·综述·

口腔和口咽鳞状细胞癌免疫治疗相关生物标志物研究现状

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【摘要】 头颈癌(HNC)是全球常见的恶性肿瘤,其中口腔鳞状细胞癌(OSCC)和口咽鳞状细胞癌(OPSCC)在口腔颌面外科学领域具有较高的发病率和极高的临床关注度。受治疗应答异质性及耐药性等因素影响,HNC患者的总体生存率在近十年来尚未取得显著改善。本文在概述HNC放疗、化疗、免疫治疗、靶向治疗及免疫联合多疗法发展现状的基础上,重点综述了预测OSCC和OPSCC免疫治疗相关的生物标志物研究现状。在放疗和化疗领域,人乳头瘤病毒(HPV)感染状态是目前较为明确的独立预后指标,而液体活检技术的应用为疗效的动态评估提供了新的手段。在免疫治疗方面,虽然程序性死亡-配体1(PD-L1)表达水平和肿瘤突变负荷(TMB)在疗效预测中具有一定参考价值,但肿瘤微环境(TME)的异质性影响了免疫治疗的结局。在靶向治疗领域,尽管以表皮生长因子受体(EGFR)为靶点的治疗已广泛应用,但仍缺乏可靠的预测性生物标志物。通过系统分析不同生物标志物的预测价值及其局限性,本文旨在为OSCC和OPSCC的个体化治疗决策及未来多维生物标志物整合策略提供理论参考。

【关键词】 头颈癌; 生物标志物; 免疫治疗; 程序性死亡-配体1

基金项目:广东省基础与应用基础研究基金(2023A1515011945);深圳市科技计划(JCYJ20240813142112017);深圳大学总医院海雅青年科学家基金(2025-HY006)

引用著录格式:江鸿宇,梁家洛,马琳,等. 口腔和口咽鳞状细胞癌免疫治疗相关生物标志物研究现状[J/OL]. 中华口腔医学研究杂志(电子版), 2026,20(2):136-148.

DOI:10.3877/cma.j.issn.1674-1366.2026.02.009

Current advances in biomarkers associated with immunotherapy in oral and oropharyngeal squamous cell carcinoma

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【Abstract】 Head and neck cancer (HNC) is a prevalent malignancy worldwide. Notably, oral squamous cell carcinoma (OSCC) and oropharyngeal squamous cell carcinoma (OPSCC) are characterized by a high incidence rate and garner significant clinical attention within the field of oral and maxillofacial surgery. Constrained by the heterogeneity of therapeutic responses and drug resistance, the overall survival rate of patients with HNC has not witnessed significant improvement over the past decade. This article provides an overview of the current status of radiotherapy, chemotherapy, immunotherapy, targeted therapy, and multidimensional combination therapies. Furthermore, it systematically reviews the research status of predictive biomarkers associated with therapeutic efficacy in OSCC and OPSCC. In the realm of radiotherapy and chemotherapy, human papillomavirus (HPV) infection status remains a well-established independent prognostic factor, while the application of liquid biopsy offers a novel approach for the dynamic evaluation of treatment outcomes. Regarding immunotherapy, although programmed cell death-ligand 1 (PD-L1) expression and tumor mutational burden (TMB) possess certain predictive value, the heterogeneity of the tumor microenvironment (TME) significantly influences treatment outcomes. In the field of targeted therapy, despite the widespread clinical application of epidermal growth factor receptor (EGFR) - targeted treatments, reliable predictive biomarkers remain lacking. By systematically analyzing the predictive utility and limitations of various biomarkers, this review aims to provide theoretical references for personalized treatment decision - making and the future development of integrated multidimensional biomarker strategies in OSCC and OPSCC.

【Key words】 Head and neck cancer; Biomarkers; Immunotherapy; Programmed death-ligand 1

Fund programs: Basic and Applied Basic Research Foundation of Guangdong Province (2023A1515011945); Science and Technology Planning Project of Shenzhen (JCYJ20240813142112017); HaiYa Young Scientist

Foundation of Shenzhen University General Hospital (2025-HY006)

DOI:10.3877/cma.j.issn.1674-1366.2026.02.009

头颈癌(head and neck cancer,HNC)是全球常见的恶性肿瘤之一。尽管近年来治疗手段不断进步,但HNC患者总体生存率和预后改善仍有限。据世界卫生组织预测,HNC发病率未来仍将持续上升,其高发病率与死亡率已构成重大的公共卫生挑战。HNC是一组高度异质性的恶性肿瘤,其中90%以上为鳞状细胞癌,而口腔鳞状细胞癌(oral squamous cell carcinoma, OSCC)和口咽鳞状细胞癌(oropharyngeal squamous cell carcinoma,OPSCC)占比较大,也是近年来免疫治疗、生物标志物及精准治疗策略研究最为活跃的亚型。现有的HNC综合治疗体系包括手术、化学治疗(化疗)、放射治疗(放疗)、靶向治疗和免疫治疗等。放疗和化疗都是以制造DNA损伤进而诱导癌细胞死亡为主要目的,临床证实对HNC有着确切的疗效。然而一些HNC细胞可以通过多种方式有效地调控DNA损伤修复机制,造成对放疗、化疗的耐受。免疫治疗方面,程序性死亡-配体1(programmed cell death-ligand 1,PD-L1)表达水平在部分癌种中与疗效呈正相关,但在HNC中预测价值有限,单一标志物难以全面指导治疗决策。因此,仍需发掘能同时克服放化疗耐受、并更准确预测免疫治疗获益的生物标志物,以推动个体化精准治疗,提升患者生存率。本文在概述HNC整体治疗现状的基础上,重点综述预测OSCC及OPSCC免疫治疗相关的生物标志物研究现状。

一、头颈癌发展现状

HNC起源于上呼吸道及上消化道的上皮组织,涵盖鼻腔、鼻旁窦、咽、口腔、喉及颈段食管等多个解剖部位,其中超过90%为头颈鳞状细胞癌(head and neck squamous cell carcinoma,HNSCC)[1]。作为全球常见的恶性肿瘤之一,HNC在我国亦具有较高的发病率,其发生与吸烟、饮酒、咀嚼槟榔及人乳头瘤病毒(human papilloma virus,HPV)感染等因素密切相关[2-3]。此外,HNC在性别和年龄分布上具有明显差异,男性发病率显著高于女性,且多见于老年人群[4-5]。由于HNC的早期症状如颈部无痛性肿块、口腔或咽喉溃疡等[6],缺乏特异性,部分患者确诊时已处于中晚期。因此,早期识别、及时采取医疗干预至关重要,以避免HNC病情进展和提高治疗成功率。

目前,HNC的治疗以手术、放疗、化疗及免疫治疗等为基础,并逐渐向多学科综合治疗模式发展(图1)。尽管近年来诊疗手段不断进步,患者生存率在一定程度上有所改善,但近十年来发病率和死亡率仍呈上升趋势,且不同患者之间存在显著的疗效差异和预后异质性[7-8]。因此,探索能够预测治疗反应及预后的生物标志物,对于实现个体化精准治疗具有重要意义。

1. 放疗、化疗的发展现状:放疗和化疗是HNC除手术外的重要治疗手段,其主要通过诱导DNA损伤抑制肿瘤细胞

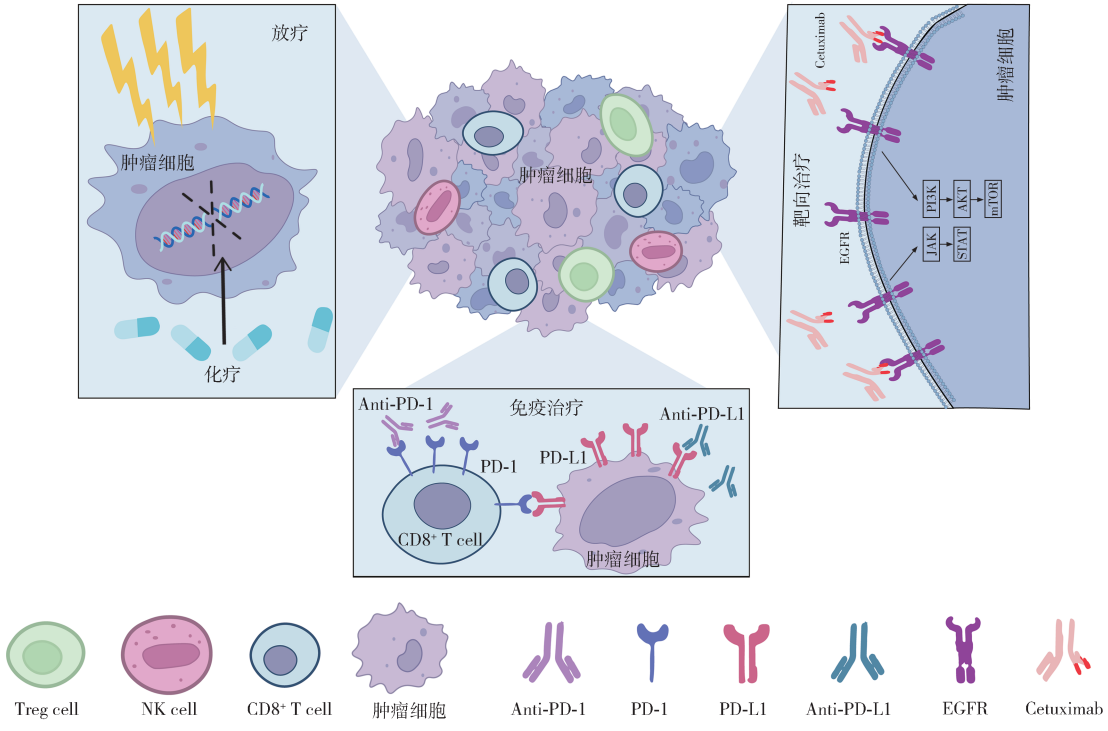

图1 头颈癌(HNC)放疗、化疗、免疫治疗及靶向治疗作用机制示意图 Treg cell:调节性T细胞;NK cell:自然杀伤细胞;$CD8^+$ T cell:$CD8^+$细胞毒性T淋巴细胞;PD-1:程序性死亡受体1;Anti-PD-1:抗PD-1单克隆抗体;PD-L1:程序性死亡-配体1;Anti-PD-L1:抗PD-L1单克隆抗体;EGFR:表皮生长因子受体;Cetuximab:西妥昔单克隆抗体;JAK/STAT通路:Janus激酶-信号转导及转录激活因子通路;PI3K/AKT/mTOR通路:磷脂酰肌醇-3-激酶-蛋白激酶-B-哺乳动物西罗莫司靶蛋白通路。

