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Venous thromboembolism in cancer patients receiving neoadjuvant chemotherapy: a systematic review and meta-analysis

Running head: Venous thromboembolism during neoadjuvant chemotherapy

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Abstract

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Summary

Background: Venous thromboembolism (VTE) is a frequent complication in cancer patients receiving adjuvant treatment. The risk of VTE during neoadjuvant chemo-radiotherapy remains unclear.

Objectives: This systematic review evaluated the incidence of VTE in patients with cancer receiving neoadjuvant treatment.

Methods: MEDLINE and EMBASE databases were searched from inception to October 2017. Search results were supplemented with screening of conference proceedings of the American Society of Clinical Oncology (2009-2016) and the International Society of Thrombosis and Haemostasis (2003-2016). Two review authors independently screened titles and abstracts, and extracted data onto standardized forms.

Results: Twenty-eight cohort studies (7827 cancer patients, range 11 to 1398) were included. Twenty-five had a retrospective design. Eighteen cohorts included patients with gastrointestinal cancer representing over two-thirds of the whole study population (n = 6002, 78%). In total, 508 of 7768 patients were diagnosed with at least one VTE during neoadjuvant treatment for a pooled VTE incidence of 7% (95% CI, 5% to 10%) in absence of substantial between study heterogeneity. Heterogeneity was not explained by site of cancer or study design characteristics. VTE presented as pulmonary embolism in 22% to 96% of cases (16 cohorts), and it was symptomatic in 22% to 100% of patients (11 cohorts). Highest VTE rates were observed in patients with bladder (10.6%) or esophageal (8.4%) cancer.

Conclusions: This review found a relatively high incidence of VTE in cancer patients receiving neoadjuvant therapy in the presence of some between study variation, which deserves further evaluation in prospective studies.

Keywords: Neoadjuvant therapy, neoplasms, venous thromboembolism, review, meta-analysis.

Essentials

- Cancer patients are at risk for venous thromboembolism (VTE).
- The risk of VTE in less advanced stage cancer on neoadjuvant chemotherapy is unclear.
- In over 7800 patients, we found a 7% pooled incidence of VTE during neoadjuvant therapy.
- Highest VTE rates were observed in patients with bladder and esophageal cancer.

Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a frequent complication in patients with solid or hematological malignancies [1]. The pro-coagulant state associated with cancer disease as well as cancer treatments increase the risk of VTE up to 50-fold compared to patients without cancer [1-7].

Although the risk of VTE has been well described in cancer patients from adjuvant and palliative settings, data on the occurrence of VTE in patients receiving neoadjuvant chemo-radiotherapy remain limited and conflicting [5]. Even though cancer may be considered as less extensive in the neoadjuvant setting and therefore amenable of surgical excision, certain tumor types with a high thrombogenic potential such as gastric or pancreatic cancer, could activate blood coagulation leading to thrombosis [1,8]. In addition, neoadjuvant chemotherapy may increase the risk of VTE by directly damaging the endothelium, reducing the levels of blood anticoagulants, and increasing tissue factor activity [8]. The occurrence of VTE during these early phases of cancer disease may have a significant impact on morbidity, cause the interruption of neoadjuvant treatment, delay surgery, and increase health resources utilization and costs.

Current guidelines suggest the use of VTE thromboprophylaxis in high-risk cancer patients receiving adjuvant chemotherapy, whereas no specific recommendations are provided for patients undergoing neoadjuvant chemo-radiotherapy [9]. A better understanding of VTE risk during

neoadjuvant treatment may inform oncologists about thrombotic risk in these patients, and potentially provide useful information to design randomized controlled studies of VTE thromboprophylaxis with the aim of reducing this burdensome complication.

The aim of this review was to summarize the evidence on the risk of VTE in ambulatory cancer patients receiving neoadjuvant chemotherapy or chemo-radiotherapy.

Methods

A systematic search of the literature was conducted in the MEDLINE and EMBASE electronic databases (from inception to October 2017). Conference proceedings of the American Society of Clinical Oncology (2009-2016) and the International Society of Thrombosis and Haemostasis (2003-2016) were screened for potentially relevant records. We used the following search terms as text and Mesh words for the search in the electronic databases: "neoadjuvant therapy", "perioperative chemotherapy", "thrombosis", "pulmonary embolism", "venous thromboembolism", and "venous thrombosis". We applied no language restriction. The search results were supplemented with screening of citation lists of related reviews and those of included studies. The review is registered in PROSPERO with accession number CRD42017080148.

Study selection

Prospective or retrospective cohort studies and randomized controlled trials reporting on the incidence of VTE during neoadjuvant chemotherapy or chemo-radiotherapy in patients with cancer were eligible. We excluded studies reporting on a mix of arterial and venous thrombotic complications as well as studies that evaluated the occurrence of VTE over the entire perioperative period if the incidence of VTE could not be extracted separately for the pre-surgical neoadjuvant phase. In addition, studies occasionally reporting on VTE as one of the adverse effects of chemotherapy were not considered as these studies may selectively report only more severe cases or fail to properly identify and classify thrombotic events.

