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Radiobiology of stereotactic radiotherapy

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ABSTRACT

This paper focuses on the radiobiological mechanisms underlying the effects of stereotactic radiotherapy (SRT) which, despite SRT expansion, have not yet been fully elucidated. Some authors postulated that radiobiology principles, as applied to conventional fractionations (5R: reoxygenation, repair, repopulation, redistribution, radioresistence), suffice in themselves to account for the excellent clinical results of SRT; others argued that the role of the 5R was limited. Recent preclinical data showed that hypofractionated ablative treatments altered the microenvironment, thus determining cell death either directly or indirectly. Furthermore, dead tumor cells released quantities of antigens, which stimulated antitumor immunity, thus reducing the risk of relapse and metastasis. Better understanding of the radiobiological mechanisms underlying response to high-dose radiation treatment is essential for predicting its short- and long-term effects on the tumor and surrounding healthy tissues and, consequently, for improving its related therapeutic index.

Key words: stereotactic radiotherapy; radiobiology; radiosurgery

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Introduction

Despite expansion of stereotactic radiotherapy (SRT), i.e., hypo-fractionated treatments with high doses per fraction, the radiobiological mechanisms underlying their effects have not yet been fully elucidated. Some authors postulated that radiobiology principles, as applied to conventional fractionations (5R: reoxygenation, repair, repopulation, redistribution and radioresistence), are enough to account for their excellent clinical results [1]; others argued that in the ablative hypofractionated setting, the role of the 5R was limited [2–7]. Recent preclinical data showed that hypofractionated ablative treatments altered the microenvironment, thus determining cell death either directly or indirectly [2–5]. Furthermore, dead tumor cells released quantities of antigens, which stimulated antitumor immunity, thus reducing the risk of relapse and metastasis [6, 7].

Better understanding of the radiobiological mechanisms underlying response to high-dose radiation treatment is essential for predicting its short- and long-term effects on the tumor and surrounding healthy tissues and, consequently, for improving its related therapeutic index. Beside the present article, this topic was recently explored in depth in excellent review articles which we refer the reader to [8–11].

The "5Rs" of radiobiology

The "5Rs" of radiobiology play a controversial role in hypofractionated schemes, especially with high doses per fraction [1, 4, 5].

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Re-oxygenation is believed to play little or no role in tumor response after single-fraction ablative treatments which are associated with widespread vascular destruction of tumors. Conversely, massive cell death with its drop in oxygen consumption, could favor re-oxygenation of surviving hypoxic cells [12]. Furthermore, vascular damage may be irrelevant after hypofractionation with doses of 3-8 Gy per fraction, which might thus lead to some reoxygenation [13, 14].

The hypofractionated schedules require prolonged delivery times, which were associated with around 10% loss of biological efficacy, particularly when they lasted over 30 minutes [15, 16]. They may interfere with sublethal damage repair, overwhelming repair mechanisms due to enzymatic pool depletion [17].

High single-dose fractionation blocks the cell in the cycle phase, thus interfering with redistribution. However, some cells may slowly progress to G2 and then die [2, 18, 19].

SRT hypofractionated schedules do not provide enough time for repopulation. In fact, the proliferation of surviving cells generally occurs 3–4 weeks after the start of radiation treatment [18]. Cell depletion could, however, determine some degree of repopulation which occurs 3–4 weeks afterwards, i.e., earlier than with conventional treatments [18].

The linear quadratic model

Mathematical formulas [biologically effective dose (BED), equivalent dose in 2 Gy fractions (EQ2)] based on the linear quadrant (LQ) model calculate the iso-effective doses for unconventional single fractions. As the LQ model derives mainly from in vitro studies, it does not perfectly reflect in vivo observations [20]. Although valid for fractions ranging from 1 to 5 Gy, its validity is doubtful when higher doses are used per fraction [20]. In vitro observations suggested the LQ model overestimated cell killing because it predicted a survival curve that continuously bent downward at high single doses whereas experimental data showed a constant slope [20]. In fact, lethal damage (linear component) predominated at large doses per fraction.

