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Review

Why should radiological oncology do translational research?

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ARTICLE INFO

Article history:
Received 28 February 2018
Received in revised form
14 August 2018
Accepted 25 October 2018
Available online 12 November 2018

Keywords:
Translational research
Radiotherapy
Nanoparticles
Gene therapy
Artificial intelligence
Networks

ABSTRACT

Radiological Oncology, like the rest of medical specialties, is beginning to provide can personalized therapies. The ongoing scientific advances enable a great degree of precision in diagnoses and therapies. To fight cancer, from a radiotherapy unit, requires up-to-date equipment, professionals with different specialties working in synchrony (doctors, physicists, biologists, etc.) and a lot of research. Some of the new therapeutic tendencies are immunotherapy, nanoparticles, gene therapy, biomarkers, artificial intelligence, etc. A new clinical paradigm in which new professional networks are inevitable is arising. The mission of translational research is to become a scientific engine in the clinical space.

1. What is translational research?

Translational research has different meanings but its overarching function is to improve human health. It is usually considered as an integrative discipline between Biomedical Research and Clinical Reality. The aim of translation research is to provide "the right care, at the right time, for the right person, in the right way".[1] A wide network of professionals is needed to achieve this.

For many, the term refers to the "bench-to-bedside" enterprise of harnessing knowledge from basic sciences to produce new drugs, devices, and treatment options for patients. The endpoint is the production of a promising new treatment that can be clinically used or commercialized. The synergy between the role of the medical doctor and the researcher is very relevant because it provides new knowledge, mechanisms, and techniques. These are generated by advances in basic science research and are responsible for new approaches for prevention, diagnosis, and treatment of diseases. Those

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https://doi.org/10.1016/j.rpor.2018.10.008

who work on clinical and basic research focus on health care as the primary outcome, so translational research provides knowledge that actually reaches patients or populations for whom they are intended.[2]

The Institute of Medicine's Clinical Research Roundtable describes two "translational blocks" named T1 and T2.[3] T1 was described as "the transfer of new understandings of disease mechanisms gained in the laboratory into the development of new methods for diagnosis, therapy, and prevention and their first testing in humans"; and it requires basic sciences and technology. T2 was described as "the translation results from clinical studies into everyday clinical practice and health decision making"; and it requires the community and ambulatory care settings that bring the results of T1 research to the public. These two translational blocks seem to be the way to reduce the gap between laboratory and clinic.[4]

However, there are other classifications of translational research. Some authors, especially the clinicians, divide the research into four groups. T1 includes biomedical research in the prognosis and treatment.[5] T2 produces protocols and work guides. T3 confirms the implementation of medical routines.[6] T4 verifies and evaluates the impact of discoveries on global health.[7]

Translational research is a train with lots of wagons with a clear destination: to improve clinical efficiency and, therefore, the quality of life. Translation research moves back and forth between discovery and utility, which makes it dynamic and recursive. It has different and hybrid domains or pathways: commercial, clinical/practical and civic.[8] The symbiosis between the different stakeholders generates new ideas that can benefit the whole. This is the greatness of this method of investigation.

2. Cancer: an international problem

The World Cancer Research Fund International announced: 'There were an estimated 14.1 million cancer cases around the world in 2012, of these 7.4 million cases were in men and 6.7 million in women. This number is expected to increase to 24 million by 2035'. There is no doubt that cancer is a great epidemic of today's society. Life expectancy is longer year after year, and so we accumulate more mutations, which are associated to a higher prevalence of cancer.

In 1977 Keyfitz said: 'At the extreme, it might be said that everyone dies of something sooner or later, so that, when the effects of the eradication of cancer had shaken down, the same number of deaths would occur as before, and the only benefit would be the substitution of heart and other diseases for cancer. A cure for cancer would only have the effect of giving people the opportunity to die of heart disease'.[9] Fortunately, medical research is progressing globally without leaving behind other pathologies of high mortality.

Nowadays, cancer treatments are much more specific and include new techniques in combination with clinical therapies (chemotherapy and radiotherapy). Some of them are immunotherapy and nanotherapy, which work because they specifically target the mutated tissue. New treatments are intended to be more precise in order to preserve the healthy tissue and reduce the toxicity to the organism.

