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Critical Considerations on the Overall Uncertainties in the Radiotherapy Treatment Process

Considerações críticas das incertezas gerais no processo de tratamento radioterápico

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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, 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 demand for accuracy of a given dosimetry procedure is very high. In this case, the measurement results must be represented the best possible reported values with their typical uncertainties to allow clinical results to be achieved and 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, and 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 all steps that lead to better tumor control and ultimately, to provoke a reflection on the theme.

Keywords: Quality assurance, disease staging, dose delivered, dose pre-scribed, translational studies, dosimetry, and overall uncertainties.

Resumo

A integração de todas as etapas envolvidas no processo de tratamento é bastante complexa, pois envolve o conhecimento correto das curvas dose-resposta desenvolvidas em experimentos de laboratório, a tradução desses resultados para a clínica, a delimitação adequada do tumor a dose apropriada prescrita para cada tipo de tumor e entregue diariamente ao paciente. Por exemplo, a avaliação correta da dose administrada a um paciente depende fortemente de uma cadeia interconectada de etapas executadas harmoniosamente, pois a precisão exigida em um determinado procedimento de dosimetria é muito alta. Nesse caso, os resultados das medições devem ser garantidos para representar os melhores valores relatados possíveis com suas incertezas típicas de forma a permitir que os resultados clínicos sejam alcançados e sejam comparáveis com os de outras instituições. A robustize da cadeia de eventos é frequentemente frágil, com incertezas em cada estágio às vezes não consideradas ou às vezes difíceis de estimar, exigindo diferentes abordagens conceituais e estatísticas em vários momentos do processo de tomada de decisão. Como resultado, como a sequência aditiva de incertezas geralmente não é totalmente considerada, o resultado clínico pode não ser o esperado.

O objetivo desta revisão é destacar de forma crítica e construtiva os pontos mais frágeis que podem ser observados na inter-relação de todas as etapas que resultam num melhor controle tumoral e, em última instância, provocar uma reflexão sobre o tema.

Palavras-chaves*: Garantia de qualidade, estudos translacionais, estadiamento da doença, dose prescrita dose administrada, dosimetria e incertezas gerais.*

1. 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, interfering with understanding 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.

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

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 (2,3,4).

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.

2. 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.

2.1 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:

$$P_B(D) = e^{-N_0 * SD} = e^{-N_0 * e - D/D_0} \quad (1)$$

where the last step is a simplification possible with a constant dose per fraction D, No is the initial clonogen number, S(D) is the relative clonogen survival after the administration of dose D, and D0 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:

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

where the middle part is a rewriting of Eq. (1) and therefore the approximate mean value of the extreme value distribution $\mu=D_0 \ln N_0$, and the "radiation resistance" $n=D_0$. The true mean value is exactly obtained as $\mu + n.\ g = D_0\ (\ln N_0+g)$, the median value is $D_{50}=\mu-n\ \ln(\ln 2) = D_0 \ln(N_0/\ln 2)$, the variance is $V=sD^2=p^2D_0^2/6$, and, finally, the relative standard deviation is $sD/=p/(\mu/n+g) = p/(\ln N_0+g))$, 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 = 107 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 g_{50} 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 carcinomas. 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.

2.2 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) 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).

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 micro irradiation 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 (19a). 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, re-peated, 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 (19a). 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 (19a), 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.

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

Table 1: List of categories

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%

Source: The Autor (2024)

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 “endpoint” (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 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 (19a,19b,19c). 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 (19c).

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 micro irradiators, 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 kilo-voltage beams must follow the most current CoPs in the area, allowing the advances to be based on prior knowledge of our own dosimetric considerations.

2.3 In the Clinical Area

**Special contribution by Dr.Daniel Przybysz

Recent advancements in molecular testing and biomarkers are reshaping radiation therapy planning, providing new strategies to mitigate pretreatment uncertainties in oncology. Molecular diagnostics now enable the identification of tumor-specific genetic profiles, informing more tailored and effective radiation therapy approaches. Biomarkers, such as PIK3CA mutations in breast cancer, are used to predict radiation sensitivity and guide dose adjustments, addressing the variability in the tumor response and reducing the risk of recurrence.

Additionally, the integration of immunotherapy with radiation has shown potential in enhancing tumor immunogenicity and systemic disease control, as reported by recent studies on the abscopal effect. This synergy can significantly influence clinical outcomes by modifying the immune environment and enhancing the efficacy of radiation therapy.

This review examines how these molecular innovations influence the accuracy of radiation therapy plans, reduce treatment uncertainties, and pave the way for more individualized cancer care. By exploring the intersection of molecular science and radiation therapy, a foundation for understanding the transformative impact of these technologies on clinical practice can be laid.

2.4 Molecular Testing and Biomarkers

Molecular testing has revolutionized cancer treatment by allowing for more accurate medicine based on the genetic and molecular characteristics of individual tumors. In breast cancer, the landmark TAILORx trial provided clear evidence that the Onco-type DX Breast Recurrence Score can significantly predict which patients with HR-positive, HER2-negative, or node-negative breast cancer can avoid chemotherapy, with a primary focus on endocrine therapy (25). Prostate cancer has undergone similar advancements with the use of the Decipher test, which analyzes genomic signatures to predict aggressive disease, guiding decisions about adjuvant or salvage radiation therapy postprostatectomy (26).

