

消化道肿瘤新辅助放化疗后的内镜评效

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【摘要】 新辅助放化疗作为局部进展期直肠癌、食管癌及食管胃结合部癌的标准治疗方案, 不但能提高肿瘤局部控制率, 还能使部分患者获得病理完全缓解。对新辅助治疗后达到临床完全缓解的患者, 等待观察策略和器官保留理念可在不降低肿瘤学疗效的前提下, 减少不必要的手术创伤并降低并发症发生风险, 大幅提高患者生活质量。目前, 包括白光内镜、内镜下活检、内镜图像增强技术、超声内镜检查、超声内镜引导下针吸活检术、内镜黏膜下剥离术和人工智能辅助技术等在内的多种手段, 已成为新辅助放化疗后疗效评估的重要参考依据, 并在临床中得到广泛应用。本文将针对临床中目前常用的以及新型内镜技术, 在直肠癌、食管癌及食管胃结合部癌新辅助放化疗疗效评估中的应用及最新进展进行介绍。

【关键词】 内镜; 直肠肿瘤; 食管肿瘤; 食管胃结合部肿瘤; 新辅助放化疗; 疗效评估

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Endoscopic response evaluation in gastrointestinal cancers after neoadjuvant chemoradiotherapy

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【Abstract】 Neoadjuvant chemoradiotherapy has emerged as the standard treatment for locally advanced rectal cancer, esophageal cancer and gastroesophageal junction cancer which can not only improve the rate of local control but also induce pathological complete response in some patients. For patients who have achieved clinical complete response after neoadjuvant therapy, the watch & wait strategy and organ preservation could reduce unnecessary surgery and minimize the risk of postoperative complications, meanwhile greatly improve patients' quality of life without affecting the oncologic outcome. At present, a variety of methods, including white light endoscopy, endoscopic forceps biopsy, image enhanced endoscopy, endoscopic ultrasound, endoscopic ultrasound guided fine needle aspiration, endoscopic submucosal dissection, artificial intelligence assisted technology, etc., have become important assistance for the evaluation of tumor response after neoadjuvant chemoradiotherapy and have been widely used in clinical practice. This review will briefly introduce the application of the endoscopic approaches mentioned above and some novel endoscopic techniques and developing trends in response evaluation for patients with locally advanced rectal cancer, esophageal cancer and gastroesophageal junction cancer patients receiving neoadjuvant chemoradiotherapy.

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【 Key words 】 Endoscopy; Rectal neoplasms; Esophageal neoplasms; Gastroesophageal junction neoplasms; Neoadjuvant chemoradiotherapy; Response assessment

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新辅助放化疗(neoadjuvant chemoradiotherapy, NCRT)作为局部进展期直肠癌、食管癌及食管胃结合部癌的标准治疗,不但提高了肿瘤局部控制率,且有 18.0%~40.6% 的患者能够获得病理完全缓解(pathological complete response, pCR)^[1-5]。临床完全缓解(clinical complete response, cCR)是指放化疗后经体格检查及辅助检查,发现局部无肿瘤残留证据(yield clinical TONO, ycTONO)的现象^[6]。对于达到 cCR 的低位直肠癌患者,等待观察策略能够实现器官保留、减少永久性造口的发生,且肿瘤学预后与接受全直肠系膜切除术(total mesorectal excision, TME)后获得 pCR 的病例相似^[7-11]。对于获得 cCR 的食管癌患者,关于器官保留的策略也还在研究中^[12]。

目前临床实践中,对于 cCR 的判断主要通过内镜检查和影像学检查(磁共振 T2WI/DWI 序列及 CT)等手段综合判断。此外,局部病理活检、外周血肿瘤标志物水平和行直肠指检(直肠癌者)等指标也有帮助^[1,13-14]。本文将针对相关常用及新型内镜技术在直肠癌、食管癌及食管胃结合部癌 NCRT 疗效评估中的应用作介绍。