Two review authors (MDN, MC) independently screened the titles and abstracts identified from the searches and any disagreements were resolved through discussion. Studies with insufficient information were reevaluated if additional data were made available from the trial authors.

Data extraction

Two review authors (MDN, MC) independently extracted the data from included studies onto standardized forms, resolving any disagreements through discussion or by involving a third review author (AR). We extracted data on patients' characteristics (e.g. age, gender), type of cancer and neoadjuvant treatment (chemotherapy, radiotherapy, or both), incidence and type of VTE (PE, DVT of the lower or upper extremities), presentation of VTE (symptomatic versus incidentally detected), and use of thromboprophylaxis during neoadjuvant treatment. The main outcome of interest was any VTE, which included symptomatic or incidentally detected DVT and PE. The components of the main outcome were considered as secondary outcomes.

Study quality assessment

For each of the included studies, we evaluated the risk of bias using the Quality In Prognosis Studies (QUIPS) tool, which considers six domains to evaluate the validity of and bias in prognostic studies. Domains are related to: a) study participation addressing the representativeness of the study population; b) attrition bias; c) adequacy of prognostic factor measurement; d) adequacy of outcome measurement; e) study confounding, which addresses potential confounding factors, and f) appropriateness of statistical analysis and completeness of reporting [10]. Each of these domains was rated as at high, moderate, low, or unclear risk of bias. The latter category was only used if insufficient details were reported to allow a judgment. We followed guidance as outlined by Hayden and colleagues [10], and only described review specific rules for interpretation here. The domain "prognostic factor measurement" was considered at "low risk of bias" if information was provided

on the type, dose, and duration of neoadjuvant treatment. Regarding the domain related to attrition, we anticipated that retrospective cohort studies could select cancer patients undergoing surgery after neoadjuvant treatment. Because the evaluation of attrition bias in these circumstances would be hampered by the lack of information on withdrawals and patients who did not reach the surgical phase, we rated this domain as moderate risk in such studies. The interpretation of the domain "adequacy of outcome measurement" was focused on the primary outcome any VTE, and considered to be adequate if VTE was objectively diagnosed using reliable and valid reference tests in all participants [11]. At the domain related to confounding, we considered the handling of potential confounders such as previous VTE, use of central vein catheters, performance status, and use of thromboprophylaxis during neoadjuvant treatment. We used the GRADE methodology to judge the overall quality of the evidence [12].

Statistical analysis

In descriptive analyses, continuous variables were reported as mean (± standard deviations) or median (range), categorical variables as number (percentages). Confidence intervals around proportions were calculated with the Wilson method. We used univariate random effects logistic regression models to summarize VTE incidences as proportions and univariable meta-regression to evaluate the effect of cancer type and QUIPS domains. The likelihood ratio test was used to compare models with and without a specific covariate. All statistical analyses were conducted using STATA version 15.1 (STATACorp LLC, Texas, USA).

Results

The initial search yielded 944 references. Four additional records were identified by screening of conference proceedings and references lists (Figure 1). Following title and abstract screening, 902 records were excluded and 46 considered potentially eligible. After full-text examination, 18 were excluded because outcome data could not be extracted separately for patients receiving

neoadjuvant treatment (n = 4), or the article reported a mix of arterial and venous thrombotic events (n = 14). Twenty-eight records (19 full-texts and 9 abstracts) including a total study population of 7827 cancer patients (range 11 to 1398 patients) were finally included in the review (Table 1) [13-40]. All studies but two were single-center [21, 37], and were conducted during a time period that spanned from 1994 to 2015. Three studies (10%) had a prospective design [22, 38, 40], while all others concerned retrospective cohorts. Overall study quality was modest, with no study judged to be at low risk of bias across all QUIPS domains. We adjudicated domains of the QUIPS tool as at moderate to high risk of bias in 55% up to 100% of the studies (Table 2).

Eighteen cohorts included patients with gastrointestinal cancer representing over two-thirds of the whole study population (n = 6002, 78%). Eight studies evaluated cancer of the genitourinary tract, whereas cancer of the lung, breast and soft tissue were included in one study each. The type of neoadjuvant treatment is shown in the Supplementary Table.

Venous thromboembolism during neoadjuvant treatment

In total, 508 of 7768 patients were diagnosed with at least one VTE during neoadjuvant treatment for an overall mean VTE incidence of 7% (95% CI, 5% to 10%; moderate quality of evidence due to risk of bias). There was low between study heterogeneity, the variation observed was mainly attributed to chance (Figure 2). Rates of VTE varied across studies ranging from less than 1% up to 28% (Figure 2). The highest risk of VTE was observed in patients with bladder (13%;95% CI, 6% to 21%) or esophageal (7%; 95% CI, 5% to 10%) cancer (Table 3). Figure 3 shows the impact of cancer type, study design, and risks of bias in the six QUIPS domains. Although VTE incidence seemed higher in genitourinary cancer and in studies at low risk of bias concerning patient participation, the evidence was weak. No differences were observed on any of the study quality domains (Figure 3).

Sixteen cohorts reported on the site of thrombosis and 11 indicated whether VTE was symptomatic or incidentally detected (Table 3). The proportion of patients presenting with PE varied between 22% and 96%, whereas that of symptomatic VTE ranged from 22% to 100%, respectively.

