

EDITORIAL

Biology-guided adaptive radiotherapy (BiGART) – more than a vision?

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Acta Oncologica can this year celebrate its 50 years jubilee as the leading Scandinavian journal in oncology. As a part of this celebration the 11th Acta Oncologica Symposium was held in Aarhus, Denmark, on June 11–13, 2013. The symposium was dedicated to aspects of Biology-Guided Adaptive Radiotherapy (BiGART). The 172 participants of the meeting included physicians, physicists, radiobiologists and other scientists with an active interest in this specific area. The format included invited presentations, proffered papers and discussion rounds. More than 100 abstracts were submitted to the conference.

Acta Oncologica has sponsored scientific symposia since 1989. The aim of this activity has been to focus on oncological issues of emerging interest, preferably with a multi-disciplinary or multi-professional approach. The current series of Acta Oncologica meetings with focus on radiotherapy (RT) have encompassed stereotactic body RT (SBRT) [1], image-guided RT (IGRT) [2,3], adaptive RT (BiGART) [4] and particle RT [5]. Other topics have over the years included sentinel lymph node biopsy in breast cancer, prostate cancer, normal tissue morbidity, breast cancer, and rehabilitation.

The goal of BiGART is adaptation of RT in time and space based on biological and anatomical features, maximizing the therapeutic ratio for each individual patient. Key topics for the BiGART2013 conference included:

1. Biology of tumors and normal tissue to guide patient selection, target volumes and dose prescription in RT;

2. Functional imaging of tumors and normal tissues with functional imaging techniques based on magnetic resonance imaging (MRI) and positron emission tomography (PET), and the use of such images for dose painting and normal tissue avoidance in RT;
3. Treatment planning and delivery challenges in adaptation of radiotherapy based on changes in tumor and normal tissue biology, anatomy and/or function;
4. Clinical outcome of adaptive RT.

The current issue of Acta Oncologica contains a collection of peer-reviewed papers from the conference, and additional papers will be published in upcoming issues of the journal.

The most relevant biological features to explore and exploit within BiGART include hypoxia, proliferation, cell density and intrinsic radio-resistance. It is evident that the biological characterization of tumors has moved towards genetic profiling, and current radio-genomic research aims at establishing the full genetic signature associated with radiation response. Several studies suggest that it is possible to use gene profiles, e.g. to predict the benefit of post-operative RT in breast cancer, to identify tumors with, e.g. hypoxia in esophageal or prostate cancer [6,7] or to predict the benefit from hypoxic cell sensitization [8]. Such genetic signature will be of value in clinical decision-making, but more studies are needed since treatment adaptation requires more detailed information than currently available.

Functional imaging modalities linked to BiGART include dynamic computed tomography (CT) with

contrast-enhancement, diffusion-weighted MRI, dynamic contrast-enhanced MRI, and PET with various tracers [9–13]. A number of studies have shown that functional imaging information on, e.g. hypoxia is prognostic for the outcome of RT. The main challenges in imaging for BiGART are resolution and dynamics. The radiobiological relevant hypoxia is likely to be distributed more heterogeneous on a microscopic level than what current imaging can pick up. If so, our current imaging and delivery techniques are probably too coarse to fully address the biological distribution. A promising novel technology that was discussed at the symposium is hyperpolarized MR which offers a considerably improved signal to noise ratio [14]. The dynamics of the biological features of interest determines how frequent the patient needs to be subjected to repetitive imaging during radiotherapy, and also this needs further studies.

The application of functional imaging on a larger clinical scale meets with a number of problems and also opens up new questions. The issues range from the mere technical, like deformable image registration for the combination of multiple images, to the very basic understanding of multi-modality functional imaging and inter-patient heterogeneity [15–17]. The development of solutions for deformable image registration is clearly moving towards specialization with respect to body site and image modalities to be combined, in order to achieve the accuracy required for treatment planning. The complementary approach is to extract more information from a single modality, or use it for multiple purposes. Due to its great versatility, MRI can play a much more dominant role in the future, and maybe also replace the obligatory CT scan for dose computation. Great efforts are being directed at the development of new imaging sequences and computer algorithms to produce an electron density map from MR images. Simultaneously, it becomes clear that the interpretation of both MR and PET images requires the support of models, algorithms and knowledge databases [18,19]. In the presence, the handling of functional images is still associated with large uncertainties and ambiguities in interpretation, which require a careful and cautious use of such means while more evidence needs to be collected.

The underlying rationale for the exploration of both biological endpoints and functional imaging parameters in adaptive RT settings is that they carry information connected to the dose-response of both tumors as well as normal tissues. Such information should therefore have considerable potential to improve the current (population-based) RT dose-response relationships – often referred to as tumor control probability (TCP) and normal tissue

complication probability (NTCP) models. So far, imaging parameters associated with tumor cell density and oxygenation status has been explored in the TCP models, derived mostly from functional MRI and/or PET [18,20]. Imaging-based functional measures are being explored also for several key normal tissues in treatment of major tumor sites [12]. A number of studies has explored CT-based imaging techniques in the lung, where local density changes have been associated with local function [12,21–23], including also a study presented at this meeting [23]. However, there are a number of confounding factors that needs to be accounted for in such studies [24,25], including also challenges related to properly account for any ‘physical’ uncertainties influencing geometry and ultimately dose [26–28].

