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• 临床指南 •

组织取样与分析

American Society of Gastrointestial Endoscopy

编者按 组织取样与分析是消化内镜在临床常见情况下的应用指南之一. 美国消化内镜学会制定了该指南. 在撰写这一指南的过程中，除MEDLINE检索到的文章外，还参考了一些专家推荐的文章. 内镜的合理应用指南基于目前一些重要的综述和专家共识，还需要大量的临床对照研究加以确定和必要的修订. 临床实际情况和指南有所差异时应适当调整.

该指南的目的是为消化内镜检查中组织分析(活检、圈套切除、细胞学和培养)提供实践基础.

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0 引言

组织病理学评价有助于区分恶性肿瘤、炎症和感染性疾病. 组织活检标本取自内镜检查中发现的可疑病变部位. 对内镜检查看似正常的部位进行组织病理分析仍然能提供有意义的信息. 组织分析有时也用来验证先前内镜检查结果及治疗效果. 当内镜检查发现是一特异性病变时，如果对治疗没帮助，可不用组织分析. 对有潜在出血倾向的患者，如凝血障碍，应禁止行组织活检.

1 技术

许多技术和设备可用来获得足够的组织样本. 用活检钳夹取活检是最常用的组织取样方法. 多点活检有助于提高诊断的阳性率. 另外活检块大小、活检部位和定位、固定、染色都很重要[1-2]. 活检钳活检标本一般都是黏膜组织，有时跳跃式活检也能取到黏膜下组织. 然而这些活检钳都需要有一个至少3.6 mm大小的活检孔道，可活检2-3倍活检孔道大小的面积，但通常不能取到深层组织[3]. 细胞刷检是活检钳很有意义的附属装置，有助于恶性肿瘤和炎症的诊断[4]. 圈套摘除有助于大息肉的摘除[5]. 联合应用各种技术有助于提高诊断的精确性[6]. 超声内镜引导下FNA有助于上皮下和胃肠道外组织如淋巴结和胰腺肿块的取样，在美国消化内镜学会情况评价报告“超声内镜中的取样”中将详述这方面内容[7].

2 食管

除了少数因梗阻而不能获得足够视野对病变部位进行活检，95%的食管恶性肿瘤均可由活检诊断，活检需要取8-10块组织[1]，活检时加用细胞刷检有助于提高诊断的阳性率[8-9]. 最常见的食管炎症是反流性食管炎，见于胃食管反流病患者. 内镜结合组织分析能发现Barrett’s食管，并能排除炎症及表现类似胃食管反流病的恶性肿瘤[10]. 内镜下见到的侵蚀性改变与组织学高度相符，但孤立性红斑并不是诊断食管炎的可靠指标. 相反，那些有反流症状而内镜检查表面看似正常的食管黏膜，组织学检查却是异常的(多型核细胞和嗜酸细胞浸润)[10-11]. 肉眼异常的食管黏膜活检及刷检标本，在诊断Barrett’s食管时，通常要排除恶性肿瘤、炎症和自身免疫性疾病[10,12].

Barrett’s食管是指正常鳞状上皮黏膜被化生的小肠黏膜上皮取代，需由内镜活检才能诊断[13]. Barrett’s食管是食管癌的高危因素，需要严密随访[14]. 通过特殊染色(阿利辛蓝)检查有无杯状细胞，能鉴别无刷状缘的柱状上皮和胃黏膜[15]. 严重溃疡性食管炎往往掩盖了原先存在的Barrett’s黏膜，而且炎症导致的非典型增生和异型增生很难鉴别. 这些情况下需要积极治疗食管炎，才能进一步明确组织病理学结果[13,15-16].

活检也用来诊断组织异型增生和腺癌. 当怀疑组织异型增生时应额外对异常黏膜取4个象限，每隔1-2 cm进行活检[17-18]. 高度异型增生者每2 cm活检较每1 cm活检可能会漏诊50%的恶性肿瘤[18]. 尽管已出现了较大容量的活检钳，但一个回顾性研究显示：分4个象限每隔2 cm取活检，恶性肿瘤的漏诊率相同，结果分别是大容量活检钳(4/12，33%)，标准容量活检钳(6/16，38%)[19]. 提倡转动吸引技术，即张开的活检钳靠近内镜头端，活检钳往管壁前进并转动抽吸再夹紧便取得活检组织[17]. 那些高度异型增生者需选择食管切除术，这种技术需3-6 mo的间隔，能准确诊断肿瘤，但96%限于黏膜层[17-18].

高清晰度放大内镜和亚甲蓝色素内镜通过直接定位活检有助于短片段Barrett’s食管的诊断[19-23]. 有报告用碘溶液和亚甲蓝色素内镜能提高Barrett’s食管区域内鳞状细胞癌和瘤分布区的发现率[21,24-26]. 亚甲蓝在检测Barrett’s食管的价值以前就提出过. 用流式细胞计量和DNA分析能确定哪些患者属非整倍体、多倍体或17p(p53)杂合缺失，从而有助于预测患癌的风险[27-29].

