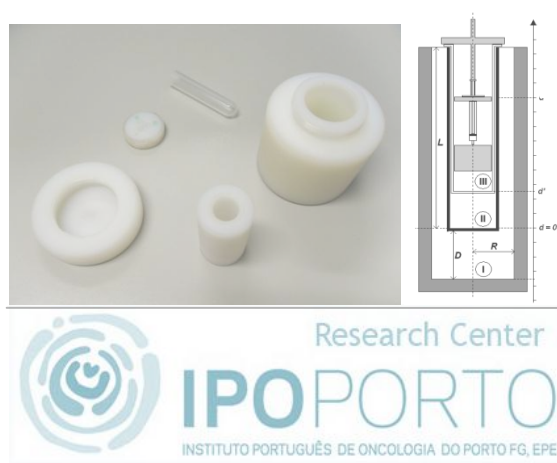
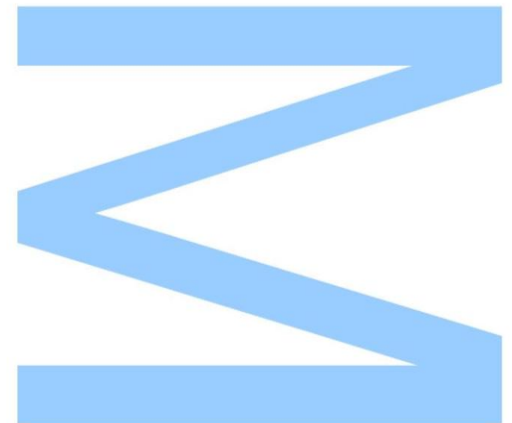




Radionuclide Calibrators Intercomparison Studies in Nuclear Medicine Centers Using *in-situ* Prepared ^{99m}Tc Sources

Innovative Methodology
Validation



Paula Alexandra da Cunha Oliveira

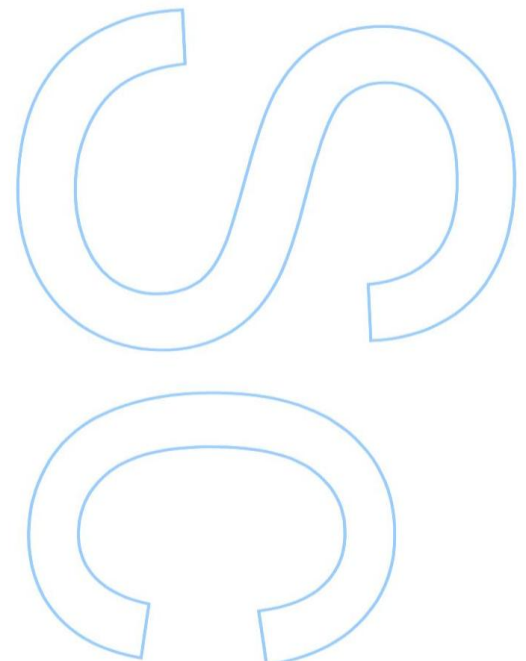
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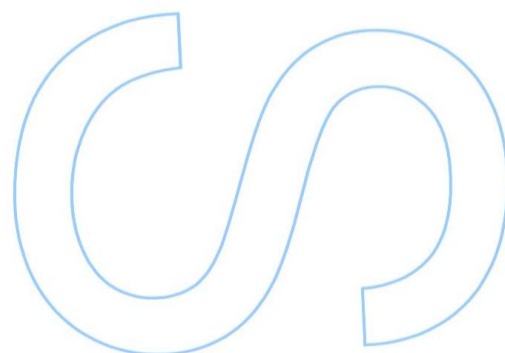
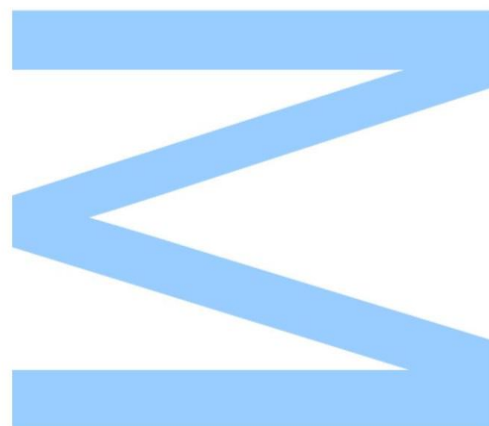




Todas as correções determinadas
pelo júri, e só essas, foram efetuadas.

O Presidente do Júri,

Porto, ____/____/____



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Abstract

In Nuclear Medicine, to perform diagnostic scans or therapeutics with high clinical value is crucial to determine accurately the activity administered to patients. To accomplish that propose is necessary to carry out periodic equipment control testing by undertaking a Quality Control Program for radionuclide calibrator. In many countries as an addition to these programs there have been conducted intercomparisons of the radionuclide calibrator's performance. Being this an assessment that heretofore implied specific resources, it has never been carried out in Portugal.

