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Risk factors of venous thromboembolism associated with Oral maxillofacial-head and neck cancer

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Abstract: *The association between venous thromboembolism (VTE) and malignancy has been demonstrated by a large number of studies, cancer is associated with thrombosis, which also has an impact on the proliferation and extension of cancer. The pathogenesis of cancer-related venous thromboembolism is complex, and the formation of thrombosis is the result of the complex interaction of multiple factors. This article reviews the pathological mechanism and related factors of venous thromboembolism associated with oral maxillofacial-head and neck malignancies as follows, by discussing the risk factors of VTE in patients with o oral maxillofacial-head and neck malignancies, more clearly understands the pathogenesis and risk factors of VTE associated with it, better prevent VTE in clinical practical application, strengthen risk assessment, improve the understanding of VTE related factors, do a good job in the education of patients and medical staff, individualized management and anticoagulant therapy for patients, close follow-up and regular review after treatment, so as to improve the life treatment of patients, prolong the survival time, and reduce the occurrence of VTE associated with oral maxillofacial head and neck malignancies.*

Keywords: *Venous thromboembolism; oral maxillofacial-head and neck cancer; related factors*

Venous thromboembolism (VTE) refers to thrombotic diseases of the venous system, mainly including deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE is considered to be one of the common and life-threatening serious complications in patients with malignant tumors[1], the overall incidence of tumor-related venous thromboembolic disease is 0.1% -15%[2], the incidence of cancer-associated venous thromboembolism (CAT) is 4% -20%, the incidence of VTE in patients with malignant tumors is 4 to 7 times higher than that in non-tumor patients[3][4], and the overall incidence of cancer-related VTE has increased threefold in recent years[5]. CAT is a major cause of death in cancer patients, second only to the progression of the tumor itself and the harm caused by metastasis, and the treatment of CAT patients is more complex because CAT patients have an increased risk of VTE recurrence and bleeding compared with non-tumor VTE patients. Compared with patients with tumors without VTE, patients with tumors who developed VTE had a significantly lower survival rate and a significantly poorer prognosis[6]. Oral maxillofacial-head and neck cancer (OMH - NC) refers to a general term for a series of malignant tumors including various organs of the oral cavity and its adjacent anatomical sites, face and neck, and its incidence still ranks sixth in human malignant tumors without thyroid cancer[7]. According to the 2021 NCCN Oncologic Clinical Practice Guideline for Cancer Associated Venous Thromboembolic Disease, the development of VTE increases the likelihood of death in cancer patients by 2- to 6-fold[8]. There are few studies on VTE in patients with oral and maxillofacial-head and neck malignancies at home and abroad. This article reviews the pathological mechanism, related risk factors, risk assessment and prevention of venous thromboembolism associated with oral and maxillofacial-head and neck cancer as follows in order to arouse clinicians' attention to VTE associated with oral and maxillofacial-head and neck malignancies.

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1. Epidemiological Overview of Venous Thromboembolism Associated with oral maxillofacial-head and neck cancer

According to the 2020 global cancer statistical analysis r[eport[9]: There are about 19.3 million new cancers worldwide, including thyroid cancer, lip cancer, oral cancer, laryngeal cancer, nasopharyngeal cancer, oropharyngeal cancer, hypopharynx (laryngopharyngeal cancer) and salivary gland cancer, accounting for about 1.52 million new cancers, accounting for about 7.9% of all new cancer patients. Thyroid cancer, lip cancer, oral cancer, laryngeal cancer, nasopharyngeal cancer, oropharyngeal cancer, hypopharynx (laryngopharyngeal cancer) and salivary gland cancer account for about 510,000 deaths, accounting for about 5.1% of all cancer deaths. The incidence of OMHNC is increasing year by year worldwide. Most oral and maxillofacial head and neck malignancies affect the patient's mouth opening and closing movement, mastication and swallowing function after surgery, which seriously affects eating and nutrition; masticatory dysfunction leads to weakened oral self-cleaning and increases the risk of local infection[10] ; it also causes displacement and deformation of normal tissues and organs in the maxillofacial region after surgery, resulting in facial deformity and dysfunction, which causes psychosocial disorders in patients. Patients with oral and maxillofacial head and neck malignancies tend to have a poor prognosis and severely reduced quality of life. According to statistics, even if active treatment is taken, the recurrence rate of head and neck malignancies is also 40% -50%[11].

