# 宫颈小细胞神经内分泌癌治疗的研究进展

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【摘要】 宫颈小细胞神经内分泌癌(small cell neuroendocrine cervical carcinoma,SCNECC)是一种罕见的妇科恶性肿瘤,早期容易出现侵袭转移,预后比宫颈鳞癌和腺癌差。目前对其临床管理尚处于探索阶段,近年来,随着国内外对SCNECC的关注越来越多,改善其预后的探索也取得一些成果。本文将SCNECC综合治疗的研究进展作一综述,对当前手术、放化疗、靶向与免疫药物等治疗策略中的一些关键问题进行探讨和展望。

【关键词】 宫颈癌; 小细胞神经内分泌癌(SCNECC); 综合疗法

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# Research progress in the treatment of small cell neuroendocrine cervical carcinoma

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【**Abstract**】 Small cell neuroendocrine cervical carcinoma (SCNECC) is a rare gynecological malignancy characterized by early invasion and metastasis, resulting in a poorer prognosis compared to cervical squamous cell carcinoma and adenocarcinoma. The clinical management of SCNECC remains in the exploratory phase. Recently, as this uncommon tumor has garnered increasing attention both domestically and internationally, some progress has been made in improving its prognosis. This article summarizes the advancements in combined modality therapy for SCNECC, discussing and providing insights into key issues related to current treatment strategies of surgery, radiotherapy and chemotherapy, as well as targeted and immunotherapies.

【**Key words**】 uterine cervical cancer; small cell neuroendocrine carcinoma (SCNECC); combined modality therapy

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宫颈小细胞神经内分泌癌(small cell neuroendocrine cervical carcinoma,SCNECC)的发病率约为0.06/10万,占所有宫颈癌的0.5%~2%,发病与人乳头瘤病毒(human papilloma virus,HPV)感染相关,诊断主要依据肿瘤细胞的病理学形态,是一种少见且独特的原发性高级别神经内分泌癌[1-2]。SCNECC的恶性程度极高,易出现淋巴结转移和血管间隙浸润,约有一半的患者在初诊时已发展至晚期[3-4]。相比类似分期的其他病理类型宫颈癌,SCNECC的病死率明显上升,局部进展期的中位生存时间仅6.4~11个月[4-5]。疾病罕见性导致既往对SCNECC的系统性研究极少,随着近年来国内外研究者对SCNECC的关注渐增,利用综合疗法改善预后的探索也取得一些进展,本文将对此展开

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综述。

**SCNECC的治疗策略沿革** 受限于疾病的罕见性，SCNECC的前瞻性研究难以开展，其临床管理的循证医学证据以回顾性分析和专家共识为主。考虑到SCNECC的组织和病理特点，美国妇科肿瘤协会和国际妇科肿瘤协作组提出的治疗策略不仅借鉴于宫颈鳞癌和腺癌，也参考了其他器官的神经内分泌肿瘤，尤其是小细胞肺癌[3,6]。2021年起，美国国立综合癌症网络（National Comprehensive Cancer Network，NCCN）的宫颈癌指南单独列出SCNECC并在近年来不断更新，2022年国内也总结了SCNECC诊疗的专家共识[7]。随着一些大样本量临床回顾性分析的开展，SCNECC综合治疗策略也在不断进步。

**SCNECC的手术治疗** 根治性手术在SCNECC的综合治疗中具有重要地位，一些多中心研究和专家共识推荐早期SCNECC患者以手术作为初始治疗方式，甚至对于ⅠB3～ⅡA2期的局部进展期患者，也可以考虑新辅助化疗后行根治手术[3,6]。但也有回顾性分析提示及早应用同步放化疗等系统治疗能使SCNECC患者获益[8-9]，这部分研究者认为，SCNECC恶性程度高，淋巴结转移阴性的病例也可能出现隐匿性转移；并且在病理类型与SCNECC类似的小细胞肺癌诊疗指南中，同步放化疗也具有重要地位。受限于病例数，这些分析的结果均有一定局限性。NCCN指南曾认为，根治性手术可以作为局限于宫颈且肿瘤直径≤4 cm的SCNECC初始治疗；而肿瘤直径＞4 cm时，若肿瘤仍局限于宫颈可以考虑新辅助化疗后行间歇性全子宫切除，若已经属于局部晚期，则建议用同步放化疗取代手术治疗；并且对所有分期的SCNECC均可考虑同步放化疗联合近距离放疗作为初始治疗方案。最近发表的一项大样本回顾性分析[10]引起了国内外的广泛关注，这项多中心研究对610例来自美国SEER（Surveillance，Epidemiology，and End Results）数据库和678例来自中国的SCNECC患者队列进行预后分析，提示手术能够明显改善预后，亚组分析显示局部进展期患者仍可从手术中获益。在此基础上，2024年的NCCN指南提出，局限于宫颈的SCNECC即使直径＞4 cm仍可在新辅助化疗后接受根治手术，但ⅠB3～ⅣA期的SCNECC患者仍建议同步放化疗而非手术作为初始治疗。

