Advances in Clinical Medicine 临床医学进展, 2022, 12(2), 1014-1021
Published Online February 2022 in Hans. http://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2022.122148

Hans汉斯

放射治疗与免疫治疗之间的关系

刘根利[1]，鲁永织[2]，陶风英[2]，李　玲[2]，杨　雪[2]，王笑荷[2]，袁胜利[2*]

[1]大连医科大学规培医院青岛市市立医院，山东　青岛
[2]青岛市市立医院肿瘤二科，山东　青岛

收稿日期：2022年1月14日；录用日期：2022年2月8日；发布日期：2022年2月17日

摘　要

放射治疗是诊断后一半以上癌症患者的主要抗癌方式，与化学疗法相比，其具有局部肿瘤控制的优势，且系统性副作用相对较少。然而，放射治疗的疗效受到获得性肿瘤耐药性的限制，导致复发和转移的风险。自从免疫疗法在癌症治疗中出现以来，现在已经确定放疗与此类治疗的关联可以促进放射诱导的抗肿瘤免疫的出现。因此，这种组合近年来引起了科学界越来越大的兴趣，并正在大量临床前模型中进行研究，也在许多临床试验中付诸实践。在这篇综述中，我们旨在总结放射治疗与免疫系统之间的相互影响以及放射治疗与免疫治疗相结合对肿瘤治疗效果的影响。

关键词

放射治疗，免疫治疗，远隔效应

The Relationship between Radiation Therapy and Immunotherapy

Genli Liu[1], Yongzhi Lu[2], Fengying Tao[2], Ling Li[2], Xue Yang[2], Xiaohe Wang[2], Shengli Yuan[2*]

[1]Qingdao Municipal Hospital, Guipei Hospital of Dalian Medical University, Qingdao Shandong
[2]The Second Department of Oncology, Qingdao Municipal Hospital, Qingdao Shandong

Received: Jan. 14th, 2022; accepted: Feb. 8th, 2022; published: Feb. 17th, 2022

Abstract

Radiation therapy is the main anti-cancer method for more than half of the cancer patients after diagnosis, it has the advantage of local tumor control over chemotherapy and has relatively few systemic side effects. However, the efficacy of radiotherapy is limited by resistance to acquired

*通讯作者。

文章引用: 刘根利, 鲁永织, 陶风英, 李玲, 杨雪, 王笑荷, 袁胜利. 放射治疗与免疫治疗之间的关系[J]. 临床医学进展, 2022, 12(2): 1014-1021. DOI: 10.12677/acm.2022.122148

tumors, leading to the risk of recurrence and metastasis. Since the advent of immunotherapy in cancer therapy, it has now been established that the association of radiation therapy with such treatments can promote the emergence of radiation-induced antitumor immunity. Therefore, this combination has attracted increasing interest in the scientific community in recent years and is being studied in a large number of preclinical models and also put into practice in many clinical trials. In this review, we aimed to summarize the inter effects between radiotherapy and the immune system and the impact of the combination of radiotherapy and immunotherapy on the effect of tumor therapy.

Keywords

Radiotherapy, Immunotherapy, Abscopal Effect

1. 引言

放射疗法是治疗癌症的基石之一，它也是最常用的癌症治疗策略，大约 60%的实体瘤患者接受治愈性或姑息性照射作为治疗的一部分[1]。如今，放射技术与先进的成像系统相结合，可以将匹配的放射剂量准确地传递到病变的精确位置，最大限度地保留邻近的正常组织[2]。除了这些最先进的技术外，随着免疫学，生理学和分子细胞生物学的发展，我们对肿瘤生物学和放射生物学的知识也有了显著增长，这使我们能够从更全面的角度分析治疗结果并更有效地进行放射治疗。

几十年来，关于改善放射治疗结果的研究几乎全部集中在癌细胞本身上，而忽略了肿瘤与其生长基质之间的复杂生物相互作用——所谓的肿瘤微环境(tumor microenvironment, TME)。在肿瘤的微环境中，辐射会诱导基质，免疫和血管的变化，这对于肿瘤的反应至关重要[3]。尽管传统上已知电离辐射会通过直接或间接破坏细胞 DNA 来诱导肿瘤细胞杀伤，但是越来越多的证据开始表明，辐射也可能通过激活局部和/或全身免疫反应来消除肿瘤。在本文中，将着重介绍放射治疗对肿瘤免疫微环境的影响及放射治疗与免疫疗法之间的互惠关系。