The incidence of VTE also varies by cancer type, with VTE associated with oral and maxillofacial head and neck malignancies being much lower than that associated with cancers at other sites, and VTE incidence and related data in patients with head and neck cancer are extremely limited in most studies of cancer-related venous thrombotic diseases. Recent results from a population-based cohort study by Mulder FI et al[12] experts in 2021 showed that the presence of cancer increased the risk of VTE by 9-fold. Multiple retrospective studies on oral maxillofacial head and neck cancer associated thrombi have shown that the overall incidence of oral maxillofacial head and neck cancer associated venous thromboembolic disease varies between 0.05% – 2%[5][13][14][15][16], and its incidence of venous thromboembolism is considered very low compared with other cancer patients, and retrospective studies are considered to potentially underestimate the true incidence. In multiple large scale retrospective studies, the data showed wide variability. One of these studies had a VTE rate of approximately 5.6% based on clinical symptoms, and another prospective study found a VTE risk of 13% after major head and neck surgery[17]. In addition, risk stratification using the Caprini risk assessment model suggests that patients at highest risk may have a VTE risk of 18.3%, although risk can be reduced by the use of appropriate prophylactic anticoagulants[18], suggesting that retrospective studies may underestimate the true incidence. Since 1823, VTE has been associated with cancer treatment discontinuation, reduced quality of life, and increased morbidity and mortality, all of which not only threaten patients' life and health, but also lead to increased length of hospital stay, increased hospitalization costs, and susceptibility to medical disputes in addition to increased health care costs, and is the leading cause of unanticipated in-hospital deaths, which, although low in incidence, are extremely harmful. In oral and maxillofacial head and neck malignancies, VTE prevention should be emphasized.

2. Pathogenesis of VTE associated with oral and maxillofacial head and neck malignancies

Venous thromboembolism (VTE) is a series of diseases caused by abnormal coagulation of blood in the venous system due to a series of factors such as blood stasis, blood hypercoagulability, and vascular wall injury, which mainly include deep vein thrombosis (DVT) and pulmonary embolism (PE) [1]. The clinical manifestations of DVT may be asymptomatic or local swelling and pain, PE is mainly characterized by hemoptysis, shortness of breath, chest tightness and chest pain, and in severe cases, hemodynamic instability or even death. DVT formation can lead to increased venous pressure distal to the thrombus, causing superficial vein dilatation and varicose veins, limb pain and swelling, once not treated promptly, thrombosis shedding occurs, which can enter and block the pulmonary artery or its branches. The cause of PE thrombosis was first explained at the cellular level by cytopathology proposed by a Berlin scientist in the 19th century, Rudolf Virchow. The three factors of Virchow triad were proposed to include intravascular vessel wall injury, blood flow arrest, and hypercoagulable state [21]. Currently, the commonly used concept of cancer-associated venous thromboembolism (CAT) is gradually developed from Trousseau's syndrome. In 1865, "Trousseau 's syndrome" was first proposed by Armand Trousseau[22] to combine cancer and hypercoagulable conditions to recognize hypercoagulable states caused by malignant tumors, and then "Trousseau' s syndrome" was gradually used to describe hypercoagulable disorders in patients with malignant tumors and is considered to be a chronic disseminated intravascular coagulation, leading to venous thromboembolism and arterial

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thrombosis in cancer patients[23].

In addition to hypercoagulable state (prothrombotic state) caused by oral maxillofacial-head and neck cancer themselves, and its treatment is often based on surgery, surgical repair and reconstruction such as vascularized free flap repair is often required due to the huge defects left by surgical resection, and such patients undergoing major surgery have experienced Virchow triad[21], long operation time, direct endothelial trauma, and cancer-related prothrombotic state, and the risk of VTE has even increased 20-fold[24]. The patient is in a state of stress before, during and after the operation, and the body 's hypobaric hypoxia activates the coagulation system[25] ; and the operation is mostly performed under general anesthesia, which causes the patient' s peripheral veins to dilate, blood flow velocity to slow, and body temperature to drop[16] ; the operation leads to local tissue damage, resulting in vascular endothelial collagen and basement membrane exposure. Inflammatory reactions increase the chance of thrombosis. Bed rest or immobilization after oral and maxillofacial surgery repair and reconstruction surgery often due to body position, wounds and other restrictions on the patient's lower limb movement, and bed rest or immobilization will lead to lower limb muscle relaxation, and then make the blood flow slower. Chemotherapy increases the risk of thrombosis 6.5-fold, due to vascular injury and release of tumor necrosis factor and interleukins [26]. Postoperative nasogastric feeding, drainage volume and tracheotomy fluid evaporation were large, and the intake was insufficient[27] ; after tracheotomy, the patient's respiratory pattern changed, and the negative thoracic pressure was lower than before, resulting in a slower return rate of venous blood[28][29] ; preoperative PICC could promote VTE and PTE[30] in patients with hypercoagulable state.

