

宫颈癌淋巴结转移的研究进展

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收稿日期: 2025年8月15日; 录用日期: 2025年9月8日; 发布日期: 2025年9月18日

摘要

宫颈癌是全球女性中最常见的恶性肿瘤之一, 其主要病因是高危型人乳头瘤病毒(HPV)感染。淋巴结转移是宫颈癌的重要转移途径, 影响疾病的分期、治疗策略和预后。本文系统综述了宫颈癌淋巴结转移的临床病理特征、诊断评估方法、分子机制及治疗策略的最新研究进展。早期宫颈癌的淋巴结转移率较低, 而晚期患者的转移率显著增加。临床研究表明, 淋巴结转移发生率随临床分期进展而显著升高, 主要危险因素包括肿瘤直径 ≥ 4 cm、深间质浸润、淋巴血管侵犯(LVSI)等。目前诊断主要依赖影像学检查(MRI, PET-CT)和前哨淋巴结活检, 但其对微转移的检测仍存在局限。分子机制研究揭示了多步骤转移过程: 上皮-间质转化(EMT)促进肿瘤细胞迁移; 血管内皮生长因子C信号通路介导淋巴管生成; 免疫检查点参与免疫逃逸; miRNA和lncRNA调控表观遗传改变。治疗方面, 早期患者可采用前哨淋巴结清扫手术, 中晚期以同步放化疗为主, 而靶向治疗和免疫治疗在临床试验中展现出潜力。未来研究应整合人工智能等前沿技术, 开发新型生物标志物, 优化个体化治疗方案, 以改善患者预后。通过多学科交叉融合, 有望实现宫颈癌淋巴结转移的精准诊疗。

关键词

宫颈癌, HPV, 分子机制, 淋巴结转移

Research Progress on Lymph Node Metastasis in Cervical Cancer

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Received: Aug. 15th, 2025; accepted: Sep. 8th, 2025; published: Sep. 18th, 2025

Abstract

Cervical cancer is one of the most common malignant tumors among women worldwide, with high-

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文章引用: 王娟, 彭亚楠, 崔晨阳, 李福霞, 周小铃. 宫颈癌淋巴结转移的临床病理特征与分子机制研究进展[J]. 临床医学进展, 2025, 15(9): 1044-1052. DOI: 10.12677/acm.2025.1592590

risk human papillomavirus (HPV) infection being its primary etiology. Lymph node metastasis (LNM) is a critical pathway for cervical cancer dissemination, significantly influencing disease staging, therapeutic strategies, and prognosis. This article systematically reviews recent advances in the clinicopathological characteristics, diagnostic evaluation methods, molecular mechanisms, and treatment strategies for cervical cancer LNM. The incidence of LNM is relatively low in early-stage cervical cancer but increases markedly in advanced cases. Clinical studies demonstrate that the rate of LNM rises significantly with disease progression, with key risk factors including tumor diameter ≥ 4 cm, deep stromal invasion, and lymphovascular space invasion (LVSI). Current diagnostic approaches primarily rely on imaging modalities (MRI, PET-CT) and sentinel lymph node biopsy (SLNB), though limitations remain in detecting micrometastases. Molecular studies have elucidated a multi-step metastatic cascade: epithelial-mesenchymal transition (EMT) facilitates tumor cell migration; the vascular endothelial growth factor-C (VEGF-C) signaling pathway mediates lymphangiogenesis; immune checkpoints participate in immune evasion; and miRNAs/lncRNAs regulate epigenetic modifications. Therapeutically, SLNB is feasible for early-stage patients, while concurrent chemoradiotherapy (CCRT) remains the mainstay for locally advanced disease. Emerging targeted therapies and immunotherapies show promising potential in clinical trials. Future research should integrate cutting-edge technologies like artificial intelligence (AI) to develop novel biomarkers and optimize personalized treatment regimens, thereby improving patient outcomes. Through multidisciplinary collaboration, precision medicine for cervical cancer LNM may be achieved.

