The future of radiotherapy is molecular

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Published online: 17 August 2020

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Introduction and overview: Clive Baldock, moderator

Very soon after the discovery of X-rays by Wilhelm Röntgen in 1895, radiation was beginning to be used to treat cancer. The field of radiotherapy, or radiation therapy, has continued to grow and evolve for over 125 years as a treatment for cancer with the translation of fundamental research through to clinical practice. In recent decades there has been significant changes in radiotherapy enabled by technological and biological advances. Clinical outcomes have improved through the introduction of innovations such as IMRT and IGRT, the use of novel therapeutic radionuclides, particle beams and the availability of advanced imaging techniques such as CT, PET, MRI.

In this Topical Debate, the proposition to be debated is that the future of radiotherapy is molecular.¹

Arguing for the Proposition is Professor Dale Bailey PhD. Prof Bailey was born and raised in Sydney and received his undergraduate and Master's degrees in Physics from University of Technology Sydney (UTS). He undertook postgraduate training at Harvard Medical School working at Beth Israel Hospital, Boston after which he returned to Sydney in 1984 to a position in the Department of Nuclear

Medicine at Royal Prince Alfred Hospital, Sydney. While in this position Prof Bailey was awarded the Australasian College of Physical Scientists and Engineers in Medicine (ACPSEM) Boyce Worthley Young Achiever Award for his work on simultaneous transmission/emission imaging in SPECT. Prof Bailey moved to London to work at the Medical Research Council Cyclotron Unit at Hammer-smith Hospital in 1990. At the same time he commenced his doctoral studies at the University of Surrey. Prof Bailey was in the UK for nearly 10 years, finishing his time as the head of Nuclear Medicine Physics at Guy's and St Thomas's Hospital. He returned to Sydney in 2002 to be appointed Principal Physicist in Nuclear Medicine at Royal North Shore Hospital, Sydney where he remains to this day. He also has an appointment as Professor in the School of Health Sciences at the University of Sydney and in 2019 was appointed the Director of the Sydney Vital Translational Cancer Research Centre. He served as the President of the Australian and New Zealand Society of Nuclear Medicine (ANZSNM) from 2016 to 2018. Prof Bailey's interests are primarily in quantitative imaging in nuclear medicine where he has made significant contributions in both SPECT and PET. More recently, prompted by the rapid expansion of radionuclide therapies for cancer treatment, he has established a radiobiology laboratory geared towards studying the effects of particle-emitting radionuclides on cancer cells to better understand how to optimise therapy.

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¹ Contributors to Topical Debates are selected for their knowledge and expertise. Their position for or against a proposition may or may not reflect their personal opinions.

Dale Bailey

Arguing against the proposition is Dr Wendy Phillips, Senior Radiation Oncology Medical Physicist from South Australia. Dr Phillips undertook her undergraduate and postgraduate studies at the University of Adelaide and has worked at the Royal Adelaide Hospital (RAH) for 15 years. After completing her PhD in Radiobiological tumour modelling with thesis commendation by the Dean of graduate studies and her Radiation Oncology Medical Physics (ROMP) certification in 2011, she served as Radiation Oncology TEAP (Training Education and Assessment Program) public preceptor, is currently an Affiliate Lecturer for the University of Adelaide. Having authored peer reviewed papers and a book chapter, Dr Phillips experience in performing and supervision within radiobiological based research teams, for both computational modelling and experimental cell and animal irradiation projects, is evident. The duties and interests currently driving Dr Phillips include high dose rate brachytherapy, computational radiobiological modelling, radiation safety and protection, clinical ethics, as well as teaching and training. She is currently the lead physics specialist for high dose rate cervix brachytherapy at the RAH. Her key achievements include being awarded the APESM Kenneth Clarke Journal award in 2011, the Boyce Worthley Young Achiever award in 2012 and poster prize at the 2014 CSM for work entitled “Stochastic predictions of tumour cell kill during SBRT: Do hypoxia and Reoxygenation matter?”.