The LQ model does not take into account in vivo vascular damage after a single fraction high dose [20] or tumor stem cells which maintain the tumor pool and were associated with radioresistence [21]. Despite these data, experimental models and some clinical trials reported that the LQ model adapted adequately to SRT treatment response and was reliable for single fractions up to 10 Gy, becoming progressively less accurate as doses rose [1, 17]. As cell death is mediated directly and indirectly [18], the LQ formula, may not overestimate its rate but may well approximate the total SRT-induced cell death. Although the LQ model is still the most common, other models, such as the Universal Survival Curve (USC), were developed to compare conventional and high dose hypofractionated schemes [22, 23], and to provide empirical and clinical rationales for SRT [23].

Are tumor or endothelial cells the main radiobiological target of high-dose radiotherapy?

The radiobiological target of high-dose radiation treatments is highly debated. Even though Leith et al. calculated [24] at least 80–90 Gy in a single fraction were needed to control a 3 cm diameter brain tumor, many clinical studies showed that 18–25 Gy in a single fraction effectively controlled primary and metastatic central nervous system neoplasms [2–7, 15, 24–27]. Furthermore, when 5–7 cm liver tumors were treated with 54 Gy in 3 fractions, local control was over 90% at 2 years [28]. To justify these surprisingly better results [24], different radiobiological mechanisms were proposed. The main control point for irradiation-induced immune responses may be the vascular endothelium, which acted as a barrier regulating immune cell rolling on the vascular surface [29]. Several pieces of experimental evidence supported the hypothesis of endothelial cell damage [5, 30–32], with consequent tumor microenvironment deterioration and indirect hypoxia-related cell death [33]. Tumor endothelial cells were more radiosensitive than normal endothelial cells because of varying intrinsic radiosensitivity and structural differences [34, 35]. Doses over 10 Gy in a single fraction caused vascular damage like occlusion, vasodilation, vasoconstriction, and rupture [4, 5, 36–41] which reduced endotheliocytes in number and, consequently, perfusion [38, 42, 43]. Irradiation-induced endothelial cell death released anti-tumor signals, such as the TNF cytokine, which activated macrophages; the C-X-C motif chemokine ligand 6 (CXCL6) chemokine, which recruited immune cells and activated Toll-like receptors on dendritic cells [44]. The efficacy of SRT

when administered in hypoxic conditions was evaluated in pre-clinical and clinical studies. Compared with conventional fractionation, SRT reduced the cell killing of hypoxic cellular lines [45]. Furthermore, in an animal model, tumor control probability was lower when SRT was delivered to tumors irradiated at low partial pressure of oxygen (pO2) [46]. In the clinical setting, some studies confirmed that hypoxia, assessed by imaging, decreased the efficacy of SRT [47, 48]. Interestingly, in patients who had received SRT for the treatment of meningiomas, the expression of the endogenous marker of hypoxia hypoxia-inducible factor 1α (HIF-1α) negatively impacted on local control [49].

A single dose of 8–16 Gy increased acid sphingomyelinase (ASMase) expression, which contributed to post-irradiation inflammation and fibrosis. Within blood vessels, irradiation generated a prothrombotic state with platelet aggregation, microthrombosis and increased inflammatory-endothelial cell adhesion, with subsequent diapedesis to the perivascular space [50]. Endothelial cell exposure to radiation doses of > 0.5 Gy or < 10 Gy primarily caused their senescence [51].

In vivo studies supported the hypothesis that irradiation played an indirect role in vascular damage. Clonogenic survival was lower in tumor-bearing mice that were irradiated with single dose 10 Gy than in *in vitro* tumor samples [5, 33].

The dose for indirect death varied with factors, such as tumor type [4, 33] and vessel diameter, as small vessels seemed more vulnerable to radiation damage than large [52]. Despite these data, consensus is not unanimous on the main target in high dose hypofractionated treatments. In a recent murine model study, Moding et al. [53] argued it was the tumor rather than the endothelial cell, providing evidence that radioinduced tumor death did not change when endothelial cells were genetically engineered by deleting the Bax pro-apoptotic gene or the DNA damage response gene. While not excluding that other stromal cells may play a role in tumor eradication after SRT, the vascular damage contribution was reduced [53].

