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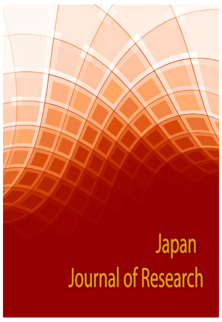

Critical Analysis of the Uncertainties in Translational and Radiobiology Studies as a Basis for Radiotherapy

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Abstract

The integration of all the steps involved in the treatment process is quite complex, as it involves the correct knowledge of the dose–response curves developed in laboratory experiments, the translation of these results to the clinic, the adequate delineation of the tumor, and the appropriate dose prescribed for each type of tumor and delivered daily to the patient. For example, the correct assessment of the dose administered to a patient strongly depends on an interconnected chain of steps executed harmoniously, as the accuracy of a given dosimetry procedure is very high. In this case, the measurement results must be ensured to represent the best possible reported values with their typical uncertainties to allow clinical results to be achieved and to be comparable with those of other institutions. The robustness of the chain of events is often fragile, with uncertainties at each stage sometimes not considered or sometimes difficult to estimate, requiring different conceptual and statistical approaches at various times in the decision-making process. As a result, as the additive sequence of uncertainties is generally not fully considered, the clinical outcome may not be as anticipated.

The objective of this review is to critically and constructively highlight the weak points observed in the interrelationship of some of all steps that ultimately lead to better tumor control and, ultimately, to provoke a reflection on the theme.

Introduction

Accelerated technological development has had significant positive impacts on tumor imaging, immunohistochemistry, disease staging and treatment equipment, including treatment planning software [1]. The introduction of artificial intelligence into this area will likely reduce the level of complexity when all the steps involving clinical radiotherapy are considered. As a result, when the immunohistochemistry results are combined with the high imaging quality and resolution of computed tomography (CT), magnetic resonance (MRI) and positron emission tomography (PET) machines, disease staging is optimized. Its use only requires additional knowledge of the correction factors related to the machine, the dosimetry process and the biology of each tumor to be treated. All these somewhat independent steps require a global view of their impacts on the final uncertainties involved in the dose delivered to the tumor and neighboring tissues.

Alternatively, the ongoing improvements in detector technology, the stability of the linear accelerators, the consistency of the monitoring chamber response and the accuracy of the dose calculation algorithms, which are now based on Monte Carlo methods, have resulted in more trust in the process. As a result, the implementation of new techniques, such as intensity-modulated therapy (IMRT), volumetric MAT, adaptive radiotherapy, and 4D imaging associated with motion management, is possible. The combination of these procedures and detailed knowledge of each procedure, including a fair analysis of its advantages and limitations, will enrich efforts toward reducing the final remaining uncertainties before the clinical treatment plan is delivered.

Clarifying the concepts of error, precision, accuracy, and uncertainty is important since they are often misused, which interferes with the understanding of their description.

Error is defined as a failure of a planned action to be completed as intended, which can be avoided if a well-designed quality assurance program is implemented.

Precision is the closeness of the agreement between repeated independent measurements, and it is independent of accuracy. The dispersion of a series of measurements n around an average value x (bar) can be characterized by its standard deviation, which can be calculated from the variance, as it is the square root of this parameter.

$$s(x_i) = \sqrt{\frac{1}{n-1}\sum_{i=1}^{n}\left(x_i - \bar{x}\right)^2} \qquad (1)$$

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Accuracy is how close a measurement is to the true value and is generally presented as an interval +/- in which the expected true value is located.

Uncertainty is characterized by a range of values within which the true value is asserted to lie with a defined level of confidence, i.e., 95% or 99%. Uncertainty represents a lack of the exact knowledge of the measured value when the systematic effects are eliminated, and the appropriate corrections are considered.

The demands for a high degree of accuracy are increasing and challenging due to the use of new treatment techniques such as hypofractionation (few fractions with high doses per fraction), the use of flattening filter–free (FFF) beams with high doses in the tumor and the substantial reduction of doses in the OARs (organs at risk). The uncertainties of new techniques known as FLASH and proton therapy also need to be assessed to be recognized as a valid option to complement or substitute the techniques currently being used [2-4].

