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低剂量放疗抗肿瘤免疫应答的机制解析与临床进展

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摘　要

放疗联合免疫治疗是解决免疫耐药问题的关键。常规放疗方式是被最广泛选择的，但是最近的研究表明，低剂量放疗(LDRT)在局部肿瘤控制方面更有效，正常组织毒性可以忽略不计。低剂量放疗(LDRT)调节肿瘤免疫微环境、增加T细胞的浸润与募集、诱导免疫反应，这些机制可能共同负责并参与局部肿瘤控制。本文重点介绍了LDRT的免疫刺激作用、临床疗效、安全性及其耐受性，同时也对LDRT的毒性进行了初步探讨。

关键词

低剂量放疗，非小细胞肺癌，免疫治疗，免疫耐药

Mechanistic Analysis and Clinical Advances of Low-Dose Radiotherapy in Antitumor Immune Responses

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Abstract

Radiotherapy combined with immunotherapy is key to overcoming immune resistance. Conventional radiotherapy remains the most widely adopted approach, but recent studies indicate that low-dose radiotherapy (LDRT) offers superior local tumor control with negligible normal tissue toxicity. Low-dose radiotherapy (LDRT) modulates the tumor immune microenvironment, enhances T-cell infiltration and recruitment, and induces immune responses. These mechanisms collectively contribute to and participate in local tumor control. This article highlights the immunostimulatory effects, clinical efficacy, safety, and tolerability of LDRT, while also providing preliminary insights into its toxicity.

Keywords

Low-Dose Radiotherapy, Non-Small Cell Lung Cancer, Immunotherapy, Immune Resistance

1. 引言

世界卫生组织国际癌症研究中心(IARC)发布 2022 年全球新发肺癌病例约 220 万，占比 11.4%；死亡约 180 万，占比 18.0%。其中中国肺癌新发 81.6 万，死亡 71.5 万[1]。晚期非小细胞肺癌(NSCLC)治疗在经历了根据病理类型和驱动基因靶向治疗显著进步后，免疫单药或免疫联合化疗已经成为晚期驱动基因阴性 NSCLC 患者一线标准方案[2]-[4]，奠定了免疫疗法在肿瘤治疗中的地位。但以上研究在显示更佳疗效的同时，也体现出免疫检查点抑制剂患者同样面临耐药问题，如何解决免疫疗法带来的耐药问题成为目前面临的主要问题。

Chen 等人提出了“癌症–免疫周期”这一核心理念，阐述了抗肿瘤免疫反应的逐步发展的七个连续的阶段。该周期以肿瘤相关抗原的释放为起点，这些抗原被树突状细胞捕获，并通过主要组织相容性复合体(MHC)依赖的途径传递给 T 细胞。T 细胞随后被激活并进入血液循环，渗透至肿瘤微环境(TIME)，通过 T 细胞受体(TCR)与抗原-MHC 复合物的相互作用识别并靶向肿瘤细胞，进而消灭它们[5]。肿瘤微环境及其复杂的内在机制，使其参与肿瘤的形成、进展及转移，同时也可阻碍肿瘤免疫，从而造成免疫逃逸。在迄今为止描述的肿瘤免疫逃逸机制中，主要组织相容性复合体(MHC)分子表达缺失及水平下调起着至关重要的作用[6] [7]。其次，癌症相关成纤维细胞(CAFs)“冷却”了免疫微环境。CAFs 作为一种物理屏障和免疫抑制分子的来源，所起的核心作用使其成为增强癌症免疫治疗的靶点[8]。而肿瘤细胞内在机制主要是通过对 PD-1/PD-L1 的调控，诱导 PD-L1 表达增加，导致效应 T 细胞失活，从而促进免疫逃逸[9]。

放疗被认为是各种恶性肿瘤治疗的基石。单次高剂量的立体定向放射治疗(HD-RT)可以通过增加肿瘤抗原暴露与释放，刺激炎症因子增强免疫应答能力，这一点已被临床观察到的远隔效应证实[10]，然而，高剂量 RT 不能在很大程度上有效解决肿瘤间质中广泛存在的免疫抑制因素：如主要组织相容性复合体(MHC) I 类分子的下调，从而掩盖了肿瘤的细胞毒性 $CD8^+$T 细胞识别；通过 CXCL8 招募髓系来源的抑制细胞(MDSCs)等。最近有一种理论认为低剂量照射(LD-RT)可以解决这些局限性。LD-RT 没有标准定义，但最常见的是每部分 0.5~2 Gy 的方式输送，总输送量为 1~10 Gy。低剂量放疗(LD-RT)重新编程缺乏