Antigen-induced damage and immune response

Other biological mechanisms are involved in the efficacy of high-dose ablative treatments. High dose hypofractionated irradiation was reported to promote antitumor immunity [6, 7], while low dose fractionated treatments suppressed host immunocompetence. Extensive cell death during hypofractionated irradiation increased expression of immunomodulatory molecules like the histocompatibility complex, adhesion molecules, heat shock proteins, inflammatory mediators, immunomodulatory cytokines and tumor cell surface death receptors [7, 54]. The massive release of tumor antigens and cytokines enhanced the innate antitumor response. In a mouse model, with an induced B16 melanoma, single dose 15 Gy increased the number of antitumor immune cells, facilitating antigen presentation, T lymphocyte priming in lymph nodes and effector T lymphocyte trafficking in tumors [55]. When the 15 Gy dose was fractionated in the same murine model, the immune response was weaker. Increasing the single dose up to 20 Gy augmented the immune response towards the primary tumor [55, 56]. Hypofractionated radiation therapy significantly inhibited tumor growth in immunocompetent, but not immunocompromised, mice [57]. Compared with conventional fractionation, hypofractionation reduced tumor recruitment of myeloid-derived suppressor cells and decreased their expression of programmed death-ligand 1 (PD-L1) [57]. Antitumor immunity was observed in clinical trials. A recent phase 1 study showed that the combination of interleukin 2 (IL-2) and SRT enhanced the immune response more than radiation therapy alone [58]. Ipilimumab, a CTL-associated antigen 4 (CTLA-4) ligand, associated with SRT (9.5 Gy in 3 fractions) was linked to an abscopal effect in metastatic melanoma [59]. The time-frames are worth noting. Generally speaking, tumor-specific radio-induced immunity cannot underlie the secondary death of tumor cells 2–3 days after radiation treatment as it completely developed within in 1–2 weeks. On the other hand, tumor-specific radio-induced immunity seemed to inhibit proliferation of surviving tumor cells, thus suppressing recurrences and metastases. As preclinical and clinical evidence continues to mount, immune-mediated tumor "rejection" is increasingly appreciated as the sixth "R" of radiobiology [60] and several clinical trials were initiated combining SRT with immunotherapy [61, 62].

The radiobiological immunologically effective dose (IED) model was recently developed for immuno-radiotherapy. Since the dose per fraction,

the time interval between fractions and the tumour radio sensitivity may all impact on the tumour antigen expression, the IED model was designed to predict the anti-tumour immune response after exposure to different RT schedules. Once this model is validated it may be used to select the most immunogenic RT schedules [63].

Conflicts of interest

The authors have no conflict of interest to declare.

