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Research progress on venous thrombosis development in patients with malignant tumors

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Abstract

The coexistence of venous thromboembolism (VTE) within patients with cancer, known as cancer-associated thrombosis (CAT), stands as a prominent cause of mortality in this population. Over recent years, the incidence of VTE has demonstrated a steady increase across diverse tumor types, influenced by several factors such as patient management, tumor-specific risks, and treatment-related aspects. Furthermore, mutations in specific genes have been identified as potential contributors to increased CAT occurrence in particular cancer subtypes. We conducted an extensive review encompassing pivotal historical and ongoing studies on CAT. This review elucidates the risks, mechanisms, reliable markers, and risk assessment methodologies that can significantly guide effective interventions in clinical practice.

Key Words: Malignant tumor; Venous thromboembolism; Cancer-associated thrombosis; Research progress

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Core Tip: Treatment-related risks involve therapies such as chemotherapy, endocrine therapy, angiogenesis inhibitors, immunotherapy, protein kinase inhibitors, blood transfusions, and cell line stimulants, all contributing to venous thromboembolism. This review summarizes the pathogenesis of cancer-associated thrombosis and treatment approaches for this condition. This review elucidates the risks, mechanisms, reliable markers, and risk assessment methodologies that can significantly guide effective interventions in clinical practice.

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INTRODUCTION

With demographic shifts and an aging population, the global incidence of tumors has steadily risen, establishing malignant tumors as a leading cause of disease mortality in the 21st century[1-3]. Cancer-associated thrombosis (CAT) stands out as a common complication of malignant tumors, affecting up to approximately 20% of individuals, according to relevant studies[4,5]. The risk of CAT is multifaceted, lacking a singular predictive risk factor or biomarker for its occurrence[6,7]. The correlation between venous thrombosis and malignancy was initially suggested by Baptiste Builaud, and later confirmed 44 years afterward by the French physician Armand Trousseau[8,9]. Among CAT patients, the risk of tumor recurrence and bleeding post-anticoagulation is notably higher than patients without tumor. Specifically, the risk of venous thromboembolism (VTE) recurrence is three times higher than that in the general population without tumor, while the risk of bleeding escalates three to six times higher than in the population without tumor[10].

The risk of recurrent VTE (rVTE) in patients with tumor significantly amplifies within one month of experiencing VTE [11]. Numerous factors may influence the risk of CAT, including patient-related, tumor-related, and treatment-related risk factors[12]. Patient factors include age, gender, smoking, alcohol consumption, obesity, and nutritional requirements [13]. Tumor-related risks are closely associated with the type and stage of malignant tumors, with brain tumors[14], pancreatic cancer[15], and gastric carcinoma[16] posing the highest CAT risk, followed by lung[17], liver[18], ovarian cancers[19], and certain hematologic tumors such as multiple myeloma[20] and acute leukemia[20].

Treatment-related risks involve therapies such as chemotherapy, endocrine therapy, angiogenesis inhibitors, immunotherapy, protein kinase inhibitors, blood transfusions, and cell line stimulants, all contributing to VTE. Chemotherapy, notably, elevates thrombotic events nearly sevenfold compared with patients with cancer who do not undergo chemotherapy[21,22]. Additionally, other treatments (*e.g.*, surgeries) and factors related to treatment (*e.g.*, hospitalization and central venous catheters) heighten VTE risk in patients with cancer.

Epidemiology of CAT

The paradigm of cancer treatment has undergone a significant shift in the past decade with the emergence of precision medicine and the development of various targeted therapies[23]. As medical care quality has improved, cancer patient survival rates have seen a proportional increase, leading to the emergence of new CAT risk groups. The GARFIELDVTE study revealed that 10.1% of patients had an active tumor upon VTE diagnosis, and patients with active tumors exhibited higher rates of mortality, rVTE, and major bleeding than patients without tumor[24]. A recent study involving 150000 cancer diagnoses during 2006-2007 identified approximately 7200 cases of VTE, showcasing substantial variations in CAT prevalence based on patient characteristics, follow-up duration, and detection/reporting methods for venous thrombosis [25]. A registry study in Denmark assessed the survival duration of patients with general tumors *vs* CAT tumors, demonstrating that CAT patients had a notably lower 1-year survival rate, at least 24% lower than those with general tumors, and a 11% higher rate of distant metastases than patients without CAT tumors[26]. Intriguingly, this study also illustrated that patients with bilateral deep vein thrombosis (DVT) had lower survival rates than those with unilateral DVT, with a 2-year survival rate of approximately 70% for unilateral proximal DVT, 64% for bilateral proximal DVT, and 66% for bilateral distal proximal DVT[27].