The majority of symptomatic events were DVTs (38/63). Only 9 of the 25 studies including patients with genitourinary or gastrointestinal cancer described the clinical presentation of VTE, which was reported to be symptomatic in 42% (91/215). In five of these studies, DVT of the upper or lower extremities represented 64% (29/45) of all symptomatic VTEs (Table 3).

In the study by Krepline and colleagues, 18% of patients with pancreatic cancer were receiving or started VTE thromboprophylaxis at time of cancer diagnosis [30]. VTE thromboprophylaxis was not provided during neoadjuvant treatment in 15 studies, whereas information about the use of thromboprophylaxis was lacking in all other cohorts.

Three studies adopted a screening strategy for VTE, which included the systematic evaluation of patients by compression ultrasonography [18, 22, 38] or computed tomography pulmonary angiography [22] before and at the end of neoadjuvant treatment.

Additional observations

Eight studies reported on the prevalence of VTE before the start of neoadjuvant treatment, which ranged between less than 1% up to 10% [17, 21-22, 26, 29-31, 36]. The clinical presentation of prevalent VTE was described only by Krepline and colleagues who reported that 69% of these events were incidentally detected [30].

The performance of the Khorana score for the prediction of VTE during neoadjuvant treatment was evaluated in two studies [30-31]. In patients with pancreatic cancer, the incidence of VTE was 10% (15/155) in patients classified by the Khorana score as at intermediate risk and 11% (11/101) in those at high risk [30]. Similar findings were reported in the other study on patients with genitourinary cancer (3/28 versus 5/42, respectively) [31].

No study reported on the incidence of bleeding that occurred either spontaneously or on thromboprophylaxis during the neoadjuvant period. In the study of Rulach and colleagues, there were 2 fatal and 3 non-fatal bleeding events, which, however, occurred during anticoagulant treatment for newly diagnosed VTE.

Discussion

This review found a relatively high incidence of VTE in cancer patients receiving neoadjuvant therapy with apparently higher VTE rates for cancer of the bladder or esophagus. Information on the site and clinical presentation of VTE was scanty and highly heterogeneous across studies. Two-thirds of the study population was represented by patients with gastroesophageal or bladder cancer with limited or no data available for cancers at other sites.

Although VTE represents a common complication in patients with cancer, the risk varies markedly among these patients depending on cancer stage and the presence of a number of clinical and laboratory risk factors [1,5]. Chemotherapy increases the risk of VTE by two- to six-folds and specific chemotherapeutic agents such as platinum-based regimens have been associated with higher rates of VTE [2,4,7]. The risk of VTE in patients with a less advanced stage cancer undergoing neoadjuvant chemotherapy is less well established. In a study population of over 7,800 patients, we found a 7% pooled incidence of VTE, consistent with rates observed in ambulatory cancer patients receiving adjuvant treatment [6, 8, 41]. In a recent narrative review of studies on patients with esophageal or gastric cancer undergoing neoadjuvant chemotherapy, Marshall-Webb and colleagues reported an incidence of VTE ranging between 4% and 19% [42]. The inclusion of studies reporting VTE incidence throughout the neoadjuvant and postoperative periods limits the interpretation of their findings.

The primary site of cancer has been identified as a significant risk factor for VTE across a variety of studies [5]. Although specific incidence rates vary based on the clinical setting, cancer types consistently associated with the highest rates of VTE include those of the pancreas, stomach, uterus, kidney, lung, and primary brain [1,5,43]. These cancer types could be associated with a pro-coagulant state even when diagnosed at an earlier stage. As two-thirds of the current review population was represented by patients with gastrointestinal cancer, the high incidence of VTE

observed in our study may be driven by the inclusion of a large proportion of these highly thrombogenic cancer types.

About half of all VTEs diagnosed in cancer patients undergoing adjuvant chemotherapy are incidentally detected [44]. Although it is still an area of investigation and debate, data suggest that incidental VTE in the cancer population has important prognostic implications and clinical practice guidelines recommend the same anticoagulant treatment as for symptomatic VTE [9,45]. In the current review, the proportion of patients presenting with an incidental VTE varied across studies, where the variation was insufficiently explained by cancer type, study design or risk of bias domains.

This review has some limitations that need to be acknowledged. Although we used robust methods of double and independent risk of bias assessment, poor reporting may have led to some misclassifications. For example, clinical presentation of VTE was reported by only one-third of the studies, and information on the diagnostic VTE workup was lacking or poorly described. All studies included were judged to have significant methodological flaws. The lack of systematic VTE diagnosis by an accepted reference method may have introduced significant bias. We found moderate quality for the incidence of VTE, where we downgraded the evidence for risk of bias, in the absence of substantial inconsistency, imprecision or indirectness. Although study estimates seemed to vary across studies and within each cancer type, this was mainly explained by chance. We are moderately confident that the actual incidence is close to the estimate, but there is a possibility that it is substantially different [12]. Information on study population characteristics and concomitant VTE risk factors were scarce, and significant residual confounding cannot be excluded. Most of the studies were relatively old and the observed VTE rates may not apply to patients undergoing contemporary neoadjuvant treatments. Poor reporting on the use of thromboprophylaxis and outcome verification may have resulted in significant underestimation of VTE incidence. Finally, the predominant inclusion of gastroesophageal and bladder cancer, limit the generalizability of these findings to cancer at other sites.

