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综 述

食管癌放疗敏感性相关生物标志物的研究进展

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【摘要】 食管癌是全球高发的消化道恶性肿瘤,放疗作为其综合治疗的核心手段之一,在局部晚期患者根治、术后辅助治疗及姑息治疗中发挥关键作用。但临床中食管癌患者放疗敏感性存在显著个体差异,部分患者因放疗抵抗导致治疗失败、肿瘤复发及转移,严重影响预后。生物标志物作为反映肿瘤细胞生物学行为、预测治疗反应的关键指标,为食管癌放疗个体化方案制定、疗效评估及预后判断提供了重要参考。文章按功能性将生物标志物分为接触(暴露)标志物、效应标志物、敏感性标志物 3 类进行综述,并重点阐述这些标志物在食管癌诊断初期、治疗过程中及治疗结束后 3 个阶段的变化特点及临床应用价值。系统梳理其作用机制与临床研究进展,探讨当前挑战与未来方向,为食管癌放疗个体化策略提供理论依据。

【关键词】 食管癌; 放疗; 敏感性; 生物标志物**【中图分类号】** R735.1 **【文献标识码】** A**Research progress on biomarkers related to radiotherapy sensitivity in esophageal cancer** He Leran^{*}, Cheng Yufeng,^{*} Shandong University, Shandong, Jinan 250012, China

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【Abstract】 Esophageal cancer is a highly prevalent malignant tumor of the digestive tract worldwide. Radiotherapy, as one of the core methods of comprehensive treatment, plays a key role in the radical treatment, postoperative adjuvant therapy, and palliative care of locally advanced patients. However, there are significant individual differences in radiotherapy sensitivity among esophageal cancer patients in clinical practice. Some patients may experience treatment failure, tumor recurrence, and metastasis due to radiotherapy resistance, which seriously affects prognosis. Biomarkers, as key indicators reflecting the biological behavior of tumor cells and predicting treatment response, provide important references for the development of individualized radiotherapy plans, efficacy evaluation, and prognosis judgment for esophageal cancer. This article categorizes biomarkers by function into three types: exposure (contact) biomarkers, effect biomarkers, and sensitivity biomarkers. It provides a comprehensive review of these biomarkers, focusing on their characteristics and clinical application value during the initial diagnosis, treatment process, and post-treatment stages of esophageal cancer. It systematically summarizes their mechanism of action and clinical research progress, explores current challenges and future directions, and provides a theoretical basis for individualized radiotherapy strategies for esophageal cancer.

【Key words】 Esophageal cancer; Radiotherapy; Sensitivity; Biomarker

食管癌是全球常见的消化道恶性肿瘤,新发病例和死亡病例分别居恶性肿瘤第七位和第六位^[1]。放疗作为局部晚期食管癌核心治疗手段,在新辅助、根治性及姑息治疗中发挥关键作用,可显著提高 5 年生存率^[2]。同时,调强放疗、图像引导放疗等精准技术的应用,使靶区剂量更精确,正常组织损伤有效降低^[3]。然而,临床分期、肿瘤位置及病理类型相似的患者接受相同放疗后疗效差异显著,部分患者反应不佳^[4]。这种放疗敏感性个体差异与肿瘤细胞生物学特性、微环境及宿主因素相关,放疗抵抗不仅导致局部控制失败,还可能通过诱导上皮-间

质转化增加远处转移风险,是制约患者预后改善的关键瓶颈。在此背景下,生物标志物作为可客观测量和评价的生物学指标,为食管癌放疗敏感性预测和个体化治疗提供了重要工具。根据功能特点可分为反映致癌因素暴露或肿瘤负荷的接触(暴露)标志物、体现放疗引起的生物学效应的效应标志物、决定肿瘤内在放射敏感性的敏感性标志物^[5-6]。同时,这些标志物在食管癌不同阶段展现出不同的变化特点和应用价值。本文系统综述近年来食管癌放疗敏感性相关生物标志物的研究进展、作用机制及临床意义,并探讨该领域面临的挑战与未来发展

方向。

1 接触(暴露)标志物

1.1 循环肿瘤 DNA(circulating tumor DNA, ctDNA) ctDNA 是肿瘤细胞凋亡、坏死或分泌释放入血的片段化 DNA,携带肿瘤特异性基因突变和甲基化修饰信息,是理想的暴露生物标志物。在诊断初期,ctDNA 突变谱可全面反映肿瘤基因组负荷及克隆演化特征。Liu 等^[7]对 132 例局部晚期食管癌患者的前瞻性队列研究显示,个性化 ctDNA 检测联合临床评估预测非病理完全缓解的敏感性达 92.0%~93.2%。在治疗过程中,ctDNA 动态变化可实时评估放疗应答。Tatalovic 等^[8]发现治疗 2 周后 ctDNA 下降>57.1%的患者中位总生存期(overall survival, OS)显著延长(13.6 个月 vs 4.1 个月, $P<0.001$)。在疗效及预后阶段, Yue 等^[9]发现放疗后 ctDNA 持续存在或再次出现可提前数月预测复发风险。此外, ctDNA 甲基化谱分析为放疗敏感性预测提供新维度,如 ZNF569、HOXA9 等甲基化位点水平变化可反映放疗过程中肿瘤克隆演化^[10-11]。ctDNA 作为暴露标志物,贯穿食管癌诊治全程,但标准化和假阳性问题仍需解决。