2.5 Impact on Treatment Planning

The identification of specific genetic mutations and biomarkers facilitates the development of targeted radiation therapy protocols. Research has revealed, for example, that breast cancer patients with PIK3CA mutations may exhibit resistance to anti-HER2 therapies but can be effectively treated with PI3K inhibitors in conjunction with radiation, modifying traditional therapeutic approaches (27). For prostate cancer, studies have shown that patients with defects in DNA repair genes, such as those in the BRCA1/2 and ATM genes, are more likely to benefit from intensified radiation therapy and the use of DNA damage response inhibitors (28).

2.6 Immunotherapy Targets

Immunotherapy combined with radiation therapy is emerging as a particularly effective approach to treat cancers traditionally viewed as resistant to immune-based therapies. The RADVAX trials, for example, are investigating the combination of radiation and dual checkpoint blockade (PD-1 and CTLA-4 inhibition) for metastatic breast and prostate cancers. Preliminary results suggest that localized radiation can prime an immune response enhanced by systemic immunotherapy to target both local and distant tumor sites, supporting the concept of the abscopal effect (29).

2.7 Prognostic Factors

The integration of molecular diagnostics has dramatically enhanced the ability to determine the patient's prognosis based on methods other than the traditional histopathological analysis. In breast cancer, the use of MammaPrint testing in early-stage breast cancer patients has been crucial in identifying those who are at high genetic risk but might benefit from less intensive treatment strategies, challenging previous overtreatment paradigms (30). In patients with prostate cancer, the presence of androgen receptor splice variant 7 (AR-V7) is correlated with poor responses to standard hormone therapies but may indicate better responses to taxane-based chemotherapies and possibly more aggressive radiation therapy strategies (31).

2.8 Future Directions

The application of liquid biopsies holds promise for monitoring tumor dynamics in real-time, potentially allowing for mid-treatment modifications in radiation therapy protocols based on the characteristics of circulating tumor DNA (32). Artificial intelligence (AI) is also becoming increasingly important, with machine learning

algorithms being developed to predict patient responses to radiation therapy based on pre-treatment imaging and genetic profiles (33).

2.9 Clinical Uncertainties and Criticisms

Despite these advancements, several latent uncertainties and potential issues persist in clinical practice.

1. Patients not receiving treatment: Clinical decision-making can sometimes lead to patients not receiving potentially beneficial treatments due to a misinterpretation of molecular testing results or a lack of access to advanced diagnostic tools. In real-world settings, accessibility to these advanced tests can be limited, leading to disparities in treatment outcomes (34).

2. Delays in treatment: Delays in initiating treatment can occur due to prolonged testing periods or logistical issues in health care systems. These delays can adversely affect patient outcomes, particularly in patients with aggressive cancer types. Real-world healthcare systems often face such delays due to administrative and resource constraints (35).

3. Errors in biopsies and guidance: Mistakes in biopsy procedures, such as sampling errors or incorrect interpretations of biopsy results, can lead to inappropriate treatment plans. Additionally, variability in radiologist expertise can impact the accuracy of imaging-based guidance for radiation therapy. These errors are not uncommon in clinical practice and affect patient management and outcomes (36).

4. Adaptive radiation therapy challenges: Implementing adaptive radiation therapy, which adjusts doses based on the real-time tumor response, poses technical challenges and requires accurate imaging and monitoring systems to be effective. The real-world implementation of such advanced techniques is often limited by their technical capabilities and resource availability (37).

Table 2. Description of how uncertainties in radiation therapy are identified and managed, with potential solutions that leverage current and emerging technologies. This study provides a clearer picture of how the accuracy of medicine continues to evolve in the management of breast and prostate cancers, addressing the complexities associated with radiation therapy.

Table 2: Description of how uncertainties in radiation therapy are identified and managed.

Aspect	Breast Cancer	Prostate Cancer
Molecular Testing	- Oncotype DX and MammaPrint guide chemotherapy and radiation decisions. - Tailors treatment based on the genetic characteristics of the tumor.	- The Decipher test predicts aggressive disease to guide radiation therapy decisions. - Focuses on genomic signatures to determine treatment strategies.
Biomarkers	- PIK3CA mutations indicate resistance to anti-HER2 therapies but responsiveness to PI3K inhibitors and radiation. - Helps modify therapeutic approaches based on specific genetic traits.	- BRCA1/2 and ATM gene defects suggest benefits from intensified radiation and DNA damage response inhibitors. - Guide personalized therapy based on genetic vulnerabilities.
Immunotherapy Targets	- Trials like RADVAX are exploring radiation with dual checkpoint blockade (PD-1 and CTLA-4 inhibition). - Enhances systemic immune response, supporting the abscopal effect.	- Investigations of a combination of radiation and immunotherapy have been conducted to enhance the systemic response against tumors. - Utilizes immunotherapy to target specific proteins expressed by tumors.
Prognostic Factors	- MammaPrint identifies patients with a high genetic risk who might benefit from less intensive treatment. - Molecular diagnostics enhance the ability to determine the prognosis and treatment strategies.	- The presence of AR-V7 correlates with a poor response to hormone therapies but potentially a better response to other therapies. - Helps determine aggressive treatment strategies based on genetic profiles.
Future Directions	- Integration of liquid biopsies for real-time tumor monitoring. - AI algorithms predict responses based on imaging and genetic profiles.	- Application of AI to refine radiation therapy plans. - Continued research on biomarkers and their implications for treatment adjustments.
Radiation Therapy Uncertainties	- Variability in the tumor response due to genetic heterogeneity. - Adaptive radiation therapy and real-time imaging techniques are being researched to dynamically adjust treatments.	- Uncertainties in tumor size and location due to prostate movement. - Use of advanced imaging modalities and real-time tracking systems to increase the precision of radiation delivery.
Solutions to Uncertainties	- Implementation of genomic-based adaptive therapy to adjust doses based on an early response. - Development of personalized radiation therapy plans using AI to manage intratreatment changes.	- Incorporation of MRI-guided radiation therapy for real-time tumor tracking. - Development of AI-driven predictive models to optimize treatment schedules and radiation dosing.