一、内镜技术用于直肠癌 NCRT 的疗效评估

1. 白光内镜检查:Habr-Gama 等^[15]提出直肠癌 NCRT 后 cCR 典型的内镜下表现,包括白光内镜下瘤床呈现白色瘢痕、可见毛细血管扩张以及瘢痕处柔韧度略下降;而溃疡残留、触及结节都视作非 cCR 的表现。尽管上述特征被认为是 pCR 病例的典型内镜下表现,但其标准过于严格,导致其仅在约 40% 的 pCR 病例中被观察到^[16-17]。这也使得医师低估了病变退缩程度和直肠癌 NCRT 后的器官保留率^[18]。既往有研究发现,对于一部分已获得明显缓解,但尚未达到 cCR 标准的患者而言,额外等待 6~12 周有可能获得 cCR,有望进一步提高器官保留率,故 near-cCR 这一概念被引入临床^[19]。目前,小而平的溃疡被认为是 near-cCR 的内镜下主要表现^[17]。在 van der Sande 等^[20]的研究中,扁平瘢痕是 cCR 的最佳预测征象,其阳性预测值为 70%~

80%,小而平的溃疡其阳性预测值为 40%~50%,而大溃疡的阳性预测值仅为 29%~33%。此外,有高达 27% 的病例尽管存在典型的黏膜 cCR 表现,但术后仍然可见到肿瘤残留^[20-21]。其原因在于,NCRT 治疗后黏膜及黏膜下层的瘤细胞最早发生退缩,残余的肿瘤往往位于深层,故即便表面黏膜连续完整,但在肠壁深层组织中依然可能有残余病灶^[22-23]。而此类病例通过内镜下活检钳常规活检往往不能获得肿瘤残留的证据^[23]。有时甚至需要进行超声引导下全层穿刺活检,或局部全层切除活检等手段以明确^[6,7,24-25]。此外,日本 Kawai 等^[26]根据其单中心的研究结果指出,尽管内镜下 cCR 判断标准与肿瘤退缩程度具有良好的一致性,但如果仅根据内镜下 cCR 表现,便对 NCRT 后患者实施等待观察策略,将会导致 41.7% 的患者发生无法挽回的局部进展,严重影响患者的预后。故目前内镜下评估常需要结合其他检查指标综合进行判断。

2. 放大染色内镜:放大染色内镜在消化道肿瘤,特别是早癌诊断中扮演着重要的角色。Chino 等^[27]通过前瞻性单中心研究,提出了通过结晶紫染色联合放大内镜判断 NCRT 后疗效的参考依据:(1)溃疡完全愈合,无白苔附着;(2)线样或扁平瘢痕;(3)无隆起结节;(4)小圆形再生腺管呈均一排列;(5)波纹状大细胞腺管呈均一排列。当上述 5 条全部满足时,可判定为内镜下 cCR;这一标准的诊断准确率为 85%,特异度为 97%,但灵敏度略低(仅 47%),而且不同医师间诊断的一致性一般($Kappa=0.57$)。因此,目前尚不能替代 Habr-Gama 等^[15]的标准,且需要采用放大内镜这一专用设备,同时色素染色较为繁琐,也在一定程度上限制了其广泛应用。

3. 窄带光成像技术:借助窄带光成像技术(narrow-band imaging, NBI),对肿瘤表面微血管进行观察,已广泛用于结直肠肿瘤的诊断^[28]。在 Ishioka 等^[29]的前瞻性研究中,61 例接受 NCRT 治疗的患者中有 19 例证实为 pCR,与单纯白光内镜检查相比,联合 NBI 技术后可将 cCR 的判断准确率从

70.5% 提高至 75.4%，同时将不同医师诊断一致率从 59.9% 提升至 75.6%。因此，虽然 NBI 技术的应用对于进一步提高诊断准确率的价值有限，但却能明显改善不同评估者对 cCR 状态判断的组间一致率，所以该技术在 cCR 临床判断中仍可发挥一定的作用。

