Venous Thromboembolism in Cancer Patients Undergoing Chemotherapy: A Systematic Review and Meta-Analysis

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**Abstract:** Objective: Venous thromboembolism (VTE) is a life-threatening complication that may exacerbate cancer prognosis. Whilst some studies indicate an increased risk of VTE in cancer patients undergoing chemotherapy, the prevalence estimates on the pooled prevalence of VTE in cancer patients undergoing chemotherapy are not known. This study aims to calculate the pooled prevalence of VTE in chemotherapy-treated cancer patients. **Methods:** Studies on VTE occurrence in cancer patients undergoing chemotherapy were retrieved after database search. The terms used included “cancer”, “chemotherapy”, and “venous thromboembolism”. A random-effects meta-analysis was conducted to obtain a pooled estimate of VTE prevalence in cancer patients undergoing chemotherapy. **Results:** A total of 102 eligible studies involving 30,671 patients (1773 with VTE, 28,898 without) were included in the meta-analysis. The pooled estimate of VTE prevalence was found to be 6%, ranging from 6% to 7% (ES 6%; 95% CI 6–7%; \(z = 18.53\); \(p < 0.001\)). **Conclusions:** The estimated pooled prevalence rate of VTEs was 6% in cancer patients undergoing CRT, which was higher than the overall crude prevalence rate (5.78%). Comprehensive cancer care should consider stratified VTE risk assessment based on cancer phenotype, given that certain phenotypes of cancer such as bladder, gastric and ovarian posing particularly high risks of VTE.

**Keywords:** cancer; chemotherapy; venous thromboembolism; prevalence; screening

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**1. Introduction**

Venous thromboembolism (VTE) is a major public health problem constituting a significant burden of disease \([1,2]\). There are around 10 million cases of VTE worldwide every year. After myocardial infarction and stroke, VTE is the third leading vascular disease \([3]\). In the first one to three months following a stroke, there is an increased risk of VTE, partly because of immobility brought on by the stroke \([4]\). Major venous and arterial thrombotic disorders share overlap in some key cardiovascular risk factors \([5]\). A higher risk of VTE is linked to specific cardiovascular risk factors such as older age, smoking, and greater adiposity \([2,6]\). Cancer, a leading cause of death and disability in the world \([7,8]\), is known to potentiate the risk of VTE and roughly 20% of VTE are linked to cancer \([9,10]\). Thrombosis in cancer patients is a clinically challenging construct which is associated with poor outcomes despite therapy \([11]\).
Recent studies have also indicated that cancer patients on chemotherapy may be at an increased risk of venous thromboembolism [12–14]. Assessment of VTE risk is critical for appropriate medical management and prophylactic treatment [15]. Given the lack of data on the prevalence estimates of VTE in cancer patients, especially in those receiving chemotherapy, further studies are required. Distinct cancer phenotypes may render cancer patients at varying levels of VTE risk [16–18]. Recent guidelines from American Society of Haematology published in early 2021 recommend stratifying cancer patients according to their VTE risk prior to the start of chemotherapy, as well as patient-specific factors, using the Khorana risk score, the major determinant of which is cancer phenotype [19]. This comes in the background of two landmark randomized clinical trials (RCTs), resulting in the change of guidelines, demonstrating VTE prophylaxis with direct oral anticoagulants (DOACs) following risk assessment lowered the incidence of VTE during chemotherapy [20–22]. Several societies or health systems beyond United States are yet to adopt these recommendations; besides, unwarranted variations in clinical care as well as poor adherence to recommendations or guidance vis-à-vis VTE risk assessment and optimal administration of thromboprophylaxis pose an ongoing real-world or systems challenge [23,24]. Moreover, literature is sparse when comparing the relative risk and prevalence of VTE across multiple cancer phenotypes—with studies only revealing VTE prevalence specific to a cancer phenotype and risk in homogenous cancer populations, vis-à-vis their ethnicity and treatment received. Understanding of, and estimates of, the pooled prevalence may also be useful to increase awareness on VTE risks in cancer patients undergoing chemotherapy as well to inform clinicians and patients on the quantum of the VTE prevalence/risk in cancer or across various types of cancer. This meta-analysis sought to investigate the pooled prevalence of venous thromboembolism in cancer patients receiving chemotherapy. There is also a gap in clinician knowledge pertaining to the specific risk that cancer phenotypes and chemotherapy poses to cancer patients. We have sought to address two key underlying questions through this meta-analysis:

1. what is the prevalence of VTE in cancer patients receiving chemotherapy?
2. what is the prevalence of VTE stratified by cancer phenotype in patients undergoing chemotherapy?

2. Materials and Methods

2.1. Literature Search: Identification and Selection of Studies

The primary search engine of this meta-analysis and systematic review was the PubMed database. Articles published between 2012 and October 2022 were included in the search. Search terms included: “cancer”, “chemotherapy” and “venous thromboembolism”. The complete search strategy is available in the Supplementary Information (Search Strategy). Studies were filtered to include those in the English language, conducted on humans, and restricted to disregard Phase I studies, accepting only those Phase II and above. Additional studies were also included through handsearching of references from included studies as well as from other sources such as Google Scholar and ResearchGate. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This study was registered in Open Science, registration number is “yn5br” (https://osf.io/yn5br/ (accessed on 6 November 2022)). The PRISMA flowchart shows the studies included in the meta-analysis (Figure 1). PRISMA checklist is also provided in the Supplementary Information (PRISMA Checklist).
Figure 1. The PRISMA flowchart showing the steps followed during the study selection process. Abbreviations: N: number of studies; n: number of patients.
2.2. Inclusion and Exclusion Criteria

Studies were eligible for inclusion if they met the following criteria: (1) age $\geq 18$ years; (2) patients with a confirmed diagnosis of cancer; (3) patients receiving chemotherapy; (4) patients not on prophylactic anticoagulation concomitant to chemotherapy; (5) availability of data on VTE occurrence noted in patients; and (6) studies with a sample size of $>20$ patients. The exclusion criteria were (1) studies not in English, (2) animal studies, (3) duplicated publications, (4) systematic reviews, meta-analyses, or narrative reviews; and (5) studies whereby relevant data on VTE occurrence not available.

3. Data Extraction

Firstly, titles and abstracts were screened on EndNote™ (Clarivate, Philadelphia, PA, USA) to identify articles that were beyond the scope of this study, were systematic reviews of meta-analyses, or for other reasons failed to match the eligibility criteria before being excluded. Remaining articles were read in full-text and comprehensively assessed to determine eligibility for inclusion in this study, with screening conducted independently by two experienced investigators. In the case of disagreement between authors, a consensus was reached through discussion. A data extraction sheet was used to extract the following data from each study: (1) baseline demographics: author, year of publication, type of publication, country of lead author, study design, and study type; (2) study population: age of patients, sample size, baseline clinical characteristics, cancer phenotype, body location of cancer, cancer stage, and treatment agent, dose, duration, and frequency; (3) outcome measures: VTE occurrence. In the grading of VTE severity, most VTEs were classified as an adverse effect within a drug trial, and thus were graded via the Common Terminology Criteria for Adverse Events (CTCAE) scale of Grade 1 through 5. Although some studies were particular in grading each adverse event into individual categories of Grade 1/2/3/4/5, the majority of studies grouped Grades 1 and 2 together, and Grades 3/4/5 together. As such, in our meta-analysis, we have extracted data based on this later, more generalised method. Studies reporting on VTE in cancer, without prophylactic anticoagulation concomitant to chemotherapy, were included in the systematic review and meta-analysis.

Quality Assessment of Included Studies

Using the modified Jadad analysis (MJA) criterion, the methodological quality of each study was assessed [25]. The MJA evaluates the quality of studies based upon: randomisation, blinding, description of withdrawals/dropouts, inclusion/exclusion criteria, assessment of adverse events and methods used for statistical analysis. Studies receive a score from 0–8 based upon their ability to fulfil aforementioned criteria [26]. The complete quality assessment of each study is available in the Supplementary Information (Jadad Analysis). Each study was also separately assessed for risk of funding bias using a 2-point scale that scored studies from 0 (low potential for bias) to 2 (high potential for bias) [27]. The absence of industry funding was not taken to signify an absence of bias, but the presence of industry funding or conflicts of interest was assumed to be an indicator of bias.

4. Statistical Analysis

Statistical analysis was performed using STATA (Version 13.0, StataCorp LLC, College Station, TX, USA). The purpose of this study was to determine the prevalence of VTE in cancer patients undergoing chemotherapy. As a result, the “metaprop” STATA command was utilised, pooling prevalence by performing a random-effects meta-analysis of proportions obtained from the individual studies [28]. The DerSimonian and Laird method was used for random effects modelling. In presenting the overall effects, forest plots were generated. Heterogeneity across the studies was estimated from the inverse-variance fixed-effect model and quantified using the $I^2$ measure ($I^2 < 40\% = \text{low}, 30–60\% = \text{moderate}, 50–90\% = \text{substantial},$ and $75–100\% = \text{considerable}$). An overall meta-analysis was performed stratified by cancer phenotype to estimate the pooled prevalence of VTE in cancer patients undergoing chemotherapy. Besides, meta-analysis for individual cancer pheno-
types were also performed provided there were minimum of 4 studies. The estimate of between-study variance (tau-squared or $\tau^2$) was also reported. Significance tests in the form of z-statistics and $p$-values were also reported. $p$-values less than 0.05 were considered significant.

5. Results

A total of 2643 and 85 studies were identified from PubMed and other sources, respectively. On screening of 2723 titles/abstracts, 2172 studies were excluded. Out of these, full texts of 551 studies were assessed for eligibility. Overall, 102 studies were included in the final synthesis.

5.1. Description of Included Studies

This meta-analysis included 102 studies, which reported on VTE prevalence within cancer patients undergoing chemotherapy, with a cumulative cohort of 30,671 patients (1773 with VTE, 28,898 without). Within a cohort of 20,420 patients for which data on sex was reported, 53.11% were male (sex data on 10,251 patients were not reported). Age ranged from 18–93 years. The mean age within a cohort of 8159 patients on which age data was reported was 59.59 years (standard deviation (SD) 33.74). Twenty-two cancer phenotypes were identified including bladder, blood, brain, breast, cervical, colorectal, endometrial, gastric, germ cell, head and neck, liver, lung, lymph, mesothelial, mixed, neuroendocrine, oesophageal, ovarian, pancreatic, prostate, renal, and skin.

The clinical characteristics of all included studies are shown in Table 1. Tables 2 and 3 further delineate treatment dose, duration, and frequency. Tabulated results for the estimated pooled prevalence and crude prevalence rates stratified by cancer phenotype are shown in Table 4. The MJA and funding bias analysis for each study can be found in Supplemental SI Tables S1 and S2.
Table 1. Clinical characteristics of studies included in the meta-analysis.

| Study ID | Author                  | Year | Study Design              | Study Phase | Country | Cancer Phenotype                        | Cancer Phenotype, Body | Age (Median) | Age (Range) | Number of Males (%) | C  | N  | P   |
|----------|-------------------------|------|--------------------------|-------------|---------|----------------------------------------|------------------------|--------------|-------------|---------------------|----|----|-----|
| 1        | Affronti et al. [29]    | 2018 | Prospective, single centre | II          | USA     | Recurrent grade IV malignant glioma    | Brain                  | 55.5         | 27–74       | 61.11                | 36 | 4  | 11.11 |
| 2        | Alexander et al. [30]   | 2012 | Prospective, single centre | II          | USA     | Newly diagnosed glioblastoma           | Brain                  | N/A          | N/A         | 62                   | 89 | 8  | 8.99 |
| 3        | Alvarez et al. [31]     | 2014 | Prospective, single centre | II          | USA     | Recurrent or persistent endometrial carcinoma | Endometrial            | 63           | 35–80       | 0                     | 49 | 1  | 2.04 |
| 4        | Assenat et al. [32]     | 2021a| Prospective, multicentre  | II          | USA     | Metastatic pancreatic cancer           | Pancreas               | 60           | 34–72       | 50                   | 58 | 18 | 31.03 |
| 5        | Assenat et al. [33]     | 2021b| Prospective, multicentre  | II          | France  | Metastatic pancreatic cancer           | Pancreas               | 62           | 35–77       | 59.7                 | 62 | 22 | 35.48 |
| 6        | Bai et al. [34]         | 2015 | Prospective, single centre | Unspecified | China  | Metastatic colorectal cancer           | Colorectal             | 55           | 20–79      | 63.4                 | 175 | 1  | 0.57 |
| 7        | Balar et al. [35]       | 2013 | Prospective, single centre | II          | USA     | Advanced unresectable/metastatic urothelial cancer | Bladder                | 67           | 42–83       | 72.5                 | 51 | 10 | 19.61 |
| 8        | Basso et al. [36]       | 2013 | Prospective, multicentre  | Unspecified | Italy  | Locally advanced/metastatic breast cancer | Breast                | 78           | 70–93       | 0                    | 32 | 3  | 9.38 |
| 9        | Bear et al. [37]        | 2015 | Prospective, single centre | III         | USA     | Early HER2-negative breast cancer      | Breast                | N/A          | N/A         | 0                    | 1206 | 37 | 3.07 |
| 10       | Buxo et al. [38]        | 2018 | Retrospective, single centre | Unspecified | Spain  | Recurrent or metastatic head and neck squamous cell carcinoma | Head and Neck         | N/A          | N/A         | N/A                  | 104 | 1  | 0.96 |
| 11       | Campbell et al. [39]    | 2012 | Prospective, multicentre  | II          | USA     | Malignant mesothelioma                | Mesothelium            | N/A          | N/A         | 84                   | 50  | 3  | 6.00 |
| 12       | Chekerov et al. [40]    | 2018 | Prospective, multicentre  | II          | Germany | Platinum-resistant ovarian cancer     | Ovary                  | N/A          | N/A         | 0                    | 174 | 10 | 5.75 |
| 13       | Chen et al. [41]        | 2015 | Prospective, single centre | II          | USA     | Relapsed/refractory indolent non-Hodgkin lymphoma | Lymph                | 62           | 44–85       | 54                   | 28  | 4  | 14.29 |
| 14       | Chibaudel et al. [42]   | 2019 | Prospective, multicentre  | II          | France  | Metastatic colorectal cancer           | Colorectal             | 62.9         | 32–86       | 53.1                 | 48  | 1  | 2.08 |
| Study ID | Author | Year | Study Design | Study Phase | Country   | Cancer Phenotype, Body | Cancer Phenotype | Age (Median) | Age (Range) | Number of Males (%) | C | N | P |
|----------|--------|------|--------------|-------------|-----------|------------------------|-----------------|--------------|-------------|----------------------|---|---|---|
| 15       | Ciombor et al. [43] | 2014 | Prospective, multicentre | II          | USA       | Hepatocellular carcinoma | Liver           | 59           | 23–76.5    | 71.1                 | 38 | 1 | 2.63 |
| 16       | Cremolini et al. [44] | 2020 | Prospective, multicentre | III         | Italy     | Unresectable metastatic colorectal cancer | Colorectal | N/A          | N/A         | N/A                  | 672 | 63 | 9.38 |
| 17       | de Vos et al. [45] | 2014 | Prospective, multicentre | II          | USA       | Diffuse large B-cell lymphoma | Lymph          | 72           | 18–85      | 61                    | 46 | 3 | 6.52 |
| 18       | DeCensi et al. [46] | 2019 | Prospective, multicentre | III         | Italy     | Ductal carcinoma in situ | Breast         | N/A          | N/A         | 0                    | 500 | 2 | 0.40 |
| 19       | Deschenes-Simard et al. [47] | 2021 | Retrospective, multicentre | Unspecified | Canada   | Non-small-cell lung cancer | Lung           | 66.7         | N/A         | 54.3                  | 593 | 64 | 10.79 |
| 20       | Donskov et al. [48] | 2018 | Prospective, multicentre | IIb         | Denmark  | Metastatic renal cell carcinoma | Renal          | N/A          | N/A        | N/A                  | 118 | 15 | 12.71 |
| 21       | Dowell et al. [49] | 2012 | Prospective, multicentre | II          | USA       | Advanced malignant mesothelioma | Mesothelium    | 66           | 24–81      | 85                    | 52  | 7 | 13.46 |
| 22       | Dummer et al. [50] | 2012 | Prospective, multicentre | II          | Switzerland | Primary cutaneous T-cell lymphoma, mycosis fungoides | Lymph         | N/A          | N/A        | N/A                  | 49  | 2 | 4.08 |
| 23       | Duvic et al. [51] | 2015 | Prospective, single centre | II          | USA       | Cutaneous T-cell lymphoma and lymphomatoid papulosis | Lymph         | 59.5         | 31–77      | 54                    | 48  | 2 | 4.17 |
| 24       | Fehr et al. [52] | 2020 | Prospective, multicentre | III         | Switzerland | Locally advanced oesophageal cancer | Oesophageal    | 61           | 36–75      | 88                    | 300 | 29 | 9.67 |
| 25       | Feliu et al. [53] | 2014 | Prospective, multicentre | II          | Spain     | Metastatic colorectal cancer | Colorectal     | 75.6         | 70.5–85.4 | 65                    | 68  | 10 | 14.71 |
| 26       | Fleming et al. [54] | 2014 | Prospective, multicentre | II          | USA       | Endometrial cancer | Endometrial | N/A          | N/A        | 0                    | 71  | 10 | 14.08 |
| 27       | Folprecht et al. [55] | 2016 | Prospective, multicentre | II          | Germany  | Metastatic colorectal cancer | Colorectal     | 62.5         | 29–87      | 61                    | 235 | 22 | 9.36 |
| 28       | Frizziero et al. [56] | 2019 | Retrospective, multicentre | Unspecified | UK       | Poorly differentiated neuroendocrine carcinomas | Neuroendocrine | 65.8         | 24–88      | 63.7                  | 113 | 7 | 6.19 |
Table 1. Cont.

