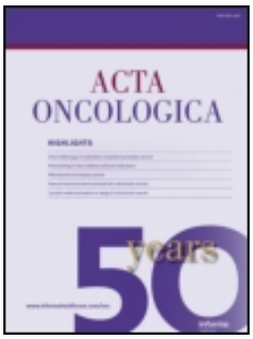

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**EDITORIAL**

# Biology-guided adaptive radiotherapy (BiGART) is progressing towards clinical reality

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The present issue of Acta Oncologica contains a large number of publications that were presented at the 13th Acta Oncologica Symposium, held recently in Aarhus, Denmark (June 2015). The symposium was dedicated to aspects of biology-guided adaptive radiotherapy (BiGART), and attracted physicians, physicists, radiobiologists and other scientists with an active interest in this specific area.

Acta Oncologica has sponsored scientific symposia since the late 1980s. The aim of these meetings has been to focus on oncological issues of emerging interest, preferably with a multi-disciplinary and multi-professional approach. The current series of Acta Oncologica meetings with focus on clinic, biology and technique in radiotherapy (RT) have encompassed stereotactic body RT (SBRT) [1], image-guided RT (IGRT) [2], particle RT [3], and BiGART [4–55].

The goal of BiGART is treatment adaptation in time and space based on biological and anatomical features, maximizing the therapeutic ratio for each individual patient. Key topics for the BiGART2015 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 RT and particle therapy based on changes in tumor and normal tissue biology, anatomy and/or function;
4) Clinical outcome of biology-guided and adaptive RT.

The current issue of Acta Oncologica contains most of the publications from the BiGART2015 conference, and several additional papers will be published in subsequent issues of the journal.

The radiobiological issues focused on the risk of late effects after RT. This included an increasing awareness of the risk of radiation-induced secondary cancer and the consequential attempt to understand and avoid this problem by, e.g. particle therapy [56–58]. Also the importance of individual variation in normal tissue radiosensitivity was highlighted with regard to different sensitivity and volume effects of different morbidity endpoints [59–62]. This has implications for the dose-response relationship applied in the model-based selection mechanism which are suggested as a basis for identifying the patients which may have benefit of proton irradiation [63–65].

Functional imaging has been explored over the last decades for characterization of tumors, for evaluation of treatment response, as well as for assessment of the function of normal tissues before and after RT. Functional imaging modalities linked to BiGART include dynamic computed tomography (CT) with contrast-enhancement, diffusion-weighted magnetic resonance imaging (MRI), dynamic contrast-enhanced MRI,

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and positron emission tomography (PET) with various tracers [9–11]. The perspectives of integrating functional imaging in RT are manifold: targeting of tumor sub-volumes, individual adaptation of treatment strategies according to the risk of recurrence, adaptations during RT according to response to treatment, adaptations according to normal tissue function, and finally having new tools which can be used to characterize, quantify and better understand tumor biology and normal tissue function. Quantitative assessment in imaging techniques have gained significant interest with the perspectives of arriving at more user-independent interpretation of images which can provide more robust measures across patients, scanners and centers in prospective multicenter studies.

A systematic model for validation of quantitative MRI in prostate cancer which included both calibration of sequences at multiple scanners as well as validation of imaging by comparison with pathology was presented by Uulke van der Heide and coworkers [66]. These efforts contribute to the movement of the field towards improved ability to identify tumor lesions and to consider more intelligent strategies for targeting of prostate cancer according to disease burden and tumor characteristics [67]. BiGART2015 was also an arena for interesting developments related to imaging in head and neck cancer. With studies showing that the recurrence rate is largest in gross tumor volume (GTV) [68,69] and hypoxic regions [70] there is a strong motivation to move ahead with further developments of imaging in head and neck cancer [71] as well as testing prospectively new strategies of dose administration which target more efficiently the regions with highest risk of recurrence [69,70].

Normal tissue imaging studies were also presented at the symposium, showing that functional imaging has the ability to assess heterogeneous distribution of function in parotid with dynamic MRI [72], in lung with single photon emission CT (SPECT) [60] as well as by biomechanical analysis of repeat MRI scans of different rectum expansions [73]. Such methods can be used to assess spatial dose-volume effects and has potential for improved treatment planning by taking heterogeneous organ function into account.

