Personalised radiation therapy taking both the tumour and patient into consideration

Jens Overgaard a,⇑, Marianne C. Aznar b, Carol Bacchus c, Rob P. Coppes d, Eric Deutsch e, Dietmar Georg f, Karin Haustermans g, Peter Hoskin h, Mechthild Krause i, Eric F. Lartigau k, Anne W.M. Lee l, Steffen Löck j, Birgitte V. Offersen a, David I. Thwaites m,n, Albert J. van der Kogel o, Uulke A. van der Heide p, Vincenzo Valentini q, Michael Baumann c

a Department of Experimental Clinical Oncology, Aarhus University Hospital, Denmark; b Division of Cancer Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, The Christie NHS Foundation Trust, United Kingdom; c Departments of Radiation Oncology and Biomedical Sciences of Cells & Systems, Section Molecular Cell Biology, University of Groningen, University Medical Center Groningen, the Netherlands; d Department of Radiation Oncology, Institut d’Oncologie Thoracique (IOT), Gustave Roussy, France; e Division Medical Radiation Physics, Department of Radiation Oncology, Medical University of Vienna/AKH Wien, Austria; f Department of Radiation Oncology, University Hospitals Leuven, Belgium; g Mount Vernon Cancer Centre and University of Manchester, United Kingdom; h Department of Radiotherapy and Radiation Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Germany; i OncRay - National Center for Radiation Research in Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Helmholtz-Zentrum Dresden - Rossendorf, Germany; j Academic Department of Radiotherapy, Oscar Lambret Comprehensive Cancer Center, Lille, France; k Department of Clinical Oncology, University of Hong Kong - Shenzhen Hospital and University of Hong Kong, China; l Institute of Medical Physics, School of Physics, The University of Sydney, Australia; m Medical Physics Group, Leeds Institute of Medical Research, School of Medicine, University of Leeds, United Kingdom; n Department of Human Oncology, University of Wisconsin School of Medicine and Public Health, Madison, USA; o Department of Radiation Oncology, the Netherlands Cancer Institute, Amsterdam, the Netherlands; p Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, UOC Radioterapia Oncologica, Fondazione Policlinico Universitario “A. Gemelli” IRCCS, Rome, Italy

The scenario

A look through almost 2000 abstracts submitted for the upcoming ESTRO 2022 meeting together with a glance back on the 2021 papers published in Radiotherapy and Oncology gives one a good impression of the (current) key focus areas in radiation oncology: Almost all of this work relates to optimal delivery of radiation therapy in terms of technology, quality assurance and morbidity reducing approaches. Thus, at present the research questions considered as most relevant for radiotherapy of e.g. lung and oesophageal cancer are not related to tumour control, but to the late risk of cardiac disease in the patients who are lucky to survive their cancer long enough to develop such problems [1]. The same scenario is found in the patient cohort that constitutes the largest indication for radiotherapy in Europe: women with early breast cancer [2]. In these examples, and in many other situations where radiotherapy is applied with a curative intent, less focus has currently been given to the aim or indication of the treatment, namely the control of loco-regional malignant disease. Of course, since Holthuizen’s seminal paper in 1936 [3] the overall aim of radiotherapy, as stated over and over again by all teachers in the field (including the authors of this editorial), is uncomplicated tumour control, i.e. loco-regional tumour control without severe normal tissue damage (therapeutic ratio). This implies that rigorous study of the effects of radiotherapy on normal, non-tumour, tissues is an absolute neces-

sity. Yet, the prescription of radiotherapy in clinical practice is done to kill tumour cells for local and loco-regional control. If the effects of radiotherapy on tumours are shifting out of focus, it might be taken for granted that the indication, dose, fractionation, and potential multidisciplinary interactions in this field are fully understood, and what remains is the fine tuning of the associated risk of morbidity.

This is in striking contrast to the first two decades of ESTRO’s activities in the 1980’s and 90’s, where attention was on optimising treatment on a radiobiological basis where the 4 or 5 R’s [4–7] were in focus, and large multinational trials explored and defined the indication, fractionation, hypoxic modification and chemo-irradiation in an attempt to improve curability. Good examples of this effort are reflected by the most cited papers from Radiotherapy and Oncology [5], and by the impressive meta-analyses activity of primary curative radiotherapy of squamous cell carcinoma of the head and neck [8–11]. These studies clearly point to improved outcome of cancer treatment if the basic radiobiological principles are considered [12,13]. But this lesson is not always learned – we are increasingly seeing a development where the tumour control is under challenge by attempts to de-escalate curative dose levels, not only in the primary treatment, but also in the adjuvant setting. The latter is not necessarily intentional, but often a consequence of the increasing use of hypofractionated regimes which de facto can result in a relatively poorer therapeutic ratio (more late damage relative to tumour control) [14], but where this is not observed because unnoticed, the “true” cancer treatment indication has been decreasing. This is likely the case with adjuvant irradiation of early breast cancer where the risk of local recurrence has