4. 超声内镜：超声内镜对 NCRT 后病灶的再分期准确率介于 38%~75%，由于放化疗导致的组织局部纤维化以及水肿在超声内镜下亦呈低回声表现，使得 EUS 难以将其与肿瘤组织进行良好的区分，从而导致超声内镜对 T 分期更容易出现过分期现象，限制了其在临床中的应用。Pastor 等^[30]的一项前瞻性研究显示，超声内镜对于 NCRT 后 T 分期和 N 分期的判断准确率分别为 54% 和 75%，但在被超声内镜判定为 ycN0 的病例中，有 20% 的病例术后被证实存在淋巴结转移。故目前超声内镜并不常规推荐用于 NCRT 后疗效的判断。但对于仅合并直肠周围系膜淋巴结肿大且原发灶考虑 cCR 的病例，可尝试通过超声内镜引导下针吸活检术 (endoscopic ultrasound guided fine needle aspiration, EUS-FNA) 对目标淋巴结进行穿刺活检以辅助明确淋巴结转移状态^[31]。

5. 定量荧光内镜：定量荧光内镜是新近报道的一种新型内镜技术。Tjalma 等^[32]对 25 例接受了 NCRT 治疗的局部进展期直肠癌患者进行了定量荧光内镜检查，发现肿瘤组织中的荧光强度明显高于正常直肠黏膜组织以及纤维化无活性肿瘤的成分；定量荧光内镜、MRI 及白光内镜对 NCRT 疗效判断的准确率依次为 92%、84% 及 80%，且与传统 MRI 联合白光内镜的判断结果相比，定量荧光内镜额外提高 16% 的诊断准确率，后续研究者将对该技术进行更大规模样本的研究，以期获得更为有价值的临床证据。

6. 探头型共聚焦激光显微内镜：探头型共聚焦激光显微内镜 (probe-based confocal laser endomicroscopy, pCLE) 可在活体组织上将图像放大 1 000 倍并进行实时观察，以期达到光学活检的目的。根据 Safatle-Ribeiro 等^[33]的报道，采用 pCLE 对 47 例 NCRT 后病例的瘤床上皮细胞及血管特征进行观察，用于疗效评估；结果显示：pCLE 对于完全缓解 (complete response, CR) 判断的灵敏度、特异度及准确率依次为 100%、71.4% 及 95.7%，作者指出，pCLE 有望在今后改变现有的 cCR 判断模式。

但鉴于现阶段 pCLE 设备尚无法普及、临床操作繁琐及诊断标准缺乏一致性，其距真正用于临床实践仍有一定距离。

7. 内镜黏膜下剥离术 (endoscopic submucosal dissection, ESD)：通常认为，NCRT 后残余肿瘤往往位于黏膜下层以深，故多采用外科经肛门局部全层切除来协助制定器官保全策略，但手术相关并发症难以避免^[34]。Elazzamy 等^[35]报道，NCRT 后 98% 的残余病变可累及黏膜下层，有望采用内镜下切除的方式进行肿瘤残余情况的评估。Leung 等^[36]对 12 例 NCRT 后的直肠癌患者实施了 ESD，评估 NCRT 效果的同时移除可能残余的病灶。虽然 NCRT 造成了黏膜肌层及黏膜下层广泛纤维化，但与未接受 NCRT 治疗患者相比，ESD 的整块切除率及完整切除率差异无统计学意义，且未增加术后并发症发生率，从技术层面指出 ESD 可用于 NCRT 后残余病灶的评估。

8. 人工智能：以上多种内镜技术及内镜手段在用于直肠癌 NCRT 后疗效评估，其准确率及有效性都不可避免地受到操作者经验的影响。而通过机器深度学习、人工智能等技术手段，有望能够缩小个体经验差异带来的诊断差距。一项来自荷兰的初步研究显示，通过深度学习网络计算进行 cCR 判断，虽然结果显示，机器学习的 cCR 判断准确率低于经验丰富的内镜医师^[37]。但随着今后人工智能技术的发展迭代，其有望能够帮助临床医师做出正确的判断，进而提高 cCR 评估的准确率。