In this thesis an original radionuclide calibrator intercomparison and survey methodology is presented for short half-life radioactive sources used in Nuclear Medicine, such as ^{99m}Tc or most Positron Emission Tomography (PET) radiopharmaceuticals. As an alternative to using a calibrated source sent to the surveyed site, which requires a relatively long half-life of the isotope, a methodology was developed using a source prepared *in-situ* and an indirect activity determination through irradiation of a radiochromic film using ^{99m}Tc under strictly controlled conditions, and cumulated activity calculation. By evaluation of the resulting net optical density (*netOD*) using a standardized scanning method, a comparison of the *netOD* measurement with a previously determined calibration curve can be made and the difference between the tested radionuclide calibrator and the primary radionuclide calibrator (used to establish the calibration curve) can be calculated. To estimate the total expected measurement errors, a careful analysis of the methodology, for the case of ^{99m}Tc , was performed: reproducibility determination, scanning conditions, and possible fadeout effects, and the overall error is approximately 1.8%. The method also evaluates correct syringe positioning inside the radionuclide calibrator, since every factor of the activity measurement procedure can influence the final result.

The methodology described shows good potential for accurate dose intercomparison studies for ^{99m}Tc between Nuclear Medicine centers and can easily be adapted to other short half-life radioisotopes.

Key words: quality audit program, intercomparison study, Nuclear Medicine, radionuclide calibrator, radiochromic film, traceability.

Resumo

Em Medicina Nuclear é fundamental determinar com precisão a atividade administrada aos doentes com vista a realização de exames de diagnóstico e terapêuticas com elevado valor clínico. De forma a alcançar esse propósito é necessário realizar periodicamente testes de controlo ao equipamento seguindo o que é designado por Programa de Controlo da Qualidade ao calibrador de radionuclídeos. Em muitos países, como suplemento deste programa foram realizadas inter-comparações de calibradores de radionuclídeos. Contudo, uma vez que até então este estudo implicava meios dispendiosos, este nunca foi realizado em Portugal.

Nesta tese é apresentada uma inter-comparação e metodologia de pesquisa de calibradores de radionuclídeos original, para fontes radioativas de curta semi-vida utilizadas em Medicina Nuclear, tais como ^{99m}Tc ou radiofármacos emissores de positrões utilizados na realização de Tomografia por Emissão de Positrões (PET). Como alternativa ao uso de uma fonte calibrada enviada para o local alvo de estudo, o que exige um tempo de semi-vida do isótopo relativamente longo, foi desenvolvido um método que recorre a uma fonte preparada *in-situ* e uma determinação indirecta da actividade através de irradiação de uma película radiocromica com ^{99m}Tc em condições estritamente controladas e cálculo da atividade cumulativa. Pela avaliação da densidade ótica resultante (*netOD*) utilizando um método de digitalização padronizado pode ser efetuada uma comparação entre a medição *netOD* com uma curva de calibração previamente determinada e a diferença entre o calibrador de radionuclídeos testado e o calibrador de radionuclídeos primário (utilizado para estabelecer a curva de calibração) determinada. Para estimar o erro total esperado desta medição foi levado a cabo uma análise cuidadosa da metodologia. Para a utilização de ^{99m}Tc foi realizada: determinação da reprodutibilidade, condições de digitalização e possíveis efeitos de desvanecimento e o erro total obtido foi cerca de 1.8%. O método avalia também o correto posicionamento da seringa no interior do calibrador de radionuclídeos uma vez que cada elemento do processo de medição da atividade pode influenciar o resultado final.

A metodologia descrita apresenta bom potencial para a realização de estudos de inter-comparação com medição da atividade de ^{99m}Tc entre centros de Medicina Nuclear e pode ser facilmente adaptada para outros radioisótopos de curta semi-vida.

Palavras-chave: programa de controlo da qualidade, estudo de inter-comparação, Medicina Nuclear, calibrador de radionuclídeos, filme radiocromico, rastreabilidade.

List of Publications Accepted/Submitted Resulting From the Developed Work

Accepted:

“Innovative methodology for dose calibration inter-comparison studies using *in-situ* prepared ^{99m}Tc sources”

Accepted as an oral presentation within the Scientific Programme of EANM'13 - Annual Congress of the European Association of Nuclear Medicine (October 19 - 23, 2013 in Lyon/France), (AP Oliveira, JAM Santos, AL Bastos)

Submitted:

“Innovative methodology for intercomparison of dose calibrators using short half-life *in-situ* prepared radioactive sources”

Article Submitted to Medical Physics (September, 2013)

“Intercomparação de calibradores de dose pertencentes a duas instituições utilizando fontes de ^{99m}Tc preparadas *in-situ*”

Accepted as a poster in the XIV Congresso Nacional de Medicina Nuclear (December 5 – 7, 2013 in Fundação Cupertino Miranda, Porto), (AP Oliveira, JAM Santos, H Duarte, R Gradim)

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List of Acronyms and Abbreviations

$\tilde{A}$ - Cumulated Activity;

A_0 - Initial Activity;

AAPM - American Association of Physics in Medicine;

ALARA - As Low As Reasonable Achievable;

ANSI - American National Standards Institute;

DLRs - Dose Reference Levels;

dpi - Dots Per Inch;

FDA - Food and Drug Administration;

GIC - Gamma Ion Chamber;

IAEA - International Atomic Energy Agency;

ICRP - International Commission on Radiological Protection;

IPO-PORTO - Instituto Português de Oncologia Francisco Gentil, EPE do Porto;

MOSFETS - Metal–Oxide–Semiconductor Field-Effect Transistor;

netOD - Net Optical Density;

netOD($\tilde{A}$) - Net Optical Density as a function of Cumulated Activity;

NPL - National Physical Laboratory;

PET - Positron Emission Tomography;

pv - Mean Pixel Value;

RGB - Red, Blue and Green components of the image;

ROI - Region of interest;

$t_{1/2}$ - Half-life time;

t_{exp} - Exposition time.

