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Radiotherapy dose painting by circadian rhythm based radiomics

Hamid Abdollahi[a,b,*]

[a] Department of Radiologic Sciences and Medical Physics, Faculty of Allied Medicine, Kerman University of Medical Sciences, Kerman, Iran
[b] Student Research Committee, Faculty of Allied Medicine, Kerman University of Medical Sciences, Kerman, Iran

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ABSTRACT

Radiotherapy dose painting is a new dose delivery technique to achieve higher treatment outcome. In this approach, does is escalated to high progressive regions which are heterogeneous and determined by advanced medical imaging. Radiomics is issued as a feasible image quantification method to reveal tumor heterogeneity by extraction of high throughput mineable texture features. On the other hand, circadian rhythm is a given biological process that studied as a critical factor to obtain more effective treatment outcome. In this study, we hypothesized that radiotherapy dose painting could be enhanced by using circadian rhythm that is determined on the radiomics maps obtained from medical images. This hypothesis is based on the idea which circadian rhythm could change the tumor heterogeneity and therefore image features.

Introduction

Radiotherapy (RT) is a feasible approach to treat several cancers. A wide range of cancer patients receive radiation in terms of palliative or curative therapy [1]. The aim of RT is to deliver high radiation dose to the tumors and preserve surrounding normal tissues [2]. Modern RT techniques such as intensity-modulated RT (IMRT) and volumetric-modulated arc therapy (VMAT), and also brachytherapy, by a complex dose distributions deliver a lethal radiation dose to tumors, while nearby healthy tissue can be optimally spared [3]. In addition, image guided techniques have facilitated modern RT techniques.

Dose painting (DP) is a new proposed strategy in modern RT, by which, radiation dose is escalated to parts of the tumor that are particularly aggressive or radiation resistant, while dose to less aggressive parts is reduced [4–7]. This approach could be achieved by biological imaging and consequently finding biological heterogeneity in the tumors. For an effective DP, previous studies, have indicated that high-quality imaging of the tumor and surrounding tissue is required [8]. In this topic, some clinical studies have applied positron emission tomography (PET) and functional magnetic resonance imaging (FMRI) as advanced molecular imaging techniques for DP [7].

Intra-tumor heterogeneity has been reported in many cancers and be associated with adverse clinical outcomes such as treatment failure, radiation/drug resistance and lower survival rate [9]. This heterogeneity has been observed more in malignant tumors at the histological and genetic levels and can be caused by variations in cellularity, angiogenesis, extracellular matrix, or necrosis [10]. Intra-tumor heterogeneity assessment is an advanced way to facilitate personalized therapy. But studies have indicated that the current methods for heterogeneity assessment suffer from several challenges and limitations such as invasiveness and low sensitivity/specificity [10].

Radiomics is a new advanced image quantification method that extract mineable data from medical images and profiles the tumor heterogeneity [11]. On the use of radiomics for tumor heterogeneity assessment, several studies have revealed that radiomics textures/features extracted from computed tomography (CT), PET and MRI could enhance the detection and prediction of tumor heterogeneity and its consequences (e.g. treatment resistance or failure) with high accuracy, sensitivity and specificity [12–17]. In addition, advanced radiomics studies have identified that radiomics features are feasible issues for tumor detection, cancer subtype classification, and treatment/survival response assessment and prediction.

Circadian rhythm (CR), is a fundamental biological system that regulates behavioral and physiological processes in a rhythmic manner, in response to external factors [18]. There is substantial evidence that, the inclusion of circadian rhythms in RT or other treatments schedules, so called chronotherapy, affects the treatment outcome in cancer patients [19]. Some studies reported that chronotherapy have a great impact on radiation-induced side effects and some others observed that this issue affects the tumor treatment response [20,21]. The chronotherapy is revealed as a more effective parameter for chemotherapy patients. However there are numerous studies on the Chrono-

* Address: Department of Radiologic Sciences and Medical Physics, Faculty of Allied Medicine, Kerman University of Medical Sciences, Medical University Campus, Haft-Bagh Highway, Kerman, Iran.
E-mail address: hamidrbp60@gmail.com.