Although certain factors such as patient age, gender, history of VTE, and various metastatic diseases have been recognized as predictive factors in some studies, the comprehensive understanding of risk factors contributing to CAT within this population remains incomplete.

Risk factors for CAT

The primary clinical presentations of malignancy-associated thromboembolism encompass DVT[28], pulmonary embolism (PE)[29], wandering thrombophlebitis, arterial thromboembolism, nonbacterial thrombotic endocarditis, portal vein thrombosis, and disseminated intravascular coagulation[30]. However, the etiology of CAT varies among cases and primarily involves stagnant blood flow due to the hypercoagulable state of blood, vessel wall injury, and tumor compression[31]. The presence of additional risk factors contributes significantly to VTE development, primarily including patient-related factors, tumor-related factors, and treatment-related factors. Patient-specific factors encompass age, gender, obesity, and history of VTE, where a prior history of VTE can independently elevate the risk for recurrent CAT, notably more prevalent in patients with malignant tumors compared to common VTE cases[32]. For instance, in the general population, the incidence of VTE escalates notably with advancing age. One study findings suggest that patient age may universally influence VTE occurrence and could impact the location of thrombus presentation[33]. Correspondingly, aging emerges as a substantial risk factor for VTE in cancer patients. In retrospective cohort analyses, cancer patients aged ≥ 65 years were notably more prone to VTE development compared to younger patients. In a case control study, Matern *et al*[34] conducted a multifactorial analysis of data related to patients with cervical cancer, and the results showed that age is an independent risk factor for CAT formation, and that attention should be paid to screening for DVT in patients of advanced age[34]. Furthermore, systemic infections also pose a risk for CAT development[35]. In a controlled study, hospitalized patients with malignant tumors who acquired infections demonstrated a 3- to 5-times

higher risk of developing CAT than non-infected patients. Infections such as respiratory, skin, intra-abdominal infections, and bacteremia all contributed to this heightened risk[35]. The second risk factor, specifically linked to malignancy-related VTE, includes the anatomical location of the tumor, tumor stage, and tissue origin. Some studies highlight that the incidence of VTE is significantly higher in patients with advanced tumors developing distant metastases than in patients whose lesions do not progress to distant metastases[36]. The third risk factor emanates from the therapeutic dimension of tumor treatment, encompassing systemic chemotherapy, hormonal therapy, anti-angiogenic therapy, major surgery, postoperative bed rest, and other factors capable of influencing CAT development. Among the predictive factors for VTE in hospitalized patients with malignancies are blood transfusions and central venous cannulation. The development of blood clots from central venous catheters may be related to venous stasis and endothelial injury after the procedure. The formation of blood clots from central venous catheters may relate to venous blood stasis and endothelial injury post-procedure[37].

Mechanisms of CAT occurrence

Malignant tumors disrupt the body's coagulation, anticoagulation, and fibrinolytic systems through various mechanisms, inducing hypercoagulability and pre-thrombotic alterations. This disruption promotes the growth and metastasis of the tumor, forming a vicious circle. Numerous reports delve into the mechanisms underlying CAT occurrence, and this review consolidates four potential aspects involved in CAT formation: Tissue factor (TF)[38], podoplanin (PDPN)[39], neutrophil extracellular traps (NETs)[40], and plasminogen activator inhibitor-1 (PAI-1)[41] (Figure 1).