增殖或促进细胞死亡[9]。局部晚期HNC的主要治疗手段是同步放化疗,其中放疗联合顺铂(100 mg/m^2,每3周1次)被推荐为标准的非手术综合治疗策略[10]。然而,临床疗效存在显著个体差异,约半数患者在治疗后仍出现复发或进展,复发/转移性患者总体预后较差[11]。尽管近年来图像引导放疗(image-guided radiation therapy,IGRT)和调强放疗(intensity-modulated radiation therapy,IMRT)等技术提高了治疗精准性并减少了对正常组织的损伤,但放疗相关毒副反应及局部复发问题仍然突出,严重影响患者生活质量[12-13]。因此,筛选能够预测放疗、化疗敏感性、毒性反应及预后的生物标志物,对于优化个体化治疗策略具有重要意义。

2. 免疫治疗的发展现状:HNC的发生、发展与免疫系统密切相关,肿瘤细胞可通过激活免疫检查点通路、抑制抗原呈递及重塑肿瘤微环境,从而逃避免疫监视[14]。HNC中免疫治疗有多种方式。一种方式是针对免疫逃逸,可以使用免疫检查点抑制剂(immune checkpoint inhibitor,ICI),这些药物[如帕博利珠单抗(Pembrolizumab)和纳武利尤单抗(Nivolumab)是两种针对程序性死亡受体1(programmed death-1,PD-1)的人源化单克隆抗体(简称单抗),而度伐利尤单抗(Durvalumab)和阿替利珠单抗(Atezolizumab)是针对PD-L1的抗体]通过靶向PD-1/PD-L1轴来恢复抗肿瘤免疫反应[15]。此外,肿瘤免疫微环境的复杂性(如$CD8^+$ T细胞、Treg及巨噬细胞等免疫细胞组成差异)进一步影响免疫治疗疗效[16]。以PD-1/PD-L1为代表的ICI开启了晚期和复发/转移性HNC免疫治疗的新时代,但据估计有70%~90%的复发/转移性HNC患者对ICI治疗无反应[11]。HNC个体差异及肿瘤本身的异质性都为免疫治疗增加了难度。寻找更有效指示免疫治疗反应的生物标志物,或者改变原有免疫钝化状态的联合治疗方法,是改善免疫治疗在HNC疗效中的关键环节。ICI在激活抗肿瘤免疫反应的同时,可因免疫系统的非特异性激活而破坏机体免疫稳态,导致自身耐受受损并引发免疫相关不良反应(immune-related adverse event,irAE)[17]。irAE可累及多个器官和系统,常见受累部位包括皮肤、内分泌系统、肺部、心脏、神经系统、肾脏、肌肉和关节等[18]。其中,皮肤毒性发生率较高且多于治疗早期出现,临床表现多样,严重程度不一,从常见的丘疹或斑丘疹、皮肤瘙痒,到需专科干预的大疱性皮疹,以及Stevens-Johnson综合征和药物超敏反应综合征(drug reaction with eosinophilia and systemic symptoms,DRESS)等重度不良反应[19]。随着治疗进程的推进,部分患者可出现内分泌系统受累,ICI相关的内分泌毒性发生率约为4%~14%,主要包括甲状腺炎、垂体炎、原发性肾上腺皮质功能不全及罕见的1型糖尿病[18,20]。而免疫性肺炎临床表现为呼吸困难和干咳,或仅表现为影像学异常而无明显症状[21]。相比之下,ICI相关心脏毒性发生率虽不足1%,但起病急骤、进展迅速且重症致死率高[22]。因此,较高的无应答率与严重的不良反应,使得精准筛选优势获益人群成为当前亟待解决的临床痛点。

3. 靶向治疗的发展现状:近年来,HNC的靶向治疗逐渐由单一受体抑制向多信号通路联合干预转变。其中,以表皮生长因子受体(epidermal growth factor receptor,EGFR)为代表的靶向治疗在HNSCC中具有重要地位,其异常激活与肿瘤细胞增殖、侵袭及不良预后密切相关[23-25]。尽管,以西妥昔单抗为代表的EGFR靶向治疗在部分患者中取得了一定疗效,但总体应答率有限且易出现耐药现象[23,26]。近年来的研究表明,Janus激酶-信号转导及转录激活因子通路(Janus kinase-signal transducer and activator of transcription pathway,JAK-STAT通路)、磷脂酰肌醇3-激酶-蛋白激酶B-哺乳动物西罗莫司靶蛋白通路(phosphatidylinositol 3-kinase-AKT-mammalian target of rapamycin pathway,PI3K/AKT/mTOR通路)及肝细胞生长因子/间质上皮转化因子通路(hepatocyte growth factor/mesenchymal-epithelial transition factor pathway,HGF/MET通路)等多条信号通路的异常激活与交叉调控在HNSCC进展中起关键作用[23-24]。其中,PI3K/AKT/mTOR通路是HNSCC中最常见的失调致癌驱动通路,在超过90%的病例中呈激活状态[27-29]。HGF/MET通路激活与西妥昔单抗耐药相关。针对性策略包括MET抑制剂(如卡博替尼)和HGF抑制剂(如非他珠单抗)。临床证据显示,卡博替尼联合帕博利珠单抗可改善复发/转移性HNSCC的无进展生存期和总生存期;非他珠单抗联合西妥昔单抗在HPV阴性患者中表现出一定抗肿瘤活性,提示双通路阻断在特定亚群中的潜力[30-32]。新兴靶点[如人表皮生长因子受体2(human epidermal growth factor receptor 2,HER2)、人表皮生长因子受体3(human epidermal growth factor receptor 3,HER3)、丝裂原活化蛋白激酶(mitogen-activated protein kinase kinase,MEK)等]研究持续推进,相关药物(如曲妥珠单抗等)已进入临床试验阶段[33-34]。目前,靶向药物与免疫检查点抑制剂、放疗或化疗的联合应用正广泛探索,以延缓耐药并提升疗效。然而,鉴于HNSCC的高度异质性和肿瘤微环境复杂性,联合方案的疗效与安全性仍需更多前瞻性研究验证[35-37]。

4. 免疫联合多疗法的发展现状:大量临床前研究证实,靶向DNA损伤的治疗(如放疗、化疗)可诱导免疫原性细胞死亡(immunogenic cell death,ICD),促进肿瘤抗原暴露、重塑肿瘤微环境,从而增强抗肿瘤免疫应答,具体机制包括:放疗诱导肿瘤细胞形成“原位疫苗”、上调CD80/CD86、STAT1磷酸化、T细胞扩增、激活补体途径辅助抗原呈递、肿瘤DNA损伤修复缺陷进一步增加基因组不稳定性与抗原性等[38-40]。因此,研究肿瘤自身DNA损伤修复缺陷,对寻找有效的联合免疫治疗靶点十分重要。这些机制为ICI与手术治疗、放疗、化疗及靶向治疗的联合提供了理论基础。

临床证据显示,免疫联合策略已在HNC中取得重要进展。KEYNOTE-048研究证实,帕博利珠单抗单药或联合化疗较西妥昔单抗+化疗显著延长复发/转移性头颈部鳞状细胞癌(Recurrent/Metastatic head and neck squamous cell carcinoma,R/M HNSCC)总生存期,获益不完全依赖PD-L1联合阳性分数(combined positive score,CPS)[41]。尽管放疗具有免疫增敏潜力,但KEYNOTE-412试验显示帕博利珠单抗

联合同步放化疗在局部晚期HNSCC中未显著改善无事件生存期(event-free survival,EFS)[42]。靶向EGFR的西妥昔单抗可增强抗肿瘤免疫(促进DC成熟、$CD8^+$ T细胞激活、NK细胞功能),与ICI联合显示协同潜力[43]。相关试验包括:NCT03370276(纳武利尤单抗+西妥昔单抗)在中位总生存率达11.4~20.2个月;NCT03082534(帕博利珠单抗+西妥昔单抗)6个月客观缓解率达45%[44-45]。而在可切除局部晚期HNSCC的联合治疗中,KEYNOTE-689研究首次证实围手术期应用Pembrolizumab能显著提高患者的EFS及主要病理缓解率(major pathologic response,MPR),确立了其在手术联合治疗中的突破性地位[46]。此外,针对高复发风险患者,NIVOPOSTOP GORTEC 2018-01研究显示,在术后标准放化疗基础上联合Nivolumab可显著延长无病生存期[47]。这些结果凸显免疫联合的多模态潜力,但疗效异质性仍需生物标志物指导患者筛选与方案优化。

二、预测口腔和口咽鳞状细胞癌治疗效果的生物标志物

上述治疗策略的异质性与耐药问题凸显了可靠生物标志物指导个体化治疗的迫切需求,所以选择合适且准确的生物标志物是制定免疫治疗方案乃至整体肿瘤治疗方案的重要参考因素之一。目前看来,PD-L1等生物标志物对于免疫治疗具有一定的指导性,但也有其局限性。综合考虑多因素并探索更多的生物标志物,有助于临床更好地筛选能从治疗中获益的人群[39]。

1. 预测放疗、化疗效果的生物标志物:局部晚期HNC患者常采用放疗、化疗作为标准治疗方案,然而患者的治疗响应及预后存在显著的个体异质性。尽管部分患者疗效显著,但仍有相当比例的患者面临治疗抵抗、肿瘤复发或严重毒副反应。因此,寻找可靠的生物标志物以预测放疗、化疗获益人群至关重要,这对实现个体化精准治疗具有重要意义。

