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EDITORIAL

Bridging imaging and therapy: the role of medical physics in development of precision cancer care

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A number of health disciplines are involved in diagnosing, staging and treating cancer, using a broad array of technologies and treatment approaches. One highly relevant discipline in this field is medical physics, where physics principles and methods are applied to medicine, contributing, in particular, to medical imaging and radiotherapy [1–3]. Magnetic resonance imaging (MRI) and positron emission tomography (PET) can be used to assess disease extension and to localize the most aggressive part of the disease in the patient. Extraction and analysis of imaging profiles of individual patients may further give prognostic information, not necessarily obtained from patient-specific clinical or genetic information [4]. Images from such modalities may further be used as input for planning of surgery and radiotherapy, giving both surgeons and radiation oncologists guidance tools for eradicating the tumor. Furthermore, in radiotherapy, medical images provide the information necessary to delineate the tumor and organs at risk. Radiotherapy is a completely digital process, where developments are seen among others in delivery techniques and image-guided adapted strategies [5–7]. With the aim of cancer care to move from the concept of *'one-size-fits-all'* to individualized treatment, the term *'Precision cancer care'* could also encompass radiotherapy tailored to the individual patient's medical image-based profile in addition to the *genetic* profile. The progress in imaging and radiotherapy towards precision cancer care relies on the development of dedicated methods for quantitative use of functional images in treatment selection, planning, delivery and response evaluation for the individual patient.

The current issue of Acta Oncologica contains contributions presented at the 4th symposium for the Nordic Association for Clinical Physics (NACP)[1] – *Bridging imaging and therapy* – arranged in Oslo, Norway in February 2017 gathering close to 200 participants. The NACP symposium has become a regular, Acta Oncologica supported, triennial meeting which started with a symposium in Aarhus, Denmark in 2008 [1] that was held together with an Acta Oncologica symposium on image-guided radiotherapy [8]. A combined NACP and Acta Oncologica symposium on proton and particle therapy followed thereafter in Uppsala, Sweden in 2011 [9,10]. In 2014 a joint meeting between the NACP and the Turku PET center, Finland, was organized with the main theme of the NACP part being imaging in oncology [11]. Looking at the decade covered by the four NACP symposia, the early years focused on developments of various modes of intensity-modulated radiotherapy and in-room image-guidance principles such as cone beam CT, now being part of clinical routine. Today, we see research on more advanced imaging methodologies such as MR-only workflow, extended use of PET, consideration of inter- and intra-fractional motion and consequences for adaptive radiotherapy as well as improvements of proton and particle therapy approaches. With the operational Skandion proton therapy clinic in Uppsala, Sweden, and the upcoming Danish particle therapy center in Aarhus, Denmark, it is a natural choice for the Nordic medical physics communities to focus on proton therapy in the years to come.

The medical physics contributions in the current issue of Acta Oncologica illustrate how this field takes part in the development of further individualized, precision cancer care. A highly relevant topic among the articles is the use of MRI in radiotherapy, which has for the last decade expanded mainly due to its superior soft tissue contrast compared to computed tomography (CT). Traditionally, MRI has been employed as a radiological modality supplementary to CT-based treatment planning, where the tumor is delineated in the CT images visually aided by high-contrast MR images. Today, MR images are often imported into the planning system and co-registered to the CT with rigid or non-rigid registration algorithms [12–14]. Furthermore, some centers also consider doing so-called 'MR-only' workflow, where CT is

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omitted in the planning approach [15–17]. However, this raises some concerns due to two distinctly different problems: (1) RT dose calculations require electron density mapping, which is well approximated by CT but not by MRI, and (2) MRI may produce more prominent geometric distortions compared to CT. Two contributions in the current issue discussed these concerns [18,19]. Both studies focused on pelvic cancers and employed the same commercially available algorithm to transform MR images into so-called pseudo-CTs. In brief, the studies showed that dosimetric accuracy was high using pseudo-CTs (error introduced typically $<1\%$). Also, the studies indicated that geometric distortions from the T1-sequence applied are very small (<1 mm). Thus, the MR-only workflow seems very robust with respect to accuracy in RT dose delivery. Still, other MR sequences may be more prone to, e.g., causing geometric distortions [20], and MR-only workflow is expected to still be a field of active research in the years to come.