2. 肿瘤与免疫系统

肿瘤在由免疫系统细胞组成的微环境中发展，免疫系统可以调节肿瘤抑制或进展。免疫系统对肿瘤的作用具有免疫保护宿主和促进肿瘤双重作用[4] [5]。R. Schreiber 提出的癌症免疫编辑理论阐述了免疫系统与肿瘤之间的相互作用分为三个阶段：消除(即癌症免疫监测)，平衡和逃脱。这个过程也被称为癌症免疫编辑的三个“E”[6]。在消除癌症的第一阶段，先天性(自然杀伤细胞——NK 和巨噬细胞)和适应性(树突状细胞——DC，CD8+和 CD4+ T 淋巴细胞)的细胞和分子与构成癌症免疫系统相互作用，存在于致癌过程开始时的高度免疫原性肿瘤细胞。在具有免疫能力的宿主内，肿瘤细胞将通过细胞毒性机制(Fas 受体与其配体之间的相互作用，诱导细胞死亡)被 CD8+ T 淋巴细胞或 NK 淋巴细胞(“自然杀手”)破坏，尤其是通过分泌细胞溶解蛋白，例如穿孔素或颗粒酶 B 等)。如果所有肿瘤细胞未完全溶解，则发生第二阶段：这是平衡阶段。在第二阶段中，其余肿瘤细胞与免疫系统之间保持平衡，实际上，免疫系统将控制肿瘤细胞，而不会成功地破坏它们。在这种免疫“编辑器”环境中长期或免疫维持，它们可能产生新的肿瘤变体群体。在那时，肿瘤细胞不仅呈现较少的抗原，而且还促进抑制局部效应细胞的免疫抑制细

胞的募集。其中，调节性 T 淋巴细胞、髓样抑制细胞(MDSC)，吲哚胺 2,3-二加氧酶(IDO)的分泌以及诸如白细胞介素 10 (IL-10)等细胞因子在高度免疫抑制的环境中是最重要的。这样，肿瘤就摆脱了免疫监视，变得可在临床上检测到[7]。

3. 放射治疗的免疫调节作用

除了直接杀死癌细胞外，放射线还可能将肿瘤微环境从免疫抑制重编程为免疫刺激表型[8]。辐射可增加 CD8 [+] T 细胞的浸润，不仅可诱导 T 淋巴细胞 CD8+表面 MHC-1 的表达，还能诱导 T 淋巴细胞 CD8+和自然杀伤(NK)淋巴细胞表面死亡受体 Fas/CD95 和 NKG2D 配体的表达，使肿瘤细胞被这些免疫细胞识别并因此破坏它们[9] [10]。同时减少髓样来源的抑制细胞，这取决于交叉呈递的树突状细胞和 IFN-γ 的存在[11]。低剂量辐射促进肿瘤脉管系统的正常化和 M2 样巨噬细胞向 M1 样 iNOS [+]表型的极化[12]，iNOS [+]巨噬细胞诱导 Th1 趋化因子的表达，将 CD8 [+]和 CD4 [+] T 细胞募集到肿瘤中，从而促进 T 细胞介导的抗肿瘤作用[12]。另一方面，辐射也刺激诱导免疫抑制的细胞因子的分泌。例如，转化生长因子-β (TGF-β)在辐射后不久就被上调，TGF-β 诱导抑制 CD8 [+] T 细胞并促进调节性 T 细胞转化，从而导致肿瘤的免疫抑制[13] [14] [15]。同时，辐射也可通过使树突状细胞，细胞毒性 T 淋巴细胞和 NK 淋巴细胞失活，以及通过募集 MDSC 和调节性 T 淋巴细胞，以及通过巨噬细胞的表型修饰，获得免疫抑制特征，并从促炎表型 M1 转变为免疫抑制表型 M2。

