Cancer Letters 355 (2014) 169–175

Contents lists available at ScienceDirect

Cancer Letters

journal homepage: www.elsevier.com/locate/canlet

Mini-review

PET/CT imaging-guided dose painting in radiation therapy

Xiaorong Shi [a,b,1], Xue Meng [a,1], Xindong Sun [a], Ligang Xing [a], Jinming Yu [a,*]

[a] Department of Radiation Oncology, Key Laboratory of Radiation Oncology of Shandong Province, Shandong Cancer Hospital, Shandong University, Jinan, Shandong Province, China
[b] Department of Oncology, Tangdu Hospital, Fourth Military Medical University, Xi'an, Shanxi Province, China

ARTICLE INFO

Article history:
Received 18 May 2014
Received in revised form 17 July 2014
Accepted 26 July 2014

Keywords:
Functional imaging
RT treatment planning
Dose painting by contours
Dose painting by numbers

ABSTRACT

Application of functional imaging to radiotherapy (RT) is a rapidly expanding field with the development of new modalities and techniques. Functional imaging of PET in conjunction with RT provides new avenues towards the clinical application of dose painting – a new RT strategy delivering optimized dose redistribution according to the functional imaging information to further improve tumour control. Two prototypical strategies of dose painting are reviewed: dose painting by contours (DPBC) and dose painting by numbers (DPBN). DPBN set a linear correlation of the boost dose and image intensity of this same voxel while homogeneous dose is given to the subvolume contoured by a threshold created in PET images in DPBC. Both comply with strict organs at risk (OAR) constraints and are alternatives for boosting subvolumes in clinical practice. This review focuses on the rationale, target validation, dose prescription verification and evaluation and recent clinical achievements in the field of integrating PET imaging into RT treatment planning. Further research is necessary in order to investigate unresolved problems in its routine clinical application thoroughly.

Introduction

It is illustrated that there is a strong correlation between local-regional control (LRC) and overall survival (OS) [1–4]. A straightforward way to improve local tumour control that proved by large bodies of evidence is to increase the radiation dose further [1,5–7]. However, we seem passive in the battle with cancer since the OS is not in keep with the clear improvement in various new modalities and techniques of treating cancer over decades. Current treatment prescriptions are already close to patient tolerance making it nearly impossible to raise the dose prescription of the whole target tumour. The failure of Radiation Therapy Oncology Group (RTOG) 0617 which beyond our widest expectation is another robust evidence. The side effects of pulmonary or cardiopulmonary from high thoracic radiation dose are the most likely explanation of the failure based on the finding of the RTOG 0617 [8]. It illustrates the need for a more stringent application of the dose escalation as the potential for heightened toxicity of the higher dose. Then limited by tolerances of organs at risk (OAR), the idea of raising the target dose only to the functional subvolumes within the tumour, which are supposed to be more radio-resistant, seems promising and practical [9].

New biological imaging methodologies, mainly based on positron emission tomography/computed tomography (PET/CT), magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) imaging, in conjunction with radiotherapy (RT), make dose painting possible. It can be used to draw a three-dimensional map of radiobiological relevant parameters as its inherent potential to trace the real target volume – volume consisting of tumour cells that requires a therapeutic dose to control the disease. PET/CT is outstanding and widely used in daily clinical practice. It offers molecular biological information about the tumour microenvironment in addition to anatomical imaging and shows significant biological heterogeneity of tumours, such as metabolism, proliferation, hypoxia, radio-resistance cell density, and perfusion [10]. Dose escalation to the definite radio-resistant subvolumes present on PET imaging makes the burden of the normal tissues constant, or even decreased. Exploration is hot regarding this new field. The new combination will revolutionize the way that RT is prescribed and planned and may improve the therapeutic outcome in terms of LRC with current available clinical data. The article here is meant to review the current status of implementation of biologic heterogeneity that showed in PET/CT imaging in dose planning and to identify whether the new combination can make a practical clinical profit. Also, the

