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Original article

Malignant ureteroenteric anastomotic stricture following radical cystectomy with urinary diversion: Patterns, risk factors, and outcomes

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Abstract

Objective: The development of a ureteroenteric anastomotic (UEA) stricture has been reported in up to 15% of patients undergoing radical cystectomy (RC) with urinary diversion. Although benign strictures are thought to be the result of ischemia, the incidence, risk factors, and outcomes of patients with malignant UEA strictures have not been well described.

Material and methods: We reviewed 2,523 patients treated with RC for bladder cancer from 1980 to 2012 at Mayo Clinic. Patients diagnosed with a UEA stricture following the surgery were identified, and a subset with malignant UEA was then analyzed. Cox proportional hazard regression models were performed to evaluate factors associated with the diagnosis of malignant UEA. Survival was assessed using the Kaplan-Meier method.

Results: At a median of 10.5 years of follow-up, 232 (9.2%) patients were diagnosed with UEA stricture, of which 38 (16.4%) had malignant strictures (MS). Median time from RC to the diagnosis of a malignant vs. benign UEA stricture was 32.4 months and 7.2 months, respectively ($P = 0.004$). Pathologic non–muscle-invasive disease stage at RC was more common among patients diagnosed with a MS compared with patients who did not develop a MS (71.1% vs. 45.9%; $P = 0.002$). The presence of carcinoma in situ on initial ureteral margin at RC was associated with a significantly increased risk of subsequent diagnosis (hazard ratio = 4.1; $P < 0.001$). Following malignant stricture diagnosis, 2- and 5-year cancer-specific survival was 50% and 30%, respectively, whereas overall survival was 44% and 23%, respectively.

Conclusions: MS are uncommon after RC, and present later than benign strictures. Ureteral margin involvement with carcinoma in situ was associated with a significantly increased risk of MS diagnosis.

Keywords: Malignant stricture; Bladder cancer; Upper tract recurrence; Anastomotic stricture; Urinary diversion

1. Introduction

In 2015, it was estimated that there were 74,000 new cases of bladder cancer and 16,000 deaths from bladder cancer [1]. Radical cystectomy (RC) with urinary diversion (UD) is a standard treatment for muscle-invasive bladder cancer and high-risk non–muscle-invasive disease [2–4].

Despite aggressive surgical management, up to 50% of patients experience disease recurrence following RC [5]. In particular, upper urinary tract recurrence has been reported in approximately 5% of patients at 15 years after RC [6]. The presentation of upper tract recurrence is heterogeneous, including asymptomatic tumors detected on postoperative surveillance, as well as presentation with flank pain and gross hematuria [5,7,8]. Meanwhile, ureteroenteric anastomotic (UEA) strictures have been reported to occur in 1.7% to 14% of patients undergoing UD [9–12]. The vast majority of these strictures are benign and occur likely

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because of ischemia. Nevertheless, upper tract recurrence may also present as a UEA [9–14]. Indeed, although benign UEA strictures have been previously well characterized, the existing literature on malignant UEA strictures (MS) is limited to case reports [11,12,15–19].

Herein, therefore, we analyzed the incidence and clinicopathologic variables associated with malignant UEA stricture development following RC.

2. Material and methods

After Institutional Review Board approval, we examined the Mayo Clinic Cystectomy Registry to identify patients treated with RC and UD for bladder cancer between 1980 and 2012 at our center who were subsequently diagnosed with a UEA stricture. After review of the medical records, we excluded patients with noted extrinsic compression of the ureter. The diagnosis of a malignant UEA stricture was confirmed by pathology or cytology or both in combination with imaging.