TF: Endothelial cells, monocytes, and tumor cells express TF. TF is now widely acknowledged as a major contributor to cancer-associated coagulation disorders and CAT. TF directly triggers the conversion of coagulation factor VII to coagulation factor VIIa, playing a pivotal role in activating the exogenous coagulation pathways. TF, a transmembrane protein, exhibits heightened expression on the plasma membrane of cancer cells or microvesicles derived from circulating cancer cells[42]. In cancer patients, TF's expression and activity are significantly elevated compared to normal tissues, often correlating with thromboembolic complications and a poorer prognosis. Several ongoing clinical studies indicate a correlation between CAT incidence and TF in pancreatic cancer, glioma, and other tumors[14]. Activated TF is frequently released from tumor cells in the form of extracellular vesicles (EV), specifically termed EVTF[43]. Patients with tumors have higher levels of EVTF activity than healthy individuals, and intriguingly, patients with tumors of different histological origins have different levels of EVTF activity, with patients with tumors originating from adenocarcinomas also having higher levels of EVTF activity than those with other histological types of tumors. Elevated EVTF activity levels are associated with an increased CAT risk in patients with multiple tumors. A recent study on the relationship between EVTF activity and VTE in patients with glioblastoma showed no direct association between EVTF activity and VTE in patients with glioblastoma during a 2-year follow-up. Notably, patients with glioblastoma and wild-type IDH1/2 displayed higher levels of TF expression and a greater CAT incidence than the mutant type[44]. However, further investigation is needed to determine whether tumor-derived TF + EV contributes to VTE in patients with glioblastoma[45]. Nick *et al*[45] collected autopsy specimens from 180 patients, including 66 patients without tumor and 114 patients with tumor. Among the patients with tumor, 30 (26.3%) showed CAT formation. Upon analyzing TF expression in this group, their results revealed that 23 (76.7%) patients exhibited higher TF levels[45]. Collectively, these TF-expressing tumor cells likely contribute to CAT formation through various pathways in this patient cohort.

PDPN: PDPN represents a class of cell surface glycoproteins that play a pivotal role in tumor development. Overexpressed in various tumors such as hepatocellular carcinoma, lung cancer, and breast cancer[46,47], PDPN induces platelet aggregation through specific binding to platelet receptors. Additionally, PDPN participates in the proliferation, differentiation, epithelial mesenchymal transition and maintenance of tumor stem cell-like properties of malignant tumor cells.

Several studies have investigated PDPN's regulatory mechanisms. Hantusch *et al*[48] initially analyzed the base-rich region upstream of PDPN's promoters and identified multiple transcription factors promoting its transcription, including SP1, AP4, NF-1, among others. Moreover, in lymphatic endothelial cells, the transcription factor PROX-1 was recognized as a potential regulator for transcription factor for the transcriptional regulation of PDPN. Interestingly, analysis confirmed by chromatin immunoprecipitation confirmed the recruitment of SP1/SP3 to the upstream promoter region of PDPN, suggesting the presence of additional transcription factor complexes in this region. Peterziel *et al*[49] demonstrated a negative correlation between PDPN expression levels in primary human glioblastoma and glioma cells at the cellular level. At the same time, they experimentally observed increased PDPN expression in the ventricles of the brain in phosphatase and tensin homolog (PTEN) knockout mice and confirmed using western blot, that the PI3K/AKT/AP-1 signaling axis activation and PTEN loss of function led to PDPN expression in glioblastoma.

The tumor microenvironment (TME) comprises extracellular matrix (ECM), cytokines, and numerous stromal cells. Oncogenic stromal cells significantly contribute to TME construction, involving ECM production, activation of cancer-associated fibroblasts (CAFs), immune suppression, and angiogenesis promotion[50]. PDPN-positive CAFs actively participate in tumor malignancy by modifying the TME. Furthermore, PDPN acts as a co-inhibitory receptor expressed on T cells[50]. Understanding this mechanism elucidates PDPN's role in immunosuppression, offering new directions for cancer immunotherapy.

