Title

High rates of venous thromboembolic events in patients undergoing systemic therapy for urothelial carcinoma: A systematic review and meta-analysis

Journal

Urologic Oncology Seminars and Original Investigations, 34(9)

ISSN

1078-1439

Authors

Gopalakrishna, Ajay
Longo, Thomas A
Fantony, Joseph J
et al.

Publication Date

2016-09-01

DOI

10.1016/j.urolonc.2016.05.009

Peer reviewed

HHS Public Access

Author manuscript

Urol Oncol. Author manuscript; available in PMC 2017 September 01.

Published in final edited form as:

Urol Oncol. 2016 September ; 34(9): 407–414. doi:10.1016/j.urolonc.2016.05.009.

High rates of venous thromboembolic events in patients undergoing systemic therapy for urothelial carcinoma: A systematic review and meta-analysis

Ajay Gopalakrishna[1], **Thomas A. Longo**[1], **Joseph J. Fantony**[1], **Uma Doshi**[1], **Michael R. Harrison**[2], **Megan Van Noord**[3], and **Brant A. Inman**[1]

[1]Division of Urology, Duke University Medical Center, 2301 Erwin Road Durham, NC, 27710

[2]Division of Medical Oncology, Duke University Medical Center, 2301 Erwin Road Durham, NC, 27710

[3]Research and Education Services, Duke University Medical Center, 2301 Erwin Road Durham, NC, 27710

Abstract

Background—Patients undergoing systemic therapy for urothelial carcinoma (UC) are at increased risk for venous thromboembolic (VTE) events. The objective of the current study was to determine the rate of VTE events in patients undergoing systemic therapy for UC and assess factors impacting this rate.

Methods—This study was registered with the PROSPERO database (CRD42015025774). We searched Pubmed, MEDLINE, EMBASE, The Cochrane Library, CINAHL, and Web of Science libraries through August 2014. As per PRISMA guidelines, two reviewers independently reviewed titles and abstracts. Disagreements were arbitrated by a third reviewer. After full text review, data was abstracted and pooled using a random effects (RE) model. Authors were contacted for clarification of data. To determine VTE risk factors, subgroup analyses and meta-regression were conducted.

Results—We identified 3635 publications in the initial search, of which 410 met inclusion criteria for full-text review. Of these, we were able to obtain data on the outcome of interest for 62 publications. A total of 5082 patients, of which 77% were male, underwent systemic therapy for UC, with 373 VTE events. The proportion of patients who had had prior surgery, chemotherapy, or radiation was 55%, 25%, and 9%, respectively. Fixed effects and random effects models were used to estimate the VTE rate, yielding event rates of 6.7% and 5.4%, respectively.

Corresponding author: Brant A. Inman, MD MS, Box 103868, 3007 Snyderman Bldg., 905 La Salle Street, Durham, NC 27710, Asst: (919) 684-1322, Fax: (919) 668-7093, brant.inman@duke.edu.

Conclusions—VTE occurs frequently in patients undergoing systemic therapy for UC. The VTE rate was affected by the country of origin, history of radiation, as well as by the systemic treatment class. The study was limited by the incomplete reporting of all variables of interest.

Keywords

Bladder cancer; urothelial carcinoma; deep venous thrombosis; pulmonary embolism; venous thromboembolism; systemic therapy; chemotherapy

1. INTRODUCTION

It is well known that malignancy is an important risk factor for thromboembolic events.[1] Cancerous cells are thought to engage the coagulation cascade and promote a hypercoagulable state.[2] Systemic therapy also dramatically increases the risk for thrombotic events.[3] Mechanisms for chemotherapy-induced thrombosis are thought to include endothelial injury, platelet activation, and decrease in natural coagulation inhibitors.[3]

High rates of venous thromboembolic (VTE) events have been documented in patients undergoing systemic treatment for a variety of cancers, including urothelial carcinoma (UC).[4] As perioperative chemotherapy is now the recommended standard of care for treatment of advanced bladder cancer,[5] evaluating the risk of VTE in these patients has become particularly important, as VTE is a significant predictor of mortality in patients with UC.[6] To the best of our knowledge, we are the first to conduct a systematic review and meta-analysis of the published literature to determine the overall rate of venous thromboembolism in patients undergoing systemic therapy for UC. Our objective in this study was to systematically review all relevant publications to determine the overall VTE rate in patients undergoing systemic therapy for UC and assess factors affecting this rate.

2. METHODS

2. 1. Protocol registration and search strategy

The protocol is registered in the PROSPERO registry (CRD42015025774). With the help of a medical information specialist, we searched MEDLINE, EMBASE, the Cochrane Library, Web of Science, and CINAHL libraries through August 2014. Search terms captured urothelial carcinoma, chemotherapy, and venous thromboembolism. The search strings are included in Appendix A.