We must not forget that these treatments are very expensive and affect patients, industry, payers and providers. Cancer has an important economic impact on society.[10]

3. The role of radiotherapy

Radiotherapy is delivered by a linear accelerator and uses ionizing radiation to control or kill malignant cells. Its treatment action is local and, in most cases, non-systemic. It can be applied as a radical treatment (when it is the only treatment), neoadjuvant (before surgery to extract a tumor in order to decrease its size), adjuvant therapy (after tumor surgery) or concomitant (when it is accompanied by other treatments). It may also be used as a palliative treatment. Radiotherapy has been driven by constant technological advances since the discovery of X-rays in 1895. Radiotherapy aims to sculpt the optimal isodose on the tumor volume while sparing normal tissues.[11]

The Radiotherapy treatment can be external, internal or systemic. Among the external radiotherapy treatments, we can highlight the virtual simulation and 3-dimensional conformal radiation therapy, which use CT or MRI scanners and planning software with External Beam Radiation Therapy (EBRT). It is the most extended technique, but the physical requirement of EBRT may not lead to an optimal outcome for an individual patient.[12] Other treatments, as Intensity-Modulated Radiation Therapy (IMRT), which is an advanced type of high-precision radiation, and volumetric modulated arc therapy (VMAT), which delivers radiation by rotating a gantry, have been used widely to improve local control rates and they are normally combined with a boost.[13] Particle therapy with protons (PBT) or carbon ions (CIRT) displays high rates of long-term local control, low rates of symptomatic deterioration, along with the potential for safe dose-escalation in selected (but not necessarily routine) cases.[14] Stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) are the delivery of a potent, ablative or nearly ablative, dose in oligofractions. Thus, SRS and SBRT basically attempt to hit the tumor while ideally altogether avoiding the normal tissue. This is a dramatically different approach from conventional radiotherapy, where large volumes of normal tissues are typically included, even in the high-dose region. Currently, both techniques require a specialized professional team to handle this high-performance technology.[15,16]

Another option is the intraoperative radiation therapy (IORT), which is the therapeutic application of radiation to the tumor bed during surgery. The hypofractionation and partial radiation seem to have good results; IORT appears to have low toxicity rates and it is a short treatment, which allows to speed up the clinical demand. Current studies show IORT as an effective technique that also reduces the time of treatment in many patients: Chowdhry et al.,[17] Silverstein et al.[18] or Guenzi et al.[19] Still, IORT is a novel treatment that requires follow-up studies.[20]

Brachytherapy is an internal radiotherapy; it consists in applying the radiation treatment internally through implants into the tumor area or cavity. It can have a low dose rate (PDR) or a high dose rate (HDR).[21] The technique requires control by image of the area to be treated; this is one of the points

that generates the most controversy and that is currently being analyzed. Another aspect is the importance of controlling the deviation between the planned and the administered radiation. These errors of precision can lead to clinical consequences in patients.[22] On the other hand, because of the high dose gradient specific of brachytherapy, the dose administered to the tumor is greater than that given by external irradiation. This treatment is shorter than external irradiation. It also allows greater control of dose in tumor, margins and healthy tissue.[23] Brachytherapy has also been commonly used as a boost in external radiotherapy, for example in prostate cancer, where the combination of HDR and EBRT can offer dose escalation with good coverage and low incidences.[24]

Finally, the systemic treatment uses radiopharmaceuticals. It consists in the oral or intravenous administration of radioactive drugs. They are frequently linked to specific antibodies which can work as a radiosensitizers in order to act more specifically on the tumor.[25]

In summary, innovation in radiotherapy technologies has resulted in remarkable progress in the quality of therapies and in outcomes, given the growing ability to identify and target tumors with a high accuracy.[26]

4. The era of personalized medicine

Immunotherapy, nanoparticles, gene therapy and artificial intelligence are widely well-known concepts. Although some of these terms seemed like things from a distant future, the reality is that they are already in our laboratories and our hospitals; why are they so important?

Some of the effects of ionizing radiation contribute to systemic antitumor immunity.[27] This natural responses cause the 'abscopal effects', i.e. tumor regression. Therefore, Radiotherapy per se is an immunomodulatory and can be used as an adjuvant to immunotherapies.[28] On the other hand, immunotherapy wants to accelerate the immune system action against the tumor cells. It seems evident that the combination of radiotherapy and immunotherapy will provide good results in the fight against cancer.[29] Obviously, dose and fractionation are likely to be key variables in determining the effects of ionizing radiation on the immune system of the patients and/or in determining the success of radiotherapy when combined with different forms of immunotherapy. Similarly, the correct sequencing of radiotherapy and immunotherapy depends on the type of immunotherapy chosen.[30] Cushman et al. show the ongoing increase in clinical trials investigating immunotherapy with radiotherapy (iRT).[31] Some of the used agents are Ipilimumab.[32–35]

