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Malignant urachal neoplasms: A population-based study and systematic review of literature

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Abstract

Objectives: To examine patient and clinicopathological features of malignant urachal neoplasms (MUN) in a population-based cohort, to investigate survival outcomes, and to review the current evidence that exists in the literature.

Material and methods: The Surveillance, Epidemiology, and End Results database was used to identify microscopically confirmed MUN cases diagnosed between 1988 and 2012. Kaplan-Meier analysis was used to determine median and 5-year overall survival (OS) as well as cancer-specific survival (CSS) rates. Cox proportional hazards model was employed to identify variables independently associated with cancer-specific mortality. A systematic literature review was conducted in line with the PRISMA statement.

Results: A total of 420 patients with MUNs were identified. The majority were white (77.6%) and male patients (59%) who presented with low-grade (62.1%), mucinous, noncystic adenocarcinomas (42.9%). From the cohort, 19%, 15.2%, 29.5%, and 30.5% of the patients presented with American Joint Committee on Cancer Stage I to IV disease, respectively. Cancer-directed surgery was performed in 86.5% of the patients. The most common procedure performed was partial cystectomy (52.4%) followed by local tumor excision (20.7%). Median OS was 57 months (95% CI: 41.6–72.4), and median CSS was 105 months (95% CI: 61.5–148.5). Five-year OS and CSS rates were 51% and 57%, respectively. Grade and stage were independently associated with cancer-specific mortality. Mortality rates did not differ between patients who underwent partial cystectomy and radical cystectomy/exenteration ($P = 0.165$), even after controlling for tumor stage. A total of 16 studies reporting on 585 patients were systematically reviewed, and relevant outcomes were summarized in the Supplemental material.

Conclusions: MUNs are usually low-grade, mucinous, noncystic adenocarcinomas diagnosed at advanced stages. Overall, the prognosis is poor, and high-grade and disease stage are independently associated with cancer-specific mortality.

Keywords: Urachus; Bladder; Malignant neoplasms; Cancer; Adenocarcinoma

1. Introduction

During embryogenesis, the urachus connects the allantois to the apex of the bladder [1–3]. It consists of an outer muscular layer, connective tissue, and a lumen lined by transitional or cuboidal epithelium [2–4]. The urachus later degenerates and transforms into a fibromuscular cord known as the median umbilical ligament [1,3]. Urachal remnants are found in almost a third of the population [4], commonly located at the apex of the bladder and less frequently along the anterior or posterior midline of the bladder wall [1,5]. Histologically, urachal remnants resemble intestinal epithelium more closely than the adjacent urothelium. Proposed theories for this paradoxical phenomenon include metaplasia of transitional/cuboidal epithelium and the persistence of cloacal remnants within the urachus

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[1,4,5]. As such, urachal tumors differ histologically and thus biologically from other bladder neoplasms.

Malignant urachal neoplasms (MUNs) account for less than 1% (0.35%–0.7%) of all bladder cancers [5–7]. The most commonly encountered histological subtype is adenocarcinoma [6]. Patients usually present at an advanced stage and thus prognosis is poor [2,8]. Given the very low incidence of these tumors, most existing evidence is derived from single-institution case series.

The aim of this population-based study was to investigate the clinicopathological features and prognosis of MUNs by using a population database, which enables the follow up of a large number of patients with this rare entity. In addition, a systematic review of the literature was performed to contextualize our results with those from historical case series.

2. Material and methods

2.1. Data source and subjects

Patients with MUNs were identified in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database [9]. This population-based database consists of 18 cancer registries, which incorporate high-quality data on the incidence and survival of patients with primary malignancies and covers approximately 27.8% of the total US population based on the 2010 census [10]. Given the comprehensive method of data collection, SEER is a unique database permitting the descriptive analysis of rare malignancies. All patient data are deidentified and available to the public for research purposes.

2.2. Data collecting and coding

To identify all eligible patients, the following selection criteria were applied: (i) malignant tumor located at the urachus (ICD-O-3/WHO 2008 site code C.67.7) [11]; (ii) tumor diagnosed between January 1, 1988, and December 31, 2012; (iii) active follow up (diagnosis not obtained from autopsy or death certificate); and (iv) microscopically confirmed tumor.

Patient demographics (age, race, sex marital status, and year of diagnosis) as well as clinicopathological parameters (tumor grade, size, stage, management, and outcome) were extracted using the "case listing" option. Disease staging information was based on the derived seventh edition of the American Joint Committee on Cancer (AJCC) staging system for patients diagnosed between 2010 and 2012, the derived sixth edition of the AJCC staging for those diagnosed between 2004 and 2009, and the SEER-modified third edition of AJCC staging for patients diagnosed between 1988 and 2003 as provided by the SEER database. For analysis purposes, patients with in situ and stage I malignant tumors were grouped together. Using the site-specific surgery codes, all patients who underwent cancer-directed surgery were identified as well as the nature of each procedure was noted. Local resection mostly refers to transurethral resection, but some cases were not defined (marked as local destruction or local excision in the SEER database).

2.3. Statistical analysis

Median, 5-year overall survival (OS) and cancer-specific survival (CSS) rates were estimated using the Kaplan-Meier method, whereas the log-rank test was used to determine significant differences in patients stratified by demographic and clinicopathologic parameters. In this study, survival represents the number of months from cancer diagnosis to the date of death. All patients were presumed alive at the time of last follow up and were censored at that point. For the estimation of CSS rates, only patients with a single tumor or the first of multiple primary malignant tumors were included; those who died of causes other than urachal cancer were censored. Finally, a multivariable Cox proportional hazard model was constructed to identify independent variables associated with cancer-specific mortality. Patients with missing information for 1 or more variables were excluded from the multivariable model. Statistical analysis was conducted using the SPSS v.22 and Stata v.14 software. The alpha level of statistical significance was set at 0.05, and all P values were 2 sided.

2.4. Systematic review methodology

A systematic review was conducted in accordance with the PRISMA statement [12]. Two independent investigators (I.Z. and D.N.) searched the PubMed database (last search: March 5, 2016) using the following MeSH terms: ("urachus" AND [adenocarcinoma OR malignan* OR cancer]). Eligible articles were published in English after 1990, included $\geq$ 10 patients, and presented information on demographic and clinicopathological parameters.

3. Results

3.1. Patient demographics

A total of 420 patients with microscopically confirmed MUNs, diagnosed between 1988 and 2012, with a median follow up of 104 months (calculated using the reverse Kaplan-Meier method) were identified in the SEER database. Median age was 59 years (interquartile range: 46–71). Most patients were white (77.6%), with 10.5% and 11.9% identifying as African-American and Asian/other race, respectively. Patients were more likely to be male, with a male to female ratio of 1.44 to 1. Table 1 summarizes the demographic and clinicopathological characteristics of patients with MUNs.