POLYTECHNIC INSTITUTE OF LISBON

LISBON SCHOOL OF HEALTH TECHNOLOGY

GEOMETRIC UNCERTAINTIES IN PROSTATE CANCER RADIOTHERAPY TREATMENTS

MÁRCIO JOSÉ PEDROSO DE ASSIS
SUPERVISOR: DR. NUNO TEIXEIRA, ESTeSL

Master in Radiation Applied to Health Technologies

Specialization Area:

Digital Imaging Technologies

(This version includes the criticisms and suggestions made by the jury.)

Lisbon, 2019

POLYTECHNIC INSTITUTE OF LISBON

LISBON SCHOOL OF HEALTH TECHNOLOGY

GEOMETRIC UNCERTAINTIES IN PROSTATE CANCER RADIOTHERAPY TREATMENTS

MÁRCIO JOSÉ PEDROSO DE ASSIS
SUPERVISOR: DR. NUNO TEIXEIRA, ESTeSL

Master in Radiation Applied to Health Technologies

Specialization Area:

Digital Imaging Technologies

(This version includes the criticisms and suggestions made by the jury.)

Lisbon, 2019

At first, this dissertation is dedicated to God for my life and blessings. For my parents, José e Cleusa, whom teach me the timeless principles and for all support necessary that only the parents can do.

Acknowledgements

I am grateful to Dr. Nuno Teixeira for his great scientific expertise, love to teach and guidance through out the master course.

Many thanks to all professors of ESTeSL, in special professor Dr. Luís Freire, which supervised us during all time and for the exciting classes.

I have the gratitude to the new friends I have made in Portugal as the old friends always somehow present.

I am very grateful for the love of all my family, in special, for the unconditional love of my father José and my mother Cleusa.

A great gratitude I feel for Our Lady of Fátima for the care over these years.

You have had the good fortune to find real teachers, authentic friends, who have taught you everything you wanted to know without holding back. You have had no need to employ any tricks to steal their knowledge, because they led you along the easiest path, even though it had cost them a lot of hard work and suffering to discover it... Now, it is your turn to do the same, with one person, and another — with everyone!

St. Josemaría Escrivá

Resumo

Procedimentos em radioterapia visam alcançar a entrega de dose com alta exatidão. Este trabalho aborda algumas considerações sobre incertezas associadas a erros sistemáticos e aleatórios em tratamentos com radioterapia conformacional de câncer de próstata que podem comprometer a entrega de dose prescrita no planeamento. Sugestões sobre como minimizar as incertezas são apresentadas nos relatórios e diretrizes da Agência Internacional de Energia Atómica (IAEA), Comissão Internacional de Unidades e Medidas Radiológicas (ICRU) e o Instituto Britânico de Radiologia (BIR), tais sugestões são amplamente discutidas e confrontadas com observações clínicas em tratamento radioterápico. Os erros geométricos e incertezas estão intimamente relacionados com a dose de radiação fornecida ao paciente. Portanto, a descoberta de margens ideais de CTV-PTV permite uma maior exatidão em entrega de dose ao tumor e preserva os órgãos circundantes os quais são altamente sensíveis à radiação. Para o entendimento dos fundamentos relacionados à sobre e subdosagem em tratamento radioterápico de câncer de próstata, deve-se levar em consideração a mudança de forma geométrica relativa às variações anatômicas do volume tratado (TV) e dos órgãos em risco (OAR). Assim como a precisão das técnicas de delineamento de CTV-PTV tal qual o uso de portal de imagem, por exemplo. Todas essas intervenções possibilitam a precisão na identificação das margens de CTV-PTV para o maximização de entrega de dose prescrita. Neste ínterim, os métodos para o cálculo de margens desenvolvidas pelo BIR e van Herk são abordados, além da discussão acerca de um estudo onde aqueles métodos foram empregados e aplicados clinicamente. Os resultados indicam uma exatidão na entrega de dose que está abaixo de 2%, valor menor que o limite de ±5% sugerido pelos relatórios das agências internacionais.

Palavras-chave: Incertezas. Exatidão. Margem. Radioterapia. Dose.

Abstract

The procedures in radiotherapy aim achieve high accuracy on dose delivery. This work covers some considerations about systematic and random errors besides the related uncertainties in prostate cancer treatments performed in conformal radiotherapy treatment which can compromise the dose delivery in the planning. Suggestions about minimizing the uncertainties are presented in reports and guidelines of International Atomic Energy Agency (IAEA), International Commission on Radiation Units and Measurements (ICRU) and The British Institute of Radiology (BIR), they are widely discussed and confronted to clinical observations inside the radiotherapy treatment. Those geometric errors and uncertainties are closely related to dose delivered to the patient. The find of the optimal CTV-PTV margins allows a better accuracy of dose delivery on the tumor and spare the surrounding high radio-sensitive organs. For the understanding of roots related to over and under-dosing in the prostate cancer radiotherapy treatment the change of the geometrical shape due the anatomical variations of the treated volume (TV) and the organ at risk (OAR) must be taken into account. As well as the precise CTV-PTV delineation techniques like the use of portal of image, for instance. All that interventions possibilities the accuracy on identifying the CTV-PTV margins for the maximum delivery of prescribed dose. In the meantime, both BIR and van Herk margins recipes are covered, therefore a study where that methods were applied clinically and analized were discussed. The results indicate the dose delivery less than 2% that is inside the limit of ±5%, which is in compliance with international reports.

Keywords: Uncertainties. Accuracy. Margin. Radiotherapy. Dose.

List of Figures

List of Tables

List of abbreviations and acronyms

AAAEA	As Accurately as Reasonably Achievable
IAEA	International Atomic Energy Agency
IARC	International Agency for Research on Cancer
ICRU	International Commission on Radiation Units and Measurements
BIPM	Bureau International des Poids et Mesures
BIR	The British Institute of Radiology
WCRF	The World Cancer Research Fund International
BPH	Belvoir Park Hospital
NICC	Northern Ireland Cancer Centre
GTV	Gross Tumor Volume
GTV-T	Primary Tumor
GTV-N	Nodal Gross Tumor Volume
GTV-M	Metastatic Gross Tumor Volume
CTV	Clinical Target Volume
TCP	Tumor Control Probability
TCPpop	Tumor Control Probability in a Population of Patients
PTV	Planning Target Volume
OAR	Organ at Risk
PRV	Planning Organ at Risk Volume
ITV	Internal Target Volume
TV	Treated Volume
RVR	Remaining Volume at Risk
IVM	International Vocabulary of Metrology
NTCP	Normal Tissue Complication Probability

CT	Computing Tomography
MLC	Multileaf Collimator
EPI	Electronic Portal Images
DDR	Digitally Reconstructed Radiograph
Gy	Gray
SD	Standard Deviation
EUD	Equivalent Uniform Dose
L	Lateral
AP	Antero-posterior
CC	Craniocaudal
CS	Cranio-spinal
SI	Superior-inferior

Contents

1 Introduction

Cancer is one of the more dangerous and complex human diseases. It has been treated with radioactivity since the first years of the 20th century [1]. Approximately one third of global population will develop cancer during their lifetime [2]. A study of International Agency for Research on Cancer (IARC) [3] guarantee there will be an estimated 18.1 million new cancer cases and 9.6 million cancer deaths in 2018. Another estimative of International Atomic Energy Agency (IAEA) [2] presents up to 65% of all cancer patients, it depends on area of world they live, will be benefited with treatment with radiation as part of their overall treatment. The World Cancer Research Fund International (WCRF) relates that from those cancer cases, the prostate cancer is the second most common cancer in men, about 1.3 million new cases in 2018, and the fourth most commonly occurring cancer between men and women [4, 5, 6]. Thereby, it is evident how the radiotherapeutic managements are important to the world-wide health population.

The radiation oncology technology has been improved very rapid over the last years. It became possible by an increase of development of radiology interventions while new techniques have been improved continuously. Is acknowledged that the principal aim of radiology treatment is to kill the malignant cells of the tumor. Thus, the increase of treatment complexity improved the primary goal of the delivering radiation dose on malignant cells with greater radiation dose although the dose delivered to surrounding normal tissue must be as minimal as possible. This goal has been reached even more by the increasing of radiation oncology technology by the better controlling of tumor and the reducing of side effects as well. The new technologies applied in radiotherapy are very significative since the control of malignant tumor is one of major problems to a cancer cure. Otherwise, the better dose distribution implies positive treatment response. Is know, how will be described here, there are uncertainties in every step of treatment of cancer with radiotherapy in the both past radiotherapy methods and in the new advanced technologies. "Therefore, it is important not only to have a quantitative understanding of uncertainties, but also to consider the propagation of these uncertainties as part of the entire treatment optimization process" [7].

External beam radiotherapy as approach to treat cancer tumors uses high energetic particles projected towards the tumor. Then, the cancerous cell has the apoptosis induced by a damage caused by a particle of that beam. As described, the principal aim is eradicate the tumor cells while the surrounding non-tumor tissue is preserved. However, that process described has several troubles to be bypassed, the principal one is that the ionizing radiation can interact with the healthy tissue as well. Conversely, the dose must be applied only to extension of the target reducing the

delivery of dose to organs of risk in order to keep off newly complications as secondary tumors. Moreover, if insufficient radiation dose is applied to a cancerous tumor its uncontrolled cells growth cannot stop. All the process of planning and delivering of fractioned radiation in radiotherapy introduces a number of inherent uncertainties [8]. In other words, the patient already has the uncertainties before the begining of its treatment. It is clear for Sonke and van Herk [8] that "Each of these uncertainties might be small in general, but the combined effect of all associated errors can be substantial and will limit the precision of treatment".

A small and concise history of the accuracy in treatments with radiation from the beggining of the first publications about the subject in 60's to the last IAEA report about that in 2016 will be described next.

The concerning about accuracy in radiology comes out in early 60's with the paper of the Wambersie's group [9], based on affirmation of the work of Flamant's group [10], which has the thesis that the dose deviations between 7 to 10% is possible to be detected clinically. Later, in 1971, Herring and Compton [11] conclude that some tumors have they probability of control significantly linked with the function of dose. For instance, the determination of the decrease of 10% of a radiation dose delivered in a cancer of larynx could change the probability of control of that tumor up to 70%. At the same decade the Report nº 24 of International Commission on Radiation Units and Measurements (ICRU) about accuracy requirements was published. Accordingly to Van Dyk et al. [7] the ICRU Report nº 24 concludes that

> "the available evidence for certain types of tumor points to the need for an accuracy of ±5% in the delivery of an absorbed dose to a target volume if the eradication of the primary tumor is sought. Some clinicians have requested even closer limits such as ±2%, but at the present time it is virtually impossible to achieve such a standard" (p.366).

Afterwards that report a lot of studies about accuracy requirements have been demonstrated that an accuracy of ±5% in delivery of radiation on target should be an objective. The most of that analyses were made in two-dimensions radiation management era. The newest IAEA Report Nº 31 "Accuracy Requirements and Uncertainties in Radiotherapy" [2] published in 2016 exhibit new recommendations for the modern era, or three-dimensions conformal radiation therapy. In addition, that IAEA Report [2] considers that "is clear that a single statement about accuracy requirements, i.e. 5% in radiotherapy, is an oversimplification. The accuracy requirements are dependent on both technological considerations as well as biological and clinical concerns". However, pursuant the IAEA Report Nº 398 "Absorbed Dose Determination in External Beam Radiotherapy" [12] "the requirement for an accuracy of 5% in the delivery of absorbed dose would correspond to a combined uncertainty of 2,5% at the level of one standard

deviation". In contrast, taking into account the uncertainties in dose generated by algorithms, a more appropriate limit for the combined standard uncertainty of the dose delivered to the target volume would be ±5% [12].

The margins are frequently reduced in radiotherapy to increase the excluding of normal-tissue. In addition, van Herk et al. [13] declare that is "unclear whether the potential clinical benefit outweighs the risk of missing the target".

The static volumes is used for the most treatment planning systems evaluation and the planned dose distribution. However, this outlook grossly simplifies geometric errors. "When a planned dose distribution is evaluated on the clinical target volume (CTV), i.e., the volume that does not include a margin for geometric uncertainties, all geometric errors are explicitly ignored" [13]. Which leads to an estimation of tumor control probability (TCP) higher than the TCP with geometric errors included. Even so, to compute the TCP or evaluate the dose using the planning target volume (PTV) without the margin for for geometric uncertainties is not correct. A method of evaluating treatment plan based on detailed knowledge of the distribution of geometric errors in the patient population, one that does not use the PTV, will be described on the Chapter 8.

Unfortunately several terms used in radiotherapy literature such as *uncertainty*, *precision*, *accuracy* and *error* are not roled clearly. Consistent and clear terminology are fundamental, then this work will use terminology of "International Vocabulary of Metrology - Basic and General Concepts and Associated Terms" from *Bureau International des Poids et Mesures* (BIPM) and from the IAEA Report nº 31 which is the newest guideline of the radiology area.

Therefore, is very clear how the safety margins are crucial to have a better cancer management. In order to reach better safety margins the ICRU Report nº 83 [14] described several categories of volume of a tumor and normal tissues that surround it as well as several procedures to take that into account. The definition of three oncological and radio-oncological volume concepts have been created for use in the treatment-planning and for reporting processes. Those volume concepts are identified as general oncological volumes, radiation oncological volumes related to the target and volumes related to normal tissues.

2 Terminology in Radiotherapy

Some of terminologies used in measurement have been defined by international organizations such as the *Bureau International des Poids et Mesures* (BIPM). The definitions of the basic terminology will be described here with the aim to minimize inconsistency of the such terms used in radiotherapy and those argued on the "International Vocabulary of Metrology – Basic and General Concepts and Associated Terms" published in 2012 by the BIPM. The definitions of basic terms that will be presented here are widely used in radiotherapy, thereby this chapter has the purpose of avoid whichever misunderstanding about the classification of measurements.

2.1 Accident

The term *accident* "refers to any unintended event, including operating errors, equipment failures or other mishaps, the consequences or potential consequences of which are not negligible from the point of view of protection or safety" [15].

2.2 Accuracy

The term *accuracy* (or measurement accuracy) is defined in International Vocabulary of Metrology (IVM) [16] as the “closeness of agreement between a measured quantity value and a true value of a measurand”. In turn, measurand is the “quantity intended to be measured” [16]. It is clear that this definition is not a quantity or a value. "A measurement is said to be more accurate when it offers a smaller measurement error" [7].

2.3 Error

The term *error* (or measurement error) is defined in IVM [16] as the “measured quantity minus a reference quantity value”. In the radiation oncology context, the word *error* tends to be used for both measurement error and mistakes [7].

2.4 Incident

The term *incident* has been defined as "an event or a series of events that has led to, or would have led to if undiscovered, dose error in a patient undergoing radiation therapy treatment" [17].

