Functional image-guided intensity modulated radiation therapy: Integration of the tumour microenvironment in treatment planning

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Radiation oncology has never been more integrated in the multidisciplinary treatment approach of cancer than it is today. This results, in part, from pivotal prospective or retrospective clinical studies that have demonstrated, with an irrefutable level of evidence, the need for radiotherapy as a sole treatment modality or in combination with other options such as surgery, chemotherapy and, more recently, biological targeted agents [1]. It results also from the tremendous technological innovations that have been made available to the radiation oncology community at large. Among these progresses, Intensity Modulated Radiation Therapy (IMRT) with on-board imaging capability enables the delivery of a radiation dose with a degree of accuracy that has never been achieved before. Such improvements in accurate dose delivery have led to improved loco-regional control probability with reduced morbidity [2].

These dramatic improvements in dose delivery have progressively shed light on the difficulties and limitations in target volume definition. Typically, the gross target volume (GTV), defined as the bulk of disease, has always been delineated using computed tomography (CT) scans and/or for some specific locations (e.g. brain or prostate tumors) with magnetic resonance imaging (MRI). More recently, functional imaging with positron emission tomography (PET), using fluoro-deoxyglucose (FDG) as tracer, has been advocated for very specific tumour sites. The clinical advantage of FDG-PET has been demonstrated for the diagnosis, staging and therapeutic response evaluation in several tumour sites such as lung, oesophagus and lymphoma [3]. For treatment planning in radiotherapy, FDG-PET has demonstrated clinical use in non-small cell lung cancers (NSCLC) where it helps to exclude the retro-obstructive atelectasis from the tumuor bulk, thus allowing a substantial sparing of normal lung tissue [4,5]. In head and neck tumours, it has been shown that FDG-PET is more specific and more sensitive for the delineation of pharyngo-laryngeal tumours compared to conventional anatomic imaging with CT or MRI [6]. These differences in volume delineation between imaging modalities translate into differences in dose distribution, in particular reducing the dose delivered to the surrounding normal tissues [7]. In brain tumours, FDG-PET has limited value for target volume delineation, but more specific tracers have been evaluated and have shown great promise [8]. In rectal cancer, FDG-PET-CT has been compared with CT for target volume delineation [9]. In short, these studies reported some conflicting data regarding the integration of FDG-PET with CT for the delineation of the GTV in rectal cancer. These findings illustrate the need to develop reliable and validated delineation methods, especially for FDG-PET volumes. These methods should be validated with a pathological specimen used as the "ground truth".

The concept of GTV as presently used, although very operational, is an oversimplification of the reality, as it does not really approach the complexity of tumour biology. First, it is indeed based on the hypothesis that a tumour is a homogeneous entity with a homogeneous distribution of tumour clonogens, thus requiring an even dose distribution; second, it is based on the hypothesis that a tumour is a static entity which does not change during the course of radiotherapy, typically spread over 5 to 7 weeks. More and more evidences are challenging these two hypotheses. Biological data have been collected indicating that tumours are highly heterogeneous and dynamic with regards to their genetic profile and microenvironment, both factors being crucial for their radiation response. For example, Geets and colleagues demonstrated that during a typical treatment with concomitant chemo-radiation, head and neck tumours progressively shrunk; the dose distribution could then be progressively adapted leading to a high dose distributed to a smaller volume enabling more

sparing of the surrounding normal tissues [7,10]. The benefit of adaptive treatment (adaptive IMRT) was more pronounced with the use of FDG-PET images compared to anatomical images with CT or MRI. Roels and colleagues investigated different biological characteristics of rectal cancer with three PET tracers. PET-CTs with FDG, fluorothymidine (FLT) and fluoro-misonidazole (FMISO) were performed in order to evaluate, respectively, glucose metabolism, cellular proliferation and hypoxia within the tumour. The authors found that the mean FDG, FLT and FMISO-PET tumour volumes showed a tendency to shrink during preoperative chemoradiation. FLT and FDG showed good spatial correspondence, while FMISO seemed less reliable due to the non-specific uptake in the normal bowel wall [11,12].

The above-mentioned data suggest that the consideration of the biological heterogeneity of tumours and its variation with time during a course of radiotherapy might be helpful for the GTV delineation. Functional imaging with PET could allow a segmentation of the anatomic tumour volume into several so-called "biological target volumes", each of them identifying a fraction of the tumour expressing a relevant prognostic factor for radiation response. We could then sculpt or paint the radiation dose according to these various volumes, delivering for example a higher dose to the sub-GTV with a high hypoxic fraction [13]. In this respect, a "proof of concept" study has been reported with ^{60}Cu-ATSM-PET, a so-called hypoxic tracer, which was used to guide IMRT in head and neck tumours [14]. Although what this hypoxic tracer really visualises is not totally understood, this study was the first to illustrate the feasibility of a biological image-guided IMRT.

In summary, recent progresses in functional imaging of relevant biological pathways for radiation response using PET open a new avenue for the delineation of target volumes before and during radiotherapy treatment. A more elaborate delineation, taking into account not only the anatomic aspects but also the biological components of tumours, should allow a more tailored and refined dose prescription and dose distribution. Altogether, such improvements offer the prospect of an increased probability of tumour response with a consequent potential gain in survival.

Conflict of interest statement

None declared.

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