

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 multi-disciplinary 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

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, multi-centre 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. ¹⁸Fluor-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 Bayesian 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].

References

- [1] Overgaard J. Management of the axilla in breast cancer. Implication for diagnosis, prognosis, treatment, and morbidity. *Acta Oncol* 2000;39:259–60.
- [2] Levitt S. Second Acta Oncologica symposium on prostate cancer controversies. *Acta Oncol* 2005;44:526–8.
- [3] Grau C, Høyer M, Lindegaard J, Overgaard J. The emerging evidence for Stereotactic Body Radiotherapy. *Acta Oncol* 2006;45: 771–4.

- [4] Høyer M, Roed H, Traberg Hansen A, Ohlhuis L, Petersen J, Nellemann H, et al. Phase II study on stereotactic body radiotherapy of colorectal metastases. *Acta Oncol* 2006; 45:823–30.
- [5] Paludan M, Traberg Hansen A, Petersen J, Grau C, Høyer M. Aggravation of dyspnea in stage I non-small cell lung cancer patients following stereotactic body radiotherapy: Is there a dose-volume dependency? *Acta Oncol* 2006;45: 818–22.
- [6] Baumann P, Nyman J, Lax I, Friesland S, Høyer M, Rehn Ericsson S, et al. Factors important for efficacy of stereotactic body radiotherapy of medically inoperable stage I lung cancer. A retrospective analysis of patients treated in the Nordic countries. *Acta Oncol* 2006;45:787–95.
- [7] Nord C, Ganz PA, Aziz N, Fosså SD. Follow-up of longterm cancer survivors in the Nordic countries. *Acta Oncol* 2007;46: 433–40.
- [8] Aziz NM. Cancer survivorship research: State of knowledge, challenges and opportunities. *Acta Oncol* 2007;46:417–32.
- [9] Overgaard J. DBCG: The Danish Breast Cancer Cooperative Group – a 30-year struggle for better breast cancer treatment in Denmark. *Acta Oncol* 2008;47:491–6.
- [10] Grau C, Muren LP, Høyer M, Lindegaard JC, Overgaard J. Image-guided adaptive radiotherapy – integration of biology and technology to improve clinical outcome. *Acta Oncol* 2008;47:1182–5.
- [11] Nielsen T, Mouridsen K, Maxwell RJ, Stødkilde-Jørgensen H, Østergaard L, Horsman MR. Segmentation of dynamic contrast enhanced magnetic resonance imaging data. *Acta Oncol* 2008;47:1265–70.
- [12] Østergaard Noe K, De Senneville B, Elstrøm U, Tanderup K, Sørensen TS. Acceleration and validation of optical flow based deformable registration for image-guided radiotherapy. *Acta Oncol* 2008;47:1286–93.
- [13] Pötter R, Kirisits C, Fidarova EF, Dimopoulos JCA, Berger D, Tanderup K, et al. Present status and future of high-precision image guided adaptive brachytherapy for cervix carcinoma. *Acta Oncol* 2008;47:1325–36.
- [14] Wright P, Redpath A, Høyer M, Grau C, Muren LP. The normal tissue sparing potential of adaptive strategies in radiotherapy of bladder cancer. *Acta Oncol* 2008;47: 1382–9.
- [15] Muren LP, Petersen JB, Hansen J, Hafslund R. Medical physics in the Nordic countries: The past, the present and the future. *Acta Oncol* 2009;48:165–8.
- [16] Webb S. The contribution, history, impact and future of physics in medicine. *Acta Oncol* 2009;48:169–77.
- [17] Jeraj R. Future of physics in medicine and biology. *Acta Oncol* 2009;48:178–84.
- [18] Søndergaard J, Høyer M, Petersen JB, Wright P, Grau C, Muren LP. The normal tissue sparing obtained with simultaneous treatment of pelvic lymph nodes and bladder using intensity-modulated radiotherapy. *Acta Oncol* 2009;48: 238–44.
- [19] Andreassen, CN, Alsner, J. Genetic variants and normal tissue toxicity after radiotherapy: A systematic review. *Radiother Oncol* 2009;92:299–309.
- [20] Ishkanian AS, Zafarana G, Thoms J, Bristow RG. Array CGH as a potential predictor of radiocurability in intermediate risk prostate cancer. *Acta Oncol* 2010;49:888–94.
- [21] Busk M, Horsman MR, Overgaard J. Resolution in PET hypoxia imaging: Voxel size matters. *Acta Oncol* 2008;47: 1201–10.
- [22] Brock KK, Hawkins M, Eccles C, Moseley JL, Moseley DJ, Jaffray, DA, et al. Improving image-guided target localization through deformable registration. *Acta Oncol* 2008;47: 1279–85.