2.5 Trueness

The VIM [16] defines the *trueness* (or measurement trueness) as the “closeness of agreement between the average of an infinite number of replicate measured quantity values and a reference quantity value”. It is used for comparative statement, and can not be expressed numerically.

2.6 Precision

The *precision* (or measurement precision) is “closeness of agreement between indications or measured quantity values obtained by replicate measurements on the same or similar objects under specified conditions” [16].

2.7 Bias

The term *Bias* (or measurement bias) is the “estimate of a systematic measurement error” [16].

2.8 Uncertainty

The term *Uncertainty* (or measurement uncertainty) is described in IVM [16] as a “non-negative parameter characterizing the dispersion of the quantity values being attributed to a measurand, based on the information used” . Van Dyk et al. [7] complement the IVM definition for repeated measurements in what way "the results can be represented by a statistical distribution, which can be summarized by specific statistical quantities such as mean, mode, standard deviation, and variance".

Since each measurement, procedure in radiation treatment and dose calculations have a corresponding uncertainty, they cannot be performed perfectly.

2.8.1 Type A evaluation of measurement uncertainty

Type A evaluation of measurement uncertainty is the “evaluation of measurement uncertainty by a statistical analysis of measured quantity values obtained under defined measurement conditions” [7].

2.8.2 Type B evaluation of measurement uncertainty

Type B evaluation of measurement uncertainty incorporates a “method of evaluation of a component of measurement uncertainty determined by means other than Type A evaluation of measurement uncertainty” [16, 18, 7].

The value of uncertainty may be taken from a resultant value of a previous measurement, a reference value from the literature, or using the value of uncertainty associated with a standard for which a calibration certificate is available [7].

Some of concepts associated with measurements cited above are better described graphically on Figure 6 from the Chapter 4 which covers better about the set-up errors and the related terms.

2.9 Systematic Error

The VIM [16] defines *systematic error* (or systematic measurement error) is defined as the “component of measurement error that in replicate measurements remains constant or varies in a predictable manner” [16]. The causes of systematic error can be known or unknown. Korreman et al. [19] complement the definition of the systematic errors for radiotherapy as "[...] reproducible consistent errors, occurring in the same direction and of similar magnitude over the course of treatment". For an individual, the systematic errors is a distance of the mean of the daily positions in relation to a ideal point in space [19].

2.10 Random Error

The *random error* (or random measurement error) is defined as the “component of measurement error that in replicate measurements varies in an unpredictable manner” [16]. Van Dyk et al. [7] complement such definition for a set of measurements as "random measurement errors of a set of replicate measurements form a distribution that can be summarized by its expectation, which is generally assumed to be zero, and its variance". In radiotherapy, the random error "varies in direction and magnitude from day-to-day and is represented by the range of different positions for each delivered treatment fraction" [19].

Figure 1 shows an example of systematic and random errors of a group of five patients.

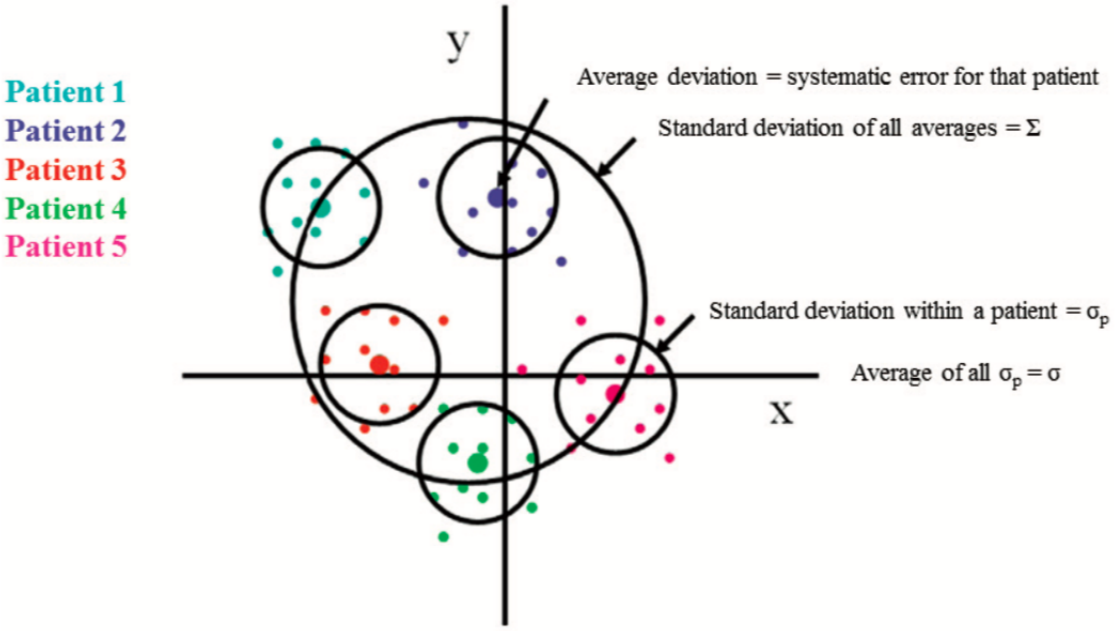

Figure 1 – Graphical presentation of systematic and random errors of a group of individuals.

Source: Korreman et al. [19], p. 132.

Where the small colored dots represent the patient's error for each measurement, the large colored dots represent the average systematic error, the standard deviation of the set-up error for an individual patient is presented in small circles while the standard deviation of all averages in the large circle [19]. Therefore, the Figure 1 illustrates that "that detailed knowledge of the set-up error of a given patient can therefore reduce the required margin compared to margins based upon group statistics alone" [19].

3 Radiobiological Framework for Considering Accuracy Requirements

Patients whom receive inadvertently a higher dose than the prescription to organ at risk (OAR) have raised the hazard of developing toxicity, whereas patients which receive inadvertently a lower dose to the target volume have an increased hazard of failure. Some authors have tried to consider the accuracy and its effects on outcome based on empiric models. These researches are important to quantify the consequences of poor accuracy and also identifying a level of accuracy which is required in radiotherapy.

The head objective is to achieve the highest reasonably achievable level of accuracy of the overall treatment planning and delivery process. "In practice, however, there is a limit beyond which further improvement would have no clinically meaningful effect on treatment outcome" [2].

3.1 Description of Dose-Response Curve

The IAEA Report Nº 31 [2] defines the *end point* or *radiation effect* as "a specific observable effect in a tissue or organ that could occur at some time after irradiation and can reasonably be attributed to the radiation". The effect for normal tissues can be a change in the morphology of a normal tissue or in its function. Insofar as the radiation dose is increased the severity of radiation effects increases, as the probability of incidence as well, or both of them. In the case of the tumors the end point in radiotherapy is the persistent tumor control and is defined as the absence of tumor at a specified period of time, about 5 years after the radiotherapy treatment.

The term dose-response relationship, or curve, is applied for the relationship between dose and the incidence of radiotherapy end point. "The dose-response curve is generally sigmoid in shape, with the incidence rising gradually from zero to 100% as dose increases from zero to infinity" [2].

When handling about assessment the IAEA Report Nº 31 [2] quotes the Zuppinger [20] explanation, i.e. "[...] assessment of radiotherapy outcome requires prolonged observation of the patient, as tumor recurrence or late side effects may occur several years after the end of therapy". Clinical curves might be fitted to actual estimative of incidence of toxicity and tumor controlling. The late effects may continue to develop for tens of years after the radiotherapy. Therefore, as cited in the IAEA Report Nº 31 [2], 5 year estimates are generally accepted

> "as a reasonable indication of the late toxicity associated with radiotherapy alone, or combined with other modalities, except for very late effects such as radiation related second malignant neoplasms"(p. 30).

Nevertheless, even the late effects is present in a population of irradiated individuals, it does not prove that very long periods of follow-up is necessary to profile the relational toxicity of treatments.

3.2 Steepness of the Dose-Response Curve

The malignant tissues, normal tissues and cells have a biological response. This behavior is described graphically as a sigmoidal shape as seen in Figure 2, where the low doses yields almost no effect and, with the increase of dose the response, it rises rapidly up to saturation [7].

An earlier description of the steepness of dose-response curves is the increase of percentage in dose required to improve the tumor control probability (TCP) from 50% to 75%. In case of normal tissue complication probability (NTCP), it used to be described as the percentage decrease in dose required to reduce the complication rate from 50% to 25%.

The data for recents descriptors of the steepness of dose-response curves can be found in the ICRU Report nº 76 [18]. There are variations on that data in reported slopes of dose-effect curves for some tumors and normal tissues, which depends on their radiobiological characteristics and the uncertainties associated with these parameter values generated [2].

The main characteristic of the steepness of the dose-response curve is described in Figure 2.

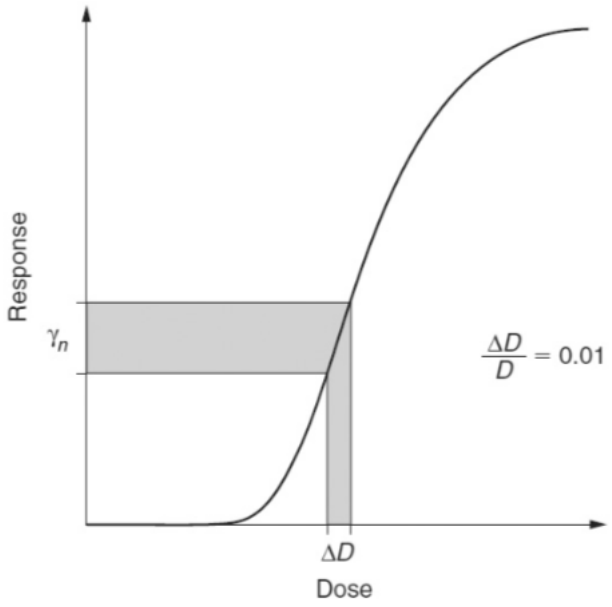

Figure 2 – The mid-range and the steepness of the dose-response curve.

Source: International Atomic Energy Agency [2], p. 33.

In relation to mid-range, the IAEA Report Nº 31 [2] explain that "the mid-range represents the steepest portion of this curve, and at this point, a 5% change in dose may result in a 10% to 20% change in TCP, at a TCP of 50%". For the complication rates in normal tissues, a 5% change in dose might result in a 20% to 30% change.

The Figure 3 published by Okunieff et al. [21] shows the clinical results generated from 90 dose-response curves of human tumors from multiple institutions.

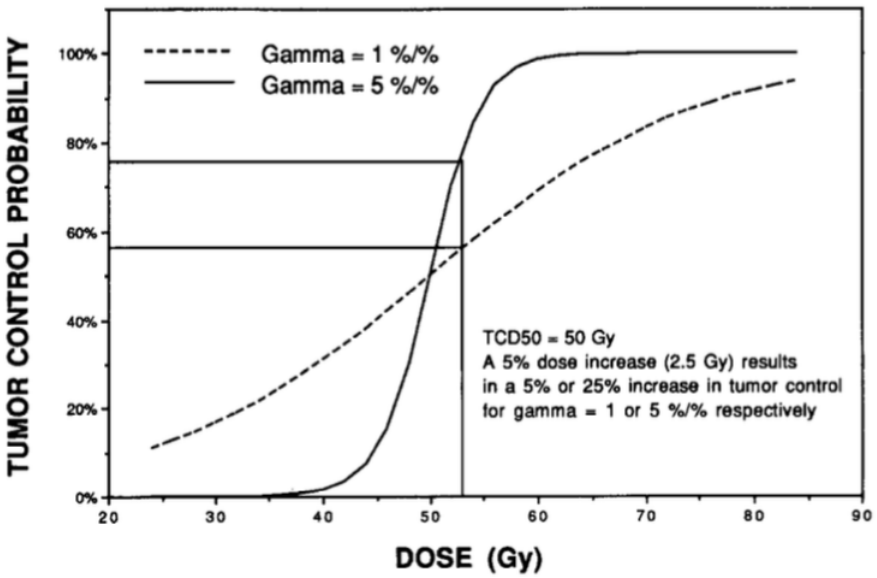

Figure 3 – Dose-response curve for a local tumor control based on data of patients from the multiple institutions.

Source: Okunieff et al. [21], p. 1234.

There is a dose which controls 50% of tumors, it is called TCD_{50}. And the γ_{50} is the percent change in TCP awaited from 1% change in dose at about the local maximum slope (TCD_{50}) [7]. It was demonstrated that values of γ_{50} "[...] varied dramatically from as low as 0.04 to as high as 47, although they are quick to point out that the very high and the very low values are probably fortuitous, and the 25% to 75% ranges of γ_{50} are more representative" [7]. For the γ_{50} range between 1 to 5, there is the following relation for the dose increasing: if the dose is increased by 5% then the TCP can be also increased by 5% for data with $\gamma_{50} = 1$, while the TCP can be increased by 25% for $\gamma_{50} = 5$ [21, 7]. However, Okunieff et al. [21] conclude that the steepness of the dose-response curves and γ_{50} are greater for each patient, differently of that reported curves in Figure 3 based on population statistics [7].

3.2.1 Measurement of the Steepness of Dose-Response Curve

For the measurement of the steepness of dose-response curve the IAEA Report Nº 31 [2] considers that "actually is more common the use of the normalized dose-response gradient γ for the measurement of the steepness of dose-response curves, its definition is

$$\gamma = D\frac{dP(D)}{dD} = DP'(D) \tag{1}$$

where *P(D)* is the function dose-response and γ is the change in percentage points for the relative increase of dose of 1%". The γ is pointed as the steepness of the dose-response curve and the curve of figure 2 lead to γ vary according to dose. It can be indicated by the notation γ_x where γ is the value at the dose to a response probability of x%. The γ value is set at the 50% response level, it is noted as γ_{50}, for a logistic dose-response curve. "This is the point where the logistic curve attains its maximum steepness (but not necessarily its maximum γ value, owing to the multiplication with dose in equation (1))" [2]. If the γ_{50} is known the steepness at any other response level can be calculated. It is useful for the tabulating steepness parameters for the dose-response relationship for several end points.

However, for practical applications is used the local value of γ at the actual clinical response level. "For a relatively small change in total dose, ΔD, the resulting absolute change in response, ΔP, can be calculated using the approximation

$$\Delta P \approx \gamma_x \frac{\Delta D}{D} \tag{2}$$

where γ_x is the local steepness of the dose-response curve and x is the response at dose D" [2].

3.3 Slope and Dose-Effect Level

Fortunately, the occurrence of severe adverse effects in radiotherapy is much lower than the rate of tumor control [2]. Consequently, in the most of times the γ_{50} is not a very meaningful parameter used at a lower response level to the slope characterization. The IAEA Report Nº 31[2] exemplifies it:

> "[...] in the case of $\gamma_{50} = 4$ for severe adverse effects, the γ value for an effect occurring in 5% of the cases, γ_{05}, is 0.62, or about 7 times lower than γ_{50} , and hence the relative steepness of the dose-response curve for tumor and normal tissues are reversed, assuming that tumor control is between 15% and 90%, and γ_{50} for the tumor control curve is 2 (p. 33).