Source: The Autor (2024)

2.10 In the Medical Physics Area

A combination of factors involving the interaction coefficients and dosimetric data, especially the stopping powers, parameters associated with the definition of the beam quality, tissue heterogeneities, and algorithms used for treatment

planning when considered as part of the whole process, are still the main contributors to the final uncertainty values associated with the doses measured and delivered to the tumor target (11,38,39,40).

Some of the main sources can be identified as follows:

- Math calculations.
- Incorrect tumor delineation by different professionals.
- A lack of care in handling the measuring system and its individual components, i.e., electrometers, cables, and chambers, plays a role in the inaccuracy of the measurement.
- The selection of incorrect values of the local influencing factors, i.e., temperature, pressure, and humidity, especially pressure, which varies significantly with altitude and is often not considered with due attention, or the temperature of the room and not of the water.
- Incorrect selection of reference conditions that must be used by the calibration laboratory, i.e., the distance to the source chamber, field size at the chamber position, depth of the detector in the phantom, and lack of lateral equilibrium.

Four main areas still need careful attention: tumor delineation, treatment planning, physical dosimetry, QA, and treatment delivery.

2.11 Tumor delineation

The delineation of the clinical targets and organs at risk is recognized as one of the most important, if not greatest, sources of uncertainty since the exact knowledge of subclinical disease depends strongly on the imaging resolution. Variations between different professionals for the same patient can be observed, such as in cases where head and neck tumors of 3.4–7.7 mm in size have been reported. Experience shows that the existing “guidelines” are not yet sufficiently accurate, although the use of software such as FALCON (Fellowship in Anatomical Lineation) or other software has become more readily available, in addition to joint training sessions, which can significantly reduce final uncertainties. The use of scripts can reduce human error, increase treatment planning efficiency, reduce confusion and promote consistency within an institution and among institutions (41).

Scripting capabilities, which record a sequence of messages or keystrokes while the user is operating the system, have been used for automated IMRT planning for simple and complex cases, such as prostate and whole-breast cases.

GTV delineation with MRI may be smaller with reduced interobserver variability than that with CT, indicating that CT and MRI are complementary, especially in head and neck cases. PET images are indeed a great asset for assessing tumor activity outside the main area of interest, although their resolution and sensitivity are still in need of further research. The inter- and intrafraction movements of organs between and during fractions are important sources of uncertainty and are often very difficult to evaluate when existing options are compared using different technologies.

The use of online imaging systems with fiducial markers, such as Calypso, tends to minimize errors due to organ movement during treatment, especially in the abdomen and pelvis. Reducing toxicity in prostate treatment, for example, has led to considerable improvements in biochemical control and a reduction in side effects such as urinary incontinence and actinic reactions.

A negative effect on survival curves can also be observed, especially for esophageal and lung tumors, because the movements toward the heart are increased by the movement of the respiratory cycle. Movements during the execution of each fraction caused by the cyclical displacement during breathing affect not only the lungs but also the liver and pancreas. This effect is also significant when the left breast is treated with tangential fields, and the dose administered to the left descending coronary artery may be impacted (42,43). These effects have been significantly improved by new technologies that monitor these movements in real-time, substantially reducing doses to the OARs and allowing larger doses to be delivered to the tumor or by proper treatment with field and field options using photons and electrons.

The traditional concept of increasing safety margins to cover organ movement errors mistakenly assumes a static spatial dose distribution in the PTV, namely, the only natural variation in the geometry of the patient's internal organs.

Considering these points, the innovative idea of using so-called robust planning (RP) (44,45) is an interesting, foreseeable approach that optimizes one of the most important sources of uncertainty associated with clinical planning. The traditional concept of the PTV associated with its uncertainties (RP) tends to generate a better and more integrated view of the process of reviewing the most important concepts, including stochastic and optimization aspects.

Interestingly, the major source of uncertainty can be related more to both the tumor geometry and its delineation than to the dose calculation and even less to the dose delivered to the tumor. The lack of information on tumor biology and the limited sensitivity of imaging methods, especially for that type of cell, limits the proper design of tumor delineation and may weaken the expected clinical outcome.

