohistochemistry examination is only performed in a small proportion of studies, with the most common tests being p53 and Ki-67 reactivity, and other tests including CK-5, CK-7, CK-20, and PAX-8. Table 3 exemplifies the less common diagnostic modalities used in diagnosing bladder cancer in children.

Sonography is the safest and most commonly used diagnostic modality for bladder cancer. With sensitivity and specificity values nearing 100%, bladder sonography is a low-cost, highly effective diagnostic tool for bladder cancer. Bladder masses usually present as a hypoechoic mass protruding into the bladder cavity from the wall and are usually located on the posterior and lateral walls. Nevertheless, the American Urological Association does not recommend the use of abdomino-pelvic ultrasonography alone for the evaluation of bladder cancer due to the insufficient anatomic detail for upper urinary tract imaging. Instead, the AUA opted to recommend contrast-based axial imaging using CT or MRI, confirmed through direct visualization with cystoscopy[34].

In children, sonography is almost universally used as the preliminary diagnostic tool in the reviewed studies. The use of immunohistochemistry examination is much less uniform in comparison, as is reflected in its use in adult bladder cancer patients.

Rajcani, *et al*. (2013) described a wide range of cell-cycle-related proteins in bladder cancer, used in the differentiation and prognostication of bladder cancer. Ki-67 and p53 are useful markers to differentiate LGPUC, HGPUC, and PUNLMP, where their specific values can be used for grading the degree of cell proliferation; while pRb and Survivin may indicate a risk of recurrence and correlates with proliferation and differentiation in HGPUC. CK-7 and CK-20 are cytokeratin antigens used for the recognition of urothelial origins of non-differentiated HGPUC, especially in prostatic area[35]. GATA3 may be used in differentiating carcinomas of urachal origin from primary bladder adenocarcinomas[36]. Other immunohistochemical markers are not specific for bladder neoplasms and may be useful for differentiating other primary tumor

Table 9: Summary of studies with reported follow-up protocols

Author	Year	Follow-up duration	Follow-up ultrasonography	Follow-up cystoscopy
Di Carlo *et al*	2014	30 months	Every 3-6 months	Every 2-12 months
Oda *et al*	2019	30 months	Every 3 months	Every 6 months
Karatzas & Vassilios	2019	12 months	Every 3 months	At 6 and 12 months
Neogi *et al*	2013	6 months	Every 1 month for 6 months	Every 6 months
Kral *et al*	2016	24 months	Every 3-6 months	Every 12 months
Ander *et al*	2015	60 months	At 3 and 9 months, then biannually	At 3 and 9 months, then biannually
Innocenzi *et al*	2019	30 months	At 3 and 9 months, then annually	At 3 and 9 months, then annually
Ucar *et al*	2018	5-120 months	At 3 and 9 months, then annually	Every 12 months
Aguiar *et al*	2015	60 months	At 1,3,6,12,18, and 24 months	At 1,3,6,12,18, and 24 months
Diaz *et al*	2019	30 months	Every 3-6 months	Every 2-12

Table 10: The AUA and EAU recommendations for the surveillance of bladder cancer post-treatment patients[46].

	AUA	EAU
All Patients	Initial cystoscopy within 3–4 months of completion of treatment	Initial cystoscopy at 3 months
Low-risk	Cystoscopy 6–9 months later, and then annually for at least 5 years	Another cystoscopy at 9 months later, then annually for 5-years. Consider stopping after 5 years without recurrence.
Intermediate-risk	Cystoscopy + cytology every 3–6 months for 2 years, then every 6–12 months for years 3–4, and then annually thereafter	Surveillance scheme between low and high-risk
High-risk	Cystoscopy + cytology every 3–4 months for 2 years, then every 6 months for years 3–4, and then annually thereafter	Cystoscopy and cytology every 3 months for 2 years, then every 6 months until 5 years, and then annually thereafter
Upper tract evaluation	Every 1–2 years in intermediate- or high-risk NMIBC, not routinely recommended for low-risk NMIBC	Yearly for high-risk NMIBC, no specific recommendations for low- or intermediate-risk NMIBC

sites[37].