4. 远隔效应

正常组织中放射疗法的全身效应被称为远隔效应。这种作用对未接受辐射的细胞造成损害[16]。远隔效应是放射生物学中的一个有趣现象，它引起针对癌细胞的免疫系统的激活。它可以用作放射治疗期间针对原发肿瘤的免疫系统的刺激物。实际上，电离辐射引起的 DNA 损伤，氧化应激和细胞死亡是免疫系统的主要刺激因素。免疫系统可以通过识别称为病原体相关分子模式(PAMPs)和损伤相关分子模式(DAMPs)的特定分子来识别病原体和受损细胞[17]。某些免疫细胞(称为抗原呈递细胞(APC))可以识别 PAMPs 以唤醒免疫系统。DAMPs 包含一些分子，可作为免疫系统的警报。高迁移率族蛋白 1(HMGB1)是细胞死亡后释放的最常见 DAMP 之一，暴露于电离辐射中的死亡细胞还可以释放一些其他警报，包括热休克蛋白(HSP)，S100，氧化的 DNA，ATP 等[18] [19]。充当 APC 的巨噬细胞也可以被炎性细胞因子激活。实际上，炎症细胞因子能够将 M2 型促肿瘤型巨噬细胞重编程为 M1 型抑制肿瘤型巨噬细胞[20]。这些变化与触发针对癌细胞的免疫系统有关，从而导致 CSC 和其他癌细胞凋亡的诱导[19]。当炎性细胞因子迁移到远处的肿瘤和转移时，可以观察到远隔效应。已经显示，局部肿瘤照射后血清 IFN-γ 水平升高会导致另一个未照射区域的肿瘤消退[21]。在一系列人类癌症中，放射治疗的 23 例临床病例对潜在的远隔效应进行了很好的总结[22]。另一项体面的研究进一步证明了通过释放 HMGB1 [23]和肿瘤新抗原(该术语用于描述由肿瘤发生或 RT 引起的突变导致的患者特异性肿瘤抗原)，由于免疫原性细胞死亡而在临床放射治疗中产生了明显的疗效[24] [25]。根据 Marconi 等人的荟萃分析，远隔效应显示出对辐射的剂量依赖性模式[26]。尽管最大程度地发挥远隔效应所需的最佳剂量仍存在争议[23] [27]，但理想的辐射方案(例如低剂量或高剂量)的确定可能在临床实践中产生突破性的优势。

5. 放射治疗与免疫治疗

在过去的十余年中，将电离辐射与免疫疗法相关联引起了科学界的广泛兴趣，这种关联可以增强放射性诱导的抗肿瘤免疫反应，同时使用许多类型的免疫疗法和放射疗法进行了许多临床前模型和临床试验。电离辐射可以诱导肿瘤微环境内的免疫学改变，包括促进肿瘤抗原释放[28]，增加效应子 T 细胞浸

润[11]和上调肿瘤细胞上的 MHC-1 分子[29]，最近的一项研究表明，辐射诱导的 DNA 双链断裂通过 ATM/ATR/Chk1 激酶上调了肿瘤细胞上 PD-L1 的表达[30]。鉴于肿瘤中 PD-L1 的过度表达与对抗 PDL1 治疗的反应改善有关[31]，放射线可作为一种有效的新辅助治疗，以提高免疫检查点封锁的有效性。但最近的证据表明癌症免疫疗法如免疫检查点抑制剂也可能具有放射增敏作用[32]，其可能机制为通过使肿瘤血管正常化改善缺氧微环境来增加肿瘤对放射治疗的敏感性[33]。

目前已经提出免疫疗法与其他抗肿瘤疗法的结合可以提高肿瘤控制的可能性[34]。在不同的治疗方式中，放射疗法与免疫疗法的结合似乎是最有效的。免疫检查点阻滞剂的机制基于防止 CTL 的凋亡诱导。CTL 在其表面上包括两个著名的检查点，即程序性细胞死亡 1 (PD-1)和细胞毒性 T 淋巴细胞相关抗原 4 (CTLA-4)，其余靶点还包括：人类白细胞抗原(HLA)、CD47、HMGB1、GRP78、CD134、TLR、CRT、细胞外基质(ECM)、DNA 核酸外切酶 Trex1、癌症相关成纤维细胞(CAF)、TAM、树突状细胞等[35]。