In conclusion, the risk of VTE in cancer patients undergoing neoadjuvant treatments appears to be not negligible. Future large prospective studies are warranted to clarify the actual burden of VTE and the potential efficacy and safety of VTE thromboprophylaxis in this setting.

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Authors contribution

M. Di Nisio, M. Candeloro and E. Porreca were responsible for the conception and design of the study; M. Di Nisio and M. Candeloro were responsible for the acquisition of data; M. Di Nisio and A. W. S. Rutjes analyzed and interpreted data; all authors drafted the article or revised it critically for important intellectual content; all authors gave final approval of the version to be published.

Disclosure of Conflict of Interests

M. Di Nisio reports personal fees from Daiichi Sankyo and Bayer, outside the submitted work. The other authors state that they have no conflict of interest.

References

1. Cohen AT, Katholing A, Rietbrock S, Bamber L, Martinez C. Epidemiology of first and recurrent venous thromboembolism in patients with active cancer. Thromb Haemost. 2016;117:57–65.
2. Barni S, Labianca R, Agnelli G, Bonizzoni E, Verso M, Mandalà M, Brighenti M, Petrelli F, Bianchini C, Perrone T, Gasparini G. Chemotherapy-associated thromboembolic risk in cancer outpatients and effect of nadroparin thromboprophylaxis: results of a retrospective analysis of the PROTECHT study. J Transl Med. 2011;9:179.

3. Qu CY, Zheng Y, Zhou M, Zhang Y, Shen F, Cao J, Xu LM. Value of bevacizumab in treatment of colorectal cancer: A meta-analysis. World J Gastroenterol 2015;21:5072-80.
4. Khorana AA1, Francis CW, Culakova E, Lyman GH. Risk factors for chemotherapy-associated venous thromboembolism in a prospective observational study. Cancer. 2005;104:2822–2829.
5. Khorana AA, Connolly GC. Assessing risk of venous thromboembolism in the patient with cancer. J Clin Oncol. 2009;27:4839-47.
6. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood. 2008;111:4902-7.
7. Moore RA, Adel N, Riedel E, Bhutani M, Feldman DR, Tabbara NE, Soff G, Parameswaran R, Hassoun H. High incidence of thromboembolic events in patients treated with cisplatin-based chemotherapy: a large retrospective analysis. J Clin Oncol. 2011;29:3466-73.
8. Ay C, Pabinger I, Cohen AT. Cancer-associated venous thromboembolism: Burden, mechanisms, and management. Thromb Haemost. 2017;117:219-230.
9. Lyman GH, Bohlke K, Khorana AA, Kuderer NM, Lee AY, Arcelus JI, Balaban EP, Clarke JM, Flowers CR, Francis CW, Gates LE, Kakkar AK, Key NS, Levine MN, Liebman HA, Tempero MA, Wong SL, Somerfield MR, Falanga A; American Society of Clinical Oncology. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update 2014. J Clin Oncol. 2015;33:654-6.
10. Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. Ann Intern Med. 2013;158:280-6.
11. Di Nisio M, van Es N, Büller HR. Deep vein thrombosis and pulmonary embolism. Lancet. 2016;388(10063):3060-3073.
12. Iorio A, Spencer FA, Falavigna M, Alba C, Lang E, Burnand B, McGinn T, Hayden J, Williams K, Shea B, Wolff R, Kujpers T, Perel P, Vandvik PO, Glasziou P, Schunemann H, Guyatt G. Use of

GRADE for assessment of evidence about prognosis: rating confidence in estimates of event rates in broad categories of patients. BMJ. 2015; 16;350:h870.

13. En Amada, Hiroya T, Fumihiko K, Hirofumi K, Kazumasa F, Rieko N, Tsunehiro T, Norihito W, Yuko K. The influence of venous thromboembolism on prognosis of esophageal cancer patients. J Clin Oncol. 2016;Suppl 4;34: abstract 29.
14. Bosch DJ, Van Dalfsen QA, Mul VE, Hospers GA, Plukker JT. Increased risk of thromboembolism in esophageal cancer patients treated with neoadjuvant chemoradiotherapy. Am J Surg. 2014; 208:215-21.
15. Mungo B, Molena D, Stem M, Yang SC, Battafarano R J, Brock MV, Lidor AO. Does neoadjuvant therapy for esophageal cancer increase postoperative morbidity or mortality? Dis Esophagus 2015;28:644-651.
16. Sabra M J, Smotherman C, Kraemer DF,Nussbaum MS, Tepas 3rd JJ, Awad ZT. The effects of neoadjuvant therapy on morbidity and mortality of esophagectomy for esophageal cancer: American college of surgeons national surgical quality improvement program (ACS-NSQIP) 2005-2012. J Surg Oncol. 2017;115:296-300.
17. Teman NR, Silski L, Zhao L, Kober M,Urba SC, Orringer MB, Chang AC, Lin J, Reddy MR. "Thromboembolic events before esophagectomy for esophageal cancer do not result in worse outcomes." Ann Thorac Surg. 2012;94:1118-1124.
18. Tetzlaff ED, Correa AM, Komaki R, Swisher SG, Maru D, Ross WA, Ajani JA. Significance of thromboembolic phenomena occurring before and during chemoradiotherapy for localized carcinoma of the esophagus and gastroesophageal junction. Dis Esophagus. 2008;21:575-81.
19. Wada T, Fujiwara H, Morita S, Fukagawa T, Katai H. Incidence of and risk factors for preoperative deep venous thrombosis in patients undergoing gastric cancer surgery. Gastric Cancer. 2017;20:872-77.

