LH Gray Memorial Trust

Meeting report: LH Gray Jack Fowler Symposium "Radiobiology foundations and Radiotherapy futures" June 19th 2015.

The first LH Gray Symposium was held in London, 19th June 2015 to mark the 90th birthday of Professor Jack Fowler. The symposium was organised for the LH Gray Memorial Trust in collaboration with the Association for Radiation Research by: Dr Ester Hammond (Oxford), Professor Jolyon H Hendry, Dr Mark Hill (Oxford), Professor Penny Jeggo (Sussex), and Professors Catharine ML West and Kaye J Williams (Manchester). The venue was the Academic of Medical Sciences, Portland Place, London, which provided a wonderful backdrop to a celebratory meeting.

The meeting programme spanned themes of precision radiotherapy, radiobiology foundations and radiotherapy futures, with 11 world leading invited speakers from around the globe. In addition, in line with their support for the meeting, a presentation was made to the winner of the British Institute of Radiology's Nic McNally prize winner, Lara Barazzuol, from the University of Sussex. To encourage participation of more junior colleagues there was also a poster session, with 25 presentations made in this format. Programme sessions were chaired by Professors Howard Thames (Houston, US), Kaye Williams (Manchester, UK) and Paul Harari (Wisconsin, US), with Professor Gillies McKenna providing a summary of the science presented on the day.

Following the scientific programme, Professor Paul Harari led a tribute to Professor Fowler and Professor Fowler was presented with a portrait painted by Professor Arthur Sun Myint to mark the occasion. The formalities were followed by a food and drinks reception for all delegates and extra guests.

The meeting had a very personal aspect, with many of Professor's former colleagues attending along with his wife and children. The overall feedback was very positive with a general consensus that the meeting had been a very fitting way to celebrate a milestone birthday for an exceptional scientist.

Soren Bentzen, Philippe Lambin, Herman Suit, Peter Wardman

Professor Fowler, meeting delegates and speakers

Catharine West, Paul Harari, ..., Jolyon Hendry, Philippe Lambin, ..., Bob Anderson, Lester Peters, Howard Thames, Jack Fowler, Liz Travis, Fiona Stewart, Klaus Trott, Soren Bentzen, ...

Part of the organising team: Penny Jeggo, Kaye Williams and Catharine West

LH Gray Memorial Trust

The LH Gray Memorial Trust Jack Fowler Symposium

Radiobiology Foundations and Radiotherapy Futures

Friday 19 June 2015

A symposium marking the year of Jack Fowler's 90th birthday supported by the Association for Radiation Research, the British Institute of Radiology, CTRad, the University of Manchester and the CRUK/MRC Oxford Institute for Radiation Oncology

The Academy of Medical Sciences, 41 Portland Place, London, W1P 1QH

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Programme

09.30	**Arrival and Coffee**	
09.50	Introduction	Catharine West, Manchester
10.00-12.10	***Precision radiotherapy***	Chair: Howard Thames, Houston
10.00-10.30	The long and the short of radiotherapy fractionation for breast cancer	John Yarnold, Institute of Cancer Research & Royal Marsden Hospital, Sutton
10.30-11.00	Personalised radiotherapy using risk adaptive optimisation	Wolfgang Tomé, Albert Einstein College of Medicine, New York
11.00-11.30	Biology-guided adaptive radiotherapy	Cai Grau, Aarhus
11.30-12.00	Radiotherapy physics: linear, quadratic, non-linear	John Fenwick, Oxford Institute
12.00-12.10	BIR Nic McNally prize winner presentation	Lara Barazzuol, University of Sussex
12.10-13.30	**Lunch and Posters** supported by Xstrahl	
13.30-15.30	***Radiobiology foundations***	Chair: Kaye Williams, Manchester
13.30-14.00	Regenerative medicine meets radiotherapy	Rob Coppes, University of Groningen
14.00-14.30	Radiation and immunotherapy	Amato Giaccia, Stanford University
14.30-15.00	Oxygen's association with aggressive tumours	Brad Wouters, University of Toronto
15.00-15.30	Gatekeeper rescue increases radiosensitivity	Ester Hammond, Oxford Institute
15.30-16.00	**Tea/coffee**	
16.00-18.00	***Radiotherapy futures***	Chair: Paul Harari, Wisconsin
16.00-16.30	From bedside to bench: hypoxia and genetic instability	Rob Bristow, PMH, Toronto
16.30-17.00	Proton therapy: pushing the frontiers of radiotherapy	Tony Lomax, Paul Scherrer Institute, Switzerland
17.00-17.30	Personalised precision radiotherapy	Søren Bentzen, University of Maryland
17.30-18.00	Discussion and round-up	Gillies McKenna, Oxford Institute
18.00-20.00	**Reception and Posters** supported by RPS Service	

