· 指南与共识 ·

乳腺癌荧光示踪前哨淋巴结活组织检查操作指南

中华医学会肿瘤学分会乳腺癌学组

癌细胞通过淋巴管转移至淋巴结是乳腺癌局部区域扩散的主要方式。通过手术切除腋窝淋巴结确定的腋窝淋巴结分期是乳腺癌预后判断和辅助治疗决策的重要依据。传统的腋窝淋巴结清扫可以获得准确的转移淋巴结数目和良好的局部控制,但上肢水肿、神经损伤等并发症长期困扰着医师和患者。前哨淋巴结活组织检查(简称活检)相对微创、并发症少,而接受前哨淋巴结活检与清扫手术的患者的局部控制率和远期生存率无明显差异,目前已经成为临床腋窝淋巴结阴性早期乳腺癌患者的腋窝分期首选。

前哨淋巴结被定义为肿瘤转移的第一站淋巴结。实际操作中首先在乳房注射示踪剂,根据示踪剂的指引切除第一站淋巴结,通过病理诊断确定转移与否。确保前哨淋巴结活检成功率和准确性的核心在于示踪技术。目前,循证医学证据最充分的方法是核素标记的大分子和蓝色染料双示踪,该方法可以获得超过95%的检出率和低于10%的假阴性率,是前哨淋巴结活检的金标准。但标记核素的制剂存在辐射防护、供药不足、配套设施要求高等现实难题,国内多数单位难以开展。因此,不含核素的乳腺癌前哨淋巴结双标记示踪技术成为了很有吸引力的探索领域。近年来,以吲哚菁绿(indocyanine green,ICG)为示踪剂的近红外荧光示踪技术因其无辐射、使用方便、实时性、学习曲线短等优势迅速获得国内外学者青睐,与蓝色染料联合成为理想的备选双示踪方案。但因为该荧光示踪技术用于乳腺癌前哨淋巴结检测的时间尚短,目前尚无公认的技术规范。

本指南通过总结国内外研究证据,结合部分单位应用经验,明确荧光示踪技术用于乳腺癌前哨淋巴结检测的适应证和操作方法,有利于该技术的推广,促进相关领域的研究。

一、基本技术原理

1. 近红外荧光成像原理

核素标记的大分子是应用最成熟的前哨淋巴结示踪剂,与染料相比,其优势在于发出的γ射线可以穿透皮肤和皮下软组织,在体表即可通过伽马探测仪探测淋巴结发出的γ射线而定位前哨淋巴结。

近红外光是波长为780~1 100 nm的光,其软组织穿透力良好,光谱与可见光无重叠因而受自然光干扰较小,是良好的在体显像工具。与常用的γ射线、X射线不同,近红外光对人体无辐射损伤,使用中无需特殊防护。近红外光成像具有γ射线组织穿透性优势且无辐射安全问题,因而成为替代核素示踪的良好选择。荧光系通过特定波长的激发光激发荧光物质产生特定波长的发射光的常见物理现象。通过在乳房内注射荧光物质,利用特定近红外光装置激发,荧光物质发出可以穿透皮肤软组织的近红外荧光,并利用体外装置接收,通过计算机处理显示成像,即可显示淋巴管、定位淋巴结,这便是近红外荧光示踪前哨淋巴结活检的原理。

2. ICG的特性

ICG是目前最常用的荧光示踪剂,其化学名为2-[7-[1,1-二甲基-3-(4-磺丁基)-2H-苯并[e]二氢吲哚-2-亚基]1,3,5-庚三烯]-1,1-二甲基-3-(4-磺丁基)-1H-苯丙[e]二氢吲哚内鎓钠盐,分子式为$C_{43}H_{47}N_2NaO_6S_2$,分子质量为774.96。ICG的荧光特性与其溶剂、浓度以及是否与其他分子结合有关。在乳房组织内注射ICG后,ICG迅速与组织间液的蛋白结合,浓度也得到稀释,其最大吸收峰约为780 nm,激发光波长为830 nm。

