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胃癌的科学预防、早期诊断与精准治疗

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[摘要] 我国胃癌防治工作面临发病率高、疾病负担重、防控体系待完善等多重挑战,构建"预防-诊断-治疗"三位一体的精准防控体系已成为当务之急。在疾病预防维度,基于循证医学的幽门螺旋杆菌根除治疗展现出显著优势;高危肠上皮化生的内镜诊断新技术已启动临床转化,可精准识别高危肠上皮化生等癌前病变。诊断技术创新方面,新近报道的内镜分子成像和液体活检等早期胃癌筛查新技术能显著提升检出率。治疗策略优化层面,免疫、靶向和放疗等综合治疗以及基于分子分型的个性化治疗新策略,为不同分子亚型的胃癌患者带来临床获益。当前,高通量多组学测序与人工智能技术紧密融合;未来,这些新兴技术有望加快解决胃癌防控领域的诸多关键科学问题,促进基础与临床研究的跨越式发展,推动我国胃癌防治从经验医学、循证医学向精准医学的范式转变,最终实现发病率和病死率"双下降"的"健康中国"宏伟目标。

[关键词] 胃癌;预防;早期诊断;治疗;精准医学

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Effective prevention, early diagnosis and precise treatment of gastric cancer

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[**Abstract**] The prevention and treatment of gastric cancer in China confront multifaceted challenges, including high incidence rates, substantial disease burden and suboptimal management system. Establishing a precision gastric cancer control infrastructure with integrated "prevention, diagnosis and treatment" strategies has become an urgent public health priority. In terms of disease prevention, evidence-based eradication therapy of *Helicobacter pylori* has demonstrated remarkable clinical advances. Novel endoscopic diagnostic technologies for precancerous lesions are under clinical translation, which accurately identify conditions such as high-risk intestinal metaplasia. Regarding innovative diagnostic technologies, cutting-edge endoscopic molecular imaging and liquid biopsy can significantly increase early detection rates of gastric cancer. In regard to treatment modalities, comprehensive clinical benefits have been achieved, largely through advances

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in immunotherapy, targeted therapy, radiotherapy, as well as treatment personalization based on cancer molecular subtyping. Moreover, high-throughput multi-omics sequencing is currently integrated with artificial intelligence technology. These pioneering technologies are projected to expedite resolution of pivotal scientific challenges in gastric cancer management, catalyzing transformative progress across basic-clinical research domains, driving China's gastric cancer control paradigm shift from empirical medicine to precision frameworks, ultimately achieving the public health dual-goal of incidence and mortality rates in the near future.

[**Key words**] gastric cancer; prevention; early diagnosis; treatment; precision medicine

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胃癌是我国第五大恶性肿瘤,但致死人数高居第三位,严重危害人民群众生命健康[1]。最新数据显示,我国每年新增胃癌患者358 700人、致死人数260 400人,分别占全球数据的37%及39%[1-2]。尽管胃癌发病率与病死率近年来缓慢降低[2],但我国人口基数大,胃癌科学预防、早期诊断、精准治疗工作依然任重道远。围绕这些问题,本文结合国内外最新进展,探讨如何开发和推广疗效确切、普及率高、依从性好的致癌因素根除方案。对于早期胃癌患者,探讨如何精准辨别高危人群、准确识别高危癌前病变,实现早诊早治和长期生存。对于进展期胃癌患者,探讨如何开展分型诊断,探索个性化的系统治疗,提高围手术期疗效,减轻肿瘤负荷,改善临床症状,提高生活质量,延长生存期。我们相信努力攻克这些关键问题,将为大幅改善胃癌预防、诊断、治疗现状提供理论依据。

1 提高胃癌的科学预防水平

胃癌是典型的感染相关肿瘤[1],其重要病原菌即幽门螺旋杆菌(*Helicobacter pylori*,*H. pylori*,Hp)被世界卫生组织公布为Ⅰ类致癌因子。Hp感染诱导"慢性非萎缩性胃炎-萎缩性胃炎-肠上皮化生-异型增生-肠型腺癌"的级联反应,在超过70%患者的胃癌发生中发挥重要作用[3]。这个"炎-癌转化"过程跨越10~30年,为胃癌预防提供了充足时间,1项随访长达15年的随机对照试验结果显示,Hp根除治疗可阻止大部分癌前病变继续发展,使胃癌风险降低40%,有效预防胃癌发生[4]。