(1)HPV感染状态:HPV相关HNC(尤其是OPSCC)的发生高度依赖高危型HPV的持续感染(persistent infection),而非短暂暴露。尽管大多数HPV感染可在1~2年内被机体免疫系统自然清除,但少数未能被有效清除的感染可演变为持续感染,持续时间可达10~30年[48-49]。在这一持久感染过程中,病毒E6和E7癌蛋白持续表达,通过分别降解p53蛋白和视网膜母细胞瘤蛋白(retinoblastoma protein,pRb),引发细胞周期失控、基因组不稳定及免疫逃逸,最终推动肿瘤发生与发展[50-51]。在OPSCC中,HPV持续感染已被证实与肿瘤发生密切相关,并可能在数年甚至十年内逐步进展为侵袭性癌症。此外,越来越多研究表明,HPV持续感染还可通过调控肿瘤微环境、促进免疫逃逸,以及与口咽部微生物组发生互作,共同参与肿瘤的发生与进展[52-54]。

大量研究证实,HPV感染状态是OPSCC放疗、化疗疗效的独立生物标志物[55-59]。Ang等[60]回顾性分析了323例Ⅲ~Ⅳ期口咽癌患者(其中63.8%为HPV阳性)的数据,结果显示HPV阳性患者的3年总生存率(82.4%)显著优于HPV阴性患者(57.1%,$P<0.001$);在对年龄、种族、肿瘤和淋巴结分期、烟草暴露情况及治疗分组情况进行调整后,死亡风险降低了58%。在机制层面,Rieckmann等[61]指出HPV阳性HNSCC细胞系由于DNA损伤修复(DNA damage repair,DDR)能力受损,使其对放射治疗更为敏感,这为临床观察到的生存优势提供了潜在的生物学解释。

然而,与OPSCC中HPV感染已被确立为明确致病因素不同,HPV在OSCC中的作用仍相对有限且存在一定争议[62-63]。OSCC中HPV的总体检出率约为10%~25%,显著低于OPSCC(约45%),且在不同地区及研究之间存在较大异质性,其作为致病因素或预测性生物标志物的作用尚未形成一致结论[62]。这种差异主要归因于解剖部位上皮结构的差异:口咽部(尤其是腭扁桃体和舌扁桃体)隐窝由特殊的网状上皮构成,上皮结构松散、基底膜不连续,使基底细胞易暴露于外界环境,从而为HPV进入和持续感染提供有利条件[64-65]。

(2)液体活检技术:尽管HPV阳性患者预后总体较好,但仍有约20%~25%的患者在5年内复发[66-68]。液体活检技术(liquid biopsy,LB)通过检测循环肿瘤DNA(circulating tumor DNA,ctDNA)等衍生物,为动态监测HNSCC放疗、化疗疗效提供了新策略[69-72]。Hilke等[73]针对HNC患者接受放疗和化疗期间的研究,验证了液体活检作为新型生物标志物的预测价值。该研究纳入20例局部晚期HNSCC患者,通过肿瘤测序明确驱动突变,动态监测放疗和化疗期间ctDNA的变化,结果发现:85%患者的ctDNA可被检测到,且其水平与肿瘤体积显著相关;首次随访时ctDNA阳性的患者后续出现了疾病复发。此外,研究还观察到3例患者体内存在高水平循环HPV DNA(circulating HPV DNA,cvDNA),其动态变化与ctDNA高度一致,且治疗后逐渐消失。这些结果提示,ctDNA和cvDNA可能成为评估放疗和化疗疗效的潜在生物标志物。另一项针对HPV相关口咽癌的研究通过检测血浆循环肿瘤HPV DNA(plasma circulating tumor human papillomavirus DNA,ctHPVDNA)发现,该指标在预测疾病复发方面表现出较高的阳性预测值和阴性预测值,提示其作为评估放疗和化疗疗效及复发风险的潜力[74]。

(3)与肿瘤微环境相关因素:HNSCC对放疗、化疗的应答还受到肿瘤微环境(tumor microenvironment,TME)复杂性的深刻影响[75]。TME中的特定组分已被识别为治疗抵抗的潜在屏障:结缔组织增生反应(desmoplastic reaction,DR)及其特征性的间质纤维化,与不良的临床预后(无病生存期和总生存期)密切相关[76]。此外,基质金属蛋白酶(matrix metalloproteinase,MMP)及其抑制剂(tissue inhibitors of metalloproteinase,TIMP)在放疗后的表达谱改变,有望作为指示治疗后生物学行为的预后标志物[77]。在分子调控层面,微小RNA(microRNA,miRNA)的异常表达与肿瘤蛋白*p53*基因(tumor protein *p53* gene,*TP53*)和磷脂酰肌醇3-激酶催化亚基α基因(phosphatidylinositol 3-kinase catalytic subunit alpha gene,*PIK3CA*)等关键基因的改变密切相关,可能介导化疗耐药[78]。而肿瘤相关成纤维细胞(cancer-associated fibroblast,CAF)分泌的外泌体miRNA则通过重塑微环境,进

一步促进了治疗耐药性的产生[79]。

综上所述,HPV感染状态是OPSCC中成熟的独立预后指标,阳性患者放射敏感性增强、生存获益,但在OSCC中的预测价值仍受限于解剖差异及异质性而存在争议。同时,基于ctDNA及ctHPVDNA的液体活检技术打破了传统检测的局限,为治疗响应的动态监测及早期复发预警提供了高灵敏度的新手段。此外,复杂的TME特征(如间质纤维化、MMP及miRNA的异常表达)在介导放化疗耐药中扮演着关键角色。全面整合这些多维生物标志物,将是未来攻克放化疗抵抗、实现个体化精准治疗的重要方向。

2. 预测免疫治疗效果的生物标志物:与放疗、化疗主要依赖HPV状态等预后指标不同,免疫治疗的疗效预测更依赖于肿瘤免疫微环境。近年来,以PD-1/PD-L1抑制剂为代表的ICI引发了R/M HNSCC治疗范式的转变[80-81]。然而,患者对ICI的响应率较低且高度可变[80-82]。因此,在将患者暴露于潜在毒性和高成本的治疗之前,识别能够预测疗效和预后的生物标志物变得至关重要[43]。

(1)PD-L1表达:PD-L1表达是目前评估ICI疗效最为成熟的生物标志物。其机制涉及阻断PD-L1与T细胞表面PD-1的结合,从而逆转肿瘤免疫抑制微环境[15],通常采用CPS或肿瘤比例分数(tumor proportion score, TPS)进行量化评估[83-84]。多项大型临床试验已确立了其预测价值:近期公布的KEYNOTE-689试验有力佐证了CPS评分在围手术期免疫治疗中的分层指导意义。结果显示,PD-L1高表达(CPS≥10)亚群作为核心获益人群,取得了最为显著的EFS改善(HR:0.66,95% CI:0.49~0.88)及最高的病理缓解率(MPR:13.7%)。而在更广泛的PD-L1阳性(CPS≥1)人群中,尽管获益幅度略逊于高表达组,但仍维持了统计学显著的EFS优势(HR:0.70,95% CI:0.55~0.89)及可靠的病理反应(MPR:9.8%)[46]。基于此,FDA已批准帕博利珠单抗用于治疗PD-L1 CPS≥1的可切除局部晚期HNSCC患者,进一步巩固了PD-L1作为治疗分层核心指标的地位[85]。此外,KEYNOTE-048研究证实CPS≥1(涵盖CPS:1~19亚组)的患者能从帕博利珠单抗单药或联合化疗中获益,疗效优于标准靶向化疗方案[41];CheckMate141和KEYNOTE-040试验也分别在TPS≥1和TPS≥50的人群中观察到了显著的生存获益[86]。尽管PD-L1在指导HNSCC免疫治疗中占据核心地位,但其作为预测标志物的临床应用仍面临严峻的标准化挑战。首先,临床常用的PD-L1检测方法(如22C3、SP263等)及对应的评分平台存在差异,导致结果的一致性受到影响[87-88]。此外,PD-L1表达具有空间和时间异质性,不同取材部位(如原发灶、转移灶等)及检测时间点(治疗前后)可能导致结果显著变异,从而限制其预测准确性[89]。因此,推动PD-L1检测方法的标准化(如统一抗体、平台和评分指南)仍是提高其临床应用价值的关键。综上所述,PD-L1高表达与帕博利珠单抗的治疗应答呈显著正相关,充分凸显了其作为预测性生物标志物的重要性。然而,单纯依赖PD-L1表达这一单一指标,尚不足以精准筛选出所有潜在获益患者,未来需探索多维度的生物标志物联合应用。

(2)细胞毒性T淋巴细胞相关抗原4(cytotoxic T lymphocyte-associated antigen 4, CTLA-4):在PD-L1作为最成熟预测指标之外,CTLA-4相关特征在双重检查点阻断策略中显示出补充价值,尤其在特定亚组中。CTLA-4与CD28竞争性结合抗原呈递细胞上的CD80/86,从而抑制T细胞的共刺激信号,限制免疫反应的激活[90]。在HPV阳性口腔癌的临床前模型中,抗PD-1与抗CTLA-4的联合治疗相比单药治疗显著提高了生存率并缩小了肿瘤体积[91]。此外,CTLA-4基因启动子的低甲基化被发现与ICI的良好应答相关,这表明CTLA-4的可能作为一种新型的预测性生物标志物[91-92]。尽管,双重检查点阻断的CheckMate651试验在全人群中未达到主要终点,但在PD-L1 CPS≥1的亚组分析中仍观察到了生存获益,提示CTLA-4相关标志物在特定联合治疗场景下的筛选价值[92]。

(3)肿瘤突变负荷(tumor mutational burden, TMB):TMB作为另一独立维度指标,已被指南推荐用于补充PD-L1预测不足的情况。TMB表示在特定癌症中测序的每百万碱基(Mut/Mb)DNA的突变数,最初于黑色素瘤中被确立为ICI的潜在生物标志物[93]。2023年,美国临床肿瘤学会(American Society of Clinical Oncology, ASCO)发布了R/M HNSCC免疫治疗和生物标志物检测指南,指出当CPS不可用时或在罕见肿瘤患者中,可对R/M HNSCC患者进行TMB检测,且TMB≥10/Mb应被解读为"高TMB",可作为PD-1抑制剂获益的补充指标[93]。Rodrigo等[94]开展的一项系统评价与Meta分析(纳入11项研究,共1 200例患者)进一步验证了TMB的预测价值,接受Pembrolizumab单抗治疗的TMB-high患者(相比TMB-low患者)具有显著更高的总缓解率(OR:2.62,95% CI:1.74~3.94,$P<0.000\ 1$)和生存优势(HR:0.53,95% CI:0.39~0.71,$P<0.000\ 1$)。尽管ASCO指南推荐TMB≥10 Mut/Mb作为高TMB标准(补充PD-L1预测),但不同测序平台、样本来源以及突变过滤算法差异,均可导致TMB测定结果存在显著异质性[95-96]。此外,临床常采用靶向基因*Panel*推算TMB,其结果与金标准全外显子组测序之间存在一定偏差[97]。甚至在低TMB患者中仍可观察到部分超预期应答者,提示TMB单一指标的预测能力有限,需结合其他生物标志物进行综合评估[98]。