Keywords

Cervical Cancer, HPV, Molecular Pathogenesis, Lymph Node Metastasis

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1. 引言

宫颈癌是全球女性中最常见的恶性肿瘤之一[1],尤其在发展中国家[2][3],其发病率和死亡率居高不下[4][5]。据世界卫生组织统计,全球每年新增超过 50 万宫颈癌病例[6][7],其中约有一半的患者因疾病进展而死亡[8]。宫颈癌的主要病因是高危型人乳头瘤病毒(HPV)感染[5][6],特别是 HPV 16 和 18 型[9][10],这两种亚型感染与宫颈癌的发生密切相关[11][12]。宫颈癌的病程进展往往伴随着局部浸润和远处转移[13],其中淋巴结转移是最常见且最重要的转移途径。淋巴结转移在宫颈癌的发生和发展中起着关键作用[14],是评估患者预后和制定治疗方案的重要依据[14][15]。淋巴结转移的存在与否直接影响宫颈癌的分期、治疗策略和预后。一般来说,淋巴结阳性患者的预后较差,五年生存率明显降低[16]。因此,早期发现和准确评估淋巴结转移对于改善宫颈癌患者的临床结局至关重要。目前,对于宫颈癌淋巴结转移的诊断和评估主要依赖于影像学检查和病理学评估[17]。然而,这些传统方法在敏感性和特异性方面存在一定局限性[18],难以全面揭示淋巴结转移的复杂生物学特性。近年来,随着生物信息学和分子生物学技术的发展,人们对宫颈癌淋巴结转移的分子机制有了更深入的了解。研究表明,淋巴结转移是一个多步骤、多因素的复杂过程,涉及基因表达调控、信号通路激活、肿瘤微环境变化以及免疫逃逸等多方面的相互作用[19][20]。这些研究为揭示淋巴结转移的分子机制和寻找新的诊断标志物提供了重要线索。本文旨在综述宫颈癌及其淋巴结转移的最新研究进展,包括其临床特征、诊断方法、分子机制和治疗策略。通过整合临床和基础研究的最新成果,我们希望为宫颈癌淋巴结转移的诊断、治疗和预后评估提供新的见解,并展望未来可能的发展方向。

2. 宫颈癌淋巴结转移的临床病理特征

淋巴结转移在宫颈癌的发生和发展中起关键作用，是影响预后和指导治疗的重要指标。早期宫颈癌患者的淋巴结转移率较低，而晚期患者的转移率显著增加。了解淋巴结转移的发生率、危险因素及其对预后的影响，有助于早期诊断和个体化治疗策略的制定。

2.1. 淋巴结转移的发生

淋巴结转移在宫颈癌患者中较为常见，且其发生率与疾病的分期密切相关[18][21]。宫颈癌患者的淋巴结转移风险随着分期的进展而增加。早期宫颈癌主要是局部肿瘤，但有少量淋巴结转移的风险。随着疾病进展到中晚期，淋巴结转移的发生率显著增加，晚期常伴有远处器官转移。总体而言，宫颈癌的分期越晚，淋巴结转移风险越高，并且是晚期患者预后较差的主要原因之一。

2.2. 淋巴结转移的危险因素

宫颈癌的淋巴结转移风险受到多种临床和病理因素的影响。首先，肿瘤大小是重要指标之一[22]，肿瘤直径超过 4 厘米的患者通常具有更高的转移可能性。这是因为较大的肿瘤往往伴随着更深的组织浸润和更高的转移潜能。其次，浸润深度与淋巴结转移呈正相关，特别是当肿瘤侵及宫颈基质的深层或子宫体时，转移风险明显升高[23]。深层组织浸润增加了肿瘤细胞进入淋巴管和血管的机会，促进转移。

血管/淋巴管侵犯(LVSI)在早期宫颈癌患者中是一个关键的预测指标[24]。LVSI 指的是肿瘤细胞侵入周围的血管和淋巴管，这显著增加了淋巴结转移的风险。LVSI 的存在通常通过病理学检查检测，并在决定患者术后辅助治疗时起重要作用。其存在往往预示着更具侵袭性的肿瘤特性。