20. Berger, AC, Scott WJ, Freedman G, Konski A, Weiner L, Cheng JD, Goldberg M. Morbidity and mortality are not increased after induction chemoradiotherapy followed by esophagectomy in patients with esophageal cancer. Semin Oncol.2005;32(6 Suppl 9):S16-20.
21. Khanna A, Reece-Smith AM, Cunnell M, Madhusudan S, Thomas A, Bowrey DJ, Parsons SL. Venous thromboembolism in patients receiving perioperative chemotherapy for esophagogastric cancer. Dis Esophagus. 2014;27:242-7.
22. Larsen AC, Frøkjær JB, Fisker RV, Iyer V, Mortensen PB, Yilmaz MK, Møller B, Kristensen SR, Thorlacius-Ussing O. Treatment-related frequency of venous thrombosis in lower esophageal, gastro-esophageal and gastric cancer--a clinical prospective study of outcome and prognostic factors. Thromb Res. 2015;135:802-8.
23. Mohan AJ, Papavasileiou V, Chatzigeorgiou V, Kamposioras K. The risk of thromboembolic events in upper GI cancer patients undergoing preoperative chemotherapy. Ann Oncol. 2016;27(Suppl 2): ii21–ii22.
24. Muthiah S., Jaretzke H, Griffi M, Wahed S, Sumpter K. Incidence of thromboembolism during neoadjuvant chemotherapy for oesophago-gastric carcinoma. Eur J Surg Oncol. 2012;38:1124–1125.
25. O'Connor EM, S. Croghan, Reynolds JV. Venous thromboembolism in patients with gastrooesophageal cancer treated with curative intent: A tertiary referral centre 14 year experience. Irish J Med Sci 2015;184(Suppl 5):127.
26. Rollins KE, Peters CJ, Safranek PM, Ford H, Baglin TP, Hardwick RH. Venous thromboembolism in oesophago-gastric carcinoma: incidence of symptomatic and asymptomatic events following chemotherapy and surgery. Eur J Surg Oncol. 2011;37:1072-7.
27. Rulach R, Evans J, McIntosh D, Grose D, Fullarton G, Forshaw M, MacKay C, Craig C, Graham J. Incidence of thrombo-embolism (TE) during neo-adjuvant chemotherapy in patients (pts)

with oesophago-gastric adenocarcinoma (OGC): Implications for surgery and survival. Ann Oncol 2016;27(Suppl 2): ii24- ii25.

28. Mezi S, Musio D, Orsi E, De Felice F, Verdinelli I, Morano F, Raffetto N, Tombolini V. Incidence of thromboembolic events in patients with locally advanced rectal cancer receiving neoadjuvant chemoradiotherapy, Acta Oncol.2013;52:187-190.
29. Smart PJ, Stocchi LL, Remzi FH. Neoadjuvant chemoradiation for rectal cancer is not associated with higher rates of thromboembolism. Colorectal Dis. 2015;17:984-9.
30. Krepline AN, Christians KK, George B, Ritch PS, Erickson BA, Tolat P, Evans DB, Tsai S. Venous thromboembolism prophylaxis during neoadjuvant therapy for resectable and borderline resectable pancreatic cancer-Is it indicated? J Surg Oncol. 2016;114:581-586.
31. Greco PS, Bazzi AA, McLean K, Reynolds RK, Spencer RJ, Johnston CM, Liu JR, Uppal S. Incidence and timing of thromboembolic events in patients with ovarian cancer undergoing neoadjuvant chemotherapy. Obstet Gynecol. 2017;129:979-985.
32. Szmal P, Bazzi AA, Reynolds RK, McLeanc K, Uppal S. Incidence and the timing of thromboembolic events in ovarian cancer patients undergoing neoadjuvant chemotherapy. Gynecol Oncol. 2016;141(Suppl. 1):66.
33. Bagrodia A, Sukhu R, Winer A, Vacchio M, Levy E, Lee B, Donahue T, Cha E, Assel M, Sjoberg D, Vickers A, Rosenberg J, Bajorin D, Dalbagni G, Bochner B. Incidence and impact of venous thromboembolism in radical cystectomy patients undergoing preoperative chemotherapy for muscle-invasive bladder cancer. J Urol. 2016;145:e65-e66.
34. Duivenvoorden WCM, Daneshmand S, Canter DJ, Lotan Y, Black PC, Abdi H, Bas W.G. Van Rhijn, Fransen EE van de Putte, Bostrom PJ, Koskinen E, Zareba P, Janet E. Baack Kukreja, Kassouf W, Traboulsi s, Pinthus jh. Incidence, characteristics, and implications of thrombo-embolic events in patients with urothelial carcinoma of the bladder undergoing neoadjuvant chemotherapy. J Clin Oncol. 2016;34(2 Suppl. 1).