优化Hp根除治疗方案对于预防胃癌至关重要。我国普遍采用"铋剂四联方案"根除Hp。但该方案药物种类多、用法复杂,患者常因头晕、恶心、呕吐、食欲下降等不良反应停药,疗程不足导致治疗失败,甚至继发性耐药,增加罹患胃癌风险。本研究团队系统分析国内多地域抗生素耐药情况,制定"优化二联方案"[5]。该方案与经典四联方案等效,但仅用抑酸药及一种抗生素,显著减少临床副作用、节约治疗费用、降低耐药风险,大幅提升患者依从性[5],被《中国幽门螺杆菌感染治疗指南》推荐为Hp感染初次和再次根除治疗的标准方案[4]。近期一系列临床研究不断优化药物剂量、频次、配伍、疗程,将Hp根除率提升到95.6%[6-11],不良反应率降低到16.7%[9],为广大Hp感染人群提供了新选择。由于全球Hp感染率高达50%[4],社会学及人口学差异大,亟需针对不同地区患者抗生素耐药特征,制定符合卫生经济学的精细化Hp根除方案。

Hp以外的微生物感染也可能导致胃癌发生,其中6.7%~9.5%[12-13]的胃癌与EB病毒(epstein-barr virus,EBV)感染相关。EBV可通过潜伏膜蛋白1(the latent membrane protein 1,LMP1)、EB病毒核抗原1(epstein-barr nuclear antigen 1,EBNA1)、非编码RNA等病毒编码产物,打破胃黏膜细胞增殖-凋亡平衡、逃避免疫监视,导致胃癌发生与进展[14]。新近研究表明,咽峡炎链球菌(*Streptococcus anginosus*,*S. anginosus*,Sa)可在胃黏膜中定植,通过表面蛋白与膜联蛋白A2(annexin A2,ANXA2)相互作用,激活上皮细胞丝裂原活化蛋白激酶(mitogen-activated protein kinase,MAPK)信号,导致胃黏膜炎症、萎缩和癌变[15]。在进展期胃癌中,Sa调控精氨酸代谢通路,抑制肿瘤免疫微环境$CD8^+$T细胞,促进肿瘤增殖和转移,造成预后不良[16]。上述多种微生物在胃黏膜定植均导致慢性炎症与局部免疫失衡,深入研究非Hp微生物感染诱发胃癌的黏膜免疫机制,揭示宿主遗传及表观调控因素在其中的具体机理,有助于开发胃癌预防新策略。

胃癌发生是一个多因素、多步骤的复杂过程,吸烟、饮酒、食用腌制食品以及新鲜蔬菜水果摄入不足等不良生活习惯,以及特定的环境因素和遗传因素,都是导致胃癌发生的重要病因[17]。建立科普宣传体系,在胃癌高发地区实地调研、筛查高危人群等方式,

均对预防胃癌意义重大。值得一提的是,高危癌前病变的内镜筛查是胃癌早期预防的关键环节,其中肠上皮化生(肠化)是胃癌发生的关键癌前病变,约有1%的肠化患者最终进展为早期胃癌。肠化分为完全小肠型(Ⅰ型肠化)、不完全小肠型(Ⅱ型肠化)、不完全大肠型(Ⅲ型肠化)。Ⅲ型肠化的癌变风险显著高于Ⅰ型及Ⅱ型[18],极易演变为早期胃癌,亟需准确识别这种高危肠化并密切随访,但目前尚无内镜下检出高危肠化的诊断方法。本团队基于肠化克隆性发育的细胞生物学特征,初步发现亮蓝嵴环形包绕的乳头状区域(light blue crest capsuling papillary lesion,LCPL)可能是Ⅲ型肠化病灶的内镜诊断征象[19],为内镜下精准识别高危癌前病变、进行胃癌极早期预警、开展个性化随访和防癌方案提供新依据。