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References

1. Brown JM, Carlson DJ, Brenner DJ. The tumor radiobiology of SRS and SBRT: are more than the 5 Rs involved? Int J Radiat Oncol Biol Phys. 2014; 88(2): 254–262, doi: 10.1016/j.ijrobp.2013.07.022, indexed in Pubmed: 24411596.
2. Song CW, Park H, Griffin RJ. et al. Radiobiology of stereotactic radiosurgery and stereotactic body radiation therapy. In: Levitt SH, Purdy JC, Perez CA, Poortmans P. ed. Technical basis of radiation therapy: practical clinical applications. 5th ed. Springer, New York 2012: 51–61.
3. Park HJ, Griffin RJ, Hui S, et al. Radiation-induced vascular damage in tumors: implications of vascular damage in ablative hypofractionated radiotherapy (SBRT and SRS). Radiat Res. 2012; 177(3): 311–327, doi: 10.1667/rr2773.1, indexed in Pubmed: 22229487.
4. Song CW, Cho LC, Yuan J, et al. Radiobiology of stereotactic body radiation therapy/stereotactic radiosurgery and the linear-quadratic model. Int J Radiat Oncol Biol Phys. 2013; 87(1): 18–19, doi: 10.1016/j.ijrobp.2013.03.013, indexed in Pubmed: 23608235.
5. Song CW, Park I, Cho LC, et al. Is indirect cell death involved in response of tumors to stereotactic radiosurgery and stereotactic body radiation therapy? Int J Radiat Oncol Biol Phys. 2014; 89(4): 924–925, doi: 10.1016/j.ijrobp.2014.03.043, indexed in Pubmed: 24969800.
6. McBride WH, Schaue D. In situ tumor ablation with radiation therapy: its effect on the tumor microenvironment and anti-tumor immunity. In: Keisari Y. ed. Tumor ablation: effects on systemic and local anti-tumor immunity and on other tumor-microenvironment interactions. Springer, New York 2013: 109–119.
7. Finkelstein SE, Timmerman R, McBride WH, et al. The confluence of stereotactic ablative radiotherapy and tumor immunology. Clin Dev Immunol. 2011; 2011: 439752, doi: 10.1155/2011/439752, indexed in Pubmed: 22162711.
8. Macià I Garau M. Radiobiology of stereotactic body radiation therapy (SBRT). Rep Pract Oncol Radiother. 2017; 22(2): 86–95, doi: 10.1016/j.rpor.2017.02.010, indexed in Pubmed: 28490978.
9. Song CW, Glatstein E, Marks LB, et al. Biological Principles of Stereotactic Body Radiation Therapy (SBRT) and Stereotactic Radiation Surgery (SRS): Indirect Cell Death. Int J Radiat Oncol Biol Phys. 2021; 110(1): 21–34, doi: 10.1016/j.ijrobp.2019.02.047, indexed in Pubmed: 30836165.
10. Li S, Shen L. Radiobiology of stereotactic ablative radiotherapy (SABR): perspectives of clinical oncologists. J Cancer. 2020; 11(17): 5056–5068, doi: 10.7150/jca.44408, indexed in Pubmed: 32742453.
11. Qiu B, Aili A, Xue L, et al. Advances in Radiobiology of Stereotactic Ablative Radiotherapy. Front Oncol. 2020; 10: 1165, doi: 10.3389/fonc.2020.01165, indexed in Pubmed: 32850333.
12. Shibamoto Y, Hashizume C, Baba F, et al. Stereotactic body radiotherapy using a radiobiology-based regimen for stage I nonsmall cell lung cancer: a multicenter study. Cancer. 2012; 118(8): 2078–2084, doi: 10.1002/cncr.26470, indexed in Pubmed: 22009495.
13. Hall EJ. Radiobiology for the Radiologist, 6th edn. Lippincott Williams and Wilkins, Philadelphia 2006.
14. Story M, Kodym R, Saha D. Exploring the possibility of unique molecular, biological, and tissue effects with hypofractionated radiotherapy. Semin Radiat Oncol. 2008; 18(4): 244–248, doi: 10.1016/j.semradonc.2008.04.006, indexed in Pubmed: 18725111.
15. Fowler JF, Welsh JS, Howard SP. Loss of biological effect in prolonged fraction delivery. Int J Radiat Oncol Biol Phys. 2004; 59(1): 242–249, doi: 10.1016/j.ijrobp.2004.01.004, indexed in Pubmed: 15093921.
16. Ling CC, Gerweck LE, Zaider M, et al. Dose-rate effects in external beam radiotherapy redux. Radiother Oncol. 2010; 95(3): 261–268, doi: 10.1016/j.radonc.2010.03.014, indexed in Pubmed: 20363041.
17. Brenner DJ. The linear-quadratic model is an appropriate methodology for determining isoeffective doses at large doses per fraction. Semin Radiat Oncol. 2008; 18(4): 234–239, doi: 10.1016/j.semradonc.2008.04.004, indexed in Pubmed: 18725109.
18. Kim MS, Kim W, Park InH, et al. Radiobiological mechanisms of stereotactic body radiation therapy and stereotactic radiation surgery. Radiat Oncol J. 2015; 33(4): 265–275, doi: 10.3857/roj.2015.33.4.265, indexed in Pubmed: 26756026.
19. Park H, Lyons J, Griffin R, et al. Apoptosis and Cell Cycle Progression in an Acidic Environment after Irradiation. Radiat Res. 2000; 153(3): 295–304, doi: 10.1667/0033-7587(2000)153[0295:aaccpi]2.0.co;2.
20. Kirkpatrick JP, Meyer JJ, Marks LB. The linear-quadratic model is inappropriate to model high dose per fraction effects in radiosurgery. Semin Radiat Oncol. 2008; 18(4): 240–243, doi: 10.1016/j.semradonc.2008.04.005, indexed in Pubmed: 18725110.
21. Thames HD, Withers HR, Peters LJ, et al. Changes in early and late radiation responses with altered dose fractionation: implications for dose-survival relationships. Int J Radiat Oncol Biol Phys. 1982; 8(2): 219–226, doi: 10.1016/0360-3016(82)90517-x, indexed in Pubmed: 7085377.
22. Tree AC, Khoo VS, van As NJ, et al. Is biochemical relapse-free survival after profoundly hypofractionated radiotherapy consistent with current radiobiological models? Clin Oncol (R Coll Radiol). 2014; 26(4): 216–229, doi: 10.1016/j.clon.2014.01.008, indexed in Pubmed: 24529742.
23. Park C, Papiez L, Zhang S, et al. Universal survival curve and single fraction equivalent dose: useful tools in understanding potency of ablative radiotherapy. Int J Ra-

