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EDITORIAL

EXPERIMENTAL RADIATION ONCOLOGY. A REAL EVOLUTION TOWARDS A PRECISION THERAPY?

Luigi **Pirtoli** [1], Marcella **Barbarino** [2], Rocco **Giannicola** [3], Pierpaolo **Correale** [1,3], Valerio **Nardone** [4,*]

[1] Sbarro Institute for Cancer Research and Molecular Medicine, Center for Biotechnology, College of Science and Technology, Temple University, Philadelphia, PA, USA
[2] Department of Medical Biotechnologies, University of Siena, Siena, Italy
[3] Medical Oncology Unit, Bianchi-Melacrino-Morelli Grand Metropolitan Hospital, Reggio Calabria, Italy
[4] Department of Precision Medicine, L. Vanvitelli University of Campania, Naples, Italy
* Correspondence to: valerio.nardone@unicampania.it, https://orcid.org/0000-0002-7347-0965

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UNDERSTANDING RADIATION THERAPY: THE EARLY SCIENTIFIC THINKING AND STILL STANDING FUNDAMENTALS

Along the last two decades an incredible amount of knowledge concerning the molecular pathways, and the immunobiological and microenvironmental mechanisms allowing cancer development, the mechanisms of metastases and treatment resistance, has risen thanks to a multidisciplinary coordinated efforts. At the present, clinicians can count on a clearer picture that allows them to define the best oncological treatment on a personalized based medicine. On these grounds, we believe that both radiation therapy (RT) and oncological pharmacology (including chemo-immuno and molecular-target therapy) are two fields in which a strong cooperation and a mutual exchange of information and scientific integration are needed. This work is, therefore, directed at both Radiotherapy and Oncology residents, with the aim of providing a common scientific perspective.
RT contributes to the success of most oncological multi-disciplinary treatments, but its inherent role is less easily understandable by clinical oncologists on mechanistic bio-molecular grounds, compared to pharmacological agents. The present manuscript addresses this shortcoming, for possible experimental developments aimed at "precision RT".

HISTORY OF RADIATION THERAPY

The early years

At the beginning of the twentieth century, a revolutionary paradigm change occurred in physics, that is, a new point of view on science, based on two conceptions: 1) a shift from the immutable natural laws to the awareness of "events", critical for any transformation; 2) the irreducibility of probability for scientific analysis (The International Conference on Electron and Photons, Brussels 1927). These concepts remarkably influenced the development of RT of human malignancies, after the WC Roentgen's and M Curie's discoveries (X-rays, 1895;

Radium, 1899, respectively) already undergoing a fast implementation in medicine (radiological diagnosis and RT) and gave rise to "quantitative" radiobiology. The involved medical scientists borrowed the physicists' approach for investigating the results derived from empirical observations, in absence of any mechanistic interpretation, with mathematical modelling of radiation effects. Skin cancer was the first field of clinical radiobiology, due to the visually perceptible response to external beam X-ray therapy in terms of both tumor regression and healthy tissue reaction. Increasing radiation doses delivered in several fractions over time, progressively achieved better therapeutic results (healing of cancer) but increased also incidence and severity of radiation adverse effects (AE: erythema, dry and moist desquamation, *etc*., up to necrosis), whereas time exerted a modulatory influence in both cases. Pioneer scientists guessed that these relationships were multi-factorial but couldn't demonstrate the causal links: they only observed non-linearity in the cause-effect plotted graphs. Non-linearity, multi-factorial interactions, opacity of the mechanisms underlying the observed emergence (that is, "complexity") were challenges the scientific thinking was facing in the years at the midst of the 20th century, thus math modelling provided useful tools for investigating complex phenomena, such as radiation biological effects. In fact, a formalism was devised (1), that is, plotting the various dose-time parameters for the same outcomes (the non-linear "isoeffects") resulting in straight lines on logarithmic graphs, whose angular coefficient is an obtainable, quantitative parameter, *i.e*., anexponential factor. This method was shown reproducible and fitting to skin (skin cancer cure and AEs), thus grounding successful applications for clinical purposes, also in other neoplasm contexts.

