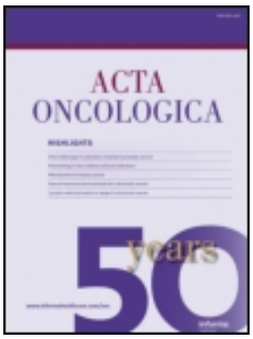

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EDITORIAL

Biology-guided adaptive radiation therapy – presence or future?

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The present issue of Acta Oncologica contains a large number of publications from the 2010 Acta Oncologica Symposium held in Aarhus, Denmark May 26–28, 2010. The symposium was dedicated to aspects of Biology-Guided Adaptive Radiation Therapy (BiGART). A broad faculty of distinguished international scientists presented state-of-the-art of the research field, and a record number of abstracts were received for the proffered paper sessions. It is our hope that both the meeting and the papers in the current issue will provide new insight into the biological background of, and potential clinical benefit from, adaptive radiotherapy.

Acta Oncologica has sponsored scientific symposia since 1989. The aim of this activity is to focus on emerging issues in oncology, preferably with a multidisciplinary approach. Topics have over the years included sentinel lymph node biopsy in breast cancer [1], prostate cancer [2], stereotactic body radiotherapy [3–6], normal tissue morbidity [7,8], breast cancer [9], and most recently, image-guided radiotherapy (IGRT) [10–14]. The 2008 IGRT conference was held in conjunction with the annual meeting of the Nordic Association of Clinical Physicists (NACP) [15–18].

On the agenda of the 2010 Acta Oncologica symposium on BiGART were three timely and instrumental topics:

1. The underlying biology of therapy response on which adaptation may be founded;
2. Molecular and functional imaging as non-invasive tools for providing the pertinent information for treatment adaptation;
3. treatment adaptation strategies – in time and space.

Adapting the treatment to the biological features of the tumour is hardly a paradigm-shifting approach, one can argue; and rightly so – to a certain extent. Boosting the gross tumour volume, escalating the dose to large tumour masses, irradiating involved nodes are all clinical decisions made based upon insight into biological features and its implications for the disease. The challenge modern radiation oncology faces is, however, how to incorporate an increasingly amount of biological information of relevance to therapy response into planning and adaptation of the treatment of *individual* patients. Understanding and validating the clinical implications of biological information is a first critical step. Investigating whether non-invasive technologies may provide the pertinent information about these biological features is a second requirement if adaptation in the time-domain is to be achieved. Lastly, developing strategies that incorporate and weight the impact of a multitude of biological inputs is a third and unresolved scientific issue on which treatment adaptation rest. This includes a number of steps from the laboratory to prospective clinical trials. These components – on which the very concept of biological guided adaptation of radiation therapy relies – must be critically addressed and the solutions and strategies validated before we can hope that the concept will enhance the therapeutic ratio on an individual patient level. The current papers from the BiGART conference show that, although significant progress is evident, there is still a long way before individualised adaptive radiotherapy is a standard approach.

Radio-genomics is a rapidly emerging translational research field in radiation oncology. Whereas earlier research aimed at identifying a few candidate

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genes associated with radiation response, both in normal tissue and in tumour tissue, current radiogenomics aim at establishing the full genetic signature associated with radiation response [19]. This endeavour requires large patient populations, multicentre involvement and well established data base infrastructure, and is thus ideal for international collaboration. A genetic signature will obviously be of value in clinical decision making; true treatment adaptation will, however require a more detailed measure than the dichotomous classification into anticipated responder/non-responder. Measures of altered copy numbers and percentage genome altered, as shown by Bristow's group for a large series of prostate patients [20], may represent examples of such continuously distributed biological variables.

Functional and molecular imaging has been postulated to the preferable non-invasive technology that provides the pertinent biological information upon which treatment adaptation can be based. To what extent has actually this postulate been tested and what are the challenges associated with the use of functional and molecular imaging in biological guided adaptive therapy?

Although imaging technologies are undergoing a revolution-like development, there are still limitations that might hamper functional imaging-guided adaptive radiation therapy. Obviously, limited resolution, image distortions, segmentation and thresholding are examples of technological and physical challenges that current and forthcoming research endeavours need to address [21,22]. However, the technological requirements should be defined by the clinical needs for detailed biological information rather than the opposite.

The hypothesis that functional and molecular imaging may meet the needs for repetitive, non-invasive acquisition of relevant biological information for treatment adaptation is to a large extent linked to the expectations of imaging 1) providing specific information about biological features of relevance to treatment response, and 2) evolving beyond the descriptive diagnostic approach and into quantitative imaging.