1.2 代谢组学标志物 肿瘤代谢重编程是重要的暴露特征。王华光等^[12]综述了食管癌代谢组学研究进展,指出特定代谢物可作为敏感性预测指标。在诊断初期,磷脂酰胆碱、溶血磷脂酸等血清脂质代谢物及谷氨酰胺等氨基酸代谢物可区分放疗敏感与抵抗人群。在治疗过程中,正电子发射断层扫描(positron emission tomography, PET)-CT 检测的葡萄糖代谢参数动态变化可实时评估代谢反应。Shen 等^[13]强调,代谢物反映肿瘤微环境及宿主状态,其作为非侵入性暴露标志物具有独特优势。在预后阶段,已有研究证实,放疗后代谢物谱恢复正常的速度与远期生存显著相关,靶向代谢通路联合放疗成为克服抵抗的新策略^[14]。

2 效应标志物

2.1 缺氧相关效应标志物 肿瘤组织缺氧是实体瘤的普遍特征,也是放疗抵抗的关键微环境因素。诊断初期,缺氧诱导因子 1 α (hypoxia inducible factor-1 α , HIF-1 α)过表达即预示放疗抵抗。于芹等^[15]研究显示,食管癌中 HIF-1 α 过表达与放疗抵抗相关, HIF-1 α 表达下调的食管癌细胞放疗敏感性增强,其机制涉及上皮间质转化与肿瘤血管生成抑制。治疗过程中,碳酸酐酶 IX(carbonic anhydrase IX, CAIX)作为 HIF-1 α 下游靶基因,其表达变化反映缺氧程度动态演变。研究发现,免疫组化显示 CAIX 高表达与食管癌放疗后局部复发风险增加相关,其通过维持细胞内 pH 稳态抑制凋亡,并通过细胞外酸化形成免疫抑制微环境^[16]。在预后阶段,治疗前 HIF-1 α 或 CAIX 高表达患者 OS 显著缩短,靶向缺氧联合放疗正在临床探索中^[17]。

2.2 免疫微环境相关效应标志物 肿瘤免疫微环境对放疗疗效具有双重调控作用,放疗既可激活免疫也可诱导免疫抑制,相应的免疫细胞及分子是关键效应标志物。Liu 等^[18]研究发现,诊断初期, CD8⁺细胞毒性 T 细胞密度与食管癌放疗敏感性呈正相关,治疗前高 CD8⁺T 细胞患者新辅助放化疗后病理完全缓解率显著提高。程序性死亡配体-1(programmed death-ligand 1, PD-L1)作为关键免疫检查点分子,其表达与放疗反应关系复杂。研究显示,在具有放疗抵抗特性的食管鳞癌细胞

中, PD-L1 的蛋白水平显著升高,其主要机制为 JunD-miR494-CUL3 的分子通路通过抑制 PD-L1 的降解,使其在细胞内累积,直接导致了肿瘤细胞对放疗产生抵抗,并同时促进了肿瘤的转移^[19]。治疗过程中,放疗可诱导免疫原性细胞死亡,表现为 CD8⁺T 细胞浸润增加和细胞因子谱改变。研究显示,放疗后血清白介素-6(IL-6)、转化生长因子- β (transforming growth factor- β , TGF- β)水平变化可反映免疫效应状态^[20-21]。在预后阶段, Habu 等^[22]研究发现,治疗前叉头框蛋白 P3(forkhead box P3, FoxP3⁺)调节性 T 细胞高浸润通常与放疗抵抗相关,而放疗后出现 T 细胞炎性微环境预示良好预后。且已有研究指出, IL-1、IL-10、肿瘤坏死因子- α (tumour necrosis factor- α , TNF- α)等亦参与了调控,多细胞因子联合检测可构建免疫评分系统以预测放疗疗效^[23-24]。

2.3 血管生成与缺氧调节相关效应标志物 异常血管生成是肿瘤微环境紊乱的核心,会导致缺氧和酸性环境,是重要的效应环节。在诊断初期,血管内皮生长因子(vascular endothelial growth factor, VEGF)高表达与放疗抵抗及不良预后相关。陈美玲等^[25]研究显示,血清 VEGF 水平与放疗敏感性呈负相关,高 VEGF 患者新辅助放化疗后病理完全缓解率显著降低。在治疗过程中,抗 VEGF 药物联合放化疗可尝试改善血管正常化,但与临床研究结果不一致,可能与患者选择、联合方案及毒性管理有关^[26-27]。在预后阶段,表皮生长因子受体(epidermal growth factor receptor, EGFR)在食管鳞癌中过表达率达 50%~70%,主要通过激活 MAPK/ERK 和 PI3K/AKT 通路促进增殖、抑制凋亡并增强 DNA 修复,其高表达与新辅助放化疗后病理完全缓解率低相关^[28-29]。

