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Editorial Open Access

Dose Rate and Dose Painting

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Editorial

Tumor heterogeneity is one of the most important factors in tumor progression and recurrence after therapy. In this situation, delivery of a non-uniform dose would be optimum. Dose painting as a non-uniform dose distribution is a feasible strategy in radiation oncology. It requires imaging biomarkers to determine treatment sites which should receive higher doses. There are two main strategies for dose painting: by numbers (DPBN) and by contours (DPBC). In DPBC, tumour sub volumes receive a boosted dose, whilst DPBN is a voxel based issue and each voxel of tumour volume receives an individual dose prescription [1]. Based on molecular imaging data, dose painting involves four distinct steps including: "determination of the correlation between the underlying tumour biology and molecular imaging; determination of dose prescription function based on molecular imaging data; planning of the treatment and dose delivery; and assessment of the clinical outcomes in comparison with standard treatments" [2]. Molecular imaging (more PET) plays a rigorous role to find more accurate target volume, called biological target volume (BTV). Bentzen et al. mentioned there are three evidence based causes of treatment failure in radiation oncology including tumor burden, tumor cell proliferation, and hypoxia. They concluded that molecular imaging of those phenotypes using specific PET tracer can lead to find ideal painted dose distribution [3]. In the other hand, by introduction of cancer stem cells (CSCs) hypothesis and their highly radiation resistance, the mentioned triplet treatment failure (tumor burden, proliferation, and hypoxia) can be correlated to CSCs. Also, the main heterogeneity of tumors is due to CSCs theoretically. Multiple studies have shown that CSCs are highly radioresistance because they are hypoxic, have strong DNA repair and radical scavenging systems and they repopulate by a fast manner [4].

Dose painting delivery is highly dependent to machine and clinical beam [5]. As the aim of dose painting is biologically conformal dose distribution, machine system and beam characteristics should provide this conformity and tailor to produce dose distributions which consider mentioned triplet treatment failure. Dose rate effect in radiotherapy has been studied for years. Splitting a given total dose into many fractions underlines in the first line of dose rate effect. Fractionation preserves normal tissues as well as tumor cells due to recovery effect. Dose can be delivered by three main approaches of low, high and pulsed rates. In the present work, we aimed to discuss on the importance of dose rate in dose painting, means dose painting planning with triplet treatment failure phenotypes may be modified by dose rate.

In recent years, developed flattening filters free (FFF) machines and technical advances in clinical approaches, have opened a new horizon of potential influence of dose-rate on radioresponse in many treatment plans [6]. In dose painting we have many BTVs with different sizes and radiosensitivity. In this condition, normal tissue sparing is of importance. New study show ultrahigh dose-rate irradiation increases the differential response between normal and tumor tissue in mice [7]. Painted dose distribution with a high dose rate to BTV can improve therapeutic ratio. Although providing a high or ultrahigh dose rate is difficult, but it can be done by newer machines.

Proliferation is a basic problem in radiation oncology. Cell proliferation has a wide variety of difference among cancers. Different modified fractionation regimens are addressed to remediate this problem. Studies show low dose rate irradiation has beneficial effects on cell proliferation [8]. High dose rate irradiation can solve the problem of proliferation, but in balance with normal tissue sparing. One of the important factors influencing the response to radiation therapy is repair of sublethal damage taking place in the time needed to deliver the fractional dose. In a recent study Dasu et al. investigated the impact of increasing fraction delivery time on the outcome of hypofractionated radiation therapy for prostate cancer. They concluded that by increasing fraction delivery time, intra-fraction repair lead to loss of biological effect [9]. Due to time prolongation in dose delivery, IMRT can be considered as a problematic approach for dose painting. Scientific researchers have shown prolonged delivery times of photon fractions could have a significant impact on treatment outcome especially for tumors with a low alpha/beta ratio and short repair halftime [10]. Moiseenko et al. showed increasing the dose delivery time from 0.5 or 1 min to 30 or 60 min produced a significant increase in cell survival from 0.45 to 0.48 after 2 Gy, and from 0.17 to 0.20 after 4 Gy. They concluded when dose delivery is prolonged DNA repair increases [11]. As the main targets of dose painting are cancer stem cells and they have a high DNA repair capacity, this prolongation Hypoxia dose painting have been studied for some tumors and satisfied results have been achieved [12,13]. There is a relation between dose rate and treatment of hypoxic cells. Studies show low dose rate radiotherapy can be more efficient to remove hypoxic cells [14,15]. Based on Ling et al. experiment, oxygen enhancement ratio (OER) increases as dose rate decreases but by a variable manner [16]. For planning a hypoxic dose painting, after determination of hypoxic targets using molecular imaging, boost dose (higher dose) can be delivered in a given lower rate to achieve more efficiency. The dose rate effect and hypoxic cells killing can be more important in IMRT and brachytherapy dose painting. It was shown that intraoperative high-dose-rate brachytherapy using dose painting technique is feasible, safe, and allows for dose escalation in locally advanced or recurrent previously irradiated tumors [17]. Due to a very hypoxic microenvironment, CSCs are main targets for dose paining.