Development of radiobiology and preclinical models

In the meanwhile, radiobiology lab experiments on cell cultures showed that the probability of cell death due to radiation is dependent on radiation dose (hit/target theory), according to the Poisson's negative exponential relationship. Surprisingly, the killing effect at low doses was less than expected as the dose-survival curve showed an initial "shoulder," suggesting the possibility that more than one target per cell should be hit to obtain cell death. All together these findings led to the definition of a "linear quadratic (LQ) model". This was based on the theory of few single- and non-repairable lethal hits at low doses (single target), and of two-target hits for cell death at higher doses (2). The conceptualization of this model came around the fifties of the last century, almost contemporarily with the discovery of the double-helix structure of DNA, thus providing a strong suggestion for the centrality of DNA as the main target for radiation cell killing.

The practice of fractionated RT (typically 2 Gy each daily session (dose-per fraction: dpf), per 5 days a week, up to total doses (TD) of 30-80 Gy in 3-8 weeks) was adopted in the meanwhile for clinical external beam radiation therapy (EBRT), even if the time factor was not considered in the LQ model. The above typical schedule - which is still largely used - is based on the flatness of the "shoulder" of the LQ function, considering that rapidly growing substrates, responding with early effects to radiation (*e.g*., cancer cells and high-renewal tissues) show a flat shoulder. Thus, fractionation impacts less on the outcome, compared to late-reacting tissues (vascular endothelia, connective, low-renewal-normal tissue in general) characterized by a more bowed shoulder. Given that the late-reacting tissues are deemed responsible for the severe, irreversible AEs of high dose of radiation (3), a markedly fractionated treatment can obtain a good outcome on cancer with tolerable AEs. In fact, early responding healthy tissues can have brisk acute AEs, reversible in most cases (but less reversible in many cancers) and late severe damages, such as necrosis, are normally avoided. In short, early *vs.* late reacting tissues are distinguished based on the " ratio" parameter: it is high in the former and low in the latter ones. Note that the ratio is – dimensionally - a dose (inGy), as an exponent is a pure number by definition; thus are the inverses of a dose. This conceptualization found a sound confirm in the isoeffects of early and late responding tissues, revisited on these bases. A plain conformation resulted for the former, compared to the greater slope of the latter isoeffect curves, respectively (4), thus providing the basis for a favorable therapeutic index achievable by fractionation.

Contribution of imaging technology in the newest era of radiation therapy

The explosive progress of the last thirty years in the field of imaging technology (CT, MRI, US), has improved the effectiveness of external beam radiation therapy (EBRT) for deep-sited tumors, en-

hancing control rates due to the reliable assessment of disease extension, shape and location, better definition of tumor response and radiation AE to surrounding healthy structures. The analysis of the available, reported data of these aspects is mandatory for the optimal benefit/damage ratio, that is, tumor control probability (TCP) *vs.* normal tissue complication probability (NTCP), respectively. An optimization of the TCP/NTCP ratio can be achieved, based on the most suitable radiation sources and treatment planning facilities: technology provided very sophisticated resources to these purposes.

Physical precision radiation delivery for precision oncology

The advanced technology of the radiotherapy machines, including particle beam sources presently allow precise high dose delivery to the tumor volume, thus sparing the surrounding healthy tissues with pronounced gradients. This impacts on the most diffused practice with linear accelerators for high-energy (6-25 MeV) photon beam EBRT, due to low surface dose, high deep dose deposition, reduced laterally scattered radiation, homogeneity in dose distribution among tissues of various mean Z-number, *etc*. Technical tools were implemented for multiple-field convergent irradiation of the target volume in three-dimensional arrangements, along with the possibility of shaping accordingly the cross-sectional conformation of each beam through multi-leaf collimators (three-dimensional conformal RT: 3D-CRT) that can also modulate the photons' intensity inside of the beam (intensity-modulated RT: IMRT), enabling the targeting of irregular shapes (or even to achieve different dose level inside of the target). Of course, this evolution was possible due to the contemporary development of advanced imaging resources, which is CT, MRI, PET-CT, *etc*., and of computer science. Shrinking of the tumor during treatment allows "adaptive RT" (ART). The sophisticated calculation algorithms, presently available, are outstanding scientific results whose coverage, however, is beyond the scope of the present paper.

High dose selectivity to the tumor is maximized in stereotactic RT (SRT, based on many thin, non-coplanar beams rigorously converging on a usually small focus, precisely defined by 3D spatial coordinates), that scales down the importance of fractionation and can achieve tumor "ablation" (stereotactic ablative RT) in a single high-dose session (stereotactic radio-surgery, SRS) or a few fractions. Particle (proton or heavy-ion) beams, produced by synchrotrons, on the other hand, give advantages in dose deposition, due to an increased ionization density at a given depth, which depends on the initial kinetic energy impressed to particles (a phenomenon denominated "Bragg peak") with improved volume selectivity. For heavy ions (*e.g.,* carbon ions), their high relative biological effectiveness (RBE) also improves cell lethality, mostly along the Bragg peak region.