3. 荧光示踪成像设备

荧光示踪成像设备包含激发光产生系统、发射光接收系统和图像处理显示系统。一般将激发光产生系统和发射光接收系统集成为体积较小的探头,通过无菌套膜包裹后可以放到手术台上。术中将探头置于距离皮肤10~30 cm处,缓慢移动探头可以获得较好的乳腺浅表淋巴管引流和乳腺前哨淋巴结的图像。

二、循证医学证据

2005年,日本Kitai等报道利用ICG进行荧光示踪前哨淋巴结活检,可以获得94%的成功率,且可以同时观察到淋巴管和淋巴结,具有良好的可视性和实时性。随后大量研究对ICG前哨淋巴结活检进行了准确性和成功率方面的验证。2004年,*Lancet Oncology*杂志发表系统综述,认为荧光示踪的成功率为93%~100%,优于蓝色染料,与核素相比,差异无统计学意义。平均检出淋巴结数目为1.5~5.4枚,多于染料或核素方法。国内多个中心对荧光示踪进行了验证,结论基本与国外研究一致。2016版德国妇科肿瘤学会(Arbeitsgemeinschaft Gynäkologische Onkologie,AGO)指南将荧光示踪方法的循证医学证据级别评定为2B类。日本乳癌学会对荧光示踪检测前哨淋巴结的推荐度为B级。

三、操作指南

1. 术者要求

术者应具备其他示踪剂指引的前哨淋巴结活检经验,并

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通信作者:王殊(100044,北京大学人民医院乳腺中心),Email:shuwang@pkuph.edu.cn

应观摩过或参加过荧光示踪乳腺癌前哨淋巴结活检手术并熟悉乳腺癌手术及相关解剖。

2. 术前准备

详细询问病史,有碘过敏史者不能接受 ICG 注射,可根据所使用的 ICG 说明书要求决定是否行碘过敏试验。建议通过经皮活检方式获得病理诊断,尽量减少开放性活检对淋巴引流的干扰。一般术前准备同常规手术。

3. 麻醉方式

可以选择气管插管全身麻醉、静脉麻醉或局部浸润麻醉。气管插管全身麻醉效果容易控制,有利于手术操作,适合大多数患者,尤其是需同时行乳房切除者。静脉麻醉或局部浸润麻醉对患者影响小,恢复更快,适合单纯前哨淋巴结活检或同期保留乳房的患者。

4. 示踪剂配置

目前市售的 ICG 剂型为粉剂,每支含 25 mg,使用前先用 10 ml 灭菌注射用水溶解,溶解后质量浓度为 2.5 mg/ml。取 2.5 mg/ml 的 ICG 0.2 ml,用灭菌注射用水稀释至 1 ml(即为 0.5 mg/ml),作为使用的质量浓度。

注意:必须以灭菌注射用水溶解和稀释 ICG,避免使用 0.9% 氯化钠溶液或其他溶剂。

5. 体位

手术体位采用仰卧位,患侧上肢外展,肩部略垫高。术者站在患侧,荧光显示屏最好置于术者对侧偏向患者头侧,便于术者和助手观察。荧光探头以无菌腔镜套包裹后置于手术台上备用。

6. ICG 注射方法

0.5 mg/ml 的荧光示踪剂 ICG 可以注射在乳晕区、乳房皮肤、皮下或肿块周围皮肤或腺体内。推荐在乳晕区皮内注射,淋巴管显示效果更佳,有利于初学者掌握该技术。

具体操作:常规皮肤消毒铺无菌巾后,在乳晕区进针,针头斜面向上倾斜 5°穿刺皮肤,使针头开口处全部刺入皮肤推注 ICG 0.2 ~ 0.3 ml,形成皮丘。可取 2、3 个注射点,勿使注射液漏出皮肤。轻轻按摩注射部位后用荧光探头进行探测,乳房皮下淋巴管即可荧光显像。