Table 1 tabulates the values of local γ for a array of response levels for the associated dose-response curves with varying steepness.

γ_{50}	5%	10%	15%	20%	30%	40%	50%	60%	70%	80%	85%	90%
1	0.05	0.16	0.29	0.42	0.66	0.86	1.00	1.06	1.02	0.86	0.73	0.56
2	0.24	0.52	0.80	1.06	1.50	1.82	2.00	2.02	1.86	1.50	1.24	0.92
3	0.43	0.88	1.31	1.70	2.34	2.78	3.00	2.98	2.70	2.14	1.75	1.28
4	0.62	1.24	1.82	2.34	3.18	3.74	4.00	3.94	3.54	2.78	2.26	1.64
5	0.81	1.60	2.33	2.98	4.02	4.70	5.00	4.90	4.38	3.42	2.77	2.00

Table 1 – Local γ value as a function of γ_{50} and the response level for a logistic dose-response curve.

Source: International Atomic Energy Agency [2], p. 34.

Other values of γ of response level and γ_{50} can be found easily by bivariate interpolation in the Table1 above [2].

The Table 1 provides a helpful and informal impression of the validity of the Equation 2 as linear approximation to the dose-response curve. The local γ values are roughly constant over a range of response levels. Thus, a satisfactory accuracy is given as a linear approximation.

4 Accuracy and Uncertainty

In this chapter the concepts accuracy and uncertainty are conceptualized and exemplified, as well as the other significant terms strictly pertaining to them. The terms presented in this chapter are often used ambiguously in the literature. Thus, it is very important to clarify one consistent terminology.

Set-up errors is present when the anatomy and the position of the patient at the planning CT is not reproduced with accuracy during the treatment [19].

4.1 Uncertainty

Each step in the radiation treatment process has a correspondent uncertainty. It is a parameter that characterizes the dispersion of values obtained for a single measurement when it is held over and over. Van Dyk et al. [7] define uncertainty as "the range of values within which the true value is asserted to lie with some level of confidence". "For such measurements, the results can be described by a statistical distribution, which can be summarized by specific statistical quantities such as mean, mode and standard deviation" [2]. The standard deviation σ is showed in a Gaussian distribution in Figure 4 (a), where the vertical axis is frequency and horizontal is the measurement value. The Type A uncertainties are evaluated by statistical methods and Type B uncertainties are evaluated by other means [2].

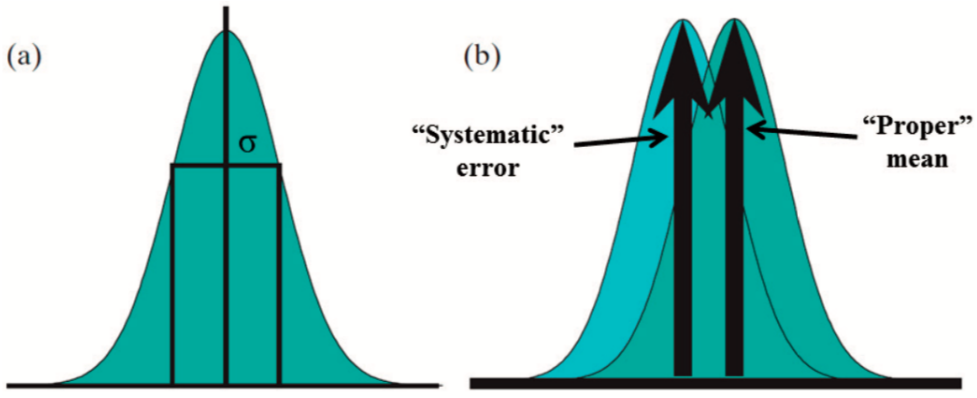

Figure 4 – Uncertainty distribution for a particular measurement (a). Comparison of two uncertainty distributions (b).

Source: International Atomic Energy Agency [2], p. 21.

Figure 4 (b) shows two uncertainty distributions, one with a systematic error and the other about the proper mean [22].

4.2 Error

Error is defined as the difference between the true value of the amount measured and the value measured, or from Monte Carlo calculations. Whereas total error is the combination of random and systematic error. The Type A and Type B uncertainties are found in measurements, while almost all calculations are subject only to Type B uncertainties [2].

4.3 Accuracy

Accuracy refers to the closeness of agreement between the calculated or measured result and the accepted reference value, or true value [2].

4.4 Precision

Precision is the intimacy agreement between repeated measurements or tests made independently under stipulated conditions. The IAEA Report Nº31 [2] complements that the "[...] precision depends only on the distribution of random errors and does not relate to the true value or to the reference value". It is quantified as a standard deviation of the test results. Thus, less precision produce a larger standard deviation.

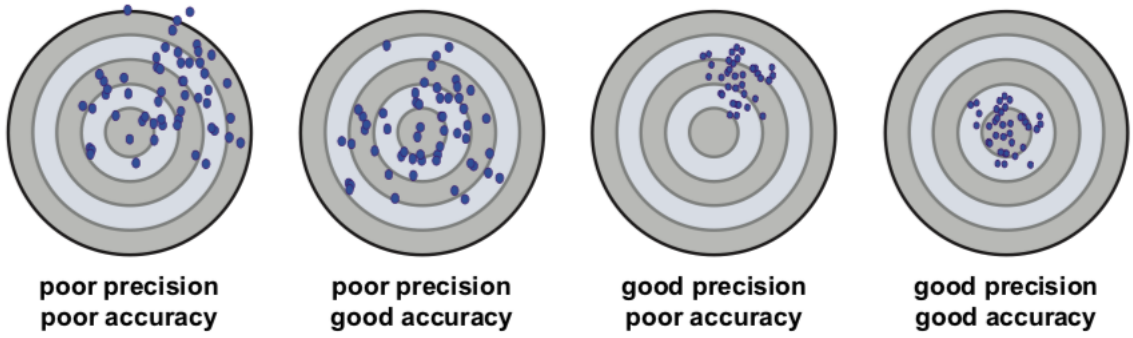

Figure 5 – Demonstration of the concepts of accuracy and precision.

Source: Goitein [23], p. 16.

Figure 5 above illustrates the relationship between the concepts of accuracy and precision, where the objective is blue dots to be in the center of the target.

4.5 Tolerance

A discussion about the tolerance is given in IAEA Report Nº 31 [2], where the concept of tolerance is set as the range of acceptability beyond which corrective action is required. Besides that, the value of tolerance can be dependent on the value defined

to the reference data. Albeit, there is a recommendation of BIPM to avoid the term *tolerance* by its somewhat ambiguous use. Instead of it, the recommendations of IAEA Report Nº 31[2] suggests an *action level,* which is presented on the Section 4.6.

4.6 Action Level

The action level or maximum permissible error for any measurable quantity is the level over which an action should be carried [24, 2].

4.7 Trueness

The trueness is the intimacy concordance between mean value of al large series of test results and the true value accepted [7].

In order to illustrate some of the terms discussed above the Figure 6 is presented for better understanding of them.

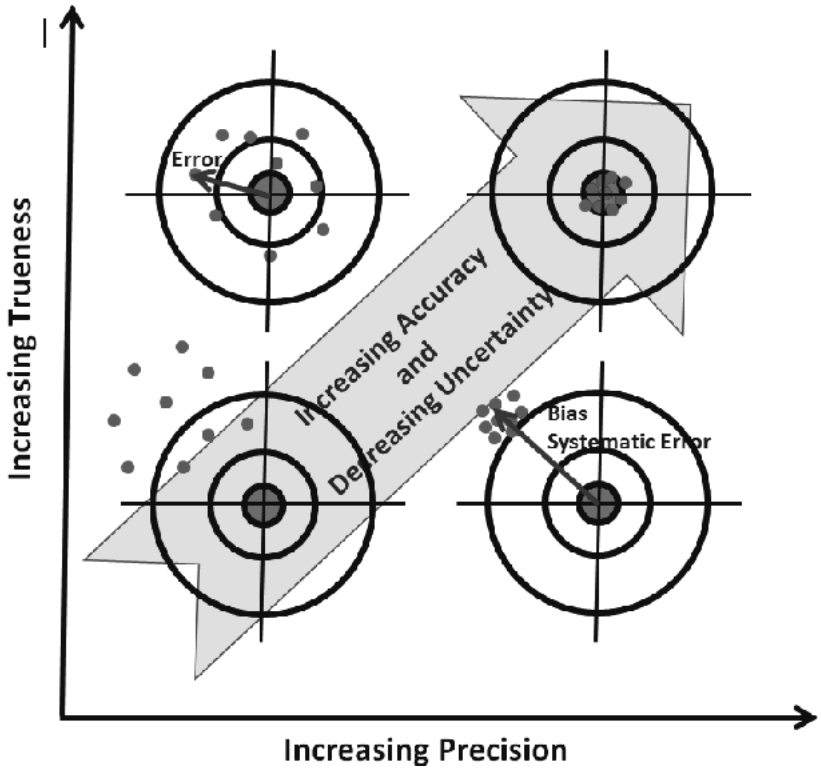

Figure 6 – Sets of measurement data points of the general concepts associated with measurements.

Source: Van Dyk et al. [7], p. 366.

The small dots are sets of measurement data points. Small random error is on data points showed on the upper right quadrant, whilst the large systematic and random

error is demonstrated on lower left quadrant. Both large and systematic random error are demonstrated on lower left quadrant. Data points with significative systematic error just small random error are illustrated on the lower right quadrant.

The shaded arrow in Figure 6 from the lower left to the upper right shows that with increasing trueness and precision, there is a decreasing of uncertainty and a increasing of accuracy.

5 Geometrical Uncertainties

A radiology treatment consists of planning session and some irradiation sessions. The patient geometry is visualized using the computing tomography (CT) or simulating images, it is necessary to the planning phase. For the treatment planning there is a necessity of the structures visualization. It is the base for construction of the treatment plan. "The ICRU considers three sources of geometrical uncertainty that may hamper the exact delivery of a plan: patient set-up variation, organ motion and deformation, and machine related errors" [25].

The errors of patient set-up have some characteristics as variations of daily positioning of the patient on the treatment couch, session-to-session variations, day-to-day tumor motion, cardiac action, respiration and so on. All of them might result in intrafraction tumor movements. The set-up and organ motion deviations are larger in comparison with the machine-related geometrical errors, i.e. gantry angles and beam sizes, of the modern radiotherapy equipment. The uncertainty is expressed in statistical quantities where the standard deviation (SD) is the most important [8].

5.1 Set-up Error Definitions

5.1.1 Systematic Error

Systematic errors are inevitable in radiotherapy, they are related to machine output, initial patient positioning and organ segmentation. It can be predicable or not. "The systematic component of any error is a deviation that occurs in the same direction and is of a similar magnitude for each fraction throughout the treatment course" [26].

- Target delineation error: For The Royal College of Radiologists (RCR)[26] it "[...] may be introduced when the CTV is first delineated and represents the difference between the defined and ‘ideal’ CTV".

- Target position and shape: The RCR [26] defines it as "[...] a change in target position and shape between delineation and treatment" and the "possible causes include tumor regression or growth, bladder filling and rectal distension".

- Phantom transfer error : The RCR report [26] describes that "either do not change (image resolution, margin algorithm) or are assumed to vary slowly (isocentre position, leaf position accuracy) and are therefore taken as constant over the typical treatment duration" and, in other hand, the "possible causes [of the phantom transfer error] include differences in laser alignment between CT and linear

accelerator, CT couch longitudinal position indication, image resolution, margin growing algorithm, field edge and multileaf collimator (MLC) leaf position, isocentre location, source to surface distance indication, gantry and collimator angle accuracy".

- Patient set-up error: "This describes all causes of treatment set-up error not accounted for by the phantom transfer error and includes all the errors listed under gross error" [26]. Some possible causes are the alterations of shape, weight loss and patient's position, for example.

The term systematic error can be used to referring to a individual patient or to a population of patients. The systematic error for an individual patient is the mean error during the treatment, while for a group of patients is an indication of the spread of individual mean error [26]. The calculation of systematic error for a group of patients is the SD of the distribution of mean errors for each single patient.

Systematic errors are present all over the patient treatment and represent a smearing and tendency. The knowledge of systematic errors "allows to consider them and to introduce counter-measures during planning and treatment delivery" [27]. Moreover, the modern safety systems allow to verify a threshold of acceptance to avoid a a exceed of uncertainties.

5.1.2 Random Error

The RCR [26] describes "the random component of any error is a deviation that can vary in direction and magnitude for each delivered treatment fraction". Moreover, the "random errors occur at the treatment delivery stage and for this reason are often referred to as treatment (or daily) execution errors" [28, 26]. They are following summarized.

- Patient set-up error: The ideal is to set-up the patient in every session in the same position as described in the planning CT. However, set-up the patient with precision as described in the planning is impossible. Although, safety margins are used to minimize the problem.

- Intrafraction errors: "The patient's anatomy is changing all along the treatment course and even during radiation delivery, due to, e.g. respiration or different amounts of bowel gas" [27]. Thus, the patient anatomy is not the same one of the planning CT time.

- Target position and shape: The change in target position and shape between fractions. For the RCR [26] "this error is essentially the same as that described

above for systematic errors but accounts for motion between fractions rather than from delineation to treatment".

The term random error also can be used to referring to a individual patient or to a population of patients. The random error for an individual patient is the SD of measured errors during the treatment quantifying the spread of errors, whilst for a group of patients the calculation of the random error is the mean of the individual errors [26].

Random errors are closely linked to patient compliance, immobilization system, and protocols followed by the institution. The online correction strategies can be used to control the random errors, whereas an off-line correction strategy cannot foresee the component of random error in subsequent fractions [26].

5.1.3 Gross Error

The *gross error* is is defined for the RCR [26] as "an unacceptably large set-up error that could under-dose part of the CTV or overdose an organ at risk". There are some possible causes of gross error like the incorrect isocentre position; the incorrect field size, orientation or shape and the incorrect patient, patient orientation or anatomical site. Several complications might be induced by the gross errors, i.e. necroses, ulceration and bleedings can be caused by overdosages and, in contrast, the risk of recividismus and a decrease of the tumor control can be caused by an under-dosage of target volume.

The CTV-PTV margins do not account for errors of such magnitude of the gross errors [26]. It is not expressed in statistical quantities, the occurrence of gross errors should be limited by quality assurance procedures [8].

The same systematic errors influence all dose fractions, while random error are different in each dose fraction. On other words, the consequence in dose delivery due to random errors is much smaller than of systematic errors [29]. Since the random errors lead to the blurring effect which provide a small decrease in the dose, at the edge of the high-dose region, that affects all patients moderately. And, in contrast, the systematic errors affect heavily some patients once there is a shift of the dose (i.e., the movement of CTV outside the high-dose region) [29].