NETs: In 2004, Brinkmann *et al*[51] identified a network of DNA-histone complexes and proteins released by activated neutrophils, naming it NETs[51]. NETs formation represents a specific cellular process leading toward death, involving the release of granule proteins and chromatin depolymerization[52]. The mechanisms underlying NETs formation primarily stem from two aspects. First, the cleavage of NETs is induced by fopferol acetate myristate or cholesterol crystals, leading to histone arginine citrullination. Subsequently, neutrophils undergo rapid actin cleavage, detachment of cytosolic membranes, and reestablishment of microtubules and the cytoskeleton, followed by rupture of the cytoplasm

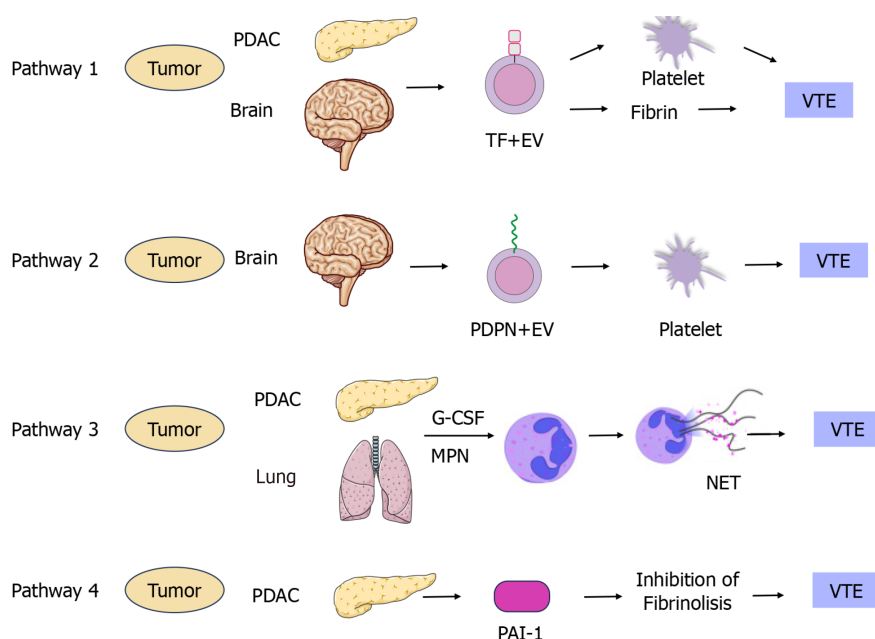


Figure 1 Pathways of cancer-related thrombosis. PDAC: Pancreatic ductal adenocarcinoma; PDPN: Podoplanin; TF: Tissue factor; EV: Extracellular vesicles; VTE: Venous thromboembolism; G-CSF: Granulocyte colony-stimulating factor; MPN: Myeloproliferative-neoplasms; NET: Neutrophil extracellular trap; PAI-1: Plasminogen activator inhibitor-1.

and nucleus to release the chromatin. Finally, NET is released after cytoplasmic membrane rupture and release of the cytoplasmic contents. Another mechanism is the formation of nonlysing NETs, mediated by the activation of Toll-like receptors by certain bacteria or by the activation of a few complement-mediated reactions, all of which occurs independent of the oxidative activity of nicotinamide adenine dinucleotide phosphate [53] (Figure 2).

Previous studies have highlighted NETs' role as a defense mechanism for host cells and their involvement in non-infectious diseases such as rheumatoid arthritis, systemic lupus erythematosus, diabetes mellitus, atherosclerosis, and periodontitis[54]. Notably, several investigations have linked NETs to tumor cells, indicating their involvement in the tumor immune microenvironment, proliferation, metastasis, and CAT[55]. NETs further facilitate tumor cell metastasis by degrading extracellular stromal components.

Interestingly, NETs are closely associated with tumor progression and metastasis, with significantly higher expression levels detected in the plasma of patients with pancreatic, bladder, and lung cancers compared to healthy individuals[56]. In colorectal cancer patients, heightened *in vitro* stimuli correlate with increased NETs expression, linking to poor patient prognosis. Park *et al*[57] demonstrated the highest expression of NETs in metastatic triple-negative breast cancer patients through immunofluorescent staining.