diat Oncol Biol Phys. 2008; 70(3): 847–852, doi: 10.1016/j.ijrobp.2007.10.059, indexed in Pubmed: 18262098.
24. Leith JT, Cook S, Chougule P, et al. Intrinsic and extrinsic characteristics of human tumors relevant to radiosurgery: comparative cellular radiosensitivity and hypoxic percentages. Acta Neurochir Suppl. 1994; 62: 18–27, doi: 10.1007/978-3-7091-9371-6_5, indexed in Pubmed: 7717130.
25. Brown JM, Koong AC. High-dose single-fraction radiotherapy: exploiting a new biology? Int J Radiat Oncol Biol Phys. 2008; 71(2): 324–325, doi: 10.1016/j.ijrobp.2008.02.003, indexed in Pubmed: 18474308.
26. Kim YJ, Cho KHo, Kim JY, et al. Single-dose versus fractionated stereotactic radiotherapy for brain metastases. Int J Radiat Oncol Biol Phys. 2011; 81(2): 483–489, doi: 10.1016/j.ijrobp.2010.05.033, indexed in Pubmed: 20800386.
27. Folkert MR, Bilsky MH, Tom AK, et al. Outcomes and toxicity for hypofractionated and single-fraction image-guided stereotactic radiosurgery for sarcomas metastasizing to the spine. Int J Radiat Oncol Biol Phys. 2014; 88(5): 1085–1091, doi: 10.1016/j.ijrobp.2013.12.042, indexed in Pubmed: 24661662.
28. Jang WII, Kim MS, Bae SH, et al. High-dose stereotactic body radiotherapy correlates increased local control and overall survival in patients with inoperable hepatocellular carcinoma. Radiat Oncol. 2013; 8: 250, doi: 10.1186/1748-717X-8-250, indexed in Pubmed: 24160944.
29. Jaillet C, Morelle W, Slomianny MC, et al. Radiation-induced changes in the glycome of endothelial cells with functional consequences. Sci Rep. 2017; 7(1): 5290, doi: 10.1038/s41598-017-05563-y, indexed in Pubmed: 28706280.
30. Cramer W. Experimental observations on the therapeutic action of radium. Tenth Sci Rep Invest Imp Cancer Research Fund. 1932: 95–12229.
31. Lasnitzki I. A quantitative analysis of the direct and indirect action of X radiation on malignant cells. Br J Radiol. 1947; 20(234): 240–247, doi: 10.1259/0007-1285-20-234-240, indexed in Pubmed: 20243691.
32. Clement JJ, Tanaka N, Song CW. Tumor reoxygenation and postirradiation vascular changes. Radiology. 1978; 127(3): 799–803, doi: 10.1148/127.3.799, indexed in Pubmed: 663181.
33. Clement JJ, Song CW, Levitt SH. Changes in functional vascularity and cell number following x-irradiation of a murine carcinoma. Int J Radiat Oncol Biol Phys. 1976; 1(7-8): 671–678, doi: 10.1016/0360-3016(76)90149-8, indexed in Pubmed: 977401.
34. Oh ET, Park MT, Song MJ, et al. Radiation-induced angiogenic signaling pathway in endothelial cells obtained from normal and cancer tissue of human breast. Oncogene. 2014; 33(10): 1229–1238, doi: 10.1038/onc.2013.70, indexed in Pubmed: 23503466.
35. Garcia-Barros M, Paris F, Cordon-Cardo C, et al. Tumor response to radiotherapy regulated by endothelial cell apoptosis. Science. 2003; 300(5622): 1155–1159, doi: 10.1126/science.1082504, indexed in Pubmed: 12750523.
36. El Kaffas A, Giles A, Czarnota GJ. Dose-dependent response of tumor vasculature to radiation therapy in combination with Sunitinib depicted by three-dimensional high-frequency power Doppler ultrasound. Angiogenesis. 2013; 16(2): 443–454, doi: 10.1007/s10456-012-9329-2, indexed in Pubmed: 23314761.
