·综　述·

甲状腺癌与静脉血栓栓塞症的研究进展

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【摘要】 **目的**　总结现阶段甲状腺癌与静脉血栓栓塞症（VTE）的研究进展。**方法**　复习近年来国内外有关甲状腺癌与静脉血栓栓塞症发生风险相关危险因素的文献并进行综述。**结果**　静脉血栓栓塞症对于甲状腺癌患者来说，其发生率虽然不高，但是相关危险因素较少，而且甲状腺癌的各类治疗药物也可能会导致 VTE 的发生。**结论**　研究甲状腺癌与 VTE 的相关因素及血栓前状态的发生对降低甲状腺癌中 VTE 发生率和改善预后有必要性。

【关键词】 静脉血栓栓塞；甲状腺癌；危险因素；综述

The research progress of venous thromboembolism and thyroid cancer

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【**Abstract**】 **Objective**　To summarize the current research progress of thyroid cancer and venous thromboembolism. **Methods**　Retrieved the literatures about risk factors associated with thyroid cancer and venous thromboembolism both at home and abroad in recent years and reviewed the literatures. **Results**　The incidence of venous thromboembolism in patients with thyroid cancer was not high, but there were few factors related to risk factors, and various types of therapeutic drugs for thyroid cancer may also lead to the occurrence of venous thromboembolism. **Conclusions**　The study of thyroid cancer and venous thromboembolism related factors and prethrombotic state occurrence are necessary to reduce the incidence of venous thromboembolism in thyroid cancer and improve prognosis.

【**Keywords**】 venous thromboembolism; thyroid cancer; risk factors; review

静脉血栓栓塞症（VTE）包括深静脉血栓形成（DVT）和肺栓塞（PE），其风险度在各种恶性肿瘤中是不同的[1]。目前关于甲状腺癌与 VTE 风险的关系的文献报道较少，在已有的 VTE 研究并未将甲状腺癌纳入其中[1-7]。甲状腺癌可以通过压迫血管[8-9]或侵入诱导血栓形成[10-13]，然而，关于甲状腺癌和 VTE 及其高凝血风险的研究很少。笔者现就甲状腺癌发生 VTE 和血栓前状态的风险进行综述。

1　甲状腺癌与高凝状态

滤泡细胞来源的甲状腺癌包括高分化的乳头状癌、滤泡状癌、低分化癌和间变性（未分化）癌[14]。在所有甲状腺癌病例中，分化癌占 95%[15]。甲状腺癌的年发病率大约是所有新发恶性肿瘤的 1%，并且在过去 10 年中有所增加，这主要是由于诊断甲状腺恶变结节的能力提高所导致的[16]。

目前已有的回顾性队列研究未发现甲状腺切除者中 VTE 与甲状腺癌之间存在独立关联性[17]，甲状腺切除术和甲状旁腺切除术后的总 VTE 发生率为 16%，比整个 VTE 研究的风险度（96%）低 5 倍，反映了其非常低的发生率[18]。在一项大型前瞻性队列研究[19]中，年龄>60 岁的甲状腺癌患者的 VTE 风险每 1 000 人年（95% *CI*）为 9.5［95% *CI* 为（4.3，21）］，而年龄<60 岁的患者为 0.6［95% *CI* 为（0.1，4.3）］，年龄>60 岁的甲状腺癌患者组的风险是年龄<60 岁的 15.8 倍。关于癌症明确诊断后发生 VTE 的时间，在 0～3 个月内，每 1 000 人年（95% *CI*）的绝对发病率为 30［95% *CI* 为（9.6，92）］，3～12 个月为 11［95% *CI* 为（3.5，33）］，而>12 个月为 0.5［95% *CI* 为（0.1，3.8）］。笔者最初认为，VTE 风险度在普通人群中没有显著差异，然而文献中数据显示年龄