PAI-1: PAI-1 acts as a serine protease (serpin) inhibitor and the principal regulator of the plasminogen activation system [58]. Studies conducted since the 1990s have consistently found high levels of PAI-1 protein in human primary malignant tumor extracts, serving as a significant biochemical marker for poor prognosis across various human cancer types. Recent research highlighted PAI-1's influence on the transition of tumor cells from G1 to S phase by regulating cell cycle proteins D1/CDK3/4 and, consequently, the transition of tumor cells from G1 to S phase[59]. However, conflicting findings exist; in breast tumor cells, PAI-1 exhibited an inhibitory effect on proliferation. The exact molecular mechanisms confirming PAI-1's direct regulation of malignant tumor cell cycles lack validation, although its role in inhibiting apoptosis is extensively reported and characterized. PAI-1's anti-apoptotic effect involves inhibiting cell adhesion to waveform proteins, prompting tumor cell separation and migration, thereby exerting its anti-apoptotic effect[60].

Extensive literature underscores PAI-1's pro-cancer role in malignant tumors. Surprisingly, despite numerous studies, there remains insufficient evidence supporting the therapeutic efficacy of targeting PAI-1 on tumor cells[60]. Notably, recent investigations over the past 3 years have seen the development of several small molecule inhibitors of PAI-1, tested in animal models. While these inhibitors have shown promise in promoting thrombus recanalization in some models, their significant impact on tumor cell growth and metastasis in animal tumor models remains limited. Placencio *et al*[61] reported that PAI-039, also known as tiplaxtinin, an inhibitor of PAI-1, demonstrated antitumor activity in T47 bladder cancer and HeLa cell tumors in mice. However, another PAI-1 inhibitor, TM554, displayed activity in certain preclinical cancer models but lacked antithrombotic activity in other models.

Treatment of CAT

Conventional anticoagulation for CAT: The current treatment program for CAT is based on DVT treatment. All patients who are considered for VTE should commence anticoagulation therapy alongside diagnostic assessments. Guidelines advocate for low-molecular-weight heparin (LMWH) as the preferred choice for both initial and prolonged anticoagulation in CAT patients. Several guidelines support LMWH as the primary option for initial and ongoing anticoagulation