2 研发早期胃癌的筛查和诊断新技术

早诊断早治疗是提高胃癌疗效和改善临床预后的重要途径。早期胃癌患者在接受内镜下切除后5年生存率超过90%,甚至可被治愈[20],但我国大多数胃癌患者确诊时已处于进展期,即使接受外科手术等综合治疗,5年生存率仍低于40%[21]。目前,主要采用内镜检查发现癌前病变和筛查早期胃癌[22],但我国早期胃癌确诊率低于20%[23],超过80%早期胃癌因各种原因未被检出[24]。尽管可以采用"可操作的与胃癌风险联系的胃炎评估"(operative link for gastritis assessment,OLGA)和"可操作的与胃癌风险联系的肠化生评估"(operative link for gastric intestinal metaplasia assessment,OLGIM)等内镜评估方法,但尚不能完全满足个性化随访需求。

早期胃癌病灶微小、临床症状不典型、内镜特征不明显,极易隐匿于慢性炎症或癌前病变背景中,对内镜医生的临床经验和耐心程度挑战较大,加之缺乏特异性的内镜诊断和血清学标志物,导致大量漏诊[23-24]。早期胃癌内镜下表现为黏膜发红、浅表隆起或凹陷等,但非癌黏膜也具有相似特征,尤其在多灶肠化或Hp根除状态下,早癌病变的隐蔽性更强,极易被漏诊。如何突破这一临床困境,是基础研究、材料科学等医工交叉领域学者面临的挑战[25],亟需从全新视角开发原创性技术,改变早癌发现率低、漏诊率高的现状。近年二代测序技术的飞速发展,逐渐揭示胃黏膜微环境中上皮[26]、免疫及间质细胞[27-28]在肿瘤发生过程中的组学特征。本团队采用高通量多组学测序技术发现:胃黏膜从肠化到早期胃癌进展过程中发生显著表观遗传重塑,大量增强子与沉默子元件功能活性变化,改变转录调控网络,引发癌变过程的细胞谱系转换[29-30]、代谢重编程[31]、免疫逃逸[32]等,并从中发现多个候选的早期胃癌分子标志物。由于早期胃癌突变负荷低[33],深度剖析表观遗传变化如何重塑转录调控网络,有助于发现诊断标志物及其调控机理,为早期胃癌的精准诊断提供新思路。

分子成像和液体活检技术为高灵敏度检出早期胃癌提供新契机。新近研究采用静脉注射或黏膜表面喷洒方式,递送早期胃癌分子标志物抗体耦联的成像发光单元(纳米微粒和荧光探针等),在蓝激光内镜的激发下发出可见荧光,可实现早期胃癌组织的靶向成像[34]、提高内镜下早期胃癌检出率。对于不愿接受或无法耐受胃镜检查者,血液检查安全快捷,但临床常用肿瘤标志物(CEA、CA19-9、CA72-4等)均对早期胃癌的灵敏度低,导致目前缺乏高效特异的体液诊断方法。近年来液体活检技术快速发展,外周血中循环肿瘤细胞(circulating tumor cell,CTCs)、循环肿瘤DNA(circulating tumor DNA,ctDNA)、循环游离DNA(circulating free DNA,cfDNA)、循环RNA(circular RNAs)和外泌体等新兴标志物,可能为早期胃癌的筛查诊断开辟新途径[35-37]。值得注意的是,肿瘤是由多种细胞类型构成的复杂生态系统,无论内镜分子成像,还是血清学液体活检,均需要深刻认识胃癌发生过程、全面揭示早期胃癌分子谱征。构建涵盖各类细胞及亚群动态演化的全景图谱,精准描绘正常组织-癌前病变-进展期肿瘤的时-空演化规律,细致刻画癌变过程中的空间结构、细胞互作和基因表达调控网络,有助于发现新型分子标志物,开发精准的胃癌早期筛查工具和诊断方法[25]。

3 探索进展期胃癌的精准治疗新模式

近年来在大量循证医学证据指导下,胃癌(含胃食管结合部腺癌,下同)治疗已从"外科手术+放化疗"的单一模式发展为综合治疗(化疗、靶向治疗、免疫治疗、放疗等)联合外科手术的新型模式。准确识别胃癌分子特征,针对不同临床阶段和分子亚型制定精准治疗方案,使患者获得最大临床受益,是进展期胃癌的重要治疗目的。

3.1 靶向治疗与抗体偶联药物

以曲妥珠单抗为代表的靶向药物标志着胃癌进入综合治疗的新时代。对于人表皮生长因子受体2(human epidermal growth factor receptor 2,*ERBB2*,又名*HER2*)基因扩增或高表达胃癌患者,美国国立综合癌症网络(national comprehensive cancer network,NCCN)