5.2 Difference between Systematic and Random Errors

In Figure 7 a graphical representation, with axis in centimeters, of systematic and random errors is observed for the case of a treatment with 9 fractions of the radiation dose. The systematic component of error is a deviation that occurs in the same direction and it has a similar magnitude for each fraction through the treatment time, while the

random component of errors is a deviation that might vary in direction and magnitude for each one of 9 fractions of the total dose. The red triangle indicates the systematic error and the blue rhombus exemplifies the daily random errors.

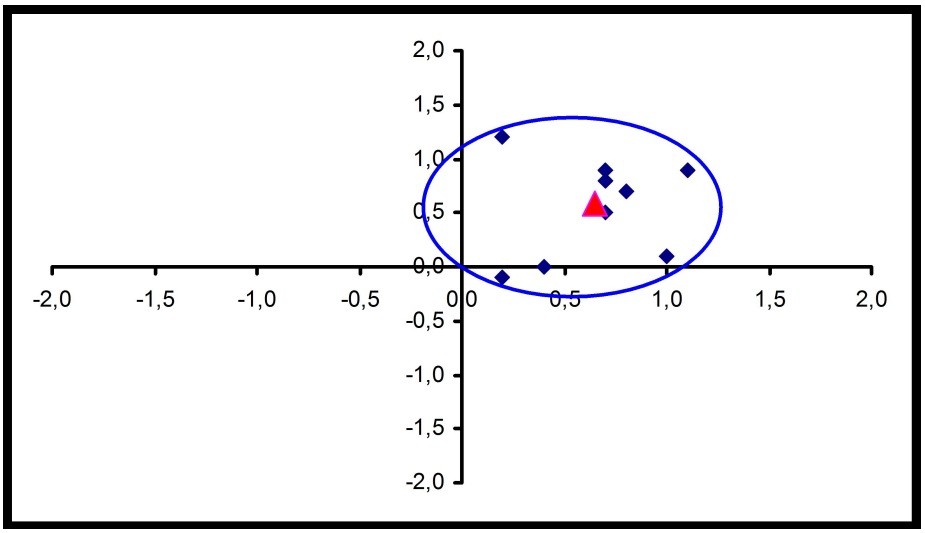

Figure 7 – Systematic and random errors.

Source: Semmelweis Uni. Inst. of Radiology and Oncotherapy et al. [30], p. 350.

The sum of systematic and random errors define the set-up errors and the CTV-PTV geometric margins as well [30]. Each of this erros are small in general, however the combined effect of all associated errors can be substantial and can limit the precision of the radiotherapy treatment [8].

5.3 Set-up Error and Treatment Margin

There are a connection between set-up errors and CTV-PTV geometric margins. The impact of systematic and random errors on CTV coverage is illustrated on the Figure 8. "It demonstrates that random errors, which vary from day to day, lead to a blurring of the cumulative dose distribution around the CTV, whereas systematic errors could lead to a cumulative under-dose to a portion of the CTV" [26].

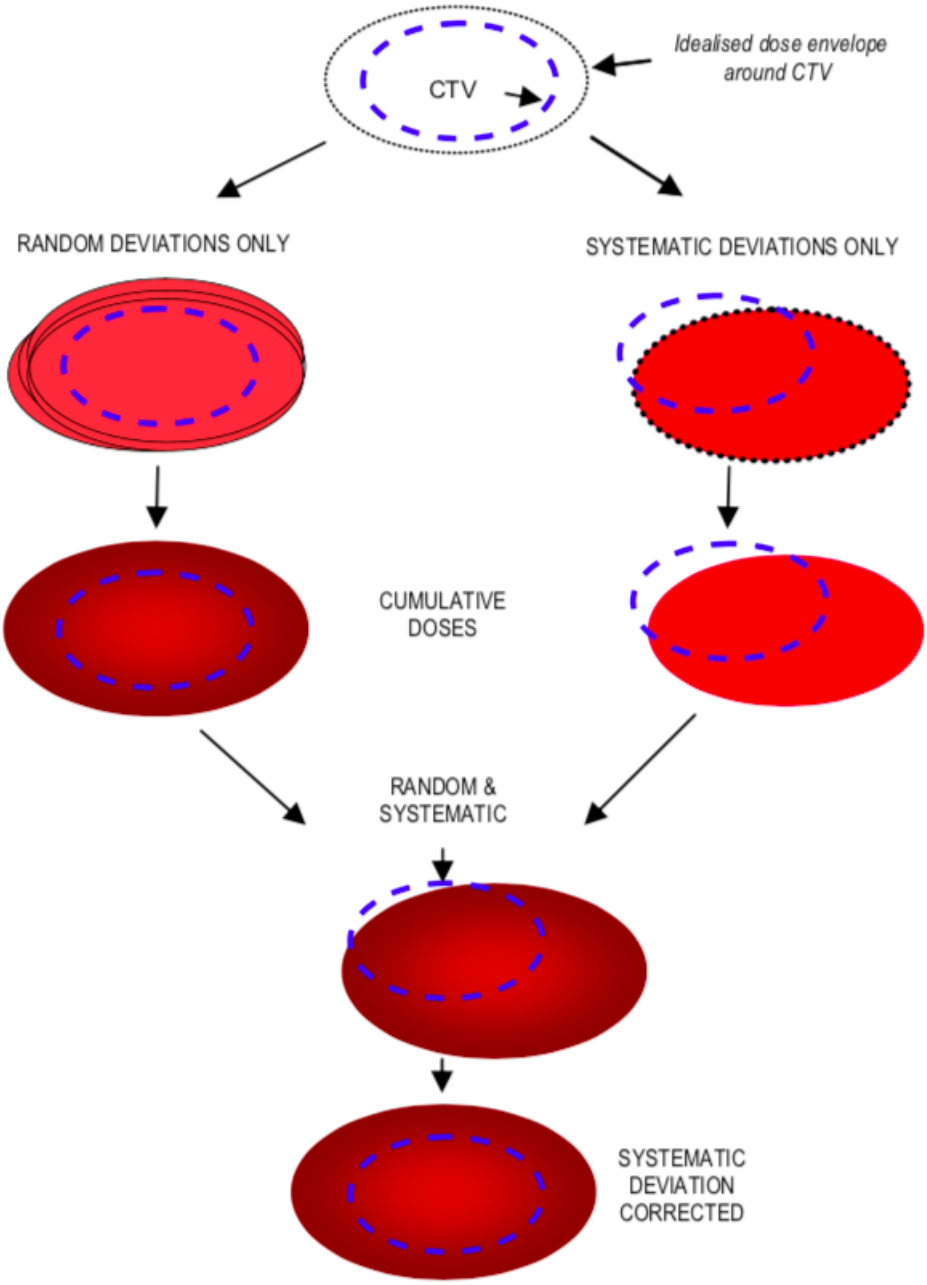

Figure 8 – The impact of geometric deviations on the dose distribution relative to the CTV.

Source: The Royal College of Radiologists [26], p. 15.

This latter effect turns on necessary the delineation of CTV-PTV margin to ensure satisfactory coverage from the sources of systematic error. The CTV-PTV margin is adaptable, it depends on the errors, which can be detected and corrected during the course of treatment. "If left uncorrected, the systematic error will remain throughout the course of treatment potentially compromising dose coverage to the CTV" [26].

5.4 The AAARA Recommendation in Radiotherapy

One of the most important recommendations in treatment with radiations considers that radiotherapy should be applied *as accurately as reasonably achievable* (AAARA). All factors as technical and biological must be considered to achieve the AAARA recommendation.

The acceptable risk versus benefit in using radiotherapy may be very different regarding the stages and types of cancer. There is for each different case the accuracy requirements to achieve preferred outcomes.

The radiotherapy is a very complex treatment, consequently to consider *ipsis litteris* a statement about accuracy requirements, i.e. 5% in radiotherapy, is a ideal simplification.

There are some very important points to count. The first one is the cost in terms of effort, the possibility of recurrence, likelihood of possible complications and, finally, the impact on other patients. The importance of this last consideration refers to resources limitation of one establishment, once "limited resources must be balanced against the benefit that will be gained for the patient in terms of cure and improved quality of life" [2].

Van Herk [29] states that is impossible to eliminate all geometrical errors even if the treatment is fully accurate, since uncertainties in CTV and GVT definition will be still present. Some of difficulties listed by van Herk are the inaccuracy of detection or observer errors in online for image-guided system, the short-term organ movement between imaging and treatment, limits of accuracy of correction procedures and movement of the structure of reference and the tumor when the finding of tumor is made by indirect methods.

6 Definitions of Volumes

The ICRU has been introduced some definitions of volumes related to tumor and normal tissues. There are actually eight volumes:

- Gross tumor volume (GTV)
- Clinical target volume (CTV)
- Planning target volume (PTV)
- Organ at risk (OAR)
- Planning organ at risk volume (PRV)
- Internal target volume (ITV)
- Treated volume (TV)
- Remaining volume at risk (RVR)

These volumes are used in reporting processes and in treatment planning. In the planning processes the delineation of these volumes are essential since the prescription of absorbed dose cannot be made, recorded and reported without the stipulation of the volume which is target and the volume of organ at risk.

"The GTV, CTV, and OAR correspond, respectively, to volumes of known (GTV), and/or suspected (CTV) tumor infiltration, and volumes of normal tissues that might be irradiated and affect the treatment prescription (OAR)" [14]. The GTV and CTV delineation are essentially out of irradiation techniques since they are influenced entirely by oncological circumstances. The ITV, PTV and the PVR are volumes that does not have any anatomical or physiological basis, they are introduced to ensure that the absorbed dose delivered to CTV and OAR is equal to prescription constraints. "For the delineation of volumes, and in their use, it is irrelevant whether photons, electrons, protons, or any other radiation is to be employed" [14].

The radiation treatment planning generally departs from the delineation of GTVs, they are primal regions for the delineation of CTVs and PTVs. "The accuracy of GTVs may affect the tumor control and adverse events related to OAR or normal tissue" [31].

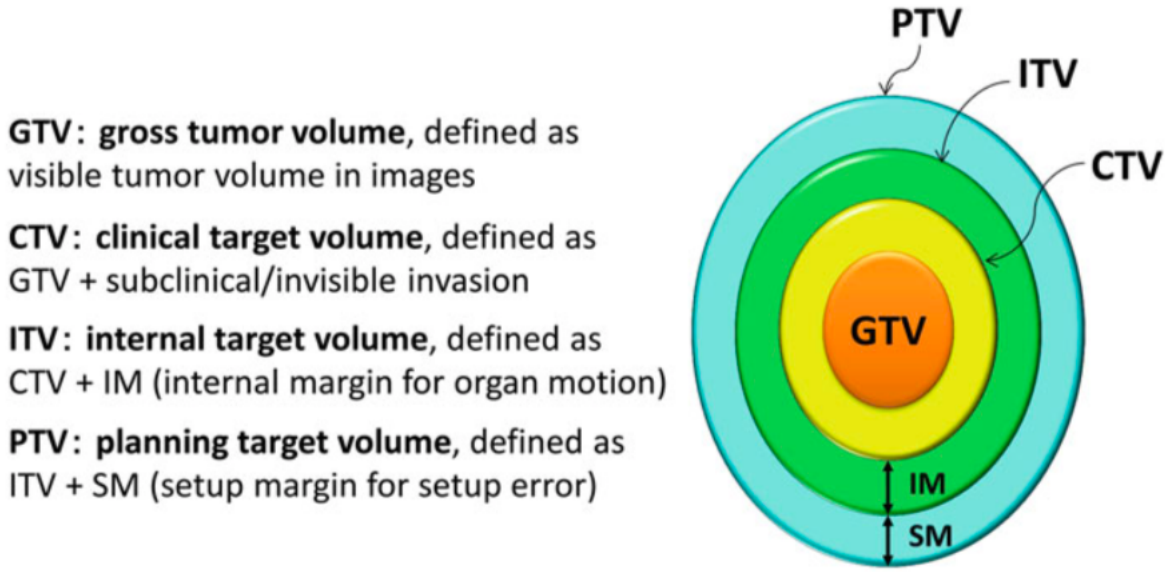

Figure 9 – Definition of target volumes.

Source: Arimura et al. [31], p. 88.

6.1 Gross Tumor Volume

The GTV is defined as the gross demonstrable extent of the tumor and its location. The GTV "may consist of a primary tumor (primary tumor GTV or GTV-T), metastatic regional node(s) (nodal GTV or GTV-N), or distant metastasis (metastatic GTV, or GTV-M)" [14].

It is common the definition of different GTVs for the primary tumor and, if applicable, the regional node(s). Though the GTV terminology in the most of cases refers to malignant tumor, it is also used for non-malignant lesions which can be treated with ionizing radiation. The GTV delineation uncertainties generally propagate to CTV delineation.

6.2 Clinical Target Volume

The CTV "is a volume of tissue that contains a demonstrable GTV and/or subclinical malignant disease with a certain probability of occurrence considered relevant for therapy" [14]. However, there is no agreement about that occurrence considered relevant, even so a probability of occult disease assumed to require treatment is higher than from 5% to 10%. It depends on the clinical judgment in which the type of malignancy need to be reasoned. On the other hand, a benign-tumor do not have a CTV associated with it, once there is no risk of microscopic or metastatic tumor infiltration. For the ICRU Report nº83 [14]

> "The selection of the tissues that bear risk for microscopic infiltration outside of the GTV is a probabilistic assessment integrating the biological and clinical behavior of the various tumor entities and the knowledge of the surrounding anatomy, including structures that are barriers to tissue infiltration (e.g., muscular fascia, bone cortex), or—on the contrary—structures that are easy conduits for tumor dissemination (e.g., fatty space)" (p. 45).

A GTV of a malignant-tumor is necessarily related to a CTV, but adjacent GTVs could be related to only one CTV.

6.3 Internal Target Volume

The ITV "represents the volume encompassing the CTV and the internal margin, which is added to the CTV to compensate for expected physiologic movements and variations in size, shape, and position of the CTV during therapy" and it is "recommended that the internal and external margins be added quadratically, however in practice they are added linearly" [32, 14]. "The ITV might be useful only in clinical situations in which uncertainty concerning the CTV location dominates setup uncertainties and/or when they are independent" [14]. It is an optional tool which might be used to help delineate de PTV.

6.4 Planning Target Volume

The PTV is used for treatment planning and evaluation. "It is the recommended tool to shape absorbed-dose distributions to ensure that the prescribed absorbed dose will actually be delivered to all parts of the CTV with a clinically acceptable probability, despite geometrical uncertainties such as organ motion and setup variations" [33, 32, 14]. The PTV surrounds with a margin the CTV representation in order that the planned absorbed dose is delivered to the CTV. That PTV margin takes the set-up and internal uncertainties in concern. "The setup margin accounts specifically for uncertainties in patient positioning and alignment of the therapeutic beams during the treatment planning, and through all treatment sessions" [14]. To the PTV delineation some considerations as the presence and impact of uncertainties and variations in tumor positioning are considered.