The choice of software used by the computerized treatment planning system (TPS) may also influence the calculated dose or the dose distribution; for example, the use of the pencil beam algorithm, although efficient, has lower accuracy than the Monte Carlo-based algorithms, as the latter model the physical interactions in the tissue directly.

2.12 Treatment Planning and Delivery

A positioning error at the time of image acquisition using CT or MRI can be interpreted as a systematic error, whereas daily positioning variation can be interpreted as random behavior. The movement of the organs has systematic and random uncertainties Sint and sint, and the setup Sext and sext contain systematic and random uncertainties that are not correlated.

The standard deviation of the systematic component can be expressed as follows:

$$S_{tot} = (S_{ext}^2 + S_{int}^2)^{½}$$

The standard deviation of the random component is calculated as follows:

$$s_{tot} = (s_{int}^2 + s_{ext}^2)^{½}$$

From an epidemiological perspective, the analysis must be performed in a more comprehensive manner, considering not only quantitatively the estimated value of the prescribed dose but also the true dose delivered to a particular organ. In addition, other factors, such as organ movement, potentially modifying the tumor response, such as the beam type, dose rate, age, sex, eating habits, genetics, and gradient of the oxygen concentration in the tumor itself, are not considered fully.

Table 3. Some examples of human- and technology-related uncertainties during the radiation treatment process require further consideration. Some are very difficult to assess fully. A more extensive list is available in a published report (1).

Human	Technology
Organ/tumor motion	Dose determination
Couch position	Beam profiles
Immobilization devices	Tissue inhomogeneities
Breathing motion	Leaf transit times
Contour change	Optimization algorithm
Organ full/empty	Machine calibration
Accuracy of lasers at set up	Electron density
Excess confidence	Virus infection
Lack of a QA program	Imaging resolution
Patient repositioning	Beam energy
Treatment plan validation	Electron density
End-to-end tests	Machine calibration

Source: The Autor (2024)

Some of the most important factors related to the treatment process that may influence the dose delivered to the tumor during daily sessions are summarized in Table 4 (2).

Table 4. Immobilization devices and typical associated uncertainties

Anatomic site	**Immobilization device**	**Expected uncertainty**
Intracranial	Head ring	1 mm
	Head fixation bite plate	< 2 mm
Head and Neck	Thermoplastic	2-8 mm
Lung	Abdominal	5-15 mm
Breast	Breast board	1.7 ± 2.8 mm
	Vac-Lok	1.8 ± 2.9 mm
Prostate	Leg support	6.5 mm
	Thermoplastic	4.6 mm
	Vac-lock	4.6 ± 3.5 mm

Source: The Autor (2024)

2.13 Physical Dosimetry and QA

As mentioned earlier, the interaction coefficients and correction factors are important components of the chain of events involving the process of measuring the absorbed dose at a given point and its contribution to the final uncertainty. The wall and electrode materials and the presence of air in the chamber cavity are indeed very sensitive to those factors.

The uncertainty evaluation should, whenever possible, be able to quantify the uncertainties associated with the measured absorbed dose through the initial calibration of the photon and electron beams directly in water. The typical final values provided by the SSDL are on the order of 1.4% for photons to 2.1% for electrons, where (k=2) is the largest contribution due to the conversion factor $k_{Q,Q0}$ [2001].

In the areas of physical dosimetry and treatment planning, this assessment is somewhat more feasible since most of the parameters are quantifiable, which allows the use of a mathematical approach to define the uncertainties.

Clarifying the concepts of absolute, reference, and relative dosimetry is important since the procedures and uncertainties are different and, in some cases, might be somewhat cumulative.

2.14 Absolute Dosimetry

Absolute dosimetry refers to the measurement of a physical quantity, in this case, the absorbed dose in water, with an instrument of the highest metrological quality, allowing its determination in accordance with its definition, which is generally conducted in primary standard laboratories (PSDLs) (47,48,49). In PSDLs, the conventional reference beam of gamma rays is the one emitted by a ^{60}Co source, and the final uncertainty is on the order of 0.7% (k=2) for the absorbed dose in water, which is normally determined with a calorimeter or Fricke

system and then used to calibrate the secondary standard chamber of an SSDL.

The values obtained by the secondary standard dosimetry laboratories (SSDLs or ADCLs in North America) with the original measurement reference conditions maintained are then transferred to the final user. In the SSDLs, the users' chambers from each radiation oncology center are calibrated using the calibration coefficients N_{D,w,Q_0} provided by the PSDL under the same reference conditions with a gamma ray beam emitted by a 60Co source. Since different classes of instruments and experimental conditions are not as rigid as those in the PSDLs are, the final uncertainty value increases to 1.5% when *k=2.*

2.15 Reference Dosimetry

Reference dosimetry refers to the measurement at the user level of the absorbed dose to water with an ionization chamber calibrated in an SSDL following the recommendations of the Code of Practice (46,47,48).