(4)癌症相关成纤维细胞(cancer-associated fibroblast, CAF):除了基因组层面的TMB,肿瘤微环境中的细胞组分如CAF异质性也深刻影响免疫治疗敏感性与耐药。CAF是HNSCC肿瘤微环境中丰度最高的基质细胞,对免疫治疗的耐药性起着关键调节作用,肿瘤微环境的异质性深刻影响免疫治疗结局[76]。CAF通过分泌转化生长因子β(transforming growth factor-β, TGF-β)等细胞因子,促进调节性T细胞的募集,并构建物理屏障阻碍效应T细胞的浸润,从而形成免疫抑制微环境[76,99]。在HNSCC中,特定的CAF亚型与免疫治疗反应密切相关。例如,HNCAF-0/3亚型具有免疫刺激特性,能够通过细胞间接触激活组织驻留记忆T细胞和细胞毒性T细胞,从而预测对Nivolumab的良好反应,而HNCAF-1

亚型则与T细胞耗竭及治疗耐药密切相关[76,100]。

(5)HPV感染状态:相比之下,HPV感染状态作为预测标志物的价值仍存在争议,但HPV作为HNC(特别是口咽癌)风险因素的作用越来越被认可,近年来在高收入国家中,所有癌症类型里OPSCC的发病率增长最为迅速。2021年的报道显示,全球范围内HPV阳性的口咽癌占口咽癌总数的33%[55]。然而,HPV感染状态作为ICI疗效预测生物标志物的价值仍待明确。Xu等[101]通过系统综述和Meta分析(7项研究,n=814)指出,HPV阳性患者接受ICI治疗后的客观缓解率(objective response rate,ORR)和总生存期优于阴性患者。但在评估Pembrolizumab单抗单药治疗HNSCC患者的KEYNOTE-012与KEYNOTE-055研究中,无论HPV状态如何,均观察到治疗反应,提示HPV可能仅作为预后指标而非单纯的ICI疗效预测因子,目前临床尚无依据HPV状态指导免疫治疗选择的明确指南[102]。尽管围绕HPV状态开展了大量治疗相关研究,但在HNC中作为免疫治疗预测性生物标志物的作用仍未明确界定。就目前而言,针对如何依据HPV状态对HNC患者进行免疫治疗,仍然缺乏明确的指南。

(6)口腔微生物组:近年来,口腔微生物组与免疫治疗疗效之间的关联成为研究的新热点。特定口腔菌群可能通过调节肿瘤免疫微环境影响免疫治疗的效果[103-104]。如Wei等[105]的研究提示特定口腔菌群或可作为OSCC的生物标志物,发现微生物与宿主的相互作用可以改变肿瘤免疫微环境影响疾病进程,这为OSCC的免疫治疗提供了理论依据,但其作为独立预测性生物标志物的临床可行性仍需前瞻性研究验证。

综上所述,HNC免疫治疗的生物标志物研究正逐步从单一维度向多维空间拓展。目前,PD-L1表达仍是临床应用最为成熟、证据等级最高的核心预测指标,而TMB则作为重要的基因组补充标志物被指南推荐。然而,两者的临床转化均面临检测标准化与阈值界定等局限性。在此基础上,CTLA-4分子特征、微环境中的CAF特定亚型及新兴的口腔微生物组,为解析肿瘤免疫微环境的复杂异质性提供了全新视角。相比之下,HPV感染状态在免疫治疗中的预测价值尚存争议。单一标志物预测效能有限,未来需通过多维度整合策略以提高免疫治疗获益人群的识别能力。

3. 预测靶向治疗效果的生物标志物:相较于免疫治疗的多维度标志物,靶向治疗目前仍缺乏成熟的预测指标,主要围绕EGFR通路相关特征。靶向治疗凭借其高特异性与低毒性,在HNC治疗中取得了重要进展。自20世纪80年代发现EGFR在HNC中高表达以来,以西妥昔单抗为代表的EGFR靶向药物逐步应用于临床,并成为局部晚期及复发/转移性HNC患者的标准治疗方案之一;然而,现有治疗策略在进一步改善生存结局方面仍存在一定局限。目前,研究重点正转向PI3K、MET等新型信号通路的靶向干预,并强调通过鉴定可靠的生物标志物以优化个体化治疗决策[23-25]。

(1)抗EGFR相关:EGFR靶向单抗(如西妥昔单抗)通过结合肿瘤细胞膜表面的EGFR发挥抗肿瘤作用,但现有临床研究显示,*EGFR*基因扩增或蛋白高表达与治疗疗效之间缺乏稳定一致的相关性,难以作为可靠的预测性生物标志物[106-107]。在结直肠癌(colorectal cancer,CRC)中,大鼠肉瘤病毒癌基因(rat sarcoma viral oncogene homolog,*RAS*)突变已被用于指导抗EGFR治疗,其中Kirsten大鼠肉瘤病毒癌基因(Kirsten rat sarcoma viral oncogene homolog,*KRAS*)突变是CRC不良预后及西妥昔单抗耐药的重要预测因素[108-109],相比之下HNSCC中*KRAS*突变率较低(约1.4%),且与西妥昔单抗疗效的相关性尚无定论,其他EGFR相关分子改变亦未显示出稳定的预测价值[110-111];此外,HPV状态与西妥昔单抗治疗反应存在一定关联,HPV阳性HNSCC患者对西妥昔单抗的疗效相对较差。De-ESCALaTE和RTOG 1016临床试验表明,在HPV阳性OPSCC患者中,西妥昔单抗联合放疗组的总生存期显著短于顺铂联合放疗组,且复发率更高,提示HPV阳性患者对西妥昔单抗响应欠佳[112-113]。鉴于缺乏指导HNSCC抗EGFR治疗的有效标志物,一项研究通过对HNC患者来源异种移植模型(patient-derived xenograft model,PDX)进行分析,鉴定出一组包含小窝蛋白1(Caveolin-1)和性别决定区Y框蛋白2(SRY-box transcription factor 2,SOX2)在内的8个蛋白分子生物标志物特征,其中Caveolin-1高表达并伴随SOX2低表达与西妥昔单抗治疗敏感性显著相关。该结果在接受西妥昔单抗治疗的HNSCC患者肿瘤样本中得到验证,并显示该标志物组合在PDX模型中的预测准确率达88%,且其预测性能优于HPV状态,提示其可能作为HNSCC中EGFR靶向治疗疗效预测的潜在替代性生物标志物[114]。

(2)血管内皮生长因子(vascular endothelial growth factor,VEGF)与其他通路抑制剂相关:VEGF抑制剂(如贝伐珠单抗、索拉非尼和舒尼替尼),是HNC靶向治疗中常用的抗血管生成药物。研究显示,细胞外基质金属蛋白酶诱导因子(extracellular matrix metalloproteinase inducer,EMMPRIN,又称CD147)在HNSCC中高表达,并在HNSCC的PDX模型中表现出预测贝伐珠单抗治疗反应的潜在生物标志物价值[23,115]。细胞周期蛋白依赖性激酶4/6抑制剂(cyclin-dependent kinase 4/6 inhibitor,CDK4/6)(如哌柏西利、阿贝西利和达尔西利)在HNSCC中的应用受到广泛关注[116-118],一项基于食管鳞癌患者来源模型的研究发现,细胞周期蛋白依赖性激酶抑制2A/2B基因(cyclin-dependent kinase inhibitor 2A/2B,*CDKN2A/CDKN2B*)缺失可作为预测药物敏感性的标志物[119]。此外,CDK4/6抑制剂在HPV阴性HNSCC患者中显示出相对较好的治疗反应,而HPV阳性患者总体获益有限;但在HPV阴性人群内部,疗效仍存在明显差异,提示需进一步阐明耐药机制并筛选精准标志物[120-121]。在PI3K通路靶向治疗研究中,PI3K抑制剂阿培利司在PDX模型中对HNSCC显示出显著的抗肿瘤活性。机制研究表明,突变型p53可通过增强骨髓细胞瘤病毒癌基因同源物(myelocytomatosis viral oncogene homolog,MYC)的稳定性及其与靶基因启动子的结合促进致癌信号传导,而抑制MYC、突变型p53或Yes

相关蛋白(Yes-associated protein,YAP)可增强阿培利司的治疗效果,提示与突变p53、MYC及YAP相关的分子特征可能作为PI3K抑制剂疗效预测的潜在生物标志物[122-123]。此外,针对mTOR通路抑制剂替西罗莫司,研究发现基线血清半胱氨酸天冬氨酸蛋白酶3(Caspase-3)高活性与较短的无进展生存期相关,提示其作为无创疗效预测标志物的临床价值[124]。

总体而言,靶向治疗已由以EGFR为核心的单一靶点干预,逐步拓展至PI3K、c-MET、VEGF、CDK4/6及mTOR等多条信号通路。以西妥昔单抗为代表的EGFR抑制剂虽已成为标准治疗方案之一,但其传统分子标志物(如*EGFR*表达或基因扩增)的疗效预测价值有限;HPV状态虽与治疗反应存在相关性,但尚不足以作为独立的治疗决策依据。相比之下,新近报道的蛋白分子特征(如Caveolin-1高表达伴SOX2低表达)在部分研究中显示出较HPV状态更稳定的预测性能。近年来,基于PDX模型及机制研究所识别的多分子特征(如CDKN2A/2B缺失、p53-MYC-YAP轴异常及基线Caspase-3活性等)为不同靶向药物的疗效预测提供了新的候选生物标志物,提示通过整合分子分型与通路特异性标志物,或可进一步优化HNSCC靶向治疗的个体化决策。