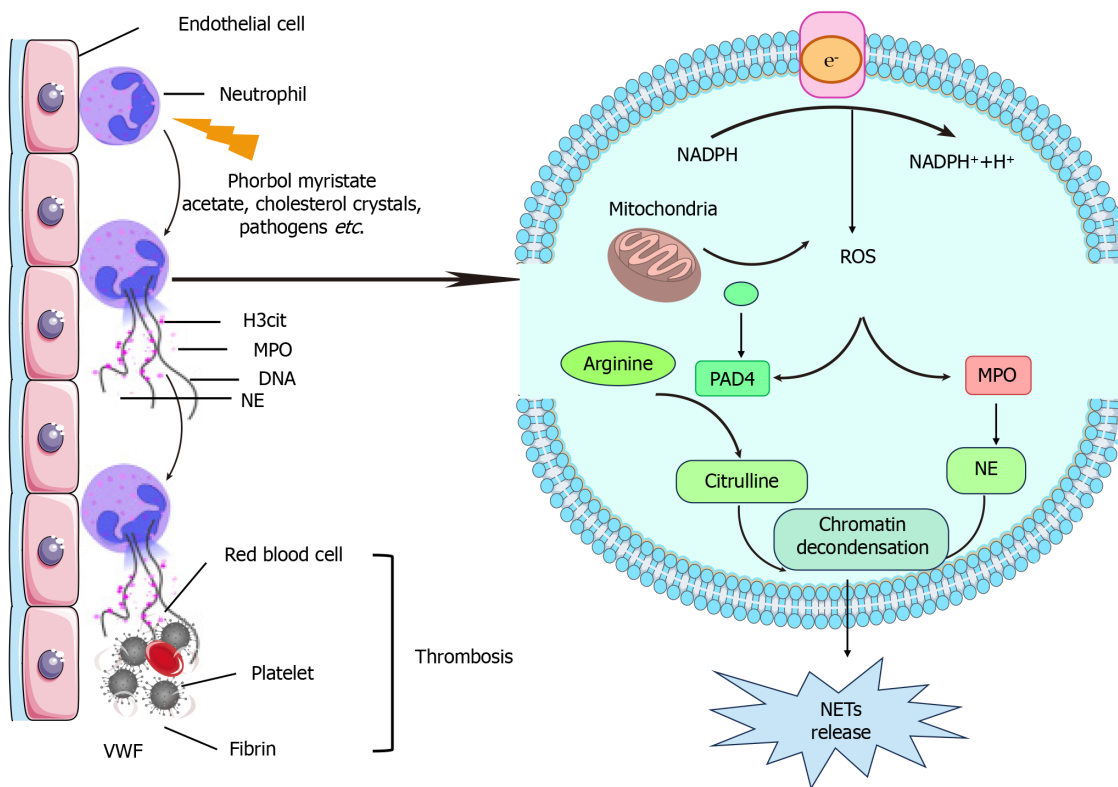


Figure 2 Diagram showing the mechanisms of neutrophil extracellular trap formation. MPO: Myeloperoxidase; NE: Neutrophil elastase; NADPH: Nicotinamide adenine dinucleotide phosphate; PAD: Peptidyl arginine deiminase; VWF: Von willebrand factor; NET: Neutrophil extracellular trap; ROS: Reactive oxygen species; H3cit: Histone 3 citrullination.

in CAT patients. According to a randomized controlled study comparing low molecular heparin to oral anticoagulants in preventing rVTE in cancer patients, a 6-month LMWH treatment notably reduced the risk of rVTE from 17% to 9% compared with conventional treatment (LMWH bridged to warfarin)[62].

While many guidelines support LMWH therapy for CAT, some analyses propose VKA bridging after 6 months of LMWH might be effective in patients with tumor. A study of 1502 patients with tumor treated with LMWH for 6 months demonstrated similar rates of rVTE [hazard ratio (HR) = 0.67, 95%CI: 0.44-1.02] and major bleeding (HR = 1.05, 95%CI: 0.79-1.55) for those continuing LMWH *vs* those transitioned to VKAs. Optimal anticoagulation duration remains inconclusive; guidelines suggest its continuation during active tumor presence or ongoing antitumor therapy[63].

ASCO guidelines recommend starting pharmacological prophylaxis preoperatively, ITAC recommends starting 2 to 12 h preoperatively[64], and ASH recommends starting postoperatively; for patients with malignancies treated with outpatient chemotherapy, risk stratification using the Khorana Risk Assessment Model recommends rivaroxaban as a primary prophylaxis for thrombosis[65]. These guidelines are applicable to all patients with malignancies, but how to more accurately individualise the regimen for gynecological patients with malignancies in different risk strata is a major challenge in prophylactic anticoagulation for a wide range of malignancies, including gynecological oncology patients.

Novel oral anticoagulation therapy for CAT

Recent advancements in novel oral anticoagulants (NOACs) mark a significant breakthrough in CAT prophylaxis and treatment, presenting an alternative to heparin and vitamin K antagonists (VKAs)[66]. However, efficacy and safety data for patients with tumor using NOACs are limited. Despite the advantages of NOACs over other anticoagulants, such as ease of administration (oral and fixed-dose regimens), no need for frequent testing, half-life similar to that of heparin, predictable anticoagulant efficacy, and minimal adverse effects, their safety and effectiveness in patients with tumor require further exploration[66].