All these technological advances have the final goals of improving the tumor control probability (TCP) and reducing the normal tissue complication probability (NTCP), leading to a substantial reduction in treatment morbidity and ensuing improvements in patients' quality of life.

Both external beam therapy and brachytherapy have also progressed significantly, creating new procedures involving the use of HDR sources of ^{192}Ir and ^{60}Co and ^{125}I LDR sources for permanent implants [5,6].

An understanding that the concept of uncertainty is clearly associated with the physical quantity measured, which is statistically characterized by the dispersion of the measured values represented by the standard deviation, is important. Moreover, the concept of uncertainty, by definition, unlike the concept of error, has no sign and its values are represented by a symmetric dispersion [7,8].

The ISO Guide on the Expression of Uncertainty in Measurement, INTERNATIONAL COMMITTEE FOR WEIGHTS AND MEASURES, Evaluation of Measurement Data—Guide to the Expression of Uncertainty in Measurement, JCGM 100:2008, BIPM, Paris (2008) provides the definitions and guidelines for reporting the values of uncertainties. The guide further suggests that the concepts of type A and B uncertainties be adopted once two distinct pathways are used [7,8]. Considering the innumerous independent but somewhat interconnected components of the chain of events, all of which are representative of the entire radiotherapy process, one must estimate, whenever possible, its individual uncertainties, specifically when quantitative values are calculated, and should follow the statistical rules recommended by the ISO Guide on the reporting of uncertainties [7,8].

The following three examples clarify the distinctions between type A and B uncertainty in dosimetry:

- *In a typical table where all the individual and identifiable uncertainties are listed, the standard deviation of a set of measurements represents type A uncertainty.*
- *The calibration coefficient, whose uncertainty results are derived from the quadratic combination of the uncertainties of types A and B, must be considered by the user as type B.*
- *The published cross-sectional values used to quantify an interaction process must be considered type B.*

This chapter addresses the possible assessment of the uncertainties in each step of the chain of events, starting with radiobiology and followed by translational research, the clinical benchmarks that support decisions, metrological processes, treatment planning, and treatment delivery.

In the Radiobiology Area

The interaction of beams of different types of ionizing radiation with living normal tissues and tumors is one of the most complex problems since it requires highly comprehensive knowledge of the atomic and nuclear physics of the therapeutic beams. Knowledge of the complex interaction process of generated secondary electrons and the molecular biology of living tissues and cells, including their multifaceted damage repair systems, is also needed. The question is how to deliver the effective dose of delta rays in a safer mode to normal cells.

Perhaps a simplified but very complex answer is to use advanced molecular radiation that has been biologically optimized inversely with electron, photon or light ion radiation therapy. It combines a low dose and ionization density with repairable damage everywhere except in the tumor.

The Dose–Response Relationship

The shape of the tumor dose–response relationship is described in a simplified manner by the binomial or Poisson statistical probability, which assumes that no surviving viable tumor clonogens are present at the end of the treatment, using the following equation:

$$P_B(D) = e^{-N0S(D)} = e^{-N0e-D/D0} \qquad (1)$$

where the last step is a simplification possible with a constant dose per fraction *D*, N_0 is the initial clonogen number, *S(D)* is the relative clonogen survival after the administration of dose *D*, and D_0 is the exponential slope. As the dose *D* increases, the number of remaining clonogens decreases until high doses are reached, the number of surviving clonogens tends to reach zero, and the cure probability approaches unity along a sigmoidal curve.

The curve shape reflects the cumulative distribution function of a random variable, which also starts from zero to finally reach one or 100% when all random events have been counted. The curve shape may be described (within a few %) by the cumulative generalized gamma distribution.