6.5 Organ at Risk

The OAR are healthy tissues that could experience morbidity and might influence the absorbed-dose prescription and the treatment planning if they are irradiated. "In

principle, all non-target tissues could be OARs" [14]. Even so, normal tissues considered as OARs depend on the CTV localization and/or the prescribed absorbed dose.

6.6 Planning Organ at Risk Volume

The PRV is analogous to the PTV. Once in both cases variations in the position of the OAR must be considered in the planning of the treatment. In other words, to avoid serious complications during the treatment the margins have to be added to the OARs to correct for these uncertainties and variations. The delineation of the PTV and the PRV can result in overlap regions. Therefore, “it is recommended that the margins not be compromised for the PTV or PRV even if overlaps occur" [14].

6.7 Treated Volume

The TV is defined as “the volume of tissue enclosed within a specific isodose envelope" [14]. In turn, “the value of the isodose selected to define the TV should be quoted either relative to the prescribed absorbed dose or in absolute terms" [14]. The irradiation techniques have some limitations, consequently the volume receiving the prescribed absorbed dose might differ than the PTV, it can be larger, smaller or simply shaped. There are several reasons to identify the position, shape and size of the TV in relation to the PTV, one of them is to evaluate causes for recurrences inside or outside the TV.

6.8 Remaining Volume at Risk

The RVR "is operationally defined by the difference between the volume enclosed by the external contour of the patient and that of the CTVs and OARs on the slices that have been imaged" [14]. The RVR is identified as the imaged volume within the patient excepting the any OAR and the CTVs. Since the RVR might be affected by absorbed dose, is critical knowing it in evaluating plans. If RVR is not specifically evaluated, unsuspected regions with high absorbed dose would go undetected. Additionally, recognizing the absorbed dose in the RVR is effective to estimating the risk of late effects in the patient.

The split of margins suggests that a linear separation of internal errors due to organ motion and set-up errors is possible to be made. However, the sources of external and internal errors are different and no correlated, which leads, in general, to incorrectness of addition of their SDs [8].

7 Prostate Cancer

The prostate gland, illustrated in Figure 10, is partly muscular and glandular situated deep in the pelvis surrounding the urethra. A healthy prostate gland has the weight about 15 to 20 grams and the size of a walnut, however it may become larger with the time.

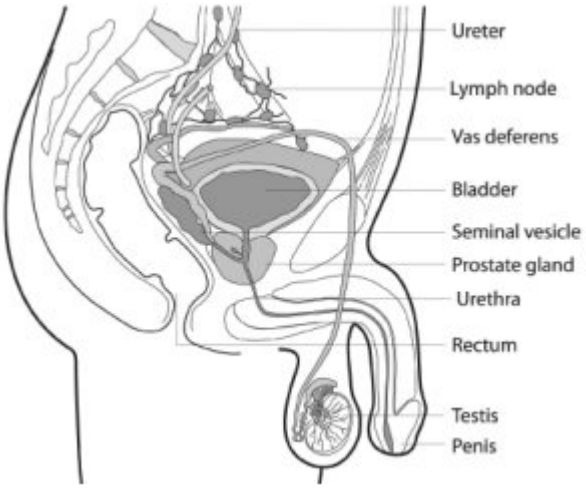

Figure 10 – Pelvis Anatomy.

Source: Prostate Cancer Canada [34].

The abnormal growth of cells in the prostate gland is denominated prostate cancer, and the primary function of the gland is to produce a slightly alkaline fluid which forms the seminal fluid. This disease is more common in man older than 65 years old. The problems caused by prostate cancer normally take years until the tumor has turned big enough, once it grows slowly. The causes of this prostate disease is unknown, however the diet and great body fatness are some of evidences that may exert some influence in development of that disease [5]. The best treatments known for the care of prostate cancer are surgery, radiation therapy, systemic treatments, targeted therapy and chemotherapy [35].

One important fact important to take into account is the movement of the prostate gland with breathing, bladder filling and/or bowel movement. "The degradation of image quality due to this motion and subsequent effects on radiotherapy dose planning and delivery have prompted medical physicists and clinicians to study the motion using a variety of imaging modalities" [36].

8 Geometric Uncertainties in Treatment Plan Evaluation

As rapidly described on Chapter 1, the margins in radiotherapy are frequently reduced to exclude the larger quantity of normal-tissue possible. However, it is unclear if the potential clinical benefit counterbalance the risk of missing the target [13].

Frequently the steady volume is used for the most treatment planning systems evaluation and the planned dose distribution, even this outlook grossly simplifying the geometric errors, see Figure 11. In this case, if the volume that does not include a margin for geometric uncertainties when a planned dose distribution is evaluated on the CTV, the totality of geometric errors will be ignored. It leads to an estimation of TCP higher than that one with geometric errors added. "When considering the CTV as a static structure, evaluation of its dose distribution is too optimistic, because it is known that in reality, the CTV will be in a different place for each patient and for every fraction" [13]. In the other hand, as the PTV is larger than the target, the dose evaluation over the PTV is frequently too pessimistic.

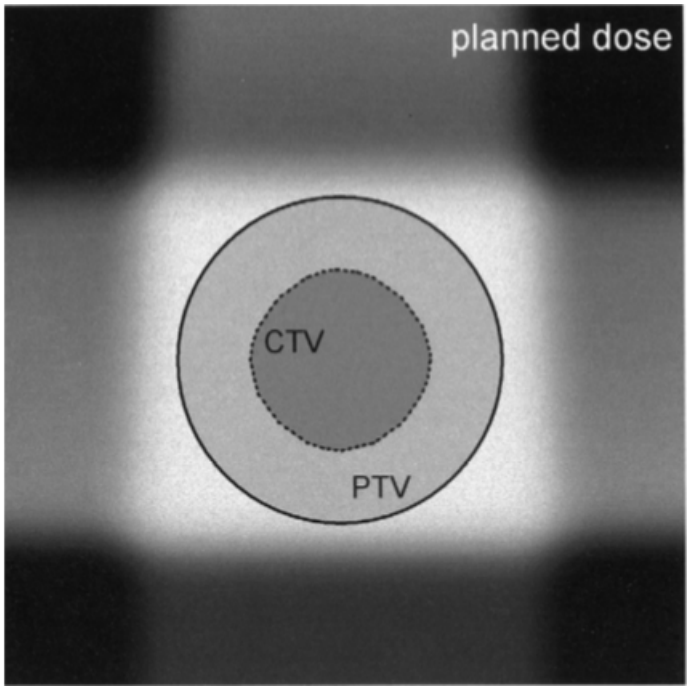

Figure 11 – CTV as a static structure.

Source: van Herk et al. [13], p.1408.

Therefore, it is a good practice to avoid the computing of the TCP or evaluate the dose using the PTV without the margin for geometric uncertainties. It is clear that the PTV chosen includes the CTV with a certain probability, but in practice, the CTV has

an unknown position within the PTV, once this one has a greater volume face to CTV. "Because of the volume difference, the tumor control probability (TCP) derived from the PTV will underestimate the real TCP" [13]. Also, the inhomogeneities dose effect in the PTV is overestimated.

A method of evaluating treatment plan which does not use the PTV is based on the detailed data of distribution of geometric errors in population patients as illustrated in figure 12. Van Herk et al. [13] relate that "a more correct evaluation of a treatment plan is obtained by blurring the dose distribution for the day-to-day variation and testing a large number of possible preparation (systematic) shifts of the CTV".

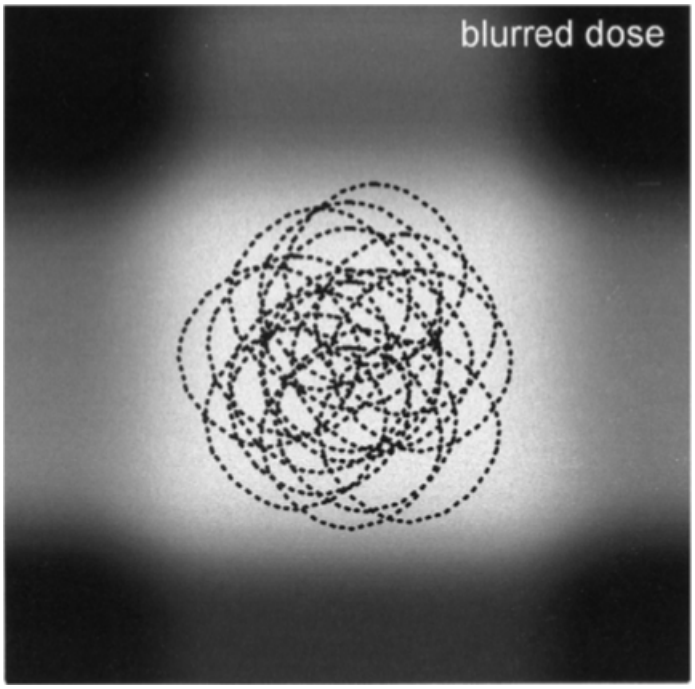

Figure 12 – Blurred dose distribution for the day-to-day variation.

Source: van Herk et al. [13], p.1408.

Procedures of correction based on image guidance as online electronic portal imaging and implanted markers can be used to reduce the level of preparation and execution errors. Although the residual preparation and execution errors will be always present, so the implementation of correction procedures is very important. Each correction procedure has its intrinsic inaccuracies. For example, the electronic portal imaging (EPI) do not correct the target volume delineation inaccuracies neither correct the organ motion. "For this reason, a margin around the CTV will always be required, and treatment plan evaluation should include the residual uncertainties" [13].

8.1 Tumor Motion

The tumor motion is one of the factors more important to consider in radiotherapy treatments. Since the GTV does not stay motionless in any time of treatment planning and/or during the treatment. The Figure 13 regards to a simulated visualization of a tumor motion, setup error, and delineation error on the dose delivery in an array of 3D images.

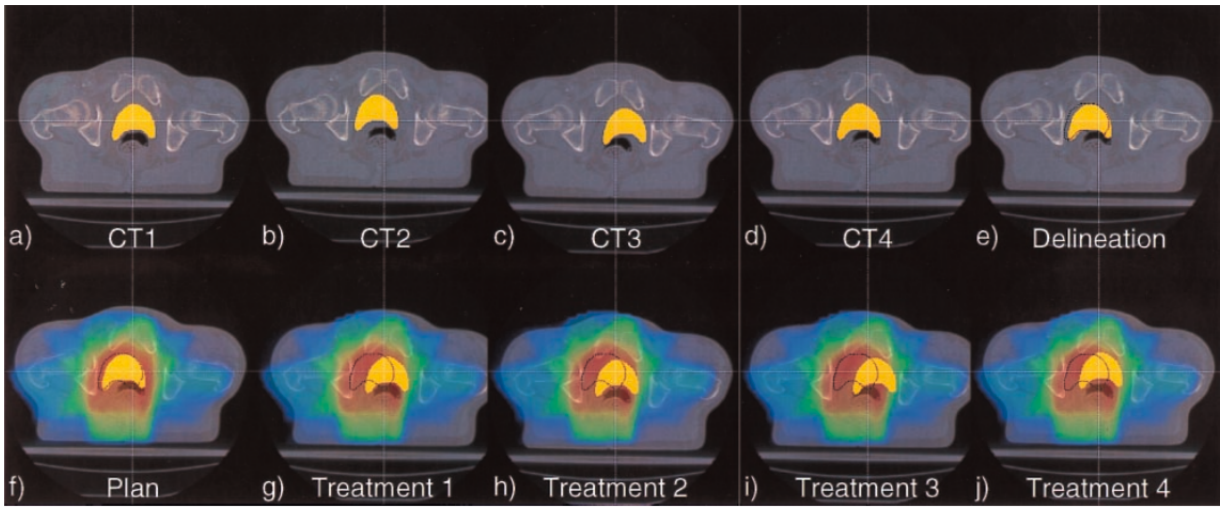

Figure 13 – Simulated visualization of a tumor motion, setup error and delineation error on the dose delivery.

Source: van Herk et al. [37], p.1123.

This simulation of organ motion and setup error is over expressed, they are 6 mm in *x* and *y* direction. And the PTV margin is 10mm. The CTV is indicated in *a*, the white cross wires indicate the room lasers. From *b* to *d* the CT scans are not identical due to organ motion and the setup error on the CT scanner. In *e* "CT4 is used for planning, and the delineation (black contour) adds some extra error, because the “true” CTV is invisible" [37]. In *f* the delineated CTV ins the base for the planning. From *g* to *i* "for each treatment fraction, the error made in the treatment preparation phase is reproduced, causing a systematic shift of the “true” CTV relative to the delivered dose distribution" [37]. Moreover, the treatment execution variations, in other words, the random movements occur due to setup error and tumor motion. "It is important to note that all of these changes cause geometric uncertainties and may give rise to systematic delivery errors and thus compromise the effect of high-precision techniques" [8].

9 Analysis of Geometric Uncertainty Calculations for Prostate Cancer

Geometric uncertainties have great contributions to normal tissue complications and in the prostate cancer tumor. And then, understanding well the main characteristics of geometric uncertainties the patient treatment might be the best outcome possible.

Nowadays, simple margin recipes are used to estimate the CTV-PTV margin that allows the net effect of residual uncertainties does not compromise the treatment, i.e. to eliminate the cancer while sparing the OAR. These simple margin recipes are based on Gaussian distributions, penumbra width in water, systematic error SD > random error SD, and in some plans with a more or less uniform dose distribution [8].

For assisting the calculation of PTV in radiotherapy the use of margins are essential. It can be determinated by analyzing the geometric uncertainties intrinsic to the radiotherapy delivery process and planning. McGarry et al. [38] complement it

> "Prescriptive geometric uncertainty analysis not only supports calculation and justification of the margins used clinically to generate planning target volumes, but may also best be used to monitor trends in clinical practice or audit changes introduced by new equipment, technology or practice" (p.140).

Therefore, margins using two different methods will be described in this chapter, the first one is the method of The British Institute of Radiology (BIR) from the book *"Geometric Uncertainties in Radiotherapy: Defining the Planning Target Volume"* [39] and the Van Herk method published on the paper *"Probability of correct dosage: dose-population histograms for deriving treatment margins in radiotherapy"* [37].

9.1 Derivation of Systematic and Random Set-up Errors and Relationship to the CTV-PTV Margin

The deviation between actual and expected position is the definition of *set-up error* (Δ), it is calculated as a shift in the isocentric position by the comparison to an image and its reference. The equations used to calculate the random and systematic errors will be given in subsections following. Those equations will be split in form to calculating a mean and another one to calculating a standard deviation (SD). "The SD is a measure of how widely values are dispersed from the mean value and in this context defines the size of the error" [26]. The population of patients treated with a

specific technique is denominated *treatment population.* "The set-up errors for this population are estimated by calculating the errors for a group of patients whose results are assumed to accurately represent those of the population from which they are drawn" [26].

