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放疗联合PD-1/PD-L1抑制剂治疗的协同机制及临床研究进展

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摘　要

放疗与以免疫检查点抑制剂(如PD-1/PD-L1抑制剂)为主的免疫治疗，是实体瘤治疗的关键手段。本文聚焦放疗的免疫调节效应与二者联合应用，阐述放疗对正向免疫调节的作用机制、放疗与PD-1/PD-L1抑制剂联合时对肿瘤免疫微环境影响，远隔效应的发生等。相关临床试验显示，该联合治疗在非小细胞肺癌、肝细胞癌等多种实体瘤中展现出良好效果，但不同癌种获益有别。目前，联合治疗的最佳剂量、分割方案及时间安排策略尚存争议，需依据肿瘤类型和治疗目标进行个体化调整。本文系统梳理现有研究，为放疗与PD-1/PD-L1抑制剂联合治疗的临床实践提供全面科学依据与实用参考。

关键词

放疗，免疫治疗，免疫检查点抑制剂，PD-1/PD-L1抑制剂

Mechanisms and Clinical Research Advances in Radiotherapy Combined with PD-1/PD-L1 Inhibitor Therapy

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Abstract

Radiotherapy and immunotherapy mainly based on immune checkpoint inhibitors (such as PD-1/PD-L1 inhibitors) are key approaches for the treatment of solid tumors. This article focuses on

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the immunomodulatory effects of radiotherapy and their combined application. It elaborates on the mechanisms of radiotherapy's positive immunomodulation, the impact of the combination of radiotherapy and PD-1/PD-L1 inhibitors on the tumor immune microenvironment, and the occurrence of the abscopal effect. Relevant clinical trials have demonstrated that this combined treatment has shown good efficacy in various solid tumors such as non-small cell lung cancer and hepatocellular carcinoma, yet the benefits vary among different cancer types. Currently, there are still controversies regarding the optimal dose, fractionation scheme, and timing strategy of the combined treatment, which need to be adjusted individually according to the tumor type and treatment goals. This article systematically reviews the existing research, providing a comprehensive scientific basis and practical reference for the clinical practice of the combined treatment of radiotherapy and PD-1/PD-L1 inhibitors.

Keywords

Radiotherapy, Immunotherapy, Immune Checkpoint Inhibitors, PD-1/PD-L1 Inhibitiors

1. 引言

放射治疗(以下简称放疗)是治疗恶性肿瘤重要的局部治疗方式之一，可作为手术的替代方法或与手术及药物治疗联合使用。20 世纪 60 年代以来，随着直线加速器发展实现了关键性飞跃，放疗技术的发展，包括调强放疗、立体定向放疗(Stereotactic Body Radiotherapy, SBRT)、图像引导调强放疗技术以及质子放疗开创了实体瘤精确放疗的时代[1]-[4]。传统观念认为，放疗利用高能射线的电离作用，直接或间接地对肿瘤细胞的脱氧核糖核酸(Deoxyribonucleic Acid, DNA)双链造成不可修复的损伤[5]，并最终通过有丝分裂灾难、细胞衰老、凋亡和自噬从而引起细胞死亡，达到治疗肿瘤的目的。近些年，越来越多突破性的研究表明，放疗能够调节局部甚至全身肿瘤特异的免疫反应[6]-[8]。发挥抗肿瘤免疫反应的主要分子机制包括免疫原性细胞死亡(Immunogenic Cell Death, ICD)，ICD 释放出损伤相关分子模式(Damage-Associated Molecular Patterns, DAMP)，增强了肿瘤细胞的免疫原性，从而刺激肿瘤肿瘤特异性 T 淋巴细胞亚群的克隆扩增[9] [10]。