如果肿块位于外上象限并已被切除,淋巴引流可能会被破坏,可在切口外上方皮内补充注射少量 ICG。

ICG 敏感性非常高,原液或稀释后注射 1.0 ml 用于前哨淋巴结活检均可取得很好的效果。如联合蓝色染料,染料注射采用常规方法。

7. 切口选择

可采用 2 种方法定位切口。如果乳房上淋巴管显示良好,可以在指向腋窝的淋巴管消失点上方 1 ~ 3 cm 处做切口。如淋巴管显示不佳可采用常规方法,即在胸大肌外缘腋褶线下两横指处做切口。从乳房切除切口手术容易受到皮下渗漏的 ICG 的影响,手术难度加大,不推荐初学者采用。

8. 手术操作

切开皮肤后,直接切开脂肪组织,注意止血,切开软组织直至腋窝筋膜,以皮肤牵开器暴露腋窝组织。以荧光探头探查腋窝,发现“发光”的淋巴结后,钳夹淋巴结周围组织,摘取淋巴结,离体淋巴结再次以探头探测确认是否发光。同样方法摘取腋窝内发光淋巴结,直至无明显荧光信号。再次触诊探查,如发现明显肿大融合的淋巴结应一并摘除。仔细止血后常规缝合腋窝筋膜及皮肤。

注意:荧光信号显示有轻微延迟,因此,荧光探头不宜移动过快。

9. 标本送检

将发光淋巴结标记为前哨淋巴结送病理检查,常规采用 HE 染色,判断困难时可增加免疫组织化学染色帮助判断。

10. 与其他示踪剂联用

尽管目前有研究者认为,单用染料或核素作为示踪剂即可获得良好的示踪效果,但大部分学者仍认为联合采用 2 种示踪原理不同的方法进行双示踪,可以减少示踪失败,降低潜在的假阴性率。双示踪法仍是前哨淋巴结示踪技术的金标准。ICG 荧光示踪与蓝色染料联用避免了核素类药物的介入,综合了荧光示踪的高敏感性、实时性、直观性以及多数医师对蓝色染料较为熟悉的优势,是良好的不含核素的双示踪方法,也是目前大多数开展荧光示踪单位采取的联用策略。ICG+核素联合应用可以避免蓝色染料带来的皮肤染色、皮下组织坏死等潜在并发症,亦是可以考虑的组合。总之,操作者可以根据本单位的条件和自身习惯选择合适的示踪剂联用方法。

四、并发症及处理

ICG 临床应用安全性良好,并发症很少,文献中仅见少量病例报告有过敏反应存在。对于潜在的过敏反应主要在于预防,谨慎用于碘过敏和过敏体质者。多数过敏反应表现为荨麻疹、轻度不适,给予抗组胺药物治疗后可缓解,重症可给予糖皮质激素治疗,过敏性休克者应按照相应流程组织抢救。另外,注射部位短期内可见皮肤染色,无需特殊处理,可自行消失。

五、荧光示踪技术的不足与注意事项

荧光示踪剂不足之处在于其敏感性高,ICG 从淋巴管内漏出后即可污染脂肪筋膜组织而发出荧光,手术过程中应注意精细操作,减少示踪剂的漏出。切除第一枚发光淋巴结后难免会出现荧光污染,继续探查时应注意鉴别发光组织是否为淋巴结。可通过形状、挤压是否变形以及触诊质地综合判断。

需要注意的是,根据腋窝的解剖特点,淋巴结均位于腋窝筋膜深层,如果切开皮肤后在脂肪内盲目游离可能会增加荧光污染机会而很难发现淋巴结,建议直接切开腋窝筋膜后再进行探查。

少数情况下,腋窝无任何发光淋巴结显示,应注意探查胸肌后方,避免遗漏胸肌间淋巴结,因为近红外光穿透力约为 1 cm,难以穿透胸大肌。

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