EXPERIMENTAL CLINICAL RADIATION THERAPY: EVIDENCE-BASED AND TRANSLATIONAL ISSUES

The evidence-based approach (EBM, evidence-based medicine) for clinical research grounds the procedure of random comparative trials (RCTs) for innovative therapeutic disclosures. However, less RCTs were carried out in oncology for emerging RT modalities, compared to new pharmacological agents. The most advanced RT technology – in terms of precision in dose delivery - should be employed whenever available, without formal RCTs: a RT practice or technology overtly outdated as a control arm is deemed unjustified from an ethic point of view. Contrarily, it is mandatory to test an innovative RT setting - as the experimental arm - against a standard and reliable-modality of care, in the context of multidisciplinary approaches, provided that suitable endpoints are selected, as it was in the case of the following examples:

(1) Radical prostatectomy was tested in a RCT against RT for cure of localized prostatic cancer, with the result of equivalent outcomes of overall- and relapse-free survival (OR and RFS, respectively) (5).

(2) Mastectomy was compared to lumpectomy and to lumpectomy plus RT in a fundamental, three-arm RCT, with the former and the latest groups showing equal OS and event-free survival, whereas 40% out of the patients assigned to lumpectomy alone experienced mammary relapse (6).

(3) Total nodal RT (supra-diaphragmatic mantle- and infra-diaphragmatic inverted Y-fields) was abandoned, for the cure of Hodgkin's disease, in favor of limited- or involved field irradiation with the advent of effective chemotherapy (CHT) schedules, given the high incidence of heavy adverse ef-

fects - including second cancers - of wide radiation volumes after prospective trials performed during the last decades of the nineties (7).
(4) Similarly, RT volumes for full- or post-operative treatment of locally advanced lung cancer were reduced in favor of limited-field treatment associated with CHT, after RCTs (8), without significant differences in survival results, but with a less incidence of lung fibrosis due to the reduced volume-RT.
Brain metastases are no longer undergoing whole brain irradiation (WBI) as a standard approach - with rare exceptions - after the RCT demonstration of better outcomes by SRS (9), even in patients undergoing Tyrosine Kinase inhibitors (10, 11).

Clinical and biological considerations

Thus, there is an evident, general trend towards a RCT-based, modulated use of RT in the context of multidisciplinary treatment of cancer. However, it can be remarked that only in the last one, out of the above examples, the hypothesis grounding the RCT was based on a biomolecular determinant. Many excellent and extensive reviews are available (12), concerning genetic and biomolecular determinants (or markers) for a precision-driven use of RT in multidisciplinary approaches, also listing a multitude of ongoing RCTs on this subject, but few, reliable translational conclusive data have been published to date (13). However, this is exactly what should be necessary for "precision medicine" (precision RT, in this case).

Biological determinants and newest radio-oncological treatments

An example of how a biological determinant of radiation sensitivity can drive clinical trials and, subsequently, real-world RT practice is the case of Human Papilloma Virus-positive oropharyngeal cancer (HPV+ OPC) after the identification of the mechanisms underlying the high radiation sensitivity of these tumors, paving the way to the development of biologically-based, precision cancer therapy protocols, tailored for an enhanced TCP/NTCP ratio (14-16). Some drugs, such as cisplatin and paclitaxel, have the same anti-proliferative effects of RT, besides acting on systemic spread. Thus, systemic therapy can cooperate for both the local effectiveness of RT and can limit the metastatic spread. The validity of this theory was tested in some clinical experiences, such as the prospective phase II ECOG 1308 study (17) in which also the monoclonal antibody (mAb) cetuximab (targeting EGFR) was used besides platinum-based chemotherapy. Patients achieving complete clinical response after initial chemo- and mAb therapy (IC), that is, 70% out of seventy-seven evaluable cases, received a reduced-dose, standard fractionated IMRT course (54 Gy) associated with cetuximab, whereas less-than-complete IC-responding cases underwent full-course (70 Gy) IMRT and cetuximab. Results showed an optimal progression free survival (PFS) and overall 2-year survival (OS) (80% and 94%, respectively) in the former patients, and also the other ones, undergoing full dose IMRT, fared fairly well (OS: 67% and PFS: 87%, respectively), but with impaired swallowing (40% in the reduced, *vs*. 89% in the full-dose group) and a poorer nutrition status (10%, *vs*. 44%, respectively), due to mucositis.