| Study ID | Author                      | Year | Study Design                  | Study Phase | Country     | Cancer Phenotype                          | Cancer Phenotype, Body | Age (Median) | Age (Range) | Number of Males (%) | C | N  | P  |
|----------|-----------------------------|------|------------------------------|-------------|-------------|------------------------------------------|------------------------|--------------|-------------|----------------------|---|----|-----|
| 29       | Fuchs et al. [57]           | 2019 | Prospective, multicentre     | III         | USA         | Metastatic, HER2-negative gastric or gastroesophageal junction adenocarcinoma | Gastric                | N/A          | N/A         | 645                  | 99 | 15.35 |
| 30       | Ghiasieddin et al. [58]     | 2018 | Prospective, single centre   | II          | USA         | Recurrent, grade 4 malignant glioma       | Brain                  | 52.4         | 32–74       | 60                   | 40 | 3   | 7.50 |
| 31       | Ghiringhelli et al. [59]    | 2012 | Prospective, single centre   | II          | France      | Metastatic colorectal cancer              | Colorectal             | 63           | 25–79       | 53                   | 49 | 1   | 2.04 |
| 32       | Goss et al. [60]            | 2016 | Prospective, multicentre     | II          | Canada      | EGFR Thr790Met-positive advanced non-small-cell lung cancer | Lung                  | 64           | 35–88       | 31                   | 210| 1  | 0.48 |
| 33       | Gronberg et al. [61]        | 2012 | Prospective, multicentre     | II          | Norway      | Brain metastases from lung cancer        | Lung                  | N/A          | N/A         | 107                  | 16 | 14.95 |
| 34       | Guigay et al. [62]          | 2015 | Prospective, multicentre     | II          | France      | Recurrent or metastatic head and neck squamous cell carcinoma | Head and Neck         | N/A          | N/A         | 96.3                  | 54 | 1   | 1.85 |
| 35       | He et al. [63]              | 2020 | Retrospective, single centre | Unspecified | China       | Advanced cervical cancer                  | Cervix                 | N/A          | N/A         | 0                    | 264| 24 | 9.09 |
| 36       | Hirsch et al. [64]          | 2017 | Prospective, multicentre     | II          | USA         | Advanced squamous cell non-small-cell lung cancer | Lung                  | N/A          | N/A         | 109                  | 3  | 2.75 |
| 37       | Honecker et al. [65]        | 2013 | Retrospective, multicentre   | Unspecified | Germany     | Germ cell tumour                          | Germ Cell              | 35           | 18–83       | N/A                  | 193| 4  | 2.07 |
| 38       | Hu et al. [66]              | 2015 | Prospective, single centre   | II          | China       | Advanced non-small-cell lung cancer       | Lung                  | 59.6         | 32–83       | 55.4                  | 56 | 12 | 21.43 |
| 39       | Idelevich et al. [67]       | 2012 | Prospective, single centre   | II          | Israel      | Locally advanced resectable esophageal cancer | Oesophageal            | N/A          | N/A         | 82                   | 28 | 3  | 10.71 |
| 40       | Ikemura et al. [68]         | 2015 | Prospective, single centre   | II          | Japan       | Advanced non-small-cell lung cancer       | Lung                  | 59.5         | 35–74       | 80.6                  | 31 | 1  | 3.23 |
| 41       | Ishida et al. [69]          | 2015 | Prospective, multicentre     | Unspecified | Japan       | Metastatic breast cancer                  | Breast                | 62           | 41–85       | 0                    | 117| 1  | 0.85 |
| 42       | Kakkos et al. [70]          | 2020 | Prospective, multicentre     | Unspecified | Greece      | Various—lung, pancreatic, ovarian, prostate | Mixed                 | N/A          | N/A         | 231                  | 17 | 7.36 |
Table 1. Cont.

| Study ID | Author | Year | Study Design | Study Phase | Country | Cancer Phenotype | Cancer Phenotype, Body | Age (Median) | Age (Range) | Number of Males (%) | C  | N  | P  |
|----------|--------|------|--------------|-------------|---------|-----------------|------------------------|--------------|-------------|---------------------|----|----|----|
| 43       | Karavasilis et al. [71] | 2014 | Prospective, multicentre | II | Greece | Metastatic non-small-cell lung cancer | Lung | 64 | N/A | N/A | 50 | 1  | 2.00 |
| 44       | Kim et al. [72] | 2018 | Prospective, multicentre | Unspecified | USA | Previously treated cutaneous T-cell lymphoma | Lymph | N/A | N/A | N/A | 372 | 7  | 1.88 |
| 45       | Kitayama et al. [73] | 2017 | Prospective, single centre | Unspecified | Japan | Mixed | Mixed | 65 | N/A | 48.5 | 97 | 29 | 29.90 |
| 46       | Konecny et al. [74] | 2015 | Prospective, multicentre | II | USA | Metastatic endometrial cancer | Endometrial | N/A | N/A | 0 | 53 | 9  | 16.98 |
| 47       | Kottschade et al. [75] | 2013 | Prospective, multicentre | II | USA | Unresectable metastatic melanoma | Skin | N/A | N/A | N/A | 93 | 7  | 7.53 |
| 48       | Lang et al. [76] | 2012 | Prospective, multicentre | III | Hungary | Locally recurrent/metastatic breast cancer | Breast | N/A | N/A | 0 | 561 | 8  | 1.43 |
| 49       | Lara et al. [77] | 2016 | Prospective, multicentre | II | USA | Advanced non-small-cell lung cancer | Lung | N/A | N/A | N/A | 59 | 1  | 1.69 |
| 50       | Larsen et al. [78] | 2015 | Prospective, single centre | Unspecified | Denmark | Gastric, esophageal, gastro-oesophageal | Gastric | 64 | 35-84 | 75.2 | 129 | 21 | 16.28 |
| 51       | Lee et al. [79] | 2020 | Prospective, multicentre | II | USA | Recurrent ovarian cancer | Ovary | N/A | 27-79 | 0 | 54 | 5  | 9.26 |
| 52       | Maio et al. [80] | 2017 | Prospective, multicentre | IIb | Italy | Relapsed malignant mesothelioma | Mesothelium | 66 | 60-72 | 74 | 571 | 17 | 2.98 |
| 53       | Makielski et al. [81] | 2015 | Prospective, multicentre | II | USA | Advanced pancreatic cancer | Pancreas | 63 | 48-83 | N/A | 24 | 1  | 4.17 |
| 54       | Matsumoto et al. [82] | 2015 | Prospective, multicentre | II | Japan | Platinum-resistant taxane-pretreated ovarian cancer | Ovary | 58 | 31-75 | 0 | 60 | 1  | 1.67 |
| 55       | Michelsen & Sorensen [83] | 2015 | Prospective, single centre | Unspecified | Denmark | Advanced non-small-cell lung cancer | Lung | N/A | N/A | N/A | 42 | 10 | 23.81 |
| 56       | Mountzios et al. [84] | 2012 | Prospective, multicentre | II | Greece | Chemoresistant relapsed small cell lung cancer | Lung | 64 | 43-82 | 90 | 30 | 1  | 3.33 |
| 57       | Nagane et al. [85] | 2012 | Prospective, single centre | II | Japan | Recurrent malignant glioma | Brain | 54 | 23-72 | 51.6 | 31 | 1  | 3.23 |
### Table 1. Cont.

| Study ID | Author              | Year | Study Design     | Study Phase | Country | Cancer Phenotype, Body | Cancer Phenotype | Age (Median) | Age (Range) | Number of Males (%) | C   | N   | P   |
|----------|---------------------|------|------------------|-------------|---------|------------------------|------------------|--------------|-------------|---------------------|-----|-----|-----|
| 58       | Okines et al. [86]  | 2013 | Prospective, multicentre | II/III      | UK      | Localised gastro-oesophageal adenocarcinoma | Gastric          | 64           | 40–80      | 82                  | 200 | 15 | 7.50 |
| 59       | Ottosson et al. [87]| 2020 | Prospective, multicentre | Unspecified | Sweden  | Muscle-invasive urinary bladder cancer | Bladder          | N/A          | N/A        | 80.6                | 126 | 45 | 35.71 |
| 60       | Peeters et al. [88] | 2013 | Prospective, multicentre | II          | Belgium | Metastatic colorectal cancer | Colorectal       | N/A          | N/A        | N/A                | 144 | 10 | 6.94 |
| 61       | Pitz et al. [89]    | 2015 | Prospective, multicentre | II          | Canada  | Glioblastoma            | Brain            | 56           | 35–78      | 63.6                | 33  | 2  | 6.06 |
| 62       | Powell et al. [90]  | 2013 | Prospective, single centre | II          | USA     | Advanced, refractory non-small-cell lung cancer | Lung             | 62.5         | 36–80      | 42.9                | 42  | 1  | 2.38 |
| 63       | Ramos et al. [91]   | 2017 | Retrospective, multicentre | Unspecified | USA     | Metastatic urothelial carcinoma | Bladder          | N/A          | N/A        | 77.5                | 1762| 144| 8.17 |
| 64       | Reck et al. [92]    | 2014 | Prospective, multicentre | III         | Germany | Non-small-cell lung cancer | Lung             | N/A          | N/A        | N/A                | 1314| 3  | 0.23 |
| 65       | Reyes-Botero et al. [93]| 2018 | Prospective, multicentre | II          | France  | Newly diagnosed glioblastoma | Brain            | 76           | 70–87      | 36                  | 66  | 3  | 4.55 |
| 66       | Rivera et al. [94]  | 2015 | Prospective, multicentre | II          | Spain   | Advanced gastric cancer | Gastric          | 73.3         | 40–87      | 74.41860465          | 43  | 4  | 9.30 |
| 67       | Saad et al. [95]    | 2021 | Prospective, multicentre | III         | Canada  | Metastatic, castration-resistant prostate cancer | Prostate         | N/A          | N/A        | 100                | 982 | 15 | 1.53 |
| 68       | Salinaro et al. [96]| 2020 | Prospective, multicentre | Unspecified | USA     | Advanced epithelial ovarian cancer | Ovary            | 64.8         | 34–84      | 0                   | 230 | 16 | 6.96 |
| 69       | Salles et al. [97]  | 2020 | Prospective, multicentre | II          | France  | Relapsed or refractory diffuse large B-cell lymphoma | Lymph            | 72           | 62–76      | 54                  | 156 | 7  | 4.49 |
| 70       | Seidel et al. [98]  | 2012 | Prospective, multicentre | Unspecified | Germany | Glioma                  | Brain            | N/A          | N/A        | N/A                | 2855| 143| 5.01 |
| 71       | Slagter et al. [99,100]| 2020 | Prospective, multicentre | Unspecified | Netherlands | Gastric cancer | Gastric          | N/A          | N/A        | N/A                | 781 | 78 | 9.99 |
Table 1. Cont.

| Study ID | Author           | Year   | Study Design                  | Study Phase | Country | Cancer Phenotype, Body          | Cancer Phenotype, Age (Median) | Cancer Phenotype, Age (Range) | Number of Males (%) | C   | N  | P  |
|----------|------------------|--------|-------------------------------|-------------|---------|--------------------------------|--------------------------------|--------------------------|---------------------|-----|----|----|
| 72       | Sonpavde et al. [100] | 2012   | Prospective, multicentre      | II          | USA     | Metastatic castration-resistant prostate cancer | Prostate                   | N/A                      | N/A                 | 100 | 220 | 9  | 4.09 |
| 73       | Stevenson et al. [101] | 2012   | Prospective, single centre    | II          | USA     | Advanced, non-squamous non-small-cell lung cancer | Lung                       | 65.3                     | 35-80               | 46  | 40  | 3  | 7.50 |
| 74       | Tahover et al. [102] | 2015   | Prospective, single centre    | Unspecified | Israel  | Metastatic colorectal cancer | Colorectal                   | N/A                      | N/A                 | N/A              | 308 | 20  | 6.49 |
| 75       | Tan et al. [103]   | 2021   | Prospective, multicentre      | III         | USA     | HER2-positive early breast cancer | Breast                      | N/A                      | N/A                 | 0    | 500 | 4  | 0.80 |
| 76       | Tryfonidis et al. [104] | 2013   | Prospective, multicentre      | II          | Greece  | Metastatic breast cancer HER-2 negative | Breast                       | 62                       | 23-75               | 0    | 83  | 1  | 1.20 |
| 77       | Tunio et al. [105] | 2012   | Prospective, single centre    | II          | Pakistan | Metastatic renal cell carcinoma | Renal                        | 51.11                    | 23-73               | 73.8          | 80  | 7  | 8.75 |
| 78       | Uetake et al. [106] | 2015   | Prospective, multicentre      | II          | Japan   | Metastatic colorectal cancer | Colorectal                    | 62.5                     | 39-80               | 58.7          | 45  | 1  | 2.22 |
| 79       | Usmani et al. [107] | 2019   | Prospective, multicentre      | III         | USA     | Multiple myeloma | Blood                       | N/A                      | N/A                 | N/A              | 301 | 2  | 0.66 |
| 80       | Vaishampayan et al. [108] | 2014   | Prospective, single centre    | II          | USA     | Metastatic castrate-resistant prostate cancer | Prostate                     | 67                       | 50-85               | 100           | 31  | 2  | 6.45 |
| 81       | Valle et al. [109] | 2021   | Prospective, multicentre      | II          | UK      | Locally advanced or metastatic biliary tract cancer | Liver                       | N/A                      | N/A                 | N/A              | 309 | 17 | 5.50 |
| 82       | Wolff et al. [110] | 2012   | Prospective, multicentre      | II          | USA     | Metastatic colorectal cancer | Colorectal                   | N/A                      | N/A                 | N/A              | 117 | 10 | 8.55 |
| 83       | Yamazaki et al. [111] | 2016   | Prospective, multicentre      | III         | Japan   | Metastatic colorectal cancer | Colorectal                   | N/A                      | N/A                 | N/A              | 395 | 26 | 6.58 |
| 84       | Yardley et al. [112] | 2012   | Prospective, multicentre      | II          | USA     | Advanced breast cancer | Breast                       | N/A                      | 35-83               | 0              | 83  | 2  | 2.41 |
| 85       | Zalcman et al. [113] | 2016   | Prospective, multicentre      | III         | France  | Newly diagnosed pleural mesothelioma | Mesothelium                  | N/A                      | N/A                 | N/A              | 448 | 15 | 3.35 |
| 86       | Baggstrom et al. [114] | 2017   | Prospective, multicentre      | III         | USA     | Non-small cell lung cancer | Lung                         | 66                       | 25-89               | 56  | 210 | 1  | 0.48 |
| Study ID | Author | Year | Study Design | Study Phase | Country       | Cancer Phenotype                          | Cancer Phenotype, Body | Age (Median) | Age (Range) | Number of Males (%) | C    | N    | P   |
|----------|--------|------|--------------|-------------|---------------|-------------------------------------------|------------------------|--------------|-------------|---------------------|------|------|------|
| 87       | Chavan et al. [115] | 2017 | Retrospective, single-centre | Unspecified | China         | Epithelial ovarian cancer                  | Ovary                  | N/A          | 26–75      | 0                    | 144  | 20   | 13.89 |
| 88       | Duivenvoorden et al. [116] | 2016 | Retrospective, multicentre | Unspecified | USA           | Muscle invasive bladder cancer              | Bladder                | N/A          | 74.8       | 761                  | 106  | 13.93 |
| 89       | Gay et al. [117] | 2010 | Retrospective, multicentre | Unspecified | USA           | Newly diagnosed multiple myeloma            | Blood                  | N/A          | N/A        | 411                  | 49   | 11.92 |
| 90       | Hong et al. [118] | 2012 | Prospective, multicentre | II          | South Korea   | Metastatic colorectal cancer                | Colorectal             | 57           | 31–75      | 51.3                 | 76   | 1    | 1.32 |
| 91       | Kang et al. [118] | 2012 | Retrospective, single-centre | Unspecified | South Korea   | Advanced gastric cancer                     | Gastric                | 57           | 18–88      | 66                    | 3095 | 103  | 3.33 |
| 92       | Li et al. [119] | 2017 | Prospective, multicentre | II          | USA           | Metastatic gastroesophageal adenocarcinoma  | Gastric                | 62           | 27–79      | 79%                   | 39   | 3    | 7.69 |
| 93       | Martella et al. [85] | 2022 | Retrospective, multicentre | Unspecified | Italy         | Newly diagnosed acute myeloid leukaemia     | Blood                  | N/A          | N/A        | 52                    | 222  | 50   | 22.52 |
| 94       | Matikas et al. [120] | 2016 | Prospective, multicentre | IV          | Greece        | Advanced non-small cell lung cancer         | Lung                   | 63           | 38–84      | 74.8                 | 314  | 9    | 2.87 |
| 95       | Monk et al. [121] | 2018 | Prospective, multicentre | II          | USA           | Recurrent or persistent platinum-resistant ovarian, fallopian tube or primary peritoneal cancer | Ovary                  | N/A          | N/A        | 0                    | 56   | 7    | 12.50 |
| 96       | Slavicek et al. [122] | 2014 | Retrospective, multicentre | Unspecified | Czech Republic | Metastatic colorectal cancer                | Colorectal             | N/A          | N/A        | 62.6                  | 3187 | 105  | 3.29 |
| 97       | Tachihara et al. [123] | 2020 | Prospective, multicentre | II          | Japan         | Resected nonsquamous non-small cell lung cancer | Lung                   | 66           | 57–75      | 57.1                 | 21   | 1    | 4.76 |
| 98       | Tewari et al. [124] | 2018 | Prospective, multicentre | III         | USA           | Advanced cervical cancer                    | Cervix                 | N/A          | N/A        | 0                    | 452  | 22   | 4.87 |
| 99       | Yildiz et al. [125] | 2012 | Retrospective, multicentre | Unspecified | Turkey        | Metastatic colorectal cancer                | Colorectal             | 53           | 18–74      | 61.7                  | 332  | 4    | 1.20 |
| 100      | Lee et al. [126] | 2013 | Prospective, multicentre | Unspecified | Taiwan        | Metastatic colorectal cancer                | Colorectal             | 57           | 32–87      | 62.5                  | 40   | 1    | 2.50 |
Table 1. Cont.