Several sources noted that rhabdomyosarcoma is the most common type of bladder malignancy found in children. Huppman & Pawel (2011) reported a single-center retrospective study by rhabdomyosarcoma as the most commonly found bladder mass in children aged 5 months to 18 years old, followed by fibroepithelial polyps and urothelial neoplasms[39].

We identified a lower number of rhabdomyosarcoma cases in other literature. Based on a retrospective analysis on the SEER database conducted by Alanee and Shukla (2009), embryonal rhabdomyosarcoma dominated the diagnosis of bladder malignancies in the first 12 years of life, while the incidence of papillary transitional cell carcinoma increases significantly afterwards[38]. Table 4 summarizes the largest identified studies concerning bladder neoplasms in children.

Currently, there is no standardized diagnostic system for bladder neoplasms in children. This is reflected in the highly diverse diagnosis made in the analyzed studies. While most studies conformed to the WHO/ISUP 2004 classification, a number of studies described the diagnosis based on muscle invasiveness and grading. Nevertheless, it seemed that the majority of bladder cancer in children is of a low grade.

Based on the histopathological features, our study showed that the most commonly made diagnosis for bladder cancer in children were low-grade papillary urothelial carcinoma (LGPUC, 29.8%), papillary urothelial neoplasm of low malignant potential (PUNLMP, 21.2%), high-grade papillary urothelial carcinoma (HGPUC, 13.8%), and papilloma (8.5%). Very few cases presented with atypical histopathological subtypes, including clear cell UC[13,14,26], myoepithelial carcinoma[40], and one case of squamous cell carcinoma of the bladder[10]. Our finding is consistent with a meta-analysis conducted by Marinoni, *et al*., where LGPUC dominated the diagnosis, followed by PUNLMP[41].

On a side note, most of the patients aged under 5 years old in our study were diagnosed with higher-grade lesions. 5 out of 6 patients aged under 5 years old were diagnosed with HGPUC. In patients aged 6-10 years old, PUNLMP contributed to 50% of the diagnoses, while LGPUC dominated the diagnoses for patients aged over 10 years old. Paner, et al. noted that LGPUC is the most common histopathological type in patients aged 10-20 years old, with an increased risk for intermediate- or high-grade PUC as the patients age[7].

TREATMENT

Currently, there are no specific guidelines or widely-accepted consensus on the treatment of bladder cancer in the pediatric population. A number of studies described different treatment approaches for bladder cancer in children, both invasive and noninvasive. The vast majority of patients in the analyzed studies underwent TURBT as the primary treatment modality, in addition to intravesical therapy and partial cystectomy. TURBT appeared highly effective in treating bladder cancer in pediatric patients, with very low recurrence rates and few adverse events. Partial cystectomy is reported in a small number of patients, usually reserved for larger masses or patients presenting with unusual diagnoses or presentation[10,14,40,42]. Recurrence usually occurs in invasive masses, and lymph node involvement may be an indicator of future recurrence[43].

The mainstay of treatment for the majority of bladder cancer cases is cystoscopic tumor resection through TURBT. In adults, bladder cancer is stratified into three risk groups, where the low-risk group may be treated with TURBT alone with further surveillance. Most of the pediatric patients in the reviewed studies fall into this category, and no further treatment was required after TURBT. Even with TURBT alone, the recurrence rate is low, and this approach may be recommended for low-grade bladder cancer in children. For intermediate- and high-risk bladder cancer, adjuvant intravesical immunotherapy with Bacillus Calmette-Guerin may be considered after TURBT. One study reported the use of this intravesical therapy with BCG, although treatment was ceased due to the patient experiencing dysuria and gross hematuria after intravesical BCG administration[42]. In addition, other studies also reported intravesical therapy with doxorubicin, mitomycin-C, and HCPT[8,17,23,30]. These treatments are less well-studied compared to BCG in adults, and the choice to use these intravesical agents should be made with caution.