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dramatically fallen (because of changed biology and/or as a consequence of other treatment modalities) in recent decades while we have maintained the same level of indication for adjuvant radiotherapy [14]. The truth is, that we are seeing some tumours changing character, despite having the same label, e.g. the increasing influence of HPV on head and neck squamous cell carcinoma [15], and the previously mentioned increasing locally less aggressive breast cancer [16], but we are still treating as we used to do.

The problem

Radiation oncology is falling behind if we do not take advantage of advances in tumour biology which will allow individualising our treatment indication. Although a large number of research groups are working on e.g. biomarkers or new combination approaches for personalised radiation oncology (see below), we are lagging behind to translate them into clinical practice. Obviously, the same considerations on biology are also relevant regarding the risk of morbidity, but here we have actively tried to explore the practical possibilities, starting with the ESTRO GENEPIC project years ago [17], then Gene-PARE [18], and currently within the framework of the Radiogenomics Consortium (RgC) [19–21]. Unfortunately, aside from dose-volume and clinical parameters (which clearly have a biological basis), we are still without any practical clinical applications so far.

In our eagerness to make the technical delivery of our therapy better, and because of the great successes of advanced computer-based treatment planning and monitoring to avoid morbidity, we may have increasingly slipped into a situation where we almost forget that we are treating cancer in sick people. Yet, we deliver radiotherapy to patients, because they have a cancer that we assume can be controlled by our modality. Tumours differ from patient to patient, as do the patients’ other comorbidities. Therefore, the individual characteristics of the tumour and patient are of prime importance to define indications and treatment with radiation alongside the interaction with other modalities.

The biology

A personalised treatment approach requires accurate prediction of the response. Current imaging based clinical response measurements are generally insufficient for predicting radiotherapy sensitivity and optimizing individual cancer treatments [22]. For normal tissue, it is clear that the adult stem cells (ASC) play a major role in the regenerative response after irradiation [23], although the clinical implementation of this knowledge is still troublesome [24,25]. However, in many tumours, only subsets of cells have been found to possess cancer stem cell (CSC) properties with associated signalling driving tumour regrowth and resistance to therapy [26]. Interestingly, ASCs and CSCs can be cultured as patient-derived normal and tumour organoids (PDO) and used to assess radiation responses. Such organoid methodology to culture, passage and expand PDO showing cancer cell stemness and derived chemoradiation response data may allow assessment of personalised therapeutic ratio and prediction of treatment response [27]. Excitingly, the first papers appeared in 2019 showing that biobank-derived tumour organoids recapitulated the responses of locally advanced rectal and pancreatic cancer to chemotherapy [28,29] and since then many more papers on this topic were published [27]. More complex culture systems such as tumour and normal tissue on a chip combining organoids with stromal cells, vasculature and immune cells could further fine tune the predictability of PDOS. Indeed, gut-on-a-chip models have successfully been shown to recapitulate the radiation response of intestinal injury in vivo [30]. However, for the development of such models to be included in predicting patient responses in personalised precision therapies, the whole process of culturing and testing needs to be accelerated. Additionally, single cell gene expression profiling PDOS could yield signatures for rapid assessment of predictor of response. Combining PDO derived biomarkers with clinical imaging parameters may allow future optimisation of personalised treatments in radiation oncology.

The patients

We also should not forget that the way a patient perceives morbidity might be different from one person to another, even when treated for the same tumour type and with similar dose-volume parameters for relevant normal tissues. That is why patient-reported outcome measures (PROMs) are becoming more and more important in the field of radiation oncology. Indeed, PROMs may be more comprehensive and sensitive than clinician assessments of treatment toxicity and symptoms, as multiple studies show low concordance between patient and clinician rating of symptoms. Furthermore, clinicians who use PROMs reported enhanced awareness of their patients’ quality of life (QoL), emotional well-being and physiological experience, enabling them to consider a more holistic view of patient functioning. The wider implementation of PROMs in our radiotherapy practice, which is a relatively easy-to-use and low-burden method to follow patients during and after their treatment, might enable further personalisation of radiation therapy. Validated PROMS tools enable us to identify patients requiring specific attention and appear to correlate in a generalisable manner with objective scores [31–34]. Prospectively collected real world data that include the patient’s perspective can also add to predictive tools for personalised radiation oncology. These sets of tools and associated data can be linked with other sets of patient data via data mining and predictive modelling developments supported by artificial intelligence (AI) methodologies, to assist in personalisation of clinical treatment decisions, including the prescription. This arises from the possibility of providing personalised risk analysis and stratification from incorporating data reflecting the heterogeneity of patient, tumour and treatment characteristics and combining data from disparate sources, such as genomics, imaging, pathology, etc.