3. Risk factors for VTE associated with oral and maxillofacial head and neck malignancies

Because the factors influencing the development of thrombosis are complex, this review mainly discusses the risk factors associated with venous thromboembolism in patients with malignant tumors. The causes of hypercoagulable state in cancer patients are complex and can be mainly divided into two categories[31]. The first type is that tumor cells break the balance of coagulation and fibrinolysis system through a variety of ways in the process of its occurrence and development, so that the body is in a hypercoagulable state. The multiple mechanisms of cancer thrombosis are currently mainly studied by the following nine aspects, including extracellular vesicles (EVs), tissue factor (TF)/tissue factor-positive extracellular vesicles (TF + EVs), neutrophil Neutrophils and neutrophil extracellular traps (NETs), inflammatory factors, polylanine and isocitellular dehydrogenase 1, extracellular microRNAs, miRNAs, polyphosphate and pathway of contact (Polyphosphate and the Pathway) polyPs, plasminogen activator inhibitor-1(PAI-1), and platelet activator [32]. The second type includes all other etiologies, Factors related to the patient itself, malignancies, and cancer treatment[33].

1) Thrombosis occurs in association with many of the patient 's own factors, including age, gender, race, obesity, systemic disease, and the presence of comorbidities (e.g., severe infections, diabetes, hyperlipidemia, hypertension, previous history of VTE, family history, etc.), but multiple studies have shown that patients with malignancies have no significant differences in age, race, sex, etc., and have fewer venous thromboembolism-related risk factors, such as hypertension, diabetes, hyperlipidemia, high BMI, cardio-respiratory disease, history of inflammatory bowel disease, family history of thrombosis, and history of hormone therapy, compared with patients without malignancies[34].

2) The risk of VTE in patients with oral maxillofacial-head and neck malignant tumors is influenced by various factors, on the one hand, it is related to the size of the tumor, and the tumor itself can lead to venous thrombosis by direct compression of blood vessels, which leads to blood stasis. On the other hand, it mainly depends on tumor type and stage, and type of treatment. Tumor types and stages have an impact on the risk of VTE. Some studies have shown that different pathological types of the same cancer have different possibilities of VTE. The incidence of VTE in poorly differentiated or undifferentiated tumors is higher than that in moderately well-differentiated tumors, and patients with advanced or distant metastasis are at higher risk of VTE than patients with early localized tumors [35].

3) Effect of oral maxillofacial-head and neck cancer therapy on the risk of VTE. Antineoplastic therapy and supportive care mostly increase the risk of VTE. Associated factors include inpatient surgery, chemotherapy, radiotherapy, angiogenesis inhibitors and other new cancer drugs[36]. Length of stay in hospital (especially bed rest) during hospitalization is closely related to the occurrence of thrombosis in cancer patients, and the longer the length of stay, the greater the probability of morbidity;

Surgery: The prothrombotic state caused by surgery is a well-known risk factor for VTE, and surgery places the body in a long-term stress state, which activates the coagulation system. Oral maxillofacial-

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head and neck malignancies mostly require surgical resection, in addition to cancer infiltration easily causing extensive vascular damage, and surgical dissection will also have an impact on blood vessels, longer operation time makes the residual tumor or nodules continue to squeeze the vein, forming stasis, causing vascular endothelial collagen and basement membrane exposure ; surgery for patients with malignant tumors is basically performed under general anesthesia, and the peripheral venous dilatation, slower blood flow velocity, and lower body temperature produced by general anesthesia also increase the risk of thrombosis[16] ; surgery will lead to local tissue damage, bed rest or immobilization of oral and maxillofacial surgery often limit the patient's lower limb movement due to body position, wounds, etc., while bed rest or immobilization will lead to lower limb muscle relaxation, and then slow blood flow. In particular, patients with oral and maxillofacial head and neck malignancies often require flap transplantation during surgery, and immobilization is often required after the site of flap transplantation[37], and prolonged recumbency after surgery is also associated with the occurrence of thrombosis. Inflammatory reactions increase the chance of thrombosis. Because some patients with oral, maxillofacial, head and neck malignancies have longer surgical sites than nasal cavity and oral cavity, the probability of postoperative infection is also greater, and the inflammatory system reactions caused by infection will also increase the risk of thrombosis. The particularity of surgical site and surgical approach for oral, maxillofacial, head and neck malignancies may increase the risk of VTE formation. Therefore, it is necessary to consider whether the patient is operated for flap transplantation and the site of flap transplantation, usually including radial forearm flap, anterolateral thigh flap, lateral leg flap, scapular system tissue flap, fibula myocutaneous flap, iliac myocutaneous flap, and arbitrary flap plasty.