Chemotherapy is used very rarely in pediatric bladder cancer patients, due to the low invasiveness of bladder cancer in these patients and the potentially serious side effects of chemotherapy in children. Treatment of chemotherapy is usually reserved for high-grade or invasive cases, such as in distant metastasis or muscle-invasive carcinomas. Chemotherapy is used in one case report with myoepithelial carcinoma, using a six-course regimen of ICpE (ifosfamide, cisplatin, and etoposide). In addition, the same study reported radiotherapy with 4,500 cGy dose over 25 sessions[40].

Other studies utilizing chemotherapy include a case report of a metastatic transitional cell carcinoma treated with gemcitabine and cisplatin[11]; large high-grade transitional cell carcinoma treated with gemcitabine, cisplatin, and paclitaxel[44]; and another case report of an atypical high-grade sarcomatoid urothelial carcinoma treated with vinblastine, adriamycin, and cisplatin[25]. A modified MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) regimen has also been used in the treatment of invasive urothelial carcinoma[45].

Intravesical therapy is a commonly used adjunct therapy for bladder cancer in adults. However, intravesical therapy is rarely utilized in children, and several case reports used either Bacillus Calmette-Guerin (BCG)[27,42], doxorubicin[23], mitomycin-C[8], or hydroxycamptothecine (HCPT)[22] as intravesical agents. In these cases, intravesical therapy is initialized after TURBT for the treatment of recurrent bladder cancer[27] and high-grade transitional cell cancer[8,42].

PROGNOSIS

Overall, bladder cancer in pediatric patients has an excellent prognosis, and mortality rates are very low. This is due to the fact that bladder cancer in children mostly present as low-grade tumors, and high-grade or metastatic disease is quite rare, and mortality rates are much lower compared to adults. All the deaths reported in the reviewed studies were attributed to high-grade or metastatic disease, and patients underwent a more aggressive treatment approach utilizing chemotherapy as neoadjuvant or adjuvant treatment. Recurrence rates are generally low in the analyzed studies. 5 studies reported 8 recurring cases, which were mostly treated with repeated TURBT. Most of the studies analyzed reported patients surviving until the date of publication, with a median follow-up duration of 21 months. The death occurred only in 4 patients (4.25%). The following table 8 summarizes the studies in which recurrence or death occurred.

There are no established protocols for follow-up of pediatric cancer patients, and the majority of studies performed follow-up using some modification of adult bladder cancer follow-up protocol. Most follow-ups were performed with serial ultrasonography in either 3, 6, or 12 months after surgery and cystoscopy in 6 and 12 months after surgery. Other studies also reported an adjunct of urinalysis or abdominal CT-scan as part of the follow-up. The following table 9 summarizes the follow up protocol of each study.

In adults, the follow-up protocol for bladder cancer patients is tailored to the patient's risk of recurrence and diagnosis. Both the American Urological Association and the European Association of Urology recommend the use of repeated cystoscopy for the surveillance of bladder cancer in adults after treatment, in addition to repeated cytology in intermediate to high-risk patients. In the reviewed studies, follow-up protocols for pediatric patients are markedly less uniform, and sonography is more often used for routine follow-up while cystoscopy is used less frequently. A number of studies used sonography in tandem with cystoscopy, while others performed sonography as the initial follow-up examination, followed by cystoscopy. Most studies seemed to agree on sonography for the follow-up of bladder cancer at 3 months, followed by another sonography in the sixth or ninth months, and then annually or biannually. Cystoscopy in the reviewed studies was performed either every six months, at the third and ninth months then annually, or every three months for one particular high-risk patient. The following table 10 summarizes the AUA and EAU recommendations for the surveillance of bladder cancer post-treatment patients.

CONCLUSION

Bladder cancer, although rarely encountered in children, is still an important clinical entity, and clinicians must be vigilant in diagnosing this potentially deadly condition. There is currently no widely-accepted consensus on the diagnosis, staging, treatment, and follow-up for bladder cancer in the pediatric population and the clinical approach must be tailored on a case-by-case basis. The body of evidence supports the use of ultrasonography as the first-line diagnostic modality, while treatment is mostly limited to cystoscopic excision through TURBT. Given an early diagnosis and proper treatment, bladder cancer has an excellent prognosis in children. Nevertheless, further study is required to establish proper diagnostic and treatment protocols for these patients.

CONFLICTS OF INTEREST

The authors declared no competing interests.

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