2.2. Eligibility criteria

The inclusion criteria were: (1) use of systemic treatment in the entire cohort or a subgroup of patients with UC, and (2) reporting of a VTE rate. The exclusion criteria were: (1) animal studies, (2) pediatric (age < 18) studies, (3) population with known heritable coagulopathy, (4) duplicate publications, and (5) case reports. No studies were excluded based on perceived quality or bias.

2.3. Manuscript screening and data abstraction

The primary outcome of interest was the overall venous thromboembolism (VTE) rate. Secondary outcomes included: (1) deep venous thrombosis (DVT) rate, (2) pulmonary emboli (PE) rate, and (3) PE case-fatality rate. Studies for which we were unable to obtain data regarding the primary outcome of interest were excluded in the final analysis.

All abstracts were evaluated independently by two reviewers and disagreements were resolved by a third arbitrator. The full text manuscript review of eligible studies was then completed. Data regarding variables of interest were abstracted and stored electronically. In cases where the primary outcome of interest was not available from the study manuscripts, we attempted to contact the study authors for whom contact information (email address) was available. We emailed the authors two times, with a one-week response period given for each email.

2.4. Statistical methods

We used fixed effects and random effects models to pool the primary and secondary endpoints. The proportions and 95% confidence intervals (95%CI) were pooled after arcsine transformation for variance stabilization and then back-transformed to a normal scale for presentation.[7] The between-study variance (τ^2) in the random effects models was determined using restricted maximum likelihood estimation.[8] The I^2 statistic and Cochran's Q test were used to evaluate and test for residual heterogeneity.[9] The random effects model was used for subgroup analyses as we assumed between-study variance in the VTE rate to be non-constant. Externally standardized residuals, covariance ratios, DFBETAS values, Cook's distances, and DFFITS values were used to assess outliers and influential studies.[10] All models were reassessed using jackknife leave-one-out analyses. Subgroup analyses were conducted to investigate potential sources of heterogeneity. Publication bias was evaluated using the Egger regression test, Begg-Mazumdar rank correlation, and Duval-Tweedie trim-and-fill funnel plots.[11] All analyses were performed using R 3.1.2 with the meta and metafor packages.[12, 13]

3. RESULTS

3.1. Search results

The initial search yielded 3635 publications. After title and abstract review, full text review was performed on 410 articles. Contact information (email address) was obtained for 167 authors, of which 15 responded with data. We were able to abstract data on the outcomes of interest for 62 publications that included a total of 5082 patients. The abstract selection process is shown in Figure 1. A list of the studies included in the meta-analysis is listed in Supplemental Table 1 and a summary of the characteristics of these studies is listed in Table 1. Additionally, specific treatment agents used across studies are listed in Supplemental Table 2.

3.2. Pooled event rate and heterogeneity

The distribution of VTE rates across studies as well as the pooled event rates are shown in Figure 2. Fixed effects and random effects estimates of the primary and secondary endpoints

are shown in Table 2. The level of heterogeneity in the primary endpoint was moderately high (I^2 = 70%).

3.3. Subgroup analyses

The high level of heterogeneity was explored further through study-level subgroup analyses (Table 3) and systemic therapy class subgroups (Table 4). Study level factors that affected VTE rate were country of origin (P = 0.005) and proportion of patients with prior radiation (P = 0.042). A more detailed analysis of country of origin is included in Supplemental Table 2. Westernized countries tended to report higher VTE rates than non-westernized countries, with a pooled VTE rate of 7.5% reported in studies originating in the United States (USA), 3.9% in non-USA Western countries, and 2.7% in non-USA non-Western countries.

Meta-regression analyses indicated that studies that had a higher proportion of patients with prior radiation had dramatically increased VTE rates (Table 3). In contrast, proportion of patients with prior chemotherapy or prior surgery did not affect VTE rates.

Classes associated with particularly high VTE rates included anti-angiogenics at 11.4% [2.3–26.1%] and anti-ErbB agents at 9.7% [2.2–21.6%]. Alkylating agents were associated with the lowest VTE rates at 1.3% [0.1–3.7%]. VTE rates pooled by specific systemic agents are included in Supplemental Table 3. Particular agents were associated with dramatically higher VTE rates. Specifically, bevacizumab was associated with the highest VTE rate at 19.7% [95%CI 10.9, 30.3%], followed by trastuzumab at 14.3% [95%CI 0.0–47.3%], and cetuximab at 10.7% [0.0–59.3%]. The findings observed among these individual agents presumably account for the high VTE rates seen in their respective classes. VTE rates for the most common combination regimens, MVAC (Methotrexate, Vinblastine, Doxorubicin, and Cisplatin) and GC (Gemcitabine and Cisplatin) were 5.1% (95%CI: 2.6–8.4%, I^2 60%) and 6.8% (95%CI: 3.4–11.2%, I^2 68%), respectively.