免疫浸润的肿瘤微环境，逆转免疫抑制表型，增加 $CD8^+$T 淋巴细胞浸润和活性[11]。本文旨在综述 LDRT 的免疫调节机制，研究目前的联合治疗策略以及其安全性及耐受性。

2. LDRT 调节肿瘤免疫微环境

2.1. DNA 损伤与新抗原

LDRT 诱导的 DNA 损伤组成的损伤簇可被视为促进慢性炎症的持续“危险”信号和免疫反应[12] [13]，受损的宿主组织中释放的“损伤相关分子模式”(DAMP)，能够识别受损的自我，作为免疫炎症反应的介质，通知宿主组织破坏，启动旨在恢复体内平衡的过程[14]。研究发现，放疗(2 Gy × 5 F)与免疫疗法联合使用可以增强 T 细胞向局部治疗肿瘤的运输，能够增强已有的抗癌 T 细胞反应，从而介导肿瘤病变的消退，但是这种特异性 T 细胞仅增加 0.5%，这表明浸润的 T 细胞针对的仅是预先存在的抗原[15]。在低突变负荷小鼠模型中，LDRT 加免疫治疗通过释放新抗原刺激细胞毒性 T 细胞的抗肿瘤作用来促进肿瘤排斥反应。非治疗性照射诱导 19 个错义突变，其中 4 个引发具有功能性细胞毒性的突变特异性 $CD8^+$T 细胞群[16]。

2.2. 树突状细胞

树突状细胞在肿瘤免疫治疗及 T 细胞抗原呈递过程中起着至关重要的作用，是肿瘤微环境中最重要的免疫监视哨兵细胞，是启动和维持有效 T 细胞介导的抗肿瘤免疫反应的关键决定因素[17]-[21]。研究表明，来自低剂量照射的骨髓细胞可以分化为具有多种不同特征的树突状细胞，例如 MHC 分子的表达、细胞因子的分泌和抗原摄取能力[22]。据报道，低剂量辐射剂量会导致 $CD4^+$T 细胞功能谱的变化，最常见的是向 Th2 表型转变[23]。暴露于 0.2 Gy 剂量的 LDRT 能够增加骨髓 DC 疫苗的抗肿瘤作用，诱导 T 细胞增殖的能力增强，细胞毒性 T 淋巴细胞(CTL)的细胞毒性作用显著增强，同时低剂量放射还会通过增加 IL-2、IL-12 和 IFN-γ DC 的产生来增强 T 细胞活化能力[24] [25]。

2.3. MHC 相关分子上调

抗原加工途径的最终结果是肽结合的主要组织相容性复合体 I (pMHC I)分子的展示，各种抗原肽的呈递均依赖于 MHC 分子[26]-[28]。研究表明，定向放疗可以提高肿瘤免疫治疗的疗效，只有在肿瘤组织放疗之前，免疫疗法才能成功根除小鼠结肠腺癌。这是由于辐射影响 MHC I 类分子抗原呈递的增加，而同时 MHC 分子的表达具有明显的剂量依赖性[29]。研究表明，与未接受电离辐射的细胞相比，LDRT 可以通过剂量依赖性方式增强与 NKG2D 结合的细胞因子诱导的 NK 细胞、MICA 和 MICB 的 mRNA 和蛋白质表达[30] [31]。另一项研究表明，LDRT 能够增强 CD28 和 B7 的共刺激作用及 IL-12/IL-10 的相互作用，上调抗原呈递细胞(APC)上的 CD28 和 CTLA-4 的表达，导致免疫增强，从而延缓肿瘤生长，减少转移，并减轻因肿瘤负荷引起的免疫抑制[32] [33]。