Prostate cancer as a possible experimental paradigm for RCTs

Advanced technology-based IMRT or SBRT (body SRT), with high dose-deposition in an accurately defined target volume and sharp dose gradients, allows treatment of cancers (typically prostate cancer, PC) characterized by a low ratio (similarly to the surrounding healthy tissues, critical for late and irreversible adverse effects), and few large dpfs in a short time (hypo-fractionation, HF). In fact, in these cases extreme HF (in general 5 fractions, 6.5-7.5 Gy each and a total dose of 32.5-37.5 Gy, overall treatment time ≤14 days) may achieve superimposable (or possibly better) therapeutic outcomes and not substantially enhanced late, severe adverse effects, when compared to the standard fractionated RT (1.8-2 Gy per fraction, 5 fractions per week, up to 70-80 Gy in 7-8 weeks or more). However, the acute urinary and rectal adverse effects of HF may be contained due to the sharp gradients of the most advanced RT facilities. These hypotheses are tested in both clinical experimental phase III RCTs on localized low- or intermediate risk-PC (18, 19), and a multitude of random prospective reports (revised in 20). Biochemical relapse-free survival was reported in the 85%-100% range at 5 years in most series, with 0%-5% intestinal- and 1%-7% genitourinary chronic adverse effects, not significantly different from conventional fractionation. As expected, these results are coherent with the low alfa-beta ratio of PC (generally identified in 1.5 Gy) and similar values for late damages to the organs immediately adjacent to prostate (that is, rectum: = 3

Gy; bladder; = 3-5 Gy), confirming similar (or even better) TCP/NTCP ratio to extreme HF treatments. The reported aggressiveness of HR-deficient PCs and their response to PARP inhibitors (21) may be a clue for in-depth investigating possible personalized, multimodality treatment strategies, based on biological selectivity and associations with target drug therapy.

The genomic risk classification, integrated with clinical data may be, instead, an appealing approach for a "precision" strategy, recently hypothesized (22) but still lacking experimental confirmation in clinics, even if prospective trials are ongoing (NCT03070886, NCT03371719).

TUMOR MICROENVIRONMENT (TME), IMMUNOTHERAPY AND NEXT GENERATION SEQUENCING (NGS)

Recent advances in understanding the interplay between TME and resistance of cancer cells to treatments have sparked the interest in investigating the effects of the different RT regimens on the modulation of inflammation and immune response. RT induces increased vascular permeability, edema, and production of cytokines by fibroblasts and endothelial cells, attraction of macrophages and white cells in general, resulting in inflammation (3). It has been extensively demonstrated, in *in vitro* studies, that high dpf IMRT and SRT techniques cause enhanced vascular damage to the TME, whereas standard fractionated (SFRT) induces less endothelial and mesenchymal damage. In fact, a still persistent oxygen perfusion was considered advantageous for cancer cells early re-oxygenation (and ROS generation) during the progressive tumor shrinkage along a SFRT course: thus, a theoretical limit of TCP for the short-course HF RT has been - probably erroneously - hypothesized for the less time allowed to inter-fraction tumor re-oxygenation. Conversely, experiments on animal fibrosarcoma models with single 20-30 Gy radiation doses have shown that the induced reduction in blood perfusion and hypoxia resulted in impaired tumor cell clonogenicity in *in vivo-in vitro* excision assays, related to overexpressed VEGF, HIF-1α, and carbonic anhydrase-9 (23). Thus, the overturning of the hypoxia paradigm in extreme HF RT may be the subject for clinical prospective research, addressing the possible molecular markers and tailored treatment modalities in different neoplasms.

Cancer immunity and Radiation therapy

Due to the established link between inflammation and cancer immunity, the immunomodulatory role of RT is, therefore, of great interest. With a typical 3 x 8 Gy schedule, regression of tumors was observed in different *in vivo* models even in distant sites not exposed to treatment, a phenomenon called "abscopal effect" (AbE) of RT (24). This term derives from the Latin (*ab*: distant from; *scopus*: intent) and describes the effect of tumor cytolysis out of the irradiated field, resulting in the regression of other neoplastic localizations, as shown by sporadic clinical observations reported in the last fifty years. Approximately 50 cases have been reported after RT alone since 1970, a number that rose to 3,500 patients when RT was associated with the most recent immuno-oncology treatments, that began their clinical development since 2012. For the potential clinical benefits of RT treatment in combination with immunotherapy, a multitude of preclinical and clinical studies, including 30 prospective clinical trials, have addressed - or are addressing - this specific topic (25). Therefore, it would be of great interest, in particular to set up the optimal biological and clinical conditions for triggering the AbE with RT in combination with PD-1/PDL-1 and CTLA-4 immune-checkpoint inhibitors (ICIs).

