Review Article

Upper Urinary Tract Recurrence Following Radical Cystectomy for Bladder Cancer: A Meta-Analysis on 13,185 Patients

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Abbreviations and Acronyms

CIS = carcinoma in situ

TCC = transitional cell cancer

UUT = upper urinary tract

For other articles on related topics see pages 2377, 2384, 2391 and 2398.

Editor's Note: This article is the first of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 2446 and 2447.

Purpose: Patients who undergo radical cystectomy for urothelial cancer are at risk for upper urinary tract disease in the remnant transitional tissue. Previous studies have identified several risk factors for upper urinary tract recurrence but the predictive value of each factor remains controversial. Furthermore, the schedule for surveillance of the upper urinary tract with imaging techniques and cytology has not been established. International guidelines do not address these topics and refer only to isolated works with a large case based analysis. We performed this meta-analysis to evaluate the effective incidence of upper urinary tract recurrence after cystectomy for bladder cancer, to analyze the risk factors so we can create subgroups of patients at high risk for recurrence and to investigate the real role of screening in the detection of upper tract lesions at an early stage.

Materials and Methods: A bibliographic search covering the period from January 1970 to July 2010 was conducted using PubMed®, MEDLINE and EMBASE®. This analysis is based on the 27 studies that fulfilled the predefined inclusion criteria. Data were analyzed using a fixed effect logistic regression approach and classic meta-analysis.

Results: A total of 13,185 participants were included in the analysis. Followup was described in 22 studies and ranged from 0.36 to 349.2 months. The overall prevalence of upper tract transitional cell cancer after cystectomy ranged from 0.75% to 6.4%. Recurrence appeared at a range of 2.4 to 164 months, and in an advanced (64.6%) or metastatic state (35.6%) as reflected in poor survival rates. Patients with low grade vs high grade lesions at cystectomy showed as strong a significant difference in incidence as those with carcinoma in situ and superficial cancer vs invasive cancers and as strong as in those without lymph node involvement, with multifocal disease, with a history of multiple urothelial recurrences, with positive ureteral margins, with positive urethral margins, with urethral involvement and a history of upper urinary tract urothelial cancer. Data do not support a statistically significant difference in recurrence among patients with a history of carcinoma in situ, solitary lesion and among various types of urinary diversion adopted. In 24 studies the followup schedule included periodic radiological assessment of the upper urinary tract and in 20 it included urinary cytology. In 14 studies in 63 of 166 patients (38%) upper urinary tract recurrence was diagnosed by followup investigation whereas in the remaining 62% diagnosis was based on symptoms. When urine cytology was used in surveillance the rate of primary detection was 7% and with upper urinary tract imaging it was 29.6%. Of 5,537 patients who underwent routine cytological examination, recurrence was diagnosed in 1.8/1,000 and of those who underwent upper urinary tract imaging recurrence was diagnosed in 7.6/1,000.

Conclusions: The recurrence values could appear low when considering the pan-urothelial field defect theory, but these values reflect, in part, the mortality associated with the initial bladder cancer. Based on anamnesis and pathological examination of cystectomy specimens, a group of patients is at high risk. Extensive regular followup with cytology, urography and loopgraphy yields insufficient benefits. Periodic computerized tomography with urography combines the ability to study the upper urinary tract oncologically and functionally, and the identification of any parenchymal, osseous or lymph node secondary lesion.

Key Words: urinary bladder neoplasms; ureteral neoplasms; carcinoma, transitional cell; recurrence; cystectomy

TRANSITIONAL cell carcinoma is often multifocal, and while it most frequently involves the bladder mucosa, the urothelial lining of the renal pelvis, the ureters and the urethra are also at risk. In fact, urothelial carcinoma is thought to be associated with a pan-urothelial field defect characterized by frequent, multifocal metachronous tumors due to the transformation of epithelial cells at different sites, and the intraluminal seeding and implantation of tumor cells derived from an initial clone.[1] Today radical cystectomy is the standard treatment for patients with invasive bladder cancer and for those with superficial disease at high risk for progression.[2,3] Patients who undergo radical cystectomy for urothelial cancer are at risk for UUT disease in the remnant transitional tissue and clearly not all patients have an equal propensity for a UUT tumor. Previous studies identified several risk factors but the predictive value of each factor remains controversial. In addition, the optimal schedule for surveillance, and the role of cytology and imaging techniques have not yet been established. International guidelines do not cover these issues, and refer only to some work with a large case based analysis.[2,3]

MATERIALS AND METHODS

In this systematic review and meta-analysis we evaluate the effective incidence of UUT recurrence after cystectomy for bladder cancer, analyze the risk factors so we can create subgroups of patients at high risk for recurrence, and study the real role of screening in the detection of upper tract lesions at an early stage.

Search Strategy

Studies were identified by searching electronic databases and scanning reference lists of articles. A bibliographic search covering January 1970 to July 2010 was conducted using PubMed, MEDLINE and EMBASE. Additional hand searches were performed of the reference lists of included studies, reviews, meta-analyses and guidelines on UUT recurrence after cystectomy. Several search terms were used for each, including bladder cancer, upper urinary tract cancer, cystectomy, recurrence, population based, incidence, treatment, urinary cytology, urography, tomography and followup. The searches were restricted to publications in English.

Study Selection

Studies were excluded from analysis if they were case reports, meeting abstracts and conference proceedings. Identified studies were reviewed and selected if they reported data related to UUT recurrence after radical cystectomy. The inclusion or exclusion of studies was performed hierarchically based first on the title of the report, then on the abstract and finally on the contents of the full text. A study was accepted for inclusion on the basis of the agreement of 2 investigators (SP and CR). Any disagreement on study inclusion was resolved by consulting a third investigator (LC). Database searches yielded 143 references. Exclusion of irrelevant references left 29 references describing studies. We excluded 2 further references because they were not in English. Thus, this analysis is based on the 27 studies that fulfilled the predefined inclusion criteria.

Data Extraction, Quality of Comparative Study and Level of Evidence

One author (SP) extracted the data and a second author (CR) checked the extracted data to ensure data quality. Disagreements were resolved by discussion between the 2 review authors, and if no agreement could be reached it was planned that a third author (LC) would decide. The quality of studies was scored using the methods of the U.S. Preventive Services Task Force.[4,5] PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were applied in the preparation of this report.[6] All the studies included in the meta-analysis were classified as good,[7–32] except that of Akkad et al,[23] which was fair due to the moderate sample size.

Statistical Analysis

Data were analyzed in 2 ways. If the survey reported incomplete data on exposure (no events reported for a given level), a fixed effect logistic regression approach was applied to all reported outcomes. To correct for overdispersion, the covariance matrix was multiplied by the estimate of the dispersion parameter using Williams or deviance criterion where appropriate.[33] The effects of factors of interest were evaluated by odds ratio estimate and 95% confidence limits.

A second approach of meta-analysis was applied to surveys reporting complete data about exposures (the outcomes rate for all factors of interest by study). For this analysis the random or fixed effect model analysis was used according to the heterogeneity among studies (random effect model was used when I^2 was greater than 50%).[34]