Chemotherapy: Chemotherapy is a systemic treatment using cytotoxic drugs to eliminate cancer cells and often requires peripherally inserted central catheter (PICC) placement. Chemotherapy is an independent and important risk factor for malignant tumor-associated venous embolism, and the mechanism of venous embolism caused by chemotherapeutic drugs is also different. As a foreign body, PICC catheter is complicated with catheter-related upper limb venous thrombosis (UEDVT) in long-term indwelling human body; chemotherapeutic drugs directly lead to vascular endothelial injury; some chemotherapeutic drugs will increase the level of procoagulant molecules and reduce endogenous anticoagulation; chemotherapeutic drugs can induce apoptosis of tumor cells and endothelial cells and release of cytokines, and then increase the expression of tissue factor activity; some chemotherapeutic drugs can activate platelets[30] ; chemotherapy can directly induce the expression of monocyte-macrophage tissue factor. These mechanisms can directly damage the endothelium, reduce endogenous anticoagulants, and affect blood fibrinolytic system capacity. For example, cisplatin induces endothelial cell apoptosis and leads to the release of procoagulant endothelial microcells[36] ; 5-fluorouracil leads to protein C depletion, increases thrombin activity and impairs endothelial cells to promote thrombosis; and antiestrogens may increase the risk of VTE through depletion of protein C and protein S.27, 28, not only chemotherapy is associated with an increased risk of VTE, but also cancer type is associated with a further increased risk of VTE[38].

Radiation therapy: There is increasing evidence that radiation therapy is associated with the development of VTE, and radiation therapy can affect the results of VTE anticoagulant therapy in cancer patients, Temraz S et al in the COMPASS-CAT trial[39] in 2021 found that radiation therapy significantly increased the occurrence of VTE, with a risk difference of 5%, and that women receiving radiation therapy had a higher risk of VTE than men (10.8% vs 2.7%). In 2017, Guy JB et al also found in RIETE[40] trial that VTE accounted for a significant proportion (12.9%) of patients with radiotherapy tumors, and the risk of VTE was at the same level between radiotherapy and chemotherapy. The risk of VTE was not higher in combination therapy with the two regimens than in monotherapy. Radiotherapy and thrombosis may be related to the following aspects. After radiotherapy, procoagulant factors promote procoagulant response with various prothrombotic molecules such as activated factor VIII, proinflammatory nuclear factor κB, increased D-dimer, platelets and prothrombin fragments, tilting the balance to a hypercoagulable state; ionizing radiation affects the protein C pathway and its thrombomodulin interaction; radiotherapy also induces primary hemostasis through TF, leading to endothelial dysfunction and thrombosis. In addition, Leith JT[41] 2018, et al investigated in vitro that tumor irradiation activated integrin αvβ3 in cancer cells, and radiation significantly increased active β3 within 1 hour ($P < 0.001$), associated with thrombosis.

4. Summary and outlook

In this review, we discuss the latest progress in the high-risk factors of VTE in oral and maxillofacial head and neck cancer in recent years, and find that many factors such as the type and stage of malignant tumors and clinical treatment methods are closely related to the occurrence of VTE, especially flap

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transplantation in patients with head and neck cancer has a closer effect on the site of VTE during surgery. Based on the various high risk factors of VTE in patients with oral maxillofacial-head and neck malignancies described in this paper, how to better prevent VTE in clinical practical application requires careful thinking, strengthening risk assessment, improving the understanding of VTE related factors, doing a good job in the education of patients and medical staff, individualizing the management and anticoagulant therapy of patients, close follow-up and regular review after treatment, so as to improve the patient's life treatment, prolong the survival time, and reduce the occurrence of VTE associated with oral maxillofacial-head and neck malignancies.

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