In fact, radiation therapy is truly the almost perfect example of an extreme value distribution, since only the last few and likely the most radiation-resistant tumor clonogens have survived the initial major part of the treatment without being killed. Instead, they remain to finally form the tumor control probability curve. Therefore, not surprisingly, Eq. (1) can be rewritten to perfectly fit the cumulative extreme value distribution as follows:

$$e^{-e(\mu-D)/n} = e^{-e(D_0 lnN_0 - D)/D_0} = e^{-N_0 e - D/D_0} \qquad (2)$$

where the middle part is a rewriting of Eq. (1) and therefore the approximate mean value of the extreme value distribution

$\mu = D_0 lnN_0$, and the "radiation resistance" $n = D_0$. The true mean value is exactly obtained as $\mu + n.\ g = D_0\,(lnN_0+g)$, the median value is $D_{50} = \mu - n\ ln(ln2) = D_0 ln(N_0/ln2)$, the variance is V=sD²=p²D0²/6, and, finally, the relative standard deviation is $^sD/=p/(\mu/n+g) = p/(lnN_0+g))$, which is an important quantity from a microdosimetric point of view (in all these equations, g ≈ 0.577, representing Euler's gamma constant).

For a common tumor size of $N_0 = 10^7$ clonogens, the relative standard deviation s≈0.0768 is only approximately 7.7%, making the shape of the tumor control curve quite steep and rather sensitive to microscopic dose fluctuations. This result is partly due to its high kurtosis of 5.4, which is independent of μ and n, as well as N_0 and D_0, along with the skewness of 1.1395, which explains the much steeper rise in the tumor control curve at low doses and the shallower extended shoulder at high doses, making achieving a 100% ideal tumor cure generally quite difficult. Therefore, approximating Eq. (2) via a Gaussian error function with a skewness of 0 may not be appropriate.

A careful assessment of the doses and all the parameters involved in radiobiology is very challenging and complex but not unsurmountable. In most cases, it requires no more than a few parameters related to key biological and physical issues, such as the steepness of the dose–response and complication curves specific for each type of tissue, the individual clinical sensitivity associated with the effects due to similar doses, the clinical outcome, the statistical considerations and assumptions to define a certain level of accuracy when a clinical trial is designed, and, finally, the level of accuracy that is practically achievable.

While other conceivable causes and factors that are currently unknown and other unaccountable factors might increase the final uncertainty in the delivered dose compared with the prescribed dose, known factors must be considered.

In principle, the responses of malignant and normal cells to radiation have sigmoidal shapes, although the steepness varies significantly from cell to cell, as reported for the analysis of 90 dose–response curves of human tumors from multiple institutions [9].

Importantly, the nominal dose that controls 50% of the tumor is known as TCD_{50}, and g_{50} is the percentage that changes in terms of the tumor control probability (TCP), which realistically ranges from 25 to 75%. Similar dose–response curves, even though they are still incomplete, are currently available and reported in QUantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) [10]. The dose–response curves for normal tissues are steeper than those for tumors, resulting in higher g50 values. Furthermore, in a lung tumor, one of the organs considered to have a parallel tissue structure, dose–volume information is highly desirable for modeling its response.

The sensitivity of the TCP (*tumor control probability*) and NTCP (*normal tissue complication probability*) curves are related to the deviation between the doses prescribed and delivered to the target volume. Uncertainties in the dose delivered to the tumor have direct effects on both probabilities, which are reflected in the slope angles of the curves and are more critical in some tumors. Normal late-responding tissues have a g_{50} region that is approximately 2–6 times steeper than that of tumors, which are on the order of 1.5–2.5. Patients with heterogeneities exhibit less steep response curves with low values of g [11].

In the case of adjuvant radiotherapy, the g values are much lower than those derived from a single dose of radiotherapy. Seeking the most accurate possible value for the dose delivered so that the tumor response is in the upper region close to the maximum of the curve and the normal tissues are in the lower part of the curve represents a crucial part of the objectives to be achieved. As a result, an improvement in the cure rate and a significant reduction in morbidity should occur, resulting in a better quality of life.

Some studies reported [12,13] a 1% improvement in the final uncertainty, with a 2% increase in the control of initial tumors. The International Committee of Radiation and Units (ICRU#24) [14] recognizes that values of 5% are still realistic, although this requirement may vary depending on the type of tumor, and a value of 3.4% is the most appropriate average value; however, in some cases, these values may need to be smaller.