SCNECC手术治疗的具体方案是近年来的另一个研究热点，比如保留卵巢的适用标准。研究显示SCNECC的发病年龄早于宫颈鳞癌和腺癌，患者保留卵巢的愿望更为强烈[6,11-12]，但是肿瘤的高度侵袭性导致临床上对根治术中保留卵巢的安全性产生担忧[13]，在目前的国内外指南中尚无统一共识。我们回顾性分析了本中心的116例SCNECC患者，结果表明保留卵巢对SCNECC患者的预后无显著影响；如果在术前或术中发现卵巢转移的相关危险因素（如FIGOⅣ期、主动脉旁淋巴结转移和宫旁累及），则不建议保留卵巢[14]。相信未来随着多中心的随访数据不断加入到研究队列，将会有更多高质量的回顾性分析进一步完善SCNECC患者的根治性手术策略。

**SCNECC的放化疗** 除了作为重要的初治方案，放化疗也常常被纳入SCNECC根治术后的辅助治疗策略。其中，依托泊苷联合顺铂（etoposide and cisplatin，EP）方案已经成为共识和指南普遍推荐的辅助化疗策略，并提出术后需要至少5个周期的化疗才能够改善无进展生存期（disease-free survival，DFS），理想目标为6个周期[7,15-16]。另一方面，术后辅助放疗的应用标准仍未得到共识。近年来的回顾性研究和荟萃分析表明，术后辅助放疗可能降低早期SCNECC患者的盆腔复发率，但无证据显示能提升DFS或总生存期（overall survival，OS）[17-19]。这些结果提示部分早期高危SCNECC患者可能会从术后放疗获益，但如何在临床实践中区分这部分患者仍有待进一步多中心、大样本量的研究结果。

SCNECC恶性程度高，近80%的患者治疗后复发，一些术后病理显示淋巴结转移阴性的患者也可能很快出现远处血行转移。近年来，多项研究通过回顾性比较复发性SCNECC患者的预后，为复发后化疗方案选择提供了重要的临床证据。2017年的回顾性宫颈神经内分泌癌登记研究（Neuroendocrine Cervical Tumor Registry，NeCTuR）发现，采用拓扑替康-紫杉醇-贝伐珠单抗方案（topotecan，paclitaxel and bevacizumab，TPB）作为复发性SCNECC一线治疗的患者中位DFS比21例其他化疗方案的患者明显延长（7.8个月 *vs.* 4.0个月，OR=0.21，$P<0.05$）[20]。这一结果被报道后，TPB方案逐渐得到广泛应用[11,21-23]。最近，NeCTuR的更新数据显示，62例以TPB方案进行复发性

SCNECC一线或二线治疗的患者相比56例采用其他化疗方案的患者,中位DFS(8.7个月 *vs.* 3.7个月,OR=0.32,$P<0.05$)和中位OS(16.8个月 *vs.* 14.0个月)均延长[24]。除TPB方案以外,其他研究也在探索改善复发SCNECC预后的用药策略。近期一项研究[25]显示,一线化疗复发后进行紫杉醇-卡铂加贝伐珠单抗治疗的SCNECC患者,继续接受贝伐珠单抗维持治疗比未接受者的中位OS(34个月 *vs.* 10.5个月)及DFS(19个月 *vs.* 5个月)长,但研究也指出,贝伐珠单抗维持治疗可能增加消化道出血和穿孔的风险。

总体来看,无论是放疗的应用标准,还是化疗的具体方案,越来越多的证据显示,SCNECC应当作为一种独特的原发性神经内分泌癌进行治疗。虽然部分放化疗方案对SCNECC患者的有效性得到初步验证,但其预后改善依然任重而道远。