| Study ID | Author                  | Year | Study Design               | Study Phase | Country | Cancer Phenotype | Cancer Phenotype, Body | Age (Median) | Age (Range) | Number of Males (%) | C    | N   | P   |
|----------|-------------------------|------|----------------------------|-------------|---------|------------------|------------------------|--------------|-------------|---------------------|------|-----|-----|
| 101      | Reynes et al. [127]     | 2016 | Prospective, multicentre  | II          | UK      | Recurrent glioblastoma | Brain                 | 56           | 42–77      | 70.4                | 27   | 1   | 3.70 |
| 102      | Pinto et al. [128]      | 2021 | Prospective, multicentre  | II          | Italy   | Malignant pleural mesothelioma | Mesothelium | 69           | 44–81      | 74              | 165  | 20  | 12.12|

Abbreviations: C: total number of patients, N: number of venous thromboembolism cases, P = crude prevalence of venous thromboembolism in individual studies, GI: gastrointestinal, VTE: venous thromboembolism, II: phase-two study, III: phase-three study.

Table 2. Prevalence of venous thromboembolism stratified by treatment regimen.

| Study ID | Author                  | Year | Cancer Phenotype, Body | Treatment Agent                                   | C  | N  | P   | Grade 1/2 (n) | Grade 3/4/5 (n) |
|----------|-------------------------|------|------------------------|---------------------------------------------------|----|----|-----|---------------|-----------------|
| 1        | Affronti et al. [29]    | 2018 | Brain                  | Bevacizumab with rilotumumab                      | 36 | 4  | 11.11 | 0             | 4               |
| 2        | Alexander et al. [30]   | 2012 | Brain                  | Thalidomide                                       | 89 | 8  | 8.99  | 0             | 8               |
| 3        | Alvarez et al. [31]     | 2014 | Endometrial            | Bevacizumab + temsirolimus                       | 49 | 1  | 2.04  | 0             | 1               |
| 4        | Assenat et al. [32]     | 2014 | Pancreas               | Nab-paclitaxel/gemcitabine and FOLFIRINOX        | 58 | 18 | 31.03 | 8             | 10              |
| 5        | Assenat et al. [33]     | 2014 | Pancreas               | Gemcitabine, trastuzumab plus erlotinib          | 62 | 22 | 35.48 | 0             | 22              |
| 6        | Bai et al. [34]         | 2015 | Colorectal             | mFOLFOX-6 or XELOX or FOLFIRI with bevacizumab   | 175| 1  | 0.57  | 0             | 1               |
| 7        | Balar et al. [35]       | 2013 | Bladder                | Gemcitabine, carboplatin and bevacizumab         | 51 | 10 | 19.61 | 0             | 10              |
| 8        | Basso et al. [36]       | 2013 | Breast                 | Liposomai doxorubicin                            | 32 | 3  | 9.38  | 2             | 1               |
| 9        | Bear et al. [37]        | 2015 | Breast                 | Various                                           | 1206| 37 | 3.07  | 0             | 37              |
| 10       | Buxo et al. [38]        | 2018 | Head and Neck          | Carboplatin, cetuximab and tegafur              | 104| 1  | 0.96  | 0             | 1               |
| 11       | Campbell et al. [39]    | 2012 | Mesothelium            | Cediranib                                         | 50 | 3  | 6.00  | 0             | 3               |
| 12       | Chekerov et al. [40]    | 2018 | Ovary                  | Sorafenib plus topotecan versus placebo plus topotecan | 174| 10 | 5.75  | 5             | 5               |
| 13       | Chen et al. [41]        | 2015 | Lymph                  | Vorinostat and rituximab                         | 28 | 4  | 14.29 | 0             | 4               |
| 14       | Chibaudel et al. [42]   | 2019 | Colorectal             | Aflibercept with FOLFOX (folic acid, fluorouracil, oxaliplatin) followed by maintenance with fluoropyrimidine | 48 | 1  | 2.08  | 0             | 1               |
| 15       | Ciombor et al. [43]     | 2014 | Liver                  | Bortezomib plus doxorubicin                      | 38 | 1  | 2.63  | 0             | 1               |
| Study ID | Author | Year | Cancer Phenotype, Body | Treatment Agent | C | N | P | Grade 1/2 (n) | Grade 3/4/5 (n) |
|---------|--------|------|------------------------|-----------------|---|---|---|--------------|-----------------|
| 16      | Cremolini et al. [44] | 2020 | Colorectal | mFOLFOX6 and bevacizumab followed by FOLFIRI plus bevacizumab after disease progression, or FOLFOXIRI and bevacizumab, followed by the same regimen after disease progression | 672 | 63 | 9.38 | 32 | 31 |
| 17      | de Vos et al. [45] | 2014 | Lymph | Dacetuzumab | 46 | 3 | 6.52 | 0 | 3 |
| 18      | DeCensi et al. [46] | 2019 | Breast | Tamoxifen | 500 | 2 | 0.40 | 0 | 2 |
| 19      | Deschesnes-Simard et al. [47] | 2021 | Lung | Various immune checkpoint inhibitors including nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, ipilimumab, tremelimumab, and M7824. | 593 | 64 | 10.79 | 0 | 64 |
| 20      | Donskov et al. [48] | 2018 | Renal | Interleukin-2 and interferon-a with or without bevacizumab | 118 | 15 | 12.71 | 0 | 15 |
| 21      | Dowell et al. [49] | 2012 | Mesothelium | Cisplatin, pemetrexed and bevacizumab | 52 | 7 | 13.46 | 0 | 7 |
| 22      | Dummer et al. [50] | 2012 | Lymph | Pegylated liposomal doxorubicin | 49 | 2 | 4.08 | 0 | 2 |
| 23      | Duvic et al. [51] | 2015 | Lymph | Brentuximab Vedotin | 48 | 2 | 4.17 | 0 | 2 |
| 24      | Fehr et al. [52] | 2020 | Oesophageal | Docetaxel and cisplatin, | 300 | 29 | 9.67 | 13 | 16 |
| 25      | Felu et al. [53] | 2014 | Colorectal | Bevacizumab, oxaliplatin and oral capecitabine | 68 | 10 | 14.71 | 3 | 7 |
| 26      | Fleming et al. [54] | 2014 | Endometrial | Tensirolimus plus megestrol acetate/tamoxifen | 71 | 10 | 14.08 | 0 | 10 |
| 27      | Fopprecht et al. [55] | 2016 | Colorectal | mFOLFOX6 with or without afliberecept | 235 | 22 | 9.36 | 1 | 21 |
| 28      | Frizziero et al. [56] | 2019 | Neuroendocrine | Carboplatin and etoposide | 113 | 7 | 6.19 | 0 | 7 |
| 29      | Fuchs et al. [57] | 2019 | Gastric | Cisplatin and capecitabine, and either ramucirumab or placebo | 645 | 99 | 15.35 | 0 | 99 |
| 30      | Ghiaseddin et al. [58] | 2018 | Brain | Bevacizumab and vorinostat | 40 | 3 | 7.50 | 1 | 2 |
| 31      | Ghiringhelli et al. [59] | 2012 | Colorectal | Bevacizumab and FOLFIRI-3 regimen (irinotecan, leucovorin and 5-fluorouracil) | 49 | 1 | 2.04 | 0 | 1 |
| 32      | Goss et al. [60] | 2016 | Lung | Osimertinib | 210 | 1 | 0.48 | 0 | 1 |
| 33      | Gronberg et al. [61] | 2012 | Lung | Enzastaurin | 107 | 16 | 14.95 | 0 | 16 |
| 34      | Guigay et al. [62] | 2015 | Head and Neck | Cetuximab, docetaxel and cisplatin | 54 | 1 | 1.85 | 0 | 1 |
| 35      | He et al. [63] | 2020 | Cervix | Cisplatin and paclitaxel chemotherapy with or without bevacizumab | 264 | 24 | 9.09 | 0 | 24 |
| 36      | Hirsch et al. [64] | 2017 | Lung | Onartuzumab, paclitaxel and carboplatin/cisplatin or placebo plus paclitaxel and carboplatin/cisplatin | 109 | 3 | 2.75 | 0 | 3 |
| Study ID | Author | Year | Cancer Phenotype, Body | Treatment Agent | C   | N   | P   | Grade 1/2 (n) | Grade 3/4/5 (n) |
|----------|--------|------|------------------------|-----------------|-----|-----|-----|---------------|-----------------|
| 37       | Honecker et al. [65] | 2013 | Germ Cell | Cisplatin-based chemotherapy | 193 | 4   | 2.07 | 0             | 4               |
| 38       | Hu et al. [66] | 2015 | Lung | Nab-paclitaxel | 56  | 12  | 21.43 | 4             | 8               |
| 39       | Idelevich et al. [67] | 2012 | Oesophageal | Cisplatin, 5-FU, bevacizumab | 28  | 3   | 10.71 | 0             | 3               |
| 40       | Ikemura et al. [88] | 2015 | Lung | S-1 and irinotecan | 31  | 1   | 3.23  | 0             | 1               |
| 41       | Ishida et al. [69] | 2015 | Breast | Fulvestrant and trastuzumab (if HER2-positive disease) | 117 | 1   | 0.85  | 0             | 1               |
| 42       | Kakkos et al. [70] | 2020 | Mixed | Various | 231 | 17  | 7.36  | 0             | 17              |
| 43       | Karamasiris et al. [71] | 2014 | Lung | Erlotinib and docetaxel | 50  | 1   | 2.00  | 0             | 1               |
| 44       | Kim et al. [72] | 2018 | Lymph | Mogamulizumab or vorinostat | 372 | 7   | 1.88  | 0             | 7               |
| 45       | Kitayama et al. [73] | 2017 | Mixed | Various | 97  | 29  | 29.90 | 0             | 29              |
| 46       | Konecny et al. [74] | 2015 | Endometrial | Dovitinib | 53  | 9   | 16.98 | 3             | 6               |
| 47       | Kortschade et al. [75] | 2013 | Skin | Temozolomide and bevacizumab or nab-paclitaxel, carboplatin and bevacizumab | 93  | 7   | 7.53  | 0             | 7               |
| 48       | Lang et al. [76] | 2012 | Breast | Bevacizumab and capecitabine or paclitaxel | 561 | 8   | 1.43  | 0             | 8               |
| 49       | Lara et al. [77] | 2016 | Lung | Erlotinib or erlotinib plus carboplatin/paclitaxel | 59  | 1   | 1.69  | 0             | 1               |
| 50       | Larsen et al. [78] | 2015 | Gastric | Various | 129 | 21  | 16.28 | 0             | 21              |
| 51       | Lee et al. [79] | 2020 | Ovary | Bevacizumab and sorafenib | 54  | 5   | 9.26  | 0             | 5               |
| 52       | Maio et al. [80] | 2017 | Mesothelioma | Tremelimumab | 571 | 17  | 2.98  | 0             | 17              |
| 53       | Makielski et al. [81] | 2015 | Pancreas | Sorafenib and oxaliplatin and capecitabine | 24  | 1   | 4.17  | 0             | 1               |
| 54       | Matsumoto et al. [82] | 2015 | Ovary | Etoposide plus irinotecan | 60  | 1   | 1.67  | 0             | 1               |
| 55       | Michelsen & Sorensen [83] | 2015 | Lung | Platinum-vinorelbine plus bevacizumab with/without pemetrexed | 42  | 10  | 23.81 | 0             | 10              |
| 56       | Mountzos et al. [84] | 2012 | Lung | Bevacizumab and paclitaxel | 30  | 1   | 3.33  | 0             | 1               |
| 57       | Nagane et al. [85] | 2012 | Brain | Bevacizumab | 31  | 1   | 3.23  | 0             | 1               |
| 58       | Okines et al. [86] | 2013 | Gastric | Epirubicin, cisplatin and capecitabine plus bevacizumab | 200 | 15  | 7.50  | 0             | 15              |
| 59       | Ottosson et al. [87] | 2020 | Bladder | Various | 126 | 45  | 35.71 | 0             | 45              |
| 60       | Peeters et al. [88] | 2013 | Colorectal | Trebananib and FOLFIRI | 144 | 10  | 6.94  | 0             | 10              |
| 61       | Pitz et al. [89] | 2015 | Brain | PX-866 | 33  | 2   | 6.06  | 0             | 2               |
Table 2. Cont.