免疫治疗，特别是免疫检查点抑制剂(Immune Checkpoint Inhibitors, ICIs)，包括程序性细胞死亡蛋白 1 (Programmed-death Protein 1, PD-1)、程序性细胞死亡配体 1 (Programmed-death protein 1 Ligand 1, PD-L1)和细胞毒性 T 淋巴细胞相关蛋白 4 (Cytotoxic T-Lymphocyte-Associated protein 4, CTLA-4)抑制剂，它们重新激活功能耗竭的细胞毒性 T 细胞，恢复其对肿瘤细胞的杀伤作用[11] [12]。PD-1 是一种表达于 T 细胞表面的分子，与程序性细胞死亡机制相关，当其与配体 PD-L1 结合后，能够通过抑制淋巴细胞的增殖及细胞因子的释放，从而增强免疫耐受性。肿瘤细胞能够通过异常表达 PD-L1 实现免疫逃避[13] [14]。临床上用于抗肿瘤治疗的 CTLA-4 抑制剂有伊匹木单抗(Ipilimumab)，PD-1 抑制剂有纳武利尤单抗(Nivolumab)、帕博利珠单抗(Pembrolizumab)，PD-L1 抑制剂有阿特珠单抗(Atezolizumab)、阿维鲁单抗(Avelumab)、度伐利尤单抗(Durvalumab)等[15]。在黑色素瘤[16]、非小细胞肺癌[17]和头颈部鳞状细胞癌[18] [19]治疗中有着广泛的应用，一定程度上改变了患者的预后。与其他肿瘤治疗方式与化疗、放疗等的联合方案，同样获得了极大的关注[20] [21]。但随着 ICIs 药物临床试验的广泛开展和不断深入，尽管 ICIs 在部分肿瘤患者中取得了显著的治疗效果，但能够对其产生有效治疗应答的患者比例仍然有限[22] [23]。

因此，放疗和免疫检查点抑制剂为主的免疫治疗作为实体瘤治疗的两大重要手段，尤其在不可手术切除的实体瘤患者的治疗中发挥着至关重要的作用。应用放疗联合免疫治疗的综合治疗这一概念于2005年首次提出[24]，不同的免疫治疗策略与放疗结合可以增强抗肿瘤效果。经此概念提出后，越来越多的报道证实了“远隔效应”，即对肿瘤局部进行放疗后，不仅照射区域肿瘤得到控制，照射野外转移病灶也出现消退的临床观察[25]-[27]。

本文系统回顾了放疗对免疫调节效应的潜在机制，重点探讨了放疗激活干扰素基因刺激蛋白信号通路、诱导免疫原性细胞死亡以及上调 MHC-I 类分子表达的作用。在此基础上，深入分析了放疗与 PD-1/PD-L1 抑制剂的协同作用，包括其协同机制、临床试验进展及联合治疗的时间点优化策略。通过对现有研究的全面梳理，本文旨在为放疗与 PD-1/PD-L1 抑制剂联合治疗的临床应用提供科学依据和实践参考。

2. 放疗对免疫调节效应的潜在机制

放疗与免疫系统之间的相互作用具有复杂性和多因素性，可能通过多种机制产生双向免疫调节效应(包括正向激活与负向抑制)，不同放射类型对免疫细胞诱导效应也不同[28]。本综述将聚焦于放疗的主要的正向免疫激活效应，对其机制及临床意义进行深入探讨。

2.1. 放疗激活干扰素基因刺激蛋白信号通路

环磷酸鸟苷–腺苷合酶(cyclic GMP-AMP synthase, cGAS) [29]是一种核苷酸转移酶，由暴露于胞质中的双链 DNA (dsDNA)激活，合成的第二信使环二核苷酸 2',3'-cGAMP1,2 (cGAMP) [30]。cGAMP 与干扰素基因刺激蛋白(Stimulator of Interferon Genes, STING)特异性结合后，诱导 STING 发生构象变化，并且转移至内质网–高尔基体中间体[31]。通过招募 TANK 结合激酶 1 (TBK1)和干扰素调节因子 3 (IRF3)，激活下游信号通路。TBK1 磷酸化 IRF3，促使 IRF3 二聚化并转位至细胞核，启动 I 型干扰素(IFN-α/β)及多种促炎细胞因子的转录与表达[31]。这一过程不仅增强了抗肿瘤免疫反应，还可能通过激活树突状细胞(DCs)和细胞毒性 T 淋巴细胞(CTLs)等免疫细胞，进一步促进肿瘤细胞的免疫识别与清除。放疗促进细胞核 dsDNA 和细胞质线粒体 DNA (Mitochondrial DNA, mtDNA)暴露，上调 cGAS-STING 信号传导通路，引发 I 型干扰素反应，由 I 型干扰素刺激 DCs 活化成熟，促进肿瘤抗原特异性 T 淋巴细胞增殖，进一步杀伤肿瘤[32] [33]。此外，关于利用 STING 激动剂增强放疗诱导抗肿瘤免疫反应的研究也有相关综述详细记载。许多临床前研究围绕 cGAS-STING 信号传导通路的激动剂增强放疗诱导抗肿瘤免疫反应开展。二聚氨基苯并咪唑是一种 STING 激动剂，被证实在非小细胞肺癌细胞系中能够通过活化 cGAS-STING 途径，促进非小细胞肺癌的凋亡，增强了放疗敏感性[34]。外核苷酸焦磷酸酶磷酸二酯酶 1 (Ectonucleotide Pyrophosphatase Phosphodiesterase1, ENPP1)是一种 cGAMP 水解酶[35]，而 cGAMP 及其类似物可以穿过细胞膜以激活大多数细胞类型中的 STING。因此采用 ENPP1 抑制剂联合放疗被证实在小鼠髓样乳腺癌模型中能够协同作用，缩小肿瘤体积[36]。此外，STING 激动剂使用的时机和剂量也是重要的，持续的 STING 激动可以导致 T 细胞因此而凋亡[37]。