Abbreviations: RT, radiotherapy; DPBC, dose painting by contours; DPBN, dose painting by numbers; OAR, organs at risk; LRC, local-regional control; OS, overall survival; RTOG, Radiation Therapy Oncology Group; PTV, planning target volume; LRF, local-regional failure; GTV, gross target volume; BTV, biological target volume; SBRT, Stereotactic Body Radiation Therapy; NSCLC, non-small cell lung cancer; SUV, standardized uptake values; MLC, multi leaf collimator; LCR, local control rates; BED, bioequivalent dose; IMRT, Intensity-modulated radiation therapy; MLD, mean lung dose; TCP, tumour control probability; NTCP, normal tissue complication probability.

* Corresponding author. Tel.: +86 531 87984729; fax:+86 531 87984079.
E-mail address: jn7984729@public.jn.sd.cn (J. Yu).

[1] Equal contributors (Co-first author).

http://dx.doi.org/10.1016/j.canlet.2014.07.042
0304-3835/

key challenges involved in daily clinical application of the new RT strategies will be addressed.

Validation of dose painting target volume in PET/CT imaging

Firstly, the validation of a dose painting target necessarily requires a complete analysis of the correlation between the patterns of failure and the planning target volume (PTV) on molecular imaging of PET/CT. There are several emerging data analyses on the relationship of the exact anatomical site of local-regional failure (LRF) and the pretreatment PET/CT defined tumour site. In a study of locally-advanced head and neck cancers treated using PET/CT based IMRT planning, the results were very impressive: the gross target volume (GTV)-recurrent was completely encompassed by PTV (70 Gy) in 19/31 cases; 8/31 patients had recurrent disease extending from inside PTV into the low dose region, 3/31 patients failed in the low dose region alone (50.4 Gy) [11]. Then Madani et al. figured out that only 33% (3/9) LRF of head and neck cancer was outside the PET-biological target volume (PET-BTV) [12]. A more encouraging evidence was given by Soto and Dirix. Soto et al. declared that 100% (9/9) of failures were inside the GTV for patients with head and neck cancer [13]. Similarly, Dirix et al. concluded that all local-regional recurrences were within the (18) F-FDG-avid regions on baseline (18) F-FDG PET [14]. Most failures after Stereotactic Body Radiation Therapy (SBRT) treatment for recurrent head and neck cancer were partial or complete within the PTV, i.e. In-field (>75% inside PTV) – 12.3%, Overlap (20–75% inside PTV) – 24.6%, Marginal (<20% inside PTV but closest edge within 1 cm of PTV) – 36.8% [15]. There were some similar results shown in the non-small cell lung cancer (NSCLC): the location of residual metabolic-active areas after therapy which indicates worse survival corresponded with the high FDG-avid regions pre-radiotherapy [16]. And in a study of Abramyuk et al., 10 patients of NSCLC who received curative RT (66 Gy) with local-regional relapse afterwards were analysed retrospectively, 6 of 10 recurrences were localized partially or completely in the irradiated target volume with high initial metabolic activities on PET images [17].

In literature, there are various segmentation strategies to define the area with high-affinity tracer uptake and metabolism, including thresholding, region growing, classifiers, clustering, edge detection, Markov random field models, deformable models and many other approaches. But in clinical trials, thresholding is commonly used: standardized uptake values (SUV) > 2.5, 38%, 42%, 47% and 50% of the maximum standardized uptake values (SUVmax) in FDG PET/CT; 80% SUVmax in FLT PET/CT; 60% and 70% SUVmax in 11C-choline PET/CT; SUV 1.4 in FMISO or FLT PET/CT et al. More researches are needed to identify the optimal image segmentation approaches which reproducibly and accurately identify the high recurrent-risk regions to match the specificity of each particular cancer imaging probe and tumour type.