9.1.1 Systematic Set-up Errors

9.1.1.1 Individual Mean Set-up Error

The mean for an individual patient is the *systematic error* ($m_{individual}$). The calculation is made by summing the measured set-up error for each imaged fraction ($\Delta_1 + \Delta_2 + \Delta_3 + ... + \Delta_n$) divided by the number of imaged fractions (n). The equation is given as

$$m_{individual} = \frac{\Delta_1 + \Delta_2 + \Delta_3 ... + \Delta_n}{n}. \tag{3}$$

9.1.1.2 Overall Population Mean Set-up Error

"The overall mean set-up error (M_{pop}) is the overall mean for the analyzed patient group and should ideally be zero" [26]. The M_{pop} is a parameter very efficient to indicate the efficacy of one treatment technique. The means for each patient is summed ($m_1 + m_2 + m_3 + ... + m_n$) and divided by the number of patients in the group (P). Thus, the equation is given as

$$M_{pop} = \frac{m_1 + m_2 + m_3 + ... + m_p}{P} \tag{4}$$

9.1.1.3 Population Systematic Error

A population has a systematic error (Σ_{set-up}) defined as the SD of the individual mean set-up errors about the overall population mean (M_{pop}). "It is calculated by summing the squares of the differences between the overall population mean derived from Equation 4, and each individual patient mean derived from Equation 3, in turn" [26]. The resultant sum is divided by the number of patients minus one ($P - 1$), hence

$$\Sigma^2_{set-up} = \frac{(m_1 - M_{pop})^2 + (m_2 - M_{pop})^2 + (m_3 - M_{pop})^2 + ... + (m_n - M_{pop})^2}{(P - 1)}. \tag{5}$$

9.1.2 Random Set-up Errors

9.1.2.1 Individual Random Error

The interfractional random set-up error for each individual ($\sigma_{individual}$) is the SD of the set-up errors around the mean individual value (m) correspondent derived from Equation 3. The calculation is made by summing the squares of the differences between

the mean and set-up error generated from each image. The resultant sum is divided by the number of images minus one $(n-1)$ as follow

$$\sigma^2_{individual} = \frac{(\Delta_1 - m)^2 + (\Delta_2 - m)^2 + (\Delta_3 - m)^2 + ... + (\Delta_n - m)^2}{(n-1)} \tag{6}$$

9.1.2.2 Population Random Error

The mean of the summing of the individual random errors $(\sigma_1 + \sigma_2 + \sigma_3 + ... + \sigma_p)$ is called the population random error (σ_{set-up}). "This equation assumes that the number of images acquired per patient is identical or that the likely differences will have minimal effect on the final result" [26]. The equation is

$$\sigma_{set-up} = \frac{\sigma_1 + \sigma_2 + \sigma_3 + ... + \sigma_p}{P}. \tag{7}$$

9.1.3 Margin Derivation

The CTV-PTV margin recipes derivations and calculations, based on some population margin, are discussed in detail in works of van Herk et al. [37], McKenzie et al. [28] and Stroom et al. [40]. The margin calculation recipes from those works can be expressed as

$$CTV - PTV = a\sum + b\sigma + c \tag{8}$$

where Σ and σ are the combined sum of the SDs of the all systematic and random errors which contribute to the margin, and a, b e c are constants. The constant c accounts for parameters which affect the margin in a linear manner, and the b and c are relative contributions of the systematic and random components which depend on facts as beam arrangement and the coverage probability chosen.

9.1.4 Correction Protocols on Margins

The interrelationship between treatment margins and treatment verification protocol to control set-up errors are discussed in this section.

The systematic and random set-up errors from a portal imaging study might be used into Equation 8, however these are not the unique contributing components. "The use of a treatment verification protocol to control set-up errors may be used as a basis to reduce or justify currently applied margins" [26]. The type of imaging protocol implemented has a direct relationship to achievable levels of margin reduction as seen in Figure 14 .

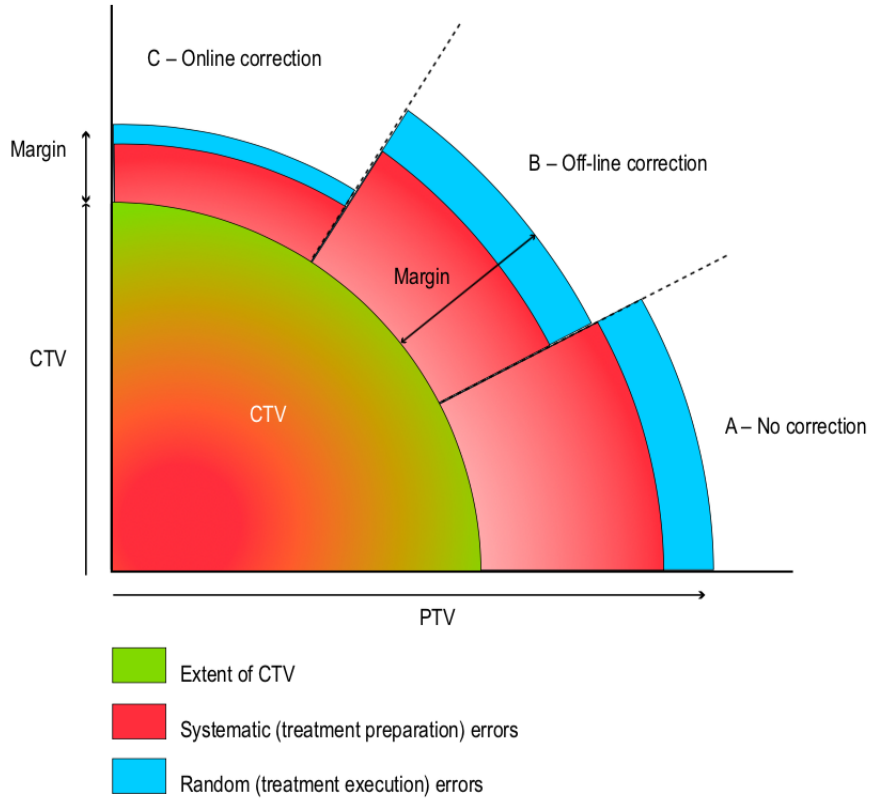

Figure 14 – Current protocols for CTV-PTV margin correction.

Source: The Royal College of Radiologists et al. [26], p. 34.

For the Case A there is no correction to measured set-up errors. However, the Case B exemplifies an off-line protocol image bony anatomy used to correct set-up errors which enables correction for the phantom transfer and the systematic set-up constituents of the patient treatment preparation error. It justify a reduction in the corresponding margin. "By definition, an off-line protocol applies any correction at the next fraction and so cannot account for the random patient set-up variations occurring from one fraction to the next" [26]. Between the Case A and B the contribution to treatment margin to random errors remain unchanged. Finally, for the Case C an on-line protocol imaging the target corrects set-up errors. This on-line protocol requires before each fraction an imaging, analysis and set-up correction. In comparison to the Case B the Case C detects in addition the random patient set-up error and errors related to variations in target position and shape. This last case is a basis to reduce both random and systematic error constituents of the margin.

9.2 The British Institute of Radiology Method

In the BIR method the source of many geometric uncertainties are identified, which turns on possible to create margins that makes possible to cover 90% of the CTV.

It begins with the radiotherapeutic treatment inspection what embraces the comparison of portal image acquired during the treatment fraction with the reference image from the beginning of treatment [41]. To determinate part of dataset used to determine geometric uncertainties can be obtained using electronic portal images (EPIs) of treatment fields, it is used to obtain the required margins. "By comparing the digitally reconstructed radiograph (DRR), calculated from the therapy CT scan, with the EPI data, an assessment of the accuracy of each delivered field can be made" [42, 38]. The BIR relates that reactive patient repositioning and online imaging can improve the accuracy and reproducibility during the radiotherapy, which in turn can lead to smaller margins surrounding the target volume. Finally, McGarry et al. [38] punctuate that

> [...] to investigate how the set-up uncertainties may be improved, and potentially lead to a reduction in target volume margins, the portal imaging data gathered were used to predict the impact of a 3 mm, rather than the current 5 mm, action level on the calculated set-up uncertainties (p.141).

The BIR method for calculating a CTV-PTV margin "separates errors into those introduced through the treatment preparation stage, in which errors will be propagated systematically through the course of the treatment, and the treatment execution errors that result from the day-to-day uncertainties of set-up, organ shape and motion" [39, 38]. The effect of different beam configurations is also considered. In this method the systematic Gaussian error (Σ) is defined as the sum in quadrature of the doctor delineation error, motion error, systematic set-up error and phantom transfer error. While the random Gaussian error (σ) is defined as the sum in quadrature of the motion error, random set-up error and beam penumbra. Hence, the total CTV-PTV margin is

$$CTV - PTV = 2.5 \sum + a + b + \beta(\sigma - \sigma_p) \tag{9}$$

where Σ is the systematic error, σ is the treatment execution error, β is the planning parameter, σ_p is the beam penumbra width, *a* is the linear treatment planning beam algorithm error and *b* is the linear breathing error [38].

9.3 The van Herk Method

The van Herk method for determining geometric uncertainties is simpler than the BIR method. Van Herk does not consider explicitly the algorithm error, planning parameter, breathing motion or penumbra, only the combined systematic error and the treatment execution error. The van Herk's margin recipe is given as

$$CTV - PTV = 2.5 \sum + 0.7\sigma \tag{10}$$

where Σ is the systematic error and σ is the treatment execution error. The margin recipe 10 above ensures that 90% of patients have an equivalent uniform dose (EUD) of 98% [13].

Then, the set-up uncertainties, as seen in Table 2, were calculated by McGarry et al. [38] with data of both Belvoir Park Hospital (BPH) and Northern Ireland Cancer Centre (NICC) on each prostate direction.

	Systematic (mm)			Random (mm)		
	L	SI	AP	L	SI	AP
BPH	3.3	2.4	2.7	2.5	1.7	1.8
NICC	2.7	2.2	2.0	2.7	1.7	1.7

Table 2 – Systematic and random errors for BPH and NICC on lateral (L), superior-inferior (SI), antero-posterior (AP) directions.

Source: McGarry et al. [38] (with modifications), p. 144.

The required CTV-PTV margins were calculated for both BPH and NICC institutions. The comparison of results of the two methods of CTV-PTV margins calculation is exhibited on Table 3, where the margins generated by van Herk method were similar to the values generated by the BIR method on each prostate direction [38].

		CTV-PTV margin		
		L	SI	AP
BIR method	BPH	8.0	11.0	11.3
	NICC	8.3	11.7	11.5
Van Herk method	BPH	11.5	13.3	13.7
	NICC	10.1	13.1	13.1

Table 3 – Values of CTV-PTV margins calculated by the BIR method and the van Herk method on lateral (L), superior-inferior (SI), antero-posterior (AP) directions.

Source: McGarry et al. [38] (with modifications), p. 145.

Van Herk et al. [13] explain that the specified margin are too generous because "it is to be expected that the reduced tumor cell density between the edge of the GTV and the CTV will reduce the required margin for some tumor types". Nevertheless, the situation to the prostate cancer is different of other tumors, "generally, the entire prostate is defined as the CTV, although the most likely location of tumor foci is in the peripheral zone, at the posterior edge of the prostate" [43, 13]. "This means that the most critical

margin lies at the posterior edge of the prostate (CTV) near the rectum, the location at which margin reduction is generally applied" [13].

As a consequence, van Herk et al. [13] have been proposed later on paper "*Inclusion of Geometric Uncertainties in Treatment Plan Evaluation*" another simple margin recipe related to prostate cancer and other spherical CTVs. So, the PTV margin must be approximately

$$CTV - PTV = 2.5 \sum + 0.7\sigma - 3mm \tag{11}$$

where Σ and σ are respectively the combined standard deviation of the preparation and execution errors. This margin recipe delivers to 90% of the patients an EUD of at least 98% for prostate treatments as well.

The calculation with the Equation (11) from van Herk method leads to CTV-PTV margins larger than those CTV-PTV margins calculated with the Equation (9) from the BIR method. In adittion, the calculations of margins with the van Herk method are easier than calculations with the BIR method, since some parameters (algorithm, planning and penumbra errors) are not included in that first method. Although, the van Herk margin recipe is simpler, it generates larger CTV-PTV margins.

One of the best uses of those calculating techniques may be for monitoring trends in clinical practice and control new changes in technology, equipment or practice [38].

10 Biological Considerations of Margins

In the paper of van Herk et al. [29] the discussion of Gotein et al. [44] about the difference between random and systematic errors applying a simple biological consideration is presented. The slope of the dose-effect curve has direct implication for importance of random and systematic errors. However, this discussion is "an oversimplification because in practice, errors will often lead only to a partial underdosage of the target and not to a complete miss" [29].

In this way, van Herk et al. [29] evaluated realistic treatment plans using the EUD and TCP with random and systematic errors. A margin of 10 mm between CTV and PTV was found as adequate for 3-field prostate treatments for this research, including rotational errors.

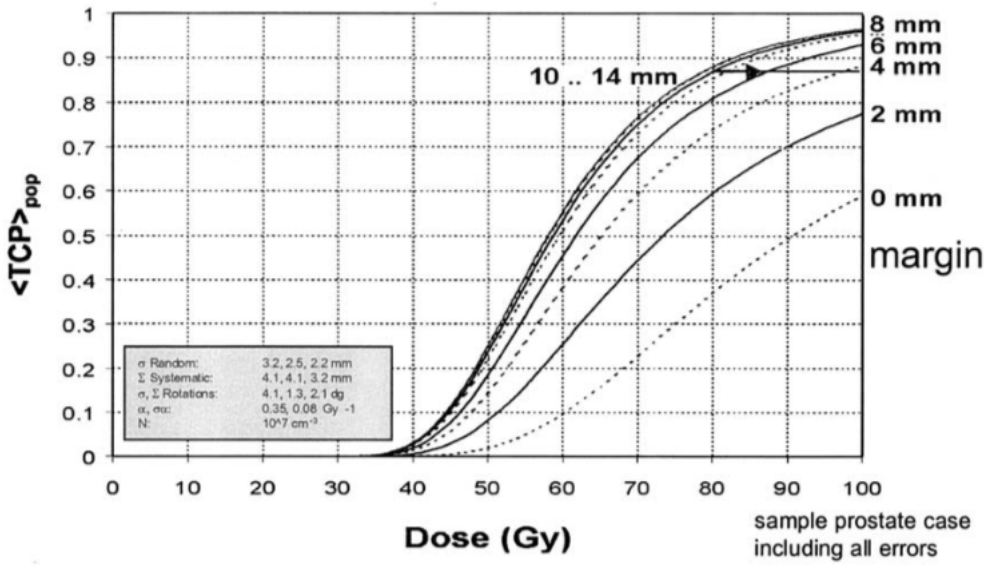

Figure 15 – Geometrical errors effect on TCP_{pop} as function of dose for different margins.

