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Editorial

Clinical research for global needs of radiation oncology

The demand for radiotherapy (RT) is increasing worldwide due to population growth as prominently seen in Africa, and increasing population age as prominently seen in Europe. Increasing age, particularly over 60 years, is associated with a significantly increased risk of cancer. Additionally, RT is more often prescribed over other modalities, such as major surgery, for frail, multimorbid and elderly patients. In some regions of the world, more cancers are now being detected earlier and treated more effectively, leading to longer survival but also to the risk of recurrence, new malignancies and late effects. More than half of all cancer patients benefit from RT [1]. However, despite its cost-effectiveness, RT is currently either not available at all or only for a small proportion of cancer patients in a disturbingly high number of countries worldwide [1]. In many other countries, including some high-income countries (HIC), the RT capacity is already limited, causing long waiting lists. In general, RT services are frequently insufficiently prepared for the growing numbers of patients expected in the coming years. These observations clearly call for major strategic investments in RT, particularly in low and middle income countries (LMIC), in parallel with general improvements in health care systems. The global radiation oncology community needs to be alert and vocal in order to accelerate relevant policy advances, which might otherwise be deprioritized, bearing in mind the many international and national crises.

Research in radiation oncology may have additional positive impact for cancer patients worldwide by addressing global needs, frameworks and resources. Conversely, rapid scientific advances have the potential to further exacerbate existing disparities in access to high quality cancer care between LMIC and HIC [2]. A recent review by Jaffrey and colleagues of the status of RT discussed how the global radiation oncology community could formulate a more integrative 'diagonal approach', in which the agendas of science-driven advances in individual outcomes and the socio-technological task of global cancer control can be aligned to bring the benefits of RT to cancer patients everywhere [3]. This 2024 Radiotherapy & Oncology New Year's Editorial looks at some contemporary examples of such a diagonal approach for global impact, with a focus on clinical research and trials.

Clinical impact through a thorough redefinition of the indication for RT and the prescription of effective treatment schemes

The indications for RT consequently need to be continuously reviewed, not least for the cancer types that take most of the beamtime. For example, recent studies in early breast cancer have described the safety of omitting RT in selected low-risk patients [4,5]. Several randomized trials are currently ongoing to explore omission of therapy in more patients (NCT02889874, NCT03646955, NCT04852887, NCT04134598). The same applies to rectal cancer [6], where the possibility of forgoing RT is currently being intensively discussed. At the same time, in selected other cases, it is an attractive option to rely on RT to avoid surgery [7].

On the other hand, a survival gain has been found in high-risk breast cancer patients when loco-regional RT includes the internal mammary nodes, so a sub-group of patients will require more advanced planning to achieve optimal target doses with low doses to organs at risk [8]. Further exploration of the relevant target for RT has revealed external beam or brachytherapy based partial breast irradiation as a new standard for selected breast cancer patients which may lead to faster treatment planning and delivery in addition to reduced morbidity without a higher risk of recurrence [9–11]. Currently not much information is available on the risk profiles for omitting or reducing RT in different global populations, and there is a general lack of clinical, and particularly of genomic and biomarker, data for cancers in LIC. Research along these lines is highly warranted before dose-modifying trials (de-escalation or escalation) of RT can be appropriately expanded beyond the populations included in clinical trials so far.

The use of hypofractionation (higher doses per fraction, lower total dose and fewer fractions) is one way to reduce the demand for RT machine capacity, and a series of large breast cancer trials have successively paved the way from 25 fractions to 15 and in some cases 5 fractions with increasing dose per fraction [12–16]. Also, in prostate cancer the number of fractions has decreased from around 39 fractions to 20 fractions being an accepted therapy, and even 7 fractions for selected patients [17–19].

Thus, hypofractionation has proven to be feasible in some early (localized) or adjuvant treated prostate and breast cancers. This is most likely due to the lower volume of normal tissue irradiated. This may be achievable for other sites using more precise radiation modalities, potentially allowing effective hypofractionation for more tumors and their affected normal tissue [20]. However, a better knowledge of the volume effect of the normal tissue is needed. Clear examples of volume-dependent differences in the mechanism of the normal tissue response have been found in preclinical models and in translational studies [21–24]. Therefore, to allow safe and optimal application of hypofractionated schedules, the limits of what levels of irradiation a specific volume in each normal tissue can tolerate what levels of irradiation need to be established.

In addition to preclinical research into mechanisms involved in the normal tissue response to hypofractionated schedules, careful monitoring and reporting of early and late responses is needed, as performed in Europe for proton therapy [25], including biomarker-related research [26].

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The apparent or practical benefit of hypofractionation is a consequence of more precise treatment delivery. It is only effective in situations where a reduced non-critical irradiated volume is involved. However, it must be clearly emphasized that hypofractionation in general is a radiobiologically inferior fractionation scheme with a poorer therapeutic ratio [27] and that, in fact, the opposite is correct: hyperfractionation with a large total dose delivered in small fractions is the biologically most advantageous way to eradicate a tumor [28]. It is important to understand, that classical radiobiology has not changed, but the physical possibilities of targeting the irradiation have allowed us to be more biologically relaxed.