Functional imaging can influence treatment planning on many levels, from target volume delineation to image intensity-guided dose escalation [20,29,30]. The rationale for the more sophisticated usages is generally still very weak and associated with many uncertainties. For example, the achievable levels of image sensitivity place very strict limits on the possibility for dose de-escalation. Dose escalation, however, can give rise to complications with a higher frequency and severity. The first clinical trials show encouraging results and also often prove that focused dose escalation can be performed with low toxicity profiles if adequate care is invested into imaging and image interpretation. The primary sites for this seem to be intermediate- and high-risk prostate cancer, based on multi-modal MRI, and head-and-neck cancer, based on FDG or hypoxia PET, with dose escalation of up to 30% and without de-escalation. For other sites like uterine cervix, evidence is mounting that radiation insensitive tumor cores exist in a sub-population of patients, which might be the next target for dose painting.

Adaptive RT also calls for advanced treatment delivery approaches. So far, photon-based intensity-modulated RT techniques have shown large promise in terms of dose shaping abilities [19,30,31]. Geometrical uncertainties are a challenge for all RT applications. Image-guided treatment strategies are therefore currently state of the art in RT, with tumor tracking showing large potential to remedy the residual uncertainties so far unaccounted for [32,33]; tracking has recently been studied together with dose painting plans [34]. However, the increased complexity in spatial dose prescription patterns might indeed call for RT with other modalities, first and foremost with protons, possibly also heavier ions. Particle beam therapy is in general receiving considerable attention currently, exemplified both by another recent Acta Oncologica symposium [17,35–38] as well as in another dedicated issue of

the present journal [5,39]. In the current issue, Combs, Debus and co-workers at the Heidelberg Ion Therapy Centre present promising results for brain and skull base tumors and provide a review of the currently available evidence for heavy ions [40,41]. Adaptive strategies may be even more important in particle radiotherapy because of the poor robustness of particles [39]. Much more attention has to be given to this research field.

The clinical aspects of anatomy-based adaptive radiotherapy have been studied in a number of clinical studies in recent years [42–50]. A number of presentations at this meeting demonstrated that there is a potential for adaptation to anatomical changes during the course of radiotherapy based on the technology that we have available today. Previous studies on cone-beam CT scans in RT for lung cancer have revealed that changes in density of the lung and atelectasis that resolves may influence the dose distribution in the liver and lung [51]. A study presented at the symposium showed that anatomical changes frequently occurred during the course of radiotherapy, and a large proportion of the patients would benefit from re-planning [52]. Another study elegantly demonstrated that changes detected with portal dosimetry during the course of radiotherapy might reveal a resolved atelectasis and a need for treatment re-planning [53].

Daily adaptive online re-planning/optimization is an ambitious strategy that involves a chain of tools, e.g. auto-segmentation, dose reconstruction/accumulation and plan evaluation that are not readily available today. A number of technical obstacles in this chain must be overcome before this concept is feasible and ready for clinical use. However, adaptation by a daily plan selection strategy can be realised with the technology that we have today [54–56]. Preliminary clinical results were presented of a study on RT for bladder cancer where one of three plans was selected based on the size and shape of the bladder on the cone-beam CT scan [54,57], and where RT technologists selected the plans on a daily basis. It was shown that with a proper training program, this was feasible within a time frame of approximately two minutes.

In brachytherapy there are convincing data showing beneficial effects by image-guided and adaptive strategies [58–60], now also with results from the retro-EMBRACE database with almost 800 cervical cancer patients, as presented at the meeting. At three years after therapy, more than 90% of the tumors were locally controlled and even the most advanced tumors were controlled in more than 80% of the cases. Similar favorable results were demonstrated in a single institution retrospective case control study of image-guided adaptive brachytherapy of cervical cancer [61].

Early assessment of treatment response is a key player in the adaptive strategies, but currently there is only limited clinical experience with this strategy. Functional imaging of the tumor may reveal metabolic changes predicting the long-term response of the therapy. This may be used for selection of patients with radio-resistant tumors for more aggressive therapy [62,63]. In cervix and head-and-neck cancer, FDG-PET response might steer the aggressiveness of chemo-radiation and in rectal and esophageal cancer the response may potentially guide decision making about organ preservation [62].

In conclusion, the current issue of *Acta Oncologica* with papers from the BiGART2013 conference shows that there is still some way before individualized adaptive radiotherapy is a standard clinical approach. However, the significant advances especially within functional molecular imaging of tumors support that BiGART will mature to become more than just a vision for the future in radiotherapy.

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