With respect to the first aspect PET and MR imaging are quite different as MR-based imaging techniques normally only provide indirect information of biological features, whereas PET can provide specific information depending on the tracer used. ^{18}Fluor-deoxy-glucose (18-FDG) is – and will still be – the most commonly used tracer in PET imaging [23]. 18-FDG is a metabolic-specific tracer, but does not provide information that is unique to malignant tissue. Although 18-FDG uptake has been shown to correlate to tumour hypoxia specific hypoxia-tracers has been developed, F-MISO and FAZA being examples of such tracers [24]. There has been number of attempts to validate various hypoxia-tracers by comparison with Eppendorf probe measurements and markers like pimonidazole, without successfully reaching at unambiguous conclusions.

A particular important feature of functional and molecular imaging for adaptive irradiation is the evolution beyond the descriptive and qualitative into the quantitative approach. This development will make integration of image information into adaptive irradiation strategies much more feasible. Contrast enhancement has been widely used both within CT and MR imaging; however, the utilisation of the dynamics of the agent uptake require a qualitative tool-set not all institutions are familiar with. Lately, also the dynamic uptake of PET tracers has been postulated to represent added value in monitoring and prediction of treatment response in tumours [25,26]. Dynamic contrast enhanced (DCE) imaging provides mainly quantitative information about the vascularity and the perfusion characteristics of tissue and has been shown to correlate to tumour hypoxia and treatment induced necrosis [11,27,28]. MR imaging is capable of measuring the diffusion of water molecules in tissue and the apparent diffusion coefficient (ADC) has been shown to be a surrogate marker of tissue and cellular intactness. The ADC-values has therefore proven to be useful in monitoring treatment response and thus a potential valuable tool for treatment adaptation [29,30]. Both DCE and ADC imaging is subjected to parameter and scan protocol dependencies; for clinical utilisation standardisation of protocols is mandatory.

IGRT is already clinically implemented in a vast number of institutions, although limited to anatomical imaging techniques [10,31–33]. Studies on the implementation of regular cone beam CT has demonstrated increased accuracy in target volume coverage allowing reduced margins [14,34–37]. Inter-fraction variations in the patient's anatomy can undoubtedly be monitored by daily cone beam CT. Inter-fraction variation in biological features, however, cannot be monitored with the same device and will require repetitive imaging with the appropriate modality. A pre-treatment snapshot of a specific biological phenomenon cannot be expected to be constant throughout the course of treatment. How frequent the patient needs to be subjected to repetitive imaging depends of the dynamics of the biological features addresses and subjected to adaptive irradiation. In practical terms this means that repetitive imaging has to be performed with an interval reflecting, e.g. the re-oxygenation processes in a tumour.

Whether biology-guided adaptive radiation therapy is feasible relies to a certain extent also on the capabilities of the radiation delivery technology. Over the last decades the radiation oncology community has become equipped with an ever increasing

versatile radiation delivery armamentarium; currently ranging from intensity modulated photons to various rotational techniques and intensity modulated particle therapy [38–40]. There will obviously be some limitations with respect to what dose gradients than can be achieved due to the laws of physics; however a number of studies indicate that with the current level of image resolution the existing radiation delivery technologies are capable of creating the requested dose distributions [41].

Quantitative information about relevant biological features in 3D of the tumour tissue can only be utilised in adaptive irradiation if the strategies for how to adapt according to the given biological feature is established. This is perhaps the most immature component of the entire biology-guided adaptive radiation therapy approach when based in functional and molecular imaging. Some theoretical studies have used tumour hypoxia as a demonstrational example since the dose-modifying factor of hypoxia – or the Oxygen Enhancement Ratio (OER) – is thought to be well known. For all other tumour biological features such a factor is far from being established. Most of the work on adaptation strategies has been on advanced tumour control probability (TCP) modelling, including spatial and temporal variations in radiation sensitivity, hypoxia and even proliferation. However, such a mechanistic approach will ultimately fail when ambiguous information from multiple image sets is to be incorporated in the dose prescription. An example would be imaging of pre-treatment apoptosis; apoptosis may be induced by hypoxia and thus be an indication on decreased radiation sensitivity, but could also be an indication of enhanced radiation sensitivity if inherently present. Second generation strategies for adaptation of irradiation – in time and space – may be based on more heuristic approaches such as Baysian statistics, artificial neural networks or other artificial intelligence systems.

The very concept of biology-guided adaptive radiation therapy rely on a number of critical components; for some a rather robust empirical support is now emerging, for others the empirical basis is yet to be established. It is therefore more than relevant to quote author William Gibson: "The future is here. It's just not evenly distributed yet." [42].

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