Therefore these results should not be transferred to treatments where we have not reached the full curative potential. Similarly, hypofractionation results obtained with advanced equipment cannot be easily transferred to RT systems that are not suitable for precision therapy. There are still many patients suffering from treatment failure and radiation sequelae after RT, and it is our responsibility to ensure that they achieve the most effective treatment in terms of therapeutic ratio, not necessarily the most resource efficient or comfortable treatment.

The interplay between technology, staffing and training

It is important to note that the successful use of advanced technology is not necessarily limited by the availability of equipment (often purchased as a one-time investment), but requires that the entire system is supported by sufficient numbers of trained personnel. Continuous training is required for all staff involved, including RTTs, physicists and oncologists, in order to apply modern image guidance and adaptive RT procedures. The European Core Curricula (https://www.efomp.org/index.php?r=news/view&id=269) provide a framework for such training and the ESTRO school courses (https://www.estro.org/courses) address some of these needs, although they can only complement high-quality local and national programs [29]. High quality educational programs always need to be adapted to specific needs, but are a basic requirement for advancing our discipline at a global level.

Using nasopharyngeal cancer as an example, a coordinated research project conducted under the auspices of the IAEA showed that the poorer outcomes in LMIC were due not only to a lack of equipment and manpower, but also to the quality of RT planning. Substantial improvement could be achieved through training and feedback from international experts and the establishment of peer review in local institutions. The shortage of highly trained and specialized personnel can be partially mitigated by the widespread adoption of carefully validated automation and artificial intelligence (AI) approaches, as described in the recent May 2023 physics special issue of Radiotherapy and Oncology (https://www.thegreenjournal.com/issue/S0167-8140(23)X0005-X). By accelerating processes such as image segmentation and treatment planning, AI may improve cost-effectiveness and help increase standardization and quality of treatment delivery. This could particularly benefit departments in smaller and non-academic centers, especially with respect to segmentation and planning. New standards and levels of quality can potentially be reached without going through the full development cycle, building on the work of the centers that have developed such tools with industry, or early adopters whose evaluation and improvements have contributed to making these tools available for the wider RT community. While AI is currently seen as a helpful tool, we must be aware that there is a long-term risk of losing knowledge by introducing AI methods. Future generations will be trained based on AI technologies, without knowing and practicing the underlying skills (e.g. contouring), which may consequently be lost. In addition, all such tools need the same levels of careful implementation, commissioning and ongoing quality assurance as any other technical RT system in each department.

Data-driven clinical trials of the future

Ideally, every cancer patient should be offered at least one clinical interventional trial during the course of treatment, but this is far from the standard. There are several obstacles to conducting a trial. First, it is challenging to secure funding for large international trials and registries. Overall, only about 6 % of cancer research papers are in the field of RT. Importantly, only about 5 % of these are related to clinical trials [30]. The radiation oncology industry is not able to fund trials to the same extent as the pharma industry because of the fundamental difference in the business model: innovations in equipment are not directly linked to one specific treatment. Thus, industry cannot monetize these inventions to the same extent as the pharma industry. The biggest challenge, however, has been low enrollment in traditional trials. It is estimated that more than half of cancer patients are not treated in hospitals where trials are available, and only 8 % are enrolled in a trial [31,32]. Radiation oncology trials not involving fancy technology are relatively simple and cheap to conduct, and the main barriers to performing clinical trials are within the radiation oncology community itself. Most clinical trials take place in a few local, national or regional clusters, and are associated with different disease or technical related environments or groups that have a tradition of collaborative activities. Greater attention to evidence-based and -generating science at ESTRO meetings may also help to stimulate and spread such activities.

While evidence-based practice should be considered the gold standard for all, it is clear that the majority of clinical trials with strict entry criteria are not necessarily representative of the general population undergoing treatment. Ethnic minorities and less privileged socioeconomic groups, patients with co-morbidities, including psychiatric problems, are under-represented in trial populations and generally have problems with RT compliance [33–35].

Real-world data consistently show under-performance compared to trial data. Greater efforts should be made in clinical trial design and patient accrual to ensure a representative population, thereby enhancing the external validity of trials and increasing the likelihood of adoption. In addition to seeking evidence from randomized trials, future evidence may increasingly come from more real life phase 4 generated data based on well-characterized (prospectively recorded) population databases which are used as a background for an inferior or superior design of new treatments [30]. This will directly give us the needed information on feasibility and impact of new activities. It will also add to our understanding of the impact and influence of recommendations and guidelines [36].