指南、欧洲医学肿瘤学会(European Society for Medical Oncology, ESMO)指南以及我国国家卫健委胃癌诊疗指南、中国临床肿瘤学会(Chinese Society of Clinical Oncology,CSCO)指南,均推荐联用曲妥珠单抗作为一线治疗方案。由于我国HER2阳性胃癌患者仅15%~20%,大部分患者无法进行曲妥珠单抗治疗。新近发现紧密连接蛋白Claudin18.2阳性胃癌患者约占38.4%,尤其在HER2阴性胃癌比例高达42.3%,提示Claudin18.2可能是一个全新的分子靶点。SPOTLIGHT、GLOW等全球Ⅲ期临床试验均显示,对于Claudin18.2阳性HER2阴性、局晚期不可切除或转移性胃癌,联用Claudin18.2靶向药物佐妥昔单抗可延长患者中位无进展生存时间1.4~2.0个月[38-39],目前已被食品药品监督管理局(food and drug administration,FDA)已批准上市。对于无特定靶点晚期胃癌,多个指南均推荐采用雷莫芦单抗通过靶向人血管内皮生长因子受体-2(vascular endothelial growth factor receptor-2,VEGFR-2)抑制肿瘤血管生成,联合紫杉醇或者单药化疗,以延长中位无进展生存时间、提高肿瘤客观缓解率。

抗体偶联药物(antibody drug conjugate,ADC)偶联单克隆抗体与细胞毒性药物,有利于克服分子靶向治疗的耐药问题。ADC药物充分发挥抗体的特异性与细胞毒素的杀伤能力,不但实现精准递送、提升抗癌效果,还可诱导"旁观者效应"、抗体依赖的细胞介导的细胞毒性作用(antibody-dependent cell-mediated cytotoxicity,ADCC)、抗体依赖的细胞吞噬作用(antibody-dependent cellular phagocytosis,ADCP)等免疫清除效应,也减少化疗的全身毒性。目前较为成熟的ADC药物包括靶向HER2的恩美曲妥珠单抗(T-DM1)、德曲妥珠单抗(T-DXd)、维迪希妥单抗(RN48)等,均已进入Ⅱ/Ⅲ期临床试验;此外,针对Claudin18.2、滋养层细胞表面抗原2(troploblast cell surface antigen 2,TROP2)的ADC药物也在积极研发阶段,有望成为胃癌靶向治疗的新选择。

除上述靶点以外,针对其他重要靶标的药物临床试验也在广泛开展。虽然靶向表皮生长因子受体(epidermal growth factor receptor,EGFR)、间质表皮转化因子(mesenchymal-epithelial transition factor, MET)、聚腺苷二磷酸核糖聚合酶[poly(ADP-ribose) polymerase, PARP]、哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin,mTOR)的临床试验受挫,但靶向成纤维细胞生长因子受体2b(fibroblast growth factor receptor 2b,FGFR2b)的贝玛妥珠单抗临床试验疗效良好[40]。当前高通量多组学测序技术呈井喷式发展,有望进一步揭示胃癌发生演进的宏观与微观驱动因素,发现更多的抗癌靶标。

3.2 免疫治疗

近年来肿瘤免疫治疗领域突飞猛进,尤其是免疫检查点抑制剂(immune checkpoint inhibitor,ICI)与嵌合抗原受体T细胞(chimeric antigen receptor T-cell,CAR-T)治疗为胃癌等多种实体瘤治疗带来全新希望。对于HER2阴性的初治局部晚期或转移性胃癌,CheckMate649[41]、ORIENT-16[42]、KEYNOTE-859[43]、RATIONALE-305[44]等重磅临床试验将化疗联合ICI推至临床一线方案;COMPASSION-15研究[45]与NO LIMIT研究[46]进一步将双免联合方案(PD-1/CTLA-4双特异抗体+化疗)拓展到更加广泛的患者群体。在联合阳性分数(combined positive score, CPS)≥1的HER2阳性患者中,KEYNOTE-811研究[47]也实现突破,将ICI治疗+靶向治疗+化疗的"三联疗法"建立为标准一线方案。这些临床研究将ICI从后线治疗推进至临床一线方案,不断改变胃癌临床治疗格局[40]。