3.4. Influence analysis

One study (Hussain M *et al.*[14]) that was a potential outlier in the random effects model was identified. However, when the jackknife leave-one-out analysis was performed, we found that the stepwise removal of the study had minimal impact on the overall VTE rate, suggesting that our random effects model was insensitive to the potential outlier (Supplemental Figure 1).

3.5. Publication bias

The Begg-Mazumdar rank correlation test yielded a Kendall's tau of 0.171 (P = 0.051). The Egger regression test for funnel plot asymmetry was insignificant (P = 0.649). The Duval-Tweedie trim-and-fill funnel plot (Supplemental Figure 2) shows that small studies with high event rates are less likely to be reported.

4. DISCUSSION

Perioperative systemic therapy is now part of the recommended standard-of-care guidelines. [5] In our meta-analysis, we found that 5.4% of patients undergoing systemic therapy had a

VTE event. In a previous study, we had found that the incidence of VTE in patients undergoing radical cystectomy (RC) for bladder cancer was 3.7%,[15] suggesting that systemic therapy increases the risk of VTE beyond the already increased risk imposed by surgery and malignancy.

Interestingly, in the current study, VTE rates were not affected by the setting (neoadjuvant vs. advanced), the number of agents (single vs. multiple), or the year of publication. There is evidence to suggest that more advanced stage of cancer is associated with higher risk of VTE.[16] One possible reason for the similar rates in treatment settings seen in our study may be a balance between risk of VTE imposed by cancer stage and that imposed by surgery. When systemic therapy is used in the neoadjuvant setting, the cancer may be of lower stage and impose lower risk of VTE. However, this is potentially offset by the increased risk of thrombosis imposed by surgery. In advanced inoperable cases, there is increased risk of VTE from the cancer, but since surgery is usually not performed in these cases, the VTE rate may consequently balance out with that seen in the neoadjuvant setting.

The subgroup analyses with respect to year of publication indicated that there was no significant change in VTE associated with systemic therapy over time. In 2004, the American College of Chest Physicians made recommendations for VTE prophylaxis in hospitalized patients though these were not widely implemented.[17] The American Society of Clinical Oncology published guidelines on VTE prophylaxis in cancer patients only recently, in 2013. In contrast, the Italian Association of Medical Oncology published guidelines in 2006, the French National Cancer Institute in 2008, and the US National Comprehensive Cancer Network in 2010.[17] A systematic review by Farge-Bancel *et al.* suggests that low levels of guideline implementation may be contributing to heterogeneity of VTE prophylaxis strategies in practice.[17] Poor adherence to prophylaxis guidelines may explain the lack of improvement in VTE rates over time seen in our study.

Similarly to a previous publication,[15] we found that the reported VTE rate differed significantly between USA and non-USA studies (8.7% vs. 5.0%, respectively). When non-USA countries were grouped based on “westernization,” we found that studies originating in non-USA western countries reported a slightly higher VTE rate than non- USA non-western countries (3.9% vs. 2.7%). As discussed before,[15] these differences may potentially be due to differences in patient characteristics, such as obesity and genetic and racial differences, or differences in practice patterns regarding thromboprophylaxis during systemic therapy. Several studies have looked at the adoption of perioperative chemotherapy in the US, and there was increasing usage from nearly 30% to 40% from 2006–2010.[18] This increase was predominantly seen in the use of neoadjuvant chemotherapy (from 10% in 2006 to 21% in 2010). Less data exists on European practice patterns of perioperative chemotherapy. However, it is also possible that there may be a reporting or surveillance bias, in which studies conducted in countries outside the United States do not record or report VTE events, or at least follow patients less closely for VTE.[19]

We found a dramatic class effect, with anti-angiogenic and anti-ErbB agents posing a notably elevated risk of VTE compared to the other classes. The thrombogenic potential of bevacizumab has been well documented.[20] The pooled VTE rate in the 4 studies that used

bevacizumab in the current study was 20%, which is significantly higher than bevacizumab-associated VTE rates reported in multiple other cancers.[20, 21] Simonietti *et al.* conducted a meta-analysis on bevacizumab-associated VTE in malignant glioma and reported a VTE rate of 7.5% in patients receiving bevacizumab and chemoradiation versus 4.3% in patients receiving bevacizumab alone.[21] A meta analysis by Nalluri *et al.* reported a bevacizumab-associated VTE rate of 11.9% among patients with multiple solid tumor types, including colorectal cancer, non-small cell lung cancer, breast cancer, and renal cell carcinoma.[20] Anti-angiogenics have been shown to inhibit resolution of venous thrombi, which may further increase the risk for thrombosis already imposed by malignancy and surgery and can present a challenge in the management of thrombotic complications in patients being treated with these agents.[22] While the mechanisms behind the thrombogenic potential of angiogenesis inhibitiors remain ill-defined, one of the main hypotheses is that the drugs cause disruption of the tumor-associated endothelial lining, leading to a prothrombotic surface that can mediate activation of the coagulation cascade.[23] Though our publication only examined venous thromboembolism, bevacizumab has also been associated with a high rate of arterial thromboembolism.[23]