With the calibration coefficient N_{D,w,Q_0} provided by the calibration laboratory (SSDL), measurements can be performed with the user's chamber to obtain the absorbed dose in water with a beam of similar quality, respecting the same reference conditions as the SSDL, namely, a distance to the source chamber of 100 cm and a radiation field of 10 × 10 cm^2 at a depth of 5 cm in water, with further consideration of the effects of the influencing factors (water temperature, atmospheric pressure and ambient humidity) measured at the time of data acquisition. Whenever the beam quality is different than ^{60}Co, the calibration coefficient can be used for a high-energy photon beam, introducing a conversion factor known as $\mathbf{K_Q}$, which is specific to each user's beam quality, as recommended by the Code of Practice (46,47,48).

The formalism below proposed as a Code of Practice, TRS#398, and universally adopted provides a detailed recommendation of the procedure for measuring the absorbed dose in water under specific reference conditions for each type of radiation beam **Q** using $\mathbf{Q_o}$ in the ionization chamber tracked to the metrological network (49).

$$D_{w,Q} = M_Q \cdot [k_{TP} \cdot (k_h)_Q \cdot (k_{elet})_Q \cdot \left(k_{pol}\right)_Q \cdot (k_S)_Q] \cdot \frac{N_{D,w,Q_0}}{\left(k_{pol}\right)_{Q_0} \cdot (k_S)_{Q_0}}$$

where

M_Q= the electrometer reading in the user's beam.

$[k_{TP}$ = correction factor for the reference temperature and pressure.

k_u=correction factor for humidity when out of the range of 30–80 %.

$(k_{elet})_Q$= electrometer calibration correction factor when its calibration is performed separately from the chamber.

$(\left(k_{pol}\right)_Q$= polarity correction factor in the user's beam.

$(k_S)_Q$= correction factor for the lack of ion recombination in the user's beam.

N_{D,w,Q_0}= chamber calibration coefficient for the 60Co radiation beam provided by the SSDL.

$\left(k_{pol}\right)_{Q_0}$ = chamber polarity correction factor different from that defined for the 60Co radiation beam; and

$(k_S)_{Q_0}$= correction factor for the lack of saturation in the chamber.

For the user's beam, the following equation must be considered:

$$M_Q^* = M_Q^* \cdot N_{D,w,Q_0} \cdot k_{Q,Q_0}$$

where

M_Q^** = the chamber reading in the user's beam.

N_{D,w,Q_0} = chamber calibration coefficient for the ^{60}Co radiation beam; and

k_{Q,Q_0}= user beam quality factor specific for each high-energy photon beam

As in a calibration laboratory, polarity and saturation effects are not corrected once they are included here to correct the MQ reading.

Assuming no correlation between the components, the combined relative uncertainty can be defined by the following equation:

$$\frac{uc^2(D_{w,Q}^*)}{(D_{w,u}^*)^2} = \frac{u^2(D_{w,u})}{(D_{w,u})^2} + \left(\frac{1}{D_{w,u}^*}\right)^2 \left[\left(\frac{\partial D_{w,u}^*}{\partial d_{SSD}}\right)^2 u^2(d_{SSD}) + \left(\frac{\partial D_{w,u}^*}{\partial d_z}\right)^2 u^2(d_z)\right]$$

As the equation contains only products and quotients, the uncertainty can be calculated as the quadratic sum of the uncertainties of each component.

2.16 Relative Dosimetry

In the clinical environment, various measurements are performed under nonreference conditions where the calibration coefficient does not need to be used. These measurements are called relative, such as dosimetry of other radiation fields relative to the value obtained by the reference field, i.e., field output factors, and wedge filter factor measurements of the depth of the dose-normalized to the values obtained at the maximum dose point for that specific radiation field and type of beam (46,47,48). In these cases, a variety of detectors can be used without the need to have their values related to the true value of the quantity. The metrological consistency between the different levels guarantees an acceptable level for the final uncertainty of the dose delivered to the patient, which is compatible with the recommendations of international organizations.

Therefore, if one maintains the instruments (electrometer + cable + camera) followed by a

quality assurance program including periodic calibrations and special care to maintain functional integrity, the final quality of the measurements is expected to always be in harmony with the concept of best practices. The best approach is to follow the recommendations outlined below.

1.18 Important parameters of the main auxiliary instruments and their associated uncertainties (50,51,52).

2.161 Electrometer

The measured signal must be approximately 1000 times greater than the leakage.

Reproducibility: The typical estimated uncertainty is on the order of 0.03%, k=1.

Resolution: For cylindrical and parallel plate chambers, the typical value is 0.01%, k=1

Linearity: the typical deviation of the linear function is 0.06%, resulting in an uncertainty of 0.03%.

Zero: For M display=M–m, with m=0, a typical value is 0.01%.

Long-term stability: a typical value is 0.29% over a year.

Typically, the type A and B uncertainties of the electrometer system and its components are 0.6% and 0.9% for photons and electrons, respectively, with instrument stability being the most significant, 0.29 and 0.48% for photons and electrons, respectively.

2.162 Transmission monitoring chamber

For a typical display resolution of ± 0.5 MUs, considering a rectangular distribution for a fixed number of 200 MUs, 0.14% is an acceptable value.

Atmospheric pressure: correction factor Po/P

If Po = 101.3 kPa with a minimum digital scale division of 0.5 mb when a rectangular distribution is used, the typical value is 0.13%. For analog displays, the parallax must be considered.