Nanomedicine is the use of nanotechnology in medical science. It refers to the manipulation of size and shape of a material at the nano-level (1–100 nm). It can be used in diagnoses and drug delivery in therapeutic treatment modalities.[36] The materials can be organic or inorganic and have tremendous impact on medical treatments.[37] Nanomaterials may also deliver the therapy itself, improving the efficacy and localization of treatment to reduce side effects. For many of the agents used to treat cancers, the side effects are often dose limiting.[38] These materials can directly target areas using ligands, perform the treatment and be eliminated or disintegrated from the body.[39] Some nanoparticles approaches to enhance cancer immunotherapy include the delivery of antigens and adjuvants as vaccines, the delivery of antibodies, targeting specific cells, such as APCs or dendritic cells even more specifically, and the modification of the tumor microenvironment to counteract many of the immunoinhibitory effects of tumors.[40] Liu et al. combine radiotherapy with adjuvant chemotherapy and a reactive oxygen species (ROS) responsive nanoparticle, which avoid the oxidation reaction on cells and reduce the tissue damage.[41] Xie et al. focus on nanomaterial as a radioprotector for healthy tissue.[42] Lechtman and Pignol present the gold nanoparticle as a radiosensitive material for malignant cells.[43]

Imaging plays an important role in clinical oncology, including diagnosis, staging radiation treatment planning, evaluation of therapeutic response, and follow-up and monitoring. Due to the importance to know the phenotypes of tumor, radiomics and radiogenomics, which integrate imaging and genomic data, are working on genomic markers.[44] Biomarker Imaging aims to find new molecules in order to detect specific tumor targets.[45] Genomic heterogeneity of aggressive tumors could translate into intratumoural spatial heterogeneity exhibited at the anatomical and functional scales. Vallières et al. describe the importance of imaging in order to determinate the risk in head and neck tumors.[46]

Advances in genetic engineering enable the identification and isolation of many hereditary illnesses. Now, with gene therapy, we can identify medical profiles to find therapeutic guidelines specific to the needs of each patient. We can also overtake diagnosis and perform hereditary control. All this depends on advancing genome project.[47] Genome can be a biomarker with predictive features that exceed the potential utility of any individual genomic perturbation. As Nesic described, specific abnormalities in DNA repair leave identifiable genomic scars, and that broad and even whole genome analysis may become a useful and usable diagnostic technology first in identifying tumors that could respond to the targeting of DNA repair abnormalities. However, genomes are constantly at risk from intracellular and extracellular agents; instability and mutations are considered to be of key relevance for cancer. If the damage causes instability, the DNA repair fails and the number of mutations increases. The organism ends up losing control, which may be the onset of a tumor process.[48] For example, concerning radiotherapy, Sjöström et al. describe the importance of gene expression profile in order to grade the tumor radiosensibility; this allows us to apply radiotherapy optimally.[49]

What about artificial intelligence? The technological systems and the possibility of programming complex structures that discriminate and choose among an immense amount of information evolve quickly. Bioinformatics is designing emulators that will allow us to predict the specific responses of tissues to certain therapies under certain biological situations.[50] In oncological radiology, just as Thompson et al. say, Artificial Intelligence will remodel the specialty; providing it with advanced computational techniques capable of minimizing errors and waiting times and of increasing the specificity of the patient's treatment, dosimetry control, etc.[51] Weidlich and Weidlich believe that "Radiation oncology has

several weak points, which are mainly found in the transcription processes of transferring information from one process of radiation oncology to the next", and so Artificial Intelligence could provide an optimization control.[52]

5. Economic impact

The source of economic resource for translational research is important. Normally, the greatest contribution of resources does not come from public but from private sources.

If health care moves, or increases, to new centers of interest, the collection and investment of funds will also be displaced to cover their needs.[53] Obviously, these funds cannot only come from the commercials of medicines and devices (although it is good that they are part of the process), but it also requires scholarships and budgets of public funds.

The large network associated with translational research requires a wide investment throughout all its sections. Although the challenge will be difficult, it seems that it is what the future demands of us. On the other hand, Jacobs et al. detected that translational research is still to be optimized and that the most frequently observed barrier is workload/lack of resources followed by high complexity and a gap between researchers and clinicians. Workload is a barrier that is generally known and very frequently identified, especially in healthcare. Therefore, it is necessary to regard research implementation not as something that comes on top of normal workload.[54]

6. Conclusions: is translational research important?

It undoubtedly is. Medicine cannot stop evolving and improving. Humans need to find answers to increasingly complicated questions. In Radiotherapy Oncology departments, as explained in this article, there are many fields that have yet to be studied (technology, immunotherapy, imaging, etc.). All of them are used at the individual level, optimized for each patient, and minimize errors. There is a need to establish translational research between clinical practice and classical research. It is necessary to generate research equipment that receives economical and professional support to allow public health to prosper as a development tool.

Conflict of interest

None declared.

Ethical approval

The study has been approved by the provincial Biomedical Research Ethics Committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. For this type of study formal consent is not required. Details that might disclose the identity of the subjects under study have been omitted.

Funding disclosure

None declared.

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