The LH Gray Memorial Trust

The L H Gray Memorial Trust was proposed at a meeting of the Association for Radiation Research in Leeds in April 1966, to commemorate the work of the late Dr Louis Harold Gray. The three founding bodies and the first Trustees were:

Association for Radiation Research	OCA Scott, FS Dainton, A Howard
British Institute of Radiology	LF Lamerton, F Ellis, MD Snelling
Hospital Physicists' Association[*]	JW Boag, J Rotblat , FW Speirs

The general purpose of the Trust and the organization of Conferences are set forth in the Trust Deed. The Trust has '*its principal purpose of furthering for the benefit of the public the knowledge and understanding of all aspects and all applications of radiation and kindred sciences … by organizing conferences … chosen from the fields of radiation physics, radiation chemistry [and] radiation biology, and the application of these fundamental studies to the treatment of disease'.*

Current trustees are: C Deehan, E Hammond, B Jones, GD Jones, A Nahum, M Hill, D Sutton, CML West (chairman), KJ Williams (secretary/treasurer)

Radiobiology Foundations and Radiotherapy Futures

This symposium was put together to mark the year of Jack Fowler's 90th birthday. The meeting is supported by the Association for Radiation Research, the British Institute of Radiology, CTRad, The University of Manchester and the Cancer Research UK Oxford Institute for Radiation Oncology.

The symposium was organised for the LH Gray Memorial Trust in collaboration with the Association for Radiation Research by: E Hammond, JH Hendry, M Hill, P Jeggo, CML West, KJ Williams

[*] Now named the Institute for Physics and Engineering in Medicine.

Jack Fowler

Dr Jack Fowler, PhD obtained his BSc in 1944, MSc in 1946, a PhD in 1955 (Radiation Physics) and his DSc in 1974 (Radiation Biology) from University of London. Jack held numerous positions as a physicist at Newcastle-upon-Tyne, King's College, and Hammersmith Hospital where he was Professor and Chair of Medical Physics from 1963-1970. He served as Director of the Gray Laboratory from 1969-1988. During this 19 year period the Gray Laboratory thrived and grew under Jack's leadership, both in expansion of space and recruitment of personnel. Research conducted by Jack and a cast of extremely talented colleagues has greatly influenced the fields of radiation biology, physics, and chemistry and has had a major impact on radiation oncology. After retiring from the Gray Laboratory Jack moved to Wisconsin.

Jack has published approximately 500 papers and is best known for his work in radiation fractionation, normal tissue injury and repair, and applying the concept of alpha/beta to better understand and rationally predict the impact of fractionation on tumour and normal tissues. He is truly a translational scientist applying basic science research to clinical research protocols and the reverse, understanding the problems in radiotherapy and going back to the lab to design experiments to attack and resolve those issues.