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和 VTE 诊断时间对风险度有明显影响[19]。总体而言，VTE 的血栓前状态可能与年龄有关，这种情况通过检测到增加的 FⅤ、FⅦ、FⅧ 和 FⅨ 而被发现[20]。许多实验室参数（如 D-二聚体）可能需要进行年龄上的校正[19]。在英国某项大型研究中由于缺乏有关甲状腺癌分期和甲状腺癌亚型的资料，因此，相对于无症状性甲状腺癌，甲状腺功能状态明显改变和经过甲状腺激素治疗后的患者，其 VTE 发生风险率更高，后者促进血栓形成的作用更大[21-23]。

在欧洲和北美目前诊断的所有甲状腺癌症中，有 10%～20% 是乳头状甲状腺癌（EFVPTC）的囊状滤泡变体[24]。最近，基于该肿瘤的无痛性和非常低的不良结局风险，又提出了新的名称，为“具有类乳头状核特征的非侵入性滤泡状甲状腺肿瘤”（NIFTP）[24-25]。这种重新分类将显著减少该类癌症的临床误诊率，减轻由此产生的相应心理负担[26]。甲状腺结节的过度诊断和治疗也引起了关注[16]。另一方面，发病率高但 VTE 率低的恶性肿瘤（例如白血病、非霍奇金淋巴瘤和甲状腺癌，在以上肿瘤中，每 100 000 名男性和女性的年发病率分别为 13.5、19.5 和 13.9）可以显著影响 VTE 总体发生率[27]。尽管胰腺癌和胃癌的 VTE 发病率最高，但非霍奇金淋巴瘤和白血病中人群由于基数较大，其 VTE 的比例超过 30%。这个同样见于甲状腺癌，本身发病率高但 VTE 发生率低。这个假设也可以类似见于甲状腺癌，发病率高但 VTE 发生率低。甲状腺癌与 VTE 发生的具体风险目前仍不清楚[17]。

甲状腺髓样癌具有代谢特征，并与副肿瘤综合征相关[28]。嗜铬细胞瘤和（或）甲状腺髓样癌使得儿茶酚胺和血清素升高，可能有助于血小板活化和聚集，从而导致血液出现高凝状态[29-30]。血清素通过增加血小板与富含组织因子的微泡和血小板活化的相互作用，或通过修改血小板表面的 N-聚糖含量，导致血小板聚集增加和促血栓形成状态[31-32]。在以前报道的 1 例复发性卒中同时伴有脑矢状窦血栓形成的转移性甲状腺髓样癌的病例中的患者的 D-二聚体和正常纤维蛋白原升高[28]，高凝状态已出现，FVIII、纤维蛋白原和抗凝血酶 III 水平均升高[33]。其他类型的甲状腺包括滤泡型和透明细胞型组织学标本[34]，许特尔氏细胞癌[35]和甲状腺未分化癌[36]患者也有高凝状态。一般而言，癌症与凝血系统中的不平衡会诱导促血栓形成的状态；然而，癌症相关性凝血的发病机制却很复杂[37-38]。癌症患者通常表现出异常的凝血因子水平，如纤维蛋白原、FV、FVIII、FIX 和 FXI 水平异常，以及纤维蛋白原/纤维蛋白降解产物比值和血小板计数升高[39]。甲状腺癌的凝血情况可能取决于疾病的严重程度[40]。目前尚未广泛研究甲状腺癌中纤溶系统的改变。平均血小板体积及其含量升高已被认为是甲状腺结节患者判定为乳头状甲状腺癌风险度的生物标志物[41]。

血氧合酶（hemeoxygenase-1）在甲状腺癌细胞系中的表达上调。一氧化碳在体外和体内可显著增强血液凝固，并且通过结合纤维蛋白原相关血红素基团来增强纤维蛋白原基质，使得血液出现高凝状态。在甲状腺癌中，碳氧血红蛋白浓度增加（2.4%），观察到一氧化碳介导的血凝进度增加，导致血浆处于高凝状态，后者已通过血栓弹性描记法确定，从而对进一步研究这种酶在甲状腺癌（特别是那些内源性一氧化碳生成增加）中的作用是有依据的[42]。