其他与淋巴结转移风险相关的因素包括患者的年龄、免疫状态、HPV 感染状况和肿瘤分化程度。年轻患者、免疫抑制状态、高危型 HPV 感染均与更高的转移风险有关。肿瘤的分化程度也会影响转移率，分化较差的肿瘤通常具有更高的侵袭性和转移潜力。这些因素在临床实践中用于评估患者的预后和制定个体化治疗方案。

2.3. 淋巴结转移的部位及其对预后的影响

淋巴结转移的位置对宫颈癌患者的预后具有重要影响。通常，淋巴结转移会遵循一定的路径[25]，最初发生在盆腔淋巴结，如髂内、髂外和闭孔淋巴结，随后可能扩散到腹主动脉旁淋巴结，甚至更远处的锁骨上淋巴结。盆腔淋巴结的转移通常与较差的预后相关，而如果扩散至腹主动脉旁淋巴结，患者的生存率会进一步降低。远处的淋巴结转移，如锁骨上淋巴结，通常预示着预后非常差。转移淋巴结的数量、微转移的存在以及双侧性转移都会使预后更加不良。研究发现，随着转移淋巴结数量的增加，患者的生存率逐渐下降，尤其当转移淋巴结数量较多时，预后会显著恶化。淋巴结转移的准确评估对于临床分期和制定治疗方案至关重要。

3. 淋巴结转移的诊断与评估方法

淋巴结转移的诊断与评估是宫颈癌治疗中的关键步骤，对患者的预后判断和治疗策略制定具有重要意义。目前，宫颈癌淋巴结转移的诊断和评估方法包括影像学检查、病理学评估、分子诊断以及新兴的生物标志物检测等。

3.1. 影像学评估

CT、MRI 和 PET-CT 是评估宫颈癌淋巴结转移的主要影像学方法[25][26]。MRI 对于评估肿瘤的局

部浸润和淋巴结肿大具有较高的敏感性[27], 而 PET-CT 可用于发现全身范围内的转移病灶[17]。然而, 这些方法的准确性受到淋巴结大小和肿瘤细胞密度的限制[26]。

3.2. 病理学评估

前哨淋巴结活检(SLNB)已成为早期宫颈癌淋巴结评估的重要手段[15][28]。SLNB 可以提供淋巴结转移的准确信息, 减少系统性淋巴结清扫的必要性, 从而降低手术相关并发症[25][29]。淋巴结清扫术仍然是评估淋巴结状态的“金标准”, 但其并发症风险较高。

3.3. 分子诊断和生物标志物

生物信息学分析已用于筛选与宫颈癌淋巴结转移相关的基因和分子标志物。循环肿瘤 DNA (ctDNA)、miRNA 和蛋白质标志物等可用于淋巴结转移的早期检测和预后评估[18]。然而, 这些分子标志物在临床实践中的应用仍需进一步验证。

4. 宫颈癌淋巴结转移的分子机制

宫颈癌淋巴结转移是一个复杂的生物学过程, 涉及多个分子和信号通路的调控, 包括肿瘤细胞侵袭、淋巴管生成、免疫逃逸、表观遗传和基因调控等。以下是与宫颈癌淋巴结转移相关的主要分子机制:

4.1. 肿瘤细胞侵袭和迁移

宫颈癌细胞通过侵袭和迁移进入淋巴管系统是淋巴结转移的第一步[13]。这个过程涉及多个关键机制, 包括细胞黏附、细胞外基质(ECM)的降解以及细胞运动能力的改变。细胞黏附分子, 如 E-钙黏蛋白(E-cadherin)[30], 在维持细胞间黏附和组织结构完整性方面发挥重要作用。然而, 在宫颈癌中, E-钙黏蛋白的表达通常下调, 这与上皮-间质转化(EMT)过程有关[31]。EMT 使肿瘤细胞获得间质表型, 从而增强其迁移和侵袭能力。与此同时, 整合素家族中的某些成员在肿瘤细胞黏附至基质并穿过基底膜的过程中起着重要作用。同时, 基质金属蛋白酶(MMPs)作为降解细胞外基质的关键酶类, 通过破坏基底膜和细胞外基质, 进一步促进了肿瘤细胞的侵袭和迁移, 推动其进入淋巴管[32]。这些机制在宫颈癌的转移过程中发挥着至关重要的作用。