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radiotherapy effectiveness in lung, breast, rectal, prostate, cervical, head and neck and brain cancers and also in bone and brain metastases [22].

It is demonstrated that circadian properties of tumors are complex and also complexity of the tumor microenvironment and cellular heterogeneity are due to complexity of tumor's CRs. On the other hand, disruption of CR is a determinant factor for tumor initiation, progression and metastasis [23]. In addition CR has crucial roles in cell proliferations, repair, apoptosis, cellular radiosensitivity and radioresistance [24].

The hypothesis

In this study, we hypothesize that radiotherapy dose painting could be enhanced by using circadian rhythm that is determined on the radiomics maps obtained from medical images. This hypothesis is based on the idea that circadian rhythm have a crucial role in tumor heterogeneity and therefore radiomics image features.

Evaluation of the hypothesis

To understand, conduct and evaluate of this hypothesis, the following items are proposed as was detailed in Fig. 1:

1. High quality medical imaging of tumor

This is the first and important section of this idea. To conduct that, there are needs to tumors be imaged by advanced medical imaging modalities including CT, MRI, PET or another imaging such as optical/fluorescence imaging and single photon emission CT (SPECT). The images have to be obtained by high resolution and details with the lowest levels of noise and artifacts and by same settings and operators.

2. Radiomics analysis

For radiomics analysis, tumors on images are segmented and after that, radiomics features are extracted. Radiomics features could be from several feature sets including first orders, textures, shape based and higher order features. Examples for radiomics feature sets are intensity histogram, co-occurrence matrix (GLCM), gray level run length matrix (GLRLM), gray level dependence matrix (GLDM); gray level size zone matrix (GLSZM) and neighboring gray tone difference matrix (NGTDM) and standard uptake value (SUV) which is extracted just form PET images. Radiomics feature maps are also obtained from images. These maps are images which could be obtained by applying feature's equations on the segmented images.

3. Radiomics based heterogeneity assessment

To assess tumor heterogeneity, radiomics feature maps are compared among tumors and different regions of tumors are observed. This heterogeneity is validated by registration of extracted biopsies from tumors on the radiomics maps and original images by several authors [25].

4. Circadian rhythm analysis

In this section, the circadian rhythm of tumors are determined by genetic, hormone, signal and image analysis.

5. Circadian rhythm based heterogeneity assessment

Circadian rhythm based heterogeneity assessment is the critical part of this idea. To make this issue feasible, it is necessary to find correlation between regions with different heterogeneity and circadian rhythms.

6. Finding correlation between circadian rhythm and radiomics

In this section heterogeneity obtained from radiomics maps and circadian rhythms are correlated and regions with high correlations are selected for dose painting.

7. Dose painting by circadian rhythm based radiomics

Finally, RT planning is done for dose painting on the correlated circadian-radiomics maps and regions with higher heterogeneities and aggressiveness receive more radiation dose. The outcome of this strategy are compared with control groups. This scenario, at first, has to be investigated in animal models and several trials are warranted before