目前，抗 PD-1 药物是与次分割放疗联合使用的最有趣的免疫疗法药物。将 PD-1/PD-L1 和其他免疫检查点作为目标，再结合放射线的辐射，可以触发更有效的抗肿瘤免疫力[36] [37]。如表 1，列出了一些目前关于放射治疗联合免疫检查点抑制剂已经有结果的一些临床试验，使用最多的还是 PD-1/PD-L1、CTLA-4 抑制剂。多数研究旨在探索放射治疗联合免疫治疗的安全性及有效性，在不同的肿瘤类型中，大多表明放射治疗与免疫治疗联合患者耐受性良好，且疗效相对于单独放射治疗来说更具有优势[38] [39]。

Table 1. Related tests of radiotherapy combined with immunocheckpoint inhibitors
表 1. 放疗联合免疫检查点抑制剂相关试验

NCT number	Study status	Phase of trial	Tumor entity	Drug	Irradiation regimen	First pdsted
NCT02298946	Has results	Phase 1	Metastatic Colorectal cancer	Anti-PD1 (AMP-224)	SBRT1 × 8 Gy or 3 × 8 Gy	2014.11.24
NCT02434081	Has results	Phase 2	NSCLC III 期	Anti-PD1 (Nivolumab)	RT	2015.5.5
NCT03115801	Has results	Phase 2	Metastatic genitourinary cancers	Anti-PD1 (Nivolumab/ Atezolizumab/ Pembrolizumab)	IMRT/IGR T3 × 10 Gy	2017.4.14
NCT03220854	Has results	Phase 2	Solid tumor	Anti-PD1	SBRT 18~60 Gy/3~5 f	2017.7.18
NCT03988647	Has results	Phase 2	Metastatic merkel cell carcinoma	Anti-PD1 (Pembrolizumab)	RT 3 × 9 Gy or 5 × 4~6 Gy	2019.6.17
NCT02303990	Has results	Phase 1	Metastatic cancers	Anti-PD1 (Pembrolizumab)	HFRT 3 × 8 Gy-1 × 17 Gy	2014.12.1
NCT02759575	Has results	Phase 1/2	Head and neck cancer	Anti-PD1 (Pembrolizumab)	RT 35 × 2 Gy	2016.5.3
NCT03051672	Has results	Phase 2	Metastatic breast cancer	Anti-PD1 (Pembrolizumab)	RT 5 × 4 Gy	2017.2.14
NCT03465891	Has results	Phase 2	Lymphoma	Anti-PDL1 (atezolizumab)	RT 2 × 2 Gy	2018.3.14
NCT02311361	Has results	Phase 1/2	Pancreatic cancer	Anti-PDL1 (Durvalumab) Anti-CTLA4 (Tremelimumab)	SBRT 1 × 8 Gy or 5 × 5 Gy	2014.12.8

Continued

NCT02934503	Has results	Phase 2	SCLC	Anti-PD1 (Pembrolizumab)	Thoracic radiotherapy	2016.12.17
NCT03617913	Has results	Phase 2	Bladder cancer	Anti-PDL1 (avelumab)	RT	2018.8.7
NCT02952586	Has results	Phase 3	Squamous cell carcinoma of the head and neck	Anti-PDL1 (avelumab)	IMRT 35 × 2 Gy	2016.9.2
NCT02336165	Has results	Phase 2	glioblastoma	Anti-PDL1 (Durvalumab)	RT 30 × 2 Gy	2015.1.12
NCT02221739	Has results	Phase 1/2	NSCLC	Anti-CTLA4 (ipilimumab)	RT 5 × 6 Gy-3 × 9.5 Gy	2014.8.20
NCT01449279	Has results	Phase 2	melanoma	Anti-CTLA4 (ipilimumab)	RT	2011.10.10
NCT01769222	Has results	Phase 1/2	Melanoma/ non-hodgkin lymphoma/colon/ rectal	Anti-CTLA4 (ipilimumab)	RT 3 × 10 Gy	2013.1.16
NCT02701400	Has results	Phase 2	Recurrent SCLC	Anti-PDL1 (Durvalumab) Anti-CTLA (Tremelimumab)	SBRT 3 × 9 Gy	2016.3.8