Personalised radiation therapy can mean many things; selection of radiotherapy over other modalities such as surgery, selection of radiotherapy modality and schedule +/- radiosensitizer according to tumour biomarker characteristics, selection of radiotherapy schedule and modality on the basis of patient preference. These are unfortunately not always mutually compatible; for example, patients wanting brachytherapy for prostate cancer because of its low toxicity profile, and short duration of treatment are not eligible for it if they have advanced disease unsuitable for brachytherapy. Patients who might benefit from cystectomy rather than bladder preserving therapy may refuse to have their bladder removed, and there are patients who refuse chemotherapy and ask for radiotherapy alone to aggressive lymphomas. Thus, true personalisation simplistically based on clinical and biological biomarkers will remain an illusion in a time in which the value of patient involvement and empowerment is increasingly recognized, calling for new partnership driven concepts — also in research! These challenges pose new demands on the clinician, who increasingly is encouraged to use shared decision making in daily routine. Making the patient understand gains and risks from a therapy is not easy, however, shared decision helpers and tools for facilitating shared decision making are being developed and tested, including in randomised trials [35].

There are situations where the decision to irradiate or not to irradiate is an open question, e.g. in selected elderly breast cancer
patients operated with breast conservation for a small luminal A cancer. Based on recent results from large randomised trials, the absolute gain from radiation therapy may be only 1–3% within 5–10 years, and such patients may prefer to omit radiation therapy and live with a slightly higher risk of local recurrence [36,37]. Indeed, several trials, such as the Danish Breast Cancer Group (DBC) Natural Trial (NCT03646955) now tests omission of radiation therapy in selected relatively low risk breast cancer patients. An expansion of these strategies is planned in the randomised DBCG Hamlet trial (‘to irradiate or not to irradiate that is the question’), which will test omission of radiation therapy in a relatively large group of patients (postmenopausal, post-lumpectomy and oestrogen receptor positive cancer, where the patient accepts systemic therapy). Such studies provide additional information to further strengthen the indication for radiation therapy.

The tools

Qualitative and quantitative imaging continues to play an increasing role in the personalisation of treatment. Images can help to assess the health status of patients before radiotherapy or during follow-up. For example, planning CT scans enable the evaluation of sarcopenia by measuring muscle density [38] or cardiovascular health by measuring calcifications [39] and ensure referral to preventive rehabilitation and specialist services (e.g. cardio-oncology). Quantitative molecular imaging from PET and MRI can help with dose painting for the individual patient and with adaptive treatment that is biologically-based, rather than simply geometrically-based, particularly with the growing availability of MRI-guided radiotherapy systems, offering the ability to monitor changes in quantitative MRI biomarkers during the course of the treatment [40]. Evidence continues to emerge that imaging biomarkers from PET and MRI have prognostic value and potentially are predictive for response [41]. More widely, the applications of radiomics are growing, using machine learning (ML) to extract combinations of image features to identify novel imaging biomarkers and to help generate predictive models [42]. Now the step needs to be made to act on the information such markers provide and test their value for personalising radiotherapy in prospective clinical trials [43].

Medical imaging can provide an important source of information and advance data science which can be used to pave new avenues in personalised radiotherapy. For example, in the context of radiomics analysis of imaging data in an automated and high-throughput manner, where finally machine learning algorithms create artificial intelligence (AI) based models to associate relevant imaging characteristics with the endpoint of interest, potentially combining different imaging modalities and time points [44].

Although promising results in tumour diagnosis or the prediction of treatment response have been obtained, mainly in retrospective radiomics studies, independent and prospective validation is often hampered by a lack of reproducibility. This may be caused by the inherent variability induced by analysing imaging data acquired in different centres, differences in the software used to perform the high-throughput analysis, and incomplete reporting. The Image Biomarker Standardisation Initiative (IBSI) was founded to improve the last two issues. It offers a reference standard for software verification, which significantly reduced differences between software packages, and suggests reporting guidelines for radiomics studies [45].