Source: van Herk et al. [29], p. 56.

As seen in Figure 15 the TCP in a population of patients (TCP_{pop}) when the margin is reduced to 6 mm the dose is increased from 80 to 87 Gy to maintain the same TCP_{pop}. "Only in regions with a high-dose gradient such a margin reduction leads to a decrease in normal tissue dose for the same TCP_{pop}" [29]. A rough correspondence of the 84% minimum dose with the 98% EUD also was observed. Thus, the Equation 11 must be used to give to 90% of patients at least 98% EUD. "This recipe corresponds accurately with 1% TCP_{pop} loss for prostate plans with clinically reasonable values of Σ and σ" [29].

"Remaining biological issues are the effect of tumor cell density distribution and the effect of unknown tumor cell presence on margin requirement" [44, 29]. A typical case for the prostate is the tumor cell density be concentrated on one side of the CTV, then the TCP_{pop} loss will decrease. This effect occurs by the effective larger margin on the side of the prostate with the lower cell density. "The effect stabilizes when the ratio of tumor cell densities exceeds 1.000, at a TCP_{pop} loss that is about 30% of the TCP_{pop} loss for a uniform cell density" [29]. An increase of 2 mm in margin reaches a similar reduction in TCP_{pop}, and the simulation of the region between the GTV and CTV of the reduced tumor cell density of the 5 mm shell propitiates the TCP_{pop} decreasing as well on behalf of the geometrical errors. The effect related is stabilized at a cell density ratio of 10.000, which indicates that the penumbral dose is adequate to eliminate a low tumor cell density if, due to geometric errors, the tumor is moved outside the region of high dose [29].

11 Impact of Random and Systematic Errors on Dose

There are differences in the effect of random and systematic errors on dose delivered to radiotherapy patient. The first ones make the dose distribution blurred, whereas a shift of cumulative dose distribution related to the target is caused by systematic errors. "The blurring can be described as a convolution of the dose distribution with the probability distribution function of the random error" [29]. However, van Herk et al. [29] admit that "this method is accurate in practice even being not completely correct".

The error in convolution is quite identical to a Gaussian distribution and its width is equal to SD of random deviations split by the square root of the number of fractions [45, 46, 47]. "Since the random errors and respiration are the causes of blurring of dose distribution, the unknown systematic error must be treated statiscally for each individual patient" [29].

Van Herk et al. [37] developed the distributions dose-population histograms which cumulative probability distributions of the dose delivered to the CTV is derived for a given treatment plan. Furthermore, as seen in Figure 16, for a spherical symmetry it was possible analytically to derive dose population histograms for the minimum dose delivered to CTV.

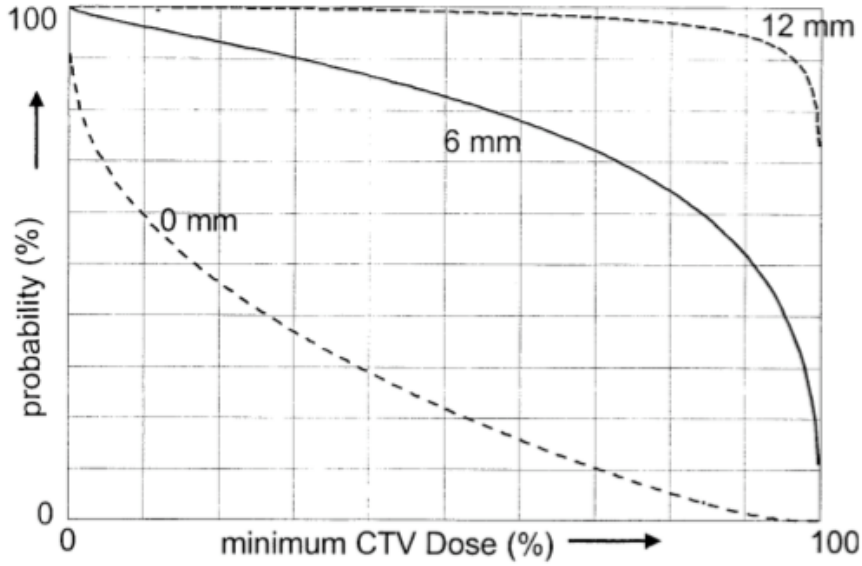

Figure 16 – Dose-population histograms for margins of 0, 6 and 12 mm over 36 fractions for the minimum total dose delivered to CTV.

Source: van Herk et al. [37], p. 54.

The probability level of reaching an acceptable minimum dose falls if the margin is reduced. For instance, the probability to give a high dose to the target is zero for zero millimeter of margin. Since "the dose distribution will completely fit around the CTV, such that only a zero error will lead to a high dose, whereas the probability of zero error is extremely small" [37].

12 Determination of Geometrical Margins for Prostate Cancer

The last paper of Bencheikh et al. [48] presents a study about evaluation of the ideal CTV-PTV margins used for radiotherapy treatment of prostate cancer utilizing the van Herk method applied to 2D prostate images as seen in Figure 17, which differs to van Herk method employed to 3D images as seen in Figure 13 of Chapter 8. The CTV-PTV margins were statiscally determined over 20 prostate cancer patients at random during four consecutive days. To achieve the lower interfraction possible the utilization of a daily portal imaging was used to ensure the reproducibility of CTV-PTV during the days of treatment. The gap between the reference image and the portal image enable the evaluation of the daily displacement in *x* (lateral direction, L), *y* (cranio-spinal direction, CS, or craniocaudal direction, CC) e *z* (antero-posterior direction, AP) axis [48] as seen in Figure 17.

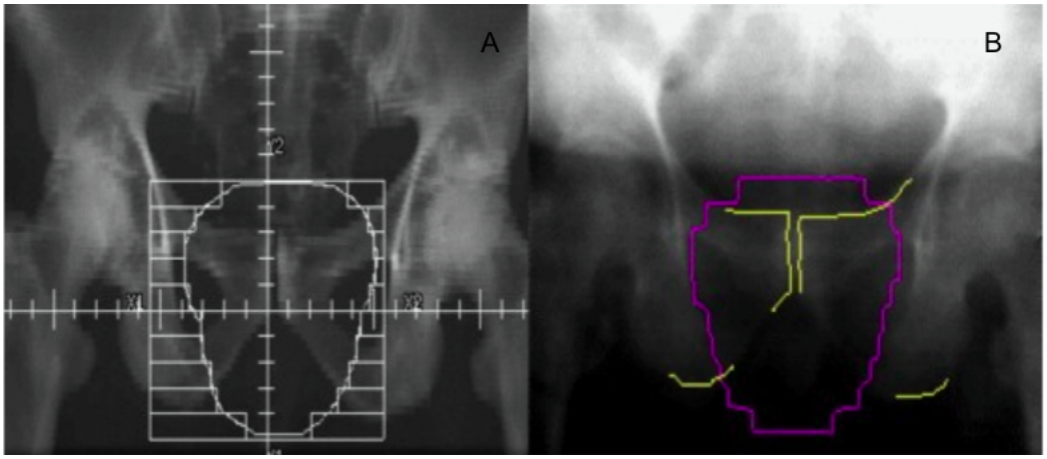

Figure 17 – Reference image (*a*) and portal image (*b*).

Source: Bencheikh et al. [48] (with modifications), p. 2.

The conditions set for displacement determination were defined as 99% for the PTV receiving at least 95% of dose in 90% of patients. The van Herk Equation 11 was used to estimate the CTV-PTV margins. The sum of uncertainties of the displacements determination are less than 2%, according to limits of IAEA [48, 12]. For each patient an average of displacements for four days of treatment for each axis is presented in Figure 18 where is realized that prostate motions are random and very different for each patient [48].

However, 3D images are better than 2D images to estimate the CTV-PTV margins. The 3D image is the option that brings more information about the localization of the

tumor once 3D image has one more direction with data obteined by the CT scans, while 2D image is limited to only two directions and it uses the pelvis bones as benchmarks.

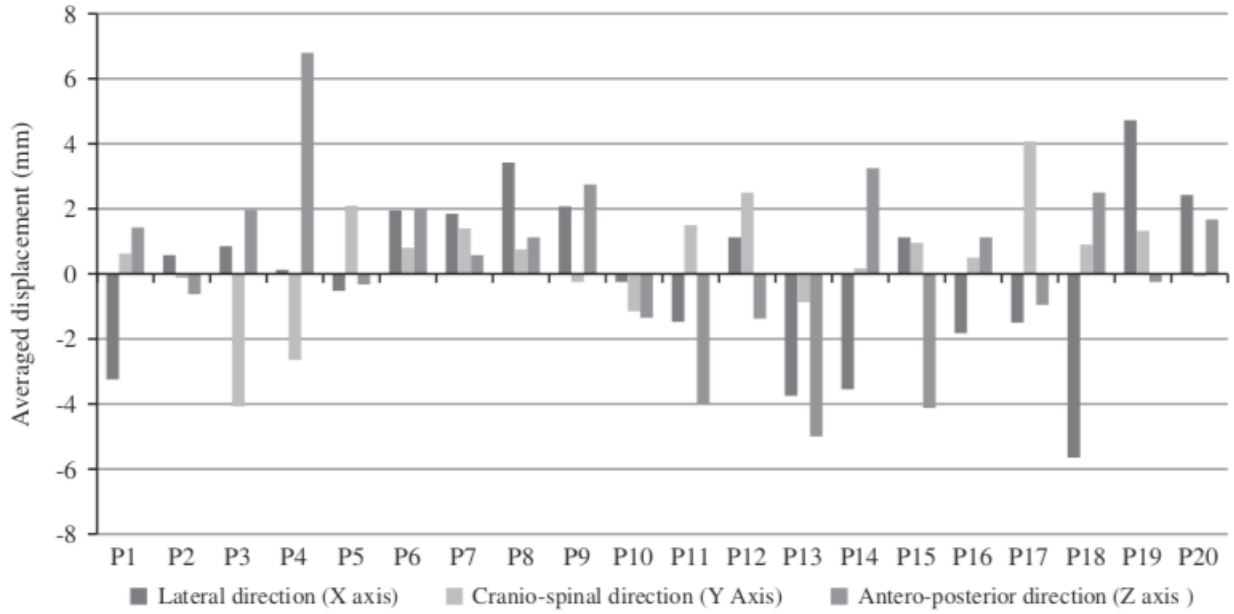

Figure 18 – Average of displacement for each patient on L (X axis), CS or CC (Y axis) and AP (Z axis) directions.

Source: Bencheikh et al. [48], p. 2.

Bencheikh et al. [48] found that the systematic error associated to SD squared and the random error is associated to SD. In addition, as seen in Figure 19, the SD changed from one direction to another and is modified from one patient to another [48].

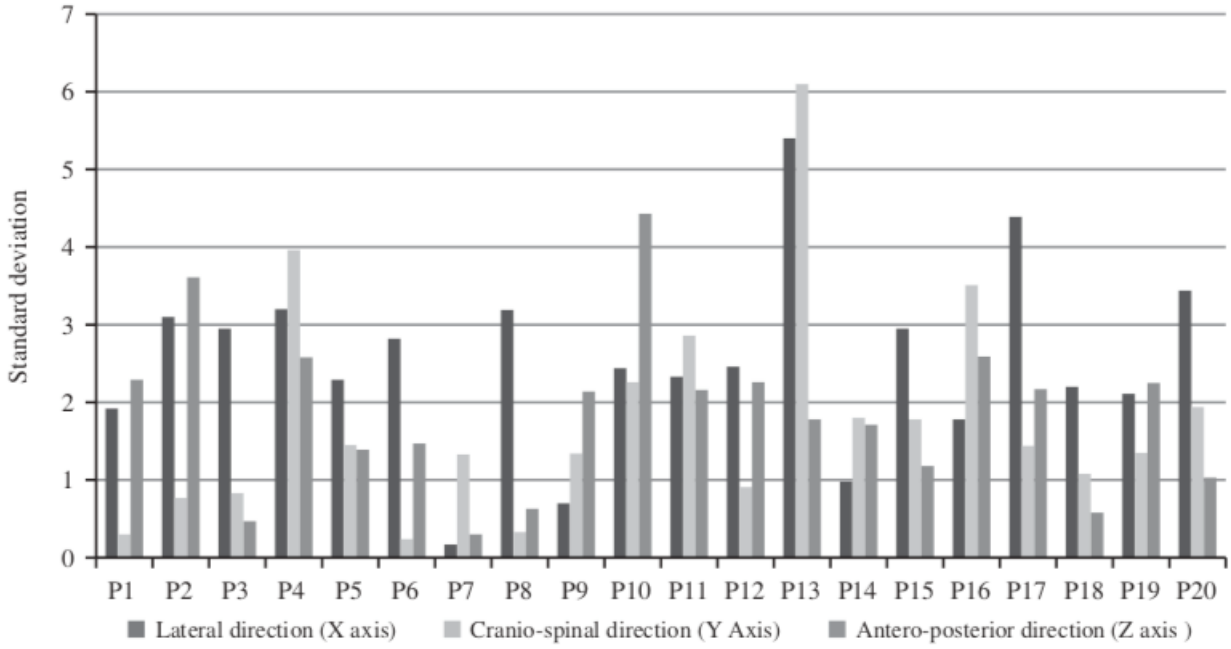

Figure 19 – SD for each patient on L (X axis), CS or CC (Y axis) and AP (Z axis) directions.

Source: Bencheikh et al. [48], p. 3.

The values of systematic error Σ, random error σ, from the Table 4 were introduced into Equation 11 in order to determinate the CTV-PTV margin on each prostate direction. [48].

Direction of space	L	CS	AP
Random error σ	2.63	1.76	2.77
Systematic error Σ	2.79	2.25	2.11
CTV-PTV margin (mm)	5.83	3.87	4.22

Table 4 – Values of systematic error Σ, random error σ and the CTV-PTV margin calculated with the van Herk method on L (X axis), CS or CC (Y axis) and AP (Z axis) directions.

Source: Bencheikh et al. [48] (with modifications), p. 3.

Van Herk [29] punctuates that "biological margin recipes are more forgiving than recipes based on physical considerations". In the face of that, is currently safer to set large margins based oneself on physics considerations because the biological effects of geometrical errors depends on the model parameters that are at the very last uncertain [29].

13 Conclusion

The both BIR and van Herk equations for CTV-PTV margins reduce the chance of tumor recurrence and are similar in order to find safe margins for a tumor treatment, which may come out on disease-free survival. Additionally, both margin recipes provide a separation between the margin of systematic errors and the margin of random errors. Since that separation is made on margin recipes it became possible visualizing what component of the margin recipe contributes to a moderate underdosage (random errors) or to a large underdosage (systematic errors). Additionally, the dose delivered to the prostate cancer using both methods is less than 2% which is inside the accuracy limit of ±5% what is the value suggested by the IAEA reports. In spite of the methods exposed took the different parameters into account there are small variations between the results of the random error, systematic error and, of course, the difference between margins. The BIR and van Herk margin recipes provide the dose delivery to the prostate cancer in lateral, craniocaudal and antero-posterior directions.