**SCNECC的靶向和免疫治疗** 随着肿瘤精准治疗的不断发展,近年来一些神经内分泌癌的测序研究陆续提示SCNECC的体细胞突变可能集中于RTK/RAS、PI3K-AKT、p53和MYC等信号通路[22,26-27]。在此基础上,一些靶向药物临床试验也开始纳入SCNECC患者。如考虑到PI3K-AKT通路在SCNECC中的聚集性突变,近期一项采用*mTOR*抑制剂依维莫司联合顺铂治疗肺外神经内分泌癌的Ⅱ期临床试验中,纳入的39例患者包括4例SCNECC,结果显示该联合治疗方案的SCNECC疾病控制率达75%[28]。应用该通路其他小分子抑制剂的Ⅰ期临床试验也在招募携带突变的宫颈癌和神经内分泌癌患者(如NCT03544905、NCT03106155)。近来,其他通路上的新一代精准靶向方案陆续进入临床试验,如*KRAS G12C*抑制剂AMG510、针对*NOTCH*配体*DLL3*开发的抗体偶联药物[29]、*MYC*抑制剂PC-002和OMO-103、以及靶向*TP53 Y220C*突变的PC14586,相信会给未来SCNECC的治疗开拓新的方向。基础研究显示,除以上通路的聚集性突变外,DNA损伤修复和细胞周期的异常调节也与神经内分泌肿瘤密切相关[22],其靶向药物逐渐进入SCNECC的临床试验中,如靶向同源重组修复靶点*BRCA*、*ATM*的*PARP*抑制剂、*ATM*抑制剂(NCT03895603),靶向细胞周期调控激酶Aurora A和Wee1的小分子药物[30-31]。

近年来,围绕PD-1等检查点开发的免疫治疗在宫颈癌综合治疗策略中越发得到重视,但是神经内分泌癌的免疫浸润与同器官其他病理类型肿瘤有较大区别。近期,一项PD-1抑制剂Pembrolizumab的Ⅱ期临床试验并未对复发性SCNECC取得良好疗效(NCT02721732)[32]。相比于宫颈鳞癌和腺癌,PD-1抑制剂在SCNECC中的应用仍需更多高级别证据支持,目前该方案也尚未进入NCCN指南。研究者提出了多种方案用于改进SCNECC免疫治疗策略。一方面是精准选择免疫治疗适用的患者,一项免疫组化研究[29]发现,70%的SCNECC患者出现局灶性*PD-L1*表达,33%的患者错配修复蛋白表达缺失;另有多项研究表明,SCNECC中*PD-L1*高表达、高肿瘤突变负荷、错配修复蛋白表达缺失的比例显著低于宫颈鳞癌[33-36]。这些研究之间的矛盾提示,免疫治疗敏感性可能与瘤间异质性密切相关,部分研究推荐在高度微卫星不稳定患者中应用免疫检查点抑制剂[26]。另一方面是调整药物作用的检查点,如联合应用PD-1和CTLA-4抑制剂的Ⅱ期临床试验SWOG-1609(NCT02834013),中期结果显示神经内分泌癌治疗反应率达44%,其中SCNECC患者治疗后均达到部分缓解[37];1年后统计仍有2例SCNECC患者,其中1例疾病控制稳定[38]。在该临床试验启发下,一项案例报道联合使用PD-1抑制剂和CTLA-4抑制剂治疗复发性SCNECC患者获得完全缓解[39]。联合治疗的可行性也推动了新药研发,目前PD-1和CTLA-4双免疫检查点抑制剂Cadonilimab(AK104)已经进入复发性SCNECC的Ⅱ期临床试验,计划招募18例高级别神经内分泌癌患者(NCT05063916)。2023年起,NCCN指南依据小细胞肺癌3期临床试验的结果[40-41],引入了PD-L1抑制剂联合含铂化疗作为复发性SCNECC一线治疗的其他推荐方案。溶瘤病毒、免疫联合靶向治疗等新兴策略也陆续进入临床评估(NCT03647163,NCT04079712)。

随着单细胞测序、类器官培养等新兴技术的应用,我们对SCNECC肿瘤生物学特性和肿瘤微环境异质性的了解也在与日俱增,相信在不远的将来,精准的个体化靶向和免疫治疗策略会使更多患者受益。

**结语** SCNECC作为一种少见且高度恶性的妇科肿瘤,仍缺少系统性研究。目前国内外对该患者群体的关注持续增加,综合治疗方案也在不断进步,尤其是初始方案和复发后患者的治疗策略成为研究

的热点。随着基础研究对肿瘤异质性的深入探索，逐步建立SCNECC的精准治疗体系，进一步辅助临床决策，将成为改善患者预后的重要方向。

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