由于局部晚期胃癌存在手术完整切除率低、术后易复发的临床难题,优化围手术期治疗方案具有重要临床意义。DANTE[48]、PERSIST[49]、NEOSUMMIT-01等[50]随机对照试验(randomized controlled trial,RCT)证实,围手术期接受含ICI方案的胃癌患者,病理完全缓解(pathological complete regression,pCR)率达22.2%~26.9%,主要病理缓解(major pathological regression,mPR)率为44.4%~69.2%,显著优于单纯化疗。然而,ATTRACTION-5等[51]研究发现,术后联用ICI未能延长无复发生存期。这些临床矛盾现象可能与ICI发挥作用的机制有关:肿瘤微环境中的终末耗竭T细胞难以响应ICI,PD-1/PD-L1抑制剂主要激活存在于肿瘤引流淋巴结中TCF-1^{+}TOX^{-}肿瘤特异性记忆CD8^{+}T细胞(T_{TSM})来发挥效应[52]。由于常规D2根治手术清扫肿瘤引流淋巴结,使得T_{TSM}大量丢失,可能导致术后使用ICI无效,提示手术前新辅助ICI治疗可能发挥更强的抗肿瘤作用。

新辅助免疫治疗可能为局晚期胃癌带来更多临床获益。近期本团队一项多中心Ⅱ期临床试验发现,76例局晚期胃癌患者中30%达到pCR、43%达到mPR;在20个月的随访期间内,mPR组中无1例复发/死亡,非mPR组6例发生疾病进展/死亡[53]。我们进一步回顾性分析多中心数据发现,新辅助免疫化疗的临床响应率显著高于新辅助化疗[54]。一项纳入33项研究、1 074例患者的Meta分析也表明,化疗联用ICI可使pCR率达24%,mPR率达49%[55]。然而这种近期获益是否能真

正转化为长期生存,正在接受KEYNOTE-585等[56]大样本研究的进一步检验。

新辅助免疫治疗的生物标志物是临床重点关注问题。目前大量临床试验仅纳入PD-L1 CPS较高患者,这类患者在胃癌人群中的占比有限。此外,一部分CPS评分低的胃癌患者也能获益于ICI治疗,而CPS高的患者获益比例往往不到半数,提示CPS评分对于预判胃癌ICI疗效的灵敏度和特异度不高。高度微卫星不稳定(high microsatellite instability,MSI-H)/DNA错配修复缺陷(deficient of mismatch repair,dMMR)肿瘤普遍对ICI治疗响应良好,但此类患者也仅占所有胃癌患者10%~15%[57]。本团队通过回顾分析295例局部晚期胃癌患者的临床病理特征发现,Lauren分型为肠型者接受新辅助免疫治疗的mPR率与pCR率均更高[58],与PANDA的RCT[59]、NEOSUMMIT-01的单臂试验[50]结果一致,该结论也在本团队后续的前瞻性研究中得到证实[53]。此外,多项晚期胃癌免疫治疗临床研究也发现Lauren分型与临床疗效密切相关[41, 50, 60],提示Lauren分型可能是胃癌免疫治疗的潜在生物标志物。

免疫治疗耐药是临床亟须解决的重大难题。大量临床研究表明,超过一半胃癌患者对于免疫治疗响应性差,存在原发性耐药;一部分初始敏感患者经4~5周期治疗后出现肿瘤进展,提示继发性耐药。鉴于此,有必要进一步研究胃癌免疫治疗的耐药机理、探索新型生物标志物,以筛选可能获益于ICI的敏感患者亚群,寻找原发/继发耐药的预警指标。深入探索肿瘤微环境中其它多种免疫检查点,有望开发免疫治疗新策略,为肿瘤免疫治疗带来新路径。