6. 小结与展望

在过去二十年来，免疫治疗在癌症治疗中的应用，以及免疫治疗与肿瘤放射疗法之间的相互影响的认识不断发展，都为开发新的治疗策略奠定了基础。正如前面提到的大量临床前研究所表明的，放疗和各种免疫疗法的结合似乎是对抗癌症的一种有前途的方法。但是，仍然存在一些问题亟待解决，例如免疫疗法和放射疗法相结合的时间以及最佳剂量。一项临床前研究表明，抗 CTLA4 和抗 CD134 相对于放射线的最佳时机不同，这表明最佳治疗顺序可能对免疫疗法的类型具有特异性[40]。有趣的是，对一项随机临床试验的分析[41]表明，与放疗后晚开始免疫治疗相比，如果同时或放疗后开始免疫治疗，患者的预后似乎更好。从机理上讲，免疫疗法的潜在放射增敏功能只有在与放射同时或放射前施用时才能有效，这是否成立还需要进一步的临床前和临床研究。同时，虽然部分研究显示两种治疗方法结合患者的耐受性可，但不可否认的是两种治疗方法的联合使不良反应增加，这可能将成为障碍。

与常规分级分离相比，单次高剂量放射可促进抗原呈递细胞的成熟[42]并增加免疫细胞向肿瘤的浸润[43]。但高剂量辐射可引起更多血管损伤，从而减少血流和灌注[44]，从理论上讲，通过免疫疗法使肿瘤血管正常化可以克服低氧的放射抵抗。然而，免疫疗法的最佳放射剂量尚不清楚，这还需要更多的临床试验去进一步验证。

另外，还需要找到一种方法来预测哪些患者将从放射疗法和免疫疗法的组合中受益最大，从而避免不必要的毒性和费用。尽管已经测试了几种此类标记，包括 DNA 修复缺陷[45]，突变负荷[46]，PDL1 表达[31]和肠道微生物组[47]，但仍然存在一些局限性。我们还需要大量的工作来推动临床实践。

基金项目

《SAMHD1 在胃癌中的调控、表达及作用机制研究》(2019WS154)。

参考文献

[1] Orth, M., Lauber, K., Niyazi, M., Friedl, A.A., Li, M., Maihöfer, C., *et al*. (2014) Current Concepts in Clinical Radiation Oncology. *Radiation and Environmental Biophysics*, **53**, 1-29. https://doi.org/10.1007/s00411-013-0497-2

[2] Baumann, M., Krause, M., Overgaard, J., Debus, J., Bentzen, S.M., Daartz, J., *et al*. (2016) Radiation Oncology in the Era of Precision Medicine. *Nature Reviews Cancer*, **16**, 234-249. https://doi.org/10.1038/nrc.2016.18

[3] Thomas, L. (1959) Cellular and Humoral Aspects of the Hypersensitive States: A Symposium Held at the New York Academy of Medicine. Hoeber-Harper, New York.

[4] Dunn, G.P., Bruce, A.T., Ikeda, H., Old, L.J. and Schreiber, R.D. (2002) Cancer Immunoediting: From Immunosurveillance to Tumor Escape. *Nature Immunology*, **3**, 991-998.

[5] Dunn, G.P., Old, L.J. and Schreiber, R.D. (2004) The Immunobiology of Cancer Immunosurveillance and Immunoediting. *Immunity*, **21**, 137-148. https://doi.org/10.1016/j.immuni.2004.07.017

[6] Dunn, G.P., Old, L.J. and Schreiber, R.D. (2004) The Three Es of Cancer Immunoediting. *Annual Review of Immunology*, **22**, 329-360.

[7] Vesely, M.D., Kershaw, M.H., Schreiber, R.D. and Smyth, M.J. (2011) Natural Innate and Adaptive Immunity to Cancer. *Annual Review of Immunology*, **29**, 235-271.

[8] Jiang, W., Chan, C.K., Weissman, I.L., Kim, B.Y.S. and Hahn, S.M. (2016) Immune Priming of the Tumor Microenvironment by Radiation. *Trends in Cancer*, **2**, 638-645. https://doi.org/10.1016/j.trecan.2016.09.007

[9] Kim, J.Y., Son, Y.O., Park, S.W., Bae, J.H., Chung, J.S., Kim, H.H., *et al*. (2006) Increase of NKG2D Ligands and Sensitivity to NK Cell-Mediated Cytotoxicity of Tumor Cells by Heat Shock and Ionizing Radiation. *Experimental & Molecular Medicine*, **38**, 474-484.