从存在方法学局限性的研究中去掉恶性肿瘤组与良性肿瘤组之间单核细胞的类似凝血活酶活性的研究是存在争议的[43]，由于甲状腺癌出现 VTE 的样本量非常小，根据以上方法的局限性来判断转移性甲状腺癌与非转移甲状腺癌中促凝血活性较高的结论缺乏普遍性[44]。

纤溶酶原激活系统（PAS）中各种组分的在 VTE 形成中的用，特别是尿激酶-纤溶酶原激活剂（uPA）和纤溶酶原激活剂抑制剂类型 1（PAI-1）在甲状腺癌进展和预后方面的作用已有报道[45-49]。尿激酶-纤溶酶原激活剂（uPA）和纤溶酶原激活剂抑制剂类型 1（PAI-1），uPA 受体在恶性肿瘤中的表现与良性肿瘤相比较具有侵袭性，并且在侵袭性较差的甲状腺癌中表现得更具有侵袭性，但其对凝血改变的作用尚未阐明。

总之，甲状腺癌是否与 VTE 风险增加相关尚未得到证实。诱发血栓前状态的甲状腺癌的机制研究更少。儿茶酚胺和（或）血清素代谢异常继发的血小板活化和（或）聚集增加是可能的机制。任何内皮功能紊乱和原发性/继发性血液凝固级联以及纤维蛋白溶解途径（尤其是 PAS 成分）的紊乱都会加强上述可能机制的趋势，但这需要进一步的研究来验证。

2　甲状腺癌与血管侵犯及压迫

甲状腺恶性肿瘤中的癌栓和压迫导致远端血管血栓形成并不是本次综述讨论的重点，但它可能在甲状腺癌中促进血栓发生。高风险乳头状和滤泡状甲状腺癌可能会侵犯颈部和上纵隔的大血管[10-13]，

但在极少数情况下，癌栓还可影响远端解剖部位，如大脑中动脉[50]。影响颈静脉的临床表现可以从无症状表现到上腔静脉综合征[51-54]。5 507 例行甲状腺切除的甲状腺恶性肿瘤患者中，有 9 例有癌栓[55]。尽管肿瘤压迫和（或）肿瘤侵袭/癌栓不被认为是 VTE 血栓形成的主要风险因素（不应该包括关于评估甲状腺癌 VTE 风险的流行病学研究），但这两种情况均有可能增加血栓形成的风险。与没有这些情况的那些甲状腺癌患者相比，伴有肿瘤压迫和（或）肿瘤侵袭/癌栓的甲状腺癌患者可能具有更高的 VTE 风险，但在这方面需要进一步的研究。

3 甲状腺癌的治疗

甲状腺癌的药物和外科管理策略在不断发展[56]，尽管左旋甲状腺素治疗可能引起血栓前状态[21-23]，但这一方法对甲状腺癌患者的 VTE 事件有何作用尚不清楚[57]。

一般来说，在癌症患者中，细胞化疗毒性与 VTE 的发生有关[58-60]。目前有几项关于阿霉素、索拉非尼、司美替尼、依维莫司、瓦他拉尼和乐伐替尼治疗各种类型甲状腺癌的临床试验正在进行[61]，所有这些正在进行的试验中，FDA 批准的用于分化型甲状腺癌的生物靶向化疗药物有阿霉素、索拉非尼和乐伐替尼[62]，用于甲状腺髓样癌的药物有凡德他尼和卡博替尼[63-64]，这些药物可能有对晚期 PDTC 和未分化甲状腺癌也具有一定前景[61]。