However, such initiatives do not bridge the gap to LMIC, where state-of-the-art RT equipment, clinical trial infrastructure or electronic infrastructure for modern data management are less widely available. To help reduce the cancer burden, these countries need adequate access to state-of-the-art RT, but also to clinical trials. The latter has been directly addressed by the IAEA PACT initiative partly funded by the 2005 Nobel Peace Prize [37], and a number of clinical trials aimed to explore and develop RT in these countries [38–41]. Ideally, such trials should focus on treatment optimization in tumor sites that have a high frequency in these countries but are rare in richer countries, e.g. liver cancer, gastroesophageal cancer or cervical cancer [42]. More importantly, such action must be accompanied by a tailored intense collaborative educational effort, as already implemented with the ESTRO school as an important partner [43,44].

All of this may not happen without placing the patient at the center. We are treating humans, not just tumors, and all aspects of the patient's life and situation should be fully integrated into the care. From the perspective of patient involvement in the care pathway, besides being the subject of studies through measurement with PROMs, the emergence of new research streams involving the use of art in its various modalities is being seen [45] to improve oncological outcomes and patients' quality of life. Through personalized services using architectural settings, digital media [46] and measurements of markers related to patients' stress

[47], the potential of humanized medicine is attracting research groups and fostering international collaborations in the field of RT. In addition, patient experts are playing an increasingly important role as research partners, for example, in helping to define trial endpoints from the patient's perspective, in assessing the attractiveness of a particular clinical trial project, and in helping other patients to learn about and access clinical trials.

The majority of clinical trials in RT have been focusing on dose modification in various organs, optimization of dose conformality (NCT05731791, NCT04909294, NCT04607694) and concurrent RT – systemic therapy strategies. It is important to note that whenever RT breaks new ground with new technologies or indications, the gains appear to be higher than by simply applying improved standards in a changing multidisciplinary approach. In this respect timelines are important, as other areas of oncology are also moving quite fast; FLASH therapy took more than two decades from first concept to early clinical application [48], similarly clinical evidence from randomized controlled clinical trials (RCT) is still awaited for protons in several tumor types. Therefore, whenever RT can address new challenges, push frontiers, and also generate evidence to fundamentally redesign treatment strategies, the impact may ultimately be greatest both for practice and patient outcomes. To illustrate this, the 50 years old concept that contact-therapy can markedly increase organ preservation in early rectal cancer is now supported by a RCT [49].

Such examples underscore the potential to integrate and constantly rethink the positioning of our discipline, expertise and tools within the multidisciplinary armamentarium available for cancer care. All aspects must therefore be considered when reassessing the positioning of RT and we need to revisit the important questions and concepts of total dose and target volumes in an era of personalized treatment [50]. Collectively, we should be able to foster challenging trial designs, and generate hypotheses for novel treatment schemes. The success of integrating SBRT in the management of oligometastases is a perfect illustration of the fact that high returns are achieved when clinical research changes not only routine but also modifies the patient's journey [51,52].

At the same time, technological developments in imaging, RT planning and delivery, together with the potential for biomarker patient stratification, are opening up the possibilities for more individualized care [53,54], Thus, increased personalization and the integration of multiple source omics into the treatment workflow is certainly the future. The cost of RNAseq, ctDNA is expected to decrease, while imaging accuracy will constantly evolve [3,50].

One might think that the systematic integration of such innovations into large scale randomized trials and cohorts, for which logistical pragmatism and budgetary issues intrinsically limit the completeness of biomarkers carried out, would be difficult. However, in-depth characterization of responders versus non-responders in selected subgroups or smaller series (repeated imaging, sequential blood and tissue sampling) is highly informative and leads to a better understanding of the biology underlying tumor response to RT [52,55], and should translate into high precision decision and treatment allocation, and to better and more informative trials. Initially costly broad research approaches can, if successful, be transferred into focused, cost-effective tests and devices that can become widely available.

While the lack of financial and industrial support for research in RT will continue to make some developments in our discipline challenging, we should continuously and collectively advocate on how basic, translational and clinical research in our field has the potential for massive changes in patient care illustrated by more organ preservation, decreased toxicity and better survival far beyond minimal incremental changes. Our field is far from plateauing, but we will need to take risks in our research hypotheses and challenge our concepts.

For the future conduct of what will hopefully be a rapidly increasing number of multicenter clinical RT trials, whether local, national, regional or global, artificial intelligence and automated treatment planning offer very significant opportunities [3,56]. For example, after uploading pseudonymized CT scans, dedicated software can centrally perform automated contouring and generate treatment plans, which can then be imported into the local treatment planning system and adapted to the specific treatment device. Finally, the plan needs to be reviewed, adapted and approved by the local team. Such software could speed up throughput, lower costs and standardize the quality of RT, thereby enabling its extended use in LMIC. It could also streamline clinical trial quality assurance and compliance. A similar approach is currently being investigated in the ARCHERY study [57], and one such potential software solution is the Radiation Planning Assistant, currently being developed at MD Anderson [58]. Based on available treatment-planning imaging and generated segmentations, radiomics analyses can provide additional information for treatment diagnosis and outcome prediction [59]. Complemented by clinical data, this offers the potential to implement personalized treatment approaches through clinical research partnerships on a global scale, in line with the ESTRO Vision 2030: "Radiation Oncology. Optimal Health for all, together".

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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