Chapter 1

Introduction

1. Introduction

Nuclear Medicine is a diagnostic and therapeutic medical specialty that utilizes radioactive components to study the function of several organ systems of the human body. In a broader sense, it can be said that "Nuclear Medicine stands to Physiology as Radiology stands to Anatomy". Once the diseases begin with functional alterations and only in an advanced state occurs the morphological changes, Nuclear Medicine came to take place to other diagnostic techniques, since it allows detecting diseases at an earlier stage compared to them.

The principle which seems complicated at first glance is actually quite simple to understand. While in the Radiology, in a Computer Tomography, for example, patients lie down on the bed and the equipment is the responsible either for focusing the x-ray beams in the patients and for being the radiation detector, enabling to obtain an image with contrast (very dense, x-ray beam highly attenuated, appears in white in the image and vice versa) in Nuclear Medicine the equipment does not emit radiation, the patient do, which makes the equipment only a detector. For such, to the patient is administered a compound known as radiopharmaceutical, which combines the radioisotope that is detected by the equipment allowing to obtain the image, with a specific chemical substance that acts as "bait" which goes (after administration to the patient) to the local where the diagnosis or treatment is desire. As different tissues have different needs, the radiopharmaceuticals must be specific to each type of organ or tissue to be studied. The pathologies are thus detected by abnormalities in the radiopharmaceutical uptake.

So it becomes vital to determine with precision and accuracy the activity administered to patients with view to realize the imaging study or therapeutic. The activity administered varies with the type of test and the patient in question, namely sex, age and weight of this, with the dosages, in most countries, being pre-established by competent authorities in the matter as International Commission on Radiological Protection (ICRP), International Atomic Energy Agency (IAEA), thus creating for clinical imaging the Dose Reference Levels (DLRs). [IAEA, 2006; ICRP, 1996;

ICRP, 2002]

The premise is then delivering a dose as low as possible, that enables the study with the higher possible quality. This is then the fundament inherent in the principle that governs the radiological protection, the principle ALARA, *As Low As Reasonable Achievable*. Ionizing radiation despite allowing obtaining the clinical image, when in high doses becomes harmful since it may induce mutations in body cells which may lead in short-term to stochastic effects and/or in long-term to deterministic effects. Therefore, all practices that use ionizing radiation should be subject to control and properly regulated. These have to be justified, limited and optimized by administering the smallest activity in order to safeguard the patient but enough activity to get image with high diagnostic value.

The instruments employed to assay the activity of a radioactive source prior to clinical use in the majority of the facilities are radionuclide calibrators, recognized by Food and Drug Administration (FDA) as a tool intended to assay radiopharmaceuticals before administration to patients. [FDA, 2011]

Besides its simplicity (when compared to an Anger Camera or a Positron Emission Tomography scanner, PET) the accuracy of radionuclide calibrators is imperative to perform a quality clinical image. Although this is not a very sensible device when compared with other detectors, the radionuclide calibrators are able to provide radioactivity measurements within the precision and accuracy levels required either by radiopharmaceutical manufacturers or clinical users [Zimmerman and Cessna, 2000]. In most countries, the regulation suggests that the administered activity should be within 10% of the prescribed one, what is attained with a radionuclide calibrator accuracy of $\pm 5\%$ [IAEA, 2006] (recommended by IAEA, whereas American National Standards Institute (ANSI) recommended accuracy of $\pm 10\%$ [ANSI, 2004]).

In AAPM Report No. 181, the task group recommended that the assayed dosage be within $\pm 10\%$ of the prescribed one for diagnostic and $\pm 5\%$ for therapeutic [AAPM, 2012].

To safeguard the good equipment performance is necessary to carry out periodic equipment control testing by undertaking a Quality Control Program for radionuclide calibrator, registering all values obtained during the conduction of these tests and also personnel training, competence testing and the details of any calibrator maintenance or repair, in locals suitable for the purpose. Therefore, the Quality Control Programs help to ensure that the calibrators performance is

adequate to attest that the activity measured previously administration to patients is within the windows aforementioned. [Zimmerman and Cessna, 2000; AERB, 2001; Joseph *et al.*, 2008]

Shortly after the radionuclide calibrator installation in the department, it should be performed acceptance tests in order to determine whether this is properly calibrated and follows the manufacturer's specifications before starting their clinical use. These tests also serve as reference tests that will provide the reference values with which it should be compare the values obtained in future regular testing [IAEA, 2006; Zimmerman *et al.*, 2006; ICRP, 1996].

If when carrying out the quality control tests the performance of radionuclide calibrator is shown to be abnormal or the values obtained are outside the manufacturer tolerance interval, the equipment should be repaired and recalibrated in order to reestablish the equipment efficiency [ANSI, 2004].