Clinical investigations mainly focus on some tumor types, including non-small lung cancer (NSCLC), melanoma, bladder, kidney, head and neck cancers, that have shown sensitivity to anti- CTLA-4, PD-1, and PD-L1 mAbs and may take advantage of RT on specific sites (26).

As we have elsewhere summarized (27), RT induces release of antigens by damaged or dyeing tumor cells and activates the immune-priming by enhancing a specific immune response. RT can potentiate a tumor-specific immune response by 1) damaging the DNA and thus inducing neoantigen processing and their presentation to modulatory T cells and cytotoxic tumor lymphocyte (CTL) precursors, which are induced to proliferate in the regional lymph nodes, 2) producing inflammatory cytokines and chemokines (*e.g.*, CXCL16) and tumor vessel-associated adhesion molecules (VCAM-1, ICAM-1) harvesting activated tumor infiltrating lymphocytes (TILs) 3) improving cancer cells susceptibility to specific immune effectors through

upregulation of HLA molecules and death receptors (FAS, NKG2DL, *etc*.).
Overall, the available studies aimed at addressing the best therapeutic conditions and at identifying suitable predictive and prognostic markers, are extremely heterogeneous for the RT technique, dosage (TD, dpf), treatment timing, and type of ICI used in combination. However, a "canonical" 8 Gy x 3 schedule (24) is usually administered with SBRT, that may be not suitable for all therapeutic applications (*e.g.*, RT for definitive cure), highlighting the need to establish a comprehensive research framework for the future studies. In fact, most RCTs on radio-immunotherapy are not primarily aimed at defining the most effective RT modality in this context (28), but mainly at optimizing the use of the immunotherapeutic agents.

Next Generation Sequencing and Radiotherapy

Precision oncology, where patients are given therapies based on their genomic profile and disease trajectory, is rapidly evolving to become a pivotal part of cancer management, supported by regulatory approvals of biomarker-matched targeted therapies and cancer immunotherapies (29).
Precision Medicine in Radiotherapy can be investigated from a point of view of sensitivity to ionizing radiation, both for healthy tissues and for cancer cells.
Radiation therapy is associated with a spectrum of early and late tissue lesions; however, within a group of identically treated patients, there is a great deal of variability in the incidence and severity of radiation sequelae (30).
This concept is also identical with regard to cancer cells, as clinicians cannot identify responders from non-responders before radiotherapy (31, 32).
From this point of view, in the clinical setting there are still no screening tests that can allow you to identify these categories a priori, which ideally would allow you to choose to perform radiotherapy or alternative methods, or even modulate technique, dose and fractionation to enhance or limit the radiobiological effects of ionizing radiation on healthy tissues and on cancer cells.
New information on the molecular mechanisms underlying this sensitivity comes from studies which evaluate associations between common polymorphisms in DNA damage detection and repair genes and the development of adverse reactions to radiotherapy (33-35).
Furthermore, this correlation between biomolecular and genetic determinants and cell damage from radiotherapy can make use of modern approaches based on artificial intelligence and neural networks, entering the world of -omics (36).

CONCLUSIVE REMARKS

Radiation therapy evolved over a time lapse of about 120 years in a scientific process based mostly on math modelling of empiric clinical observation and lab experiments, leading to coherent and reliable conceptual paradigms, that are still reference points in many oncologic clinical settings. On the other hand, mechanistic investigations on the bio-molecular determinants grounding RT have been also implemented since the half of the last century, not only concerning the DNA damage and repair, but also the RT-induced effects on cell membranes, lipids and proteins, and including also TME and healthy tissues. For brevity, we did not attempta general coverage of these subjects, that have been extensively and in-depth treated by other authors (37).
A limited translational outlet of biomolecular disclosures followed, apart from pre-clinical studies on RT interactions with anticancer drugs. Many efforts in lab radiation research have been devoted to disentangle the opacity laying beyond the math models by explicative genomic and molecular disclosures, however without strict connections with clinical investigations. Further - since the last decades of the nineties - the overwhelming developments of the RT facilities and the related computer science provided effective tools for optimal dose/volume arrangements that "personalizes" cancer RT for safe and effective TCP/NTCP ratios, often sidelining the relevance of the mechanistic, molecular radiobiology. The paradigm of 1.8-2 Gydpf over long treatment times was progressively left behind, in favor of the short-course HF schedules aiming at sub-ablative or ablative effects on cancer. Satisfactory outcomes followed in many cases, due to the sharp fall-off of the dose at the borders of the treated volume. In the meanwhile, the categorical imperative of the RCTs caught on in the medical scientific thinking, to support EB results. In fact, as we hinted at before, RCTs do not necessarily require a sound, experimentally grounded mechanistic hypothesis that is almost considered an added value. More, the highly circumscribed