Over the course of his career, Jack has worked with and interacted with some great names in radiation biology and physics. Jack has received prestigious awards including an Honorary MD from the University of Helsinki (1981), Honorary DSc from the Medical College of Wisconsin (1989), the Roentgen Prize from the British Institute of Radiology (1964), the Barclay Medial from the British Institute of Radiology (1985), the Marie Curie Medal of the Polish Society of Radiation Research (1986) and the Gold Medal from ASTRO (1995), to name a few. He has served as President of the Hospital Physicists' Association (1968), the European Society for Radiation Biology (1974), and the British Institute of Radiology (1977).

The long and the short of radiotherapy fractionation for breast cancer

John Yarnold

The Royal Marsden, Downs Road, Sutton, Surrey SM2 5PT, UK

As a general rule, human cancers are less sensitive to fraction size than the dose-limiting, late-reacting normal tissues, but breast cancer appears to be an exception. Based on clinical data published by Cohen in 1952, and re-analysed by Douglas in 1985 using the linear-quadratic model, a series of randomised trials was initiated >20 years ago that report no disadvantages for fractions in the range 2.7-3.3 Gy, compared to 50 Gy in 25 fractions, in terms of adverse effects and local tumour control provided appropriate adjustments to total dose are made. A classic regimen, 40 Gy in 15 fractions of 2.7 Gy devised by Paterson, is the current UK standard, but it is unlikely to represent the limit of accelerated hypofractionation. Against this background, I shall describe current trials testing 5-fraction regimens of whole breast radiotherapy and discuss correlative research aimed at identifying biomarkers of fractionation sensitivity.

Personalised radiotherapy using risk adaptive optimization (RAO)

Wolfgang A Tomé. Ph.D., FAAPM

Professor and Director, Division of Therapeutic Medical Physics, Department of Radiation Oncology, Montefiore Medical Center, Bronx, NY, 10461, USA

Professor and Director of Medical Physics, Institute for Onco-Physics, Department of Radiation Oncology, Albert Einstein College of Medicine, Bronx, NY, 10461

The potential of RAO to personalize radiotherapy is discussed and the impact of limited diagnostic accuracy of Functional Imaging (FI) on personalized radiotherapy is explored. Since RAO yields highly non-uniform dose distributions within target volumes, Iso-TCP maps are introduced as a tool to aid in their evaluation. Iso-TCP maps are akin to isodose maps in 3D conformal radiotherapy. Utilization of biological parameters in the generation of personalized radiotherapy plans results in an increase of the therapeutic ratio as compared to dose painting plans in which fixed preset population based dose levels are used. It is demonstrated that for the assessment of personalized radiotherapy plans Iso-TCP maps present a promising tool. However, the presence of a detection threshold, which is inherent in all currently used FI- techniques, limits the detection of high-risk tumor voxels. Hence, risk classification parameters for the parts of the PTV that are predicted to be at low risk using FI should be chosen such that current minimal peripheral prescription doses are achieved for the entire PTV so that patients have the same probability of expected local control as with current radiotherapy. With this caveat personalized radiotherapy employing RAO appears to be a promising approach to personalize radiotherapy.

Biology-guided adaptive radiotherapy

Cai Grau

Department of Oncology, Aarhus University Hospital, Aarhus, Denmark

Deformations in internal soft tissue due to e.g. weight loss or tumor shrinkage during the course of radiotherapy can lead to significant anatomical changes, which in turn can cause potential overdosage of critical normal structures. This is the motivation for the clinical concept of adaptive radiotherapy (ART). ART involves systematic modification of treatment using frequent imaging and a feedback of the geometric and dosimetric information from previous fractions. Widespread access to in-room volumetric imaging, e.g. cone-beam CT, has facilitated such this process by enabling daily imaging also of tumours and soft tissues. Although the exact clinical role of ART in head and neck cancer remains uncertain, technical solutions are now emerging, using deformable registration, auto-segmentation, dose accumulation, and fast recalculation to enable smooth re-planning for ART.