Subgroup and meta-analyses of six phase III clinical trials investigating long-term oral anticoagulant therapy using NOACs in patients with CAT who have a prior history of tumor or are currently in an active tumor stage (approximately 5% of the total population) revealed that NOACs exhibit comparable safety and efficacy in both patients with and without tumor[67]. In the Zhang *et al* study[68], a randomized subgroup meta-analysis examining the treatment of active CAT with rivaroxaban (15 mg/dose, twice daily), compared to the Select-D study—a randomized, unblinded trial contrasting rivaroxaban (15 mg/dose, twice daily for 21 d, followed by 20 mg/dose once daily) with dalteparin (200 IU/kg for the initial month, then 150 IU/kg/d)—explored the efficacy of prolonged anticoagulant therapy. This evaluation assessed the incidence of hemorrhagic events and clinically relevant non-major hemorrhagic events in patients over 6 months, revealing that the rVTE at 6 months stood at 4% in the rivaroxaban group and 11% in the dalteparin group. Moreover, major and non-major clinically relevant bleeding rates were 17% and 6% in the rivaroxaban group, respectively. A meta-analysis indicated a decrease in rVTE following LMWH treatment in contrast to patients treated

with VKAs [relative risk (RR) = 0.52, 95%CI: 0.36-0.74]. However, direct oral anticoagulants (DOACs) did not exhibit a significant reduction in rVTE (RR = 0.66, 95%CI: 0.39-1.11). Neither LMWH nor DOACs were linked to the development of major bleeding events[69]. Contrary to these findings, the International Society on Thrombosis and Haemostasis Guidance Statement suggests that NOACs might not be suitable for use in all patients with CAT due to the elevated risk of gastrointestinal bleeding. The statement emphasizes the necessity for more comprehensive and rigorous examination of the efficacy and safety of these medications through randomized, controlled trials.

Endoluminal therapy for CAT

In situations where anticoagulation is contraindicated for CAT, caution should be exercised when placing an IVCF in patients with CAT because of the high risk of thrombotic recurrence risks in this population[70]. IVTE treatment strategies encompass mechanical thrombus removal, catheter-directed thrombolysis, angioplasty, and other endoluminal therapies[71].

In cases where CAT leads to severe functional impairment or significantly affects the quality of life, such as when a tumor compresses nearby major blood vessels or metastasizes in lymph nodes, more aggressive treatment approaches may be considered. These may involve venous stenting, either with or without Contact thrombolysis with preserved catheter. The aim is to prevent further deterioration in patients' quality of life[72] due to tumor-related issues. For acute malignant superior vena cava obstruction syndrome, the primary treatment is endovascular stenting of the superior vena cava, either solely or in conjunction with radiotherapy and/or chemotherapy[72].

Although endovascular interventions prove effective and safe in alleviating symptoms and enhancing the quality of life, there's a scarcity of comprehensive data from international researchers on endoluminal treatment for tumor-related VTE. Existing data are mainly obtained from case reports and studies with small sample sizes. This limited information might be attributed to the shorter life expectancy of most patients with tumor, where preventing potentially fatal PE becomes a therapeutic priority. Additionally, patients with advanced tumors often lack sufficient survival time to develop post-thrombotic syndrome or chronic thromboembolic pulmonary hypertension[73]. Moreover, individuals with tumors have a heightened risk of rVTE and are more susceptible to in-stent reocclusion post-thromboplasty than patients without tumor. Hence, the risk-benefit analysis of angioplasty in patients with CAT should be thoroughly evaluated.

CONCLUSION

The risk associated with CAT varies based on the malignancy type, stage of development, and the patient's susceptibility to both thrombosis and anticancer therapies. However, CAT significantly impacts patient survival, mortality rates, and the overall quality of life in individuals with tumors. Consequently, enhancing risk assessment models to predict thrombosis risk and comprehending the pathogenesis of CAT are crucial. These steps aid in identifying high-risk CAT patients and devising suitable preventive measures.

Therapeutic approaches for CAT remain uniquely challenging, demanding tailored anticoagulation durations aligned with tumor activity and ongoing anticancer treatments. In the era of personalized medicine, frequent individualization of drugs, doses, and durations is imperative. While endoluminal therapy gains attention in CAT research, various aspects of its clinical application require further exploration.

FOOTNOTES

Author contributions: Wang TF and Chen Q conceived and presented the idea; Deng J, Xu Y and Ma SX wrote the manuscript with the support of Ma SX, Xu Y, Li SL and Wang TF; Ma SX supervised the results of this work; Ma SX oversaw the process and was responsible for the overall planning and management. All authors discussed the results and contributed to the final manuscript.

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