Dose rate is highly dependent on the type of machines. In conventional linacs it is governed by the overall beam-on-time and is different with newer linac versions such as volumetric-modulated arc therapy (VMAT) which may works with continuously variable dose rate (CVDR) or binned dose rates (BDR). The radiobiological effects of

dose rate need more animal and trial studies. Isotoxic planning by applying dose rate effects on TCP and NTCP may be a remedial approach.

As conclusion remark, it may be notified that CSCs are the main target of dose painting and heterogeneous dose should be delivered by a given dose rate. Since CSCs are highly hypoxic and repopulate fast, dose rate should be modified accordingly.

References

1. Shi X, Meng X, Sun X, Xing L, Yu J3 (2014) PET/CT imaging-guided dose painting in radiation therapy. Cancer Lett 355: 169-175.
2. Grégoire V, Jeraj R, Lee JA, O'Sullivan B (2012) Radiotherapy for head and neck tumours in 2012 and beyond: conformal, tailored, and adaptive? Lancet Oncol 13: e292-300.
3. Bentzen SM, Gregoire V (2011) Molecular imaging-based dose painting: a novel paradigm for radiation therapy prescription. Semin Radiat Oncol 21: 101-110.
4. Peitzsch C, Kurth I, Kunz-Schughart L, Baumann M, Dubrovska A (2013) Discovery of the cancer stem cell related determinants of radioresistance. Radiother Oncol 108: 378-387.
5. Galvin JM, De Neve W (2007) Intensity modulating and other radiation therapy devices for dose painting. J Clin Oncol 25: 924-930.
6. Ling CC, Gerweck LE, Zaider M, Yorke E (2010) Dose-rate effects in external beam radiotherapy redux. Radiother Oncol 95: 261-268.
7. Favaudon V, Caplier L, Monceau V, Pouzoulet F, Sayarath M, et al. (2014) Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice. Sci Transl Med 6: 245ra93.
8. Steel GG, Deacon JM, Duchesne GM, Horwich A, Kelland LR, et al. (1987) The dose-rate effect in human tumour cells. Radiother Oncol 9: 299-310.
9. Dasu A, Toma-Dasu I2 (2015) Will intrafraction repair have negative consequences on extreme hypofractionation in prostate radiation therapy? Br J Radiol 88: 20150588.
10. Joiner MC, Mogili N, Marples B, Burmeister J (2010) Significant dose can be lost by extended delivery times in IMRT with x rays but not high-LET radiations. Med Phys 37: 2457-2465.
11. Moiseenko V, Banáth JP, Duzenli C, Olive PL (2008) Effect of prolonging radiation delivery time on retention of gammaH2AX. Radiat Oncol 3: 18.
12. Thorwarth D, Eschmann SM, Paulsen F, Alber M (2007) Hypoxia dose painting by numbers: a planning study. Int J Radiat Oncol Biol Phys 68: 291-300.
13. Lin Z, Mechalakos J, Nehmeh S, Schoder H, Lee N, et al. (2008) The influence of changes in tumor hypoxia on dose-painting treatment plans based on 18F-FMISO positron emission tomography. Int J Radiat Oncol Biol Phys 70: 1219-1228.
14. Pettersen EO, Bjørhovde I, Søvik A, Edin NF, Zachar V, et al. (2007) Response of chronic hypoxic cells to low dose-rate irradiation. Int J Radiat Biol 83: 331-345.
15. Spiro IJ, Ling CC, Stickler R, Gaskill J (1985) Oxygen radiosensitisation at low dose rate. Br J Radiol 58: 357-363.
16. Ling CC, Spiro IJ, Mitchell J, Stickler R (1985) The variation of OER with dose rate. Int J Radiat Oncol Biol Phys 11: 1367-1373.
17. Morikawa LK, Zelefsky MJ, Cohen GN, Zaider M, Chiu J, et al. (2013) Intraoperative high-dose-rate brachytherapy using dose painting technique: evaluation of safety and preliminary clinical outcomes. Brachytherapy 12 :1-7.