In addition to Quality Control Programs adequately elaborated, following international standards, in many countries there have been conducted comparisons of activity measurements with radionuclide calibrators. These studies aim is quality assessment and improvement of Quality Control Programs in Nuclear Medicine facilities, in so far as it is used a methodology to study the performance of several calibrators in the same country in order to comprise if they are properly calibrated, otherwise corrective measures are applied promoting the proper functioning of this equipment which is vital to the realization of successful exams and therapeutics. The intercomparison of accuracy performance and traceability achievement of dose calibrators between Nuclear Medicine centers through measurement with calibrated sources is commonly recommended [AAPM, 2012].

The first intercomparison of radionuclide calibrators was carried out by the College of American Pathologists in United States of America in the early 1980s [Herrera and Paras, 1983]. Since then, several countries implemented comparison programs for several radioisotopes: United Kingdom [Woods, 1981, 1986; Woods *et al.*, 1996, 1997a, 1997b; Ciocanel *et al.*, 1999; Baker and Woods, 2000, 2001; Woods and Baker, 2003], India [Srivastava and Kamboj, 1982; Joseph *et al.*, 2003], Argentina [Rodríguez *et al.*, 1983; Furnari *et al.*, 1992], Hungary [Szörényi and Vágvolgyi, 1983; Szörényi *et al.*, 1998], Germany [Debertin and Schrader, 1992], Australia [Smart, 1995], Canada [Santry, 1998], Brazil [Iwahara *et al.*, 2001, 2002; dos Santos *et al.*, 2003, 2004], Czech Republic [Olšovcová, 2004; Olšovcová and Dryák, 2003], Swiss [Wastiel *et al.*, 2005] and Cuba [Oropesa *et al.*, 2003].

The comparison methodology, as well as the radionuclides used, in the comparisons, varied between studies. Mostly, gamma-emitters with relatively high effective energy (140 to 364 keV) such as ^{99m}Tc , ^{67}Ga , ^{201}Tl , ^{131}I ²⁹ have been used. This is because radionuclide calibrator measurements of pure β -emitters is difficult. Moreover, the measurements have high variability due to its dependence on Bremsstrahlung production by the β -particles in the source and surrounding materials, and thus in the source geometry and positioning ^[NRC, 2002; Wastiel *et al.*, 2005].

In countries where more than one intercomparison study was carried out, a visible improvement in radionuclide calibrator performance was found. This shows that intercomparisons are a useful way to improve the quality control program outcome ^[Oropesa *et al.*, 2008].

In most cases the participants themselves provided the radioactive sources to which was measured the activity with their calibrators and then sent the sources to the authors of the study that determined the standard/real activity with calibrated equipment as Centronic IG12 or 4 π high-pressures gamma ion chamber (GIC). In the other cases the authors either sent the sources to participants or went to the departments with the sources to make the radionuclide calibrators measurements, with the standard/real activity previously determined with the equipment mentioned above.

The major problems in our case focuses on the fact that we also want to test the methodology adopted by each facility, therefore being the participants responsible to provide the radioactive sources and since the ^{99m}Tc was the selected radionuclide once this is the principle used one in conventional Nuclear Medicine, then there is the problem with the relatively short half-life (± 6 h) which implies that if the whole process is not carried out in the same day, with the rapid decay of this radionuclide, the measurement of the standard activity becomes difficult. Besides, the transportation, if not done by competent authorities, is problematic since it is an unsealed radioactive source. To further complicate this assay we did not possess the Centronic IG12 or the 4 π high-gamma ion chamber pressures to measure the standard activity.

Thus, a new method was devised where it is not necessary to send or receive radioactive sources. The intercomparison procedure we propose involves an *in-situ* preparation of a ^{99m}Tc source, which will then be used to irradiate a radiochromic

film (Gafchromic XRQA2) inside a specially designed irradiator under strict conditions. The cumulated activity, $\tilde{A}$, is calculated based on the initial activity and total irradiation time, by integrating $A(t)$ for all the irradiation time. This irradiation will produce an increase in the film optical density (OD) dependent on the cumulated activity, $OD(\tilde{A})$. The OD can be defined as [Ohuchi, 2007].

$$(1) \quad OD = \log_{10} \left(\frac{2^n}{pv} \right)$$

where n is the bit depth of the image and pv is the mean pixel value of a given region of interest (ROI).

A calibration curve can be established for a given irradiator geometry and a primary dose calibrator. It is thus possible for a National Metrology Institute to mail the irradiator plus detailed procedure instructions to a distant Nuclear Medicine center to be exposed using a locally prepared source. The dose calibrator activity read-out, as well as the accurate irradiation time, is recorded and used to calculate the cumulated activity. Back at the controlling center, the corresponding OD is measured using a dedicated scanner (EPSON Expression 10000XL), and compared with a reference value obtained from a previous measured calibration curve. If the irradiation time is accurately determined, the differences between the measured OD and the calibration curve $OD(\tilde{A})$ can only be attributed to the initial activity (dose calibrator read-out), or to the errors associated with the Gafchromic XRQA2 measurement. This allows the comparison of both activity read-outs and the deviation between the primary and the tested device.

In order to estimate the total expected measurement errors, a careful analysis of the above methodology was performed: reproducibility determination (<0.1%), scanning conditions optimization, and possible fadeout effects. This methodology can be also alert to syringe miss positioning inside the radionuclide calibrator [Santos et al, 2009].