The introduction of online imaging solutions, primarily through the invention of on-board cone-beam CT (CBCT) has radically increased the use of image-guided RT, opening the door also to exploration and introduction of adaptive RT, as shown in a number of recent papers [74–76]. For several tumor sites CBCT imaging offers sufficient and reliable soft tissue contrast to allow adaptive RT protocols to be established in clinical practice [77].

To address some of the limitations of CBCT-based adaptive RT, there is increasing interest in MRI-guided RT, in particular due to the improved soft tissue visualization, also with adaptive implications [78]. Several technical solutions are available, and were presented at the symposium. There is clearly a huge potential in combining the many advanced anatomical as well as functional MRI acquisition techniques with a frontline linear accelerator [79]. Another adaptive RT-related issue that has received considerable attention is the challenge of short-term target/tissue motion [75], ultimately addressed through real-time adaptation [80–82].

Several of the image-guided and adaptive challenges that have been addressed, and now also partially solved, for photon-based RT are re-appearing for proton- and particle-based RT. Besides being more complex to handle for protons/particles, these modalities also have new and specific challenges, usually materializing in so-called range uncertainties [76,83,84]. This is probably the largest current challenge before more widespread use of proton therapy to new indications [3]. Present and future challenges in this field are discussed by Seco and Spadea in (this issue) [85].

The combinations of advanced repetitive imaging with advanced external beam RT and brachytherapy (BT) are now providing clinical evidence for improved local control and reduced morbidity. BIGART2015 showed several examples on how dose painting of resistant sub-volumes and adaptation to a regressing tumor and moving organs during fractionated RT is now being successfully employed in clinical studies in cancer of the head and neck, lung, rectum and urinary bladder [70,71,74,86–88]. Also image-guided BT using preferably MRI is now in routine use in many centers for both prostate cancer and cervix cancer, showing a substantially improvement in the therapeutic ratio [89,90]. In addition, the use of four-dimensional (4D) imaging (time and space) provides improved knowledge on dose-response and dose-effect relationships that are constantly being fed back into an ever growing evidence-based improvement in the planning aims and dose-volume constraints.

Proton therapy was a major topic at BiGART2015, both due to its considerable current interest, and due to the high relevance of biological and adaptive aspects [85,91]. The number of centers providing proton therapy will increase rapidly during the next decennium. Proton therapy is more expensive than conventional RT [92], and with the present technology and resources proton therapy should only be offered to patients who are most likely to benefit from this treatment. Patient selection should be based on a high level of evidence, but so far there are no results of sufficiently powered randomized studies. Randomized studies are not

feasible in many situations, most often due to the lack of clinical equipoise. The model-based approach is attractive for decision making and selection of the appropriate individuals for proton RT [63,64]. However, measuring relevant endpoints for normal tissue complication probability (NTCP) modeling is not trivial. It includes identification of the proper endpoints, preferentially prioritized and reported by the patient. Patient-reported outcomes (PRO) are dependent on specific patient-related circumstances at the time of the assessment and we need experience on how to extrapolate and utilize PRO-data [61,93]. PRO must be related to the radiation exposure dose-volume data, but dose-volume parameters are sensitive to day-to-day motion of the normal tissue structures [27,94].

The final session of the BiGART2015 symposium was dedicated to the future of RT, with special emphasis on balancing the ever growing need for more and more complex RT with the costs [95,96]. This challenge is being addressed by ESTRO in the HERO project [97,98]. One solution is to reduce RT costs by automation [99].

In conclusion, the current issue of Acta Oncologica with papers from the BiGART2015 conference shows that there is now substantial clinical experience with individualized adaptive RT. For some of the major RT indications, adaptation based on anatomical changes is now a standard clinical approach. Further integration also of biological information into the RT process chain, still awaits clinical testing but there is little doubt that the significant advances especially within functional molecular imaging of tumors and normal tissues will also be integrated in future RT.

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