Patient clinical characteristics, including age, sex, body mass index, and type of diversion, were reviewed. RC was performed by various surgeons at our institution during the study period. All RC cases were done with an open surgical approach. Management of the distal ureter was per individual surgeon discretion and not standardized; that is, some surgeons at our institution routinely obtain frozen section analysis of the ureteral margins during RC, whereas others do not. Likewise, the management of carcinoma in situ (CIS) returned on frozen section was surgeon specific, but it typically involved resecting additional ureter in an attempt to obtain a negative margin, pending technical feasibility. Thus, the initial ureteral margin reported here refers to the first (and in some cases, only) ureteral margin obtained, whereas the designation final ureteral margin refers to the last section taken in patients with more than 1 section obtained. All pathological specimens were reviewed by 1 urologic pathologist, and tumors were classified using the 2010 American Joint Committee on Cancer TNM staging system [20].

Owing to the retrospective nature of this study, postoperative surveillance after RC (as well as after MS excision) was not standardized. However, at our institution, patients are typically followed every 3 months for the first 2 years after surgery, every 6 months for the next 2 years, and then annually thereafter. Oncologic surveillance includes history, physical examination, urine cytology, and imaging of the chest/abdomen/pelvis. Follow-up was not altered in the case of positive ureteral margins at the time of RC. If recurrence is suspected on the basis of cytology or imaging findings, tissue diagnosis is routinely obtained either retrograde via endoscopic evaluation or antegrade via percutaneous approach by interventional radiology. Ureteroscopic evaluation is performed at the discretion of the surgeon, typically in the event of a positive cytology result without an obvious source identified on imaging or cystoscopic evaluation. In the event of suspected metastatic disease, computed tomography-guided biopsy is performed. To evaluate survival end points, we obtained vital status from death certificates or physician correspondence. For patients followed elsewhere, our institutional Cystectomy Registry prospectively monitors outcomes annually by correspondence with the patient and local treating physician.

2.1. Statistical analyses

Patients were stratified for analyses by type of stricture as benign or malignant. Time to UEA presentation was defined as the time to diagnosis of UEA stricture from the date of RC. Manner of presentation (symptomatology) and management after diagnosis was additionally assessed. Continuous variables were summarized with medians/interquartile ranges (IQR) and compared using *t*-test. Categorical variables were summarized using frequencies/percentages and were compared using Fisher's exact test and chi-square tests. Univariate Cox proportional hazard regression models were used to evaluate the association of clinicopathologic factors with the diagnosis of MS. Survival was estimated using the Kaplan-Meier method. Post-MS cancer-specific survival (CSS) was estimated as time from MS diagnosis to death from urothelial carcinoma (UC). All tests were 2-sided with $P \leq 0.05$ considered statistically significant. Statistical analyses were done with SAS Version 9.4 (Cary, NC).

3. Results

A total of 2,523 patients underwent RC at our center between 1980 and 2012, of whom 232 (9.2%) were subsequently diagnosed with a UEA stricture. Median follow-up after surgery was 10.5 (IQR 7.7, 19.0) years. Malignant UEA stricture was diagnosed in 38/232 (16.4%) of these patients. Clinicopathologic demographics for patients with a UEA stricture are provided in Table 1. Interestingly, compared with patients with a benign UEA, patients with a MS were diagnosed at a significantly later time after RC (median 32.4 mo vs. 7.2 mo; $P = 0.004$) (Fig.). Overall, 30 (78.9%) patients with MS were symptomatic at presentation, and in particular, patients with a MS were significantly more likely to present with gross hematuria compared with patients with a benign UEA stricture (29% vs. 6%; $P < 0.0001$).

We next examined the clinicopathologic features associated with the diagnosis of a MS (Table 2). We noted that patients who developed a MS were significantly more likely to have CIS on the initial ureteral margin at RC than patients without a MS (25% vs. 7.3%; $P = 0.0001$), CIS present in the RC specimen (68.4% vs. 48.7%; $P = 0.001$), and tumor located in the trigone at RC (58.3% vs. 33.2%; $P = 0.01$). Patients with an initial positive ureteral margin had a median of 3.5 margins (IQR 2.5, 4.5) taken in the MS group vs. 2.0 (IQR 2.0, 4.0) in the group without a MS