The next step in adaptive radiotherapy is called Biology-Guided Adaptive Radiotherapy (BiGART). Relevant biological features for BiGART include hypoxia, proliferation, cell density and intrinsic radioresistance. The principle in dose painting is redistribution and escalation of the radiation dose to these radioresistant parts of the tumour. Hereby, a biologically more effective dose distribution might be achieved while simultaneously sparing normal tissues. Functional imaging modalities for BiGART include dynamic CT with contrast, diffusion weighted MRI, and dynamic contrast enhanced MRI and PET/CT with various tracers. A number of studies have shown that functional imaging information on e.g. hypoxia is prognostic for the outcome of radiotherapy.

The main challenges in BiGART are resolution and dynamics: The biological features are likely to be more heterogeneous on a microscopic level than what current imaging can pick up. If so, our current imaging and delivery techniques are probably too coarse to fully address the biological distribution. The dynamics of the biological features of interest determines how frequent the patient needs to be subjected to repetitive imaging during radiotherapy. A few early studies have shown that dose-painting and BiGART in principle is possible, although not yet practical or cost-effective on a daily or even weekly basis.

Radiotherapy physics: linear, quadratic, non-linear

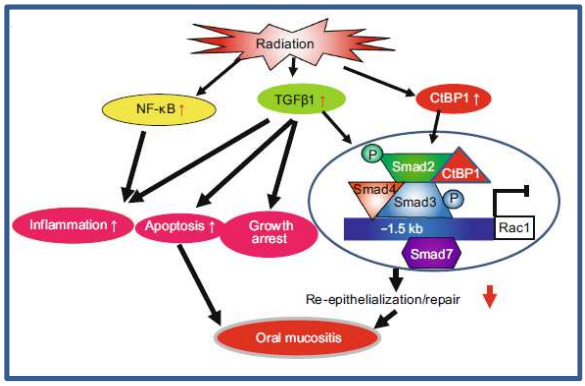
John Fenwick, Ph.D.

Cancer Research UK and Medical Research Council Oxford Institute for Radiation Oncology, Department of Oncology, The University of Oxford, Oxford, OX3 7DQ, UK

Radiotherapy physics has historically been linear: radiation dose scales linearly with fluence; IMRT optimizes trade-offs between linear fluence combinations; and probabilities of complications and tumour control are related via sigmoid link functions to biologically effective dose, a quantity varying linearly with physical dose, dose squared and treatment duration. CT and PET images used in treatment planning were reconstructed as linear combinations of transmission or emission fluences.

Non-linear techniques are, however, now being used more frequently in radiotherapy. Here I focus on two applications: the use of delay differential equation (DDE) modelling to predict early reaction tolerance, and the development of iterative approaches for simultaneous reconstruction and kinetics analysis of dynamic PET images.

DDEs have been used in mathematical biology to describe systems in which delays exist between stimuli and responses to them, sometimes due to the existence of amplification compartments between stem and functional cells. DDEs describe early reaction dose-tolerance data well, and predict waves of increasing and diminishing mucositis intensity following radiotherapy, an observed phenomenon. They are more complex than conventional modelling, but given current knowledge of cell signalling networks their level of complexity appears justified.



Potential mechanisms of Smad7-mediated protection and healing of oral mucositis (From Han et al., Nature Medicine 2013).

Kinetics modelling of dynamic PET data is used to estimate rate-constants of tumour uptake processes. The rate-constants are more directly linked to specific aspects of tumour function than is uptake at a single time-point. Parametric images obtained from kinetics analyses are noisy, however, and iterative algorithms which simultaneously perform reconstruction and kinetics analysis are being developed with the aim of reducing noise propagation. The rationale, methodology and scope of these approaches is described, alongside their potential application to radiotherapy.