37. Solesvik OV, Rofstad EK, Brustad T. Vascular changes in a human malignant melanoma xenograft following single-dose irradiation. Radiat Res. 1984; 98(1): 115–128, indexed in Pubmed: 6718687.
38. Kioi M, Vogel H, Schultz G, et al. Inhibition of vasculogenesis, but not angiogenesis, prevents the recurrence of glioblastoma after irradiation in mice. J Clin Invest. 2010; 120(3): 694–705, doi: 10.1172/JCI40283, indexed in Pubmed: 20179352.
39. Matsuya Y, Sasaki K, Yoshii Y, et al. Integrated Modelling of Cell Responses after Irradiation for DNA-Targeted Effects and Non-Targeted Effects. Sci Rep. 2018; 8(1): 4849, doi: 10.1038/s41598-018-23202-y, indexed in Pubmed: 29555939.
40. Merwin R, Algire GH, Kaplan HS. Transparent-chamber observations of the response of a transplantable mouse mammary tumor to local roentgen irradiation. J Natl Cancer Inst. 1950; 11(3): 593–627, indexed in Pubmed: 14824918.
41. Rubin P, Casarett G. Microcirculation of tumors part II: The supervascularized state of irradiated regressing tumors. Clin Radiol. 1966; 17(4): 346–355, doi: 10.1016/s0009-9260(66)80052-1, indexed in Pubmed: 5924244.
42. Wong HH, Song CW, Levitt SH. Early changes in the functional vasculature of Walker carcinoma 256 following irradiation. Radiology. 1973; 108(2): 429–434, doi: 10.1148/108.2.429, indexed in Pubmed: 4719050.
43. Song CW, Levitt SH. Vascular changes in Walker 256 carcinoma of rats following X irradiation. Radiology. 1971; 100(2): 397–407, doi: 10.1148/100.2.397, indexed in Pubmed: 5147407.
44. Venkatesulu BP, Mahadevan LS, Aliru ML, et al. Radiation-Induced Endothelial Vascular Injury: A Review of Possible Mechanisms. JACC Basic Transl Sci. 2018; 3(4): 563–572, doi: 10.1016/j.jacbts.2018.01.014, indexed in Pubmed: 30175280.
45. Carlson DJ, Keall PJ, Loo BW, et al. Hypofractionation results in reduced tumor cell kill compared to conventional fractionation for tumors with regions of hypoxia. Int J Radiat Oncol Biol Phys. 2011; 79(4): 1188–1195, doi: 10.1016/j.ijrobp.2010.10.007, indexed in Pubmed: 21183291.
46. Kirkpatrick JP, Cárdenas-Navia LI, Dewhirst MW. Predicting the effect of temporal variations in PO2 on tumor radiosensitivity. Int J Radiat Oncol Biol Phys. 2004; 59(3): 822–833, doi: 10.1016/j.ijrobp.2004.02.015, indexed in Pubmed: 15183486.
47. Qian Y, Von Eyben R, Liu Y, et al. F-EF5 PET-based Imageable Hypoxia Predicts Local Recurrence in Tumors Treated With Highly Conformal Radiation Therapy. Int J Radiat Oncol Biol Phys. 2018; 102(4): 1183–1192, doi: 10.1016/j.ijrobp.2018.03.045, indexed in Pubmed: 29859786.
48. Goodman KA, Sneed PK, McDermott MW, et al. Relationship between pattern of enhancement and local control of brain metastases after radiosurgery. Int J Radiat Oncol Biol Phys. 2001; 50(1): 139–146, doi: 10.1016/s0360-3016(00)01584-4, indexed in Pubmed: 11316557.
49. Jensen RL, Minshew L, Shrieve AF, et al. Stereotactic radiosurgery and radiotherapy for meningiomas: biomarker predictors of patient outcome and response to therapy. J Radiosurg SBRT. 2012; 2(1): 41–50, indexed in Pubmed: 29296341.