Classical reports [15-17] that are available but still currently incomplete suggest that a dose deviation of 7–10% could be detected clinically, and a variation of 7% caused different clinical outcomes in two different patient groups [12]. Currently, the International Atomic Energy Agency (IAEA) report [11] indicates that a maximum acceptable clinical uncertainty of 3% for late-reacting tissue might be acceptable, and I is added for the moment. However, considering the physical dose measured, the dose calculated by the TPS and other related uncertainties, 5% and k=2, might be a better number, although in some cases, the dose delivered to the patient may be underestimated.

Dose–response curves for both tumor and normal tissues are not commonly reported, and whenever mentioned, they refer to the upper end of the curve for tumors and the lower end of the curve for normal tissues. The only single comprehensive study reported thus far [18] has separated both curves for ^{137}Cs LDR brachytherapy trials for stage I and II cervical carcinoma. Based on the analysis of the steepness of the curves for local control, complications, and survival versus the nominal dose, a tendency was observed that clearly suggests 5% or a slightly lower value as an acceptable level of accuracy.

In the Translational Area

Although radiotherapy is recognized as one of the main modalities for the treatment of cancer, preclinical radiotherapy is defined as a set of studies on the effects of ionizing radiation on biological systems with the purpose of translation to the clinic. Optimizing the resources invested in the effective control of this disease is the main objective [2]. A recent literature review [19-21] analyzed the characteristics of the information reported by preclinical studies involving ionizing radiation and the dose–response relationships. This information is needed to define the impact of ionizing radiation on the application of the results within the concepts of clinical radiotherapy. The lack of dosimetric proposals for conformal biological irradiators is critical, especially when small animals are irradiated with X-ray beams with energies up to 225 kVp using millimetric radiation field dimensions, which is only possible with the SARRP (small animal radiation research platform). The present recommendations for reference and relative dosimetry for small fields, which are less than 5 mm in diameter, are still insufficient for this energy range, leaving important gaps related to the uncertainties involved and their impacts on the results.

This type of equipment allows research to be conducted on small animals, enabling the different stages and protocols of the radiotherapy process with humans to be reproduced, such as 3D-CT (computed tomography) simulations, delineation of the tumor and organs at risk, treatment planning and improved precision and accuracy in delivering targeted doses [19-21].

The diagnosis and treatment of cancer involve dissimilar experiences for individuals affected by this disease, and their life expectancy unfortunately depends on the country where the patients live and the resources available for disease staging and treatment. This premise is especially delicate considering the differences in investments in health care in Latin America, including the Caribbean, compared with Europe and North America [1].

Importantly, when radiobiological studies are conducted, the protocols must be as close as possible to the rigor required in treatments and clinical studies, most likely increasing the chance of achieving transferable results. The difficulty in accessing appropriate technology and the lack of dosimetric protocols for the dosimetric characterization of microirradiation systems make replicating the findings in other laboratories or translating them to clinical trials difficult. Only approximately one-third of published animal research is translated to the level of randomized human trials of radiotherapy [3]. Robust preclinical data and translational strategies are key factors for improving these results [19]. Determining the radiation dose correctly is essential for establishing a relationship between the radiation dose and the magnitude of the effects, whether on tumors or healthy tissues. The accuracy and precision of dose measurements and descriptions of measurement details must be sufficient to allow the results to be interpreted, repeated, and validated by different laboratories. As most radiobiology publications lack a detailed description of the irradiation geometry, beam energy characteristics, dosimetry equipment and techniques, and measurement uncertainties, the reproducibility and reliability of those findings may be compromised [19]. In the statistical analysis of studies conducted in laboratories performing animal research, the sample size n is decisive in the significance and statistical power of the tests. However, an extremely large sample size results in extensive experiments and a high workload for researchers, sometimes making analyses unfeasible and extending the time to publish the results. On the other hand, this large sample size can also result in difficulties in proposals being accepted by the institution's ethics committees. Therefore, reducing the final uncertainties by reducing the uncertainties in the dosimetric processes could result in possible decreases in the sample size needed for the study [6].