| Study ID | Author                  | Year | Cancer Phenotype, Body | Treatment Agent                                                                 | C  | N  | P      | Grade 1/2 (n) | Grade 3/4/5 (n) |
|----------|-------------------------|------|------------------------|---------------------------------------------------------------------------------|----|----|--------|---------------|-----------------|
| 62       | Powell et al. [90]      | 2013 | Lung                   | Topotecan                                                                        | 42 | 1  | 2.38   | 0             | 1               |
| 63       | Ramos et al. [91]       | 2017 | Bladder                | Varied                                                                           | 1762 | 144 | 8.17   | 0             | 144             |
| 64       | Reck et al. [92]        | 2014 | Lung                   | Docetaxel plus nintedanib or docetaxel plus placebo                              | 1314 | 3  | 0.23   | 0             | 3               |
| 65       | Reyes-Botero et al. [93]| 2018 | Brain                  | Temozolomide plus bevacizumab                                                   | 66  | 3  | 4.55   | 0             | 3               |
| 66       | Rivera et al. [94]      | 2015 | Gastric                | Reduced dose docetaxel, oxaliplatin and capecitabine                           | 43  | 4  | 9.30   | 0             | 4               |
| 67       | Saad et al. [95]        | 2021 | Prostate               |                                                                                  | 982 | 15 | 1.53   | 0             | 15              |
| 68       | Salinaro et al. [96]    | 2020 | Ovary                  | Neoadjuvant                                                                      | 230 | 16 | 6.96   | 0             | 16              |
| 69       | Salles et al. [97]      | 2020 | Lymph                  | Tafasitamab and lenalidomide                                                   | 156 | 7  | 4.49   | 2             | 5               |
| 70       | Seidel et al. [98]      | 2012 | Brain                  | Bevacizumab                                                                      | 2855 | 143 | 5.01   | 0             | 143             |
| 71       | Slagter et al. [99,100] | 2020 | Gastric                | Epirubicin, cisplatin, oxaliplatin and capetitabine                           | 781 | 78 | 9.99   | 0             | 1               |
| 72       | Sonpavde et al. [100]   | 2012 | Prostate               | Docetaxel plus prednisone with placebo or AT-101                              | 220 | 9  | 4.09   | 0             | 9               |
| 73       | Stevenson et al. [101]  | 2012 | Lung                   | Bevacizumab plus pemetrexed and carboplatin followed by maintenance BVZ        | 40  | 3  | 7.50   | 0             | 3               |
| 74       | Tahover et al. [102]    | 2015 | Colorectal             | Bevacizumab with other chemotherapies                                          | 308 | 20 | 6.49   | 0             | 20              |
| 75       | Tan et al. [103]        | 2021 | Breast                 | Pertuzumab and trastuzumab                                                   | 500 | 4  | 0.80   | 0             | 4               |
| 76       | Tryfonidis et al. [104] | 2013 | Breast                 | Docetaxel, epirubicin and bevacizumab                                         | 83  | 1  | 1.20   | 0             | 1               |
| 77       | Tunio et al. [105]      | 2012 | Renal                  | Thalidomide                                                                      | 80  | 7  | 8.75   | 0             | 7               |
| 78       | Uetake et al. [106]     | 2015 | Colorectal             | mFOLFOX6 + bevacizumab                                                        | 45  | 1  | 2.22   | 0             | 1               |
| 79       | Usmani et al. [107]     | 2019 | Blood                  | Pembrolizumab plus lenalidomide and dexamethasone                             | 301 | 2  | 0.66   | 0             | 2               |
| 80       | Vaishampayan et al. [108]| 2014| Prostate               | Bevacizumab and satraplatin in docetaxel-pretreated                            | 31  | 2  | 6.45   | 0             | 2               |
| 81       | Valle et al. [109]      | 2021 | Liver                  | All patients received intravenous cisplatin 25 mg/m² and gemcitabine 1000 mg/m² on days 1 and 8 in 21-day cycles, for a maximum of eight cycles + additional treatment | 309 | 17 | 5.50   | 0             | 17              |
| 82       | Wolff et al. [110]      | 2012 | Colorectal             | Enzastaurin with 5-FU/leucovorin plus bevacizumab                             | 117 | 10 | 8.55   | 0             | 10              |
| 83       | Yamazaki et al. [111]   | 2016 | Colorectal             | Bevacizumab + FOLFIRI or Bevacizumab + mFOLFOX6                                | 395 | 26 | 6.58   | 0             | 26              |
| 84       | Yardley et al. [112]    | 2012 | Breast                 | Sunitinib                                                                       | 83  | 2  | 2.41   | 0             | 2               |
### Table 2. Cont.

| Study ID | Author                  | Year | Cancer Phenotype, Body | Treatment Agent                                                                 | C   | N   | P     | Grade 1/2 (n) | Grade 3/4/5 (n) |
|----------|-------------------------|------|------------------------|----------------------------------------------------------------------------------|-----|-----|-------|----------------|-----------------|
| 85       | Zalcman et al. [113]    | 2016 | Mesothelium            | Bevacizumab, pemetrexed and cisplatin                                            | 448 | 15  | 3.35  | 0              | 15              |
| 86       | Baggstrom et al. [114]  | 2017 | Lung                   | Sunitinib after platinum-based chemotherapy                                      | 210 | 1   | 0.48  | 0              | 0               |
| 87       | Chavan et al. [115]     | 2017 | Ovary                  | Various                                                                          | 144 | 20  | 13.89 | 0              | 20              |
| 88       | Duivenvoorden et al. [116]| 2016| Bladder                | Various                                                                          | 761 | 106 | 13.93 | 0              | 106             |
| 89       | Gay et al. [117]        | 2012 | Blood                  | Thalidomide or lenalidomide, and dexamethasone                                   | 411 | 49  | 11.92 | 0              | 49              |
| 90       | Hong et al. [118]       | 2012 | Colorectal             | Bevacizumab plus doublet combination chemotherapy                                | 76  | 1   | 1.32  | 0              | 1               |
| 91       | Kang et al. [118]       | 2012 | Gastric                | Various                                                                          | 3095| 103 | 3.33  | 0              | 103             |
| 92       | Li et al. [119]         | 2017 | Gastric                | Modified FOLFOX6                                                                 | 39  | 3   | 7.69  | 0              | 3               |
| 93       | Martella et al. [85]    | 2022 | Blood                  | Various                                                                          | 222 | 50  | 22.52 | 0              | 50              |
| 94       | Matikas et al. [120]    | 2016 | Lung                   | Bevacizumab-containing chemotherapy treatments, in conjunction with paclitaxel/docetaxel/cisplatin/carboplatin | 314 | 9   | 2.87  | 0              | 9               |
| 95       | Monk et al. [121]       | 2018 | Ovary                  | Paclitaxel and elesclomol sodium                                                 | 56  | 7   | 12.50 | 5              | 2               |
| 96       | Slavicek et al. [122]   | 2014 | Colorectal             | Various                                                                          | 3187| 105 | 3.29  | 0              | 105             |
| 97       | Tachihara et al. [123]  | 2020 | Lung                   | Cisplatin-based adjuvant chemotherapy and pemetrexed                             | 21  | 1   | 4.76  | 0              | 1               |
| 98       | Tewari et al. [124]     | 2018 | Cervix                 | Various regimens involving cisplatin/paclitaxel/topotecan/bevacizumab           | 452 | 22  | 4.87  | 0              | 22              |
| 99       | Yildiz et al. [125]     | 2012 | Colorectal             | FOLFIRI and bevacizum                                                            | 332 | 4   | 1.20  | 0              | 4               |
| 100      | Lee et al. [126]        | 2013 | Colorectal             | Bevacizumab and standard chemotherapy combinations                               | 40  | 1   | 2.50  | 0              | 1               |
| 101      | Reynes et al. [127]     | 2016 | Brain                  | Temozolomide and irinotecan                                                      | 27  | 1   | 3.70  | 0              | 1               |
| 102      | Pinto et al. [128]      | 2021 | Mesothelium            | Gemcitabine with/without ramucirumab                                            | 165 | 20  | 12.12 | 15             | 5               |

Abbreviations: GI: gastrointestinal, VTE: venous thromboembolism, C: total number of patients, N: number of venous thromboembolism cases, P = crude prevalence of venous thromboembolism in individual studies.
## Table 3. Study characteristics stratified by frequency, dosage, and duration of treatment regimen.

| Study ID | Author | Year | Treatment Dose | Treatment Duration | Treatment Cycle Frequency |
|----------|--------|------|----------------|--------------------|--------------------------|
| 1        | Affroni et al. [29] | 2018 | Bevacizumab (10 mg/kg IV) and Rilotumumab (20 mg/kg IV) | Bevacizumab (every 2 weeks for up to 12 cycles, with three infusions of Avastin every 2 weeks). Rilotumumab (every 2 weeks following the administration of Avastin for up to 12 cycles. Three infusions of Avastin at 10 mg/kg followed by rilotumumab at 20 mg/kg) | 6 weeks |
| 2        | Alexander et al. [30] | 2012 | Thalidomide (200 mg daily from Day 1 of radiation therapy, increasing by 100-200 to 1200 mg every 1–2 weeks until tumour progression or unacceptable toxicity) | N/R | N/R |
| 3        | Alvarez et al. [31] | 2014 | Bevacizumab (10 mg/kg IV every other week, e.g., day 1 and 15) plus temsirolimus (25 mg IV weekly, e.g., day 1, 8, 15 and 22) or a 4 week cycle | Until disease progression or adverse event prohibits further therapy | 4 weeks |
| 4        | Assenat et al. [32] | 2021a | Patients received AG [IV injection of nab-paclitaxel over 30 min followed by gemcitabine] at day 1, 8 and 15, while FFX was delivered at day 29 and 43 (IV injection of oxaliplatin for 2 h, irinotecan for 90 min and leucovorin for 2 h after 1 h rest, followed by fluorouracil bolus injection and then continuous 46 h infusion). | Median of 4 (1–9) cycles in 8.5 months (0.5–19.8 months) | N/R |
| 5        | Assenat et al. [33] | 2021b | Patients received 1000 mg/m² IV gemcitabine, 30 minutes infusion, on days 1, 8, 15, 22, 29, 36 and 43, during the first 8 weeks of treatment, then on days 1, 8 and 15, 3 weeks out of a 4-week cycle. They also received weekly IV trastuzumab, 4 mg/kg 90 min infusion on Day 1, 2 mg/kg on Days 8 and 15, 30 min infusion, and 100 mg/day erlotinib per os. | Median duration of 16.1 weeks | N/R |
| 6        | Bai et al. [34] | 2015 | mFOLFOX-6 (oxaliplatin 85 mg/m² d1, 5-FU bolus 400 mg/m² d1, 5-FU 2400 mg/m² continuous infusion for 46 h, every 2 weeks), XELOX (oxaliplatin 130 mg/m² d1, capcitabine 2000 mg/m² d1-14 every 3 weeks), or modified FOLFIRI (irinotecan 180 mg/m² d1, 5-FU bolus 400 mg/m² d1, 5FU 2400 mg/m² continuous infusion for 46 h every 2 weeks), in combination with bevacizumab 5 mg/kg every 2 weeks (5-FU-based regimens) or 7.5 mg/kg every 3 weeks (capcitabine-based regimens). | N/R | N/R |
| 7        | Balar et al. [35] | 2013 | Patients initially received bevacizumab 10 mg/kg intravenously (IV) followed 2 weeks later with combination therapy. Gemcitabine 1000 mg/m² on days 1 and 8 and carboplatin IV at area under the [concentration-time] curve (AUC) 5.0 on day 1 were administered every 21 days. Bevacizumab 15 mg/kg IV was administered on day 1 of each 21-day cycle | Median of 6 cycles administered | 3 weeks |
| 8        | Basso et al. [36] | 2013 | PLD was administered at 20 mg/m² every two weeks for a maximum of 12 cycles. | Mean of 7.8 cycles | 2 weeks |
Table 3. Cont.

| Study ID | Author | Year | Treatment Dose | Treatment Duration | Treatment Cycle Frequency |
|----------|--------|------|----------------|--------------------|--------------------------|
|          |        |      | Patients received one of three docetaxel-based neoadjuvant regimens for four cycles: docetaxel alone (100 mg/m²) with addition of capecitabine (825 mg/m²) oral twice daily days 1–14, 75 mg/m² docetaxel) or with addition of gemcitabine (1000 mg/m²) days 1 and 8 intravenously, 75 mg/m² docetaxel, all followed by neoadjuvant doxorubicin and cyclophosphamide (60 mg/m²) and 600 mg/m² intravenously) every 3 weeks for four cycles. Those randomly assigned to bevacizumab groups were to receive bevacizumab (15 mg/kg, every 3 weeks for six cycles) with neoadjuvant chemotherapy and postoperatively for ten doses. | Various | Various |
| 10       | Buxo et al. [38] | 2018 | Carboplatin IV at an area under the curve of 5 mg/mL/min on day 1; cetuximab at an initial dose of 400 mg/m² IV as a 2 h intravenous infusion, followed by 250 mg/m² IV weekly as a 1 h infusion; and oral tegafur 500 mg/m² every 12 h for 21 consecutive days | Median of 4.5 cycles, for 13.5 weeks | N/R |
| 11       | Campbell et al. [39] | 2012 | Administered orally once daily on days 1 through 28 of a 28-day cycle. Cediranib was initially dosed at 45 mg daily, but due to substantial rates of toxicity the protocol was amended in June 2007 to decrease the starting dose to 30 mg daily. | Median of 2 cycles, range 1–14 | N/R |
| 12       | Chekerov et al. [40] | 2018 | Topotecan (1.25 mg/m² on days 1–5) plus either oral sorafenib 400 mg or placebo twice daily on days 6–15 | 6 cycles | 3 weeks |
| 13       | Chen et al. [41] | 2015 | One cycle of therapy consisted of oral vorinostat 200 mg twice daily for 14 days followed by a 7-day break, and intravenous rituximab 375 mg/m² on day 1 of a 21-day cycle. | Median of 11.5 cycles, range 1–69, median duration is 17.8 months | N/R |
| 14       | Chibaudel et al. [42] | 2019 | Modified FOLFOX7 (5-FU/folinic acid and oxaliplatin) with aflibercept at 4 mg/kg every 2 weeks followed by maintenance therapy with fluoropyrimidine with aflibercept until disease progression or limiting toxicity. | 6 cycles | 2 weeks |
|          | Ciombor et al. [43] | 2014 | Bortezomib was administered at a dose of 1.3 mg/m² IV push over 3–5 s on days 1, 4, 8, 11 of a 21-day cycle. Doxorubicin was administered at a dose of 15 mg/m² IV over 5–15 min on days 1, 8 of each 21-day cycle. The first dose of doxorubicin was administered on day 8 of cycle 1 after the first two doses of bortezomib (cycle 1, day 8). On days when both bortezomib and doxorubicin were administered (days 1 and 8), doxorubicin was administered before bortezomib. Patients continued to receive chemotherapy until progression. Doxorubicin discontinued after receiving 12 cycles, regardless of response. | 12 cycles maximum, median 3.8 | 3 weeks |
| Study ID | Author            | Year | Treatment | Treatment Dose                                                                 | Treatment Duration | Treatment Cycle Frequency |
|---------|-------------------|------|-----------|--------------------------------------------------------------------------------|--------------------|--------------------------|
| 16      | Cremolini et al.  | 2020 |           | In the control group, patients received first-line mFOLFOX6 (85 mg/m² of intravenous oxaliplatin concurrently with 200 mg/m² of leucovorin over 120 min; 400 mg/m² intravenous bolus of fluorouracil; 2400 mg/m² continuous infusion of fluorouracil for 48 h) plus bevacizumab (5 mg/kg intravenously over 30 min) followed by FOLFIRI (165 mg/m² of intravenous irinotecan over 60 min; 85 mg/m² intravenous oxaliplatin concurrently with 200 mg/m² of leucovorin; 400 mg/m² intravenous bolus of fluorouracil; 2400 mg/m² continuous infusion of fluorouracil for 48 h) plus bevacizumab after disease progression. In the experimental group, patients received FOLFOXIRI (165 mg/m² of intravenous irinotecan over 60 min; 85 mg/m² intravenous oxaliplatin concurrently with 200 mg/m² of leucovorin over 120 min; 3200 mg/m² continuous infusion of fluorouracil for 48 h) plus bevacizumab followed by the reintroduction of the same regimen after disease progression. | Maximum 8 cycles | 2 weeks |
| 17      | de Vos et al.     | 2014 |           | For Cycle 1, all patients were treated using an intra-patient dose-escalation schedule. 1 mg/kg Day 1, 2 mg/kg Day 4, 4 mg/kg Day 8, 8 thereafter. Subsequent cycles consisted of 4 doses of 8 mg/kg on Days 1, 8, 15, and 22. Patients were treated with 2 cycles after a complete remission (CR) or until disease progression for a maximum of 12 cycles. | up to 12 cycles | 6 weeks |
| 18      | DeCensi et al.    | 2019 |           | 5 mg/daily                                                                      | 3 years            | Daily                    |
| 19      | Deschenes-Simard et al. | 2021 | Various   | IFN 3 MIU subcutaneously (SC) daily and IL2 2.4 MIU/m² twice daily, 5 days per week for two consecutive weeks every 28-day-cycle, for 9 months; or supplemented with BEV 10 mg/kg, every 2 weeks intravenously (IV) until progression, unacceptable toxicity, or 1 year following no evidence of disease (NED) | N/R                | N/R                      |
| 20      | Donskov et al.    | 2018 |           | Previously untreated MM patients with advanced, unresectable disease received cisplatin (75 mg/m²), pemetrexed (500 mg/m²), and bevacizumab (15 mg/kg) intravenously every 21 days for a maximum of 6 cycles. Patients with responsive or stable disease received bevacizumab (15 mg/kg) intravenously every 21 days until progression or intolerance. | 9 months          | 4 weeks                  |
| 21      | Dowell et al.     | 2012 |           | Brenuximab vedotin was administered intravenously at 1.8 mg/kg every 21 days for a maximum of eight doses. Patients with partial or stable response were eligible to receive up to eight additional doses. Patients with complete response could receive two additional doses.Patients with breakthrough lesions could receive 1.2 mg/kg every 2 weeks at the discretion of the principal investigator. | Median of 6 cycles of chemotherapy | 3 weeks |
| 22      | Dummer et al.     | 2012 |           | PD 20 mg/m² on days 1 and 15                                                   | Maximum 6 cycles   | 4 weeks                  |
| 23      | Duvic et al.      | 2015 |           | Maximum 8 cycles                                                              | Maximum 8 cycles | 3 weeks                  |
Table 3. Cont.