35. Pugashetti N, Chandrasekar T , Lurvey R, Durbin-Johnson B, Dall'Era MA, deVere White RW, Evans CP, Yap SA. Perioperative Outcomes following Neoadjuvant Chemotherapy and Radical Cystectomy-Is There Room for Improvement? Urol Practice 2016;3:364-370.
36. Syed A. Hussain, Gomberg S, Probert C, Hickerton B, Jackson R, Weston R. Thrombo-embolic events (TEE) during neoadjuvant chemotherapy for muscle invasive bladder cancer. J Clin Oncol. 2017:35 (Suppl 6S):abstract 339.
37. Zareba P, Patterson L, Pandya R, Margel D, Hotte SJ, Mukherjee SD, Elavathil L, Daya D, Shayegan B, Pinthus JH. Thromboembolic events in patients with urothelial carcinoma undergoing neoadjuvant chemotherapy and radical cystectomy. Urol Oncol. 2014;32:975-80.
38. Kirwan CC, McCollum CN, McDowell G, Byrne GJ. Investigation of proposed mechanisms of chemotherapy-induced venous thromboembolism: endothelial cell activation and procoagulant release due to apoptosis. Clin App Thromb Hemost. 2015;21:420-427.
39. Patel A, Anraku M, Darling GE, Shepherd FA, Pierre AF, Waddell TK, Keshavjee S, de Perrot M. Venous thromboembolism in patients receiving multimodality therapy for thoracic malignancies. J Thorac Cardiovasc Surg. 2009;138:843-8.
40. Kane JM, Harris J, Kraybill WG, Harmon DC, Ettinger DS, Lucas DR, DeLaney TF, Wang D, Curran WJ, Eisenberg BL. Thromboembolic events associated with thalidomide and multimodality therapy for soft tissue sarcomas: Results of RTOG 0330. Sarcoma. 2012;2012:659485.
41. van Es N, Di Nisio M, Cesarman G, Kleinjan A, Otten HM, Mahé I, Wilts IT, Twint DC, Porreca E, Arrieta O, Stépanian A, Smit K, De Tursi M, Bleker SM, Bossuyt PM, Nieuwland R, Kamphuisen PW, Büller HR. Comparison of risk prediction scores for venous thromboembolism in cancer patients: a prospective cohort study. Haematologica. 2017;102:1494-1501.

42. Marshall-Webb M, Bright T, Price T, Thompson SK, Watson DI.Venous thromboembolism in patients with esophageal or gastric cancer undergoing neoadjuvant chemotherapy. Dis Esophagus. 2017;30:1-7.
43. Timp JF, Braekkan SK, Versteeg HH, Cannegieter SC. Epidemiology of cancer-associated venous thrombosis. Blood. 2013;122:1712-23.
44. Di Nisio M, Carrier M. Incidental venous thromboembolism: is anticoagulation indicated? Hematology Am Soc Hematol Educ Program. 2017;(1):121-127.
45. Di Nisio M, Lee AY, Carrier M, Liebman HA, Khorana AA; Subcommittee on Haemostasis and Malignancy. Diagnosis and treatment of incidental venous thromboembolism in cancer patients: guidance from the SSC of the ISTH. J Thromb Haemost. 2015;13:880-3.

Tables

Title Table 1: Characteristics of included studies.

Title Table 2: Study design and quality assessment.

Legend Table 2: *QUIPS: the Quality In Prognosis Studies tool used for risk of bias assessments in prognostic studies. Risk of bias is classified as high, moderate, low or unclear.

Title Table 3: Incidence and clinical presentation of venous thromboembolism.

Legend Table 3: * 43 PE events, 88 total VTE events; ** Two additional patients had an incidental pulmonary embolism, but it is not reported whether these occurred in the neoadjuvant group; ***Symptomatic VTE reported on 47 patients. CVC-DVT = Central vein catheter DVT; DVT = deep vein thrombosis; NR = not reported; PE = pulmonary embolism; VTE = venous thromboembolism.

Title Supplementary Table: Type of neoadjuvant therapy

Figures

Title Figure 1: Search results and study selection.

Title Figure 2: Incidence of venous thromboembolism according to cancer type.

Title Figure 3: Incidence of venous thromboembolism according to cancer type, study design, and risks of bias domains.