dose/volume around the tumor target of the most updated RT regimens requires combinations with anticancer drugs, similarly to surgery. Thus, the experimental trials in clinical oncology usually include RT as a merely debulking or even a palliative tool, hampering its scientific development as a still evolving, molecular based "precision medicine" field. For instance, these considerations apply for hormone dependent tumors, such as the estrogen positive-HER2 negative breast cancer where RT combined with aromatase- and CDK inhibitors may further modulate the cell cycle at the G1/S restriction point (recently revised in (38)), in which the outcomes may be impacted by the modalities of irradiation. Few systematic prospective research projects seem to meet this point.

However, an exciting stimulus comes from cancer immunotherapy but, also in this case, some processes must be reconsidered. As has been suggested (28), the algorithms of RCTs and the related pre-clinical investigations should address the RT modalities (TD, dpf, volumes, timing, *etc*.) as primary, independent variables, whose biologically-related mechanics should ground the leading hypothesis. This research mode may be elective particularly for RT as a primary treatment for definitive cure in cancer immunotherapy settings, obviously besides the metastatic domain where the systemic therapy remains the main subject. The so called "cold tumors" from the immunotherapy standpoint (breast, prostate, pancreatic cancers, glioblastoma, *etc*.), are an interesting field of investigation in this context. In fact, much work remains to do to this regard, concerning also the factors related to adverse effects.

The biomedical research requires huge funding, especially for clinical RCTs: the independent, academic institutions rarely can face such economic loads. On the other hand, the pressure of drug industry is obviously oriented to the marketing of new agents, tumultuously succeeding each other, and focuses primarily on achieving statistically significant results as soon as possible, for obtaining the approval by the pharma authorities. More, the tested hypotheses are sometimes based on preclinical investigations cursorily developed in-house and not always available for peer-reviewing. Further, the trials' outcomes are reported in form of surrogate endpoints (*e.g*., PFS). In this perspective, no adequate role is left to therapeutic tools considered as ancillary in the above context, as RT seems to be. Briefly, "*c'est l'argent qui fait la guerre*". On practical grounds, it is almost impossible to modify this framework. Thus, a change in basic assumptions is necessary for experimental RT. Large collections of suitable results from both preclinical lab, and reliable clinical case studies (that is, using a common "ontology"), together with advanced statistical methods and in-silico analyses, are mandatory and must be pursued by the radiation oncology scientific communities, which must also vigorously solicit public funding. Only the soundest hypotheses, thus selected, should be chosen for prospective RCTs in radiation oncology, always keeping in mind that "*big data need big theory too*" (39).

CONFLICT OF INTERESTS

The authors have declared no conflict of interests.

REFERENCES

1. Strandqvist M. Studien über die kumulative Wirkung der Röntgenstrahlen bei Fraktionierung. Erfahrungen aus dem Radiumhemmet an 280 Haut- und Lippenkarzinomen. Acta Radiol 1944;(Suppl 55):1-300. doi: 10.1016/0167-8140(95)01656-2.
2. Douglas BG, Fowler JF. The effect of multiple small doses of-Xrays on skin reactions in the mouse and a basic interpretation. Rad Res 1976;60:401-26.
3. Koukourakis MI. Radiation damage and radioprotectants: new concepts in the era of molecular medicine. British J Radiol 2012;82:318-30. doi: 10.1259/bjr/16386034.
4. Withers HR, Thames HDJr, Peters LJ. Differences in the fractionation response of acute and late responding tissues. 1982, in: Kracher KH, Kogelnik HD, Reinartz G (eds). Progress in radio-oncology II. Raven Press, New York. p 287.
5. Hamdy FC, Donovan JL, Lane JL, et al. 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. N Engl J Med 2016;131:1415-24. doi: 10.1056/NEJMoa1606220.
6. Fisher B, Anderson S, Bryant J. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002;347(16):1233-41. doi: 10.1056/NEJMoa022152.
7. Hoskin PJ, Smith P, Maughan TS, et al. Long-term results of a randomised trial of involved