| Study ID | Author [Year] | Treatment | Treatment Duration | Treatment Cycle Frequency |
|----------|---------------|-----------|--------------------|--------------------------|
| 24       | Fehr et al. [52] 2020 | Docetaxel 75 mg/m² and cisplatin 75 mg/m² (duration of cycle 3 weeks) | 2 cycles | N/R |
| 25       | Feliu et al. [53] 2014 | Intravenous bevacizumab 7.5 mg kg⁻¹ and oxaliplatin 130 mg m⁻² on day 1 of each cycle, plus oral capecitabine 1000 mg m⁻² twice daily (BID) on days 1–14 of each cycle (patients with a baseline creatinine clearance of 30–50 mL min⁻¹ had a 25% reduction in their initial capecitabine dose to 750 mg/m² BID). Treatment was repeated every 3 weeks for 6 cycles. After 6 cycles, oxaliplatin was discontinued and patients continued to receive bevacizumab and capecitabine following the same regimen until progression or study discontinuation. | Median of 6.8 months, range 0.2–25.2 | 3 weeks |
| 26       | Fleming et al. [54] 2014 | Temsirolimus 25 mg IV weekly plus megestrol acetate 80 mg orally twice a day for 3 weeks alternating with tamoxifen 20 mg orally twice a day for 3 weeks | 3 weeks | Twice a day |
| 27       | Folprecht et al. [55] 2016 | MFOLFOX6 (5 mg/m² oxaliplatin [2 (h) IV]) together with 350 mg/m² leucovorin (2 h IV) followed by 5-FU (400 mg/m² as bolus and 2400 mg/m² IV over 46 h). Patients in the experimental arm received 4 mg/kg aflibercept (1 h IV) before chemotherapy. | The median number of aflibercept cycles was 7.0 (range 1–43). In the mFOLFOX6 and the aflibercept/mFOLFOX6 arms, the median number of oxaliplatin cycles was 10.0 (1–31) and 9.0 (1–40), and the median number of 5-FU cycles was 11.0 (1–43) and 10.0 (1–44), respectively. The median duration of exposure to aflibercept was 17.1 weeks (range 2–94). In the mFOLFOX6 and the aflibercept/mFOLFOX6 arms, the median duration of exposure to oxaliplatin was 23.2 (2–77) and 22.0 (2–84), and to 5-FU was 25.9 (2–95) and 24.1 (2–106) weeks, respectively. | N/R |
| 28       | Frizziero et al. [56] 2019 | CarboEtop-1; etoposide 50 mg twice daily orally from day 1 to day 7 (inclusive) followed by carboplatin area under the curve (AUC) 5, intravenously on day 8, every 28 days; CarboEtop-2; etoposide 120 mg/m² intravenously on days 1, 2, and 3, and carboplatin AUC 5 or 6 intravenously on day 1, every 21 days; CarboEtop-3; etoposide 100 mg/m² intravenously on days 1, 2, and 3, and carboplatin AUC 4 or 5 intravenously on day 1, every 21 days; A higher proportion of patients received intravenous etoposide compared to oral etoposide, both in first-line (54.7% versus 45.3%) and second/third-line (58.8% versus 41.2%). | Median of 3.6 months, range 0.4–9.9 | Various |
| 29       | Fuchs et al. [57] 2019 | Temsirolimus 25 mg IV weekly plus megestrol acetate 80 mg orally twice a day for 3 weeks alternating with tamoxifen 20 mg orally twice a day for 3 weeks | 3 weeks | Twice daily |
| Study ID | Author | Year  | Treatment | Dose | Treatment Duration | Treatment Cycle Frequency |
|---------|--------|-------|-----------|------|-------------------|---------------------------|
| 30      | Ghiaseddin et al. [58] | 2018  | Bevacizumab, 10 mg/kg IV every 2 weeks combined with VOR 400 mg PO daily for 7 days, then 7 days off in a 28-day cycle, vorinostat VOR 400 mg PO daily for 7 days, then 7 days off, in a 28-day cycle | N/R  | 4 weeks            |
| 31      | Ghiringhelli et al. [59] | 2012  | Bevacizumab given at a dose of 5 mg/kg on day 1 every 2 weeks. FOLFIRI-3 regimen was given every 14 days as follows: on day 1, irinotecan 100 mg/m² as a 1 h infusion, running concurrently with leucovorin 200 mg/m² as a 2 h infusion via a Y-connector, followed by 5-FU 2000 mg/m² as a 46 h infusion using an electric pump. On day 3, irinotecan 100 mg/m² as a 1 h infusion was repeated, at the end of 5-FU infusion. | N/R  | 2 weeks            |
| 32      | Goss et al. [60] | 2016  | Osimertinib 80 mg orally once daily | N/R  | Daily              |
| 33      | Gronberg et al. [61] | 2012  | Oral maintenance enzastaurin (1125 mg on Day 1 followed by 500 mg daily) or placebo | N/R  | Daily              |
| 34      | Guigay et al. [62] | 2015  | docetaxel 75 mg/m² IV day 1, cisplatin 75 mg/m² IV day 1, and cetuximab on days 1, 8, and 15 (400 mg/m² IV day 1 of cycle 1 and 250 mg/m² IV weekly on subsequent administrations) | N/R  | 4 weeks            |
| 35      | He et al. [63] | 2020  | Intravenous chemotherapy regimen consisted of cisplatin (at a dose of 50 mg per square metre of body surface area) plus paclitaxel (at a dose of 175 mg/m² on day 1), the intravenous BEV regimen was a dose of 15 mg/kg on day 1 | N/R  | 3 weeks            |
| 36      | Hirsch et al. [64] | 2017  | Carboplatin was applied either as single-agent adjuvant treatment for pure seminoma or combined with etoposide as high-dose first-salvage treatment after cisplatin-based chemotherapy. Cisplatin-based combination chemotherapy consisted of 2 cycles with etoposide and bleomycin (PEB) as adjuvant therapy in nonseminoma or of 3–4 cycles combined with etoposide plus bleomycin (PEB), etoposide plus ifosfamide (VIP), or ifosfamide plus paclitaxel (TIP) for metastatic disease. | N/R  | N/R                |
| 37      | Honecker et al. [65] | 2013  | Nab-paclitaxel 100 mg/m² (IV) on days 1, 8 and 15 of a 28-day cycle | up to 6 cycles | 4 weeks            |
| 38      | Hu et al. [66] | 2015  | Bevacizumab 7.5 mg/kg followed by cisplatin 80 mg/m² infusion on day 1 followed by 5-FU 1000 mg/m² as a 96 h continuous infusion on days 1–4, separated by a 3-week interval. | 4 days per cycle | 3 weeks            |
| 39      | Idelevich et al. [67] | 2012  | Irinotecan was administered at 60 mg/m² on Days 1 and 8. Oral S-1 was administered on Days 1-14 every 3 weeks at 80 mg/day for patients with a body surface area of <1.25 m², 100 mg/day for patients with a body surface area of 1.25–1.5 m² and 120 mg/day for patients with a body surface area of >1.5 m² | N/R  | 3 weeks            |
| Study ID | Author | Year | Treatment | Dose | Treatment Duration | Treatment Cycle Frequency |
|----------|--------|------|-----------|------|--------------------|--------------------------|
| 41       | Ishida et al. [69] | 2015 | fulvestrant | 500 mg as two 5-mL intramuscular injections, one in each buttock, on days 0, 14, and 28 and every 28 days thereafter. | 4 weeks |
| 42       | Kakkos et al. [70] | 2020 | Erlotinib | N/R | N/R |
| 43       | Karavasilis et al. [71] | 2014 | Erlotinib for 12 consecutive days prior to docetaxel (Arm A) or after docetaxel (Arm B). Erlotinib was taken orally at a dose of 150 mg every day for 12 consecutive days and docetaxel was administered intravenously at a dose of 75 mg/m². | N/R | 3 weeks |
| 44       | Kim et al. [72] | 2018 | Mogamulizumab (1 mg/kg intravenously on a weekly basis for the first 28-day cycle, then on days 1 and 15 of subsequent cycles) or vorinostat (400 mg daily) | N/R | 4 weeks |
| 45       | Kitayama et al. [73] | 2017 | Various | N/R | N/R |
| 46       | Konecny et al. [74] | 2015 | Dovitinib | 500 mg per day, orally, on a 5 days-on and 2 days-off schedule | N/R | N/R |
| 47       | Kottschade et al. [75] | 2013 | Temozolomide (200 mg/m² on d. 1–5) and bevacizumab (10 mg/kg IV d. 1 and 15) every 28 days (Regimen temozolomide/bevacizumab [TB]) or nab-paclitaxel (100 mg/m² post addendum 5-secondary to toxicity] days 1, 8 and 15), bevacizumab (10 mg/kg on days 1 and 15), and carboplatin (AUC 6 day 1 [AUC 5 post addendum 5]) every 28 days (Regimen ABC) | N/R | 4 weeks |
| 48       | Lang et al. [76] | 2012 | Arm A: bevacizumab 10 mg/kg days 1 and 15; paclitaxel 90 mg/m² days 1, 8, and 15, every 4 weeks; or Arm B: bevacizumab 15 mg/kg day 1; capcitabine 1000 mg/m² BID, days 1–14, every 3 weeks, until disease progression, unacceptable toxicity or consent withdrawal. | Various | Various |
| 49       | Lara et al. [77] | 2016 | Erlotinib 150 mg orally daily (Arm 1) or erlotinib 150 mg orally daily on days 2–16 plus 4 cycles of carboplatin (AUC 5 day 1) and paclitaxel (200 mg/m² IV day 1), followed by erlotinib 150 mg orally (Arm 2) | N/R | N/R |
| 50       | Larsen et al. [78] | 2015 | Various | N/R | N/R |
| 51       | Lee et al. [79] | 2020 | Bevacizumab (5 mg/kg IV every 2 weeks) was given with sorafenib 200 mg bid 5 days-on/2 days-off. | N/R | N/R |
| 52       | Maio et al. [80] | 2017 | Intravenous tremelimumab (10 mg/kg) or placebo every 4 weeks for 7 doses and every 12 weeks thereafter until a treatment discontinuation criterion was met. | N/R | Various |
| 53       | Makielski et al. [81] | 2015 | Sorafenib 200 mg orally twice daily along with oxaliplatin 85 mg/m² IV on days 1 and 15, followed by capcitabine 2250 mg/m² orally every 8 h for six doses starting on days 1 and 15 of a 28-day cycle | N/R | 4 weeks |
Table 3. Cont.

| Study ID | Author                     | Year | Treatment Dose                                                                 | Treatment Duration | Treatment Cycle Frequency |
|----------|----------------------------|------|---------------------------------------------------------------------------------|-------------------|--------------------------|
| 54       | Matsumoto et al. [82]      | 2015 | Oral etoposide (50 mg/m² once a day) from day 1 to day 21 and IV irinotecan (70 mg/m²) on days 1 and 15 | up to 6 cycles    | 4 weeks                  |
| 55       | Michelsen & Sorensen [83]  | 2015 | Various                                                                        | N/R               | N/R                      |
| 56       | Mountzios et al. [84]      | 2012 | Aclitaxel (90 mg/m², days 1, 8 and 15) along with bevacizumab (10 mg per kg of body weight, days 1 and 15) in cycles of 28 days. | N/R               | 4 weeks                  |
| 57       | Nagane et al. [85]         | 2012 | 10 mg/kg bevacizum as an intravenous infusion administered over 90 (± 15) min on Day 1 of each cycle, which could be reduced to 30 min by Cycle 3 if no infusion reactions occurred. | N/R               | N/R                      |
| 58       | Okines et al. [86]         | 2013 | ECX comprises 3-weekly epirubicin 50 mg/m² and cisplatin 60 mg/m² IV (day 1), with capecitabine 1250 mg/m²/day (divided doses days 1-21), plus bevacizumab 7.5 mg/kg IV (day 1) added in the ECX-B arm. Surgery was scheduled 5 to 6 weeks after the last capecitabine dose of the third cycle and postoperative chemotherapy (three cycles) restarted 6–10 weeks after surgery. ECX-B patients then received six 3-weekly cycles of maintenance bevacizumab 7.5 mg/kg IV. | N/R               | N/R                      |
| 59       | Ottosson et al. [87]       | 2020 | Various                                                                        | N/R               | N/R                      |
| 60       | Peeters et al. [88]        | 2013 | Intravenous trebananib 10 mg kg⁻¹ once weekly (QW) (Arm A) or placebo QW (Arm B) | N/R               | Weekly                   |
| 61       | Pitz et al. [89]           | 2015 | 8 mg daily                                                                      | N/R               | 8 weeks                  |
| 62       | Powell et al. [90]         | 2013 | topotecan (4.0 mg/m²) on days 1, 8, and 15, and bevacizumab (10 mg/kg) on days 1 and 15 as intravenous infusions on a 28-day treatment cycle | N/R               | 4 weeks                  |
| 63       | Ramos et al. [91]          | 2017 | Gemcitabine, cisplatin, nonplatinum regimens, etc.                              | N/R               | N/R                      |
| 64       | Reck et al. [92]           | 2014 | Nintedanib 200 mg orally twice daily or matching placebo on days 2–21          | N/R               | 3 weeks                  |
| 65       | Reyes-Botero et al. [93]   | 2018 | TMZ administered at 130–150 mg/m² per day for 5 days every 4 weeks plus Bev administered at 10 mg/kg every 2 weeks | N/R               | N/R                      |
| 66       | Rivera et al. [94]         | 2015 | “miniDOX” regimen (D: 40 mg/m² IV, day 1; O: 80 mg/m² IV, day 1; C: 625 mg/m² PO BID, day 1 to day 21, every 21 days; after six courses, only C was maintained) | N/R               | 3 weeks                  |
| 67       | Saad et al. [95]           | 2021 | Oral apalutamide 240 mg once daily plus oral abiraterone acetate 1000 mg once daily and oral prednisone 5 mg twice daily (apalutamide plus abiraterone-prednisone group) or placebo plus abiraterone acetate and prednisone (abiraterone-prednisone group) | N/R               | 4 weeks                  |
| 68       | Salinaro et al. [96]       | 2020 | Various                                                                        | N/R               | N/R                      |
| Study ID | Author | Year | Treatment Dose | Treatment Duration | Treatment Cycle Frequency |
|----------|--------|------|----------------|--------------------|--------------------------|
| 69       | Salles et al. [97] | 2020 | Afasitamab was administered intravenously at a dose of 12 mg/kg, over approximately 2 h. For cycles 1–3, tafasitamab was administered weekly on days 1, 8, 15, and 22; an additional loading dose was administered on day 4 of cycle 1. From cycle 4, tafasitamab was administered every 14 days, on days 1 and 15 of each cycle. Patients self-administered lenalidomide capsules orally, starting with 25 mg daily on days 1–21 of each 28-day cycle. A stepwise dose reduction (decrease by 5 mg per day in each step, only once per cycle, without re-escalation) of lenalidomide was done in cases of protocol-defined toxicities. | N/R | 4 weeks |
| 70       | Seidel et al. [98] | 2012 | Bevacizumab 5 mg/kg (n = 12) or 10 mg/kg (n = 34) every 2 weeks until disease progression or treatment-limiting toxicity | N/R | 2 weeks |
| 71       | Slagter et al. [99,100] | 2020 | Epirubicin (50 mg/m² on day 1), cisplatin (60 mg/m² on day 1), or oxaliplatin (130 mg/m² on day 1), and capecitabine (either 1000 mg/m² twice daily on day 1–14 in combination with epirubicin and cisplatin or 625 mg/m² twice daily on day 1–21 in combination with epirubicin and oxaliplatin) (ECC/EOC) | 3 cycles | 3 weeks |
| 72       | Sonpavde et al. [100] | 2012 | Docetaxel (75 mg/m² day 1) and prednisone 5 mg orally twice daily every 21 days with either AT-101 (40 mg) or placebo twice daily orally on days 1–3 | N/R | 3 weeks |
| 73       | Stevenson et al. [101] | 2012 | Bevacizumab 15 mg/kg, pemetrexed 500 mg/m² and carboplatin at an area under the concentration-time curve of 6 intravenously on day 1 every 21 days. Responding or stable patients who completed 6 cycles then received bevacizumab maintenance every 21 days until disease progression. | N/R | 3 weeks |
| 74       | Tahover et al. [102] | 2015 | Bevacizumab was administered in combination with FOLFOX (modified FOLFOX6-oxaliplatin, leucovorin, 5-fluorouracic [5-FU]) in 40.3%, FOLFIRI (leucovorin, 5-FU, irinotecan) in 19.8%, FOLFOX-FOLFIRI/FOLFIRI-FOLFOX in sequence in 24.0%, CapeOx (oxaliplatin, capecitabine) in 6.5%, and 5-FU/LV or capecitabine monotherapy in 9.4%. | N/R | N/R |
| 75       | Tan et al. [103] | 2021 | Intravenous pertuzumab (840 mg loading dose, followed by 420 mg maintenance doses) plus intravenous trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg maintenance doses) or the fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection (1200 mg pertuzumab plus 600 mg trastuzumab loading dose in 15 mL, followed by 600 mg pertuzumab plus 600 mg trastuzumab maintenance doses in 10 mL) | N/R | 3 weeks |
| 76       | Tryfonidis et al. [104] | 2013 | received B (15 mg/kg), E (75 mg/m²) and D (75 mg/m²) with prophylactic G-CSF support every 3 weeks (q3w) for up to 9 cycles followed by B (15 mg/kg q3w) until disease progression | up to 9 cycles | 3 weeks |
### Table 3. Cont.