Table 1. Characteristics of included studies

Study	Cancer site	Cancer stage, n	Patients, n	Mean Age (SD or range)	Gender, n	Recruitment period
Gastrointestinal cancer						
Amada 2016	Esophagus	-	172	-	-	2008 - 2012
Bosch 2014	Esophagus	TNM I-II: 19 (17%) TNM III-IV: 91 (83%)	110	63 (-)	27 (24%)	2006 - 2012
Mungo 2014	Esophagus	-	708	62 (10.2)	107 (15%)	2005 - 2011
Sabra 2016	Esophagus	-	548	63 (56 - 70)	90 (16%)	2005 - 2012
Teman 2012	Esophagus	-	534	VTE: 61 (8.6) No VTE: 60 (8.8)	71 (13%)	1999 – 2010
Tetzlaff 2008	Esophagus	EUS T I-II: 26 (13%) EUS T III-IV: 162 (82%) Unknown T: 10 (5%)	198	65 (34 - 86)	35 (18%)	2001 - 2004
Berger 2005	Esophagus - stomach	TNM I-II: 100 (76%) TNM III-IV: 30 (23%) Unknown: 1 (1%)	131	-	-	1994 - 2002
Khanna 2014	Esophagus - stomach	UICC I-II: 356 (93%) UICC III-IV: 28 (7%)	384	63 (24 - 81)	102 (26%)	2004 - 2011
Larsen 2015	Esophagus - stomach	-	54	-	-	2008 - 2011
Mohan 2016	Esophagus - stomach	-	42	63 (-)	6 (14%)	2013 - 2015
Muthiah 2012	Esophagus - stomach	-	140	-	-	2009 - 2011
O'Connor 2015	Esophagus - stomach	-	1398	-	-	2000 - 2014
Rollins 2011	Esophagus - stomach	-	133	-	-	2004 - 2008
Rulach 2016	Esophagus - stomach	-	120	-	-	2013 - 2014
Wada 2017	Stomach	-	47	-	-	2012 - 2015
Mezi 2013	Rectum	TNM I-II: 32 (42%) TNM III-IV: 45 (58%)	77	64 (-)	23 (30%)	2000 - 2010
Smart 2015	Rectum	-	946	-	-	2000 - 2013
Krepline 2016	Pancreas	Resectable: 109 (42%) Borderline resectable: 151 (58%)	260	64 (-)	127 (49%)	2009 - 2014
Subtotal			6002			
Genitourinary cancer						
Greco 2017	Ovary, fallopian tube, peritoneal	TNM III-IV: 125 (100%)	125	-	112 (100%)	2009 - 2014
Szmal 2016	Ovary, fallopian tube, peritoneal	-	161	-	NR	2009 - 2014
Bagrodia 2016	Bladder	TNM I-II: 198 (55%) TNM III-IV: 159 (45%)	357	66 (58 - 71)	104 (29%)	2001 - 2013
Duivenvoorden 2016	Bladder	TNM I-II: 394 (54%) TNM III-IV: 125 (17%) TxN+: 207 (29%)*	761	-	192 (25%)	2002 - 2014
Pugashetti 2016	Bladder	cTa,cTis,cT!:0 (0%)** cT2 - cT4: 66 (100%)	66	66 (61 - 72)	12 (18%)	2003 - 2014
Syed 2017	Bladder	TII-III: 75 (80%)	94	67 (63 - 72)	28 (30%)	2012 - 2015
Zareba 2014	Bladder, prostate, urethra	Ta-T II: 17 (40%) T III-T IV: 8 (19%) TXN I-N III: 17 (40%)	42	62 (53 - 67)	18 (43%)	2005 - 2013
Subtotal			1606			
Other						
Kirwan 2015	Breast	-	11	-	11 (100%)	-
Patel 2009	Lung, pleura	-	186	60 (21 - 80)	64 (34%)	1996 - 2007
Kane 2012	Soft Tissue Sarcoma	Grade 1-2, >5 cm: 7 (32%) Grade 3-4, ≥8 cm:15 (68%)	22	- (20 – 81)	9 (41%)	2004 - 2007
Subtotal			219			
Total			7827			

*Cancer stage available on 726 patients; **cT = clinical stage; VTE = venous thromboembolism

Table 2. Study design and quality assessment

Study	Design	QUIPS Risk of Bias assessment					
		Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Confounding	Statistical analysis and Reporting
Amada 2016	Retrospective	High	High	High	High	High	High
Bosch 2014	Retrospective	Low	Low	Low	Low	High	Low
Mungo 2014	Retrospective	Low	Moderate	Moderate	Moderate	High	High
Sabra 2016	Retrospective	Low	Moderate	Moderate	Moderate	High	Moderate
Teman 2012	Retrospective	Low	Moderate	Moderate	Moderate	High	Moderate
Tetzlaff 2008	Retrospective	Moderate	Low	Moderate	Moderate	High	Moderate
Wada 2017	Retrospective	Moderate	Low	Moderate	Moderate	High	High
Berger 2005	Retrospective	Moderate	Moderate	Moderate	Moderate	High	Moderate
Khanna 2014	Retrospective	Moderate	Low	Low	Moderate	High	Moderate
Larsen 2015	Prospective	Moderate	Low	Low	Moderate	Moderate	High
Mohan 2016	Retrospective	Low	Moderate	Moderate	Moderate	High	Moderate
Muthiah 2012	Retrospective	Moderate	Moderate	Moderate	Moderate	High	High
O'Connor 2015	Retrospective	High	High	High	High	High	High
Rollins 2011	Retrospective	Low	Moderate	Low	Moderate	Moderate	Moderate
Rulach 2016	Retrospective	High	High	High	High	High	High
Mezi 2013	Retrospective	Moderate	Low	Moderate	High	Moderate	Moderate
Smart 2015	Retrospective	Moderate	Low	Moderate	Moderate	High	High
Krepline 2016	Retrospective	Moderate	Low	Low	Moderate	High	Moderate
Greco 2017	Retrospective	Low	Low	Moderate	Moderate	Moderate	Moderate
Szmal 2016	Retrospective	Moderate	High	High	High	High	High
Bagrodia 2016	Retrospective	Moderate	High	Moderate	Moderate	High	Moderate
Duivenvoorden 2016	Retrospective	Moderate	High	High	Moderate	High	High
Pugashetti 2016	Retrospective	Low	Low	Moderate	Moderate	Moderate	Moderate
Syed 2017	Retrospective	Moderate	High	High	High	High	High
Zareba 2014	Retrospective	Moderate	Low	Moderate	Moderate	High	Moderate
Kirwan 2015	Prospective	Moderate	Moderate	Moderate	Moderate	High	High
Patel 2009	Retrospective	Moderate	Low	Moderate	Moderate	High	High
Kane 2012	Prospective	Low	Moderate	Moderate	Moderate	High	Moderate