This project is thus innovative, ambitious and necessary. Innovative, since in Portugal it was never been performed an intercomparison of the measurements obtained with radionuclide calibrators in the Nuclear Medicine facilities and the methodology used has, as far as we know, never been used before. Ambitious since it was created an innovative method to determine the standard activity value. Needed once there is several measurement errors associated to this device, which are not detected with the quality control tests routinely performed in the departments, which may lead to administrating activities that do not correspond to the desired values, thus changing the clinical quality of the diagnosis and therapy.

Chapter 2

Materials

2. Materials

2.1. Radionuclide Calibrator

Gaseous phase detectors, scintillation detectors, and solid-state detectors can be used for measuring the activity of a radioactive source. Radionuclide calibrators are gaseous phase detectors and they are routinely used in Nuclear Medicine departments, especially for measuring the activity present in the radiopharmaceutical administered to the patient. It is usually an ionization chamber constituted by a gas enclosure between two conducting electrodes, the anode and the cathode, where the source is positioned along the longitudinal z-axis inside a cylindrical shaped cavity in order to maximize its efficiency, as can be seen in figure 1.

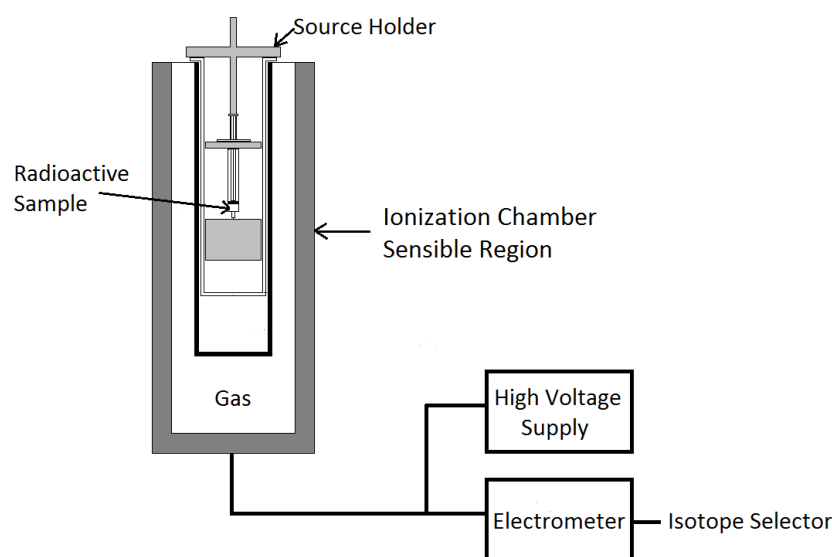


Figure 1 - Block diagram of a Radionuclide Calibrator.

The activity is therefore determined by the ionization current generated at the time of interaction between the radiation emitted by the source present in the sample with the gas [Laboratorio de Metrol gia de Radiaciones Ionizantes *et al.*, 2003; Solano, 2006].

The radionuclide detector consists in a chamber containing filling gas sealed at elevated pressure, around 10 to 20 atmospheres. The two co-axial electrodes are kept with a potential difference provided by a voltage source. The chamber should be sealed to eliminate the need for temperature and pressure correction and the high pressure is used to increase the detection sensitivity. The chamber wall is aluminum alloy with a few millimeters thick. The size of the chamber is crucial in the source positional dependence which can be decreased utilizing calibrators with larger chamber due to a longer longitudinal z-axis uniform efficiency. The chamber is shielded with lead to reduce the influence of background radiation and to minimize the radiation exposure of the operator. Although the shielding is essential for the proper and safe operation of the calibrator, backscatter and the emission of lead x-rays from shielding can affect the accuracy of the equipment, therefore the radionuclide calibrator manufactures should certify to the purchasers that the calibration settings accurately reflect the contributions from the supplied chamber shielding. These calibration settings are measured for sources in a specific source container and using the source holder. Once the chamber sensitivity varies in horizontal and vertical directions, is essential to use properly the supplied source holder [AAPM, 2012; Knoll, 2000; NCRPM, 1985].

When a photon or particle interacts with the air within the ionization chamber occurs an ionization leading to two loads: one positive and other negative, figure 2. Each load is electrically attracted to the electrode of opposite polarity, which generates a small electric current.