Because of the growing interest in this area, during 2011, the National Institute of Standards and Technology (NIST), the National Institute of Allergy and Infectious Diseases (NIAID) and the National Cancer Institute (NCI) of the United States promoted a workshop with experts from both the fields of radiobiology and radiation physics, aiming to highlight the importance of dosimetric standardization in radiobiology. As a result, recommendations were proposed, highlighting the need to define standards for the procedures involved both *in vitro* and *in vivo*. In joint work between the Department of Medical Physics at the University of Wisconsin and the United States School of Medicine and Public Health in 2016 [19], the information reported in 28 articles with a radiobiological profile over the last 10 years was evaluated, as were the proposals from the NIST 2011 Workshop, which are presented in Table 1.

The items with the lowest information index correspond to dosimetric parameters; this information at the level of dosimetry in radiotherapy corresponds to the baseline of scientific publications, in addition to the corresponding descriptions of the associated uncertainties. Since this description is considered insufficient, the publications may suggest inadequate dosimetry.

Small deviations in both the gradient in the dose–response curves and the dose values can lead to different interpretations between institutions regarding the dose–effect relationship, thus limiting the possibility of continuing in the same line of work or generating further research based on previous results. In addition to deviations in the delivered dose, many implicit biological factors are inherent to this type of research, such as genetic sensitivity, age, type of cells and environmental factors that could influence the response to radiation. Many researchers emphasize the reproducibility of the dose (precision) within the laboratory itself, without noting the importance of the accuracy (proximity to the real value) of the dose prescribed and delivered in the experiment. Therefore, even if the statistics are based on the isolated concept of standard deviation, systematic dose error may often be disregarded. Hence, the result may deviate from the real value determined and be wrongly associated with a biological "end point" (survival curves, apoptosis, mutations, specific morphological changes, radiotherapy-induced necrosis, changes in the blood–brain barrier (BBB), etc.).

After a careful literature review, the work reported here shows the characteristics of the information reported in preclinical studies involving ionizing radiation and dose–response relationships. This information is correlated with the impact on the applicability of the results within the concepts of clinical radiotherapy. The evolution of dosimetric proposals for conformational biological irradiators for small animals using medium-energy X-ray photon beams with applied voltages of up to 225 kVp and millimetric radiation field dimensions was also presented, mainly for the SARRP system. Proposals for reference and relative dosimetry for small fields close to 5 mm in diameter

Table 1. *List of categories recommended in the 2011 NIST Workshop and the percentage of articles, including the items reported in the publications.*

Category	Item	% of Articles
Reference dosimetry Calibration	Standards used from publications	6,9%
	Type of detector used	3,4%
Dose determination	Standards used in publications	10,3%
	Measured material (medium)	6,9%
Specification of the type of radiation or source	Type of detector used	27,6%
	Radioisotope	86,2%
	kV, filter material, HVL	50,0%
Irradiation details	Animal/cell type	100,0%
	Prescribed dose details	100,0%
	Field size and format	0%
	Field geometry	24,1%
	Animal restraint	100,0%

are currently scarce for the abovementioned energy range. The need for new dosimetric proposals in this field of study with the same metrological rigor required in clinical radiotherapy should be encouraged [19-21]. Dosimetric methods also involve materials other than water, such as polymethylmethacrylate (PMMA), acrylonitrile—styrene (ABS) and solid water® (Sun Nuclear Corp., Melbourne, FL).

These materials have well-controlled densities and properties for these purposes, but correction factors must be inserted mainly in the PDD when the electronic density relative to the water of these materials and the dosimetric variations because of the orientations of the dosimeters within the simulator (for example, vertical radiochromic films or axial films) are considered. Encouraging dosimetric procedures with detectors in water would allow the most sensitive and most critical aspects to be independently analyzed in the standardization of measurements, ultimately reducing uncertainties.