2.163 Temperature

A correction factor is determined using the following relationship:

(273.2 +T)/273.2 + To), where To = 20 °C

If the resolution is 0.1 °C, assuming a rectangular distribution, its value is 0.06 °C.

The calibration certificate for the range of 15–25 °C has an estimated uncertainty value of 0.29%.

Notably, the response of a chamber can be affected by the temperature of the water, which expands or contracts its walls and causes a change in its volume, potentially generating a correction of 0.19% if the temperature ranges from 15 to 25 °C. This effect is called the thermal effect.

2.164 Humidity

If no correction is made over the range between 0% and 100%, assuming a rectangular distribution, the uncertainty associated with this component must be ± 0.17%. In the working range of 30%-70%, no correction is needed.

2.165 Electrometer calibration (k_{elec})$_Q$

If the calibration coefficient has been assigned to the set (chamber + electrometer), the value to be considered a typical uncertainty is 0.14%. Only a few laboratories in our network offer the option to calibrate the electrometer separately.

2.166 Polarity effects (kpol)Q/(kpol)Qo

Maximum variations of 0.2% and 0.3% may be easily observed for photon and electron beams, respectively, depending on the linac.

2.167 Recombination (ks)Q/(ks)Qo

The typical combined uncertainty when the two-voltage method is used is the corrected reading, which is on the order of 0.49% for photons with a cylindrical chamber and 0.70% for electrons measured with a parallel plate chamber (48,49).

2.168 Calibration coefficient NDw,Qo

Uncertainties in the calibration coefficients may vary slightly from SSDLs, as they depend slightly on which primary laboratory from which it is traced and on which SSDL laboratory infrastructure it is traced.

For SSDLs, such as the SSDL in Brazil, whose reference is an ionometric standard traced to the BIPM, the uncertainty associated with the calibration certificate provided to the user for ^{60}Co gamma ray measurements is on the order of 1.5% for (k=2) (50,51,52).

2.169 Beam Quality Factor Correction Value $k_{Q,Qo}$

This factor is undoubtedly the one with the greatest uncertainty. Many variables affect its value, such as the difference between the energy fluence of the beam used in the calibration laboratory. Only primary standard laboratories have experimental conditions to evaluate this parameter; therefore, the user's beam quality is assessed via theoretical calculations using the Monte Carlo method while considering the different materials used in the construction of the chamber. As a result, their values are specific to each chamber, as recommended by TRS#398 (48).

The uncertainties are on the order of 0.9% for a photon beam in a cylindrical chamber and 1.7% for an electron beam in a parallel plate chamber because of cross-calibration with the cylindrical chamber. When experimental values of $K_{Q,Qo}$ are used, small reductions to 0.7% and 0.8% can be observed. The P_{wal} factor is one that contributes most to the variation in the chamber response due to the interaction process.

The qualities of the beams are estimated using empirical values, in the case of photons, via the TPR20,10 relationship and, in the case of electrons, via R_{50}, according to previous definitions. In this case, the uncertainties associated with the determination of TPR(20,10) and interpolation must be assessed (48).

2.17 Measurements conducted under reference conditions

Many possibilities for errors may occur when recording the results of measurements under reference conditions at the user level.

Source surface distance: A maximum deviation of 1 mm from the source to the distance indicator line may cause a maximum possible error in a uniform distribution of 0.06 cm.

Field size: The maximum acceptable deviation of the luminous field must be 1 mm, and the deviation between the light field and the radiation field must be the same value of 2 mm or an uncertainty of 0.12%.

Detector position depth: Considering the difference in the water density, for example, at 20 °C, whose real density is 0.9982 g/cm3, the position of the detector will be tenths of a mm deeper, namely, 0.2 mm for photons and 0.1 mm for electrons, due to the relation to the reference depth of R50.

Relative and reference dose values at a given point in the QA of EBRT patients

The uncertainties associated with and inherent to a quality assurance program must be estimated individually so that the global uncertainty of the planned dose to be delivered in each target volume can be reduced. As mentioned earlier, any reduction should aim for a positive impact on the probability of local control and the reduction of complications in normal tissues, which are generally dependent on the type of tumor (53 – 57).

However, a 0.2 cc small-volume ionization chamber calibrated in an SDDL for the absorbed dose in water with the calibration coefficient N_{DwQo} might be considered an interesting option for reference dosimetry in IMRT. The present uncertainty provided by the SSDL due to cross-calibration may be greater, on the order of 2.2% (k=1).

Due to the complexity of the dose distribution with the IMRT technique, the accumulated dose must be considered instead of the sum of its segments, including the transmission in the sleeves and the effect of the MLC that contributes to the signal in the chamber, depending on the type of MLC. A specific measurement to verify the dose calculated by the TPS must be performed before starting treatment, preferably with an equivalent tissue chamber to assess the uncertainty (53 – 57).

In general, in terms of the accuracy requirements and uncertainties in radiation oncology, the overall uncertainties associated with external radiotherapy can be summarized in a rather simplified manner, according to Table 5 below 11.

Table 5. Typical uncertainties achievable at different metrological levels[2].

