Radiation oncology enters the era of individualised medicine

In 2004, Bernier and colleagues published a timeline named *Radiation Oncology: a century of achievements*, stating that "We are now at a turning point in radiation oncology—techniques have been refined to allow accurate delivery and we now need the insight of molecular biology and genetics to further refine targeting".[1] More than a decade later, radiotherapy prescription is extensively adapted to patient, tumour, and other treatment-related characteristics. Dose delivery too is more accurate than ever as a result of better modulation and shaping of radiation beams, and advances in imaging, treatment planning, and delivery.

The recent introduction of tumour genomics (mutation or expression profiles) allows for the subclassification of tumours, which can be used as prognosticators or as predictive assays for response to systemic treatment. However, its application in the field of radiotherapy is lagging behind, notwithstanding that about 50% of cancer patients require radiotherapy during the course of their disease, with radiation oncology accountable for the second most cures of patients after surgery.[2] However, only 1·6% of the total US National Institutes of Health funding for cancer research is devoted for radiation oncology.[3] Also, private and governmental support for research in radiation oncology is substantially lower than for medical oncology.[3] This scarcity of funding is an important contributor to the fact that, so far, genomics has not been clinically applied in the field of radiation oncology. The development of the genomic-adjusted radiation dose (GARD) as a clinical model to individually adapt the prescription of radiotherapy is an important step in remediating this omission, and we congratulate Jacob Scott and colleagues for their study in *The Lancet Oncology*.[4]

In their previous investigations, Scott and colleagues identified a tumour molecular signature based on the expression of ten genes (*AR*, *c-Jun*, *STAT1*, *PKC*-beta, *RelA*, *cABL*, *SUMO1*, *PAK2*, *HDAC1,* and *IRF1*) that correlated with radiosensitivity (expressed as tumour cell survival fraction per 2 Gy fraction; SF2) in a large number of cancer cell lines. This was named the radiosensitivity index. The gene expression score was validated by the investigators in the preclinical and clinical setting in various tumour types (eg, rectal, breast, oesophageal, head and neck cancers).[5]

In their most recent study,[4] the investigators calculated GARD, which includes the radiosensitivity index, for a large cohort of 8271 tissue samples from 20 tumour sites. Next, they used data from five clinical cohorts (Erasmus Breast Cancer Cohort [n=263]; Karolinska Breast Cancer Cohort [n=77]; Moffitt Lung Cancer Cohort [n=60]; Moffitt Pancreas Cancer Cohort [n=40]; and The Cancer Genome Atlas Glioblastoma Patient Cohort [n=98]) to successfully correlate low or high GARD with clinical outcomes, including 5-year distant metastasis-free survival in the Erasmus Breast Cancer cohort (low GARD *vs* high GARD; multivariate hazard ratio 2·11, 95% CI 1·13–3·94, p=0·018). Their results show that GARD is superior to radiosensitivity index alone in predicting the radiotherapy effect of a given dose.

It is inevitable to question when we will be ready for the next step of adopting GARD for clinical decision making. We should be cautious not to generalise the current findings, especially in cases of unconventional radiotherapy (ie, hypofractionation, ablative radiotherapy, intraoperative radiotherapy, and particle therapy). Before applying this model into daily clinical practice—by increasing the dose for more resistant tumours and lowering the dose for more sensitive tumours—further validation will definitely be required in independent subsets of patients for whom tumour material as well as clinical outcomes are available. An important step would be to modify the ten gene predictor into a qPCR-type assay that can be performed on biopsy material, frozen or formalin-fixed, either in the local hospital or centrally. This would allow prospective, multicentre validation trials to obtain sufficient evidence for using GARD. Finally, for real individualisation of radiotherapy, known clinicopathological factors should continue to be taken into account in a proportion that still needs to be defined and that can vary based on a shared decision-making process between health-care givers and their patients. Moreover, we need to add other important components of individualisation when treating macroscopic disease, including intratumoral heterogeneity and the potential of functional adaptation of radiotherapy during the course of the treatment.[6,7] Ballistically targeting heterogeneity and adapting radiotherapy not only to morphological changes but also to functional changes during treatment will put

Science Photo Library

Lancet Oncol 2016

Published Online
December 16, 2016
http://dx.doi.org/10.1016/S1470-2045(16)30660-X

See Online/Articles
http://dx.doi.org/10.1016/S1470-2045(16)30648-9

radiotherapy ahead of systemic treatment in terms of individualisation, and are currently being investigated using the new MRI-guided hybrid radiotherapy delivery treatment systems.

In the meantime, these findings should be considered as an excellent way to pave the road for biologically directing the dose of radiation therapy for individual tumours. The efforts of Scott and colleagues and others who are working to improve patient outcome by enhancing one of the most effective modalities to treat cancer should be recognised, supported, and funded by our community.[8]

Philip Poortmans, Orit Kaidar-Person, Paul Span
Department of Radiation Oncology, Radboud University Medical Center, 6500 HB Nijmegen, Netherlands (PP, PS) and Department of Radiation Oncology, University of North Carolina, Chapel Hill, NC, USA
philip.poortmans@radboudumc.nl

We declare no competing interests.

1 Bernier J, Hall EJ, Giaccia A. Radiation oncology: a century of achievements. *Nat Rev Cancer* 2004; **4:** 737–47.
2 Borras JM, Lievens Y, Dunscombe P, et al. The optimal utilization proportion of external beam radiotherapy in European countries: an ESTRO-HERO analysis. *Radiother Oncol* 2015; **116:** 38–44.
3 Steinberg M, McBride WH, Vlashi E, Pajonk F. National Institutes of Health funding in radiation oncology: a snapshot. *Int J Radiat Oncol Biol Phys* 2013; **86:** 234–40.
4 Scott JG, Berglund A, Schell MJ, et al. A genome-based model for adjusting radiotherapy dose (GARD): a retrospective, cohort-based study. *Lancet Oncol* 2015; published online Dec 16. http://dx.doi.org/10.1016/S1470-2045(16)30648-9.
5 Eschrich S, Zhang H, Zhao H, et al. Systems biology modeling of the radiation sensitivity network: a biomarker discovery platform. *Int J Radiat Oncol Biol Phys* 2009; **72:** 497–505.
6 Even AJ, van der Stoep J, Zegers CM, et al. PET-based dose painting in non-small cell lung cancer: Comparing uniform dose escalation with boosting hypoxic and metabolically active sub-volumes. *Radiother Oncol* 2015; **116:** 281–86.
7 Hoeben BA, Bussink J, Troost EG, Oyen WJ, Kaanders JH. Molecular PET imaging for biology-guided adaptive radiotherapy of head and neck cancer. *Acta Oncol* 2013; **52:** 1257–71.
8 Sharma RA, Plummer R, Stock JK, et al. Clinical development of new drug-radiotherapy combinations. *Nat Rev Clin Oncol* 2016; **13:** 627–42.