Wendy Phillips

For the proposition: Dale Bailey

Opening statement

The science and radiobiology behind External Beam Radiotherapy (EBRT) is extremely well understood and the technology has become increasingly sophisticated over the past two decades. Nevertheless, EBRT suffers from a number of fundamental limitations: (i) in general, the target tissues must be large enough to be visible on some form of structural or functional imaging, (ii) the radiation must pass through the overlying tissues to reach the target thereby causing damage to those normal tissues, and (iii) the number of sites than can be irradiated in a cycle of treatment remains limited.

Radionuclide therapy (RNT) with radioactive iodine has been used for over 75 years to treat benign thyroid conditions and metastatic thyroid neoplasia [1]. Today, there is great interest to build on this using the so-called “theranostic paradigm”² [2], which employs the same vector (e.g., molecule, peptide, mAb) in a diagnostic imaging/treatment planning role using a suitable imaging radionuclide, and then, if there is demonstrable targeting and acceptably low radiation exposure to organs at risk, using the same vector to treat the disease with a therapeutic radionuclide substituted for the imaging one [3].

Advances in identification of specific receptors expressed by cancer cells has led to considerable renewed interest in RNT [3]. Until very recently only β^- -emitting radionuclides (e.g., ^{90}Y , ^{131}I , ^{177}Lu) have been used for therapy but now there is increasing interest in α^{2+} -emitting radionuclides such as ^{223}Ra , ^{225}Ac and ^{213}Bi due to their much higher Linear Energy Transfer (LET) and exceedingly short range (tens of microns).

So why, given the above, do I suggest that the future of radiation therapy is “molecular”?

For a start, EBRT is not well suited to the metastatic setting. It is, of course, incredibly useful when treating a primary lesion, or addressing oligometastatic or limited disease, but for widespread disease as in the case in Fig. 1 a systemic approach is required [4].

Secondly, molecular targeting can be used against micro-metastatic disease, as long as the receptor or other target is expressed by the microscopic lesions [5]. We may never know that we have treated such undetectable lesions unless there is an independent biomarker (e.g., serum PSA) that demonstrates a response after treatment.

² The term “theranostic” is attributed to the American John Funkhouser in a press release from the company *Cardiovascular Diagnostics* in August 1998.

Fig. 1 70 year old patient with metastatic castrate-resistant prostate cancer, before and after theranostic molecular radionuclide therapy using [^{177}Lu]-PSMA-617. The PET images shown used [^{68}Ga]-PSMA

Finally, at the ASTRO 2019 Meeting, based on an analysis of the number of clinical trials of RNT underway at present, the NIH predicted that by 2035 around 60% of all radiation therapy procedures would be delivered using radiopharmaceuticals. The successful trials of today will become the standard-of-care tomorrow.

Against the proposition: Wendy Phillips

Opening statement

As a Scientist my first thoughts turn to the fact that almost everything in our existence is made of molecules. In Radiation Therapy (RT) we aim to damage very complex molecules, i.e. DNA, of tumour cells. But, will we fulfil our aim solely by targeting RT beams or radiolabelled-drugs at the molecular level? No.

Radiation alone may be effective for some patients; however, it is not likely to be the ultimate stand-alone treatment modality. The current mainstream external beam and brachytherapy regimens are not able to target radiation down to the sub-mm level, due to organ/tumour movement on the sec-min timescale, x-ray or functional imaging resolution, machine accuracy). Geometric accuracy is improving; however, there will a limit to what is

achievable with RT alone, even if we achieve “real-time biology-guided RT” [6].

Within a few generations, we may be able to detect and eliminate microscopic disease through screening, e.g. circulating tumour-DNA in blood [7], and discover how to eliminate environmental factors of carcinogenesis and even viral/genetic causes, e.g. through immunisations and genetic therapies. The ultimate future for RT may be that we unemployed! For now, let’s define the “future” as within the average ROMP lifetime, i.e. 3–4 decades.

Half of cancer patients (48% in Australia) have been predicted to receive benefit from RT [8]. Chemotherapy plus modalities such as molecular targeted therapies (targeting hormones, proteins or genes) could provide an alternative or compliment to the directly cytotoxic assaults on tumours cells. One example of RT with a molecular basis is targeted alpha therapy; a form of unsealed radioisotope treatment. With promising clinical trial results and implementation in some countries, this form of treatment modality can provide improved outcomes such as length and quality of life, especially for intractable blood, brain and metastatic cancers [9]. However, it is not often utilised for large volume tumours or as a sole radical treatment modality.