多激酶抑制剂（MKI）或酪氨酸激酶抑制剂（TKI）可用于各种类型的甲状腺癌，如甲状腺髓样癌和放射性碘难治的分化型甲状腺癌[65-66]。MKI 如 FDA 批准的索拉非尼用于分化型甲状腺癌，其与动脉血栓形成和 VTE 都有关[65, 67-68]。TKIs 与甲状腺机能减退相关，凡德他尼治疗组的 VTE 发病率高达 32%[66, 69]。由于中度和（或）亚临床甲状腺功能减退可能诱发血栓前状态，因此药物引起的甲状腺功能减退症是否有助于这些 VTE 不良事件尚不清楚。卡博替尼已用于治疗局部晚期或转移性甲状腺髓样癌，其癌症患者的 VTE 发生率约为 4%[70]，已经有研究[71]报道，莫泰沙尼在治疗具有各种组织学的侵袭性分化型甲状腺癌过程中可以导致甲状腺功能减退症和 VTE。使用乐伐替尼治疗甲状腺癌组与安慰剂组之间治疗相关的 PE 发生率比较无显著差异[72]。尽管 VTE 被列入 TKIs 的药理学不良反应，但使用凡德他尼或卡博替尼是否与甲状腺癌治疗中 VTE 增加相关尚待阐明[63-64, 73-74]。

有 11% 的来那度胺使用者发生了 PE[75]。使用泊马度胺、来那度胺和沙利度胺治疗者的 VTE 发生率为 9% 至 22%[65]。依维莫司已用于甲状腺未分化癌的治疗[76]，癌症患者每日使用依维莫司加低剂量顺铂静脉，可使血栓形成发生率每周增加 11%[77]。威罗菲尼用于间变性癌，可以导致晚期恶性黑色素瘤患者出现 DIC[78]。伏立诺他是一种组蛋白去乙酰化酶抑制剂，已用于治疗分化型和甲状腺髓样癌，并且有研究[79]报道出现了由于药物使用而出现的 DVT，系 3 级不良事件。

4 甲状腺癌中 VTE 的预防

关于各种类型的甲状腺癌，其严重程度、发展阶段及其治疗副作用与 VTE 发生风险报道不足，需要以人群为基础的前瞻性队列研究和临床试验。在此之前，我们在各种临床情况下对甲状腺癌血栓预防的建议均由美国癌症协会提供，用于预防和治疗癌症相关的 VTE[80-84]，对患者 VTE 的体征和症状的评估应该是由肿瘤专业人员完成[85]。建议使用经过验证的风险评估工具，例如 Khorana 评分来区分低危、中危和高危患者[58, 83]。

5 小结

尽管癌症通常会增加血栓形成倾向，但几乎没有甲状腺癌对血栓形成的影响研究。年龄较大（> 60 岁）被报道为 VTE 的可能危险因素，但是，由于缺乏足够为文献支持，这些假设需要进一步确认[19]。目前有必要对各种亚型和（或）严重程度甲状腺癌的 VTE 发病率进行研究。甲状腺癌不仅可能易患原发性血栓前状态，而且其治疗，例如生物靶向化学疗法和抑制性左旋甲状腺素治疗和（或）其治疗的副作用[65, 67-68, 70, 86-88]，例如生物学化疗引起的甲状腺机能障碍可能会增加 VTE 发生的风险[21, 23, 66, 69]。有关甲状腺癌及其亚型和血液凝固改变机制的文献很少。关于血小板黏附和聚集，各种凝血因子，PAS 成分，内皮功能和促凝血分子[29, 39, 43, 45-49, 86]，例如组织因子阳性微肽、癌症衍生组织因子、癌症促凝血和乙酰肝素酶的变化的研究在甲状腺癌的 VTE 研究也是需要的[37-38, 45-49]。开展设计良好的大规模前瞻性研究和临床试验，用以阐明 VTE 是否与甲状腺癌的各种类型和阶段相关，这也是非常有必要的。

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