In our study, the pooled VTE event rate in patients taking anti-ErbB agents was 9.7%, with the highest rates attributable to trastuzumab and cetuximab. Anti-ErbB agents, and specifically anti-EGFR agents, such as cetuximab have also been associated with a high rate of VTEs in other cancers.[24] A recent meta-analysis by Petrelli *et al.* found that the relative risk of venous and arterial thrombotic events associated with anti-EGFR agents was 1.32 and 1.34, respectively.[24] Monoclonal antibodies were found to be associated with a higher risk (RR 1.34) of thrombosis than oral tyrosine kinase inhibitors (RR 1.16).[24]

Studies with a larger proportion of patients with prior history of radiation treatment tended to have higher VTE rates, indicating that prior radiation treatment may potentially predispose to increased risk of VTE. There is very little in the literature regarding risk for VTE in relation to radiation therapy, particularly in patients with a remote history. Our finding warrants further investigation into whether remote history of radiation treatment increases risk for thrombosis with subsequent cancer therapy. Notably, proportion of patients with prior chemotherapy or surgery did not affect VTE rate.

The National Comprehensive Cancer Network (NCCN) guidelines currently do not recommend routine VTE prophylaxis in the medical oncology patient undergoing systemic chemotherapy in the ambulatory setting.[25] The high rates of VTE events associated with anti-angiogenic and anti-ErbB agents seen in our study suggest that prophylaxis should be considered in patients being treated with these agents. However, thromboprophylaxis would not be without risks. A recent meta-analysis by Phan *et al.* found that primary VTE prophylaxis in patients with solid tumors decreased VTE events by 47% but increased bleeding events by 60%.[26] Further studies may be warranted to investigate the benefits and risks of thromboprophylaxis in the use of specific high-risk classes or individual agents.

4.1. Limitations

The current study had several limitations. First, all studies for which we were able to at least obtain the primary outcome of interest were included. However, many studies did not

necessarily have complete data for all the other variables of interest we examined for secondary outcomes as well as subgroup analyses, limiting the power of these analyses. Second, while most studies reported the use of a single chemotherapy regimen, there were a few studies that reported multiple regimens but did not discern VTE rates among regimens. For the purposes of the meta-analysis, the data in these studies was pooled, resulting in a potential distortion of the VTE rate associated with individual chemotherapy agents. Third, the absence of information in studies regarding the specific timing of VTEs was a limitation. Lastly, searches were restricted to "English-language only," though this has been shown to introduce minimal bias.[27]

5. CONCLUSIONS

The incidence of venous thromboembolism in patients undergoing systemic therapy for urothelial carcinoma is 5.4%, with particular treatment classes being associated with a dramatically higher rate. There is a significant difference in reported VTE rates between US and non-US countries, which may underlie a potential reporting or surveillance bias in non-US countries. Given the significant prognostic implications of VTE in patients with urothelial carcinoma, its reporting should become standardized across studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Research reported in this publication was supported by the National Center For Advancing Translational Sciences of the National Institutes of Health under Award Number TL1TR001116. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

REFERENCES

1. Posch F, Riedl J, Reitter EM, Kaider A, Zielinski C, Pabinger I, et al. Hypercoagulabilty, venous thromboembolism, and death in patients with cancer. A Multi-State Model. Thrombosis and haemostasis. 2016; 115
2. Falanga A, Schieppati F, Russo D. Cancer Tissue Procoagulant Mechanisms and the Hypercoagulable State of Patients with Cancer. Seminars in thrombosis and hemostasis. 2015; 41:756–764. [PubMed: 26408922]
3. Haddad TC, Greeno EW. Chemotherapy-induced thrombosis. Thrombosis research. 2006; 118:555–568. [PubMed: 16388837]
4. Khorana AA, Dalal M, Lin J, Connolly GC. Incidence and predictors of venous thromboembolism (VTE) among ambulatory high-risk cancer patients undergoing chemotherapy in the United States. Cancer. 2013; 119:648–655. [PubMed: 22893596]
5. Clark PE, Agarwal N, Biagioli MC, Eisenberger MA, Greenberg RE, Herr HW, et al. Bladder cancer. Journal of the National Comprehensive Cancer Network : JNCCN. 2013; 11:446–475. [PubMed: 23584347]
6. Sandhu R, Pan CX, Wun T, Harvey D, Zhou H, White RH, et al. The incidence of venous thromboembolism and its effect on survival among patients with primary bladder cancer. Cancer. 2010; 116:2596–2603. [PubMed: 20336780]
7. Trikalinos, TA.; Trow, P.; Schmid, CH. Simulation-Based Comparison of Methods for Meta-Analysis of Proportions and Rates. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013.