2.4. T 细胞的运输和浸润

T 细胞转化是使肿瘤对 T 细胞免疫治疗敏感的关键。细胞外超氧化物歧化酶(SOD3)改变了内皮基底膜(EC-BM)的组成，提供允许信号，增强效应 T 细胞的肿瘤浸润，而细胞间粘附分子(ICAM-1)的下调和对促炎细胞因子的反应性降低是肿瘤衍生的细胞溶解效应白细胞逃逸机制[34] [35]。低剂量放疗的加入，通过促进 M1 巨噬细胞极化、增强自然杀伤(NK)细胞浸润和降低 TGF-β 水平，从而增强 T 细胞的细胞毒性，改善免疫检查点抑制剂的抗肿瘤效果，重新编程肿瘤环境[36] [37]。研究表明，在局灶 2 Gy/F LDRT 治疗的小鼠肿瘤中，参与 T 细胞吸引的趋化因子(如 CXCL9、CXCL10、CXCL11、CCL4 和 CCL5)的分

泌增加[38]，将抗肿瘤效应 T 细胞募集到肿瘤部位[39]，且 LDRT 能够建立良好的反应及耐受。

2.5. 效应细胞的激活和杀伤

LDRT 的刺激抗氧化能力、修复 DNA 损伤、细胞凋亡和诱导免疫反应能力，在局部肿瘤控制方面更有效，且正常组织毒性可忽略不计[40]。研究表明，辐射可通过刺激效应 T 细胞基因的表观遗传调节，导致 OX40L 和 4-1BBL 的表达上调[41]。4-1BBL 是在单核细胞/巨噬细胞上表达的肿瘤坏死因子超家族的成员，其配体及其受体在激活后均在 T 细胞上被诱导，数据表明，在 T 细胞上表达的 4-1BBL 可以抑制效应 T 细胞的发育，在致耐受条件下创造更有利的调节性 T 细胞与效应细胞平衡[42] [43]。

低剂量放疗触发了具有 Th1 特征的 $CD4^+$细胞的浸润，以稀缺的免疫浸润对肿瘤的肿瘤微环境进行重编程，并与免疫疗法一起诱导先天免疫和适应性免疫(主要是 $CD4^+$效应 T 细胞)的同时动员，以实现依赖于 NKG2D 的肿瘤控制，逆转肿瘤免疫荒漠化[11]。早期研究表明，2 Gy 的放射治疗能够诱导依赖于 P53 的 Fas 受体及 CD95 表达上调，在细胞凋亡中起重要作用[11] [44]，也可以打破 PD-1/PD-L1 介导的基于 T 细胞的过继疗法的耐受性，增强其 T 细胞的细胞毒性[45]。

此外，在先天性免疫中，低剂量放疗可增强 NK 细胞的活性，刺激其细胞溶解功能，从而诱导谷胱甘肽水平的增加和抗体依赖性细胞毒性(ADCC)的出现，达到抑制肿瘤的作用，其内在机制可能是与 P38-MAPK 通路诱导 NK 细胞的直接扩增和激活有关[46]-[49]。

2.6. Tregs 的抑制

Treg 细胞被鉴定为 $CD4^+CD25^+Foxp3^+$淋巴细胞亚群，自然产生的表达 Foxp3 的 $CD25^+CD4^+$调节性 T 细胞积极维持免疫自我耐受，而肿瘤诱导其转化扩增是独立的[50]-[52]。既往报告表明，RT 可以显著增加 TME 中的肿瘤浸润性 Tregs (TIL-Treg)，与未照射肿瘤中的 Tregs 相比，TIL-Tregs 具有更高的 CTLA-4、4-1BB 表达[53]。此外，低剂量全身照射可选择性降低 $CD4^+CD25^+Foxp3^+$调节性 T 细胞的比例和数量，导致肿瘤负荷减轻和生存期延长，研究表明，低剂量放疗改变了 $CD4^+CD25^+$ Treg 细胞表面 CTLA-4 分子的表达，降低了其对 $CD4^+$ $CD25^-$T 细胞增殖的抑制作用，以及 $CD4^+$的抑制作用[54] [55]。