field radiotherapy vs extended field radiotherapy in stage I and II Hodgkin lymphoma. Clin Oncol (R Coll Radiol) 2005;17:47-53. doi: 10.1016/j.clon.2004.07.004.
8. Yun S, Sun X, Li M, et al. A randomized study of involved-field irradiation versus elective nodal irradiation in combination with concurrent chemotherapy for inoperable stage III nonsmall cell lung cancer. Am J Clin Oncol 2007;30:239-44. doi: 10.1097/01.coc.0000256691.27796.24.
9. Garsa A, Jang JK, Baxi S, Chen C, et al. Radiation Therapy for Brain Metastases. Comparative Effectiveness Review No. 242. (Prepared by the Southern California Evidence-based Practice Center under Contract No. 290-2015-00001-I.) AHRQ Publication No. 21-EHC021. PCORI Publication No. 2020-SR-02. Rockville, MD: Agency for Healthcare Research and Quality 2021. doi: 10.23970/AHRQEPCCER242.
10. Magnuson WJ, Lester-Coll NH, Wu AJ, et al. Management of brain metastases in tyrosine kinase inhibitor-naïve epidermal growth factor receptor-mutant non-small-cell lung cancer: a retrospective multi-institutional analysis. J Clin Oncol 2017;35:1070-7. doi: 10.1200/JCO.2016.69.7144.
11. Nardone V, Correale P, Mutti L, et al. Comparing addition of radiotherapy in EGFR- and ALK-positive NSCLC with brain Metastases: are we evaluating the optimal end point? J Thor Oncol 2021;17:e10-11. doi: 10.1016/j.jtho.2021.11.017.
12. Kamran SC, Mouw KW. Applying precision oncology principles in radiation oncology. JCO Precis Oncol 2018. doi: 10.1200/PO.18.00034.
13. Bunge, M. Medical Philosophy: Conceptual Issues In Medicine. World Scientific Publishing Co Pte Ltd.: Singapore, 2013; ISBN 9814508942.
14. Bentzen SM, Johanson LV, Overgaard J. Clinical radiobiology of squamous cell cancer of the oropharynx. Int J Rad Oncol Biol Phys 1991;20:1197-206. doi: 10.1016/0360-3016(91)90228-v.
15. Andl T, Kahn T, Pfuhl A, et al. Etiological involvement of oncogenic human papillomavirus in tonsillar squamous cell carcinomas lacking retinoblastoma cell cycle control. Cancer Res 1998;58:5-13.
16. Taberna M, Mena M, Pavon MA. Human papillomavirus-related oropharyngeal cancer. Ann Oncol 2017;28:2386-98. doi: 10.1093/annonc/mdx304.
17. Marur S, Li S, Cmelak A, et al. E1308: Phase II trial of induction vhemotherapy followed by reduced-dose radiation and weekly cetuximab in patients with HPV-associated resectable squamous cell carcinoma of the oropharynx—ECOG-ACRIN Cancer Research Group. J Clin Oncol 2017;35:490-7. doi: 10.1200/JCO.2016.68.3300.
18. Widmark A, Gunnlauqsson A, Beckham L, et al. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomized, non-inferiority trial. Lancet 2019;394:385-95. doi: 10.1016/S0140-6736(19)31131-6.
19. Brand DH, Tree AC, Ostler P, et al. Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): acute toxicity findings from an international, randomised, open-label, phase 3, non-inferiority trial. Lancet Oncol 2019;20:1531-43. doi: 10.1016/S1470-2045(19)30569-8.
20. Gomez-Aparicio MA, ValeroJ, Caballero B, et al. Extreme hypofractionationwith SBRT in localized prostate cancer. Curr Oncol 2021;28:2933-49. doi: 10.3390/curroncol28040257.
21. Mateo J, Carrera S, Sandhu S, et al. DNA-repair defects and olaparib in metastatic prostate cancer. N Engl J Med 2015;373:1697-708. doi: 10.1056/NEJMoa1506859.
22. Spratt DE, Zhang J, Santiago-Jmenénez M, et al. Development and validation of a novel integrated clinical-genomic risk group classification for localized prostate cancer. J Clin Oncol 2018;36:581-90. doi: 10.1200/JCO.2017.74.2940.
23. Song CW, Lee YJ, Griffin RJ, et al. Indirect tumor cell death after high-dose hypofractionated irradiation: implications for stereotactic body radiation therapy and stereotactic radiation surgery. Int J Radiat Oncol Biol Phys 2015;93:166-72. doi: 10.1016/j.ijrobp.2015.05.016.
24. Formenti S, Demaria S. Combining radiotherapy and cancer immunotherapy: a paradigm shift? JNCI Commentary 2013;105:256-65. doi: 10.1093/jnci/djs629.
25. Link B, Torres-Crigna A, Hölz M, et al. Abscopal effects in metastatic cancer: Is a predictive approach possible to improve individual outcomes? J Clin Med 2021;10(5214):1-50. doi: 10.3390/jcm10215124.