食管散在病变可行内镜黏膜切除术. 这种技术是在黏膜下注射盐水使病变隆起，然后用圈套烧灼切除[30]. 该技术已成功应用于Barrett’s食管的瘤性病变和良性食管肿瘤切除[31-33].

感染性食管炎常见于免疫功能低下患者，如接受

系统性抗免疫治疗者、吸入激素者、肿瘤患者(尤其化疗患者)以及有糖尿病或艾滋病病史患者[34]. 最常见的病原体是念珠菌属、单纯疱疹病毒、巨细胞病毒. 霉菌性食管炎内镜表现是黏膜炎性白斑，刷检细胞学和活检有助于诊断，但刷检细胞学更敏感[35-36]. 病毒性食管炎表现为溃疡，活检标本需取自溃疡中央和边缘部位. 组织病理学检查有助于诊断，但艾滋病患者需多点活检(多达10块组织)[17]. 病毒培养是最权威的诊断，但对于巨细胞病毒，组织学更敏感[35, 37-39].

3 胃

胃肿瘤可表现为溃疡性、息肉样、黏膜下损害或者胃壁增厚. 足够的组织取样有时需要几种技术联合使用. 对息肉样肿块和溃疡行夹取活检是最有效的诊断方法[1]. 对溃疡边缘4个象限及溃疡基底部多点活检是必要的[40]. 加用刷检细胞学检查能提高阳性率[41]. 对息肉样病变应进行活检，技术许可情况下对大于2 cm的息肉应摘除[42]. 胃息肉切除比肠息肉切除危险性大，因此术后应常规抑酸治疗[43].

内镜黏膜切除术用来对胃壁增厚的组织取样，也用来治疗早期胃癌. 早期胃癌的内镜黏膜切除术适用于经超声内镜或内镜检查肿瘤直径小于20 mm并局限于黏膜者. 切除方法是内镜下在病变处黏膜下注射液体，然后进行切除(见内镜下黏膜切除术技术状况评价报告)[30].

消化性溃疡和胃黏膜组织相关淋巴瘤患者及潜在发展为胃癌患者(如家族或个人有胃癌史)应该进行幽门螺杆菌检查[44-47]. 基于组织的检查来源于组织活检取得的胃黏膜. 这些检查包括尿素酶活力(快速尿素酶试验)、典型弯曲菌的组织学检查和培养[47-48]. 在未治疗的患者，活检标本应取自胃窦小弯靠近胃角处[49]. 快速尿素酶试验具有价廉、特异性高、能在内镜检查室里检查且1 h后出结果等优点[48]. 但快速尿素酶试验敏感性低，结果阴性时应选择其他方法检查[50]. 对标本进行组织学检查时应注意有无炎症细胞和典型弯曲菌，后者检测需要特殊染色[48,51-52]. 组织学检查发现有显著胃炎症细胞浸润而未发现细菌时，应快速进行其他检查，比如血清学检查、尿素呼气试验或粪抗原检测. 考虑到有抗菌剂耐药时可进行细菌培养，但敏感性较差且比较昂贵. 最近接受质子泵抑制剂及抗生素治疗的患者及消化道出血者，基于组织的检查敏感性降低，对这些患者，应在胃窦部及胃体部进行多点活检，快速尿素酶试验阴性时应选择其他方法检查[53-56]. 若病情允可应停止质子泵抑制剂治疗1 wk后进行 *Hp* 检查[57].

4 小肠

对怀疑有小肠疾病的患者进行活检是必须检查之一. 经口活检组织传统上取自屈氏韧带区域. 现在更常用的是内镜活检，具有操作时间短、患者更舒适、能直接多点活检等优点[58]. 弥散性黏膜病变者应在十二指肠球部远端至少取3块活检组织以免误诊为Brunner’s腺[59-60]. 有些疾病内镜表现为斑片状病变，在小肠远端多点活检要求更长和更小口径的内镜. 即使肉眼看似正常的组织，活检也有助于诊断[61]. 小肠活检对于精确诊断肠黏膜吸收不良综合征具有参考标准. 怀疑腹腔疾病时，仍然需要进行小肠活检，即使血液学筛选检查(如谷氨酰转氨酶及肌内膜抗体)结果阳性[59,62]. 血液学检查应在治疗前完成，否则，检查结果会出现假阳性.

小肠感染性疾病的诊断需靠组织学检查. 蓝氏贾第鞭毛虫和其他许多原生虫病原体和小肠黏膜炎性改变有关. 在上皮表面发现成熟体、滋养体或其生活周期组成部分能作出特异性诊断. 有些患者内镜表现类似嗜酸细胞性胃肠炎，故嗜酸细胞性胃肠炎诊断需排除寄生虫感染[22,26].

免疫缺陷患者包括器官移植后及HIV感染者，在小肠活检组织中常发现隐匿性病原体如贝氏等孢子球虫、隐孢子虫、环孢菌及微孢子等. 在免疫缺陷患者小肠活检组织中还可发现巨细胞病毒、真菌如念珠菌和组织胞质菌及鸟-胞内分支杆菌复合群[22]. 2块组织需系列活检时建议使用大的杯状活检钳，而不用传统活检钳，在退出活检钳前系列钳取(双咬合技术). 建议用针把活检标本从活检钳上移到固定液里，避免采取抖动的方式移到固定瓶里，以免黏附在上皮表面的渗出液丢失[63].