三、结论及展望

综上所述,OSCC和OPSCC免疫治疗相关生物标志物研究已取得重要进展。本文在概述HNC各治疗发展现状的基础上,系统梳理了不同生物标志物在预测OSCC和OPSCC放疗、化疗、免疫治疗及靶向治疗疗效中的作用(表1)。PD-L1表达和TMB作为最成熟的预测指标已在临床指南中获得应用,而CAF亚型、HPV状态、口腔微生物组等新兴标志物正逐步揭示TME异质性的深层机制。然而,单一标志物的预测效能仍然有限,检测标准化不足及多维度整合困难仍是制约其临床转化的关键问题。

未来研究应重点聚焦以下方向:构建基于多组学数据的整合模型,并结合机器学习算法开发复合预测评分体系,以提高疗效预测的准确性[125];加强液体活检的动态监测(如ctDNA/ctHPVDNA)及其纵向研究,实现治疗过程中疗效评估与早期耐药预警[126-127];开展大规模、多中心的前瞻性研究,以验证并优化不同患者亚群的个体化治疗策略[128];借助

表1 预测口腔和口咽鳞状细胞癌治疗效果的主要生物标志物总结

治疗方式	生物标志物	预测价值	临床应用现状	主要局限性
放疗、化疗	HPV感染状态[60]	阳性患者总生存率显著改善	独立标志物[55-59]	主要适用于OPSCC,对复发预测能力有限
	ctDNA、cvDNA[73]/ctHPVDNA[74]	动态检测,可预测疗效及复发	研究阶段	新兴技术,检测成本较高
	肿瘤微环境[76-79]	与耐药相关	研究阶段	临床验证有限
免疫治疗	PD-L1(CPS/TPS)[41,46,86]	预测ICI疗效及生存获益;CPS≥1:FDA批准用于围手术期帕博利珠单抗治疗[85]	最成熟	单独不足以识别所有获益患者
	CTLA-4[91-92]	双重检查点阻断中CPS≥1亚组获益	研究阶段	特定场景适用
	TMB[93]	在CPS不可用时作为PD-L1的补充	ASCO指南推荐	特定人群推荐应用
	CAF[76,99]	特定CAF亚型与免疫治疗敏感性或耐药相关	研究阶段	技术复杂,临床验证有限
	HPV感染状态[101-102]	预测价值仍待明确	未用于治疗决策	临床研究结果不一致
	特定口腔菌群[105]	特定菌群可能通过调节免疫微环境影响疗效	早期研究	新兴热点,需验证
靶向治疗	EGFR表达[106-107]	与西妥昔单抗疗效相关性差	不推荐使用	不可靠
	HPV感染状态[112-113]	阳性患者对西妥昔单抗联合放疗的疗效劣于顺铂联合放疗(复发率更高)	不推荐使用	不适合
	Caveolin-1高表达+SOX2低表达[114]	可预测西妥昔单抗敏感性(PDX准确率88%)	研究阶段	需临床验证
	EMMPRIN(CD147)[23,115]	预测贝伐珠单抗疗效	研究阶段	基于HNSCC的PDX模型研究,数据有限
	*CDKN2A/2B*缺失[119]	预测CDK4/6抑制剂疗效	研究阶段	数据有限
	突变型p53-MYC-YAP轴[122-123]	增强PI3K抑制剂(如BYL719)敏感性	研究阶段	数据有限
	基线Caspase-3活性[124]	预测mTOR抑制剂疗效	研究阶段	数据有限

注:HPV为人乳头瘤病毒;OPSCC为口咽鳞状细胞癌;ctDNA为循环肿瘤DNA;cvDNA为循环HPV DNA;ctHPVDNA为血浆循环肿瘤HPV DNA;PD-L1为程序性死亡-配体1;CPS为联合阳性分数;TPS为肿瘤比例分数;ICI为免疫检查点抑制剂;FDA为美国食品药品监督管理局;CTLA-4为细胞毒性T淋巴细胞相关抗原4;TMB为肿瘤突变负荷;ASCO为美国临床肿瘤学会;CAF为癌症相关成纤维细胞;EGFR为表皮生长因子受体;Caveolin-1为小窝蛋白1;SOX2为性别决定区Y框蛋白2;PDX模型为人源肿瘤移植模型;EMMPRIN为细胞外基质金属蛋白酶诱导因子,又称CD147;HNSCC为头颈部鳞状细胞癌;*CDKN2A/CDKN2B*为细胞周期蛋白依赖性激酶抑制2A/2B基因;MYC为骨髓细胞瘤病毒癌基因同源物;YAP为Yes相关蛋白;PI3K为磷脂酰肌醇3-激酶;Caspase-3为半胱氨酸天冬氨酸蛋白酶3。

单细胞分析等前沿技术深挖新型标志物,探索其与现有指标的协同互补机制[129-130]。上述方法有望提高OSCC和OPSCC患者的整体治疗获益,为HNC精准医学提供新的理论依据与实践路径。

利益冲突 所有作者均声明不存在利益冲突

参 考 文 献

[1] Sun Q, Chen X, Luo H, et al. Cancer stem cells of head and neck squamous cell carcinoma; distance towards clinical application; a systematic review of literature[J]. Am J Cancer Res, 2023,13(9):4315-4330.

[2] 滕琳,王斌,冯前进. 头颈癌放疗计划剂量分布的预测方法:基于深度学习的算法[J]. 南方医科大学学报, 2023,43(6):1010-1016. DOI:10.12307/j.issn.1673-4254.2023.06.17.

[3] Chow LQM. Head and neck cancer[J]. N Engl J Med, 2020,382(1):60-72. DOI:10.1056/NEJMra1715715.

[4] Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2021[J]. CA Cancer J Clin, 2021,71(1):7-33. DOI:10.3322/caac.21654.

[5] Guo K, Xiao W, Chen X, et al. Epidemiological trends of head and neck cancer:A population-based study[J]. Biomed Res Int, 2021:1738932. DOI:10.1155/2021/1738932.

[6] Yan K, Agrawal N, Gooi Z. Head and neck masses[J]. Med Clin North Am,2018,102(6):1013-1025. DOI:10.1016/j.mcna.2018.06.012.

[7] 杨小庆,王丽丽,王珍珍,等. 头颈癌核心基因筛选及其预后分析[J]. 现代预防医学, 2022,49(16):3056-3062. DOI:10.20043/j.cnki.MPM.202201177.

[8] Gormley M, Creaney G, Schache A, et al. Reviewing the epidemiology of head and neck cancer:Definitions, trends and risk factors[J]. Br Dent J, 2022,233(9):780-786. DOI:10.1038/s41415-022-5166-x.

[9] National Cancer Institute. Radiation therapy to treat cancer[EB/OL]. (2019-01-08)[2026-02-09]. https://www.cancer.gov/about-cancer/treatment/types/radiation-therapy.

[10] Alterio D, Marvaso G, Ferrari A, et al. Modern radiotherapy for head and neck cancer[J]. Semin Oncol, 2019,46(3):233-245. DOI:10.1053/j.seminoncol.2019.07.002.

[11] 韩福军,赵玲玲,崔久巍. 头颈部鳞状细胞癌免疫治疗的进展与展望[J]. 中华医学信息导报, 2021,36(17):16. DOI:10.3760/cma.j.issn.1000-8039.2021.17.127.

[12] García-Anaya MJ, Segado-Guillot S, Cabrera-Rodríguez J, et al. Dose and volume de-escalation of radiotherapy in head and neck cancer[J]. Crit Rev Oncol Hematol, 2023,186:103994. DOI:10.1016/j.critrevonc.2023.103994.

[13] 林丽玉,许丽春,张鑫,等. 头颈癌患者放射性口腔干燥症预防与管理的最佳证据总结[J]. 护士进修杂志, 2022,37(21):1961-1965. DOI:10.16821/j.cnki.hsjx.2022.21.009.

[14] Economopoulou P, Agelaki S, Perisanidis C, et al. The promise of immunotherapy in head and neck squamous cell carcinoma[J]. Ann Oncol, 2016, 27(9): 1675-1685. DOI: 10.1093/annonc/mdw226.

[15] Wu Y, Chen W, Xu ZP, et al. PD-L1 distribution and perspective for cancer immunotherapy-blockade, knockdown, or inhibition[J]. Front Immunol, 2019,10:2022. DOI:10.3389/fimmu.2019.02022.

[16] Hargadon KM. Tumor microenvironmental influences on dendritic cell and T cell function:A focus on clinically relevant immunologic and metabolic checkpoints[J]. Clin Transl Med, 2020,10(1):374-411. DOI:10.1002/ctm2.37.

[17] Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade[J]. N Engl J Med, 2018,378(2):158-168. DOI:10.1056/NEJMra1703481.

[18] Thompson JA, Schneider BJ, Brahmer J, et al. Management of immunotherapy-related toxicities, version 1.2022, NCCN clinical practice guidelines in oncology[J]. J Natl Compr Canc Netw, 2022,20(4):387-405. DOI:10.6004/jnccn.2022.0020.

[19] Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American society of clinical oncology clinical practice guideline[J]. J Clin Oncol, 2018,36(17):1714-1768. DOI:10.1200/jco.2017.77.6385.

[20] Barroso-Sousa R, Barry WT, Garrido-Castro AC, et al. Incidence of endocrine dysfunction following the use of different immune checkpoint inhibitor regimens: A systematic review and Meta-analysis[J]. JAMA Oncol, 2018,4(2):173-182. DOI:10.1001/jamaoncol.2017.3064.

[21] Wang H, Zhao Y, Zhang X, et al. Clinical characteristics and management of immune checkpoint inhibitor-related pneumonitis: A single-institution retrospective study[J]. Cancer Med, 2021,10(1):188-198. DOI:10.1002/cam4.3600.

[22] Vitale G, Lamberti G, Comito F, et al. Anti-programmed cell death-1 and anti-programmed cell death ligand-1 immune-related liver diseases:From clinical pivotal studies to real-life experience[J]. Expert Opin Biol Ther, 2020,20(9):1047-1059. DOI:10.1080/14712598.2020.1762562.