- [23] Newbold KL, Partridge M, Cook G, Sharma B, Rhys-Evans P, Harrington, KJ, et al. Evaluation of the role of 18FDG-PET/CT in radiotherapy target definition in patients with head and neck cancer. *Acta Oncol* 2008; 47:1229–36.
- [24] Roels S, Slagmolen P, Nuyts J, Lee JA, Loeckx D, Maes F, et al. Biological image-guided radiotherapy in rectal cancer: Is there a role for FMISO or FLT, next to FDG?. *Acta Oncol* 2008;47:1237–48.
- [25] Busk M, Munk OL, Jakobsen S, Wang T, Skals M, Steiniche T, et al. Assessing hypoxia in animal tumor models based on pharmacokinetic analysis of dynamic FAZA PET. *Acta Oncol* 2010;49:922–33.
- [26] Røe K, Aleksandersen TB, Kristian A, Nilsen LB, Seierstad T, Qu H, et al. Preclinical dynamic 18F-FDG PET – tumor characterization and radiotherapy response assessment by kinetic compartment analysis. *Acta Oncol* 2010;49: 914–21.
- [27] Nielsen T, Murata R, Maxwell RJ, Stødkilde-Jørgensen H, Østergaard L, Ley CD, et al. Non-invasive imaging of combretastatin activity in two tumour models: Association with invasive estimates. *Acta Oncol* 2010;49:906–13.
- [28] Søvik Å, Kippenes Skogmo H, Bruland S, Olsen DR, Malinen E. DCEMRI monitoring of canine tumors during fractionated radiotherapy. *Acta Oncol* 2008;47:1249–56.
- [29] Haack S, Morre-Pedersen E, Jespersen SN, Kallehauge JF, Lindegaard JC, Tanderup K. Apparent diffusion coefficients in GEC ESTRO target volumes for image guided adaptive brachytherapy of locally advanced cervical cancer. *Acta Oncol* 2010;49:978–83.
- [30] Kallehauge JF, Tanderup K, Haack S, Nielsen T, Fokdal L, Lindegaard JC, et al. Apparent diffusion coefficient (ADC) as a quantitative parameter in diffusion weighted MR imaging in gynecologic cancer: Dependence on b-values used. *Acta Oncol* 2010;49:1017–22.
- [31] Van Herk M. Will IGRT live up to its promise? *Acta Oncol* 2008;47:1186–7.
- [32] Verellen D, De Ridder M, Tournel K, Duchateau M, Reynnders T, Gevaert T, et al. An overview of volumetric imaging technologies and their quality assurance for IGRT. *Acta Oncol* 2008;47:1271–8.
- [33] Baumann M, Hölscher T, Zips D. The future of IGRT – Cost benefit analysis. *Acta Oncol* 2008;47:1188–92.
- [34] Vestergaard A, Søndergaard J, Petersen JB, Høyer M, Muren LP. A comparison of three different adaptive strategies in image-guided radiotherapy of bladder cancer. *Acta Oncol* 2010;49:1069–76.
- [35] Gottlieb KL, Hansen CR, Hansen O, Westberg J, Brink C. Investigation of respiration induced intra- and inter-fractional tumour motion using a standard Cone Beam CT. *Acta Oncol* 2010;49:1192–8.
- [36] Elstrøm UV, Wysocka BA, Muren LP, Petersen JB, Grau C. Daily KV cone-beam CT and deformable image registration as a method for studying dosimetric consequences of anatomic changes in adaptive IMRT of head and neck cancer. *Acta Oncol* 2010;49:1101–8.
- [37] Røthe Arnesen M, Eilertsen K, Malinen E. Optimal treatment margins for radiotherapy of prostate cancer based on interfraction imaging. *Acta Oncol* 2008;47:1373–81.
- [38] Bedford JL, Hansen VN, McNair HA, Aitken AH, Brock JEC, Warrington AP, et al. Treatment of lung cancer using volumetric modulated arc therapy and image guidance: A case study. *Acta Oncol* 2008;47:1438–43.
- [39] Korreman S, Medin J, Kjær-Kristoffersen F. Dosimetric verification of RapidArc treatment delivery. *Acta Oncol* 2009;48:185–91.
- [40] Kjær-Kristoffersen F, Ohlhues L, Medin J, Korreman S. RapidArc volumetric modulated therapy planning for prostate cancer patients. *Acta Oncol* 2009;48:227–32.
- [41] Deveau M, Bowen SR, Westerly DC, Jeraj R. Feasibility and sensitivity study of helical tomotherapy for dose painting plans. *Acta Oncol* 2010;49:991–6.
- [42] William Gibson, in NPR Talk of the Nation (30 November 1999).