2.2. 放疗诱导免疫原性细胞死亡

放疗诱导肿瘤发生免疫原性细胞死亡(Immunogenic Cell Death, ICD)，该细胞死亡形式能够在没有外源性佐剂的情况下启动针对死亡细胞所表达的抗原的适应性免疫反应[38]。其主要过程是，处于 ICD 过程中的肿瘤细胞会释放肿瘤特异性抗原和损伤相关分子模式(Damage-Associated Molecular Patterns, DAMPs) [9] [39] [40]，如高迁移率族蛋白 1 (High Mobility Group Box 1, HMGB1)、钙网蛋白(Calreticulin，CRT)、腺苷三磷酸(Adenosine Triphosphate, ATP)、热休克蛋白(Heat Shock Proteins, HSPs)等，增加肿瘤相关性抗原(Tumor-Associated Antigens, TAAs)的表达。抗原呈递细胞(Antigen-Presenting Cell, APC)通过捕

捉 TAAs 并将其与主要组织相容性复合体(Major Histocompatibility Complex, MHC)结合，完成抗原呈递过程，进而激活辅助性 T 细胞(T Helper Cell, Th)。活化的 T 细胞主要包括细胞毒性 T 淋巴细胞(Cytotoxic T Lymphocyte, CTL)和自然杀伤细胞(Natural Killer Cell, NK)，这些细胞能够通过抗肿瘤免疫反应有效清除肿瘤细胞。

在接受术前放化疗的食管鳞状患者组织样本中观察到 HMGB1 的上调，而在未接受术前放化疗的患者中免疫观察到，并且 HMGB1 的上调程度与患者生存率呈正相关[41]。HMGB1 作为一种典型的的 DAMP 分子，能够通过与 Toll 样受体(Toll-like Receptor)和晚期糖基化终产物受体(Receptor for Advanced Glycosylation End Products, RAGE)结合，能够诱导树突状细胞的成熟[41]，并且介导适应性免疫和先天性抗肿瘤免疫的诱导。同时，HMGB1 作为一种氧化还原蛋白，能够对放疗引起的氧化应激产生反应，导致其从细胞核转移到细胞质，并最终释放到细胞外，介导免疫原性细胞死亡[42]。也有研究表明，放疗能够促进 CD8+ T 细胞向肿瘤的浸润，增强其抗肿瘤活性[43]。

2.3. 放疗上调 MHC-I 类分子表达

MHC-I 是一类广泛表达于有核细胞表面的重要免疫分子，其主要功能是参与内源性抗原的呈递过程，肿瘤细胞表面同样存在 MHC-I 类分子。然而，在多种恶性肿瘤的发展过程中，肿瘤细胞常通过下调或完全缺失 MHC-I类分子的表达来实现免疫逃逸。这种机制使肿瘤细胞能够逃避 T 淋巴细胞的识别与杀伤，从而在宿主体内存活和增殖[44]。MHC-I类分子的表达缺失不仅削弱了先天性免疫系统对肿瘤的监视功能，还显著降低了适应性免疫应答的抗肿瘤效应，最终导致肿瘤免疫逃逸的加剧和疾病进展的恶化[44]。放疗可以上调肿瘤表面 MHC-I 类分子的表达，增强抗原呈递能力[45] [46]。