[23] Li Q, Tie Y, Alu A, et al. Targeted therapy for head and neck cancer: Signaling pathways and clinical studies[J]. Signal Transduct Target Ther, 2023,8(1):31. DOI:10.1038/s41392-022-01297-0.

[24] Nakano K. Progress of molecular targeted therapy for head and neck cancer in clinical aspects[J]. Mol Biomed, 2021,2(1):15. DOI:10.1186/s43556-021-00032-5.

[25] Hwang W, Ahn JS, Jung HA, et al. Emerging EGFR-targeted therapy in head and neck cancer: A review[J]. JAMA Oncol, 2025,11(11):1373-1384. DOI:10.1001/jamaoncol.2025.3136.

[26] Solomon B, Young RJ, Rischin D. Head and neck squamous cell carcinoma: Genomics and emerging biomarkers for immunomodulatory cancer treatments[J]. Semin Cancer Biol, 2018, 52(Pt 2): 228-240. DOI: 10.1016/j.semcancer.2018.01.008.

[27] Marquard FE, Jücker M. PI3K/AKT/mTOR signaling as a

molecular target in head and neck cancer [J]. Biochem Pharmacol, 2020, 172: 113729. DOI: 10.1016/j. bcp. 2019. 113729.

[28] Lee MJ, Jin N, Grandis JR, et al. Alterations and molecular targeting of the GSK-3 regulator, PI3K, in head and neck cancer [J]. Biochim Biophys Acta Mol Cell Res, 2020, 1867(6): 118679. DOI:10.1016/j.bbamcr.2020.118679.

[29] Wang Z, Valera JC, Zhao X, et al. mTOR co-targeting strategies for head and neck cancer therapy[J]. Cancer Metastasis Rev, 2017,36(3):491-502. DOI:10.1007/s10555-017-9688-7.

[30] Desilets A, Pfister DG, Stein S, et al. A phase 1 study of concurrent cabozantinib and cetuximab in recurrent or metastatic head and neck squamous cell cancer[J]. Oral Oncol, 2024,154: 106861. DOI:10.1016/j.oraloncology.2024.106861.

[31] Bauman JE, Saba NF, Roe D, et al. Randomized phase Ⅱ trial of ficlatuzumab with or without cetuximab in pan-refractory, recurrent/metastatic head and neck cancer[J]. J Clin Oncol, 2023,41(22):3851-3862. DOI:10.1200/jco.22.01994.

[32] Bauman JE, Ohr J, Gooding WE, et al. Phase Ⅰ study of ficlatuzumab and cetuximab in cetuximab-resistant, recurrent/metastatic head and neck cancer[J]. Cancers (Basel), 2020,12(6):1537. DOI:10.3390/cancers12061537.

[33] Saddawi-Konefka R, Schokrpur S, Lui AJ, et al. HER2 and HER3 as therapeutic targets in head and neck cancer[J]. Cancer J, 2022,28(5):339-345. DOI:10.1097/ppo.0000000000000622.

[34] Gandullo-Sánchez L, Ocaña A, Pandiella A. HER3 in cancer: From the bench to the bedside[J]. J Exp Clin Cancer Res, 2022, 41(1):310. DOI:10.1186/s13046-022-02515-x.

[35] Liu Y, Zhang N, Wen Y, et al. Head and neck cancer: Pathogenesis and targeted therapy [J]. MedComm (2020), 2024,5(9):e702. DOI:10.1002/mco2.702.

[36] Wang D, Lu Y, Nannapaneni S, et al. Combinatorial approaches targeting the EGFR family and c-Met in SCCHN[J]. Oral Oncol, 2021,112:105074. DOI:10.1016/j.oraloncology.2020.105074.

[37] Chai AWY, Yee PS, Cheong SC. Rational combinations of targeted therapy and immune checkpoint inhibitors in head and neck cancers[J]. Front Oncol, 2022,12:837835. DOI:10.3389/fonc.2022.837835.

[38] Brown JS, Sundar R, Lopez J. Combining DNA damaging therapeutics with immunotherapy: More haste, less speed[J]. Br J Cancer, 2018,118(3):312-324. DOI:10.1038/bjc.2017.376.

[39] 丁瑞,张弓. 头颈部癌放疗联合免疫治疗研究进展[J]. 肿瘤研究与临床, 2021,33(10):721-724. DOI:10.3760/cma.j.cn115355-20210326-00143.

[40] Chabanon RM, Rouanne M, Lord CJ, et al. Targeting the DNA damage response in immuno-oncology: Developments and opportunities[J]. Nat Rev Cancer, 2021, 21(11): 701-717. DOI:10.1038/s41568-021-00386-6.

[41] Burtness B, Rischin D, Greil R, et al. Pembrolizumab alone or with chemotherapy for recurrent/metastatic head and neck squamous cell carcinoma in KEYNOTE-048: Subgroup analysis by programmed death ligand-1 combined positive score[J]. J Clin Oncol, 2022, 40(21): 2321-2332. DOI: 10.1200/jco.21.02198.

[42] Machiels JP, Tao Y, Licitra L, et al. Pembrolizumab plus concurrent chemoradiotherapy versus placebo plus concurrent chemoradiotherapy in patients with locally advanced squamous cell carcinoma of the head and neck (KEYNOTE-412): A randomised, double-blind, phase 3 trial[J]. Lancet Oncol, 2024,25(5):572-587. DOI:10.1016/s1470-2045(24)00100-1.

[43] Liu X, Harbison RA, Varvares MA, et al. Immunotherapeutic strategies in head and neck cancer: Challenges and opportunities [J]. J Clin Invest, 2025, 135(8): e188128. DOI: 10.1172/jci188128.

[44] Chung CH, Bonomi M, Steuer CE, et al. Concurrent cetuximab and nivolumab as a second-line or beyond treatment of patients with recurrent and/or metastatic head and neck squamous cell carcinoma: Results of phase Ⅰ/Ⅱ study[J]. Cancers (Basel), 2021,13(5):1180. DOI:10.3390/cancers13051180.

[45] Sacco AG, Chen R, Worden FP, et al. Pembrolizumab plus cetuximab in patients with recurrent or metastatic head and neck squamous cell carcinoma: An open-label, multi-arm, non-randomised, multicentre, phase 2 trial[J]. Lancet Oncol, 2021, 22(6):883-892. DOI:10.1016/s1470-2045(21)00136-4.

[46] Uppaluri R, Haddad RI, Tao Y, et al. Neoadjuvant and adjuvant pembrolizumab in locally advanced head and neck cancer[J]. N Engl J Med, 2025,393(1):37-50. DOI:10.1056/NEJMoa2415434.

[47] Bourhis J, Aupérin A, Borel C, et al. Nivolumab added to cisplatin and radiotherapy versus cisplatin and radiotherapy alone after surgery for people with squamous cell carcinoma of the head and neck at a high risk of relapse (GORTEC 2018-01 NIVOPOST-OP): A randomised, open-label, phase 3 trial[J]. Lancet, 2026,407(10526):363-374. DOI:10.1016/s0140-6736(25)01850-1.

[48] Lim YX, D'Silva NJ. HPV-associated oropharyngeal cancer: In search of surrogate biomarkers for early lesions[J]. Oncogene, 2024,43(8):543-554. DOI:10.1038/s41388-023-02927-9.

[49] D'Souza G, Clemens G, Strickler HD, et al. Long-term persistence of oral HPV over 7 years of follow-up[J]. JNCI Cancer Spectr, 2020, 4(5): pkaa047. DOI: 10.1093/jncics/pkaa047.

[50] Alsahafi E, Begg K, Amelio I, et al. Clinical update on head and neck cancer: Molecular biology and ongoing challenges[J]. Cell Death Dis, 2019,10(8):540. DOI:10.1038/s41419-019-1769-9.

[51] Scarth JA, Patterson MR, Morgan EL, et al. The human papillomavirus oncoproteins: A review of the host pathways targeted on the road to transformation[J]. J Gen Virol, 2021,102(3):001540. DOI:10.1099/jgv.0.001540.

[52] Taberna M, Mena M, Pavón MA, et al. Human papillomavirus-related oropharyngeal cancer[J]. Ann Oncol, 2017, 28(10):

2386-2398. DOI:10.1093/annonc/mdx304.

[53] Lo Cigno I, Calati F, Girone C, et al. High-risk HPV oncoproteins E6 and E7 and their interplay with the innate immune response: Uncovering mechanisms of immune evasion and therapeutic prospects [J]. J Med Virol, 2024, 96(6): e29685. DOI:10.1002/jmv.29685.

[54] Chung RS, Wong S, Lin D, et al. Mechanisms of crosstalk between the oropharyngeal microbiome and human papillomavirus in oropharyngeal carcinogenesis: A mini review [J]. Front Oncol, 2024, 14: 1425545. DOI: 10.3389/fonc.2024.1425545.

[55] Lechner M, Liu J, Masterson L, et al. HPV-associated oropharyngeal cancer: Epidemiology, molecular biology and clinical management[J]. Nat Rev Clin Oncol, 2022, 19(5): 306-327. DOI:10.1038/s41571-022-00603-7.

[56] Eriksen JG, Lassen P. Human papilloma virus as a biomarker for personalized head and neck cancer radiotherapy [J]. Recent Results Cancer Res, 2016, 198: 143-161. DOI: 10.1007/978-3-662-49651-0_7.

[57] Festa BM, Schaefer N, Reschly W, et al. P16/HPV-negative oropharyngeal squamous cell carcinoma survival: Comparing primary surgery to primary chemoradiotherapy. A systematic review and Meta-analysis[J]. Eur J Surg Oncol, 2025, 51(7): 109739. DOI:10.1016/j.ejso.2025.109739.

[58] Dong H, Shu X, Xu Q, et al. Current status of human papillomavirus-related head and neck cancer: From viral genome to patient care[J]. Virol Sin, 2021, 36(6): 1284-1302. DOI: 10.1007/s12250-021-00413-8.

[59] Ramesh PS, Devegowda D, Singh A, et al. NRF2, p53, and p16: Predictive biomarkers to stratify human papillomavirus associated head and neck cancer patients for de-escalation of cancer therapy[J]. Crit Rev Oncol Hematol, 2020, 148: 102885. DOI:10.1016/j.critrevonc.2020.102885.