[10] Chakraborty, M., Abrams, S.I., Camphausen, K., Liu, K., Scott, T., Coleman, C.N., *et al*. (2003) Irradiation of Tumor Cells Up-Regulates Fas and Enhances CTL Lytic Activity and CTL Adoptive Immunotherapy. *The Journal of Immunology*, **170**, 6338-6347.

[11] Filatenkov, A., Baker, J., Mueller, A.M., Kenkel, J., Ahn, G.O., Dutt, S., *et al*. (2015) Ablative Tumor Radiation Can Change the Tumor Immune Cell Microenvironment to Induce Durable Complete Remissions. *Clinical Cancer Research*: *An Official Journal of the American Association for Cancer Research*, **21**, 3727-3739. https://doi.org/10.1158/1078-0432.CCR-14-2824

[12] Klug, F., Prakash, H., Huber, P.E., Seibel, T., Bender, N., Halama, N., *et al*. (2013) Low-Dose Irradiation Programs Macrophage Differentiation to an iNOS^{+}/M1 Phenotype that Orchestrates Effective T Cell Immunotherapy. *Cancer Cell*, **24**, 589-602. https://doi.org/10.1016/j.ccr.2013.09.014

[13] Wang, Y., Deng, W., Li, N., Neri, S., Sharma, A., Jiang, W. and Lin, S.H. (2018) Combining Immunotherapy and Radiotherapy for Cancer Treatment: Current Challenges and Future Directions. *Frontiers in Pharmacology*, **9**, Article No. 185. https://doi.org/10.3389/fphar.2018.00185

[14] Thomas, D.A. and Massague, J. (2005) TGF-β Directly Targets Cytotoxic T Cell Functions during Tumor Evasion of Immune Surveillance. *Cancer Cell*, **8**, 369-380. https://doi.org/10.1016/j.ccr.2005.10.012

[15] Gorelik, L. and Flavell, R.A. (2001) Immune-Mediated Eradication of Tumors through the Blockade of Transforming Growth Factor-Beta Signaling in T Cells. *Nature Medicine*, **7**, 1118-1122. https://doi.org/10.1038/nm1001-1118

[16] Heeran, A.B., Berrigan, H.P. and O'Sullivan, J. (2019) The Radiation-Induced Bystander Effect (RIBE) and Its Connections with the Hallmarks of Cancer. *Radiation Research*, **192**, 668-679. https://doi.org/10.1667/RR15489.1

[17] Turgeon, G.A., Weickhardt, A., Azad, A.A., Solomon, B. and Siva, S. (2019) Radiotherapy and Immunotherapy: A Synergistic Effect in Cancer Care. *Medical Journal of Australia*, **210**, 47-53. https://doi.org/10.5694/mja2.12046

[18] Krombach, J., Hennel, R., Brix, N., Orth, M., Schoetz, U., Ernst, A., Schuster, J., Zuchtriegel, G., Reichel, C.A. and Bierschenk, S. (2019) Priming Anti-Tumor Immunity by Radiotherapy: Dying Tumor Cell-Derived DAMPs Trigger Endothelial Cell Activation and Recruitment of Myeloid Cells. *OncoImmunology*, **8**, e1523097. https://doi.org/10.1080/2162402X.2018.1523097

[19] McLaughlin, M., Patin, E.C., Pedersen, M., Wilkins, A., Dillon, M.T., Melcher, A.A. and Harrington, K.J. (2020) Inflammatory Microenvironment Remodelling by Tumour Cells after Radiotherapy. *Nature Reviews Cancer*, **20**, 203-217. https://doi.org/10.1038/s41568-020-0246-1

[20] Mehla, K. and Singh, P.K. (2019) Metabolic Regulation of Macrophage Polarization in Cancer. *Trends in Cancer*, **5**, 822-834. https://doi.org/10.1016/j.trecan.2019.10.007

[21] Yang, X., Guo, Y., Guo, Z., Si, T., Xing, W., Yu, W. and Wang, Y. (2019) Cryoablation Inhibition of Distant Untreated Tumors (Abscopal Effect) Is Immune Mediated. *Oncotarget*, **10**, 4180-4191. https://doi.org/10.18632/oncotarget.24105

[22] Reynders, K., Illidge, T., Siva, S., Chang, J.Y. and De Ruysscher, D. (2015) The Abscopal Effect of Local Radiotherapy: Using Immunotherapy to Make a Rare Event Clinically Relevant. *Cancer Treatment Reviews*, **41**, 503-510.