十二指肠肿瘤应用内镜和活检诊断. 选用前视或侧视镜取样由肿瘤大小及位置决定.

33-100%的家族性腺瘤性息肉病患者有十二指肠、空肠和胃息肉[64-69]. 家族性腺瘤性息肉病患者一般是胃底腺息肉，没有恶性变倾向，但仍需活检除外腺瘤. 而十二指肠息肉一般是典型的腺瘤性，首先出现在壶腹部或壶腹周围区域. 同时或先后出现的上消化道息肉有助于对结肠息肉的识别[70]. 由壶腹周围腺瘤发展成的腺癌是公认的实体瘤，除结直肠癌外，他是家族性腺瘤性息肉病患者最常见死因，应该进行严密随访[68-71]. 有个案报告乳头部位活检会引起胰腺炎，尽管如此，内镜活检或远离乳头的十二指肠腺瘤摘除相关的并发症罕见[72-73].

5 大肠

以前的指南已经概述了大肠息肉和炎症性肠病患者结肠镜检查和活检的指征[74-76]. 肉眼看到的病变是组织病理学评价的保证. 如果病变太多而不能逐一摘除，应进行有代表性的取样分析. 乙状结肠镜筛查发现的小息肉应摘除活检，较大的息肉在随后的结肠镜检查时摘除. 检出腺瘤或癌应进行全结肠检查. 有报告乙状结肠镜检出的增生性息肉的重要性存在争议[77-78]. 大多数美国胃肠病学家认为这些增生性息肉不是近段肠管肿瘤形成的危险因素.

内镜和活检能区别不同原因引起的大肠炎，能确

定累及肠管的程度, 有助于炎症性肠病的治疗. 从急性期血性腹泻患者肠管获取的活检标本有助于急性自限性大肠炎与初发或复发的慢性溃疡性结肠炎及缺血性结肠炎鉴别[79-80]. 回肠末端活检有助于克罗恩病、感染性回肠炎及淋巴样结节性增生的诊断[81]. 溃疡性结肠炎及克罗恩病都是大肠癌的危险因素. 在其病程 8 a 时患癌危险性开始增加[82-83]. 这些患者应定期随访. 仅有左半结肠病变者一般在病程15 a时患癌危险性增加. 全大肠炎患者常用活检方法是每隔10 cm肠管在肠壁的4个象限上各取活检, 在下段的25 cm开始, 每5 cm取活检. 左半结肠炎患者近段肠壁也应活检以重新评估疾病程度[84-86].

慢性结肠炎异型增生处活检方法有所改进. 当异型增生的肿块性病变较大、不规则伴狭窄时, 应外科手术处理. 大肠炎肠段发现典型的腺癌时应摘除, 且其周边黏膜应活检. 腺瘤完全摘除而周边黏膜活检正常时, 可认为腺瘤是散发性的, 不需进一步治疗, 随访即可[74,86-88].

慢性腹泻患者结肠镜检查大体看起来正常时, 很难确定在哪里进行活检以及需要活检几块组织. 显微镜下大肠炎见于慢性水样腹泻而内镜及微生物检查正常的患者. 可屈性乙状结肠镜检查取样的活检组织检查足以诊断这种疾病[89-91].

总之, 组织取样对于鉴别恶性肿瘤、炎症及感染性疾病是有益的. 组织取样技术包括活检钳夹取、刷检细胞学及圈套摘除和FNA等. 对于恶性肿瘤病变最多应取8-10块组织. 对Barrett's食管患者应有规则的活检以评价异型增生程度. 对高度异型增生的Barrett's食管患者应在管壁的4个象限及每隔1-2 cm取活检, 有利肿瘤的发现. 内镜黏膜切除术可用来切除恶性及恶性变前的黏膜病变. 感染性病变应多点活检, 存在溃疡者, 在溃疡中心及周边都应取样. 刷检及病毒培养是附属技术. 胃组织学检查及快速尿素酶试验能确定有无 *Hp* 感染. 对未治疗的患者在胃角部进行取样, *Hp* 检出率较高. 治疗过或正在接受质子泵抑制剂及抗生素治疗者, 应在胃底及胃体部活检. 如果可行, 胃息肉应广泛取样或摘除. 胃息肉摘除术较结肠息肉摘除术出血风险大, 术后建议抑酸治疗. 腹泻及腹腔疾病者建议在小肠随机活检. 十二指肠腺瘤呈散发性或者与家族性腺瘤性息肉病有关, 如果可行, 应取样或摘除. 结肠病变应在内镜下切除(息肉切除术, 内镜下黏膜切除术), 病变太大或不能切除时应取样. 对急性大肠炎患者进行活检取样有助查找病因. 对慢性大肠炎患者严密观察有利检出使患癌风险增加的异型增生病变. 慢性腹泻患者即使结肠黏膜肉眼观察正常, 随机活检有时也能发现显微镜下大肠炎.

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