Bibliography

[1] The American Cancer Society Medical and Editorial Content Team. Evolution of Cancer Treatments: Radiation; 2019. Accessed: 02-08-2019. Available from: https://www.cancer.org/cancer/cancer-basics/history-of-cancer/cancer-treatment-radiation.html.

[2] International Atomic Energy Agency. Accuracy Requirements and Uncertainties in Radiotherapy. No. 31 in IAEA Human Health Series Publications. Vienna; 2016.

[3] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2018 sep;68(6):394–424.

[4] Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al.. Global Cancer Observatory: Cancer Today. Lyon: International Agency for Research on Cancer; 2018.

[5] World Cancer Research Fund/American Institute for Cancer Research. Diet, Nutrition, Physical Activity and Prostate Cancer. In: Diet, Nutrition, Physical Activity and Cancer: a Global Perspective; 2018. p. 3–52.

[6] World Cancer Research Fund/American Institute for Cancer Research. Prostate cancer statistics: Prostate Cancer is the Second most Common Cancer in Men Worldwide; 2019. Accessed: 2019-01-29. Available from: https://www.wcrf.org/dietandcancer/cancer-trends/prostate-cancer-statistics.

[7] Van Dyk, J and Batista, J and Bauman, G S. Accuracy and uncertainty considerations in modern radiation oncology. In: The Modern Technology of Radiation Oncology. vol. 3. Medical Physics Pub Corp Madison, WI; 2013. p. 361–412.

[8] Sonke J , van Herk, M . Errors, Margins, Localization, and Correction. In: Image-guided and adaptive radiation therapy. Philadelphia: Lippincott Williams & Wilkins; 2010. p. 41–53.

[9] Wambersie A, Dutreix J, Dutreix A. Dosimetric precision required in radiotherapy. Consequences of the choice and performance required of detectors. Journal of the Belgian Society of Radiology. 1969;52:94–104.

[10] Flamant R, et al. A clinical therapeutic study of irradiating tonsil neoplasms with 20 MeV photon or electron beams. European Journal of Cancer 3. 1967;p. 169–181.

[11] Herring D F, Compton D M J. Special Report No. 5. Symposium Proceedings of Third International Conference of Computers in Radiotherapy. London: British Institute of Radiology; 1971.

[12] International Atomic Energy Agency. 398. Absorbed dose determination in external beam radiotherapy: An International Code of Practice for Dosimetry based on standards of absorbed dose to water. Vienna; 2000.

[13] van Herk M, Remeijer P, Lebesque JV. Inclusion of geometric uncertainties in treatment plan evaluation. International Journal of Radiation Oncology Biology Physics. 2002;52(5):1407–1422.

[14] International Commission on Radiation Units and Measurements. ICRU Report 83 Prescribing, Recording, and Reporting Photon-Beam Intensity-Modulated Radiation Therapy (IMRT). Journal of the International Commission on Radiation Units and Measurements. 2010 Apr;10(1).

[15] International Atomic Energy Agency. Lessons Learned from Accidental Exposures in Radiotherapy. No. 17 in Safety Report Series. Vienna; 2000.

[16] Bureau International des Poids et Mesures. International Vocabulary of Metrology - Basic and General Concepts and Associated Terms (VIM). Paris; 2012. 3rd ed.

[17] Yeung TK, Bortolotto K, Cosby S, Hoar M, Lederer E. Quality assurance in radiotherapy: evaluation of errors and incidents recorded over a 10 year period. Radiotherapy and Oncology. 2005 mar;74(3):283–291.

[18] Allisy-Roberts P, Ambrosi P, Bartlett D T, et al. Report 76. Journal of the International Commission on Radiation Units and Measurements. 2016 06;6(2).

[19] Korreman S, Rasch C, McNair H, Verellen D, Oelfke U, Maingon P, et al. The European Society of Therapeutic Radiology and Oncology–European Institute of Radiotherapy (ESTRO–EIR) report on 3D CT-based in-room image guidance systems: A practical and technical review and guide. Radiotherapy and Oncology. 2010 feb;94(2):129–144.

[20] Zuppinger A. Spätveränderungen nach protrahiert-fraktionierter Röntgenbestrahlung im Bereich der oberen Luft-und Speisewege. Strahlentherapie. 1941;70:361–442.

[21] Okunieff P, Morgan D, Niemierko A, Suit, H D . Radiation dose-response of human tumors. International Journal of Radiation Oncology*Biology*Physics. 1995 jul;32(4):1227–1237.

[22] International Atomic Energy Agency. Commissioning and quality assurance of computerized planning systems for radiation treatment of cancer. Technical Reports Series No. 430. Vienna; 2004.

[23] Goitein M. Radiation Oncology: A Physicist's-Eye View. 1st ed. New York: Springer-Verlag New York; 2008.

[24] International Atomic Energy Agency. IAEA Safety Glossary: Terminology Used in Nuclear Safety and Radiation Protection. Vienna: IAEA; 2007.

[25] Stroom, J C Heijmen, B J M. Geometrical uncertainties, radiotherapy planning margins, and the ICRU-62 report. Radiotherapy and oncology. 2002;64(1):75–83.

[26] The Royal College of Radiologists, Society and College of Radiographers, Institute of Physics and Engineering in Medicine. On target: ensuring geometric accuracy in radiotherapy. London; 2008.

[27] Wessels C. Uncertainties in modern radiotherapy: Tomotherapy and RapidArc [dissertation on the Internet]. Ruperto-Carola University of Heidelberg. Heidelberg; 2017. Available from: `http://archiv.ub.uni-heidelberg.de/volltextserver/22535/`.

[28] McKenzie A, Coffey M, Greener T, Hall C, van Herk M, Mijnheer B, et al. Technical overview of geometric uncertainties in radiotherapy. Geometric uncertainties in radiotherapy. 2003;p. 11–27.

[29] van Herk M. Errors and margins in radiotherapy. In: Seminars in radiation oncology. vol. 14. Elsevier; 2004. p. 52–64.

[30] Semmelweis University Institute of Radiology and Oncotherapy, Budapest University of Technology and Economics Institute of Nuclear Techniques. Development of an electronic educational material for the analysing of the structures and the bio-chemical processes of living organisms by imaging technology: For Physicists. Budapest: Budapest University of Technology and Economics; 2012.

[31] Arimura H, Shibayama Y, Haekal M, Jin Z, Ikushima K. Computer-assisted target volume determination. In: Image-Based Computer-Assisted Radiation Therapy. Singapore: Springer; 2017. p. 87–109.

[32] International Commission on Radiation Units and Measurements. Report 62 Prescribing, Recording and Reporting Photon Beam Therapy (Supplement to ICRU Report 50). Journal of the International Commission on Radiation Units and Measurements. 1999;os32(1).

[33] Jones D. ICRU Report 50 Prescribing, recording and reporting photon beam therapy. Medical Physics. 1994;21(6).

[34] Prostate Cancer Canada. Pelvis Anatomy: The Prostate. Canada; 2019. Accessed: 01-10-2019. Available from: `http://www.prostatecancer.ca/Prostate-Cancer/About-Prostate-Cancer/The-Prostate`.

[35] American Society of Clinical Oncology (ASCO). Prostate Cancer: Types of Treatment; 2020. Accessed: 2020-07-21. Available from: `https://www.cancer.net/cancer-types/prostate-cancer/types-treatment`.

[36] Keall, P J, Mageras, G S, Balter, J M and Emery, R S, Forster, K M and Jiang, S B, Kapatoes, J M, Low, D A, et al. The management of respiratory motion in radiation oncology report of AAPM Task Group 76 a. Medical physics. 2006;33(10):3874–3900.

[37] van Herk M, Remeijer P Rasch C, Lebesque J V. The probability of correct target dosage: dose-population histograms for deriving treatment margins in radiotherapy. International Journal of Radiation Oncology Biology Physics. 2000;47(4):1121–1135.

[38] Mcgarry C K, Cosgrove V P, Fleming V A L, O'Sullivan J M, Hounsell A R . An analysis of geometric uncertainty calculations for prostate radiotherapy in clinical practice. The British Journal of Radiology. 2009 feb;82(974):140–147.

[39] The British Institute of Radiology. Geometric uncertainties in radiotherapy: defining the planning target volume. London; 2003.

[40] Stroom J C, de Boer H C J, Huizenga H, Visser A G. Inclusion of geometrical uncertainties in radiotherapy treatment planning by means of coverage probability. International Journal of Radiation Oncology Biology Physics. 1999;43(4):905–919.

[41] Herman M G, Balter J M, Jaffray D A, McGee K P, Munro P, Shalev S, van Herk M, Wong J W. Clinical use of electronic portal imaging: report of AAPM Radiation Therapy Committee Task Group 58. Medical Physics. 2001;28(5):712–737.

[42] Bijhold J, Van Herk M, Vijlbrief R, Lebesque J. Fast evaluation of patient set-up during radiotherapy by aligning features in portal and simulator images. Physics in Medicine & Biology. 1991;36(12):1665.

[43] Chen M E, Johnston D A, Tang, K, Babaian R J, Troncoso P. Detailed mapping of prostate carcinoma foci: biopsy strategy implications. Cancer. 2000;89(8):1800–1809.

[44] Goitein M, Schultheiss T E . Strategies for treating possible tumor extension: Some theoretical considerations. International Journal of Radiation Oncology Biology Physics. 1985 aug;11(8):1519–1528.

[45] van Herk M, Witte M, van der Geer J, Schneider C, Lebesque JV. Biologic and physical fractionation effects of random geometric errors. International Journal of Radiation Oncology* Biology* Physics. 2003;57(5):1460–1471.

[46] McCarter S, Beckham W. Evaluation of the validity of a convolution method for incorporating tumour movement and set-up variations into the radiotherapy treatment planning system. Physics in Medicine & Biology. 2000;45(4):923.

[47] Craig T, Battista J, Moiseenko V, Van Dyk J. Considerations for the implementation of target volume protocols in radiation therapy. International Journal of Radiation Oncology* Biology* Physics. 2001;49(1):241–250.

[48] Bencheikh M, Maghnouj A, Tajmouati J, Dadouch A, Benjelloun Z. Determination of geometrical margins in external beam radiotherapy for prostate cancer. Journal of Radiotherapy in Practice. 2018;p. 1–4.

[49] Leong J. Implementation of random positioning error in computerised radiation treatment planning systems as a result of fractionation. Physics in Medicine & Biology. 1987;32(3):327.

[50] McKenzie A, van Herk M, Mijnheer B. Margins for geometric uncertainty around organs at risk in radiotherapy. Radiotherapy and Oncology. 2002;62(3):299–307.

[51] Jiang R. Impact of geometric uncertainties on dose calculations for intensity modulated radiation therapy of prostate cancer [dissertation on the Internet]. University of Waterloo; 2008. Available from: `http://hdl.handle.net/10012/3570`.

[52] Van Dyk J, et al. The Modern Technology of Radiation Oncology: A Compendium for Medical Physicists and Radiation Oncologists. vol. 1. Van Dyk JMJ, editor. USA: Medical Physics Publishing Madison, WI; 1999.

[53] Booth, J T. Modelling the impact of treatment uncertainties in radiotherapy [dissertation on the Internet]. University of Adelaide; 2002. Available from: `http://hdl.handle.net/2440/37817`.

[54] Thwaites D. Accuracy required and achievable in radiotherapy dosimetry: have modern technology and techniques changed our views? In: Journal of Physics: Conference Series. vol. 444. IOP Publishing; 2013. .

[55] van der Merwe D, van Dyk J, Healy B, Zubizarreta E, Izewska J, Mijnheer B, et al. Accuracy requirements and uncertainties in radiotherapy: a report of the International Atomic Energy Agency. Acta Oncologica. 2017;56(1):1–6.

[56] International Commission on Radiation Units and Measurements. Report 29 Dose Specification for Reporting External Beam Therapy with Photons and Electrons. Journal of the International Commission on Radiation Units and Measurements. 1978 apr;os15(2).

[57] International Commission on Radiation Units and Measurements. Report 24. Journal of the International Commission on Radiation Units and Measurements. 1976 sep;os13(1).

[58] Thomas S J. Margins between clinical target volume and planning target volume for electron beam therapy. The British Journal of Radiology. 2006 mar;79(939):244–247.

[59] Smitsmans M H P. Towards image-guided radiotherapy of prostate cancer [dissertation on the Internet]. The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital. Amsterdam; 2010. Available from: `http://hdl.handle.net/11245/1.342310`.

[60] Khan H. Determinants of Prostate Cancer: The Birmingham Prostatic Neoplasms Association Study [dissertation on the Internet]. School of Health & Population Sciences. Birmingham; 2011. Available from: `http://etheses.bham.ac.uk/3170/`.

[61] Xu, H, Gordon, J J, Siebers, J V. Coverage-based treatment planning to accommodate delineation uncertainties in prostate cancer treatment. Medical physics. 2015;42(9):5435–5443.

[62] Verellen D, De Ridder M, Linthout N, Tournel K, Soete G, Storme G. Innovations in image-guided radiotherapy. Nature Reviews Cancer. 2007;7(12):949.

[63] Hurkmans C W, Remeijer P, Lebesque J V, Mijnheer B J. Set-up verification using portal imaging; review of current clinical practice. Radiotherapy and Oncology. 2001 feb;58(2):105–120.

[64] National Radiotherapy Implementation Group Report. Image Guided Radiotherapy (IGRT). England: The National Cancer Action Team; 2012.

[65] Lujan A E, Larsen E W, Balter J M, Haken R K T. A method for incorporating organ motion due to breathing into 3D dose calculations. Medical Physics. 1999 may;26(5):715–720.

[66] Karlsson M, Ahnesjö A, Georg D, Nyholm T. Independent Dose Calculations, Concepts and Models, ESTRO Booklet No. 10. Brussels: ESTRO; 2010.

[67] Aaltonen P, Brahme A, Lax I, Levernes S, Näslund I, Reitan JB, et al. Specification of Dose Delivery in Radiation Therapy. Recommendations by the Nordic Association of Clinical Physics (NACP). Acta Oncologica. 1997 jan;36(sup10):1–32.

[68] Craig T, Wong E, Bauman G, Battista J, Van Dyk J. Impact of geometric uncertainties on evaluation of treatment techniques for prostate cancer. International Journal of Radiation Oncology* Biology* Physics. 2005;62(2):426–436.

[69] Stroom J, Gilhuijs K, Vieira S, Chen W, Salguero J, Moser E, et al. Combined recipe for clinical target volume and planning target volume margins. International Journal of Radiation Oncology* Biology* Physics. 2014;88(3):708–714.