二、内镜技术用于食管癌及食管胃结合部癌 NCRT 的疗效评估

1. 胃镜检查及常规活检：在一项前瞻性队列研究中，患者于 NCRT 后 6 周及 12 周分别接受胃镜检查，将胃镜下表现与术后病理结果比较；结果发现，胃镜下可疑肿瘤残留这一征象对非 pCR 的阳性预测值为 91% (NCRT 后 6 周) 及 100% (NCRT 后 12 周)；而食管管腔狭窄、局部瘢痕形成以及溃疡形成这 3 种镜下表现均与肿瘤残留无关^[38]。在 Taghizadeh Kermani 等^[39]的前瞻性研究中，NCRT 后 4~6 周对患者实施胃镜检查，同时对瘤床或病灶进行常规活检，结果显示：无论是内镜下表现抑或活检病理结果，其阳性预测值及阴性预测值均较低，故两种手段均不适合单独用于 NCRT 后是否存在残留病变的判断。

2. 深挖活检：鉴于常规内镜下活检较低的诊断

率,深挖活检(也称 bite-on-bite)也被用于 NCRT 效果的评估。van der Bogt 等^[40]报道,通过该技术将食管残留病灶检出率提高了 20%,检出率提高主要得益于活检次数的增加,而非通过局部深挖获得了更深层次的标本。同时,由于活检后出血等因素影响,即便是经验丰富的医师,仍然难以精准地做到在同一部位连续深挖活检,且合适的活检次数目前尚无定论。

3. 超声内镜: van der Bogt 等^[41]通过前瞻性多中心研究提出,食管癌 NCRT 后 12 周经超声内镜测量获得的瘤床厚度及截面积与肿瘤退缩分级(tumor regression grade, TRG)3~4 级有关。其中瘤床厚度 >4.5 mm 对 TRG 3~4 级病变诊断灵敏度可达 87%,而截面积 >0.92 cm² 的诊断灵敏度为 89%。Chen 等^[42]回顾性分析了 148 例 NCRT 后接受根治性外科手术的食管鳞癌病例,虽然没有给出短期疗效的判断,但 NCRT 后肿瘤最大厚度 ≤8.8 mm 和肿瘤最大厚度缩小 ≥52% 两项指标与术后更长的总生存时间有关。关于 EUS-FNA 在食管癌再分期中的价值, Vazquez-Sequeiros^[43]指出,如果需要基于淋巴结状态做出食管癌的后续治疗策略,则应当进行 EUS-FNA,即便是那些看起来像是良性的淋巴结。

4. 多种内镜技术联合应用: 在 Noordman 等^[44]的前瞻性多中心研究 preSANO 中,采用胃镜检查联合常规活检、深挖活检、超声内镜测量残余病变厚度及 EUS-FNA 淋巴结穿刺等手段,评估了其对 NCRT 后食管及食管胃结合部癌 TRG 3~4 级病例检出的能力;结果显示:胃镜检查联合常规活检加 EUS-FNA 遗漏了 31% 的 TRG 3~4 级病例,深挖活检加 EUS-FNA 遗漏了 10% 的病例,超声内镜测量遗漏了 28% 的病例。据此, Noordman 等^[44]认为,联合应用上述多种技术已经能够为 NCRT 后病灶及周围淋巴结残余判断提供足够的证据。

5. ESD 技术: ESD 也有用于食管癌 NCRT 后病例的报道。在 Nakajo 等^[45]的回顾性研究中,与未接受 NCRT 的病变相比, NCRT 后食管癌瘤床 ESD 的技术成功率及整块切除率更低,但包括穿孔在内的严重并发症发生率未见明显升高。鉴于放疗后局部纤维化及瘢痕造成的操作困难、潜在并发症风险,以及其他手段对疗效评估的充分性,目前 ESD 多用于 NCRT 失败后的挽救治疗,鲜有用于疗效评估的报道。

三、总结

综上,基于目前的临床实践,内镜检查在局部进展期消化道肿瘤 NCRT 后疗效的判断中发挥着重要的作用。但因其固有的局限性,尚不适合单独用于疗效的判断,临床中通常需要多种手段联合应用,并根据患者情况对结果进行综合判断,并制定个体化诊疗方案。随着更多内镜新技术及新设备的问世,在人工智能等新技术的加持下,未来内镜技术必将能够在 NCRT 实施中提供更加准确的疗效判断,为患者带来更大的获益。

利益冲突 所有作者均声明不存在利益冲突

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