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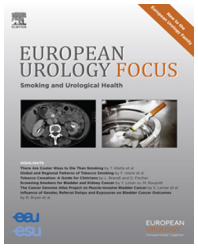

Review – Bladder Cancer

Referring to the article published on pp. x–y of this issue

Reporting Bias Leading to Discordant Venous Thromboembolism Rates in the United States Versus Non-US Countries Following Radical Cystectomy: A Systematic Review and Meta-analysis

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Abstract

Context: Postcystectomy bladder cancer (BCa) patients are at high risk for developing venous thromboembolism (VTE). The literature varies widely in the reporting of VTE in this population.

Objective: To determine the VTE rate in subjects undergoing radical cystectomy (RC) and highlight specific factors affecting this rate.

Evidence acquisition: This meta-analysis was registered with the International Prospective Register of Systematic Reviews (PROSPERO) database, registration number: CRD42015016776. We queried MEDLINE, the Cochrane Library, Embase, Scopus, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Web of Science. Search terms captured BCa, RC, and VTE. Per the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines, abstracts were reviewed for inclusion/exclusion criteria by two reviewers, and disagreements were resolved by a third reviewer. A search of the gray literature and references of pertinent articles was also performed. The date of our last search was December 15, 2014. For unreported data, authors were contacted. Data were abstracted in duplicate and pooled using a random effects (RE) model. Subgroup analyses and meta-regression were performed to determine risk factors for VTE.

Evidence synthesis: We identified 2927 publications, of which 223 met inclusion criteria for this review. A total of 1 115 634 surgeries were performed on patient population (80% men) with a total of 51 908 VTEs. The VTE rate estimated by the RE model was 3.7%. Due to significant heterogeneity, subgroup and meta-regression analyses were undertaken. These revealed a higher rate of VTE in US studies at 4.49% compared with "westernized" non-US studies at 3.43% and "nonwesternized" non-US based studies at 2.50%. Other important modifiers included minimally invasive surgery at 5.54% versus open surgery at 3.55%, and age. The case-fatality rate of pulmonary emboli was 44%.

Conclusions: VTE is common in patients undergoing RC. Reporting of VTE is heterogeneous and the rate varies according to study-level factors, including surgery type and country of origin. Limitations of this study include the preponderance of observational studies in the final analysis and lack of complete reporting of all variables of interest within each study.

Patient summary: In this review, we determined the venous thromboembolism (VTE) rate in postsurgical bladder cancer patients. VTE events did vary significantly among certain subgroups.

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1. Introduction

Cancer is a well-known risk factor for thrombotic events. Venous thromboembolism (VTE) includes pulmonary embolism and deep vein thrombosis, and is the most common form of malignancy-associated thrombosis. Arterial thrombosis and systemic thrombotic syndromes (eg, disseminated intravascular coagulation) can also occur. Previously published data report 2% of bladder cancer (BCa) patients will experience a VTE event within 2 yr of diagnosis, a probability that is five times higher than the overall population [1–3]. When VTE occurs in a patient with BCa, it is associated with a threefold increased risk of death [1,2]. The rate of VTE changes significantly depending on patient-specific characteristics such as age, disease stage, and modality of treatment. However, once a VTE event occurs, the prognostic weight it carries is independent of these patient-specific factors [4].

BCa is considered among the high-risk cancers for development of VTE [5]. Interestingly, radical cystectomy (RC) has been shown to confer a 2.1-fold increase in the risk of VTE compared with muscle-invasive bladder cancer patients who did not undergo the procedure [5]. This is unique when compared with other surgically treated malignancies such as breast, lung, and colorectal cancers, as their risk of VTE decreases significantly after surgical excision of the tumor [1,6–8]. The increased risk of VTE seen in BCa likely has a multifactorial etiology and risk factors include complex pelvic surgery, extended lymphadenectomy, prolonged time in the lithotomy position, and biochemical alterations in the coagulation cascade known to occur in BCa [4]. However, to date, there has never been a systematic review of the published literature to determine the overall rate of VTE in surgical BCa patients.

Our objective in this study was to systematically amass all relevant publications to estimate the overall rate of VTE in adult patients undergoing RC for BCa and the study-level factors affecting this rate.

2. Evidence acquisition

2.1. Protocol registration and search strategy

Our protocol is registered in the International Prospective Register of Systematic Reviews (PROSPERO) registry (CRD42015016776). An experienced information specialist searched MEDLINE, the Cochrane Library, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Web of Science through August 2014 with no limit on the earliest date. We used MeSH terms, Emtree terms, CINAHL headings, and keywords as search terms, and we combined specific terms for urinary bladder neoplasms, venous thrombosis, and bladder surgery, according to our inclusion criteria. We limited electronic searches to *humans* and *English*. Exact search strings can be found in Supplementary Table 1. All citations were imported into an electronic database and, to minimize retrieval bias, we also used semiautomatic manual searches of reference lists of pertinent articles, using the Scopus citation database. To identify relevant "gray literature," ClinicalTrials.gov, the National Cancer Institute's clinical trial database, PROSPERO, and COS Conference Papers Index were also searched [9].

2.2. Eligibility criteria

To be eligible, retrieved articles had to (1) describe a surgical treatment for BCa and (2) report a VTE rate (either explicitly or calculable). No article was excluded on the basis of method of analysis or perceived quality/bias, since such assessments are subjective and lack reproducibility [9–12]. Studies that dealt primarily with animals, pediatric patients, RC performed for reasons other than BCa, or subgroups with known coagulopathies were excluded. Duplicate publications and case reports were also excluded.

2.3. Manuscript screening and data abstraction

Two reviewers independently assessed study abstracts for eligibility, with disagreements adjudicated by a third reviewer. The full text of eligible abstracts was obtained and reviewed whenever possible. Variables of interest were abstracted into an electronic data capture form. In cases where variables were missing or unreported in the study manuscript, we attempted to contact study authors for this information. Authors were e-mailed twice, each followed by a 2-week response period, after which further response was deemed unlikely and missing data for the study considered unrecoverable. The primary end point of interest was the overall VTE rate, which included both pulmonary emboli (PE) and deep venous thrombosis (DVT) events, expressed as a summary proportion of VTE events divided by the total number of subjects at risk. Secondary end points were the DVT rate, PE rate, mortality rate from PE, and the PE case-fatality rate (ie, patients who died from PE). Studies missing both the primary end point (VTE) and key secondary end points (DVT or PE) were excluded from further analysis.

2.4. Statistical methods

For the primary and secondary end points, fixed effects and random effects (RE) models were constructed for pooling proportions. For variance stabilization, proportions were pooled after arcsine transformation [13], and restricted maximum likelihood estimation was used to calculate the between-study variance (τ^2) in the RE models [14]. Pooled arcsine-transformed proportions and their 95% confidence intervals (CIs) were then back-transformed to the normal scale for presentation. The presence of residual heterogeneity was assessed using the I^2 statistic and tested using the Cochran Q test [15]. Since we hypothesized that the VTE rate would vary from study to study, the RE model was used in all subgroup analyses and meta-regressions.

To determine if any individual study was an outlier or had significant influence on the pooled results, we examined externally standardized residuals, DFFITS values, DFBETAS values, Cook's distances, and covariance ratios (Supplementary Fig. 1) [16]. Additionally, we performed a jackknife sensitivity analysis (ie, leave-one-out analysis) of all our

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