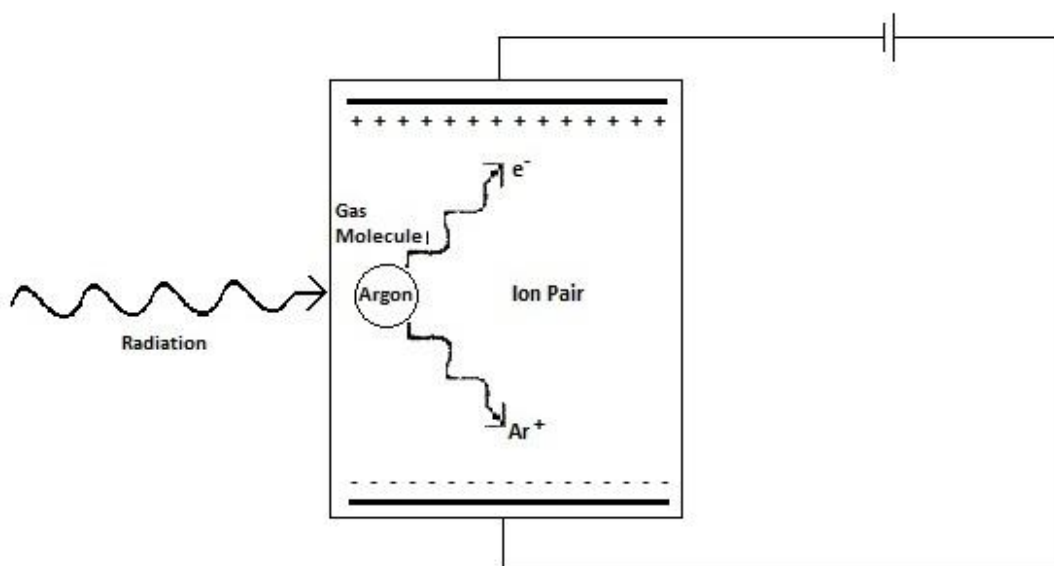


Figure 2 - Interaction between radiation provided from the radioactive source with Argon (filling gas molecule), occurring a ionization which produces a positive and a negative load, generating thus a electric current.

In the electrometer, the ionization current is converted into a signal which is amplified, processed and finally displayed in activity units as curie (Ci) or becquerel (Bq). This is only possible since the ionization current is directly proportional to the activity in the sample if it has a fixed geometry and linear response of the radioactive source ^[Laboratorio de Metrológia de Radiaciones Ionizantes *et al.*, 2003]. One of the main disadvantages of radionuclide calibrators is that these equipments have no intrinsic photon energy discrimination capability.

The majority of radionuclide calibrators used are the ionization chambers type. The design of this type of detectors presents no major influence in the outcome with large variation in the volume of sample to be measured or its position. However, manufacturer specifies the volume and type of container appropriate for each model, as well as correction factors for other volumes and containers, used in the daily routine of Nuclear Medicine departments. To overcome these errors, nowadays it is possible to find on the market calibrators using two Geiger-Müller tubes placed one on the right and another on the left of the chamber which enables a reduction in variations that comes from the source volume and positioning. Although, the intrinsic efficiency of a Geiger-Müller detector for counting gamma or X photons is very low due to the output of a pulse of

electromagnetic radiation requires the formation of secondary electrons which resulted of the interaction with the tube material. Once the atomic number of this material is low, the absorption coefficient is only high for low energy radiation and is negligible for high energy photons, the main reason why the ionization chamber type is the most used one [Solano, 2006].

The different types and energies presented in the sources of radiation produce different amounts of ionization, similarly, the same activity for different radionuclides generates different amounts of ionization. Therefore, the response of an ionization chamber to different radionuclides, varies according to the type, the energy and abundance of them, being the rate of emission of the photon energy the most important consideration. This is why is necessary to appropriately adjust the amplification of the voltage signal.

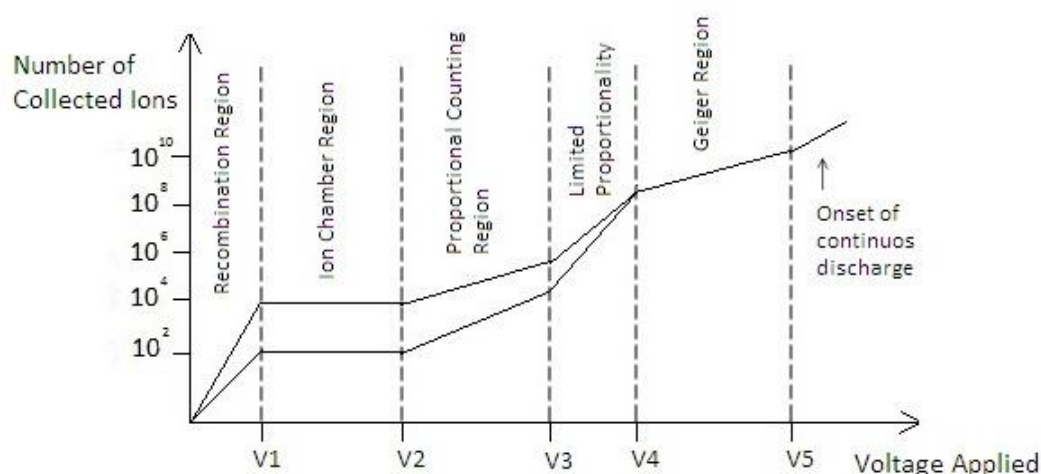


Figure 3 - Working areas of gaseous phase detectors, taking into account the voltage applied.

The figure 3 represents the different regions for each type of gaseous phase detectors taking into account the relationship between the amplitude of the output signal or number of collected ions and the voltage applied. It is possible to see that radionuclide calibrators are in the saturation region (ion chamber region), where it

is possible to collect all the charges formed till the detector reaches the saturation thus presenting a relative insensitivity to polarization voltage [Solano, 2006].

This type of phase gaseous presents a typical sensitivity curve as a function of photon energy, figure 4.