8. Veroniki AA, Jackson D, Viechtbauer W, Bender R, Bowden J, Knapp G, et al. Methods to estimate the between-study variance and its uncertainty in meta-analysis. Research synthesis methods. 2015
9. Huedo-Medina TB, Sanchez-Meca J, Marin-Martinez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? Psychological methods. 2006; 11:193–206. [PubMed: 16784338]
10. Viechtbauer W, Cheung MW. Outlier and influence diagnostics for meta-analysis. Research synthesis methods. 2010; 1:112–125. [PubMed: 26061377]
11. Soeken KL, Sripusanapan A. Assessing publication bias in meta-analysis. Nursing research. 2003; 52:57–60. [PubMed: 12552177]
12. Viechtbauer W. Conducting meta-analyses in R with the metafor package. Journal of Statistical Software. 2010; 36:1–48.
13. Schwarzer G. meta: General Package for Meta-Analysis. 2015
14. Hussain M, Daignault S, Agarwal N, Grivas PD, Siefker-Radtke AO, Puzanov I, et al. A randomized phase 2 trial of gemcitabine/cisplatin with or without cetuximab in patients with advanced urothelial carcinoma. Cancer. 2014; 120:2684–2693. [PubMed: 24802654]
15. Fantony J, Gopalakrishna A, Van Noord M, Inman BA. 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. European Urology Focus. 2015
16. Wun T, White RH. Epidemiology of cancer-related venous thromboembolism. Best practice & research Clinical haematology. 2009; 22:9–23. [PubMed: 19285269]
17. Farge-Bancel D, Bounameaux H, Brenner B, Buller HR, Kakkar A, Pabinger I, et al. Implementing thrombosis guidelines in cancer patients: a review. Rambam Maimonides medical journal. 2014; 5:e0041. [PubMed: 25386357]
18. Reardon ZD, Patel SG, Zaid HB, Stimson CJ, Resnick MJ, Keegan KA, et al. Trends in the use of perioperative chemotherapy for localized and locally advanced muscle-invasive bladder cancer: a sign of changing tides. European urology. 2015; 67:165–170. [PubMed: 24472710]
19. Haut ER, Pronovost PJ. Surveillance bias in outcomes reporting. Jama. 2011; 305:2462–2463. [PubMed: 21673300]
20. Nalluri SR, Chu D, Keresztes R, Zhu X, Wu S. Risk of venous thromboembolism with the angiogenesis inhibitor bevacizumab in cancer patients: a meta-analysis. Jama. 2008; 300:2277–2285. [PubMed: 19017914]
21. Simonetti G, Trevisan E, Silvani A, Gaviani P, Botturi A, Lamperti E, et al. Safety of bevacizumab in patients with malignant gliomas: a systematic review. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology. 2014; 35:83–89.
22. Evans CE, Grover SP, Humphries J, Saha P, Patel AP, Patel AS, et al. Antiangiogenic therapy inhibits venous thrombus resolution. Arteriosclerosis, thrombosis, and vascular biology. 2014; 34:565–570.
23. Elice F, Rodeghiero F, Falanga A, Rickles FR. Thrombosis associated with angiogenesis inhibitors. Best practice & research Clinical haematology. 2009; 22:115–128. [PubMed: 19285278]
24. Petrelli F, Cabiddu M, Borgonovo K, Barni S. Risk of venous and arterial thromboembolic events associated with anti-EGFR agents: a meta-analysis of randomized clinical trials. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2012; 23:1672–1679. [PubMed: 22241897]
25. Streiff MB, Bockenstedt PL, Cataland SR, Chesney C, Eby C, Fanikos J, et al. Venous thromboembolic disease. Journal of the National Comprehensive Cancer Network : JNCCN. 2013; 11:1402–1429. [PubMed: 24225973]
26. Phan M, John S, Casanegra AI, Rathbun S, Mansfield A, Stoner JA, et al. Primary venous thromboembolism prophylaxis in patients with solid tumors: a meta-analysis. Journal of thrombosis and thrombolysis. 2014; 38:241–249. [PubMed: 24233387]
27. Morrison A, Polisena J, Husereau D, Moulton K, Clark M, Fiander M, et al. The effect of English-language restriction on systematic review-based meta-analyses: a systematic review of empirical studies. International journal of technology assessment in health care. 2012; 28:138–144. [PubMed: 22559755]

Highlights

- VTE in patients undergoing systemic therapy for urothelial carcinoma is unknown.
- We found that VTE occurs in 5.4% of these patients.
- Systemic agent class, country of origin, and history of radiation affect VTE rate.
- Anti-angiogenics and anti-ErbB classes are associated with highest VTE rates.
- US studies tend to report higher VTE rate than non-US studies.
- History of radiation is associated with higher VTE rates.