CAR-T治疗是免疫治疗领域的另一大前沿热点。CAR-T治疗在血液系统肿瘤,尤其对淋巴瘤疗效显著,但在胃癌等多种实体肿瘤中仍处于起步阶段。目前,靶向于Claudin18.2的CAR-T细胞治疗胃癌已经展示出一定的临床疗效[61]。在接受二线以上化疗伴转移的胃癌患者,靶向EpCAM的CAR-T治疗也具有初步疗效,安全性较好[62]。嵌合抗原受体自然杀伤细胞(chimeric antigen receptor natural killer cell,CAR-NK)治疗胃癌的Ⅰ/Ⅱ期临床试验也正在进行。尽管如此,胃癌CAR-T细胞疗法的广泛临床应用仍可能经历较长时间,除治疗费用高昂等因素外,制备CAR-T的特异性肿瘤相关抗原(tumor-associated antigen,TAA)也是关键环节,与临床疗效和不良反应密切相关,仍有待深入研究。

3.3 放射治疗

放疗与其他治疗手段联合应用,可以显著提高治疗响应,是进展期胃癌综合治疗的重要组成部分。尽管CRITICS[63]、ARTIST[64]研究提示放疗并不能显著延长胃癌患者术后生存期,但对于高复发风险(非R0切除、淋巴结转移比例高)胃癌患者仍有应用价值[17]。

新辅助放化疗是目前临床关注热点。POET研究[65]报道:新辅助放化疗能显著提升胃食管结合部癌pCR率与无瘤淋巴结比例,具有良好近期疗效,并能转化为3年及5年生存率获益[66]。在Neo-AEGIS研究[67]中也可获得相似的近期疗效获益,但未显著延长总生存期。此外,大规模真实世界研究显示,接受新辅助放化疗的近端胃癌患者(n=6 000)总生存时间比围手术期单纯化疗患者(n=3 745)短[68]。TOPGEAR[69]研究也发现新辅助放化疗虽然带来近期获益,但远端胃癌患者生存期反而有缩短的趋势。目前,多项大样本临床研究(CRITICS-Ⅱ、ESOPEC、PREACT等)正在进行中,新辅助放化疗能否带来远期获益仍待揭晓。

放射治疗可能增强肿瘤免疫治疗的敏感性。放疗诱导肿瘤细胞损伤及崩解,暴露肿瘤特异抗原,为激活后续抗癌免疫反应提供条件,因此为ICI联合放疗的治疗方案提供了理论依据。近期一项多中心Ⅱ期临床研究显示,“放化免”新辅助治疗局晚期胃癌的pCR率达38.2%、mPR率达79.4%、R0切除率100%、中位无病生存期为17个月、1年生存率为92.6%[70],提示可能获得长期获益。随着调强放疗、图像引导放疗、自适应放疗等技术的不断优化,我们有理由期待胃癌放疗将取得更佳的临床疗效。

3.4 制定个性化治疗方案

尽管胃癌临床治疗进展迅猛,但总体5年生存率仍不足40%[71]。胃癌异质性极大,包括患者间异质性和瘤内异质性可能是临床疗效差的重要原因[17,72]。患者间的异质性体现为不同患者的肿瘤恶性行为、药物敏感差异大,导致相同治疗方案对不同患者的疗效迥异,产生原发性耐药。瘤内异质性则指同一患者的不同肿瘤细胞亚群存在异质性,癌细胞在治疗压力下发生达尔文进化和亚克隆竞争,容易产生获得性耐药。这两种异质性机制协同导致治疗失败,深入解析胃癌时-空异质性规律,建立胃癌多组学分子分型,是精准抗癌策略的必要条件。

近年来,高通量测序技术的广泛应用,使得人们能够全面分析肿瘤的进化模式,从而不断深化对肿瘤异质性产生及演变规律的理解。这一技术进步为开

展肿瘤的分子分型、筛选亚型特异性生物标志物以及分子靶标提供了有力支撑。癌症基因图谱计划(the cancer genome atlas program,TCGA)基于胃癌体细胞拷贝数、全外显子序列等多组学分子特征提出的四分型系统[13]已应用于指导患者治疗[72]。临床实践表明,EBV阳性亚型(epstein-barr virus positive,EBV$^+$)、MSI-H亚型的转移性胃癌患者对免疫治疗的响应率分别达100.0%[73]、85.7%[74],但基因组稳定亚型(genome stable,GS)和染色体不稳定亚型(chromosomal instability,CIN)则响应不佳。GS和CIN这两类亚型占胃癌总数近70%,目前缺乏精准治疗方案,预后极差[75]。未来利用表观遗传组、单细胞转录组、空间转录组、空间代谢组等新视角和新技术,深入解析胃癌异质性及其调控机制,整合多维信息形成分型系统,有利于开发诊治新策略。