Understanding the full biological impact and mechanisms of RT at the molecular level will form part of the way forward, however even if there is a push towards highly modulated techniques, e.g. micro-beam RT [10], this will not be the full answer. Expense and the immature theoretical/mechanistic basis for the impacts on non-irradiated tissue (with long researched, but still little understood mechanism-wise, bystander and adaptive responses [11]) will impact translation.

Radiobiological theories that have been investigated, and gained significant clinical evidence for multiple decades, are the levels of oxygenation [12] and hyper-fractionated accelerated treatment of rapidly proliferating tumours [13]. Despite the pre-clinical and clinical trial evidence, logistical factors such as longer working days and 6 day-per-week staffing have dominated decision making. With longstanding, but not widely implemented examples considered, molecular target-based RT for the majority of our patients will not be feasible for a long time.

In summary, as factors that we know will help are not yet a priority for first world countries, molecular based radiation treatment techniques will be a long time in their application, and will form only one part of an optimal and mainstream treatment strategy.

Rebuttal statement: Dale Bailey

It seems that Dr Phillips is in agreement with me that there is a big future ahead for radiation treatment delivered using radiolabelled vectors. Where we differ, however, is her

assertion that “molecular target-based RT for the majority of our patients will not be feasible for a long time”. A visit to a comprehensive nuclear medicine department today will reveal an increasing number of patients who formerly would have been sent to the Medical or Radiation Oncology clinic for treatment now being given molecular-based radionuclide therapy as a single dose, outpatient procedure. It is highly likely any such visit would also find a radiation oncologist or urologist in the nuclear medicine department as well—certainly my experience is that the drive to offer radionuclide therapy treatment is coming from the clinicians who are managing the patients’ cancers recognising the limitations of their current treatment regimes. Dr Phillips’ “long time” is already here—it is happening now!

The delivery of radionuclide therapy is, however, still in its infancy with respect to the protocols being used, with very little experimental basis or evidence of being an optimal approach. I believe that we can learn much from “traditional” radiotherapy to investigate improving on the already outstanding successes seen with, for example, [^{177}Lu]DOTA-Octreotate in the NETTER-1 trial [14]. Fractionation, for example, may have a future role, using higher therapeutic amounts of shorter half-life radionuclides that emit particles (α , β^- , β^+ , Auger e^-).

In years to come I believe our professional descendants will look back on this time with disbelief and wonderment that we thought that firing MV X-rays through normal tissues to target an underlying cancerous lesion seemed like a good idea at the time.

Rebuttal statement: Wendy Phillips

Sophistication of EBRT has indeed advanced dramatically over the past decades, but is the mechanistic radiobiology really that well understood and then translated in many clinics? No. Very few Australian patients receive EBRT accounting for effects such as tumour oxygenation, accelerated repopulation, clonogenic density and intrinsic radiosensitivity in planning process. Brachytherapy should be mentioned here (the oldest form of RT), because currently this technique is reducing in popularity in some Australian centres and is under-utilised, for various financial and logistical reasons. Access to this type of treatment or technology, to allow clinics to apply more optimal fractionation and dose conformity, is falling behind what is needed to translate much that we already know to improve patient outcomes.

With EBRT “not suited to the metastatic setting”, we will still need to rely on external treatment modalities into the 2030s for primary/oligometastatic/limited disease, with molecular-based treatments gradually utilised in the metastatic setting or widespread disease. However, will we not aim to diagnose cancer well before this point, with sophisticated imaging and blood/DNA techniques? If so, it may

only be the systemic diseases requiring molecular-RT, with genetic-, proteomic- or immuno-therapies (that need not be radioactive) being utilised for most other forms of cancer.

Due to the timeframes required for clinical trials and their follow-ups, the financial, logistical and safety surrounding main stream radiopharmaceutical treatments and that almost half of patients predicted will not receive molecular-RT by 2035, it will be well beyond our lifetimes before we see mainstream molecular-RT emerge as a sole treatment option for non-systemic disease. Understanding the underlying causes and processes of carcinogenesis, very early detection, and treatments administered such as immunotherapy [15, 16] (with EBRT providing possible roles such as increased antigen production), will be the most likely final frontier for Oncology.

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