[60] Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer[J]. N Engl J Med, 2010, 363(1): 24-35. DOI: 10.1056/NEJMoa0912217.

[61] Rieckmann T, Tribius S, Grob TJ, et al. HNSCC cell lines positive for HPV and p16 possess higher cellular radiosensitivity due to an impaired DSB repair capacity [J]. Radiother Oncol, 2013, 107(2): 242-246. DOI: 10.1016/j.radonc.2013.03.013.

[62] Fonsêca TC, Jural LA, Marañón-Vásquez GA, et al. Global prevalence of human papillomavirus-related oral and oropharyngeal squamous cell carcinomas: A systematic review and Meta-analysis[J]. Clin Oral Investig, 2023, 28(1): 62. DOI: 10.1007/s00784-023-05425-0.

[63] Lin Y, Li Z, Zhang K, et al. Correlation and prognosis analysis of human papillomavirus infection and P16 expression in oral and oropharyngeal squamous cell carcinomas [J]. Sci Rep, 2025, 15(1): 11270. DOI: 10.1038/s41598-025-95643-1.

[64] Ferris RL, Westra W. Oropharyngeal carcinoma with a special focus on hpv-related squamous cell carcinoma [J]. Annu Rev Pathol, 2023, 18: 515-535. DOI: 10.1146/annurev-pathmechdis-031521-041424.

[65] Shinomiya H, Nibu KI. Etiology, diagnosis, treatment, and prevention of human papilloma virus-associated oropharyngeal squamous cell carcinoma[J]. Int J Clin Oncol, 2023, 28(8): 975-981. DOI: 10.1007/s10147-023-02336-8.

[66] Mirghani H, Lang Kuhs KA, Waterboer T. Biomarkers for early identification of recurrences in HPV-driven oropharyngeal cancer [J]. Oral Oncol, 2018, 82: 108-114. DOI: 10.1016/j.oraloncology.2018.05.015.

[67] García-Chávez JN, Contreras-Paredes A, González-Espinosa C, et al. Association of gene expression profiles in HPV-positive head and neck squamous cell carcinoma with patient outcome: In search of prognostic biomarkers [J]. Int J Mol Sci, 2025, 26(12): 5894. DOI: 10.3390/ijms26125894.

[68] Flach S, Maniam P, Hey SY, et al. The molecular characteristics of recurrent/metastatic HPV-positive head and neck squamous cell carcinoma: A systematic review of the literature [J]. Clin Otolaryngol, 2024, 49(4): 384-403. DOI: 10.1111/coa.14161.

[69] Ribeiro IP, de Melo JB, Carreira IM. Head and neck cancer: Searching for genomic and epigenetic biomarkers in body fluids: The state of art[J]. Mol Cytogenet, 2019, 12: 33. DOI: 10.1186/s13039-019-0447-z.

[70] Economopoulou P, Kotsantis I, Kyrodimos E, et al. Liquid biopsy: An emerging prognostic and predictive tool in Head and Neck Squamous Cell Carcinoma (HNSCC). Focus on circulating tumor cells (CTCs)[J]. Oral Oncol, 2017, 74: 83-89. DOI: 10.1016/j.oraloncology.2017.09.012.

[71] Mishra V, Singh A, Chen X, et al. Application of liquid biopsy as multi-functional biomarkers in head and neck cancer[J]. Br J Cancer, 2022, 126(3): 361-370. DOI: 10.1038/s41416-021-01626-0.

[72] Ghiyasimoghaddam N, Shayan N, Mirkatuli HA, et al. Does circulating tumor DNA apply as a reliable biomarker for the diagnosis and prognosis of head and neck squamous cell carcinoma?[J]. Discov Oncol, 2024, 15(1): 427. DOI: 10.1007/s12672-024-01308-2.

[73] Hilke FJ, Muyas F, Admard J, et al. Dynamics of cell-free tumour DNA correlate with treatment response of head and neck cancer patients receiving radiochemotherapy [J]. Radiother Oncol, 2020, 151: 182-189. DOI: 10.1016/j.radonc.2020.07.027.

[74] Chera BS, Kumar S, Shen C, et al. Plasma circulating tumor HPV DNA for the surveillance of cancer recurrence in HPV-associated oropharyngeal cancer [J]. J Clin Oncol, 2020, 38(10): 1050-1058. DOI: 10.1200/jco.19.02444.

[75] Denaro N, Solinas C, Garrone O, et al. The role of cytokinome in the HNSCC tumor microenvironment: A narrative review and our experience[J]. Diagnostics (Basel), 2022, 12(11): 2880. DOI: 10.3390/diagnostics12112880.

[76] Okuyama K, Tsuchiya M, Debnath KC, et al. Desmoplastic reaction in the microenvironment of head and neck and other

solid tumors: The therapeutic barrier[J]. Ther Adv Med Oncol, 2025, 17: 17588359251317144. DOI: 10.1177/17588359251317144.

[77] Fornieles G, Núñez MI, Expósito J. Matrix metalloproteinases and their inhibitors as potential prognostic biomarkers in head and neck cancer after radiotherapy[J]. Int J Mol Sci, 2023, 25(1): 527. DOI: 10.3390/ijms25010527.

[78] Vahabi M, Blandino G, di Agostino S. MicroRNAs in head and neck squamous cell carcinoma: A possible challenge as biomarkers, determinants for the choice of therapy and targets for personalized molecular therapies[J]. Transl Cancer Res, 2021, 10(6): 3090-3110. DOI: 10.21037/tcr-20-2530.

[79] Golestannejad P, Monkaresi M, Zhian Zargaran F, et al. Role of cancer associated fibroblast (CAF) derived miRNAs on head and neck malignancies microenvironment: A systematic review[J]. BMC Cancer, 2025, 25(1): 582. DOI: 10.1186/s12885-025-13965-9.

[80] Elbehi AM, Anu RI, Ekine-Afolabi B, et al. Emerging role of immune checkpoint inhibitors and predictive biomarkers in head and neck cancers[J]. Oral Oncol, 2020, 109: 104977. DOI: 10.1016/j.oraloncology.2020.104977.

[81] Wang HC, Yeh TJ, Chan LP, et al. Exploration of feasible immune biomarkers for immune checkpoint inhibitors in head and neck squamous cell carcinoma treatment in real world clinical practice[J]. Int J Mol Sci, 2020, 21(20): 7621. DOI: 10.3390/ijms21207621.

[82] Wang Q, Zhang W, Guo Y, et al. A mutational signature and significantly mutated driver genes associated with immune checkpoint inhibitor response across multiple cancers[J]. Int Immunopharmacol, 2023, 116: 109821. DOI: 10.1016/j.intimp.2023.109821.

[83] Emancipator K, Huang L, Aurora-Garg D, et al. Comparing programmed death ligand 1 scores for predicting pembrolizumab efficacy in head and neck cancer[J]. Mod Pathol, 2021, 34(3): 532-541. DOI: 10.1038/s41379-020-00710-9.

[84] Tsujikawa T, Ohno K, Morita KI, et al. Clinical, genomic and immune microenvironmental determinants of nivolumab response in head and neck squamous cell carcinoma[J]. Front Immunol, 2024, 15: 1390873. DOI: 10.3389/fimmu.2024.1390873.

[85] Imamura Y, Kanno M, Fujieda S. Comparative review of KEYNOTE-689 and NIVOPOSTOP trials and their impact on perioperative immunotherapy in locally advanced head and neck cancer[J]. Cancer Treat Rev, 2025, 140: 103018. DOI: 10.1016/j.ctrv.2025.103018.

[86] Le X, Ferrarotto R, Wise-Draper T, et al. Evolving role of immunotherapy in recurrent metastatic head and neck cancer[J]. J Natl Compr Canc Netw, 2020, 18(7): 899-906. DOI: 10.6004/jnccn.2020.7590.

[87] de Ruiter EJ, Mulder FJ, Koomen BM, et al. Comparison of three PD-L1 immunohistochemical assays in head and neck squamous cell carcinoma (HNSCC)[J]. Mod Pathol, 2021, 34(6): 1125-1132. DOI: 10.1038/s41379-020-0644-7.

[88] Cerbelli B, Girolami I, Eccher A, et al. Evaluating programmed death-ligand 1 (PD-L1) in head and neck squamous cell carcinoma: Concordance between the 22C3 PharmDx assay and the SP263 assay on whole sections from a multicentre study[J]. Histopathology, 2022, 80(2): 397-406. DOI: 10.1111/his.14562.

[89] Zhou KI, Peterson B, Serritella A, et al. Spatial and temporal heterogeneity of PD-L1 expression and tumor mutational burden in gastroesophageal adenocarcinoma at baseline diagnosis and after chemotherapy[J]. Clin Cancer Res, 2020, 26(24): 6453-6463. DOI: 10.1158/1078-0432.Ccr-20-2085.

[90] Wang CW, Biswas PK, Islam A, et al. The use of immune regulation in treating head and neck squamous cell carcinoma (HNSCC)[J]. Cells, 2024, 13(5): 413. DOI: 10.3390/cells13050413.

[91] Miniuk M, Reszeć-Giełażyn J, Bortnik P, et al. Novel predictive biomarkers in the head and neck squamous cell carcinoma (HNSCC)[J]. J Clin Med, 2024, 13(19): 5876. DOI: 10.3390/jcm13195876.

[92] Aboaid H, Khalid T, Hussain A, et al. Advances and challenges in immunotherapy in head and neck cancer[J]. Front Immunol, 2025, 16: 1596583. DOI: 10.3389/fimmu.2025.1596583.

[93] Addeo A, Friedlaender A, Banna GL, et al. TMB or not TMB as a biomarker: That is the question[J]. Crit Rev Oncol Hematol, 2021, 163: 103374. DOI: 10.1016/j.critrevonc.2021.103374.

[94] Rodrigo JP, Sánchez-Canteli M, Otero-Rosales M, et al. Tumor mutational burden predictability in head and neck squamous cell carcinoma patients treated with immunotherapy: Systematic review and Meta-analysis[J]. J Transl Med, 2024, 22(1): 135. DOI: 10.1186/s12967-024-04937-x.