Ionization Chamber Reference Dosimetry	Dose Uncertainty (k=1)	Dose Uncertainty (k=2)
^{60}Co (PSDL) transfer to the SSDL	0,35%	0.7%
^{60}Co (SDL)	0,75%	1,5%
^{60}Co (user level)	0,9%	1,8%
High photon energy (user level), cylindrical chamber	1,5%	3.0%
Electrons (user level), parallel plate chamber	1.4-2.1%	5,0%
Combined uncertainty	1,6-2,6%	3.2-5.2%

Source: The Autor (2024)

The greatest uncertainty associated with the measurement at a given point results from a calibration with the beam quality correction factor being relative to the beam reference ($K_{Q, Qo}$), which contributes more significantly, in general, on the order of 1.7% (k=1),

For the sake of completeness and to obtain a clear understanding of the clinical environment where the reference measurements are made, the additional uncertainties of some parameters are presented in Table 6.

Table 6. Typical uncertainty values for two typical chambers used for photons and electrons.

Parameter	Photons, PTW 30013%	Electrons, Markus %
Reproducibility	0.03	0.03
Resolution	0.01	0.01
Linearity	0.03	0.03
Zero Temperature	0.01	0.01
Long-term stability of the electrometer factor	0.29	0.48
Leakage	0.01	0.01
Combined Uncertainty (*k*=2)	0.28	0.48

Source: The Autor (2024)

3. Final Remarks

3.1 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.

3.2 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 (21–24). This standardization might help to narrow the gaps between translation and preclinical research.

3.3 Clinical level

As a result of the integration of molecular diagnostics, biomarkers, and immunotherapy, radiation therapy is becoming increasingly personalized and effective. These advances allow for more precise targeting of therapies, better prognostication, and ultimately improved patient outcomes. Continuous innovation and research in these fields are expected to drive further changes in clinical practice, leading to more refined and effective cancer treatments in the future.

The conventional and mathematical statistical quantification of the uncertainties in each of the above steps that may result in different clinical outcomes is rather difficult to perform since the individual professional judgment of the above parameters normally prevails, but we feel that noting this issue is important.

Soon thereafter, theranostics, a new procedure that represents the targeting of cancer via two pathways that involve locating cancer cells anywhere in the body and delivering targeted radiation to kill those cells, might be our focus for evaluating new uncertainties in a practical and accessible manner.

Positron emission tomography (PET) is used to locate the cancer, followed by an infusion of medicine to destroy it, reducing the risk of harming nearby healthy tissues.

4. Medical Physics Level

The reduction in overall uncertainty with a positive impact on the clinic is fundamental for establishing an integrated quality assurance program, with an emphasis on the accuracy of those parameters that influence the accuracy of patient treatment.

The use of one commercially available software program for organ delineation will certainly reduce one of the main components that strongly affects the dose distribution in the tumor and surrounding organs.

Considering the complexity and the interrelation of physical, biological, and engineering parameters in the process, periodic, up-to-date exercises using the current code of practice should be encouraged.

5. 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 bio-logical 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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Annex. THE CONCEPTS RELATED TO THE UNCERTAINTY ANALYSIS

The uncertainty associated with a measurement is a parameter that can be characterized by the dispersion of measured values and is identified by their standard deviation. The concept of uncertainty, unlike error, has no sign, and its values represent a symmetric dispersion.

Additionally, uncertainty represents the lack of exact knowledge of the measurement value once systematic effects are eliminated after applying appropriate corrections.

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 methods to report the values of uncertainties.

The Guide suggests that we treat the concepts and uncertainties as types A and B, indicating that two different assessment paths must be considered. 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.

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

The quantity s2 (x_i) is called the empirical variance (which is useful for determining the deviation from the mean of the data from an analyzed set). For this calculation, the average value of the squared differences in the mean of a group of measurements *n* is determined. Typically, the interest is in the standard deviation of the mean value written as $s\left(\bar{x}\right)$, for which the following general relationship applies:

$$s\left(\bar{x}\right) = \frac{1}{\sqrt{n}}s(x_i)$$

TYPE A STANDARD UNCERTAINTY

The type A standard uncertainty, called u_A, is described as the standard deviation of the mean value of statistically independent observations, which, in principle, can have its value reduced with a greater number of readings with a smaller dispersion, for example, when the electrical leak significantly interferes with the signal.

$$u_A = s\left(\bar{x}\right)$$

Thus, type A uncertainty is estimated from the analysis of several measurements that are never less than 5.

TYPE B STANDARD UNCERTAINTY

Many standard uncertainties cannot be estimated by repeated measurements; for this reason, they are called type B. For this reason, data obtained from the literature are used, e.g., the shock section, the braking power, the KQ for a given chamber, and the values of the calibration coefficients, for example, those of the chamber, barometer and thermometer provided by the calibration laboratories, whose values are the result of a quadratic combination of uncertainties of types A and B.

Although some researchers believe that type B uncertainty can be determined, a prudent approach is to accept the idea that a probability distribution can correspond to an unknown shape. For example, L can be considered within the 95% confidence limit to be reasonably certain of this limit, and if we are quite sure of the distribution, we can assume a 99% confidence limit. Thus, type B uncertainty can be estimated using the following relationship:

$$s\left(\bar{x}\right) = \frac{1}{\sqrt{n}}s(x_i)$$

where *k=2* can be used when the assumption is reasonably safe and *k=3* when the assumption is quite certain that the limits ±L are Gaussian distributions.