2.7. 巨噬细胞复极化

单核细胞被认为是单核吞噬系统的前体细胞，巨噬细胞是该细胞系统的主要成员之一，其亚群除了 M1 和 M2 巨噬细胞之外，还有肿瘤相关巨噬细胞、$CD169^+$和 TCR^+巨噬细胞，多样性和可塑性是单核细胞－巨噬细胞谱系细胞的标志，诱导它们采用不同的表型以响应细胞外和细胞内信号，这一过程定义为 M1/M2 极化[56]-[58]。其中肿瘤相关巨噬细胞(TAM)是许多肿瘤基质的主要炎症成分，可表达多种 M2 相关的促肿瘤功能，包括促进血管生成、基质重塑和抑制适应性免疫。M2 极化的肿瘤相关巨噬细胞和相关的髓源性抑制细胞是驱动肿瘤进展的关键原型成分，因此，TAM 独特的 M2 偏向骨髓细胞群是抗癌治疗的潜在靶点[59]-[61]。低剂量放疗可以诱导 M1 相关效应细胞因子以及促致癌和 M2 相关效应细胞因子减少[62]，通过下调受照射肿瘤中的 HIF-1 的影响，从而促进幼稚巨噬细胞向 M1 表型分化[63]。此外，LDRT 编程 $iNOS^+$ M1 巨噬细胞的分化，通过诱导内皮激活和 Th1 趋化因子的表达以及抑制血管生成、免疫抑制、和肿瘤生长因子，从而协调 T 细胞的细胞免疫[64]。总之，低剂量放疗改变了巨噬细胞在肿瘤微环境中的平衡。

2.8. 肿瘤脉管系统

实体瘤的脉管系统特征是扩张和脆弱的血管、密集的血管发芽和层次结构的丧失，肿瘤相关的血管生成支持肿瘤生长，会阻止免疫效应细胞迁移到已建立的肿瘤实质中，其生成改变的机制是免疫治疗过

程中难以破解的障碍[65] [66]。肿瘤血管相比于正常血管来说，对于辐射会更加敏感[67]，局部 LDRT 可导致异常脉管系统的正常化和肿瘤特异性 T 细胞的有效募集[64]。

2.9. 细胞因子平衡

研究已发现辅助性 T 细胞 1 型(Th1)和 2 型(Th2)在正常免疫系统中维持功能平衡，LDRT 实际上以剂量和时间依赖的方式影响 Th1/Th2 移位，可促进 Th1 细胞因子的产生，减少 Th2 细胞因子的表达，从而维持免疫系统的平衡状态[68] [69]。Sonanini D 等人的研究表明全身的 LDRT 可通过支持 Th1 驱动的抗肿瘤免疫来促进基于 $CD4^+$T 细胞的癌症免疫疗法[70]。此外，白细胞介素 1β (IL-1β)由多种免疫细胞类型中的炎症信号诱导，主要由肿瘤浸润巨噬细胞在肿瘤微环境中产生的 IL-1β 通过多种机制来促进肿瘤的生长和转移[71]。LDRT 通过以 NF-κB 依赖性方式降低分泌的 IL-1β 量来诱导活化巨噬细胞的抗炎表型[72]。先前已经表明，LDRT 促进 DC 产生 IL-12，导致 DC 活性增加，其分子机制则是通过激活 ATM/NF-κB 通路对 DC 产生关于 CCR7 介导的迁移和 IL-12 产生的兴奋效应[73]，在 T 细胞活化及 Th1 极化中具有重要作用[74] [75]。

3. LDRT 改变全身肿瘤免疫环境(STIE)

全身肿瘤免疫环境(STIE)由免疫细胞和免疫分子组成，是机体抗肿瘤反应的全局环境[76]，肿瘤进展通常会导致免疫系统的紊乱，例如中性粒细胞、单核细胞以及树突状细胞的变化[77]-[79]。免疫细胞有效剂量(effective dose to immune cells, EDIC)模型表明，RT 对循环免疫细胞的影响与预后相关，可推荐作为预测淋巴细胞减少和较差临床结果的有用工具[80] [81]。