[95] Zhou C, Chen S, Xu F, et al. Estimating tumor mutational burden across multiple cancer types using whole-exome sequencing[J]. Ann Transl Med, 2021, 9(18): 1437. DOI: 10.21037/atm-21-4227.

[96] Mo SF, Cai ZZ, Kuai WH, et al. Universal cutoff for tumor mutational burden in predicting the efficacy of anti-PD-(L)1 therapy for advanced cancers[J]. Front Cell Dev Biol, 2023, 11: 1209243. DOI: 10.3389/fcell.2023.1209243.

[97] Fang H, Bertl J, Zhu X, et al. Tumour mutational burden is overestimated by target cancer gene panels[J]. J Natl Cancer Cent, 2023, 3(1): 56-64. DOI: 10.1016/j.jncc.2022.10.004.

[98] McGrail DJ, Pilié PG, Rashid NU, et al. High tumor mutation burden fails to predict immune checkpoint blockade response across all cancer types[J]. Ann Oncol, 2021, 32(5): 661-672. DOI: 10.1016/j.annonc.2021.02.006.

[99] Magan M, Wiechec E, Roberg K. CAFs affect the proliferation and treatment response of head and neck cancer spheroids during co-culturing in a unique *in vitro* model[J]. Cancer Cell Int, 2020, 20(1): 599. DOI: 10.1186/s12935-020-01718-6.

[100] Chen S, Yang Y, He S, et al. Review of biomarkers for response to immunotherapy in HNSCC microenvironment[J]. Front Oncol,

2023,13:1037884. DOI:10.3389/fonc.2023.1037884.

[101] Xu Y, Zhu G, Maroun CA, et al. Programmed death-1/programmed death-ligand 1-axis blockage in recurrent or metastatic head and neck squamous cell carcinoma stratified by human papillomavirus status: A systematic review and Meta-analysis[J]. Front Immunol, 2021, 12: 645170. DOI: 10.3389/fimmu.2021.645170.

[102] Pfister DG, Haddad RI, Worden FP, et al. Biomarkers predictive of response to pembrolizumab in head and neck cancer[J]. Cancer Med, 2023, 12(6): 6603-6614. DOI: 10.1002/cam4.5434.

[103] Pratap Singh R, Kumari N, Gupta S, et al. Intratumoral microbiota changes with tumor stage and influences the immune signature of oral squamous cell carcinoma[J]. Microbiol Spectr, 2023,11(4):e0459622. DOI:10.1128/spectrum.04596-22.

[104] Burcher KM, Burcher JT, Inscore L, et al. A review of the role of oral microbiome in the development, detection, and management of head and neck squamous cell cancers[J]. Cancers (Basel), 2022, 14(17): 4116. DOI: 10.3390/cancers14174116.

[105] Wei K, Ma Y, Xu J, et al. Oral and intratumoral microbiota influence tumor immunity and patient survival[J]. Front Immunol, 2025, 16: 1572152. DOI: 10.3389/fimmu.2025.1572152.

[106] Licitra L, Mesia R, Rivera F, et al. Evaluation of EGFR gene copy number as a predictive biomarker for the efficacy of cetuximab in combination with chemotherapy in the first-line treatment of recurrent and/or metastatic squamous cell carcinoma of the head and neck: EXTREME study[J]. Ann Oncol, 2011,22(5):1078-1087. DOI:10.1093/annonc/mdq588.

[107] Sepulveda AR, Hamilton SR, Allegra CJ, et al. Molecular biomarkers for the evaluation of colorectal cancer: Guideline from the American society for clinical pathology, college of American pathologists, association for molecular pathology, and the American society of clinical oncology[J]. J Clin Oncol, 2017,35(13):1453-1486. DOI:10.1200/jco.2016.71.9807.

[108] Fornasier G, Francescon S, Baldo P. An update of efficacy and safety of cetuximab in metastatic colorectal cancer: A narrative review[J]. Adv Ther, 2018,35(10):1497-1509. DOI:10.1007/s12325-018-0791-0.

[109] Wang C, Fakih M. Targeting KRAS in colorectal cancer[J]. Curr Oncol Rep, 2021,23(3):28. DOI: 10.1007/s11912-021-01022-0.

[110] Weidhaas JB, Harris J, Schaue D, et al. The KRAS-variant and cetuximab response in head and neck squamous cell cancer: A secondary analysis of a randomized clinical trial[J]. JAMA Oncol, 2017, 3(4): 483-491. DOI: 10.1001/jamaoncol.2016.5478.

[111] Bastit V, Bon-Mardion N, Picquenot JM, et al. Benefit of cetuximab addition to a platinum-fluorouracil-based chemotherapy according to KRAS-LCS6 variant in an unselected population of recurrent and/or metastatic head and neck cancers[J]. Eur Arch Otorhinolaryngol, 2019,276(2):541-550. DOI:10.1007/s00405-018-5235-6.

[112] Mehanna H, Robinson M, Hartley A, et al. Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): An open-label randomised controlled phase 3 trial[J]. Lancet, 2019, 393(10166):51-60. DOI:10.1016/s0140-6736(18)32752-1.

[113] Gillison ML, Trotti AM, Harris J, et al. Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): A randomised, multicentre, non-inferiority trial[J]. Lancet, 2019, 393(10166):40-50. DOI:10.1016/s0140-6736(18)32779-x.

[114] Bouhaddou M, Lee RH, Li H, et al. Caveolin-1 and Sox-2 are predictive biomarkers of cetuximab response in head and neck cancer[J]. JCI Insight, 2021,6(20):e151982. DOI:10.1172/jci.insight.151982.

[115] Newman JR, Helman EE, Safavy S, et al. EMMPRIN expression is required for response to bevacizumab therapy in HNSCC xenografts[J]. Cancer Lett, 2009, 274(2): 313-318. DOI:10.1016/j.canlet.2008.09.033.

[116] Adkins D, Ley J, Cohen J, et al. The potential for selective cyclin-dependent kinase 4/6 inhibition in the therapy for head and neck squamous cell carcinoma[J]. Cancer J, 2022,28(5):377-380. DOI:10.1097/ppo.0000000000000617.

[117] Burtness B. Integrating targeted therapies in the management of head and neck cancers[J]. Cancer J, 2022, 28(5): 329-330. DOI:10.1097/ppo.0000000000000624.

[118] van Caloen G, Schmitz S, van Marcke C, et al. Preclinical evaluation of the association of the cyclin-dependent kinase 4/6 inhibitor, ribociclib, and cetuximab in squamous cell carcinoma of the head and neck[J]. Cancers (Basel), 2021,13(6):1251. DOI:10.3390/cancers13061251.

[119] Su D, Zhang D, Jin J, et al. Identification of predictors of drug sensitivity using patient-derived models of esophageal squamous cell carcinoma[J]. Nat Commun, 2019, 10(1): 5076. DOI:10.1038/s41467-019-12846-7.

[120] Billard-Sandu C, Tao YG, Sablin MP, et al. CDK4/6 inhibitors in P16/HPV16-negative squamous cell carcinoma of the head and neck[J]. Eur Arch Otorhinolaryngol, 2020,277(5):1273-1280. DOI:10.1007/s00405-020-05891-2.

[121] Verhees F, Demers I, Legemaate D, et al. Exploring the antiproliferative effect of PI3K/Akt/mTOR pathway and CDK4/6 inhibitors in human papillomaviruspositive and negative head and neck squamous cell carcinoma cell lines[J]. Int J Oncol, 2025,66(2):e5719. DOI:10.3892/ijo.2025.5719.

[122] Ganci F, Pulito C, Valsoni S, et al. PI3K inhibitors curtail MYC-dependent mutant p53 gain-of-function in head and neck squamous cell carcinoma[J]. Clin Cancer Res, 2020,26(12):2956-2971. DOI:10.1158/1078-0432.Ccr-19-2485.

[123] Meister KS, Godse NR, Khan NI, et al. HER3 targeting

potentiates growth suppressive effects of the PI3K inhibitor BYL719 in pre-clinical models of head and neck squamous cell carcinoma[J]. Sci Rep, 2019,9(1):9130. DOI:10.1038/s41598-019-45589-y.

[124] John K, Rösner I, Keilholz U, et al. Baseline caspase activity predicts progression free survival of temsirolimus-treated head neck cancer patients[J]. Eur J Cancer, 2015, 51(12): 1596-1602. DOI:10.1016/j.ejca.2015.05.021.

[125] Yin J, Xu L, Wang S, et al. Integrating immune multi-omics and machine learning to improve prognosis, immune landscape, and sensitivity to first- and second-line treatments for head and neck squamous cell carcinoma[J]. Sci Rep, 2024, 14(1): 31454. DOI:10.1038/s41598-024-83184-y.

[126] Ruiz-Torres DA, Merkin RD, Bryan ME, et al. Personalized circulating tumor DNA dynamics inform survival and response to immune checkpoint blockade in recurrent/metastatic head and neck cancer[J]. NPJ Precis Oncol, 2025, 9(1): 298. DOI: 10.1038/s41698-025-01084-4.

[127] Nassar SI, Suk A, Nguyen SA, et al. The role of ctDNA and liquid biopsy in the diagnosis and monitoring of head and neck cancer: Towards precision medicine[J]. Cancers (Basel), 2024, 16(18): 3129. DOI:10.3390/cancers16183129.

[128] Saini KS, Somara S, Ko HC, et al. Biomarkers in head and neck squamous cell carcinoma: Unraveling the path to precision immunotherapy[J]. Front Oncol, 2024, 14: 1473706. DOI: 10.3389/fonc.2024.1473706.

[129] Wu K, Chen X, Wu Q, et al. Single-cell transcriptomics identifies novel prognostic signatures in HNSCC Immunotherapy response[J]. Cancer Sci, 2025, 116(11): 2959-2971. DOI: 10.1111/cas.70171.

[130] Xie H, Liao S, Liang L, et al. Single-cell analysis of tumor microenvironment immune homeostasis and identification of prognostic biomarkers in head and neck squamous cell carcinoma[J]. Transl Cancer Res, 2025, 14(10): 7089-7101. DOI: 10.21037/tcr-2025-999.

(收稿日期:2026-02-09)

(本文编辑:王嫚)