26. Theelen WS, Chen D, Verma V, et al. Pembrolizumab with or without radiotherapy for metastatic non-small-cell lung cancer: a pooled analysis of two randomised trials. Lancet Respir Med 2021;9:467-5. doi: 10.1016/S2213-2600(20)30391-X.
27. Correale P, Giannicola R, Saladino RE, et al. On the way of the new strategies aimed to improve the efficacy of PD-1/PD-L1 immune checkpoint blocking mAbs in small cell lung cancer. TranslLungCancer Res 2020;9:1712-9. doi: 10.21037/tlcr-20-536.
28. Demaria S, Guha C, Schoenfeld J, et al. Radiation dose and fraction in immunotherapy: one size regimen does not fit all settings, so how does one choose? J Immunother Cancer 2021;9:e002038 doi:101136/jitc-2020-002038.
29. Le Tourneau C, Perret C, Hackshaw A, et al. An Approach to Solving the Complex Clinicogenomic Data Landscape in Precision Oncology: Learnings From the Design of WAYFIND-R, a Global Precision Oncology Registry. JCO Precis Oncol 2022;6:e2200019. doi: 10.1200/PO.22.00019.
30. Bentzen SM, Overgaard J. Patient-to-Patient Variability in the Expression of Radiation-Induced Normal Tissue Injury. Semin Radiat Oncol 1994;4(2):68-80. doi: 10.1053/SRAO00400068.
31. Ma J, Setton J, Morris L, et al. Genomic analysis of exceptional responders to radiotherapy reveals somatic mutations in ATM. Oncotarget 2017;8(6):10312-23. doi: 10.18632/oncotarget.14400.
32. Chen X, Zheng J, Zhuo ML, Zhang A, You Z. A six-gene-based signature for breast cancer radiotherapy sensitivity estimation. Biosci Rep 2020;40(12):BSR20202376. doi: 10.1042/BSR20202376.
33. Riou O, Bourgier C, Brengues M, et al. Outils pour la prediction de la réponse tumorale et des tissus sains en oncologie radiothérapie [Predictive assays for responses of tumors and normal tissues in radiation oncology]. Cancer Radiother 2019;23(6-7):666-73. doi: 10.1016/j.canrad.2019.07.152. Epub 2019. doi: 10.1016/j.canrad.2019.07.152.
34. Brahme A, Lind BK. A systems biology approach to radiation therapy optimization. Radiat Environ Biophys 2010;49(2):111-24. doi: 10.1007/s00411-010-0268-2.
35. Lacombe J, Solassol J, Pouget JP, Coelho M, Azria D. Les tests de radiosensibilité des tissus sains [Radiosensitivity assays of normal tissues]. Bull Cancer 2011;98(12):1469-75. doi: 10.1684/bdc.2011.1497.
36. Pavlopoulou A, Bagos PG, Koutsandrea V, Georgakilas AG. Molecular determinants of radiosensitivity in normal and tumor tissue: A bioinformatic approach. Cancer Lett 2017;403:37-47. doi: 10.1016/j.canlet.2017.05.023.
37. Puget JP, Georgakilas AG, Ravanat JL. Targeted and off-target (bystander and abscopal) effects of radiation therapy: redox mechanisms and risk/benefit analysis. Antioxidant Redox Signaling 2018;29:1447-87. doi: 10.1089/ars.2017.7267.
38. Nardone V, Barbarino M, Angrisani A, et al. CDK4, CDK6/cyclin-D1 complex Inhibition and radiotherapy for cancer control: a role for autophagy. Int J Mol Sci 2021;22(16):8391. doi: 10.3390/ijms22168391.
39. Coveney PV, Dougherty ER, Highfield RR. Big data need big theory too. Philos Trans A Math Phys Eng Sci 2016;374(2080):20160153. doi: 10.1098/rsta.2016.0153.