在头颈部鳞状细胞癌中，Hanne 等人[47]发现，经过照射的 A223 肿瘤细胞在体内外实验中都均表现出细胞表面的 MHC-I 类蛋白的显著上调，同时 MHC-I 的重要组成成分 β2m、MHC-I 反式激活因子(NOD-like Receptor family CARD Domain-containing Protein 5, NLRC5)以及抗原呈递相关基因的表达水平也显著升高[47]。此外，接受治疗剂量辐射的肿瘤细胞能够释放放射治疗相关微粒(Radiation Therapy-Microparticles, RT-MPs) [48]，这些微粒通过诱导肿瘤细胞中的 DNA 双链断裂，激活 ATM-ATR-Chk1 介导的 DNA 损伤修复信号通路，从而进一步上调 MHC-I 的表达[49]。值得注意的是，ATM-ATR-Chk1 激酶途径还能直接促进肿瘤细胞表面 PD-L1 的表达上调，这一机制为放疗联合 PD-L1/PD-1 抑制剂的协同作用提供了理论基础，显著增强了抗肿瘤效果。

另一方面，一项基于乳腺癌细胞系的研究表明，放疗能够通过激活干扰素信号通路的激活(如增强 IFN-β 信号传导通路)来刺激 MHC-I 的表达[50]。在 B16/OVA 黑色素瘤细胞模型中也发现，IFN-γ 能够直接作用肿瘤细胞促进 MHC-I 的上调，这一上调与激活的 STAT 水平升高相关[51]。

3. 放疗联合 PD-1/PD-L1 抑制剂的协同作用

3.1. 放疗联合 PD-1/PD-L1 抑制剂的协同机制

PD-1 主要表达与 T 细胞、B 细胞和骨髓细胞表面，而 PD-L1 在大多数正常组织中通常不表达，但在 IFN-γ 的诱导下于几乎所有有核细胞中表达。当 PD-1 与 PD-L1 结合时，会抑制 CD8+ T 细胞的活性，削弱其杀伤功能，从而介导肿瘤细胞的免疫逃逸[14]。PD-1/PD-L1 抑制剂是一类重要的免疫检查点抑制剂，通过阻断 PD-1 与其配体 PD-L1 的结合，解除肿瘤对 T 细胞的免疫抑制，从而恢复抗肿瘤免疫应答[13]。这一机制为肿瘤免疫治疗开辟了新的方向，但其疗效受肿瘤微环境中多种因素的影响。

近年来，研究发现放疗与免疫治疗的联合应用能够产生协同作用，不仅能够提升局部肿瘤控制效果，

还能激发全身性抗肿瘤免疫反应，重塑肿瘤免疫微环境[40]。Tumeh 等[52]的研究揭示了 PD-1/PD-L1 抑制剂的疗效与肿瘤局部 CD8+ T 细胞的浸润状态密切相关。通过对 46 例转移性黑色素瘤患者接受帕博利珠治疗前后的样本分析发现，对治疗有反应的患者在其治疗前的样本中，肿瘤侵袭边缘和内部有更多的 CD8+ T 细胞以及 PD-1、PD-L1 表达细胞[52]。这一结果进一步证实，PD-1/PD-L1 抑制剂发挥治疗作用依赖于肿瘤微环境中预先存在的 CD8+ T 细胞。此外，在非小细胞肺癌的小鼠模型中，观察到放疗联合抗 PD-L1 抗体通过促进 CD8+ T 细胞浸润并减少髓源性抑制细胞(Myeloid-derived Suppressor Cells, MDSCs)和肿瘤浸润调节性 T 细胞(Regulatory T Cells, Tregs)的积累，从而协同增强了抗肿瘤免疫反应[53]。该实验还观察到，放疗可能通过 PI3K/AKT 和 STAT3 信号通路上调 PD-L1 的表达[53]。也就是说，放疗可以通过改变肿瘤微环境，募集相关免疫细胞，达到增强 PD-1/PD-L1 抑制剂的作用。