As indicated above, implementation of MRI in radiotherapy is expected to facilitate tumor delineation [21–23]. In the current paper by Damkjær et al. [24], multiparametric MRI was used to define MRI-positive parts of the seminal vesicles in prostate cancer patients treated with external beam radiotherapy. It was shown by mathematical modeling that targeting the MRI-positive regions potentially could increase the tumor control probability, albeit to a small extent, without increased normal tissue toxicity compared to a conventional RT strategy. However, it is interesting to note that only a minority of the lesions was positive in all the MR image series, and considerable inter-observer variability in MRI-based tumor delineation has further been reported [25]. This substantiates the need for more robust and objective methodologies and/or guidelines for delineation. In this issue, Torheim et al. explored a computer-assisted method to extract cervical tumor volume from multi-parametric MRI and machine learning [26]. T1- and T2-weighted alongside dynamic contrast enhanced (DCE) MRI scans were used in discriminant analysis to identify tumor from normal tissue. The similarity between the radiologists' contours and the auto-delineated contours varied considerably, indicating that the methodology is not yet mature for clinical implementation. However, methodological refinements and inclusion of, e.g., diffusion weighted MR images (DWI) or PET images may well improve this technique. DWI was indeed used in the current study by Bakke et al. [27] on outcome of rectal cancer after chemoradiotherapy and surgery. In DWI, MR sequences sensitive to motion of water molecules can be used to calculate parameters like the ADC (Apparent Diffusion Coefficient), where low ADCs may reflect high-tumor cellularity [28]. However, with appropriate image sampling, the analysis of DW image series can be extended to also include estimates of tumor perfusion. Bakke et al. [27] estimated the tumor perfusion fraction from DWI, and used this metric per tumor volume (F/V) as a marker of treatment resistance. It was found that low F/V was prognostic for worse outcome, indicating that the patients with low F/V had large and/or hypoxic (hypoperfused) tumors.

Hypoxia is a known cause of treatment resistance, and targeting hypoxic tumors, or tumor regions, with increased radiation dose may improve disease control [29,30]. Traditionally, positron emission tomography (PET) with suitable hypoxia tracers have been employed to depict tumor hypoxia [29]. Still, it is not straightforward how to interpret hypoxia PET images in terms of oxygenation level and how to find the best threshold to extract hypoxic subvolume(s). This was elaborated in the present article by Lindblom et al. [31], where patients with non-small cell lung cancer had 18F-HX4 PET prior to therapy. It was found that 18F-HX4 uptake resembled that of 18F-FMISO (a better characterized hypoxia tracer), and that using a specific link function between image intensity and tumor oxygenation gave reasonable hypoxic subvolumes. The authors concluded that more work has to be done with 18F-HX4 PET before radiobiologically optimized hypoxia planning with e.g., dose painting [32,33] is clinically applicable. In the current study by Holm et al. [34], dose painting of PET-positive tumor regions was explored *in silico* for glioma patients. 18F-fluoro-ethyl-tyrosine (FET) PET for target definition and risk-adapted treatment planning with X-rays (IMRT/volumetric modulated arc therapy, VMAT) or protons was employed. It was shown that the PET-positive part of the tumor could be boosted with an additional dose of typically 33% without noteworthy increase in dose burden to organs at risk. However, protons gave the most favorable dose distribution in the patients, indicating that a higher therapeutic gain can be achieved from dose painting with protons.

Proton therapy, as mentioned above, is expected to provide enhanced dose delivery to the patient compared to X-ray based, conventional radiotherapy [35]. However, in the current work by Mondlane et al. [36], proton therapy was shown to be more sensitive to simulated density changes in the abdomen compared to VMAT for patients with gastric cancer. This indicates that more extensive imaging and replanning have to be performed for such cancers in order to reach the full dosimetric potential of protons. Furthermore, organ motion is generally a problem in radiotherapy and may become an additional challenge in proton therapy due to the sharper dose gradients. Busch et al. [37] used repeat CT scans of prostate cancer patients taken during the course of fractionated radiotherapy to simulate the effects of organ motion during proton therapy or VMAT. It was found that proton therapy gave large reductions in the mean dose to organs at risk compared to VMAT, although considerable patient-to-patient variations in predicted normal tissue complication probabilities were evident. Still, to maximize the therapeutic gain from protons one also should consider optimizing the protons beams and beam angles employed, which was done in the current articles by Andersen et al. [38] and Gorgisyan et al. [39]. The studies looked at water equivalent path lengths of protons (WEPL), related to density variations discussed above, for patients with lymph node positive prostate cancer and locally advanced non-small cell lung cancer, respectively. Both studies employed repeat CT scans during the course of radiotherapy, and it was found that WEPL could serve as a plan robustness tool to find optimal beam angles and to identify patients at risk of over/underdosage.

As shown above, the Nordic medical physics community is an active contributor to the international research field of cancer diagnostics and therapy. The contributions to the *Bridging imaging and therapy* conference and the current issue of Acta Oncologica shows how medical physicists employ imaging, patient outcome data, radiotherapy simulations, mathematical modeling and more together with clinical judgments to move the cancer field forward. We anticipate that such physics contributions will play an even greater role for future cancer patients.

Note

1. Following its restructuring around 2005.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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