Bystander Effect and Second Primary Cancers following Radiotherapy: What are its Significances?

Sir,

Over last two decades, there has been an increasing interest in bystander effect in radiotherapy. Now, millions of people around the world undergo radiotherapy. On the other hand, in parallel with recent progresses in cancer therapy, there is an increasing life expectancy for cancer patients. However, these may cause growing concerns related to long-term consequences of radiotherapy including secondary malignancies. These concerns are more important for pediatric cancer patients. The risk of secondary cancer among pediatric patients who have undergone radiotherapy is considered to be up to ten folds than in adult patients.[1]

Possibly, bystander effect is one of the most interesting biological responses to ionizing radiation that may be involved in second primary cancer occurring years after radiotherapy. According to the *in vitro* and *in vivo* studies conducted so far, there is a direct link between bystander effect and cancer hallmark in non-irradiated cells. The direct role of the bystander effect in the induction of medulloblastoma in the non-targeted brain of mice has been investigated by Mancuso *et al*.[2]

In clinical studies, the best example of the role of the bystander effect in second primary cancer induction, is a high incidence of secondary lung cancer among patients who have had radiotherapy for prostate, ovarian, and rectal cancer. Induction of secondary cancers is more obvious for long-term survivors.[3] The prevalence of secondary lung cancer among these patients has been one of the most common malignancies within years after treatment, while received radiation dose with lung has been reported as lower than 0.5 Gy.[4] Hence, in addition to the need to understand the importance of this phenomenon in different situations, it is crucial to consider bystander effect as an important factor in selecting the treatment modalities.

According to different studies that have been conducted so far, different biological and physical factors are involved in damages induced by bystander effect. Two important biological factors are sex specificity and tissue specificity. Similar to direct irradiation, bystander signals are more obvious in males as compared to females.[5] Among physical factors, the role of dose, dose rate, linear energy transfer (LET), and fractionation have been investigated in several *in vitro* and *in vivo* studies.[6] Although it is predictable that an increase in cell damage, along with the increased LET, results in more obvious damages in bystander cells, the effect of fractionation against direct irradiation has less sparing effect on bystander cells.[7] Moreover, the effect of dose and dose rate are controversial.[8]

To the best of our knowledge, the basic mechanisms of bystander effect include inflammatory responses, antioxidant system suppression, epigenetic modulators, and so on.[5,9,10] Although, it seems that complete mechanisms of this phenomenon remain to be elucidated. Based on the importance of bystander effect in radiation treatment of cancer, it seems that the risk of secondary malignancies caused by this phenomenon should be considered in the near future. For this aim, it is crucial we consider life expectancy and sex of patients, numbers of fractionation, LET, and other factors.

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Conflicts of interest

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Masoud Najafi, Ashkan Salajegheh[1], Abolhasan Rezaeyan[2]

Department of Medical Physics and Biomedical Engineering, Faculty of Medicine, Tehran University of Medical Sciences, [2]Department of Medical Physics, Faculty of Medicine, Iran University of Medical Sciences, Tehran, [1]Department of Radiology, School of Paramedical, Shiraz University of Medical Sciences, Shiraz, Iran

Address for correspondence: Dr. Masoud Najafi, Department of Medical Physics and Biomedical Engineering, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran.
E-mail: masoudnajafi67@yahoo.com

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