远隔效应(abscopal effect)是指局部放疗诱导的非照射区域肿瘤消退现象，其机制主要与免疫系统的激活密切相关。研究表明，PD-1/PD-L1 抑制剂与放疗联合应用可通过协同作用显著增强远隔效应，进而提升抗肿瘤疗效[1]。目前相关研究主要集中在临床前研究阶段，其机制尚未完全阐明。以 4T1 小鼠三阴性乳腺癌(一种相对放射敏感的细胞系，具有人乳腺癌的几个特征，包括自发地从原发性乳腺肿瘤转移至多个远端部位，因此被广泛用于人类乳腺癌研究的实验动物模型)模型中，研究发现，联合 PD-1 抑制剂并对小鼠右侧原发肿瘤的放疗后，不仅右侧原发灶显著缩小，左侧未行放疗的继发灶也出现了明显消退[54]。一项针对膀胱癌的研究同样使用小鼠模型评估了联合治疗的远隔效应，放疗联合 PD-L1 抑制剂治疗显著抑制了放疗野内外的肿瘤生长速率[55]。流式细胞术分析表明，联合治疗组中细胞毒性 T 细胞(CTL)浸润增加，且免疫抑制细胞与 CTL 的比例向细胞毒性活性倾斜，并且下调了免疫抑制相关基因(如 CCL22、IL22 和 IL13)，同时上调了 CTL 激活标志物(如 CXCL9、GZMA 和 GZMB) [55]。另一项研究中，双侧腹部皮下种植 MC38 结直肠癌细胞系的小鼠被随机分为接受或不接受近距离放疗组，仅照射一侧肿瘤，另一侧作为模拟转移灶观察。所有小鼠接受 PD-1 抑制剂或对照试剂治疗。结果显示，仅同时接受放疗和 PD-1 抑制剂的小鼠，远端未照射肿瘤显著缩小，即远隔效应[56]。

3.2. 放疗联合 PD-1/PD-L1 抑制剂的临床试验进展

基于放疗与 PD-1/PD-L1 抑制剂协同机制的理论支持，放疗联合免疫治疗(即放疗免疫疗法)在多种实体瘤中展现出显著的有效性和良好的安全性，为肿瘤治疗提供了新的策略和希望[57]。以下将重点探讨放疗联合 PD-1/PD-L1 抑制剂的临床试验进展。

立体定向体部放疗(Stereotactic Body Radiation Therapy, SBRT)是临床试验中最常用的治疗方法，现有的研究主要集中在非小细胞肺癌，在一项评估帕博利珠在晚期非小细胞肺癌患者中的安全性和抗肿瘤作用的临床研究(NCT 01295827)次要结果发现，在接受帕博利珠治疗前曾接受过放疗的患者的总生存期(Overall Survival, OS)和无进展生存期(Progression-free Survival, PFS)显著长于未接受过放疗的患者，即使放疗和免疫治疗的间期长达 9.5 个月[27]。患者 PD-L1 表达水平对放疗联合 PD-1/PD-L1 抑制剂的治疗效果有关，PEMBRO-RT (NCT02492568)招募了转移性非小细胞肺癌患者，分别接受单药帕博利珠或 SBRT 联合帕博利珠(放疗后 7 天内给药)，结果显示 PD-L1 阴性肿瘤患者中联合放疗的获益最大，可显著改善 PFS 和 OS [58]。尽管放疗联合 PD-1/PD-L1 抑制剂在非小细胞肺癌的临床研究中展现出显著的疗效，但这种联合治疗的获益并非在所有癌种中普遍存在。在其他类型肿瘤中，临床研究的获益结果相对有限[59]。一项针对 III 期及以上肝细胞癌及门静脉癌栓患者的临床研究将受试者分为两组，分别接受卡瑞利珠单抗联合阿帕替尼药物治疗联合或不联合 SBRT。结果显示，联合 SBRT 组的中位 OS 和 PFS 均显著优于非联合组[60]。此外，该研究证实联合治疗的毒性在临床可接受范围内，为这类患者提供了新的治疗希望。对于免疫荒漠型肿瘤(如微卫星稳定型结直肠癌和胰腺导管腺癌)，尽管其单独对免疫治疗的反应较差，但

一项 II 期临床试验(NCT03104439)表明，放疗能够增强这类肿瘤对免疫治疗的敏感性，为免疫治疗在难治性肿瘤中的应用提供了新的思路[61]。

4. 放疗与 PD-1/PD-L1 抑制剂联合治疗的时间安排策略

潜在的临床应用前景，但不同剂量和分次方案对免疫反应的调控机制及其疗效差异仍需进一步深入研究。目前，关于放疗与 PD-1/PD-L1 抑制剂联合治疗的最佳剂量、分割方案及时间安排策略仍存在争议，但学界普遍认为，针对不同肿瘤类型和治疗目标，需采取个体化的治疗策略[62]。