3 敏感性标志物

3.1 自噬与代谢相关敏感性标志物 自噬在放疗抵抗中发挥双重作用,适度自噬清除受损成分促进存活,而过度自噬则会导致细胞死亡。代谢重编程作为肿瘤细胞适应应激的核心特征,同样与放疗敏感性密切相关。脯氨酸 4-羟化酶 α 多肽 II(prolyl 4-hydroxylase subunit alpha-2, P4HA2)是脯氨酸羟化酶家族成员,可通过催化胶原脯氨酸残基羟化参与胶原合成。近年研究发现,在诊断初期,其在食管癌中过表达且与放疗抵抗相关, P4HA2 高表达组新辅助放化疗后病理完全缓解率显著低于低表达组^[30]。机制上, P4HA2 通过胶原重塑激活整合素/FAK/YAP 信号,并通过调节 HIF-1 α 稳定性影响代谢,同时, P4HA2 参与线粒体自噬,自噬抑制剂氯喹可逆转其诱导的抵抗^[31]。在治疗过程中,代谢重编程标志物如 M2 型丙酮酸激酶(pyruvate kinase M2, PKM2)作为糖酵解关键酶,研究证实其在食管癌组织中呈高表达且与放疗抵抗相关^[32]。Zhang 等^[33]体外实验表明, PKM2 可通过调控含血小板白细胞 C 激酶底物和 Sec7 域 3 来调节上皮间质转化进程,促进食管鳞状细胞的生长和转移。

3.2 新型细胞死亡调节相关敏感性标志物 细胞死亡调控异常是肿瘤放疗抵抗的核心机制,除凋亡外,铁死亡、焦亡、坏死性凋亡等细胞死亡方式也参与了放疗反应。在诊断初期,研究发现,含 pleckstrin 同源结构域家族 A 成员 7(pleckstrin homology domain containing A7, PLEKHA7)作为新发现的细胞死亡调节分子,其低表达与放疗抵抗及不良预后相关。孟凡伟

等^[34]构建的食管癌预后模型中发现,包含 PLEKHA7 在内的 6 个铜死亡相关基因构建的风险模型,可较好地预测食管癌的预后。另外,一项功能实验证实,敲低 PLEKHA7 可增加食管癌细胞放射抵抗性,过表达则增强放射敏感性^[35]。在预后阶段,PLEKHA7 作为多细胞死亡方式调节节点,展现出作为放疗敏感性标志物和治疗靶点的潜力。此外,研究发现,焦亡效应分子和坏死性凋亡分子的表达水平也与放疗后细胞死亡方式及预后相关^[36]。

3.3 其他组织敏感性标志物 G 蛋白偶联受体 56 (G protein-coupled receptor 56, GPR56) 是黏附 G 蛋白偶联受体家族成员,参与细胞黏附和抑制治疗抵抗。诊断初期,GPR56 高表达通常与放疗抵抗及不良预后相关^[37]。Chen 等^[38]开展的一项回顾性分析中,纳入了 60 例食管癌患者,发现 GPR56 高表达患者新辅助放疗后 OS 显著缩短。在食管癌治疗过程中及预后阶段,GPR56 则可能通过激活 TGF- β 信号通路促进抵抗,但功能实验尚缺乏,具体机制待深入研究,进一步解析 GPR56 的功能及其与其他分子标志物的交互作用,将有助于完善食管癌放疗敏感性的预测体系。

4 小结与展望

近年来,食管癌放疗敏感性生物标志物研究取得显著进展,从功能性分类和时间阶段两个维度,逐步揭示了放疗抵抗的复杂网络。然而,当前研究仍面临挑战,大部分研究多为单中心小样本回顾性分析,缺乏统一标准和大规模前瞻性验证,且单一标志物预测效能有限,难以捕捉肿瘤时空异质性,临床转化障碍突出。

未来研究亟须从以下方向突破:首先,需推动多组学整合与人工智能的深度融合,通过联合基因组学、影像组学等多维度数据构建高精度预测模型,显著提升个体化疗效评估能力。其次,需发展液体活检动态监测技术,借助 ctDNA 甲基化、外泌体 miRNA 等连续采样,实现治疗过程中的实时疗效评估与耐药人群早期识别。同时,应深入探索放疗联合免疫及靶向治疗的协同机制,挖掘指导联合方案优化的关键生物标志物。此外,建立标准化体系和开展多中心前瞻性临床试验是临床转化的基石,需通过国际协作统一检测与质控标准,以大型随机对照试验验证标志物的实用价值。

随着精准医学理念的深入与技术手段的进步,食管癌放疗有望突破当前瓶颈,从“经验化”迈向“精准化”,最终实现真正意义上的个体化治疗,改善患者预后。

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