Dose painting strategies in PET/CT imaging

For a nonuniform radiosensitivity distribution of tumour, a distribution that delivers a relatively higher proportion of the integral tumour dose to the more resistant regions of the tumour (the core of dose painting) seems more logical compared with an uniform dose distribution. Different dose painting strategies to shape the radiation dose according to the functional image information have been proposed recently: dose escalation and dose redistribution. Dose escalation applies an additional dose to the functional subvolumes of the target whereas dose redistribution consists of increasing the dose to the radio-resistant areas while reducing the dose to the rest of the tumour in a way to keep the mean dose constant. The researches now mainly focus on dose escalation.

There are two strategies for the realization of dose escalation: dose painting by contours (DPBC) and dose painting by numbers (DPBN). DPBN intends to increase the additional dose gradually, according to the local PET voxel intensities, while a homogeneous dose of BTV which contoured by a threshold created in PET image is given in DPBC.

DPBC creates a boost subvolume within the tumour by a certain threshold. The areas of relatively lower and higher risk for recurrence are set fixed to voxels with a corresponding standardized uptake value (SUV) < threshold and SUV > threshold, respectively. In general, treatment application and also planning for DPBC can be realized by using the simultaneous integrated boost (SIB) technique. Troost et al. thinks that dose escalation to a relatively small subvolume by DPBC can be realized with meeting the limited dose criterion of the surrounding normal tissues and thus might be better tolerated by patients [18]. The strategy that a homogeneous boost dose is assigned to the subvolume has been fulfilled in many clinical trials.

DPBN is a method in which a continuously increasing relationship is set between the voxel values of the functional imaging and the risk of local recurrence by using a linear correlation of the boost dose and image intensity of this same voxel. The technical feasibility of DPBN is already shown by many groups [19–21]. Dose prescription with applicable steep gradients can be delivered to the numerous mini-subvolumes by means of a conventional linear accelerator equipped with a high resolution micro multi leaf collimator (MLC) [22]. Rickhey et al. showed that the DPBN approach in brain tumours by 18F-FET-PET was achievable with high accuracy [23]. Alternatively, 18[F]-FDG-PET-guided DPBN using currently available technique was proved to be feasible in phase I clinical trial by Berwouts et al. in head and neck RT [24].

For both DPBC and DPBN plans, strict planning constraints set for the OAR should be complied, in addition, the feasibility of technique is proved by the evidence mentioned above, thus both are therefore considered clinically acceptable and alternatives for boosting subvolumes.

Verification of maximum dose and evaluation of dose painting planning

With the current evidence, it tends to believe that higher dose prescription leads to lower risk of local failure. Given the fact that a dose range of 1–5 Gy per fraction is suitable in modelling of tumour response by the linear–quadratic equation and the dose–response curves presents a negative correlation between cell survival with dose, the higher dose of subvolumes in dose painting could prominently decrease the amount of tumour cells and thus improve the local control [25]. In the viewpoints of Bradley [6] and Fowler et al. [26], local control rates (LCR) over 90% can be reached when 120 Gy is given to the tumour. Similar opinions have been expressed that the potency of the dose regimen was significantly associated with LCR, patients received bioequivalent dose (BED) < 100 Gy had a 16.7% risk of local failure compared with 2.3% for patients BED >100 Gy, suggesting that high dose regimens (BED >100 Gy) should be adopted because of lower risk for local failure [27]. In a previous study by Shaw et al., it was shown that larger target volume had a potential of being delivered with lesser dose because of normal issues tolerance [28]. Thus, we attempt to push the dose of small subvolumes with acceptable toxicity to resolve the paradox. DPBC results in relatively steeper dose gradients as it is binary, contrary to that, the escalated dose in DPBN takes place within numerous subvolumes inside the target volume according to the level of tracer uptake. The dose gradients at the boundary of the target volume remain almost the same as in conventional IMRT treatment planning. Therefore, the dose to the tracer-avid areas on PET imaging can be raised remarkably at an acceptable normal tissue burden simultaneously [23].