Endogenous and radiation-induced DNA damage and apoptosis in the embryonic and adult neural stem cell compartments

Lara Barazzuol, Nicole Rickett, Limei Ju, Shreya Saha, Lisa Woodbine, Penelope A. Jeggo

Genome Damage and Stability Centre, University of Sussex, Brighton, BN1 9RQ, UK

Replication-associated DNA double strand breaks (DSBs) arise during embryonic neurogenesis and sensitively activate apoptosis. Both the level of DSBs and apoptotic sensitivity diminish temporally as replication ceases. Additionally, the embryonic brain is characterized by high sensitivity to apoptosis from exposure to low radiation doses. In this study, we ask whether the adult neural stem cell compartments, the subventricular zone (SVZ) of the lateral ventricle and the subgranular zone (SGZ) of the dentate gyrus of the hippocampus, are also characterised by high endogenous DSB formation and apoptotic sensitivity; questions relevant for evaluating the use of radiological procedures.

To aid this analysis, we used mice with a hypomorphic mutation in DNA ligase IV (*Lig4*^{Y288C}), which rejoin DSBs with slow kinetics, ataxia telangiectasia mutated (*Atm*$^{-/-}$) and double mutant mice (*Atm*$^{-/-}$/*Lig4*^{Y288C}). We observed the presence of endogenous DNA damage, in the form of DSBs, in all tissues of the adult nervous system with similar levels observed in replicating versus non-replicating cells in the SVZ and SGZ compared to other tissues, demonstrating that DSBs do not arise at a higher frequency in the adult neural stem cell compartments. Importantly, we found that apoptosis is sensitively activated in the adult SVZ, with detectable apoptosis being observed endogenously in *Lig4*^{Y288C} mice or after exposure to 50 mGy X-rays in wild type mice. In contrast, apoptosis is not activated in the differentiated neuronal tissues nor it is significantly activated in the SGZ. Analysis of *Atm*$^{-/-}$ and *Atm*$^{-/-}$/*Lig4*^{Y288C} mice showed that apoptosis in the SVZ is predominantly dependent upon ATM. We also revealed a developmentally regulated stage of high apoptosis in the SVZ immediately post-birth, which occurs independently of ATM, most likely reflecting the establishment of the adult stem cell niche.

Our findings indicate that although the SVZ stem cell compartment in the adult brain does not show excessive endogenous DSB formation, this region is extremely sensitive to DSB-induced apoptosis, with a magnitude of sensitivity similar to that observed in the embryonic brain.

Regenerative medicine meets radiotherapy

R P Coppes

Departments of Cell Biology and Radiation Oncology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Recent progress in the field of stem cell research has opened novel avenues for disease modelling, toxicity studies and regenerative medicine. In the current presentation the response of tissue stem cells to radiation and regenerative potential upon radiation will be discussed using the salivary gland and thyroid gland as models. Hyposalivation and hypothyroidism are common and often irreversible side effects of head and neck cancer treatment for which stem cell therapy may be a therapeutic option. We have developed models to isolate, culture and expand salivary and thyroid gland stem cells as organoids. These organoids closely resemble the tissue of origin and contain all the tissues major cell lineages. Organoid forming potential after irradiation can be used as a measure of the stem cells radiation response. Moreover, both expanded salivary gland and thyroid gland have a high potential to regenerate radiation-damaged tissues. The clonal expansion of adult stem cells opens novel avenues for the study of radiation responses and the use of regenerative medicine in the prevention and treatment of radiation-induced side effects. Currently, our method is under GMP translation for future clinical application.

Supported by grants of the Dutch Society for Cancer Research, NIRM, EU-FP7 project ANDANTE and ZonMW-TAS

Tumour Immunologic Heterogeneity Influences Response to Radiation and anti-PD-1 Immunotherapy

Todd A Aguilera MD PhD, Marjan Rafat PhD, Mihalis S Kariolis PhD, Edward E Graves PhD, and Amato J Giaccia PhD

Purpose/Objective(s)

Clinical trials of CTLA-4 and PD-1/PD-L1 antibodies (Ab) have shown responses limited to 10-30% of patients. Increasing evidence suggests radiation (RT) can enhance responses to checkpoint therapies. However, understanding of tumor-derived factors that influence response is limited, and many preclinical models are manipulated to expressing specific antigens. We sought to develop a model of immunologic heterogeneity to study factors that influence responses to RT and immunotherapy.