| Study ID | Author | Year | Treatment Dose | Treatment Duration | Treatment Cycle Frequency |
|----------|--------|------|----------------|--------------------|--------------------------|
| 77       | Tunio et al. [105] | 2012 | Treatment consisted of gemcitabine in a 6 h infusion on days 1 and 8, and cisplatin at 75 mg/m on day 2 of a 3-week cycle. During phase I of the trial, the dose of gemcitabine was escalated from 130 to 170, 210 and 250 mg/m. In phase I of the trial, groups of six, seven, eight and eight patients were treated at the four dose levels of gemcitabine. In phase II, the remaining 32 patients all received gemcitabine at 250 mg/m. | N/R | Daily |
| 78       | Uetake et al. [106] | 2015 | On day 1, bevacizumab (5 mg/kg), levohorinate (200 mg/m²), 5-fluorouracil (5-FU; 400 mg/m²), and oxaliplatin (85 mg/m²) were rapidly injected intravenously, followed by a 46 h continuous intravenous infusion of 5-FU (2400 mg/m²). Each cycle of the treatment steps was repeated every 2 weeks. | N/R | 2 weeks |
| 79       | Usmani et al. [107] | 2019 | Oral lenalidomide 25 mg on days 1–21 and oral dexamethasone 40 mg on days 1, 8, 15, and 22 every 4 weeks, with or without intravenous pembrolizumab 200 mg every 3 weeks | N/R | 4 weeks |
| 80       | Vaishampayan et al. [108] | 2014 | Bevacizumab treatment was administered at 10 mg/kg intravenously on day 1, and 15 mg/kg on day 15, of each 35-day cycle. Premedications were allowed at the treating physician’s discretion. Satraplatin 80 mg/m² was taken orally with fasting for 1 h prior, and 2 h after dosing. Prednisone 5 mg twice daily was taken with meal. | N/R | 35 days |
| 81       | Valle et al. [109] | 2021 | Intravenous ramucirumab 8 mg/kg or placebo (on days 1 and 8 in 21-day cycles) or oral merestinib 80 mg or placebo (once daily) until disease progression, unacceptable toxicity, death, or patient or investigator request for discontinuation. All participants received intravenous cisplatin 25 mg/m² and gemcitabine 1000 mg/m² (on days 1 and 8 in 21-day cycles), for a maximum of eight cycles | Maximum 8 cycles | 3 weeks |
| 82       | Wolff et al. [110] | 2012 | Both arms received LV5FU2 plus bevacizumab (Genentech/Roche, South San Francisco, CA, USA) on day 1 of each cycle (2 weeks): leucovorin 400 mg/m² intravenously (IV), then 5-fluorouracil 400 mg/m² bolus followed by 2400 mg/m² IV over 46 h, and bevacizumab 5 mg/kg IV. | N/R | 2 weeks |
| 83       | Yamazaki et al. [111] | 2016 | Bevacizumab (5 mg/kg) followed by FOLFIRI (irinotecan 150 mg/m²; l-leucovorin 200 mg/m²; intravenous bolus of fluorouracil 400 mg/m², continuous infusion of fluorouracil 2400 mg/m²), or bevacizumab followed by mFOLFOX6 (oxaliplatin 85 mg/m² instead of irinotecan) | N/R | 2 weeks |
| 84       | Yardley et al. [112] | 2012 | Sunitinib monotherapy at a starting dose of 37.5 mg orally on a continuous daily dosing schedule; one treatment cycle was considered to be 4 weeks. | N/R | 4 weeks |
| 85       | Zalcman et al. [113] | 2016 | Intravenously 500 mg/m² pemetrexed plus 75 mg/m² cisplatin with (PCB) or without (PC) 15 mg/kg bevacizumab | Maximum 6 cycles | 3 weeks |
| 86       | Baggstrom et al. [114] | 2017 | Patients received maintenance sunitinib, 37.5 mg/d continuously, or placebo until disease progression or intolerable toxicity. | N/R | N/R |
| Study ID | Author | Year | Treatment Dose | Treatment Duration | Treatment Cycle Frequency |
|---------|--------|------|----------------|--------------------|--------------------------|
| 87      | Chavan et al. [115] | 2017 | Various | Various | Various |
| 88      | Duivenvoorden et al. [116] | 2016 | Various | Various | Various |
| 89      | Gay et al. [117] | 2012 | Thalidomide was given at a dose ranging from 100 mg/day to 400 mg/day continuously; lenalidomide dose was 25 mg/day, days 1 to 21 on a 28-day cycle. All patients received dexamethasone, either at high dose (40 mg orally on days 1–4, 9–12, and 17–20) or at low dose (40 mg orally on days 1, 8, 15, and 22). | N/R | 4 weeks |
| 90      | Hong et al. [118] | 2012 | FOLFOX or FOLFIRI consisted of leucovorin 200 mg/m² on day 1, 5-FU 400 mg/m² bolus infusion on day 1, and 5-FU 2400 mg/m² continuous infusion for 46 h, either with oxaliplatin 85 mg/m² or with irinotecan 150 or 180 mg/m² on day 1, respectively, and repeated every 2 weeks. CapeOX consisted of capecitabine 1000 mg/m² twice daily on days 1–14 and oxaliplatin 130 mg/m² on day 1 and again every 3 weeks. | N/R | N/R |
| 91      | Kang et al. [118] | 2012 | Various | Various | Various |
| 92      | Li et al. [119] | 2017 | mFOLFOX6 (leucovorin 400 mg/m, fluorouracil 400 mg/m bolus and 2400 mg/m continuous infusion over 46 h, oxaliplatin 85 mg/m) and bevacizumab (10 mg/kg) every 2 weeks until disease progression or intolerance. | Median 12 cycles, range 4–86 | 2 weeks |
| 93      | Martella et al. [85] | 2022 | Various | Various | Various |
| 94      | Matikas et al. [120] | 2016 | Various | Various | Various |
| 95      | Monk et al. [121] | 2018 | Paclitaxel 80 mg/m² and elesclomol sodium 200 mg/m² (equivalent of free elesclomol) were administered as two separate 1 h IV infusions weekly × 3 with a one-week rest | Various | weeks |
| 96      | Slavicek et al. [122] | 2014 | Various | Various | Various |
| 97      | Tachihara et al. [123] | 2020 | Adjuvant chemotherapy with four cycles of cisplatin-based treatment (75 mg/m²) plus pemetrexed (500 mg/m²) with vitamin supplementation every three weeks. | N/R | N/R |
| 98      | Tewari et al. [124] | 2018 | Various | Various | Various |
| 99      | Yildiz et al. [125] | 2012 | Various | Various | Various |
| 100     | Lee et al. [126] | 2013 | Eligible patients received bevacizumab (Avastin, Roche Products Ltd.), plus standard 5-fluoropyrimidine (5-FU)-based chemotherapy per physician’s choice (single-agent 5-FU or 5-FU plus oxaliplatin or irinotecan) until disease progression, unacceptable toxicity or death. The bevacizumab dose was fixed at 5 mg/kg every 2 weeks. | Various | Various |
Table 3. Cont.

| Study ID | Author            | Year | Treatment Dose                                                                 | Treatment Duration | Treatment Cycle Frequency |
|----------|-------------------|------|--------------------------------------------------------------------------------|---------------------|---------------------------|
| 101      | Reynes et al. [127] | 2016 | All patients received oral TMZ at a fixed and continuous dose of 50 mg/m$^2$ divided into three daily intakes, except for a single 100 mg/m$^2$ dose, administered between 3 and 6 h before every irinotecan infusion. Irinotecan was given intravenously at the previously established dose of 100 mg/m$^2$ on days 8 and 22 of 28-day cycles. | N/R                | 4 weeks                   |
| 102      | Pinto et al. [128] | 2021 | Patients received intravenous gemcitabine 1000 mg/m$^2$ on days 1 and 8 every 3 weeks, combined with either intravenous ramucirumab 10 mg/kg or matching placebo on day 1 of a 3-week cycle, until progressive disease, unacceptable toxicity, or withdrawal of consent to treatment occurred. | N/R                | 3 weeks                   |

Abbreviations: N/R: not reported; IV: intravenous; SC: subcutaneous; CR: complete remission; NED: no evidence of disease; 5-FU: 5-fluorouracil; PO: medication taken orally; BID: medication taken twice a day; FOLFOX: 5-fluorouracil/leucovorin combined with oxaliplatin; FOLFIRI: 5-fluorouracil/leucovorin combined with irinotecan; TMZ: Temozolomide; CapeOx: oxaliplatin and capecitabine.
Table 4. Pooled and crude prevalence of venous thromboembolism across various cancer phenotypes.

| Cancer Phenotype | Number of Studies (N) | Total Number of Patients (n) | Crude Prevalence Rate | Pooled Prevalence Rate (Derived from Meta-Analysis) | 95% CI | z-Score | p-Value |
|------------------|-----------------------|----------------------------|-----------------------|---------------------------------------------------|--------|---------|---------|
| Overall          | 102                   | 30671                      | 5.78%                 | 6%                                                | 0.06–0.07 | 18.53   | <0.001  |

**Cancer Phenotype**

| Cancer Phenotype | Number of Studies (N) | Total Number of Patients (n) | Crude Prevalence Rate | Pooled Prevalence Rate (Derived from Meta-Analysis) | 95% CI | z-Score | p-Value |
|------------------|-----------------------|----------------------------|-----------------------|---------------------------------------------------|--------|---------|---------|
| Bladder          | 4                     | 2700                       | 11.30%                | 18%                                                | 0.10–0.28 | 6.53   | <0.001  |
| Blood            | 3                     | 934                        | 10.81%                | N/A                                               | N/A     | N/A     | N/A     |
| Brain            | 8                     | 3177                       | 5.19%                 | 4%                                                | 0.04–0.05 | 17.72  | <0.001  |
| Breast           | 8                     | 3082                       | 1.88%                 | 1%                                                | 0.00–0.03 | 4.17   | <0.001  |
| Cervical         | 2                     | 716                        | 6.42%                 | N/A                                               | N/A     | N/A     | N/A     |
| Colorectal       | 15                    | 5891                       | 4.69%                 | 5%                                                | 0.03–0.07 | 8.16   | <0.001  |
| Endometrial      | 3                     | 173                        | 11.56%                | N/A                                               | N/A     | N/A     | N/A     |
| Gastric          | 7                     | 4932                       | 6.55%                 | 9%                                                | 0.05–0.15 | 5.89   | <0.001  |
| Germ Cell        | 1                     | 193                        | 2.07%                 | N/A                                               | N/A     | N/A     | N/A     |
| Head and Neck    | 2                     | 158                        | 1.27%                 | N/A                                               | N/A     | N/A     | N/A     |
| Liver            | 2                     | 347                        | 5.19%                 | N/A                                               | N/A     | N/A     | N/A     |
| Lung             | 16                    | 3228                       | 3.97%                 | 5%                                                | 0.02–0.09 | 4.32  | <0.001  |
| Lymph            | 6                     | 699                        | 3.58%                 | 4%                                                | 0.02–0.07 | 4.69   | 0.05    |
| Mesothelial      | 5                     | 1286                       | 4.82%                 | 6%                                                | 0.03–0.11 | 5.24   | <0.001  |
| Mixed            | 2                     | 328                        | 14%                   | N/A                                               | N/A     | N/A     | N/A     |
| Neuroendocrine   | 1                     | 113                        | 6.19%                 | N/A                                               | N/A     | N/A     | N/A     |
| Oesophageal      | 2                     | 328                        | 9.76%                 | N/A                                               | N/A     | N/A     | N/A     |
| Ovarian          | 6                     | 718                        | 8.22%                 | 8%                                                | 0.05–0.12 | 7.47   | 0.02    |
| Pancreatic       | 3                     | 144                        | 28.47%                | N/A                                               | N/A     | N/A     | N/A     |
| Prostate         | 3                     | 1233                       | 2.11%                 | N/A                                               | N/A     | N/A     | N/A     |
| Renal            | 2                     | 198                        | 11.11%                | N/A                                               | N/A     | N/A     | N/A     |
| Skin             | 1                     | 93                         | 7.53%                 | N/A                                               | N/A     | N/A     | N/A     |

Abbreviations: CI: confidence interval, N: number of studies, n: number of patients. Note: N/A = could not be generated as meta-analysis could not be performed due to limited number of studies (minimum of four studies required).

5.2. Overall Prevalence of VTE in Cancer Patients Undergoing Chemotherapy

One hundred and two included studies, encompassing 30,671 patients, reported on the prevalence of VTE in cancer patients receiving chemotherapy only. The meta-analysis revealed a pooled estimated prevalence of 6%, ranging from 6% to 7% (ES 6%; 95% CI 6–7%; z = 18.53; p < 0.001) (Table 4 and Figure 2). Notably, there was considerable heterogeneity between the included studies ($I^2 = 91.84%$, $p < 0.001$). The estimate of between-study variance ($\tau^2$) was 0.04. The estimated pooled prevalence of VTE in cancer patients undergoing chemotherapy was higher than the crude prevalence rates of 5.78% observed in this study. The heterogeneity chi$^2$ was 1237.89 ($p < 0.001$, d.f. = 101). Figure 3 provides findings of the overall meta-analysis on the pooled estimated prevalence stratified by cancer phenotype.
## Proportion of VTE in cancer patients undergoing chemotherapy

| StudyID | Author            | Year | N  | C  | P  | ES (95% CI) |
|---------|-------------------|------|----|----|----|-------------|
| 2       | Alexander et al.  | 2012 | 8  | 89 | 8.98 | 0.09 (0.04, 0.17) |
| 11      | Campbell et al.   | 2012 | 3  | 50 | 6   | 0.06 (0.01, 0.17) |
| 21      | Dowell et al.     | 2012 | 7  | 52 | 13.46 | 0.13 (0.06, 0.26) |
| 22      | Dummer et al.     | 2012 | 2  | 49 | 4.08 | 0.04 (0.00, 0.14) |
| 89      | Gay et al.        | 2012 | 49 | 411| 11.92 | 0.12 (0.09, 0.15) |
| 31      | Ghiringhelli et al.| 2012 | 1  | 49 | 2.04 | 0.02 (0.00, 0.11) |
| 33      | Gronberg et al.   | 2012 | 16 | 107| 14.95 | 0.15 (0.09, 0.23) |
| 90      | Hong et al.       | 2012 | 1  | 76 | 1.31 | 0.01 (0.00, 0.07) |
| 39      | Idelevich et al.  | 2012 | 3  | 28 | 10.71 | 0.11 (0.02, 0.28) |
| 91      | Kang et al.       | 2012 | 103| 3095| 3.32 | 0.03 (0.03, 0.04) |
| 48      | Lang et al.       | 2012 | 8  | 561| 1.42 | 0.01 (0.01, 0.03) |
| 56      | Mountzios et al.  | 2012 | 1  | 30 | 3.33 | 0.03 (0.00, 0.17) |
| 57      | Nagane et al.     | 2012 | 1  | 31 | 3.22 | 0.03 (0.00, 0.17) |
| 70      | Seidel et al.     | 2012 | 143| 2855| 5  | 0.05 (0.04, 0.06) |
| 72      | Sonpavde et al.   | 2012 | 9  | 220| 4.09 | 0.04 (0.02, 0.08) |
| 73      | Stevenson et al.  | 2012 | 3  | 40 | 7.5  | 0.08 (0.02, 0.20) |
| 77      | Tunio et al.      | 2012 | 7  | 80 | 6.75 | 0.09 (0.04, 0.17) |
| 82      | Wolff et al.      | 2012 | 10 | 117| 8.54 | 0.09 (0.04, 0.15) |
| 84      | Yardley et al.    | 2012 | 2  | 83 | 2.4  | 0.02 (0.00, 0.08) |
| 99      | Yildiz et al.     | 2012 | 4  | 332| 1.2  | 0.01 (0.00, 0.03) |
| 7       | Balar et al.      | 2013 | 10 | 51 | 19.6 | 0.20 (0.10, 0.33) |
| 8       | Basso et al.      | 2013 | 3  | 32 | 9.37 | 0.09 (0.02, 0.25) |
| 37      | Honecker et al.   | 2013 | 4  | 193| 2.07 | 0.02 (0.01, 0.05) |
| 47      | Kottschade et al. | 2013 | 7  | 93 | 7.52 | 0.08 (0.03, 0.15) |
| 100     | Lee et al.        | 2013 | 1  | 40 | 2.5  | 0.03 (0.00, 0.13) |
| 58      | Okines et al.     | 2013 | 15 | 200| 7.5  | 0.08 (0.04, 0.12) |
| 60      | Peeters et al.    | 2013 | 10 | 144| 6.94 | 0.07 (0.03, 0.12) |
| 62      | Powell et al.     | 2013 | 1  | 42 | 2.38 | 0.02 (0.00, 0.13) |
| 76      | Tryfonidis et al. | 2013 | 1  | 83 | 1.2  | 0.01 (0.00, 0.07) |
| 3       | Alvarez et al.    | 2014 | 1  | 49 | 2.04 | 0.02 (0.00, 0.11) |
| 15      | Ciombor et al.    | 2014 | 1  | 38 | 2.63 | 0.03 (0.00, 0.14) |
| 25      | Feliu et al.      | 2014 | 10 | 68 | 14.7 | 0.15 (0.07, 0.25) |
| 26      | Fleming et al.    | 2014 | 3  | 50 | 6    | 0.06 (0.01, 0.17) |