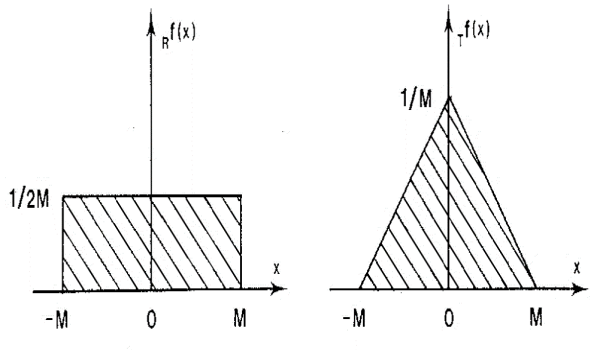
Sometimes, this probability density function can be described as a rectangular distribution, which means that the probability is equal at any point within the limits -M and +M and zero outside this limit, using the following relationship:

$$u_B = \frac{M}{\sqrt{3}}$$

Another option is to use the triangular distribution with the same limits of the relationship as follows:

$$u_B = \frac{M}{\sqrt{6}}$$

Figure 1 shows a representation of the probability density functions for the rectangular Rf(x) and triangular Tf(x) distributions; the latter is used in cases where the distribution is not known.



As no rigid rule has been established for estimating type B uncertainty, for this reason, we must use our best knowledge and experience to estimate its values or use values published in the literature from recognized sources.

COMBINATION OF UNCERTAINTY AND EXPANDED UNCERTAINTY

Types A and B can be combined using statistical rules for combining variances, which are the squares of the deviations. If u_A and u_B represent the relative standard uncertainties, types A and B, of a given quantity u_C, the relationship below is valid only when the sources of uncertainty are not correlated.

$$u_C = \sqrt{u_A^2 + u_B^2}$$

If the probability density is considered a Gaussian distribution, the confidence limit should be 68%, and multiplication by a coverage factor *k* to determine the expanded uncertainty U according to the following relationship is highly desirable:

$$U = ku_C$$

Coverage values with more than one significant number do not seem to be justifiable; therefore, the typical values are *k =2* or *k =3*, which correspond to confidence limits of 95% and 99%, respectively.

COMBINED STANDARD UNCERTAINTY

A practical example is the determination of the calibration coefficient provided by a laboratory, which is the result of a set of measurements, factors, and physical constants, as well as its traceability to primary laboratories. All these numerical values contain type A and B uncertainties that combine to a final value that is provided as part of the calibration coefficient.

In general, a variable y is a function of several variables,

$x_1, x_2, x_3, \ldots$, according to the following relationship:

$$y = f(x_1, x_2, x_3, \ldots)$$

When the influencing quantities $x_1, x_2, and\ x_3$ (e.g., temperature, pressure, and humidity) are independent of each other, the value of *u(y)* can be calculated using the following simple relationship:

$$u(y) = \sqrt{c_1^2 u^2(x_1) + c_2^2 u^2(x_2) + c_3^2 u^2(x_3) + \cdots} \quad (1)$$

Therefore, independent variables can be added or subtracted, the variances are also added, and the uncertainty of the sum is obtained by the square root of the sum of squares with the coefficients $c_1, c_2, c_3, \ldots$ and their relative weights.

Another situation that could occur would be with the product of independent variables whose dependence will be calculated using the following relationship:

$$y = x_1^{\alpha} x_2^{\beta} x_3^{\gamma} \ldots$$

where the exponents $\alpha, \beta, and\ \gamma$ are constants; in this case, the relative uncertainty *y* can be obtained from the following equation:

$$r(y) = \sqrt{\alpha^2 r^2(x_1) + \beta^2 r^2(x_2) + \gamma^2 r^2(x_3) + \cdots}$$

where

$$r(x_i) = \frac{u(x_i)}{|x_i|}$$

and x_i is the relative uncertainty.

Therefore, for the product or ratio of independent variables, the relative weight of the added variances is the square of the exponents $\alpha, \beta, and\ \gamma$. The ratio $y = x_1/x_2$ is very common, where the quantities x_1 and x_2 contain measurements and correction factors.

The rules for combined standard uncertainties also apply to expanded uncertainties if both have the same coverage factor k. The uncertainties normally published generally have a factor of k=2, and if they are not indicated, this value is assumed.

The final table (uncertainty budget) should be created by separating types A and B, as defined in the Annex, which allows any value that is modified over time to be changed more easily.

In summary, as both uncertainties (A and B) are based on probabilistic distributions, those of type A are obtained from a series of measurements and presented as the value of their standard deviations, and those of type B are evaluated using other nonstandard methods, statistics, or a series of observations.

On the other hand, the limits that define a variation may be well known, but its distribution may not be known. In this case, the best approach is to use a previously mentioned rectangular (or uniform) distribution that considers a constant value within a certain range and zero outside it.

If the maximum variation of the limit is given for -a a + a, the uncertainty of type B will be given by the relation uB-a/31/2 with the coverage factor k =1, which corresponds to a confidence limit of 68.0%.