Finally, the combination of dosimetric methods must consider the uncertainties in the use of different detectors according to the field size used, the energetic response and the response of the detector in the medium. The evaluation of dose distributions in several fields based on methods such as those used in the clinic would also be beneficial for the integration of new dosimetric proposals for the commissioning and validation of small animal irradiation systems [21].

In addition to methodological considerations, preclinical investigations should be a structural part of the radiotherapy chain. For consistency with the rigor of modern radiotherapy techniques applied to humans, different geometric and dosimetric parameters must be evaluated in microirradiators, guiding efforts to standardize the characterization and calibration techniques for the medium energy kVp X-ray beams currently used for research.

Considering that the current dosimetry method depends on the manufacturer, who also provides specifications for the SARRP micro irradiator system, even with consistent results reported by different users, a manufacturer-independent standardization system traceable to the metrological network is necessary with a greater approximation to international recommendations in clinical radiotherapy dosimetry, mainly in water-based dosimetry for small fields. Advances in small-field dosimetry proposals for kilovoltage beams must follow the most current CoPs in the area, allowing the advances to be based on prior knowledge of our own dosimetric considerations.

Final Remarks

Radiobiology level

The impact of dosimetry on dose–response curves with very low uncertainties must be registered in epidemiological studies that seek to correlate a dose with a particular effect, especially for low doses.

The uncertainties contained in published dose–response curves for different tissues are significant, and the exact values assigned to tumors and normal tissue are still critical and challenging to assess.

One argument against the use of radiobiology models relates to the difficulty of predicting biological outcomes with a sufficient level of accuracy since several parameters, in addition to dosimetry, are not well controlled and are poorly reported [1]. Additionally, tremendous technological advancements have occurred in terms of tumor localization in organs, ensuring the control of organ motion. However, very few studies related to the variation in tissue sensitivity inside tumors and the more accurate perception of subclinical disease are tempting to include in the use of adaptative treatment.

The foreseeable future will be remarkable if one aims to assess the variation in the sensitivity of the cells inside the tumor instead of overestimating the significance of the present resolution obtained for organ localization only. A balance between the cost benefit associated with the specific knowledge needed to optimize the use of the constantly evolving advancement of technology is also a goal. AI might be of much assistance in this area since, in most cases, individual interpretation and clinical judgment prevail.

Translational research level

An available report [20] on the output verification of 12 laboratories (7 gamma units and 5 X-ray units) revealed that only one delivered an output within 5% of the target dose. The dose differences for the other four X-ray irradiators ranged from 12–42%. These results indicate the need for standardization of dose determination and further additional surveillance of radiobiology investigations.

A consensus is that more studies should be performed to encourage the next phase—translation of the results to the clinic. The data in Table 1 strongly indicate a lack of standard reference conditions to standardize the measurement procedures and the need to improve the comprehensiveness of the experimental reports [22-25]. This standardization might help to narrow the gaps between translation and preclinical research.

Final Comments

Reducing the overall uncertainty requires coordinated efforts in several interconnected areas, such as the following:

- Better integration of radiobiology, translation research, clinical protocols and dose delivery;
- Research on radiobiological models and the treatment planning process;
- Comprehensive QA programs;
- Clinical trials reporting the associated uncertainties;
- Internal and external audits of the whole process;
- Description of the inter- and intraclinical variability in defining the target volume and OARs;
- Clarifying the concept of PTV in brachytherapy.

Despite all efforts made thus far, the remaining and intriguing question that needs reflection is ***what level of uncertainty would be acceptable to allow an adequate correlation among the dose–response curves with the physical measurement of the dose delivered to the target volume and to the normal tissues.***

Notably, when we are dealing with the clinical outcome of a treatment, the response to a treatment following the same protocol may vary from patient to patient, especially because of many biological variables, as described previously. As a result, subjective and incomplete assessments are not infrequent since the mathematical quantification of the overall uncertainties for a particular end point is rather difficult to achieve.

As a possible paradigm, one must state that ***radiation oncology must be applied as accurately as reasonably achievable, considering the biochemical and biological information, imaging resolution, machine-specific factors, dosimetric parameters and overall changes during daily treatment.***

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