*Figure 2. Cont.*
Figure 2. Cont.
Figure 2. Forest plot showing the estimated overall pooled prevalence of VTE in cancer patients undergoing chemotherapy [29–128]. Abbreviations: VTE: venous thromboembolism.
### Proportion of VTE in cancer patients undergoing chemotherapy

| StudyID | Author                  | Year | N   | C   | P   | ES (95% CI) |
|---------|-------------------------|------|-----|-----|-----|-------------|
|         | **Brain**               |      |     |     |     |             |
| 2       | Alexander et al.        | 2012 | 6   | 88  | 8.98| 6.00 (0.40, 0.17) |
| 57      | Nago et al.             | 2012 | 1   | 31  | 3.22| 6.03 (0.00, 0.17) |
| 70      | Swietel et al.          | 2012 | 143 | 2655 | 5  | 6.00 (0.04, 0.08) |
| 61      | Fix et al.              | 2015 | 2   | 53  | 8.06| 6.06 (0.51, 0.39) |
| 101     | Rayner et al.           | 2015 | 1   | 27  | 3.7 | 6.04 (0.00, 0.19) |
| 1       | Affandi et al.          | 2018 | 4   | 56  | 11.11| 6.11 (0.09, 0.96) |
| 39      | Dhesodin et al.         | 2018 | 3   | 46  | 7.5 | 6.08 (0.02, 0.30) |
| 65      | Reyes-Rivero et al.     | 2018 | 3   | 66  | 4.54| 6.05 (0.01, 0.13) |
| **Subtotal (I² = 0.00%, p = 0.56)** |      |     |     |     |     | 6.04 (0.04, 0.05) |
|         | **Endometrial**         |      |     |     |     |             |
| 3       | Alvarez et al.          | 2014 | 1   | 49  | 2.04| 6.02 (0.00, 0.11) |
| 26      | Flerring et al.         | 2014 | 3   | 50  | 6   | 6.06 (0.01, 0.17) |
| 46      | Korecny et al.          | 2015 | 9   | 53  | 15.98| 6.17 (0.08, 0.38) |
| **Subtotal (I² = 0.0%, p = .)** |      |     |     |     |     | 6.07 (0.01, 0.18) |
|         | **Pancreas**            |      |     |     |     |             |
| 53      | Makelisky et al.        | 2015 | 1   | 24  | 4.16| 6.04 (0.00, 0.21) |
| 4       | Asselan et al.          | 2014 | 18  | 56  | 31.63| 6.31 (0.05, 0.54) |
| 5       | Asselan et al.          | 2014 | 22  | 62  | 36.48| 6.36 (0.04, 0.49) |
| **Subtotal (I² = 0.0%, p = .)** |      |     |     |     |     | 6.03 (0.08, 0.43) |
|         | **Colorectal**          |      |     |     |     |             |
| 31      | Ghiringhelli et al.     | 2012 | 1   | 49  | 2.04| 6.02 (0.00, 0.11) |
| 90      | Hong et al.             | 2012 | 1   | 76  | 1.21| 6.07 (0.00, 0.07) |
| 82      | Wolff et al.            | 2012 | 16  | 117 | 8.94| 6.09 (0.04, 0.15) |
| 99      | Yildiz et al.           | 2012 | 4   | 332 | 1.2 | 6.01 (0.00, 0.03) |
| 100     | Lee et al.              | 2013 | 1   | 40  | 2.5 | 6.03 (0.01, 0.13) |
| 69      | Peeters et al.          | 2013 | 16  | 144 | 6.84| 6.07 (0.03, 0.12) |
| 25      | Fellu et al.            | 2014 | 16  | 68  | 14.7| 6.15 (0.07, 0.25) |
| 96      | Stalovets et al.        | 2014 | 165 | 3187 | 3.29 | 6.03 (0.02, 0.04) |
| 6       | Bai et al.              | 2015 | 1   | 175 | 57  | 6.01 (0.00, 0.03) |
| 74      | Tahovet et al.          | 2015 | 26  | 508 | 6.49| 6.06 (0.04, 0.10) |
| 78      | Uetake et al.           | 2015 | 1   | 45  | 2.22| 6.02 (0.00, 0.12) |
| 27      | Foldre et al.           | 2016 | 22  | 231 | 9.36| 6.09 (0.00, 0.14) |
| 83      | Yamazaki et al.         | 2016 | 26  | 395 | 6.98| 6.07 (0.04, 0.09) |
| 14      | Chiboulet et al.        | 2019 | 1   | 48  | 2.08| 6.02 (0.05, 0.11) |
| 16      | Demoliti et al.         | 2022 | 62  | 672 | 9.57| 6.09 (0.07, 0.12) |
| **Subtotal (I² = 66.36%, p = 0.00)** |      |     |     |     |     | 6.13 (0.03, 0.07) |
|         | **Bladder**             |      |     |     |     |             |
| 7       | Bark et al.             | 2013 | 16  | 51  | 19.6| 6.20 (0.10, 0.33) |
| 88      | Duivensvoden et al.     | 2016 | 165 | 761 | 13.92| 6.14 (0.12, 0.17) |
| 63      | Ramos et al.            | 2017 | 144 | 1792| 8.17| 6.08 (0.07, 0.10) |
| 59      | Ottonen et al.          | 2020 | 45  | 125 | 35.71| 6.36 (0.27, 0.45) |
| **Subtotal (I² = 56.86%, p = 0.00)** |      |     |     |     |     | 6.18 (0.10, 0.28) |

**Figure 3. Cont.**
| Study (Year, Authors) | Year | Study Type | Mean | SD | p-value |
|----------------------|------|------------|------|----|---------|
| Breed | 48 | Lang et al. | 2012 | 8 | 561 | 1.42 | 0.01 (0.01, 0.03) |
| | 84 | Yardley et al. | 2012 | 2 | 83 | 2.4 | 0.02 (0.00, 0.03) |
| | 6 | Bassi et al. | 2013 | 3 | 32 | 9.37 | 0.09 (0.02, 0.25) |
| | 70 | Tryfonidou et al. | 2013 | 1 | 83 | 1.2 | 0.01 (0.00, 0.07) |
| | 9 | Bear et al. | 2015 | 37 | 1209 | 3.06 | 0.03 (0.02, 0.04) |
| | 41 | Ishida et al. | 2015 | 1 | 117 | .95 | 0.01 (0.00, 0.05) |
| | 18 | DeCensi et al. | 2019 | 1 | 253 | .39 | 0.00 (0.00, 0.02) |
| | 76 | Tan et al. | 2021 | 4 | 500 | .8 | 0.01 (0.00, 0.02) |
| Subtotal (I² = 86.76%, p = 0.00) | | | | | 0.01 (0.01, 0.03) |
| Head and Neck | 34 | Guigay et al. | 2015 | 1 | 54 | 1.85 | 0.02 (0.00, 0.10) |
| | 10 | Boku et al. | 2018 | 1 | 104 | .96 | 0.01 (0.00, 0.05) |
| Subtotal (I² = %, p = .) | | | | | 0.01 (0.00, 0.04) |
| Mesothelium | 11 | Campbell et al. | 2012 | 3 | 50 | 6 | 0.06 (0.01, 0.17) |
| | 21 | Dowell et al. | 2012 | 7 | 52 | 13.46 | 0.13 (0.06, 0.26) |
| | 85 | Zelcerman et al. | 2016 | 15 | 448 | 3.34 | 0.03 (0.02, 0.05) |
| | 52 | Makio et al. | 2017 | 14 | 382 | 3.66 | 0.04 (0.02, 0.08) |
| | 102 | Pinto et al. | 2021 | 20 | 165 | 12.12 | 0.12 (0.08, 0.18) |
| Subtotal (I² = 81.37%, p = 0.00) | | | | | 0.07 (0.03, 0.11) |
| Ovary | 54 | Matsumoto et al. | 2015 | 1 | 60 | 1.66 | 0.02 (0.00, 0.09) |
| | 67 | Chavarrí et al. | 2017 | 20 | 144 | 13.88 | 0.14 (0.08, 0.21) |
| | 12 | Chetkov et al. | 2018 | 10 | 174 | 5.74 | 0.06 (0.03, 0.10) |
| | 95 | Morik et al. | 2018 | 7 | 58 | 12.5 | 0.12 (0.05, 0.24) |
| | 51 | Lee et al. | 2020 | 5 | 54 | 9.25 | 0.09 (0.03, 0.20) |
| | 69 | Sakinara et al. | 2020 | 16 | 230 | 6.95 | 0.07 (0.04, 0.11) |
| Subtotal (I² = 61.47%, p = 0.02) | | | | | 0.08 (0.05, 0.12) |
| Lymph | 22 | Dummar et al. | 2012 | 2 | 49 | 4.06 | 0.04 (0.00, 0.14) |
| | 17 | de Vos et al. | 2014 | 3 | 48 | 6.52 | 0.07 (0.01, 0.18) |
| | 13 | Chen et al. | 2015 | 4 | 28 | 14.28 | 0.14 (0.04, 0.33) |
| | 23 | DukÁ et al. | 2015 | 2 | 48 | 4.16 | 0.04 (0.01, 0.14) |
| | 44 | Kim et al. | 2018 | 7 | 372 | 1.88 | 0.02 (0.01, 0.04) |
| | 69 | Selle et al. | 2020 | 7 | 156 | 4.48 | 0.04 (0.02, 0.09) |
| Subtotal (I² = 54.86%, p = 0.05) | | | | | 0.04 (0.02, 0.07) |
| Liver | 15 | Cimbro et al. | 2014 | 1 | 38 | 2.63 | 0.03 (0.00, 0.14) |
| | 81 | Velle et al. | 2021 | 17 | 309 | 5.5 | 0.06 (0.03, 0.09) |
| Subtotal (I² = %, p = .) | | | | | 0.05 (0.03, 0.07) |
| Lung | 33 | Gronberg et al. | 2012 | 16 | 107 | 14.95 | 0.15 (0.08, 0.23) |
| | 56 | Mountzios et al. | 2012 | 1 | 30 | 3.33 | 0.03 (0.00, 0.17) |
| | 73 | Stevenson et al. | 2012 | 3 | 40 | 7.5 | 0.08 (0.02, 0.20) |
| | 62 | Powell et al. | 2013 | 1 | 42 | 2.38 | 0.02 (0.00, 0.13) |
| | 43 | Karavastis et al. | 2014 | 1 | 50 | 2 | 0.02 (0.01, 0.11) |
| | 64 | Reck et al. | 2014 | 3 | 1214 | 32 | 0.00 (0.00, 0.01) |
| | 58 | Hu et al. | 2015 | 12 | 56 | 21.43 | 0.21 (0.12, 0.34) |
| | 40 | Ikenura et al. | 2015 | 1 | 31 | 3.22 | 0.03 (0.00, 0.17) |
| | 55 | Michelsen & Sorensen | 2015 | 10 | 42 | 23.8 | 0.24 (0.12, 0.39) |
| | 32 | Goss et al. | 2016 | 1 | 210 | 47 | 0.00 (0.00, 0.03) |
| | 49 | Lara et al. | 2016 | 1 | 50 | 1.69 | 0.02 (0.00, 0.09) |
| | 94 | Matkias et al. | 2016 | 9 | 314 | 2.86 | 0.03 (0.01, 0.05) |
| | 86 | Bugnion et al. | 2017 | 1 | 210 | 47 | 0.00 (0.00, 0.03) |
| | 56 | Hirsh et al. | 2017 | 3 | 109 | 2.75 | 0.03 (0.01, 0.06) |
| | 97 | Tacchini et al. | 2020 | 1 | 21 | 4.76 | 0.05 (0.00, 0.02) |
| | 19 | DeSouza-Simard | 2021 | 64 | 593 | 10.79 | 0.11 (0.06, 0.14) |
| Subtotal (I² = 93.22%, p = 0.00) | | | | | 0.05 (0.02, 0.09) |

Figure 3. Cont.
Figure 3. Forest plot showing the estimated pooled prevalence of VTE in cancer patients stratified by cancer phenotype [29–128]. Abbreviations: VTE: venous thromboembolism.
5.3. Prevalence of VTE in Cancer Patients Stratified by Cancer Phenotype

5.3.1. Prevalence of VTE in Bladder Cancer Patients

Four included studies encompassing 2700 patients reported on the prevalence of VTE in bladder cancer patients undergoing chemotherapy [35,87,91,116]. The meta-analysis revealed a pooled estimated prevalence of 18%, ranging from 10% to 28% (ES 18%; 95% CI 10–28%; z = 6.53; p < 0.001) (Table 4 and Supplemental SI Figure S1). Notably, there was considerable heterogeneity between the included studies (I² = 95.85%, p < 0.001). The estimate of between-study variance (τ²) was 0.05. The estimated pooled prevalence of VTE in blood cancer patients (18%) was higher than the crude prevalence rate of 11.30% observed in this study. The heterogeneity chi² was 72.22 (p < 0.001, d.f. = 3).

5.3.2. Prevalence of VTE in Blood Cancer Patients

Three included studies, encompassing 934 patients, reported on the prevalence of VTE in blood cancer patients [85,107,117]. However, a meta-analysis could not be performed due to insufficient number of studies. The crude prevalence rate of VTE in blood cancer patients was 10.81% (Table 4).

5.3.3. Prevalence of VTE in Brain Cancer Patients

Eight included studies encompassing 3177 patients reported on the prevalence of VTE in brain cancer patients undergoing chemotherapy [29,30,58,89,93,98,127,129]. The meta-analysis revealed a pooled estimated prevalence of 4%, ranging from 4 to 5% (ES 4%; 95% CI 4–5%; z = 17.72; p < 0.001) (Table 4 and Supplemental SI Figure S2). Notably, there was low heterogeneity between the included studies (I² = 0.00%, p = 0.56). The estimate of between-study variance (τ²) was 0.00. The estimated pooled prevalence of VTE in brain cancer patients (4%) was lower than the crude prevalence rate of 5.19% observed in this study. The heterogeneity chi² was 72.22 (p = 0.56, d.f. = 3).

5.3.4. Prevalence of VTE in Breast Cancer Patients

Eight included studies encompassing 3082 patients reported on the prevalence of VTE in breast cancer patients undergoing chemotherapy [36,37,46,69,76,103,104,112]. The meta-analysis revealed a pooled estimated prevalence of 1%, ranging from 0% to 3% (ES 1%; 95% CI 0–3%; z = 4.17; p < 0.001) (Table 4 and Supplemental SI Figure S3). Notably, there was substantial heterogeneity between the included studies (I² = 73.31%, p < 0.001). The estimate of between-study variance (τ²) was 0.01. The estimated pooled prevalence of VTE in breast cancer patients (1%) was lower than the crude prevalence rate of 1.88% observed in this study. The heterogeneity chi² was 26.23 (p < 0.001, d.f. = 7).

5.3.5. Prevalence of VTE in Cervical Cancer Patients

Two included studies, encompassing 716 patients, reported on the prevalence of VTE in cervical cancer patients [63,124]. However, a meta-analysis could not be performed due to insufficient number of studies. The crude prevalence rate of VTE in cervical cancer patients was 6.42% (Table 4).