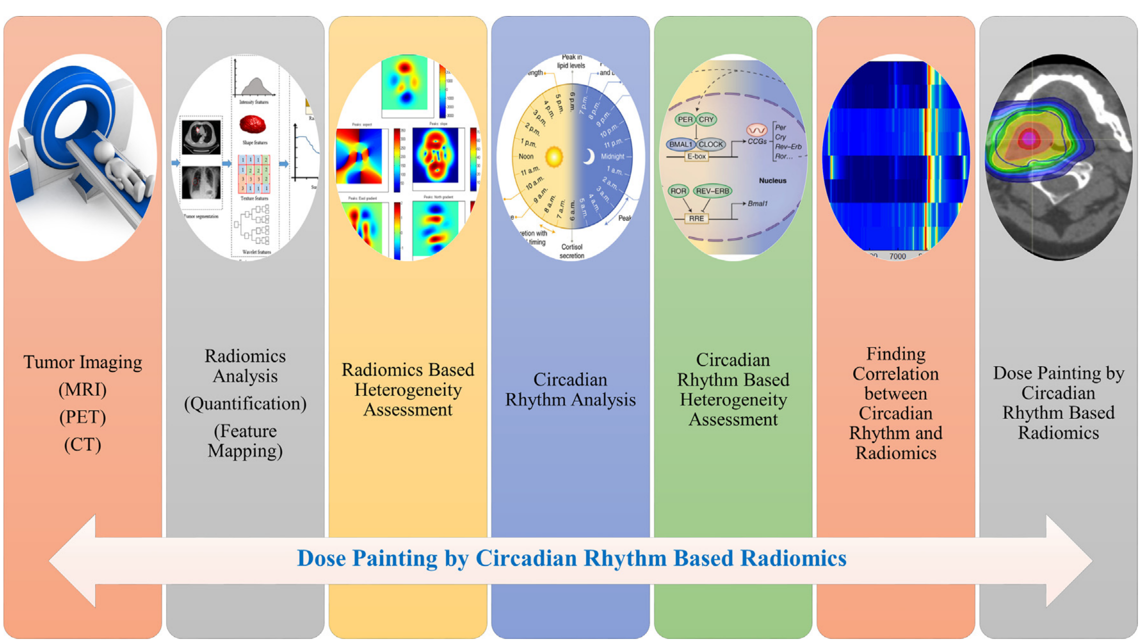

Fig. 1.

any clinical settings.

Discussion

Radiation dose delivery remains the main and critical part of radiotherapy planning. In previous studies, two dose painting strategies including by numbers and by contours are described. By number is voxel based and each voxel of tumor volume receives an individual dose prescription and in by contour, tumor sub volumes receive a boosted dose [26]. These suggested scenarios have been tested in several studies and have several limitations in their commissioning [27–31].

In the present hypothetical research, we suggested radiotherapy dose painting by circadian rhythm based radiomics which is a combination of imaging and circadian rhythm in tumors with high heterogeneity. Our idea is based on these facts that 1) radiomics maps are polished mirrors of tumor heterogeneity and 2) circadian rhythm is an approved biological system which has crucial role in tumor heterogeneity. By these facts and by more understand biological mechanisms, our idea could be translated to the clinics.

Radiomics features are mathematical equations that are applied on the images and convert them to high throughput minable data or image with different maps. These parameters have been found much interests among researchers, but their biological mechanisms are not clearly understood. Comprehensive radiogenomics studies have significantly increased our understanding of tumor heterogeneity by correlation of radiomics and genomics analysis [32–35]. These studies have identified that genomics alterations in many cancers such as "mutations in DNA sequence, DNA copy number changes, aberrant DNA promoter methylation, changes in mRNA, microRNA (miRNA) and protein expression, as well as changes in the tumor microenvironment" could be decoded by radiomics features extracted from cancer images [36].

On the use of circadian rhythm, chronotherapy is found as a feasible paradigm to treat cancers more effectively [37,38]. In our idea, we hypothesized that because circadian rhythm is a key regulator of tumor cell cycle and its microenvironment, it has a critical role in tumor heterogeneity [39,40]. In this light, radiotherapy dose enhancement in terms of dose painting based on the circadian rhythm may be an alternate strategy for more effective cancer therapy.

Conclusion

In this study we suggested radiotherapy dose painting by circadian rhythm based radiomics. It is an idea which could be tested by several radiogenomics, radiometabolomics and radioproteomics trials in cellular, animal and trial levels. At the clinical level, this idea may results in elevated treatment outcome in terms of higher tumor control and lower normal tissue complications. Mathematical modelling based on the biological and imaging findings will results in more accurate dose painting by circadian rhythm based radiomics.

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