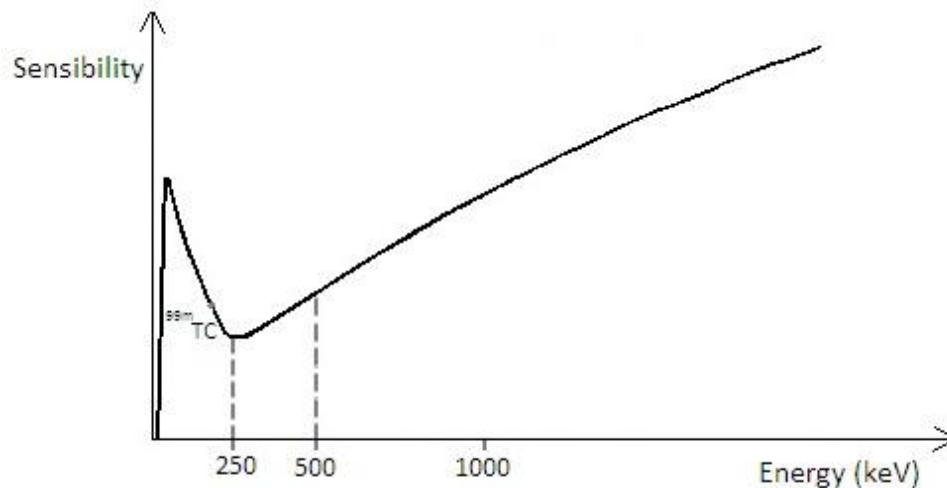


Figure 4 – Radionuclide calibrator's response characteristic curve as a function of radiation energy.

The first peak, around 40 to 45 keV demonstrates a high sensibility for the detection of ionizations induced by the increase in the probability of occurring photoelectric effect, prevalent phenomenon for low energies. Below this value, for chambers with aluminum walls, the detector sensitivity is very low since the low energy photons are attenuated while going through the walls of the radionuclide calibrator which preclude them to reach the sensitive volume of the chamber. The sensitivity threshold depends upon the source volume, the wall material and thickness of the source container and the thickness of the source holder. Above 45 keV the probability of occurring photoelectric effect decreases rapidly, becoming the Compton effect the most probable interaction which motivates a monotonous rising from 200 keV. Above 200 keV, the sensitivity increases approximately linearly with increasing photon energy [Laboratorio de Metrológia de Radiações Ionizantes, 2003; AAPM, 2012].

Radionuclide calibrators are usually pre-calibrated by the manufactures for daily-used radionuclides. Calibration is the process of determining the calibration coefficients or calibration settings for each radionuclide to be assayed. It is only possible to obtain a nominal activity through the application of a calibration coefficient to the measurement obtained with the ionization chamber. These coefficients or calibration factors are usually available on the radionuclide calibrator console for each radionuclide and the calibration coefficient value depends not only in the radionuclide properties, but also on the wall thickness, gas pressure, chamber design and operating voltage of the ionization chamber and the source geometry as the container type and wall thickness, source volume and position of the container in the chamber.

Table 1 - Examples of Calibration Coefficients for Vials from the NPL Secondary Standard Radionuclide Calibrator.

Radionuclide	Calibration Coefficient (pA/MBq)
^{99m}Tc	1.240
^{123}I	1.721
^{131}I	4.073
^{131}I (capsule)	4.053
^{67}Ga	1.565
^{201}Tl	0.886
^{111}In	4.129
^{90}Y	0.0721
^{32}P	0.03518
^{18}F	10.39

It is recommended by ANSI No 42 to perform calibration with standard sources of each radionuclide for a specific geometry. A typical calibration for radionuclide calibrators can take place with a low-energy photon emitter like ^{57}Co and a high-energy photon emitter as ^{60}Co or ^{137}Cs , measured with identical geometry. The instrument is then adjusted to read accurately at two arbitrarily assigned calibration setting numbers [ANSI, 2004].

In addition to the initial calibration undertaken by the manufacturer, there are other types of calibrations that can, and most often, should be made to the equipment. Subsidiary calibrations are performed in addition to those provided by the manufacturer to establish the response to radiopharmaceuticals in containers or volumes that are different from the containers and volumes used to initial calibrate the instrument, although it must be taken into account that these are procedures that should only be performed at facilities with necessary equipment and expertise. Recalibration is recommended by manufacturers to be performed periodically (every 4 or 5 years) to guarantee that the instrument's high reliability is maintained.

According to the general practice and international recommendations the activity administered to the patient for performing a Nuclear Medicine therapeutic or scan should be measured with an error not greater than 5% and 10%, respectively [Parkin *et al.*, 1992].

One of the most common sources of error comes from the measurement of radioactive sources into containers different from those used by the manufacturer for the determination of calibration factors, especially with beta emitters. Some radionuclide calibrators operators have no instructions for proper handling of equipment, which means that in many Nuclear Medicine departments the samples are measured without carefully use the same parameters used by the manufacture, including container source, source volume, and source position in the chamber. Once the radionuclide calibrator is not calibrated for each radionuclide and sample configuration to be used in clinical practice, the user must calculate the difference between the new measurement conditions and the ones used by the manufacture. If the difference exceeds 5%, new correction factors should be calculated and then applied [AAPM, 2012].