[23] Hu, Z.I., McArthur, H.L. and Ho, A.Y. (2017) The Abscopal Effect of Radiation Therapy: What Is It and How Can We Use It in Breast Cancer? *Current Breast Cancer Reports*, **9**, 45-51. https://doi.org/10.1007/s12609-017-0234-y

[24] Sun, Z., Chen, F., Meng, F., Wei, J. and Liu, B. (2017) MHC Class II Restricted Neoantigen: A Promising Target in Tumor Immunotherapy. *Cancer Letters*, **392**, 17-25. https://doi.org/10.1016/j.canlet.2016.12.039

[25] Sethuraman, S.N. and Ranjan, A. (2016) Neoantigen Activation, Protein Translocation and Targeted Drug Delivery in Combination with Radiotherapy. *Therapeutic Delivery*, **7**, 377-385. https://doi.org/10.4155/tde-2016-0005

[26] Marconi, R., Strolin, S., Bossi, G. and Strigari, L. (2017) A Meta-Analysis of the Abscopal Effect in Preclinical Models: Is the Biologically Effective Dose a Relevant Physical Trigger? *PLoS ONE*, **12**, e0171559. https://doi.org/10.1371/journal.pone.0171559

[27] Johnson, C.B. and Jagsi, R. (2016) The Promise of the Abscopal Effect and the Future of Trials Combining Immunotherapy and Radiation Therapy. *International Journal of Radiation Oncology*, *Biology*, *Physics*, **95**, 1254-1256.

[28] Twyman-Saint Victor, C., Rech, A.J., Maity, A., Rengan, R., Pauken, K.E., Stelekati, E., *et al*. (2015) Radiation and Dual Checkpoint Blockade Activate Non-Redundant Immune Mechanisms in Cancer. *Nature*, **520**, 373-377. https://doi.org/10.1038/nature14292

[29] Reits, E.A., Hodge, J.W., Herberts, C.A., Groothuis, T.A., Chakraborty, M., Wansley, E.K., *et al*. (2006) Radiation Modulates the Peptide Repertoire, Enhances MHC Class I Expression, and Induces Successful Antitumor Immunotherapy. *Journal of Experimental Medicine*, **203**, 1259-1271. https://doi.org/10.1084/jem.20052494

[30] Sato, H., Niimi, A., Yasuhara, T., Permata, T.B.M., Hagiwara, Y., Isono, M., *et al*. (2017) DNA Double-Strand Break Repair Pathway Regulates PD-L1 Expression in Cancer Cells. *Nature Communications*, **8**, Article No. 1751. https://doi.org/10.1038/s41467-017-01883-9

[31] Herbst, R.S., Soria, J.C., Kowanetz, M., Fine, G.D., Hamid, O., Gordon, M.S., *et al*. (2014) Predictive Correlates of Response to the Anti-PD-L1 Antibody MPDL3280A in Cancer Patients. *Nature*, **515**, 563-567. https://doi.org/10.1038/nature14011

[32] Sharabi, A.B., Lim, M., DeWeese, T.L. and Drake, C.G. (2015) Radiation and Checkpoint Blockade Immunotherapy: Radiosensitisation and Potential Mechanisms of Synergy. *The Lancet Oncology*, **16**, E498-E509. https://doi.org/10.1016/S1470-2045(15)00007-8

[33] Zheng, X., Fang, Z., Liu, X., Deng, S., Zhou, P., Wang, X., *et al*. (2018) Increased Vessel Perfusion Predicts the Efficacy of Immune Checkpoint Blockade. *The Journal of Clinical Investigation*, **128**, 2104-2115.