5.3.6. Prevalence of VTE in Colorectal Cancer Patients

Fifteen included studies encompassing 5891 patients reported on the prevalence of VTE in colorectal cancer patients undergoing chemotherapy [34,42,44,53,55,59,88,102,106,110,111,118,122,125,126]. The meta-analysis revealed a pooled estimated prevalence of 5%, ranging from 3 to 7% (ES 5%; 95% CI 3–7%; z = 8.16; p < 0.001) (Table 4 and Supplemental SI Figure S4). Notably, there was substantial heterogeneity between the included studies (I² = 85.28%, p < 0.001). The estimate of between-study variance (τ²) was 0.02. The estimated pooled prevalence of VTE in colorectal cancer patients (5%) was higher than the crude prevalence rate of 4.69% observed in this study. The heterogeneity chi² was 95.10 (p < 0.001, d.f. = 14).
5.3.7. Prevalence of VTE in Endometrial Cancer Patients

Three included studies, encompassing 173 patients, reported on the prevalence of VTE in endometrial cancer patients [31,54,74]. However, a meta-analysis could not be performed due to insufficient number of studies. The crude prevalence rate of VTE in endometrial cancer patients was 11.56% (Table 4).

5.3.8. Prevalence of VTE in Gastric Cancer Patients

Seven included studies encompassing 4932 patients reported on the prevalence of VTE in gastric cancer patients undergoing chemotherapy [57,78,86,94,99,119,130]. The meta-analysis revealed a pooled estimated prevalence of 9%, ranging from 5% to 15% (ES 9%; 95% CI 5–15%; z = 5.89; p < 0.001) (Table 4 and Supplemental SI Figure S5). Notably, there was considerable heterogeneity between the included studies (I² = 95.94%, p < 0.001). The estimate of between-study variance (τ²) was 0.05. The estimated pooled prevalence of VTE in gastric cancer patients (9%) was higher than the crude prevalence rate of 6.55% observed in this study. The heterogeneity chi² was 147.92 (p < 0.001, d.f. = 6).

5.3.9. Prevalence of VTE in Germ Cell Cancer Patients

One included study, encompassing 193 patients, reported on the prevalence of VTE in endometrial cancer patients [65]. However, a meta-analysis could not be performed due to insufficient number of studies. The crude prevalence rate of VTE in germ cell cancer patients was 2.07% (Table 4).

5.3.10. Prevalence of VTE in Head and Neck Cancer Patients

Two included studies, encompassing 158 patients, reported on the prevalence of VTE in head and neck cancer patients [38,62]. However, a meta-analysis could not be performed due to insufficient number of studies. The crude prevalence rate of VTE in head and neck cancer patients was 1.27% (Table 4).

5.3.11. Prevalence of VTE in Liver Cancer Patients

Two included studies, encompassing 347 patients, reported on the prevalence of VTE in liver cancer patients [43,109]. However, a meta-analysis could not be performed due to insufficient number of studies. The crude prevalence rate of VTE in liver cancer patients was 5.19% (Table 4).

5.3.12. Prevalence of VTE in Lung Cancer Patients

Sixteen included studies encompassing 3228 patients reported on the prevalence of VTE in lung cancer patients undergoing chemotherapy [47,60,61,64,68,71,77,83,84,90,92,101,114,120,123]. The meta-analysis revealed a pooled estimated prevalence of 5%, ranging from 2 to 9% (ES 5%; 95% CI 2–9%; z = 4.32; p < 0.001) (Table 4 and Supplemental SI Figure S6). Notably, there was considerable heterogeneity between the included studies (I² = 93.22%, p < 0.001). The estimate of between-study variance (τ²) was 0.08. The estimated pooled prevalence of VTE in lung cancer patients (5%) was higher than the crude prevalence rate of 3.97% observed in this study. The heterogeneity chi² was 221.28 (p < 0.001, d.f. = 15).

5.3.13. Prevalence of VTE in Lymph Cancer Patients

Six included studies encompassing 699 patients reported on the prevalence of VTE in lymph cancer patients undergoing chemotherapy [41,45,50,51,72,97]. The meta-analysis revealed a pooled estimated prevalence of 4%, ranging from 2% to 7% (ES 4%; 95% CI 2–7%; z = 4.69; p < 0.001) (Table 4 and Supplemental SI Figure S7). Notably, there was substantial heterogeneity between the included studies (I² = 54.86%, p = 0.05). The estimate of between-study variance (τ²) was 0.01. The estimated pooled prevalence of VTE in lymph cancer patients (4%) was higher than the crude prevalence rate of 3.58% observed in this study. The heterogeneity chi² was 11.08 (p = 0.05, d.f. = 5).
5.3.14. Prevalence of VTE in Mesothelial Cancer Patients

Five included studies encompassing 1286 patients reported on the prevalence of VTE in mesothelial cancer patients undergoing chemotherapy [39, 49, 80, 113, 128]. The meta-analysis revealed a pooled estimated prevalence of 6%, ranging from 3% to 11% (ES 6%; 95% CI 3–11%; z = 5.24; p < 0.001) (Table 4 and Supplemental SI Figure S8). Notably, there was substantial heterogeneity between the included studies ($I^2 = 84.17\%$, $p < 0.001$). The estimate of between-study variance ($\tau^2$) was 0.02. The estimated pooled prevalence of VTE in mesothelial cancer patients (6%) was higher than the crude prevalence rate of 4.82% observed in this study. The heterogeneity $\chi^2$ was 25.27 ($p < 0.001$, d.f. = 4).

5.3.15. Prevalence of VTE in Neuroendocrine Cancer Patients

One included study, encompassing 113 patients, reported on the prevalence of VTE in neuroendocrine cancer patients [56]. However, a meta-analysis could not be performed due to insufficient number of studies. The crude prevalence rate of VTE in neuroendocrine cancer patients was 6.19% (Table 4).

5.3.16. Prevalence of VTE in Oesophageal Cancer Patients

Two included studies, encompassing 328 patients, reported on the prevalence of VTE in oesophageal cancer patients [52, 67]. However, a meta-analysis could not be performed due to insufficient number of studies. The crude prevalence rate of VTE in oesophageal cancer patients was 9.76% (Table 4).

5.3.17. Prevalence of VTE in Ovarian Cancer Patients

Six included studies encompassing 718 patients reported on the prevalence of VTE in ovarian cancer patients undergoing chemotherapy [40, 79, 82, 96, 115, 121]. The meta-analysis revealed a pooled estimated prevalence of 8%, ranging from 5% to 12% (ES 8%; 95% CI 5–12%; z = 7.47; $p = 0.02$) (Table 4 and Supplemental SI Figure S9). Notably, there was substantial heterogeneity between the included studies ($I^2 = 61.47\%$, $p = 0.02$). The estimate of between-study variance ($\tau^2$) was 0.01. The estimated pooled prevalence of VTE in ovarian cancer patients (8%) was lower than the crude prevalence rate of 8.22% observed in this study. The heterogeneity $\chi^2$ was 12.98 ($p = 0.02$, d.f. = 5).

5.3.18. Prevalence of VTE in Pancreatic Cancer Patients

Three included studies, encompassing 144 patients, reported on the prevalence of VTE in pancreatic cancer patients [32, 33, 81]. However, a meta-analysis could not be performed due to insufficient number of studies. The crude prevalence rate of VTE in pancreatic cancer patients was 28.47% (Table 4).

5.3.19. Prevalence of VTE in Prostate Cancer Patients

Three included studies, encompassing 1233 patients, reported on the prevalence of VTE in prostate cancer patients [95, 100, 108]. However, a meta-analysis could not be performed due to insufficient number of studies. The crude prevalence rate of VTE in prostate cancer patients was 2.11% (Table 4).

5.3.20. Prevalence of VTE in Renal Cancer Patients

Two included studies, encompassing 198 patients, reported on the prevalence of VTE in renal cancer patients [48, 105]. However, a meta-analysis could not be performed due to insufficient number of studies. The crude prevalence rate of VTE in renal cancer patients was 11.11% (Table 4).

5.3.21. Prevalence of VTE in Skin Cancer Patients

One included study, encompassing 93 patients, reported on the prevalence of VTE in skin cancer patients [75]. However, a meta-analysis could not be performed due to
insufficient number of studies. The crude prevalence rate of VTE in skin cancer patients was 7.53% (Table 4).

6. Discussion

Our meta-analysis revealed an overall pooled estimated prevalence of VTEs in cancer patients undergoing chemotherapy, as well for various cancer phenotypes. Our findings indicate that the estimated pooled prevalence of VTEs in cancer patients undergoing chemotherapy is approximately 6%, ranging from 5% to 7%, which is higher than the crude prevalence rate of 5.78%. To the best of our knowledge, this is one of the first reports in which prevalence estimates of VTE have been conducted on a relatively large cohort of patients. Our findings also reveal phenotypic variability in VTE risk, indicating need for prophylactic management of VTE risk in cancer patients undergoing chemotherapy, with certain phenotypes of cancer such as bladder, gastric and ovarian posing particularly high risks of VTE.

One explanation for why cancer patients have a higher risk of having VTE is that tumours can express various procoagulant molecules and alter tissue factor expression [131,132]. Certain tumours may also raise the risk of thrombosis by compressing blood vessels, changing blood flow, or causing injury to the vascular endothelium through intravascular growth [9]. Subsequent cancer diagnosis within the first year of first VTE diagnosis have been reported in up to 10% of patients [133]. Therefore, VTE, especially in the lower limbs, can also be useful as marker for occult cancer [134].

This pooled estimate of 6% is higher than other estimates of 2.3% prevalence rates of VTE in cancer patients in the first 12 months after their diagnosis, with other estimates ranging from 4–20% of cancer patients developing VTE in their lifetime [12,135]. Amongst the normal population, VTE prevalence is at 1–2% [136]. In a retrospective study on 40,787,000 hospitalised cancer patients from 1979 through 1999, patients with malignancy were found to have a 2% prevalence of thromboembolism, although, were not necessarily on chemotherapy or radiotherapy treatment [137]. This suggests that cancer itself, without the interference of external treatment regimens, may not pose a significant risk to VTE but rather, it is the accompanying therapies which may confer additional VTE risk.

The prevalence of VTE may vary across cancer phenotype. This is of clinical interest as it may aid in the risk-staging and appropriate tailored management specific to cancer phenotype. We found that the pooled VTE prevalence varied across cancer phenotype in the range of 1–18%, with lowest prevalence of 1% observed in breast and head and neck cancer and highest prevalence of 18% observed in bladder cancer. This indicates a need for more aggressive VTE screening for specific cancer phenotypes. From a policy standpoint, beyond the hospital-based risk factors, such as recent surgery, cancer, and congestive heart failure, to prevent VTE, dietary counselling as well as public health strategies around encouraging the adoption of heart-healthy habits for cancer patients undergoing chemotherapy may be beneficial [138]. Moreover, concomitant preventative measures targeting arterial thrombosis and VTE are also important [2].

6.1. Pathophysiology of VTE in Cancer Patients

The pathophysiological process behind VTE prevalence in cancer patients is multifaceted and can be attributed to multiple aetiological pathways, spanning the hypercoagulable state induced by malignancy itself to the thrombotic risk posed by treatment regimens of chemotherapy and radiotherapy [139]. The inflammatory state induced by malignancy, stemming from tumour biology and activation of the coagulation cascade, increases cancer patients’ risk of VTE occurrence [139]. On a molecular level, several factors increase the risk of VTE, with increased concentrations of procoagulants on a cellular level amplifying thrombosis prevalence. These include tissue factor, microparticles, plasminogen activator inhibitor-1, cancer procoagulant, mucin, tumour-derived platelet agonists and inflammatory cytokines such as IL-6, IL-8 and IL-10 [140–145]. Alterations to thrombomod-
ulin expression due to interference from tumour necrosis factor-a and IL-1B also contribute to a prothrombotic state [146].

6.2. Chemotherapy and VTE

Chemotherapy has been shown to increase VTE risk by six-fold in cancer patients [12]. Multiple chemotherapy drugs which are used to treat cancer are associated with increased thrombotic events [147]. Cisplatin is a major component of several treatment regimens—and its thrombotic potential and vascular toxicity has been identified since 1986 [148]. Through direct drug-induced damage to the endothelium and by indirectly increasing the expression of TF procoagulant activity of monocytes and macrophages, chemotherapy poses a serious risk of increasing VTE within a cancer patient [148].

7. Limitations

There are several limitations to this study due to variance across the quality of studies included and therefore ability to accurately process the data extracted. Firstly, the types of studies included vary from being retrospective in design to being randomised controlled trials (RCT)—therefore, whilst some studies noted VTE as one of multiple adverse effects within an RCT for a novel chemotherapy regimen, others purely sought to document VTE occurrence within a cohort of cancer patients which oftentimes varied in cancer phenotype, staging and treatment. Furthermore, whilst some studies were robust in being double-blinded, randomised, placebo-controlled and multi-institutional, others were single institution studies conducted on a relatively small cohort size, without an appropriate control group or blinding. As such, this wide variance in included study quality could confound the overall pooled estimated prevalence. Within these studies, their documentation of patients’ cancer history is highly limited. Reporting of time of diagnosis to treatment, the duration, drug regimen and frequency of previous treatments are inconsistent and rarely available. As such, it is difficult to determine whether previous treatment regimens played a confounding role in patients developing VTE. We are also unable to determine whether variance in time of diagnosis to treatment plays a role. Moreover, there was a lack of standardised reporting and insufficient detail in the description of VTEs across the studies. As the majority of studies included were RCTs, VTEs were often a side effect as opposed to the focus of the study, and thus less attention was given toward the VTE. VTE pooled prevalence stratified by cancer severity grade was not investigated in this meta-analysis. In few cases, studies neglected to document the severity of thrombotic events altogether—in which we have assumed a Grade 3/4/5 event in that case. Besides, detailed analysis into the association between severity of VTE event, and any relationship with cancer phenotype, time to treatment, staging, drug regimen, or patient profile could not be performed. Additionally, documentation on certain groups such as atrial fibrillation and VTE recurrence were not available across all studies. It would be ideal to understand whether VTE events occurred before therapy, during, or how long post-diagnosis and post-treatment. As such, more robust future studies with more detailed information and reporting on VTE occurrence, recurrence and adverse effects is necessary. Another limitation of this study and in the studies gathered is the lack of accounting for baseline underlying comorbidities in all the patients. Important factors such as atherosclerosis, cardiovascular disease, histories of smoking, histories of VTE, obesity and age were not detailed in the original studies.

Although patients on prophylactic anticoagulation concomitant to chemotherapy were not included in this study, we acknowledge that previous history of anticoagulation may presumably not have been reported in some studies. In light of recent guidelines [19], as adherence to prophylactic anticoagulation grows to reduce VTE risk, it is likely that VTE prevalence will show a downward trajectory. Finally, for the patients who did experience VTE prevalence, often these patients were not followed longitudinally for VTE recurrence, and specific time to disease progression and overall survival. Typically, follow-up was not provided for longer-term complications and recurrence. The discrepancy in protocol
for VTE diagnosis and follow-up between hospitals and studies leads to the inconsistent reporting and treatment of patients across the clinical decision making, imaging and diagnosis pipeline. Despite these limitations, the use of random-effects modelling would have mitigated some of the random biases and risks above.

8. Conclusions

In conclusion, this meta-analysis demonstrated a pooled prevalence estimate of 6%, with a range of 5% to 7%, of VTEs amongst cancer patients undergoing chemotherapy. Our study indicates there is substantial risk of developing VTE as a cancer patient on chemotherapy showing a compelling need for robust screening and subsequent prophylactic management to prevent future VTE. More efforts should be undertaken to implement adherence of American Society of Haematology guidelines on VTE risks and management in cancer patients undergoing chemotherapy [19].

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/diagnostics12122954/s1, Figure S1: Forest plot showing the estimated pooled prevalence of VTE in bladder cancer patients; Figure S2: Forest plot showing the estimated pooled prevalence of VTE in brain cancer patients; Figure S3: Forest plot showing the estimated pooled prevalence of VTE in breast cancer patients; Figure S4: Forest plot showing the estimated pooled prevalence of VTE in colorectal cancer patients; Figure S5: Forest plot showing the estimated pooled prevalence of VTE in gastric cancer patients; Figure S6: Forest plot showing the estimated pooled prevalence of VTE in lung cancer patients; Figure S7: Forest plot showing the estimated pooled prevalence of VTE in lymph cancer patients; Figure S8: Forest plot showing the estimated pooled prevalence of VTE in mesothelial cancer patients; Figure S9: Forest plot showing the estimated pooled prevalence of VTE in ovarian cancer patients; Table S1: Modified Jadad Analysis for Methodological Quality; e.g., S2: Funding bias scores for studies.

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