无论采用何种放疗剂量(消融剂量、低分割或常规分割模式)，放疗与 PD-1/PD-L1 抑制剂同步使用或放疗后序贯免疫治疗的疗效均优于免疫治疗后序贯放疗的方案。一种可能的机制解释是，当免疫治疗先行时，耗竭的 T 细胞被重新激活并释放大量 IFN-γ 和 TNF-α，但随后的放疗可能会削弱这些新近激活的 T 细胞的抗肿瘤作用。相比之下，放疗与免疫治疗同步或放疗后序贯免疫治疗的策略能够更好地保护并持续发挥 T 细胞的抗肿瘤功能，从而提升治疗效果[63]。因此放疗联合 PD-1/PD-L1 抑制剂治疗的序贯顺序与放疗剂量也是许多研究的关注重点，PACIFIC 临床试验发现在同步放化疗后 2 周内进行度伐利尤单抗治疗的患者比在 4 周时开始的患者存活时间更长[64]。一项以肺癌小鼠模型为基础的临床前研究中发现，放疗后 3~14 天内肿瘤微环境中的 CD8+ T 细胞均润显著增加并达到峰值，并 3~7 天内终末耗竭的 T 细胞比例却尚未达到峰值，提示放疗后 3~7 天可能是联合免疫检查点抑制剂治疗的适宜时间窗[65]。然而，现有研究多集中于特定肿瘤类型(如非小细胞肺癌)，将结论外扩至其他肿瘤仍需要进一步验证。此外，尽管同步方案或放疗后序贯免疫治疗的策略在一些临床前和临床试验中展现优势，但是其长期安全性和耐受性仍需大规模临床试验证实。Shunsuke 等人[66]通过单细胞 RNA 测序和空间转录组分析，系统研究了食管癌患者在放疗过程中肿瘤微环境的动态变化。基于数学模型，研究者预测了五种免疫检查点抑制剂(包括抗 PD-1、抗 PD-L1、抗 CTLA4、抗 LAG3 和抗 TIGIT)在放疗不同时间点(放疗前、放疗中、放疗后)的疗效。结果显示抗 PD-1/PD-L1 抑制剂在放疗期间(同步治疗)效果最佳，而抗 CTLA4 和抗 TIGIT 治疗在放疗后(辅助治疗)仍能维持显著的治疗效果[66]。

放疗与免疫检查点抑制剂的协同作用与放疗的分割方式和剂量大小密切相关。SBRT 或立体定向放射外科(Stereotactic Radiosurgery, SRS)联合 PD-1/PD-L1 抑制剂在晚期非小细胞肺癌患者中可能比常规放疗联合 PD-1/PD-L1 抑制剂更有效[67]。值得注意的是，高剂量放射治疗(High Dose Radiation Therapy, HDRT)能够启动原位肿瘤疫苗接种效应，促进全身性抗肿瘤免疫反应，并引发显著的远隔效应。然而，HDRT 的使用对正常周围组织和肿瘤浸润淋巴细胞(Tumor Infiltrating Lymphocytes, TIL)的活力均存在潜在风险[68] [69]。低剂量放疗(Low Dose Radiation Therapy, LDRT)被发现能有效重塑肿瘤微环境，可能克服 HDRT 引起的免疫抑制[62]。一项针对转移性黑色素瘤的研究发现，LDRT 能够刺激免疫系统，通过重塑肿瘤微环境，诱发系统性的抗肿瘤活性[70] [71]。尽管低剂量放疗已展现出潜在的临床应用前景，但不同剂量和分次方案对免疫反应的调控机制及其疗效差异仍需进一步深入研究。

5. 结语

放疗与免疫治疗的联合治疗，尤其是与 PD-1/PD-L1 抑制剂的协同作用，为实体瘤治疗带来了新的曙光。放疗通过激活干扰素基因刺激蛋白信号通路、诱导免疫原性细胞死亡以及上调 MHC-I 类分子表达等机制，调节肿瘤免疫微环境，与 PD-1/PD-L1 抑制剂产生协同作用，增强抗肿瘤免疫反应。相关开展的临床试验已在以非小细胞肺癌为主的实体瘤中展现出联合治疗的有效性与安全性，但不同癌种间获益仍然存在差异，且最佳的联合治疗时间安排、剂量及分割方案仍有待进一步探索。未来需深入研究联合治疗的分子机制，优化治疗策略，以实现个体化精准治疗，为更多肿瘤患者带来生存获益。

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