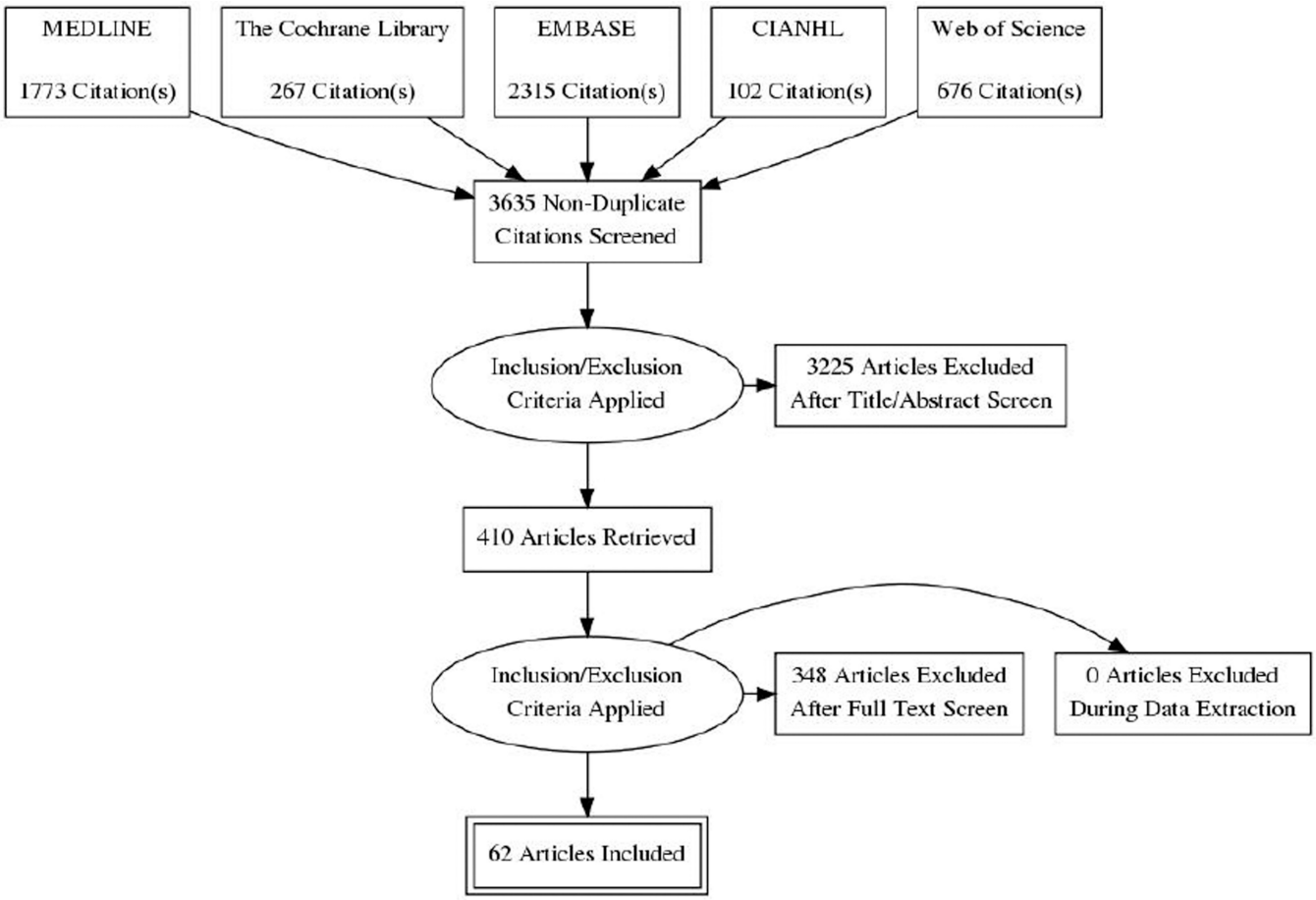

Figure 1.
PRISMA flowchart of the abstract selection process

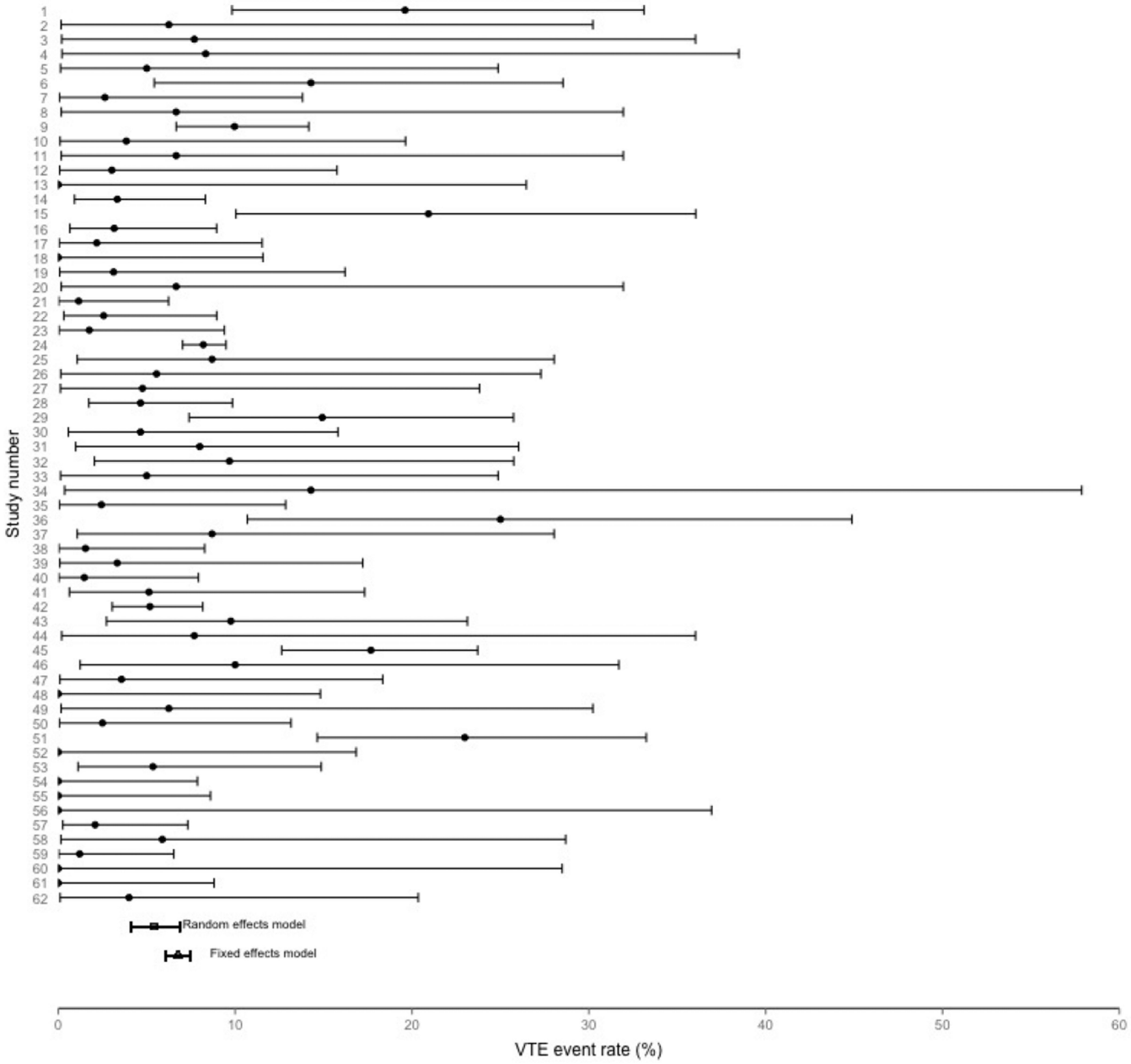

Figure 2.

Forest plot of venous thromboembolic event rates associated with systemic therapy for urothelial carcinoma

Table 1

Pooled cohort characteristics

Sample (62 studies, 5082 patients)	Summary measure
Gender	
Male	77.0%
Female	23.0%
Age, median	65
Site	
Bladder	92.2%
Upper tract	7.3%
Urethra	0.2%
Multifocal	0.3%
ECOG score	
0	50.8%
1	41.0%
2	8.3%
Prior treatment	
Surgery	54.9%
Chemotherapy	25.1%
Radiation	8.6%
Setting	**No. Studies**
Neoadjuvant	13
Locally advanced/metastatic	38
Mixed	7
Study design	**No. Studies**
Retrospective Cohort	13
Prospective	
Nonrandomized clinical trial	41
Randomized clinical trial	8
Systemic therapy classes	**No. Studies** [1]
Platinum	47
Antimetabolites	44
Vinca alkaloids	15
Anthracyclines	15
Taxanes	13
Anti-angiogenics	6
Anti-ErbB agents	6
Alkylating agents	4

Sample (62 studies, 5082 patients)	Summary measure
SERM[2]	2
Other	2
Arsenic trioxide	1
Etoposide	1
Number of agents	**No. Studies**
Single	15
Multiple	44
Combination regimens	**No. Studies**
MVAC[3]	11
GC[4]	12

[1] Studies using multiple classes were counted separately within each class

[2] Selective estrogen receptor modulator

[3] Methotrexate, Vinblastine, Doxorubicin, Cisplatin

[4] Gemcitabine, Cisplatin

Table 2

Pooled thromboembolic event rates for subjects undergoing systemic chemotherapy for urothelial carcinoma.