4.2. 淋巴管生成

淋巴管生成是肿瘤细胞向淋巴结转移的重要机制之一[33]-[35]。在这一过程中, 肿瘤细胞通过分泌各种促淋巴管生成因子, 刺激淋巴管内皮细胞的增殖和迁移, 进而形成新的淋巴管。

这些新生淋巴管为肿瘤细胞进入淋巴系统提供了必要的通道。主要的调控因子包括一些关键的生长因子, 这些因子通过与特定的受体结合, 促进淋巴管内皮细胞的增殖和迁移, 从而支持新的淋巴管的形成。

在宫颈癌的研究中, 某些生长因子, 如血管内皮生长因子 C 和 D, 已被确定为重要的淋巴管生成调控因子[34]。它们通过与淋巴管内皮细胞生长因子受体结合, 显著促进了淋巴管内皮细胞的增殖和迁移。研究表明, 宫颈癌组织中这些因子的高表达与淋巴结转移的发生有密切关系, 因此它们被认为是潜在的淋巴结转移预测标志物。除了血管内皮生长因子 C 和 D, 其他一些促淋巴管生成因子也在这一过程中发挥作用。例如, 血小板衍生生长因子、碱性成纤维细胞生长因子以及血管生成素等都参与调控淋巴管的生成[34]。这些因子的作用不仅体现在直接刺激淋巴管内皮细胞, 还涉及肿瘤微环境中的细胞, 如巨噬细胞、成纤维细胞, 这些细胞通过分泌相应的因子进一步促进淋巴管的形成[20]。因此, 淋巴管生成在肿瘤

转移过程中扮演了关键角色,了解其机制对于改进癌症治疗策略具有重要意义。值得注意的是,有研究发现[36]-[39],肿瘤大小通过缺氧微环境调控淋巴管生成。当肿瘤直径超过临床临界值时,其中心区域形成的缺氧微环境会诱导 HIF-1 α 表达上调,进而激活 VEGF 等促淋巴管生成因子的转录。这种缺氧诱导的分子级联反应显著促进了新生淋巴管形成,为肿瘤细胞扩散创造了有利条件,这也从分子层面解释了为何大肿瘤患者的淋巴结转移风险更高。

4.3. 免疫逃逸

肿瘤细胞逃避免疫系统的识别和清除是其在淋巴系统中生存和扩散的关键步骤[40]-[42]。宫颈癌细胞通过多种机制抑制宿主的免疫反应,从而促进淋巴结转移。一个重要的机制是免疫检查点抑制[43][44],宫颈癌中某些免疫检查点分子的高表达会抑制 T 细胞的活化,阻碍免疫系统对肿瘤的监视。特别是肿瘤细胞表面的某些分子,通过与免疫细胞的受体结合,进一步抑制免疫应答,这与宫颈癌的淋巴结转移及预后不良密切相关。此外,宫颈癌微环境中存在大量的免疫抑制细胞,这些细胞通过分泌免疫抑制因子,抑制宿主的免疫应答,促进肿瘤的生长和转移[40]。总体而言,宫颈癌细胞通过这些机制有效地逃避免疫系统的攻击,为其在淋巴系统中的扩散提供了有利条件。

4.4. 表观遗传和基因调控

基因表达的调控和表观遗传改变在宫颈癌的淋巴结转移中发挥着关键作用。小分子 RNA,如某些特定的 microRNA (miRNA),在肿瘤的发生和转移过程中具有重要影响[18][42][45]。这些 miRNA 通过调控基因表达来促进肿瘤的侵袭和转移。例如,一些 miRNA 可以通过抑制细胞间黏附分子的表达,推动上皮-间质转化(EMT),从而增强淋巴结转移的能力。此外,特定 miRNA 还能靶向抑癌基因,促进肿瘤细胞的生存和侵袭[46]。

长链非编码 RNA (lncRNA)也是调控宫颈癌侵袭和转移的重要分子[18][46]。研究表明,某些 lncRNA 在宫颈癌组织中高表达,它们通过调节基因表达和改变染色质结构,进一步促进肿瘤细胞的侵袭和转移。总体而言,这些基因表达的调控和表观遗传改变通过多种机制影响肿瘤细胞的行为,为宫颈癌的淋巴结转移提供了有利条件。