Most AI in medicine thus far is machine learning and there are a range of emerging applications in radiation oncology [46–49], linked to analysis and use of images or of other large digital data sets, and these are often used to support standardisation of methods and processes, e.g. in auto-contouring, knowledge-based planning, process control, quality assurance, etc. However, one significant application is in outcome prediction, of both survival and toxicity, including by modelling previous patient data from routine clinical databases and applying the models to future patients [50–53].

It may be expected that digitisation in radiation oncology will improve the performance of AI-based models for personalised treatment in the future due to the acquisition, analysis, and exchange of increasingly large multi-centre datasets, integrated analysis of medical imaging, biological, patient-related and environmental data, and accelerated validation of AI models in prospective trials. Such use of AI-based models for treatment personalisation will pose new challenges for both clinicians and patients. One specific aspect is model interpretability, i.e. to understand why models suggest a specific action, which is less clear for more complex models. Easily understood dashboards have to be developed, which show the key features on which the automated decision is based, their impact on the decision process, and inherent interactions. Probability estimates and confidence intervals may demonstrate the certainty of the algorithm for the different potential options and to guide clinicians and patients. [54,55].

Discrimination of specific patient groups may be incorporated into AI algorithms by imbalanced training data. To avoid such biases these data should reflect the actual patient population and important characteristics, such as age, gender, ethnicity, education, comorbidities, medication, and should be assessed and incorporated. Generally speaking, large data sets are better suited to derive AI algorithms, calling for data sharing in the community. Continuous model update and improvement is required to include demographic, procedural and technological changes and to increase the accuracy of the models. To empower patients in their treatment decision, open-source software demonstrating the impact of the input parameters on model output can be provided as web-based or using mobile apps, combined with relevant information on the available treatment options. With sufficient expertise and interest, motivated patients may even be able to study the source code of the algorithm to understand its function or to participate in its further development. Such active participation in the treatment decision process may increase the acceptance of AI-based personalised radiation oncology and general patient satisfaction with the treatment process [56,57].

AI also has the potential to provide evidence-based clinical decision support systems (DSS) that support and augment personalised clinical decisions, particularly as models extend to include additional data items including those above. Beyond merely informing the clinician, there is also the potential from knowledge of the personalised risks to include the patient’s individual risk preferences and concerns into a shared decision-making (SDM) process. However, there are many remaining issues and challenges with AI/ML-based predictive models and DSSs [47,53,58,59]. These include: standardisation of tools and data extraction methods; data completeness, robustness and diversity; data privacy and security; model validation for applicability and performance accuracy; commissioning and clinical implementation and ensuring such tools are integrated into radiation oncology workflows; transparency, interpretability, clinical user confidence and patient acceptance. Nevertheless, they provide powerful potential to integrate all possible sources of evidence to inform clinical decisions for personalised treatment and are gradually moving closer to larger scale implementation and evaluation. In time, these may form the basis of a wider ‘learning health system’ infrastructure in oncology [53].
The challenge
In addition to the developments described above, the multidisciplinary platform on which we operate in cancer treatment is dramatically changing, and not least the interaction between radiotherapy and the immune system which has recently been highlighted, paving the way for new combined approaches that may improve local control and enhance systemic anti-tumour immunity [60]. A direct consequence of this emerging concept is to rethink the optimal radiation dose, fractionation, and scheduling of radiation and immunotherapy delivery to maximize the synergy between irradiation and immune response. An additional level of complexity is represented by the strong immunosuppressive effects of radiotherapy that induce lymphopenia which inversely correlates with survival and suggests that irradiated volumes (in instances involving larger blood vessels potentially also dose-intensity) could be optimized to minimize deleterious radiation-induced leukopenia. Finally, the complexity of the immune consequences of irradiation on tumour antigenicity, on the different cellular components of the innate and adaptive response, combined with the great heterogeneity of the tumour immune stroma, suggests that personalised medicine will be needed to get the most out of combinations of immunotherapy and radiotherapy, highlighting the need for more complex biomarkers [61].

While radiotherapy is developing in a technical sense, even more than most other medical specialties, and has taken advantage of modern computer technology, it is at risk of falling behind in the multidisciplinary treatment approach, because we are at risk of forgetting to focus on the cancer diseases we are treating, while giving treatment-related morbidity all our attention. What is needed without neglecting normal tissues, is to regain focus on the tumour and not least their individual biological differences which in turn may influence the indication for, and magnitude of our therapeutic effort. The future demands personalized radiotherapy taking both the tumour, the healthy tissues, and the individual patient into consideration.

Thus, it is our foremost task to develop such personalised radiotherapy ontology within the multidisciplinary framework of cancer treatment – it’s so obvious that we can tend to forget about it.

References


