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Systematic review of bladder cancer outcomes in patients with spina bifida

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Summary

Background
In patients with congenital bladder anomalies, bladder augmentation is used as a last resort to reduce intravesical pressure, but concerns about malignant transformation in augmented patients were first raised in the 1980s. The best evidence to date indicates that augmentation does not appear to increase the risk of bladder cancer in spina bifida patients. To date, oncologic outcomes from patients with spina bifida with and without augmentation have only been available in small case reports.

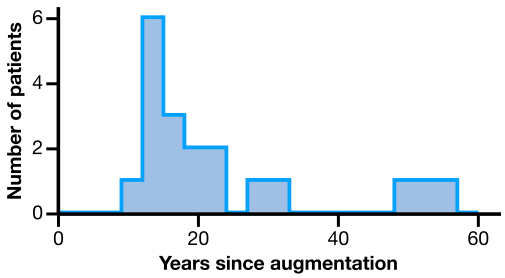
Objective
To systematically evaluate factors in myelomeningocele patients with bladder cancer, including bladder augmentation, that contribute to overall survival (OS).

Study Design
A systematic review using PubMed was conducted by cross referencing terms 'myelomeningocele,' 'cystoplasty,' 'bladder cancer' and respective synonyms according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Inclusion criteria were studies with patients with an underlying diagnosis of myelomeningocele and bladder cancer with data on age, stage, and mortality status. Studies were excluded for spinal cord injury, history of tuberculosis or schistosomiasis, or prior ureterosigmoidostomy.

Results
Fifty-two patients were identified from 28 studies with a median age at bladder cancer diagnosis of 41 years (range 13–73); 37 (71%) presented with stage III or IV bladder cancer. Overall survival at 1 year and 2 years was 48.5% and 31.5%, respectively. Overall survival was different between those with and without augmentation ($P = 0.009$) by log-rank analysis. No between-group differences in OS were seen based on age, management with indwelling catheter, diversion with ileal conduit or being on a surveillance program. Only stage remained a significant predictor of OS on multivariate analysis (HR 2.011, 95% CI 1.063–3.804, $P = 0.032$). Secondary analysis was performed after removing patients with gastric augmentation ($n = 8$), and no difference in OS was seen between patients with ($n = 8$) and without augmentation ($n = 36$, $P = 0.112$). Of augmented patients, latency to development of bladder cancer was variable (Summary Figure).

Discussion
Bladder cancer is a deadly diagnosis in patients with congenital bladder anomalies like spina bifida, and while overall prevalence of the two conditions occurring together is low, bladder cancer will go on to affect 2–4% of spina bifida patients. The present study examined overall survival, and further characterized outcomes in these patients. Presence of a bladder augment did not appear to worsen overall survival.

Conclusions
Patients with myelomeningocele who developed bladder cancer had aggressive disease. Augmentation did not worsen OS, based on cases reported in the literature. Risk of bladder cancer should be discussed with all myelomeningocele patients.



Summary Fig Histogram of latency to development of bladder cancer in patients that had previously undergone augmentation ($n = 16$).

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Introduction

Bladder augmentation is widely recognized in providing increased bladder capacity, reducing intravesical pressures, protecting upper urinary tracts, and improving continence in patients with neurogenic bladder who fail medical management [1,2]. Since its original description in the 1950s, the long-term risks of bladder augmentation are now well known and must be taken into consideration when counseling patients regarding treatment options for neurogenic bladder, particularly since patients with congenital bladder anomalies like spina bifida are living longer [3].

Concerns about malignant transformation in augmented patients were first raised in the 1980s [4–6]. In the absence of known causes for bladder cancer, augmentation was felt to be a potential independent risk factor for the development of bladder cancer [7]. This has been thrown into some dispute and doubt, with recent reports noting that both augmented and non-augmented patients with spina bifida develop bladder cancer [8,9]. However, to date, only a handful of case reports and series have been published about spina bifida patients with bladder cancer, limiting general knowledge about how these patients do and what factors, like bladder augmentation, might otherwise contribute to outcomes.

The present study sought to perform a systematic review to quantify patient characteristics that influence overall survival (OS) in spina bifida patients who develop bladder cancer. It was hypothesized that patients with myelomeningocele and bladder cancer who have previously undergone bladder augmentation do not have decreased OS as compared with patients without bladder augmentation.

Methods

Search strategy

A systematic literature search of the PubMed database was conducted in April 2016 and updated in December 2016 to identify human studies by cross-referencing the terms: 'myelomeningocele,' 'cystoplasty,' 'bladder cancer' and respective synonyms. The full list of search terms and combinations is listed in Appendix Table 1. The methodology used to identify and select studies for patient inclusion in the quantitative synthesis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [10]. Duplicate studies were identified and removed.

Studies were included if they contained one or more patients with an underlying diagnosis of spina bifida and bladder cancer, with data available on age, stage, and mortality status. Study exclusion criteria were: those written in languages other than English or for which no medical translation could be obtained; studies with patients with an underlying congenital bladder anomaly other than myleomeningocele (e.g., PUV, sacral agenesis, classic bladder exstrophy or cloacal exstrophy); patients with cancer arising from non-bladder locations (e.g., catheterizable channel or upper urinary tracts); spinal cord injury patients; and patients with a history of tuberculosis or schistosomiasis, or prior ureterosigmoidostomy.

Unique articles returned in the literature search were screened, and those that did not meet inclusion criteria on examination of title or abstract were excluded. Of the full-text articles that remained, references were further analyzed to locate any studies not returned in the original search, and these were also screened. Finally, full-text articles were assessed for eligibility based on the stated inclusion and exclusion criteria, leaving studies with patients for final quantitative analysis (Fig. 1). Data on demographics, clinical symptoms, bladder management, diagnosis, treatment, follow-up and survival were recorded. Attempts were made to contact authors of those studies with missing data by email, to maximize numbers of patients and completeness of the data.

Institutional database query

Institutional Review Board-approved databases at the authors' respective institutions were retrospectively searched to locate patients with co-diagnoses of bladder cancer and myelomeningocele who met the inclusion and exclusion criteria. Patients meeting these criteria were then abstracted and included in the analysis.

Clinical definitions

Symptoms and bladder management were recorded when described. Patients who were noted to have used one bladder management for a period of time and transitioned to another were recorded as having used both treatments. No attempt was made to differentiate time or sequencing of each management strategy secondary to heterogeneity and limited information provided within the case reports. Similarly, the study attempted to determine if patients were being followed regularly in a urology clinic; surveillance, in this regard, was defined as any of the following: regular annual or biannual visits with ultrasound and/or cystoscopy. Finally, it was recorded whether patients had a history of solid organ transplantation or were immunosuppressed, as this has been reported to increase the risk of malignancy [9,11].

Length of time from bladder augmentation to diagnosis of bladder cancer was calculated. Bladder autoaugmentation was not counted as bladder augmentation for the purposes of this paper. Type of intestinal segment used in the creation of the augment was recorded. In some cases, patients with prior ileal conduits underwent undiversion and bladder augmentation. In these cases, length of time to develop bladder cancer was recorded from the time of ileal conduit to diagnosis of bladder cancer; this was consistent with the total amount of time the bowel segment was exposed to urine.

Stage was recorded or interpreted from the available data in each report, according to the American Joint Committee on Cancer (AJCC) bladder cancer staging system. Treatments and follow-up times were noted. If no

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