Event type	Fixed Effects	Random effects	Heterogeneity		Number of studies
	Event rate [95%CI]	Event rate [95%CI]	τ^2	I^2 [95%CI]	
DVT	3.4% [2.7–4.2%]	2.9% [2.1–3.8%]	0.003	33% [0–47%]	43
PE	3.0% [2.3–3.9%]	2.9% [2.0–4.1%]	0.004	39% [2–58%]	42
VTE [1]	6.7% [6.0–7.4%]	5.4% [4.1–6.8%]	0.009	70% [51–78%]	62
Death from PE	0.5% [0.2–1.1%]	0.5% [0.3–0.9%]	0.000 [2]	0% [0–0%] [2]	27
PE case-fatality rate	13.7% [4.1–27.6%]	23.1% [44.0–50.6%]	0.095	46% [0–82%]	13

[1] Includes all DVT or PE events

[2] Highly homogenous data

Table 3

Subgroup analyses of factors affecting overall venous thromboembolism rates.

Subgroup	Number of studies	Random effects model	P-value	I^2
		Event rate [95%CI]		
Country of origin	62			
-USA		7.5% [5.5–9.9%]	0.005	63% [40–73%]
-Non-USA		3.8% [2.5–5.4%]		
Year of publication[1]	62			
-1985		5.2% [2.1–9.6%]		
-1995		5.8% [3.6–8.4%]	0.465	64% [39–72%]
-2005		6.4% [5.1–7.9%]		
-2015		7.1% [5.2–9.3%]		
Number of centers	62			
-Single center		5.4% [4.1–6.9%]	0.112	57% [25–65%]
-Multiple centers		7.6% [5.4–10.1%]		
Male proportion	52			
-0%		8.3% [0.4–24.9%]		
-25%		7.5% [1.5–17.7%]		
-50%		6.8% [3.2–11.6%]	0.688	58% [30–66%]
-75%		6.0% [4.7–7.5%]		
-100%		5.3% [2.5–9.2%]		
Age	52			
-45		5.8% [0.6–15.9%]		
-55		5.9% [2.5–10.6%]	0.977	52% [21–63%]
-65		5.9% [4.7–7.3%]		
-75		6.0% [2.5–11.0%]		
-85		6.1% [0.6–16.6%]		
ECOG 0 proportion	21			
-0%		6.8% [2.3–13.3%]		
-25%		6.4% [3.3–10.5%]		
-50%		6.1% [3.7–9.0%]	0.754	66% [33–81%]
-75%		5.7% [2.9–9.5%]		
-100%		5.4% [1.6–11.3%]		
Number of agents	59			
-Single		5.9% [4.4–7.6%]	0.237	57% [30–65%]
-Multiple		7.7% [5.3–10.4%]		
Chemotherapy setting	58			
-Neoadjuvant		6.3% [4.0–9.1%]		

Subgroup	Number of studies	Random effects model	P-value	I^2
		Event rate [95%CI]		
-Advanced/metastatic		6.8% [5.1–8.7%]	0.751	66% [43–73%]
-Mixed		6.6% [5.3–8.1%]		
Proportion prior radiation	15		0.042	0% [0–30%]
-0%		3.4% [2.3–4.7%]		
-25%		6.1% [4.0–8.6%]		
-50%		9.5% [4.3–16.6%]		
-75%		13.6% [4.4–26.8%]		
-100%		18.3% [4.6–38.5%]		

[1] Analyzed as a continuous variable, but presented as a categorical variable for ease of interpretation

Table 4

Overall venous thromboembolism rate pooled by chemotherapy class

Chemotherapy class	Random effects model Event rate [95%CI]	I^2 [95%CI]
Anti-angiogenics	11.4% [2.3–26.1%]	79% [46–96%]
Anti-ErbB	9.7% [2.2–21.6%]	67% [21–93%]
Antimetabolites	6.5% [4.8–8.4%]	67% [48–78%]
Platinum	6.1% [4.5–8.0%]	70% [53–79%]
Vinca alkaloids	4.6% [2.7–7.1%]	52% [8–80%]
Anthracyclines	4.6% [2.8–7.0%]	51% [8–79%]
Other	4.5% [0.0–55.6%]	0% [0–100%]
Taxanes	2.5% [1.4–3.8%]	0% [0–63%]
SERM	1.9% [0.0–94.6%]	40% [0–100%]
Alkylating agents	1.3% [0.1–3.7%]	0% [0–90%]