Review Article

Gender Specific Differences in Disease-Free, Cancer Specific and Overall Survival after Radical Cystectomy for Bladder Cancer: A Systematic Review and Meta-Analysis

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Abbreviations and Acronyms

CSS = cancer specific survival
DFS = disease-free survival
OS = overall survival
UCB = urothelial bladder cancer

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Supplementary references 51 to 93 are available at http://jurology.com/.

Purpose: We summarize the evidence on gender specific differences in disease-free, cancer specific and overall survival after radical cystectomy for bladder cancer.

Materials and Methods: We performed a systematic literature search of MEDLINE®, Embase® and the Cochrane Library in July 2017. Studies evaluating gender specific differences in disease-free, cancer specific or overall survival after radical cystectomy for bladder cancer were included in study. Analyses included random effect meta-analysis, subgroup analyses, meta-influence and cumulative meta-analyses. Funnel plots and the Egger test were used to assess publication bias.

Results: Of the 3,868 studies identified during the literature search 59 published between 1998 and 2017 were included in analysis. Of the studies 30 in a total of 38,321 patients evaluated disease-free survival, 44 in a total of 69,666 evaluated cancer specific survival and 26 in a total of 30,039 evaluated overall survival. Random effect meta-analyses revealed decreased disease-free, cancer specific survival and overall survival in female patients than in their male counterparts. Pooled estimates showed a HR of 1.16 (95% CI 1.06−1.27, p = 0.0018) for disease-free survival, 1.23 (95% CI 1.15−1.31, p <0.001) for cancer specific survival and 1.08 (95% CI 1.03−1.12, p = 0.0004) for overall survival. Subgroup analyses confirmed impaired disease-free, cancer specific and overall survival in female patients in all strata. Publication bias was evident only for studies of cancer specific survival (Egger test p = 0.0029). After adjusting for publication bias by the trim and fill method the corrected pooled estimated HR of cancer specific survival was 1.13 (95% CI 1.05−1.21, p = 0.0012).

Conclusions: Female patients who underwent radical cystectomy for bladder cancer demonstrated worse disease-free, cancer specific and overall survival than their male counterparts. The multifactorial etiology might include epidemiological differences, gender specific health care discrepancies and hormonal influences.

Key Words: urinary bladder neoplasms, cystectomy, mortality, female, male

Bladder cancer is one of the most common malignancies of the urinary tract with annual incidence rates of 34.9/100,000 among men and 8.4/100,000 among women between 2010 and 2014 in the United States.[1] In Europe comparable incidence rates have been published of 26.9/100,000 among men and 5.3/100,000 among women.[2]

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Surgical treatment options for bladder cancer include local resection as well as more extensive procedures such as radical cystectomy. Approximately 21% of patients with bladder cancer undergo radical cystectomy, which is recommended for muscle invasive, high risk or bacillus Calmette-Guérin refractory bladder cancer.[3]

In the past many groups aimed to identify risk and protective factors to improve the survival of patients with bladder cancer and investigated outcomes after radical cystectomy. While the incidence of bladder cancer is higher in men, large-scale studies have demonstrated impaired outcomes in female patients.[4] Moreover, evidence suggests that there are gender specific differences not only for survival but also for cystectomy complication rates or recurrence after local resection.[5,6] Yet the literature on gender specific differences is ambiguous as some studies have shown contradicting results with reduced survival in male patients.[7,8] Moreover, most of the literature on gender specific differences in other oncologic entities, such as lung or colorectal cancer, has described superior outcomes in female patients.[9,10]

To date only 1 study has been done to review the evidence on gender specific differences in CSS after cystectomy.[11] The investigators disregarded crucial outcomes such as DFS and OS which potentially provide a more comprehensive inference on gender specific differences after radical cystectomy. Moreover, recent advances in adjuvant chemotherapy regimens might well influence gender specific outcomes.

We aimed to systematically investigate gender specific differences in DFS, CSS and OS after radical cystectomy for bladder cancer, summarize the existing evidence in meta-analyses and assess whether any differences would remain after stratifying by tumor characteristics or treatment regimens.

MATERIAL AND METHODS

Search Strategy

In July 2017 we performed a systematic literature search using MEDLINE, Embase and the Cochrane Library. The search algorithm broadly included the search term clusters gender, cystectomy, bladder cancer and survival. The supplementary Appendix (http://jurology.com/) shows the full search algorithm. Reference lists of included articles as well as review articles were searched to identify additional records. No restrictions were made with respect to publication date, language, study region or publication type.

This study was prospectively registered at PROSPERO (https://www.crd.york.ac.uk/prospero/, ID 42017067125).

Study Inclusion and Exclusion Criteria

The predefined outcomes were gender specific differences in DFS, CSS and OS after radical cystectomy for bladder cancer.

Only studies were included which fulfilled certain criteria, including a peer reviewed publication source, evaluation of at least 1 outcome (DFS, CSS or OS) after radical cystectomy of bladder cancer, multivariable Cox regression analysis, inclusion of gender as a covariate in multivariable statistical models and HR reported with the associated 95% CI. If only HR and p values were given, CIs were back calculated according to the method proposed by Altman and Bland.[12] If more than 1 publication included the same patient cohort, the more comprehensive study was included in analysis.

Exclusion criteria were an evaluation of gender only in univariate regression models or missing effect sizes for gender in multivariable models as well as studies focusing on schistosomiasis associated bladder cancer. Editorials, case reports, review articles and meta-analyses were excluded if they failed to report primary patient level data which was otherwise unpublicized.

Data Extraction

A standardized data extraction process was used for every included record. Extracted variables included author(s), year, country, size, percent of female patients, patient age, cancer stage and grade, histopathological cancer subtype, followup, radiotherapy/chemotherapy, variables adjusted for in multivariable Cox regressions and HR measures with the associated 95% CI for DFS, CSS and OS.

Study extraction was independently performed by 2 authors (JU and AU). Inconsistencies were resolved by consensus.

Study Quality Assessment

We used the Downs and Black instrument[13] to rate study quality separately for each outcome as recommended by Deeks et al.[14] For study quality 5 domains were assessed, including reporting, external validity, bias, confounding and statistical power. Since retrospective calculations of statistical power were impracticable, study sample size served as a proxy. Sample size was rated from 0 to 5 points, equivalent to 100 or fewer, 101 to 200, 201 to 400, 401 to 800, 801 to 1,600 and greater than 1,600 patients, respectively.

The total score of the Downs and Black instrument[13] ranged between 0 and 32 points with 32 points indicating best study quality. Study quality assessment was independently performed by 2 of us (JU and AU). Inconsistencies were resolved by consensus.

A score of 0 to 8 points was rated as poor study quality. Moderate study quality included studies with a score of 9 to 16 points. A score of 17 to 24 points was defined as good quality and scores of 25 points and above indicated excellent study quality.

Statistical Analyses

Comparison of gender specific differences of DFS, CSS and OS among patients undergoing radical cystectomy was performed using a random effects meta-analysis with the DerSimonian and Laird method to account for clinical