5. 淋巴结转移的治疗策略和挑战

对于早期宫颈癌患者,前哨淋巴结活检可以帮助评估淋巴结状态,从而避免不必要的系统性淋巴结清扫[29]。对于淋巴结阳性的患者,扩大手术范围或辅助手段可能改善预后。放射治疗是针对淋巴结阳性宫颈癌患者的重要治疗方法之一。放疗可与化疗结合,增强治疗效果[17]。顺铂为主要的化疗药物[47],可与放疗联合用于治疗局部晚期和淋巴结阳性宫颈癌患者。

靶向治疗和免疫治疗在宫颈癌的治疗中展现出潜力[48][49],但距离临床普及仍存距离。动物实验显示,VEGFR-3 抑制剂、SAR131675 和抗 VEGF-C 单抗、VGX-100 可显著减少盆腔淋巴结转移;然而进入 I 期临床后,外周水肿、狭窄的治疗窗和肿瘤异质性成为跨越到 III 期的拦路虎[50]。miR-34a 脂质体 MRX34 在 I 期试验中安全可耐受,并使淋巴结病灶缩小,却因递送效率低、易降解及潜在脱靶毒性而难以快速推广[51]。免疫治疗方面,PD-1/PD-L1 抑制剂(如 socazolimab)已在复发/转移性宫颈癌中展现持久应答,NiCOL I 期试验进一步证实 PD-L1 抑制剂联合放化疗对淋巴结阳性患者安全可行,但单药有效率仍偏低[52]。综上,尽管 VEGF-C/VEGFR-3 轴和免疫检查点/微环境通路为精准阻断宫颈癌淋巴结转移提供了坚实机制基础,这些疗法在宫颈癌及其淋巴结转移中的应用仍停留在临床试验阶段,亟需更大规模研究验证其疗效与安全性[14]。

6. 未来研究方向与展望

未来对宫颈癌淋巴结转移的研究将整合生物信息学和免疫组化技术,以深入理解其机制并改善临床应用。首先,生物信息学将利用单细胞测序和多组学数据,揭示肿瘤细胞侵袭、淋巴管生成和免疫逃逸的关键分子及其相互作用,包括 EMT 相关的信号通路和肿瘤微环境中的免疫调控机制。免疫组化则可以用于验证这些分子在宫颈癌组织中的表达和分布,进一步确认其在转移过程中的作用。其次,结合生物信息学数据和免疫组化结果,将开发新型非侵入性早期诊断标志物,如基于血液的 miRNA 和外泌体,提升淋巴结转移的检测灵敏度。同时,生物信息学可以帮助筛选和评估靶向治疗和免疫治疗的潜在靶点,免疫组化则用于评估这些治疗的效果和机制。通过这些方法的结合,能够实现对宫颈癌淋巴结转移机制的全面理解,推动个体化治疗策略的应用,最终改善患者的诊断和治疗效果

7. 结论

宫颈癌的淋巴结转移在疾病的发生、发展及预后评估中具有重要意义。淋巴结转移的发生率与宫颈癌的分期、肿瘤大小、浸润深度等因素密切相关。尽管目前的诊断方法不断进步,传统影像学 and 病理学评估仍存在一定的局限性,生物信息学和分子生物学技术的发展为淋巴结转移的早期检测和精准评估提供了新的途径。未来的研究应重点关注分子机制的深入解析和新型生物标志物的开发,特别是结合生物信息学和免疫组化技术,以推动个体化治疗策略的应用。通过这些努力,期望能够实现更有效的宫颈癌诊断和治疗,显著改善患者的生存预后。

基金项目

新疆生产建设兵团科技计划项目(2024ZD055);新疆石河子大学校级科研项目(ZZZC201958A);新疆生产建设兵团天山英才医药卫生领军人才(CZ001214);新建生产建设兵团科技计划项目(2022ZD097);2024 年师市科技计划(2024ZDYL09)。

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