



· 综述 ·

# 子宫内膜癌前哨淋巴结应用的研究进展与展望

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**[摘要]** 前哨淋巴结 (sentinel lymph node, SLN) 检测为子宫内膜癌患者的精准淋巴结切除提供了选择, 极具应用前景, 但仍有部分问题和争议亟待解决, 如SLN检测在高危患者中的标准临床应用规范、SLN最佳算法、评估SLN的最佳方式、低体积转移的临床意义, 均值得探究。目前子宫颈注射吲哚菁绿为最常用的示踪方法, 病理学超分期可提高对低体积转移的检出率, 但病理学超分期操作流程、应用指征及低体积转移的临床管理需进一步规范。此外, 高危型子宫内膜癌并非SLN检测的绝对禁忌证, 但此类患者行SLN检测的标准临床应用规范有待进一步研究。现就近年来子宫内膜癌SLN检测研究现状及进展进行综述。

**[关键词]** 子宫内膜癌; 前哨淋巴结; 微转移; 病理学超分期

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**Research progress and prospect of sentinel lymph node mapping in endometrial carcinoma** LU Yuanyuan, YANG Fan, ZHENG Ying (Department of Gynecology and Obstetrics, West China Second Hospital, Sichuan University; Key Laboratory of Birth Defects and Related Diseases of Women and Children, Sichuan University, Ministry of Education, Chengdu 610041, Sichuan Province, China)

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**[Abstract]** Sentinel lymph node (SLN) mapping has been proposed as a more “targeted” alternative for accurate lymph node resection in endometrial cancer (EC). However, there are still some problems and disputes to be resolved. For example, the standard clinical application of SLN mapping in high-risk patients, the optimal SLN algorithm, the optimal approach to evaluate SLN and the clinical significance of low volume metastasis (LVM) are worth exploring. At present, the cervical indocyanine green injection is the most commonly used tracer method, and the detection rate of LVM can be improved by ultrastaging. However, the procedures and indications of ultrastaging and clinical management of LVM need to be further standardized. In addition, high-risk EC is not an absolute contraindication for SLN mapping, however, the standard clinical application of SLN mapping in such patients needs further clinical study. This article reviewed the research status and progress of SLN mapping in EC in recent years.

**[Key words]** Endometrial cancer; Sentinel lymph node; Micrometastasis; Ultrastaging

子宫内膜癌 (endometrial cancer) 是妇科常见恶性肿瘤之一, 近年来发病率逐渐升高, 2015年中国新发病例约6.9万例<sup>[1]</sup>。对淋巴结状态的评估是子宫内膜癌手术分期的关键步骤之一, 精准评估子宫内膜癌患者淋巴结转移与否对指导辅助治疗、评估预后具有重要意义。然而据文献报道早期子宫内膜癌患者淋巴结转移率低 (1.0%~9.0%)<sup>[2]</sup>, 且此类患者多合并肥胖、糖尿病等并发症, 手术难度增加、术后易出现淋

巴囊肿、淋巴水肿、血管神经损伤等并发症。根据淋巴结转移规律的研究, 前哨淋巴结 (sentinel lymph node, SLN) 检测技术应运而生。SLN指原发肿瘤区域淋巴引流的第一站淋巴结, SLN检测旨在获得病理学分期信息的同时减少手术相关并发症, 为子宫内膜癌患者的精准淋巴结切除提供新的选择。目前, 多部指南提出子宫内膜癌的SLN检测标准以规范临床治疗, 但尚存少数灰色争议地带亟待讨论解决<sup>[3-6]</sup>。本综述对子宫内膜

癌SLN检测的研究现状及进展进行分析总结,以期指导临床应用。

## 1 SLN检测的适应证

目前国内外指南及专家共识主张早期低危子宫内膜癌患者可获益于SLN检测,在避免系统性淋巴结清扫术相关并发症的同时获取分期信息,指导后续治疗。但SLN检测在高危子宫内膜癌中的应用仍有争议。

高危子宫内膜癌指 I B期G3级子宫内膜样癌、II型或II期及以上的子宫内膜癌<sup>[7]</sup>,恶性程度高,预后差,即使处于早期仍有可能存在远处转移,SEPAL研究强调系统盆腔淋巴结清扫+腹主动脉旁淋巴结切除可改善此类患者预后<sup>[8]</sup>。部分学者主张高危子宫内膜癌淋巴结转移是多灶性、不可预测的,不建议高危患者常规行SLN检测。Ye等<sup>[9]</sup>前瞻性纳入了131例子宫内膜癌患者(其中低危患者106例,高危患者25例)行SLN检测,结果显示高危患者SLN检测敏感性降低(20.0% vs 100.0%)而假阴性率显著上升(80.0% vs 0.0%)。高危患者SLN假阴性率及非SLN转移率均较高<sup>[9-11]</sup>,这可能与高危患者肿瘤转移堵塞淋巴管改变了原始淋巴循环相关。但随着技术的革新和研究的深入,支持SLN检测在高危子宫内膜癌中应用的呼声渐高<sup>[12-14]</sup>。Soliman等<sup>[13]</sup>对101例高危患者进行SLN检查,结果显示其SLN检出率、敏感性和假阴性率分别为89.0%、95.0%和5.0%,同时术者对未显影侧加行盆腔淋巴结清扫术+主动脉旁淋巴结切除术可使假阴性率进一步降至4.3%,Touhami等<sup>[14]</sup>的研究中SLN检出率与前者相当,且假阴性率仅为1.4%(1/128)。此外,研究发现与系统性淋巴结清扫术相比,SLN检测不影响高危子宫内膜癌患者的预后<sup>[15-17]</sup>。Schiavone等<sup>[17]</sup>将248例浆液性子宫内膜癌患者分别纳入SLN检测组( $n=153$ )和淋巴结清扫组( $n=95$ ),术后患者均接受辅助治疗,结果发现两组无进展生存率差异无统计学意义(77.0% vs 71.0%, $P=0.30$ )。2021年美国国立综合癌症网络(National Comprehensive Cancer Network, NCCN)指南认为SLN检测可能使高危患者获益<sup>[3]</sup>,中国专家共识持相同观点,但也指出高

危患者行SLN检测是否需同时系统性清扫淋巴结尚待进一步研究<sup>[4]</sup>。

综上所述,高危型子宫内膜癌已不再是SLN检测的绝对禁忌证,但如何选择患者、术中方案的制定及术后辅助治疗的决策,尚需更多高质量研究来充实循证医学证据。

## 2 示踪剂的选择及注射方式

临床常见示踪剂包括荧光染料、生物活性染料(如蓝色染料、纳米碳)及放射性锝-99(Tc-99)等,上述示踪剂可单用或联合使用。目前国内外指南多推荐荧光染料吲哚菁绿(indocyanine green, ICG)为子宫内膜癌SLN示踪剂<sup>[3-5]</sup>,ICG荧光信号穿透性强、可显示深部淋巴结,尤适用于肥胖患者,以0.50~1.25 mg/mL、2~4 mL经子宫颈注射时示踪效果最佳<sup>[18-19]</sup>,但需借助特殊成像设备,某些医疗条件较差地区应用受限。ICG示踪SLN检出率高,2018年1篇Meta分析显示ICG的SLN总检出率高于蓝色染料和Tc-99(94%、86%和86%)<sup>[19]</sup>。相较于其他示踪剂,ICG更易致淋巴管肿胀干扰识别SLN,术中借助近红外成像设备不同显像模式辨识标本形态(线形或圆形)、触诊检查或送冰冻病理学检查有助于确保所取标本为淋巴结<sup>[20]</sup>。纳米碳(carbon nanoparticles, CNP)此前多用于乳腺癌、甲状腺癌等浅表肿瘤,近年来作为一种新兴示踪剂应用于子宫内膜癌诊治中,其SLN总检出率超92%<sup>[21]</sup>,示踪效果令人满意。蓝色染料及Tc-99则因易弥散或具放射性、保存运输复杂等弊端而使临床应用受限。

现有子宫内膜癌SLN示踪剂注射方式多样,主要包括子宫颈注射、子宫腔镜下注射、子宫体(底)注射等。子宫颈注射因操作简便、可重复性强、盆腔SLN检出率高而倍受青睐,是目前国内外指南及研究的首选<sup>[3-4]</sup>。但由于病灶位于宫腔,且常为多灶性分布,对于子宫颈注射是否反映癌灶周围的真实淋巴引流尚存疑问。同时,该注射方式对腹主动脉旁SLN显影效果欠佳<sup>[22]</sup>,但近期学者发现子宫颈注射深度改为3~4 cm或联合双侧宫角注射可提高腹主动脉旁SLN的检出率<sup>[23-24]</sup>。子宫体(底)注射SLN检出率相对较低,且肿

瘤或子宫肌瘤致子宫体严重变形时较难实施。子宫宫腔镜下于癌周注射理论上可真实地反映癌灶淋巴结引流, SLN总检出率优于子宫体(底)注射(82% vs 73%)而与子宫颈注射相近(82% vs 87%), 腹主动脉旁SLN检出率则高于后两者(45%、21%和5.8%), 但操作复杂, 不适用于体积较大或多灶分布难以辨识的癌灶, 且子宫腔镜操作是否会引起肿瘤细胞腹腔播散尚存争议<sup>[18, 22, 25]</sup>。此外, 有学者提出了新型注射方式, 2014年Mücke等<sup>[26]</sup>尝试经阴道于子宫颈峡部肌层注射示踪剂, 最终SLN总检出率及腹主动脉旁SLN检出率分别为90.3%和18.0%。近期也有研究者使用带鞘导管自子宫颈外口进入子宫腔注射示踪剂, 该法操作简便, 单用或联合子宫颈注射可在保障盆腔SLN检出率(70.0%~93.5%)的同时获得更高的腹主动脉旁SLN检出率(41.5%~66.9%)<sup>[27-28]</sup>。但上述新型注射方式多为小样本研究, 需进一步研究验证其安全有效性。

### 3 SLN算法

子宫内膜癌盆腔SLN引流有3个主要通路: 上子宫颈旁通路(upper paracervical pathway, UPP), 沿子宫动脉引流髂外淋巴结和(或)闭孔淋巴结; 下子宫颈旁通路(lower paracervical pathway, LPP), 沿子宫静脉引流髂内和(或)骶前淋巴结; 骨盆漏斗韧带通路(infundibulopelvic pathway, IPP): 沿骨盆漏斗韧带引流腹主动脉旁淋巴结。

据报道示踪剂显影多位于UPP通路(髂外淋巴结及闭孔淋巴结), 但考虑到部分高危患者可能出现骶前淋巴结转移, LPP通路的SLN检测不应忽略。鉴于UPP及LPP两条通路持续引流盆腔淋巴至低位腹主动脉旁淋巴结区域, 为确保术中所取腹主动脉旁淋巴结为SLN而非次级淋巴结, Geppert等<sup>[29]</sup>主张只有在UPP、LPP两条通路均无SLN显影的前提下, 才能将IPP通路显影的淋巴结视作SLN。Persson等<sup>[30]</sup>于2017年首次提出一种旨在实现UPP、LPP两条通路双侧显影的SLN算法, 检出效果优异但程序较为繁琐且研究中重复注射示踪剂可能导致多个相邻淋巴结显影影响辨识SLN。随后Bollino等<sup>[31]</sup>简化了此SLN算法, 根据患者风险分层决定处理方式, 最终要

求所有患者均应实现UPP通路SLN检测, 仅对高危患者要求UPP、LPP双通路显影, 对UPP通路未能显影的患者行髂外淋巴结及近端闭孔淋巴结切除术, 高危患者LPP通路未能显影需行骶前淋巴结清扫术。但上述SLN算法目前尚未广泛应用于子宫内膜癌SLN检测中, 尚需积累更多临床资料。

目前研究多依照NCCN指南中的SLN算法, 即若未能实现双侧显影, 应清扫未显影侧淋巴结。术中可疑淋巴结均应切除, 腹主动脉旁淋巴结是否切除则取决于术者决策<sup>[3]</sup>, 严格遵循SLN算法可提高SLN检出率、降低假阴性率, 进而为临床决策提供准确信息。