恶性肿瘤面对治疗压力将产生适应性演进,临床治疗方案也应动态调整。临床实践中需深入思考:结合肿瘤分子特征与患者体力状态,当前最适宜哪种治疗模式?如何在治疗获益与不良反应风险之间取得平衡?如何利用影像组学特征评估肿瘤病理状态、进而结合转录组等多组学特征,关联治疗敏感性?这些问题都为临床个性化治疗带来重大挑战与机遇。

4 未来展望

癌症防控对于国民健康非常重要,我国《"健康中国2030"规划纲要》、《中国防治慢性病中长期规划(2017-2025年)》、《健康中国行动——癌症防治行动实施方案(2023-2030年)》等系列战略规划,为胃癌预防、诊断和治疗工作提供全面指导。在举国努力之下,近年来胃癌疾病负担呈下降趋势,表明我国癌症防控措施初见成效。

由于我国是全球胃癌疾病负担最重的国家,防、诊、治等任务仍然面临巨大挑战。在科学预防方面,由于抗生素耐药愈发广泛,迫切需要研发新一代药物根除Hp等致病菌;胃癌由多种病因协同致病,针对易感者遗传背景、生活习惯及所处社会环境结合制定个性化预防方案至关重要;针对胃黏膜慢性炎-癌转化过程,目前尚缺乏有效逆转肠化等癌前病变的治疗药物。在早期诊断方面,是否有成本更低、普及性更高、准确性更佳的无创性筛查技术或方法?在精准治疗领域,胃癌的分子靶向和免疫治疗药物数量相对有限,迫切需要发现更多有效的抗癌新靶点。目前,临床上尚未建立完善的分子分型系统,难以针对肿瘤的异质性提供精准的个体化治疗方案。此外,对于肿瘤的动态演变过程,缺乏实时监测疾病进展、复发和耐药情况的技术手段,这限制了精准治疗方案的制定和实施。

虽然挑战巨大,但未来已来。在精准医学、大数据以及人工智能(artificial intelligence,AI)的时代浪潮中,胃癌的预防、诊断与治疗领域正迎来一场深刻的变革。大量临床病理数据,以及海量高通量多组学测序数据,成为了AI模型学习资料和模型构建的基础。在胃癌预防方面,Kettles食管和贲门腺癌预测(kettles esophageal and cardia adenocarcinoma prediction,K-ECAN)机器学习模型可从健康档案中推测食管和贲门腺癌的发生率,其预测的受试者工作特征曲线下面积(area under the receiver operating characteristic curve,AUROC)达0.85[76]。基于卷积神经网络的图片学习AI模型已应用临床,在内镜检查过程中实时辅助诊断Hp感染状态、巴雷特食管和胃部肿瘤的AUC分别达到0.92、0.96、0.96,诊断效能已经优于高年资内镜医生,有助于减少临床漏诊[77-78]。在研究胃癌发生机制方面,利用多模态多组学数据及AI算法,可以系统描绘胃炎-癌转化规律,寻找全新的防癌分子靶点[79]。在胃癌分子诊断方面,AI模型可基于数字化HE切片准确预测HER2表达情况(内部测试、外部验证集的准确性分别为0.904、0.892)[80]、预判EBV感染(AUC为0.859)及MSI状态(AUC为0.863)[81]。在影像诊断方面,AI模型也能基于胃癌CT图像推测腹膜转移和复发概率(内部测试、外部验证集的AUROC分别为0.856、0.843)[82],为胃癌精准治疗提供关键参考。2024年9月Nature杂志发表基于弱监督机器学习的临床组织病理学图像评估基础(clinical histopathology imaging evaluation foundation, CHIEF)模型,通过全视野数字病理切片图像,可对胃癌等19种恶性肿瘤进行病理诊断、确定肿瘤起源、预测突变谱征和推测生存时间等多项任务,显著提高肿瘤数字病理评估的准确性[83]。

我们坚信,随着AI技术与临床诊疗的深度融合,将为临床医生和患者提供更为精准的循证医学依据,全方位助力肿瘤临床管理的各个环节。这不仅将推动胃癌预防、诊断与治疗水平实现质的飞跃,更将在减轻胃癌疾病负担、提升全民健康水平方面发挥重要作用。

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