[34] O'Donnell, J.S., Teng, M.W.L. and Smyth, M.J. (2019) Cancer Immunoediting and Resistance to T Cell-Based Immunotherapy. *Nature Reviews Clinical Oncology*, **16**, 151-167. https://doi.org/10.1038/s41571-018-0142-8

[35] Ozpiskin, O.M., Zhang, L. and Li, J.J. (2019) Immune Targets in the Tumor Microenvironment Treated by Radiotherapy. *Theranostics*, **9**, 1215-1231. https://doi.org/10.7150/thno.32648

[36] Liu, Y., Dong, Y., Kong, L., Shi, F., Zhu, H. and Yu, J. (2018) Abscopal Effect of Radiotherapy Combined with Immune Checkpoint Inhibitors. *Journal of Hematology & Oncology*, **11**, Article No. 104. https://doi.org/10.1186/s13045-018-0647-8

[37] Levy, A., Chargari, C., Marabelle, A., Perfettini, J.L., Magné, N. and Deutsch, E. (2016) Can Immunostimulatory Agents Enhance the Abscopal Effect of Radiotherapy? *European Journal of Cancer*, **62**, 36-45.

[38] Shaverdian, N., Lisberg, A.E., Bornazyan, K., *et al*. (2017) Previous Radiotherapy and the Clinical Activity and Toxicity of Pembrolizumab in the Treatment of Non-Small-Cell Lung Cancer: A Secondary Analysis of the KEYNOTE-001 Phase 1 Trial. *The Lancet Oncology*, **18**, 895-903. https://doi.org/10.1016/S1470-2045(17)30380-7

[39] Maity, A., Mick, R., Huang, A.C., *et al*. (2018) A Phase I Trial of Pembrolizumab with Hypofractionated Radiotherapy in Patients with Metastatic Solid Tumours. *British Journal of Cancer*, **119**, 1200-1207. https://doi.org/10.1038/s41416-018-0281-9

[40] Young, K.H., Baird, J.R., Savage, T., Cottam, B., Friedman, D., Bambina, S., *et al*. (2016) Optimizing Timing of Immunotherapy Improves Control of Tumors by Hypofractionated Radiation Therapy. *PLoS ONE*, **11**, e0157164. https://doi.org/10.1371/journal.pone.0157164

[41] Antonia, S.J., Villegas, A., Daniel, D., Vicente, D., Murakami, S., Hui, R., *et al*. (2017) Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. *The New England Journal of Medicine*, **377**, 1919-1929.

[42] Lee, Y., Auh, S.L., Wang, Y., Burnette, B., Wang, Y., Meng, Y., *et al*. (2009) Therapeutic Effects of Ablative Radiation on Local Tumor Require $CD8^+$ T Cells: Changing Strategies for Cancer Treatment. *Blood*, **114**, 589-595. https://doi.org/10.1182/blood-2009-02-206870

[43] Lugade, A.A., Moran, J.P., Gerber, S.A., Rose, R.C., Frelinger, J.G. and Lord, E.M. (2005) Local Radiation Therapy of

B16 Melanoma Tumors Increases the Generation of Tumor Antigen-Specific Effector Cells that Traffic to the Tumor. *The Journal of Immunology*, **174**, 7516-7523. https://doi.org/10.4049/jimmunol.174.12.7516

[44] Kim, M.S., Kim, W., Park, I.H., Kim, H.J., Lee, E., Jung, J.H., *et al*. (2015) Radiobiological Mechanisms of Stereotactic Body Radiation Therapy and Stereotactic Radiation Surgery. *Radiation Oncology Journal*, **33**, 265-275. https://doi.org/10.3857/roj.2015.33.4.265

[45] Le, D.T., Uram, J.N., Wang, H., Bartlett, B.R., Kemberling, H., Eyring, A.D., *et al*. (2015) PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *The New England Journal of Medicine*, **372**, 2509-2520.

[46] Khagi, Y., Goodman, A.M., Daniels, G.A., Patel, S.P., Sacco, A.G., Randall, J.M., *et al*. (2017) Hypermutated Circulating Tumor DNA: Correlation with Response to Checkpoint Inhibitor-Based Immunotherapy. *Clinical Cancer Research*: *An Official Journal of the American Association for Cancer Research*, **23**, 5729-5736. https://doi.org/10.1158/1078-0432.CCR-17-1439

[47] Gopalakrishnan, V., Spencer, C.N., Nezi, L., Reuben, A., Andrews, M.C., Karpinets, T.V., *et al*. (2018) Gut Microbiome Modulates Response to Anti-PD-1 Immunotherapy in Melanoma Patients. *Science*, **359**, 97-103.