Materials/Methods

Tumor clones PyA1 and PyB2 exhibiting efficient orthotopic engraftment were derived from the PyMT mammary mouse carcinoma model. Cells were assayed by flow cytometry for MHCI and PD-L1 expression to evaluate antigen presentation and responses after interferon-γ (IFNγ) and 10 or 20 Gy RT treatment. Tumors were then grafted into naïve mice and radiated to 12 or 20 Gy. Immune infiltrates were evaluated by flow cytometry after tumor dissociation. With evidence of an immunologic response that involved PD-L1, mice were treated with 12 Gy and PD-1 Ab in addition to a single pretreatment dose of CTLA-4 Ab to evaluate combination therapy. To elucidate factors influencing responsiveness of combination treatment in PyA1 but not PyB2 tumors, we inoculated mixed tumor cell populations at 80/20, 50/50, and 20/80 ratios.

Results

PD-L1 and MHCI expression increased significantly after INF-γ and RT to a greater extent in PyA1 than PyB2 cells. Upon orthotopic implantation and RT, PyA1 but not PyB2 tumors regressed significantly. Dissociated tumors 10 days after 12 Gy treatment revealed a significant increase in CD45 leukocytes, CD8 effector T cells, and decreased CD4 T cells, myeloid derived suppressor cells, and macrophages in PyA1 tumors but minimal changes in PyB2 tumors. Secondly, there was elevated MHCI and induced PD-L1 expression in the responsive PyA1 compared to PyB2 tumors suggesting a greater anti-tumor response may be obtained with immunotherapy. Mice were treated with 12 Gy, 12Gy + PD-1 Ab, and a single dose of CTLA-4 Ab 3 days prior to RT and PD-1 therapy. There was prolonged tumor suppression in the combination RT + PD-1 and RT + PD-1 + CTLA-4 groups with repeated measures p-values of 0.0003 and 0.0039, respectively. Notably 2/8 tumors treated with RT + PD-1 and 6/8 mice treated with RT + PD-1 +CTLA-4 were undetectable at day 81. Mixing tumors with different ratios of PyA1 and PyB2 revealed that 50% inoculation of PyA1 is sufficient for an immune response against both tumor clones. This suggests a mechanism where responsive tumors can induce antitumor activity against unresponsive tumors.

Conclusion

These results support that tumor immunologic heterogeneity can influence immune responses after radiation. This is an excellent model to study tumor-derived factors that enhance or suppress the immune response after RT and could inform clinical approaches to radiation and immunotherapy combinations.

AKT inhibition restores hypoxia-induced p53-dependent apoptosis and radiosensitivity

Ester M Hammond

Cancer Research UK and Medical Research Council Oxford Institute for Radiation Oncology, Department of Oncology, The University of Oxford, Oxford, OX3 7DQ, UK

Restoring hypoxia induced apoptosis to p53 mutated tumours is an attractive therapeutic strategy. The mechanism of hypoxia-induced p53-dependent apoptosis has been elusive and in particular the identity of key transcriptional targets. We show that hypoxia-induced p53-dependent apoptosis is reliant on the DNA binding and transactivation domains of p53 but not on the acetylation sites K120 and K164, which in contrast are essential for DNA-damage induced p53-dependent apoptosis. We have identified and validated hypoxia-inducible pro-apoptotic targets of p53. Importantly, we have verified that a group of 6 of the hypoxia-inducible p53-dependent genes identified (INPP5D, PHLDA3, SULF2, BTG2, CYFIP2 and KANK3) are regulated by p53 in human cancers. The loss of expression of the hypoxia-inducible p53 targets results in poor patient prognosis, suggesting a crucial role for hypoxia-induced apoptosis in p53-mediated tumour suppression and treatment response. We further investigated the function of p53 in hypoxia and found that two targets, PHLDA3 and a specific INPP5D transcript, mediate apoptosis through AKT inhibition. This led us to demonstrate that pharmacological inhibition of AKT leads to apoptosis in the hypoxic regions of tumours with non-functional p53 and consequently increases radiosensitivity.