4. LDRT 的临床前证据

LDRT 的免疫调节功能已经在多种肿瘤模型上得到了验证。在 3LL 和 4T1 肿瘤小鼠模型中，消融后调制(PAM)和四次每日低剂量分割(22 Gy + 0.5 Gy × 4)增加了免疫效应细胞的浸润，并减少了受照射肿瘤和次级淋巴器官中的 Treg 和 M2 巨噬细胞[82]。在致癌基因 sv40-tag 诱导的 RT5 胰腺癌小鼠模型中，LDRT 可导致过继 T 细胞和内源 T 细胞的有效募集，通过编程 $iNOS^+$ M1 巨噬细胞的分化，缩小肿瘤体积，改善肿瘤预后，延长了肿瘤患者生存期[64]。在 344SQ 肺腺癌肿瘤的 129Sv/Ev 小鼠中，RadScopal + 抗 TIGIT + 抗 PD1 的三联疗法降低了 TIGIT + 耗竭 T 细胞和 TIGIT + 调节性 T 细胞的百分比，延长了治疗小鼠的存活时间并阻止原发性和继发性肿瘤的生长[83]。在卵巢癌 ID8 肿瘤模型中，化疗、免疫及低剂量全腹放疗联合使用增加了 T 细胞的浸润，特别是 1 Gy 的剂量在第 5 天后诱导了最高的 $CD8^+$、$CD4^+$和 $CD11b^+$细胞浸润[11]。以上临床前数据表明，LDRT 可增强抗肿瘤反应，从而延长肿瘤的生存期。

5. 低剂量放疗联合免疫治疗及其毒性

一项事后分析发现，接受了低剂量放疗的病灶的客观缓解率远高于未接受放疗辐射的病灶(58% VS 18%) [84]，然而，LDRT 单一的治疗方式不足以达到抗肿瘤效果，需联合治疗。HDRT + LDRT + 免疫检查点抑制剂的联合治疗，使得接受 LDRT 的病灶的有效率大于 50% [36]，临床研究显示 HD-RT 与 LD-RT 联合免疫检查点抑制剂，改善了免疫检查点抑制剂进展患者的治疗反应率，其 ORR (HD-RT + LD-RT)为 26% vs HD-RT 13%, P = 0.27)。与 HD-RT + LD-RT (23%, P = 0.002)和 HD-RT (11%, P < 0.001)未接受放疗的病变相比，LD-RT 客观缓解率(53%)得到显著改善[85] (见表 1)。

至于 LDRT 的毒性，在上文提到的 II 期临床研究中，其 HDRT + LDRT 组与 LDRT 组相比，发生剂量限制性毒性的概率无显著差异[85]。在一项前瞻性的临床研究中，应用 LDRT + SBRT + 信迪利单抗三联疗法治疗非小细胞肺癌，观察其安全性及有效性，结果显示，未观察到 3 级或以上治疗相关毒性，2 级

或以上放射相关肺炎和免疫相关肺炎的发生率 < 10% [86]。一般来说，LDRT 是安全且可耐受的。

Table 1. Study on low-dose radiotherapy combined with immunotherapy
表 1. 低剂量放疗联合免疫研究

试验类型	患者人群	LDRT 剂量	联合免疫药物	主要终点
回顾性	转移性疾病	每病灶中位 7.3 Gy (范围 1.1~19.4 Gy)	抗 CTLA-4/抗 PD-1	ORR
前瞻性	既往免疫治疗进展的转移性疾病	0.5~2 Gy/次，最多至 1~10 Gy	抗 PD-1/抗 PD-L1/抗 CTLA-4	ORR
前瞻性	晚期 NSCLC	2 Gy × 1/2/5 次	抗 PD-1	ORR

6. 总结

综上所述，尽管 LDRT 具有良好的应用前景，但在实际应用中仍有许多问题有待解决。卢铀教授及其研究团队进行了剂量比较试验(2 Gy/5F, 2 Gy/3F, 2 Gy/1F)，发现 2 Gy/1F 的放疗方式相较于其他剂量，能够更好地增加免疫细胞浸润。因此，LDRT 的最佳剂量目前仍无法确定，尚需进一步探索。但是 LDRT 改变了放疗作为局部治疗手段的思路，相比于传统放疗方式，低剂量放疗特别适用于多发转移、大病变或重要器官附近特异性病变的患者，但其作用机理及疗效仍需进一步挖掘及研究；此外，LDRT 提供了多部位照射的可能性，可以更大程度地发挥免疫调节作用，而没有 HDRT 的高危毒性。本文综述了 LDRT 的临床前理论基础和初步临床数据，旨在为探索新型 LDRT 的临床应用提供理论依据，为经历免疫治疗耐药及化疗耐受性差的晚期非小细胞肺癌患者提供新的治疗思路，但其疗效及安全性仍需进行大规模临床试验进行进一步验证。

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