* QUIPS: the Quality In Prognosis Studies tool used for risk of bias assessments in prognostic studies. Risk of bias is classified as high, moderate, low or unclear.

Table 3. Incidence and clinical presentation of venous thromboembolism

Study	Cancer site	VTE					
		Any VTE	PE ± DVT	DVT	Symptomatic VTE	Type symptomatic VTE	Fatal VTE
Gastrointestinal cancer							
Amada 2016	Esophagus	6/172 (3.5%)	-	-	-	-	-
Bosch 2014	Esophagus	9/110 (8.2%)	7 (78%)	2 (22%)	2 (22%)	1 PE; 1 DVT	-
Mungo 2014	Esophagus	55/708 (7.8%)	-	-	-	-	-
Sabra 2016	Esophagus	40/548 (7.3%)	15 (37%)	25 (63%)	-	-	-
Teman 2012	Esophagus	73/534 (13.7%)	43 (49%)*	45 (51%)*	30 (41%)	-	1
Tetzlaff 2008	Esophagus	8/190 (4.2%)	5 (62%)	3 (38%)	-	-	0
Berger 2005	Esophagus - stomach	11/131 (8.4%)	-	-	-	-	-
Khanna 2014	Esophagus - stomach	12/363 (3.3%)	6 (50%)	6 (50%)	6 (50%)	1 CVC-DVT; 5 DVT	-
Larsen 2015	Esophagus - stomach	4/53 (7.5%)	-	-	-	-	-
Mohan 2016	Esophagus - stomach	8/42 (19.0%)	3 (37%)	5 (63%)	-	-	-
Muthiah 2012	Esophagus - stomach	7/140 (5.0%)	6 (86%)	1 (14%)	-	-	-
O'Connor 2015	Esophagus - stomach	16/1398 (1.1%)	-	-	-	-	-
Rollins 2011	Esophagus - stomach	12/132 (9.1%)	6 (50%)	6 (50%)	6 (50%)	6 DVT	-
Rulach 2016	Esophagus - stomach	22/120 (18.3%)	-	-	8 (36%)	-	-
Wada 2017	Stomach	4/47 (8.5%)	1 (25%)	3 (75%)	-	-	0
Mezi 2013	Rectum	8/77 (10.0%)	-	-	2 (25%)	-	1
Smart 2015	Rectum	9/944 (0.9%)	2 (22%)	7 (78%)	-	-	-
Krepline 2016	Pancreas	23/247 (9.3%)	-	-	-	-	-
Genitourinary cancer							
Greco 2017	Ovary, tube, peritoneal	13/112 (11.6%)	-	-	-	-	1
Szmal 2016	Ovary, tube, peritoneal	13/161 (8.1%)	-	-	-	-	-
Bagrodia 2016	Bladder	57/357 (15.9%)	-	-	-	-	-
Duivenvoorden 2016	Bladder	48/761 (6.3%)	24 (50%)	24 (50%)	29 (62%)***	20 DVT; 9 PE ± DVT	-
Pugashetti 2016	Bladder	4/66 (6.1%)	2 (50%)	2 (50%)	-	-	-
Syed 2017	Bladder	26/94 (27.6%)	25 (96%)	1 (4%)	6 (23%)	-	-
Zareba 2014	Bladder, prostate, urethra	5/42 (11.9%)	3 (60%)	2 (40%)	2 (40%)	1 DVT; 1 UEDVT	-
Other							
Kirwan 2015	Breast	0/11 (0.0%)	0	0	0	0	0
Patel 2009	Lung, pleura	11/186 (5.9%)	9 (82%)	2 (18%)	11 (100%)	9 PE; 2 DVT	-
Kane 2012	Soft Tissue Sarcoma	4/22 (18.2%)	2 (50%)	2 (50%)	3 (75%)	2 PE; 1 UEDVT	0

* 43 PE events, 88 total VTE events; ** Two additional patients had an incidental pulmonary embolism, but it is not reported whether these occurred in the neoadjuvant group; ***Symptomatic VTE reported on 47 patients. CVC-DVT = Central vein catheter DVT; DVT = deep vein thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism.