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前哨淋巴结检测方法及其在肿瘤中的研究进展*

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摘要: 前哨淋巴结(sentinel lymph node, SLN)是肿瘤淋巴结转移的第一站, SLN 活检肿瘤阳性的患者需要做系统性淋巴结清扫; SLN 活检阴性的患者, 不需要做系统性淋巴结清扫, 可以缩短手术时间, 降低手术费用, 减少手术并发症; 目前识别 SLN 的方法包括生物活性染料示踪法, 放射性核素示踪法, 联合示踪法, 纳米炭(carbon nanoparticles, CNP)标记前哨淋巴结活检技术以及吲哚菁绿(Indocyanine Green, ICG)荧光标记法。SLN 活检技术在乳腺癌、甲状腺癌、胃癌、恶性黑色素瘤、宫颈癌、子宫内膜癌等肿瘤中皆有不同程度的研究。本文通过复习文献, 对前哨淋巴结检测方法予以归纳及其在常见肿瘤中的研究进展予以综述, 旨在为恶性肿瘤临床治疗提供参考。

关键词: 前哨淋巴结; 检测方法; 肿瘤

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Sentinel Lymph Node Detection and Its Progress in Tumors*

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ABSTRACT: Sentinel lymph node is the first station of lymph node metastasis, Patients with positive sentinel lymph node biopsy require systematic lymph node dissection, whereas the negative patients do not which can shorten the operation time, reduce the cost of operation and complications. Currently, recognition method of sentinel lymph nodes including the biological activity of dye tracer method, radionuclide tracer method, combined tracer method, carbon nanoparticles labeled sentinel lymph node biopsy and indocyanine green fluorescence labeling method. Sentinel lymph node biopsy has been studied in various degrees, including breast cancer, thyroid cancer, gastric cancer, malignant melanoma, cervical cancer and endometrial carcinoma. This article reviewed the literature and summarized the methods of sentinel lymph node detection and its progress in common tumors, aiming to provide reference for the clinical treatment of malignant tumors.

Key words: Sentinel lymph node; Test method; Tumour

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SLN 是指肿瘤部位淋巴引流的第一站, 也是最早发生转移的淋巴结。SLN 最早研究是在 1997 年 Cabanas^[1]对阴茎癌患者行淋巴管造影研究时发现的, 故命名为前哨淋巴结。近年来随着精准医学的发展以及肿瘤患者对术后生活质量的追求, 肿瘤全淋巴结清扫手术的并发症越来越多, 如果前哨淋巴结活检阴性的肿瘤患者可以避免全淋巴结清扫术, 那么对于患者将是极大的福音。SLN 活检在恶性黑色素瘤、乳腺癌^[2]治疗中的应用已经取得了较好效果, 而 SLN 在宫颈癌治疗方面尚在起步阶段, 其示踪结果报道不一^[3]目前 SLN 检测方法包括生物活性染料示踪法, 放射性核素示踪法, 联合示踪法, 纳米炭标记前哨淋巴结检测技术以及吲哚菁绿荧光标记法。

1 前哨淋巴结检测技术

1.1 生物活性染料示踪法

又可分为比色法^[4](Colorimetric methods), 比色淋巴图是指在白色光线下用有色染料对淋巴道和淋巴结进行视觉检测。这种技术需要最少复杂的设备, 适用于开放式、腹腔镜和机器人的方法。异硫蓝(Isosulfan blue)是美国食品和药品管理局(Food and Drug Administration, FAD)批准的用于淋巴结定位的试剂。通常情况下, 宫颈注射异硫蓝后在淋巴结及淋巴管聚集约 10-20 分钟, 注射后延迟定位将导致检出率降低, 因为染料可通过淋巴道弥散。注射位置应该在浅层以减少染料进入更深的组织。异硫蓝的缺点是费用高、使用的限制性、过敏反应。术前注射给药并观察 60 分钟可以考虑用来降低过敏反应的风险。亚甲蓝(Methylene blue)是异硫蓝的低成本替代品, 尽管有证据表明在其他肿瘤中与异硫蓝有等效的淋巴结定位作用, 然

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而它是非 FDA 批准使用的。

1.2 放射性核素示踪法

放射性胶体得 99 注射液和核成像和或者术中 r 计数器检测是一种在乳腺癌、黑色素瘤、外阴癌中进行前哨淋巴结定位原创技术,它常常是协同蓝染法或吲哚菁绿优化检测。放射性同位素的优点是通过深部组织穿透信号,这对子宫内癌患者来说是有利的,因为淋巴盆地可能是脂肪组织,淋巴引流也是不可预知的。对于开放式手术和腹腔镜下 r- 探测仪探测均可行。结合术前影像学来定位前哨淋巴结的位置,但是需要核医学中的一个单独核素注射程序,增加了成本和不便。r 探测仪可识别 " 热点 " 示踪信号区域。在识别了核素摄取增加区域后手术医师通过精细解剖在 r 信号增加区域直观的识别出蓝染淋巴结。

1.3 联合示踪法

通常是放射性核素法结合蓝染法或者吲哚菁绿荧光成像法。优点是集中了两种方法的优点,检出率高,假阴性率低,盲目性小。缺点是检测费用高,技术要求高,工作量大。

1.4 纳米炭标记前哨淋巴结活检术

CNP^[6]混悬液是由纳米级炭颗粒制备而成的一种生物活性淋巴示踪染料,其团粒粒径平均为 150 nm,注射到肿瘤周围时可由吞噬细胞吞噬,只进入毛细淋巴管,不进入血管,在淋巴管及淋巴结中保持持久清晰显色,在体内能够全部代谢无残留,尚未见其对人体有害的相关报道。CNP 具有淋巴系统趋向性和吸附抗癌药物等特点,能在淋巴管、淋巴结高密度且长时间聚集,有利于指导恶性肿瘤的淋巴结清除及淋巴化疗。

1.5 吲哚菁绿荧光标记法

ICG 是荧光示踪剂的代表,又称为靛菁绿,是一种具有近红外特征吸收峰的三碳吲哚染料,最大发射波长在 795-845 nm 之间,且具有亲水和亲油的亲两性结构。ICG 在稀释后使用效果最优。ICG 荧光信号在近红外成像仪进行过滤,得到 830 nm 光波。近红外热像仪可用于开腹、腹腔镜和机器人手术。ICG 信号穿透组织,结合比色法和放射性核素法也允许在实时可视化下解剖。ICG 已被证明优于蓝色染料法,尤其是对于肥胖患者。这种示踪剂的唯一缺点是对专用的近红外成像设备的要求,不良事件的风险是极低的,但是,应该避免患者严重的碘过敏或肝功能衰竭,因为它是完全由肝脏排泄的。

2 前哨淋巴结在肿瘤中的研究进展

2.1 前哨淋巴结与乳腺癌

乳腺癌是女性常见恶性肿瘤,近年来发病趋于年轻化。单纯的乳腺切除术和腋窝淋巴结清扫术是最常用的手术方式。而研究表明乳腺癌患者腋窝淋巴结清扫术有 25.3 % 淋巴结均为阴性,且术后并发症率较高,所以前哨淋巴结活检已经成为临床淋巴结阴性患者的治疗标准^[6]。乳腺癌前哨淋巴结活检的应用范围很广泛,导管内癌及早期浸润性乳腺癌,临床腋窝淋巴结阴性或淋巴结穿插活检阴性都是其适应症^[7]。同时,前哨淋巴结活检技术可被用于新辅助化疗后淋巴结阳性转阴性后的乳腺癌中,炭标记细胞学证实有转移的腋窝前哨淋巴结在技术上是可行的,没有额外术前定位的炭标记步骤对于新辅助化疗后淋巴结由阳转阴的乳腺癌前哨淋巴结活检技术的诊断是有利

的^[8]。DeSnyder SM 等^[9]人研究发现前哨淋巴结活检在炎性乳腺癌中并不适用。Zhou YT 等^[10]人研究表明染料法、放射性核素法及联合法前哨淋巴结检出率分别为 88.2 %、93.0 % 和 97.4 %。近年来,ICG 荧光成像作为一种全新的前哨淋巴结检测方法,因其操作简单且具有较高的 SLN 检出率,检出数目,准确率,逐渐应用于临床^[11]。Osako T 等^[12]人研究发现一种新型前哨淋巴结肿瘤转移核酸拷贝分类法可以指导乳腺癌患者的预后和治疗决策。然而乳腺癌患者前哨淋巴结活检的假阴性率也不容忽视,Lee SA 等^[13]人研究发现导致假阴性的危险因素有可疑的影像学评估、上外象限乳腺癌和少数淋巴结肿大。Zhou YT^[10]研究发现假阴性率与主观因素也有关。

2.2 前哨淋巴结与甲状腺癌

甲状腺癌是最常见的甲状腺恶性肿瘤,约占全身恶性肿瘤的 1 %。甲状腺癌其病理类型可以分为乳头状癌、滤泡状癌、髓样癌及未分化癌 4 类。目前手术治疗是甲状腺癌首选治疗手段,但国际上对其手术方式,切除标准以及淋巴结清扫范围和适应症存在较大争议^[14]。Yan X 等^[15]人研究发现纳米炭标记前哨淋巴结活检在发现甲状腺乳头状癌隐匿性癌淋巴结转移中是安全可行的,其敏感性、特异性、阳性预测值、阴性预测值、假阳性率和假阴性率分别为 78.8 %、100 %、100 %、84.3 %、0 % 和 21.2 %,尤其适用于男性、多发病灶和伴有甲状腺外扩散的患者。有研究表明^[16]前哨淋巴结活检有助于甲状腺微小癌的诊断,另一方面前哨淋巴结活检可以减少因癌转移或者漏诊甲状腺微小癌而进行的二次手术。Gelmini R^[17]研究发现在对分化型甲状腺癌前哨淋巴结活检技术还有待进一步验证和优化。对于低危型甲状腺癌,Saliba J 等^[18]人研究发现前哨淋巴结活检可以纳入到指南中指导治疗,因为前哨淋巴结活检阴性患者术后刺激甲状腺球蛋白水平明显较低。

2.3 前哨淋巴结与胃癌

胃癌在我国各种恶性肿瘤中居于首位,好发年龄在 50 岁以上,男女发病率比为 2:1。胃切除术和区域性淋巴结清扫术是胃癌患者常见手术方式。早期胃癌(early gastric cancer,EGC)是指肿瘤组织浸润局限在胃壁黏膜或黏膜下层,而无关肿瘤大小及有无淋巴结转移。据悉,早期胃癌淋巴结转移率约 15 % -20 %,前哨淋巴结导航手术在早期胃癌中的创新应用可以防止不必要的淋巴结清扫术以及显著降低胃切除量^[19]。Nam KH 等^[20]人研究发现淋巴结转移与肝细胞生长因子和 CD133 过表达密切相关,提示这些蛋白作为早期胃癌淋巴结转移的独立预测指标是有用的。进展期胃癌(advanced gastric cancer,AGC)是指肿瘤组织浸润肌层或浆膜层,无关肿瘤大小和有淋巴结转移。淋巴结转移是胃癌转移的主要途径之一,Xie Y 等^[21]人研究发现与传统的根治性胃切除术相比,II 期进展期胃癌前哨淋巴结活检在术中出血量和住院天数延长的前提下均能提高 2 年生存率。也有研究表明,胃癌的淋巴引流具有多向性和跳跃性等特点,所以对于进展期胃癌行前哨淋巴结活检的临床价值不大^[22]。

2.4 前哨淋巴结与黑色素瘤

黑色素瘤又称为恶性黑色素瘤,是来源于黑色素细胞的一类恶性肿瘤,常见于皮肤,亦可见于黏膜、眼脉络膜等部位。在世界范围内,前哨淋巴结活检确定分期已经是大于等于 1 mm

黑色素瘤患者检查的一部分^[23]。目前,对于微小黑色素瘤沉积前哨淋巴结检测并没有标准化协议,Jonjin N 等^[24]人研究发现术中细胞学染色识别前哨淋巴结转移的特异性、敏感性分别为 99 %、57 %,对避免再次手术是有用而且有利的。前哨淋巴结活检指南集中在病理因素,Sinamon AJ 等^[25]人研究发现年龄是淋巴结转移分级重要因素,年龄小于 40 岁、肿瘤大小 0.5-0.75 mm 的 T1b 期患者并不推荐前哨淋巴结活检,淋巴结阳性率仅 5.6 %;相反,年龄大于 65 岁、肿瘤大小 0.76 mm 的 T1b 期患者一般推荐前哨淋巴结活检。Moody 等^[26]人研究发现,黑色素瘤患者治疗性淋巴结切除术后并发症总发生率为 39.3 %,包括伤口感染裂开 25.4 %、淋巴水肿 20.9 %和血肿 20.4 %;完全性淋巴结清扫术后并发症总发生率为 37.2 %,包括伤口感染裂开 21.6 %、淋巴水肿 18 %和血肿 17.9 %,并发症略低,但仍有统计学意义。MSLT-II 研究却表明前哨淋巴结转移的黑色素瘤患者,完成淋巴结清扫术增加了区域性疾病控制率并提供了预后信息,但并没有改善黑色素瘤患者的特异性生存率,所以具有极低前哨淋巴结病变的患者常常已经放弃淋巴结清扫术,然而这并不适用于所有的患者^[27]。

2.5 前哨淋巴结与宫颈癌

宫颈癌是常见的女性生殖系统恶性肿瘤,其发病率居于我国女性恶性肿瘤的首位且近年呈上升趋势,常用手术方式是根治性全子宫切除术和双侧盆腔淋巴结清扫术,必要时行腹主动脉旁淋巴结清扫。淋巴结转移是宫颈癌最重要的预后因素之一,尽管淋巴结状态并不影响 FIGO(International Federation of Gynecology and Obstetrics,FIGO)宫颈癌分期^[28]。而早期宫颈癌盆腔淋巴结转移率仅仅 10 %-30 % 左右^[29],发生淋巴结转移者预后较差,5 年生存率不足 30 %^[30]。宫颈癌的淋巴引流途径有一定规律性,1979 年 Buchsbaum 详细描述了宫颈癌淋巴结转移的三种途径,最常见的侧方转移到闭孔淋巴结,然后到髂内、髂外淋巴结,最后到髂总淋巴结;第 2 条途径是向前转移,最终转移到髂外淋巴结;第 3 条是向后注入髂总、骶淋巴结以及腹主动脉旁淋巴结^[31]。Zigras T 等^[32]人研究发现前哨淋巴结活检与盆腔淋巴结清扫术相比,具有高灵敏性、假阴性率、降低发病率和同等生存率的显著优势。Malur 等^[33]研究者应用染料法、核素法和联合示踪法对 50 例 I-IV 期宫颈癌患者分三组进行研究,结果显示染料法、核素法及联合示踪法 SLN 检出率分别为 55.9 % (5/9)、76.21 % (16/21)、90.0 % (18/20),准确率分别为 80 %、100 % 和 100 %。Lu Y 等^[34]人研究发现纳米炭标记法对 I-A2-IIA 期宫颈癌前哨淋巴结检出率为 95 %,阴性预测值为 100 %,假阴性率为 0 %,最常见的检出部位是闭孔淋巴结 47.97 %。Lopez 等^[35]人研究发现 ICG 荧光成像有很高的盆腔双侧淋巴结检出率,彩色荧光成像可以提高前哨淋巴结检出率。近年来肿瘤免疫研究层出不穷,Balsat C 等^[36]人研究发现转移前哨淋巴结区炎症反应物质 CD8⁺、Foxo3、CD20⁺ 和 PD-1 表达显著增加。值得注意的是,CD20⁺B 细胞和 PD-1 表达生发中心密度与淋巴管密度成正比。这些数据有力的支持了原发肿瘤和前哨淋巴结之间的转移前哨对话,有利于阐明前哨淋巴结的特异性转移微环境。

2.6 前哨淋巴结与子宫内膜癌

子宫内膜癌是女性生殖道常见的恶性肿瘤之一,在发达国

家中,子宫内膜癌是最常见的妇科肿瘤,在国内发病率也逐渐上升。I 期无转移的内膜癌患者 5 年生存率为 90 %,若盆腔或腹主动脉旁淋巴结受累,5 年生存率则降至 44 %-52 %^[37]。现代医学肿瘤学的重点是 "精准" 和 "个性化" 医学,这就意味着通过靶向治疗提高疗效。前哨淋巴结定位最近被引入子宫内膜癌的分期手术,目的是减少盆腔淋巴结清扫术相关并发症的发病率,并且根据淋巴结状态指导辅助治疗,提高预后^[38]。然而,也有研究表明前哨淋巴结定位指导子宫内膜癌手术 - 病理再分级可以识别低量转移,如极低细胞数量淋巴结转移和孤立肿瘤细胞,但是它的临床意义和理想管理方法仍然不确定^[39]。Liu CY 等^[40]人研究证明前哨淋巴结活检在子宫内膜癌腹腔镜手术 - 病理分期中可以减少主观因素影响,增加淋巴结检出率,减少术后并发症。子宫内膜癌前哨淋巴结定位的最佳方法研究发现 ICG 荧光成像定位与放射性核素结合蓝色染料法有相当的前哨淋巴结检出率,但是 ICG 实时双边淋巴结定位检出率更高^[41]。虽然盆腔淋巴结引流途径和前哨淋巴结位置独立于示踪剂注射部位,宫颈^[42]注射有更高的技术成功率,目前数据支持 ICG 宫颈注射定位前哨淋巴结^[43]。

3 小结与展望

随着对肿瘤前哨淋巴结及其检测方法的深入研究发现,前哨淋巴结活检技术在多数肿瘤中的应用是有益并且有效的,可以减少不必要的淋巴结清扫及脏器切除,提高了患者的术后生活质量。前哨淋巴结检测技术多种多样,其检出率及准确率也不尽相同,CNP 标记前哨淋巴结检测技术以及荧光标记法的出现给前哨淋巴结检测带来了新的契机,其独特的优越性,可行性提高了前哨淋巴结的检出率,也为将来恶性肿瘤的靶向治疗药物的研制带来了新方法,为目前提倡的肿瘤精准治疗奠定了基础。前哨淋巴结的检出率及准确性与检测技术方法、手术医师技能及病理诊断密切相关,同时肿瘤淋巴结的跳跃性转移也不容忽视,更加精准科学的前哨淋巴结活检技术需要各方同行的通力合作,协同完成,希望在不久的将来给肿瘤患者带来新的希望,为精准医学的发展增添新的篇章。

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