From bedside to bench: hypoxia and genetic instability in prostate cancer

Robert G Bristow MD PhD FRCPC

Clinician Scientist, Princess Margaret Cancer Centre, Professor, Departments of Radiation Oncology and Medical Biophysics, University of Toronto

Clinical prognostic groupings for localised prostate cancers are imprecise, with 30-50% of patients showing inter-patient heterogeneity for recurrence after image-guided radiotherapy or radical prostatectomy. DNA-based indices alone or in combination with intra-prostatic hypoxia measurements can be used to develop prognostic indices in 126 low-risk to intermediate-risk patients (Toronto cohort) who will receive image-guided radiotherapy. Combined genomic-hypoxia indices were validated in two independent cohorts (Memorial Sloan Kettering Cancer Center cohort [MSKCC] cohort) and (Cambridge cohort) radical prostatectomy specimens from low-risk to high-risk patient to stratify patients for risk of biochemical relapse 5 years after primary treatment. Using a combination of copy number alterations, mutations and hypoxia scores, we identified four genomic subtypes for prostate cancer, which had different 5-year biochemical relapse-free survival. Genomic instability is prognostic for relapse in both image-guided radiotherapy and surgery patients. We also assessed intra-prostatic heterogeneity by undertaking a detailed molecular analysis of the spatial heterogeneity of clinically localized, multifocal prostate cancer in order to delineate new oncogenes or tumor suppressors. Using 5 radical prostatectomy patients, we whole-genome sequenced 23 distinct tumor regions to assess focal genomics. Multifocal tumors are highly heterogeneous for single-nucleotide variants (SNVs), CNAs and genomic rearrangements. We identified and validated a new recurrent amplification of MYCL, which is associated with TP53 deletion and unique profiles of DNA damage and transcriptional dysregulation. Moreover, we demonstrate divergent tumor evolution in multifocal cancer and, in some cases, tumors of independent clonal origin and the first systematic relation of intraprostatic genomic heterogeneity. These data are useful to predict clinical outcome and inform the development of novel biomarkers that reflect individual prognosis. Patients exhibiting these aggressive features after biopsy should be entered into treatment intensification trials.

Proton therapy: pushing the frontiers of radiotherapy

Tony Lomax

Paul Scherrer Institute, Switzerland

Proton therapy has a long history, but a history that until now has not led to large numbers of treated patients. In the near future this could inevitably change however. There are now over 50 proton and heavy ion facilities in operation worldwide, with another 50 either being built or planned, and by the end of 2018, it is likely that there will be over 90 facilities in operation. There is certainly no doubt therefore that proton therapy is becoming main stream. This boom is being driven mainly by one thing – the improved dose distributions that result from the proton Bragg peak. However, in contrast to other recent developments in radiotherapy, the gain from protons is not necessarily in high dose conformation, but more in the reduction of the irradiated volume and/or overall integral dose. The hope of course is that this reduction will bring significant clinical gains. But will these be predominantly just in the reduction of secondary tumour incidence, or are there other potential gains that may result? In this presentation, we will first look at the basics of proton therapy and its clinical applications, but also look at other, perhaps not so obvious, consequences of ever increasing spread of proton therapy, including the idea that in the long term, proton therapy may help us understand more about the underlying macro-biology of the response of organs and tissues to radiation therapy.

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The organising bodies gratefully acknowledge

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