50. Carvalho Hd, Villar RC. Radiotherapy and immune response: the systemic effects of a local treatment. Clinics (Sao Paulo). 2018; 73(suppl 1): e557s, doi: 10.6061/clinics/2018/e557s, indexed in Pubmed: 30540123.
51. Wang Y, Boerma M, Zhou D. Ionizing Radiation-Induced Endothelial Cell Senescence and Cardiovascular Diseases. Radiat Res. 2016; 186(2): 153–161, doi: 10.1667/RR14445.1, indexed in Pubmed: 27387862.
52. Song CW, Levitt SH. Effect of x irradiation on vascularity of normal tissues and experimental tumor. Radiology. 1970; 94(2): 445–447, doi: 10.1148/94.2.445, indexed in Pubmed: 5412822.
53. Moding EJ, Castle KD, Perez BA, et al. Tumor cells, but not endothelial cells, mediate eradication of primary sarcomas by stereotactic body radiation therapy. Sci Transl Med. 2015; 7(278): 278ra34, doi: 10.1126/scitranslmed.aaa4214, indexed in Pubmed: 25761890.
54. Matsumura S, Wang B, Kawashima N, et al. Radiation-induced CXCL16 release by breast cancer cells attracts effector T cells. J Immunol. 2008; 181(5): 3099–3107, doi: 10.4049/jimmunol.181.5.3099, indexed in Pubmed: 18713980.
55. Lugade AA, Moran JP, Gerber SA, et al. Local radiation therapy of B16 melanoma tumors increases the generation of tumor antigen-specific effector cells that traffic to the tumor. J Immunol. 2005; 174(12): 7516–7523, doi: 10.4049/jimmunol.174.12.7516, indexed in Pubmed: 15944250.
56. Lee Y, Auh SL, Wang Y, et al. Therapeutic effects of ablative radiation on local tumor require CD8+ T cells: changing strategies for cancer treatment. Blood. 2009; 114(3): 589–595, doi: 10.1182/blood-2009-02-206870, indexed in Pubmed: 19349616.
57. Lan J, Li R, Yin LM, et al. Targeting Myeloid-derived Suppressor Cells and Programmed Death Ligand 1 Confers Therapeutic Advantage of Ablative Hypofractionated Radiation Therapy Compared With Conventional Fractionated Radiation Therapy. Int J Radiat Oncol Biol Phys. 2018; 101(1): 74–87, doi: 10.1016/j.ijrobp.2018.01.071, indexed in Pubmed: 29619980.
58. Seung SK, Curti BD, Crittenden M, et al. Phase 1 study of stereotactic body radiotherapy and interleukin-2--tumor and immunological responses. Sci Transl Med. 2012; 4(137): 137ra74, doi: 10.1126/scitranslmed.3003649, indexed in Pubmed: 22674552.
59. Postow MA, Callahan MK, Barker CA, et al. Immunologic correlates of the abscopal effect in a patient with melanoma. N Engl J Med. 2012; 366(10): 925–931, doi: 10.1056/NEJMoa1112824, indexed in Pubmed: 22397654.
60. Golden EB, Formenti SC. Is tumor (R)ejection by the immune system the „5th R" of radiobiology? Oncoimmunology. 2014; 3(1): e28133, doi: 10.4161/onci.28133, indexed in Pubmed: 24800177.
61. Kang J, Demaria S, Formenti S. Current clinical trials testing the combination of immunotherapy with radiotherapy. J Immunother Cancer. 2016; 4: 51, doi: 10.1186/s40425-016-0156-7, indexed in Pubmed: 27660705.
62. Gong J, Le TQ, Massarelli E, et al. Radiation therapy and PD-1/PD-L1 blockade: the clinical development of an evolving anticancer combination. J Immunother Cancer. 2018; 6(1): 46, doi: 10.1186/s40425-018-0361-7, indexed in Pubmed: 29866197.
63. Serre R, Barlesi F, Muracciole X, et al. Immunologically effective dose: a practical model for immuno-radiotherapy. Oncotarget. 2018; 9(61): 31812–31819, doi: 10.18632/oncotarget.25746, indexed in Pubmed: 30159124.