### 4 SLN的病理学检测与微转移

对SLN的病理学评估, NCCN指南及国内专家共识建议使用病理学超分期(ultrastaging)<sup>[3-5]</sup>。病理学超分期指连续超薄H-E染色切片联合或不联合免疫组织化学, 该方法不仅能够提高淋巴结转移检出率, 还可根据转移灶大小划分宏转移(转移灶直径>2 mm)和低体积转移(low volume metastasis, LVM), 并进一步细分LVM为微转移(micrometastasis, MM), 即转移灶直径为0.2~2.0 mm; 以及孤立肿瘤细胞(isolated tumor cells, ITC), 即转移灶直径≤0.2 mm<sup>[10]</sup>。但超分期耗时久且需经验丰富的病理科医师操作, 不利于指导术中决策, 其具体实施流程及应用指征需进一步研究。除超分期外, 术中快速冷冻切片(frozen section, FS)病理学检查能有效识别宏转移, 鉴于宏转移时非SLN转移率显著高于低体积转移<sup>[32]</sup>, 中国专家共识及部分学者提出术中可酌情行FS评估SLN, 根据FS结果决定手术范围<sup>[4, 10, 33]</sup>, 但FS识别LVM敏感性较低, 且可能使淋巴结组织扭曲, 不利于进一步病理学超分期<sup>[34]</sup>, 术中未识别的LVM是否会影响患者预后尚未明确, FS评估SLN的安全可行性及具体指征需要进一步研究。此外, 既往多用于乳腺癌临床诊治的一步核酸扩增分析法(one-step nucleic acid amplification assay, OSNA)近年来也有研究将其引入子宫内膜癌SLN检测中, OSNA耗时短, 有利于指导术中决策且相较于超分期转移检出率更高(20.69%

vs 8.15%)<sup>[35]</sup>，但无法评估转移灶形态学特征且成本高，目前尚未在子宫内膜癌诊治领域广泛应用。

LVM的临床意义及管理尚存争议。2021年NCCN指南认为ITC不作为分期升级的依据，但ITC可指导辅助治疗方案的制定<sup>[10]</sup>。研究发现LVM可能与盆腔外复发有关，辅助治疗可改善此类患者预后，但存在过度治疗的可能<sup>[36-39]</sup>。一项回顾性队列研究对所有存在淋巴结转移证据的患者予以辅助治疗，最终LVM者无复发生存率（recurrence-free survival, RFS）与淋巴结转移阴性者相当（86% vs 90%），优于宏转移者（86% vs 71%）<sup>[38]</sup>。而Plante等<sup>[36]</sup>的研究中视ITC为淋巴结转移阴性，仅对淋巴结转移阳性（宏转移、MM）及淋巴结转移阴性的高危患者予以辅助治疗，结果发现存在ITC患者无进展生存率（progression-free survival, PFS）与存在MM、淋巴结转移阴性患者相近（95.5%、85.5%和87.6%）而明显优于宏转移者（58.5%），由此提出存在ITC的低风险患者从辅助治疗中获益有限，辅助治疗方案应结合组织病理学检查结果、子宫状态及患者整体情况制定。目前看来在临床实践中对于LVM患者的管理应结合患者具体情况个体化分析，需要进一步临床研究以指导诊疗实践。

综上所述，SLN检测作为系统性淋巴结清扫与免淋巴结切除的一种折衷方法，在子宫内膜癌中的应用日趋成熟、极具前景。目前ICG是国外研究及指南最为推荐的示踪剂，而子宫颈注射也因其操作的简易性、可重复性、高成功率及高盆腔淋巴结检出率备受青睐。但SLN检测在子宫内膜癌患者中的应用仍有许多争议，譬如SLN检测在高危子宫内膜癌中标准临床应用规范、SLN最佳算法、评估SLN的最佳方式、低体积转移的临床意义等仍需进一步研究予以明确，期待未来更多大规模研究指导子宫内膜癌SLN检测的临床应用。

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