According to ANSI standards [ANSI, 2004] and NPL Report No. 93 [NPL, 2006] the most common sources of uncertainty in the assay of radionuclides with ionization chambers are: errors in calibration of standard reference sources; errors in calibration by interpolation using “master” chamber response-energy curve and published decay schemes as extrapolated to “field” instruments, variation in “field” instrument wall thickness and chamber gas pressure, backscatter from chamber shielding, inherent accuracy and linearity of electronics, including range changing errors (with and without with auto-ranging electrometers) and rounding or truncation errors, ion pair recombination with high-activity sources, variations in radiation background with low-activity sources, differences between calibration containers and sample containers, variation in attenuation due to variations in sample containers’ wall thickness or material and sample volume.

Notwithstanding, source geometry is the most significant error source. The geometry of the standard source should be identical to the geometry of the source being assayed, if they are not identical the error in the measurement should be quantified and a correction factor applied. Thereat, calibrator manufacturers and some credited protocols recommend calibration corrections for syringes, bottles, vials and other containers of different sizes and types, but the suggested values may be significantly underestimated [Santos *et al.*, 2009]. In addition, source position in the chamber introduces additional uncertainty, even with the utilization of source holders which ensure vertical position, some vertical and horizontal changes like syringe angle in holder and source volume, may affect chamber response. These problems could be solved with the use of a much larger chamber compared to the sample size. Despite the size of the chambers have been increasing, it is still not large enough to solve this problem and it is unfeasible to manufacturing a chamber wide enough since it would implies the utilization of much space in the hotte and increased cost of radionuclide calibrator.

Santos *et al.* [Santos *et al.*, 2009] have study the location and size of the optimum measuring region or “sweet spot” and they noticed two regions inside the cylindrical dose calibrator. The first region corresponds to the locations where the deviation from the maximum efficiency is less than 5% and the second where it is less than 10%, suggesting that these parameters can be used for source position optimization, for the characterization of new radionuclide calibrators during acceptance tests and as a quality control tool for constancy.

To prevent the improper radionuclide calibrator functioning is crucial to perform periodically an appropriate quality control program. The data obtained in the tests should be recorded and plotted for better visualization of the parameters evolution, in order to analyze and take appropriate corrective actions.

As part of a Quality Control Program, once the radionuclide calibrator has been installed in the facilities, it should be implement the acceptance tests for establishing the proper calibration and to see if it meets the manufacturer's specifications. Simultaneously, it should be perform reference tests to obtain values which will be used as reference for the periodic checks. These tests must be repeated after equipment reparation or when the equipment is relocated.

The tests recommended by ANSI ^[ANSI, 2004], IAEA ^[IAEA, 2006] and Santos et al ^[Santos et al., 2009] are presented in the follow table.

Table 2 – Tests frequencies of recommended Quality Control Programs.

	Acceptance	Daily	Annually
Clock Accuracy	V	V	
System Electronic	V	V	
High Voltage	V	V	
Physical Inspection	V	V	
Check Source	V	V	
Background	V	V	
Zero Adjustment	V	V	
Accuracy Test	V		V
Reproducibility	V		V
System Linearity	V		V

Physical inspection consists in the visual inspection of calibrator and source holder for damage whereas system electronics test uses the manufacturer-provided diagnostic testing to compare the results with the manufacturer's tolerances. Clock accuracy is performed to check the accuracy of the stored time, which should be synchronized to a standard time. High voltage should be tested and the results compared to the manufacturer's tolerances and zero adjust should be tested and adjust each day before start the clinical utilization of the equipment.

Background response or contamination check can be caused by external radiation fields, contamination or electronic noise, which becomes even more important in facilities that perform PET scanning and ^{131}I therapies, where additional shielding is most of the times required. The value obtained should be compared with the one calculated in the acceptance test. The check source test or constancy response test consists in measuring a long half-life check source to allow the demonstration of the constancy of the calibrator's response. The value obtained should be compared to the initial measurements performed at acceptance testing and it should be within $\pm 5\%$ of the decay-corrected initial values.

The accuracy test and reproducibility or precision test can be performed the same way. Is generally used a ^{137}Cs source with an activity greater than $100\text{ }\mu\text{Ci}$ ($3.7 \times 10^6\text{ Bq}$) [ANSI, 2004]. The source should be placed in the chamber with the source holder, the activity should be recorded and the source removed from the radionuclide calibrator. This procedure should be repeated 10 times. Accuracy measure is how close the measured value is from the actual value whose difference should be within $\pm 5\%$ [AAPM, 2012]. Precision is the percentage deviation of the measured values from the average value and the measurements for precision test should be within $\pm 1\%$ of the average measured activity for that source [IAEA, 2006].

System linearity test can be carried out using different methods, the decaying source method, the shield method and the graded source method, being the first and the second methods the most used since the graded source method involves manipulation and accurate measurement of stock solution aliquots which is not recommended for most facilities. Measurements should be within $\pm 5\%$ of the expected values [AAPM, 2012].

In Instituto Português de Oncologia do Porto Francisco Gentil, EPE (IPO-PORTO), it was used a Capintec CRC-15R as the reference calibrator to obtain the calibration curve used as the reference *netOD value*.

2.2. Gafchromic Film Dosimetry

To perform radiation dosimetry and image acquisition during clinical imaging or therapeutic procedures, a vast range of techniques that can be characterized by its sensitivity to the specific photon energies, spatial resolution, difficulty of use, and capacity to measure absolute dose, can be employed. Several techniques can be used such as ionization chambers, thermoluminescent dosimeters, radiographic films, MOSFETS, etc. Although, there are many problems associated to the use of each one of these modalities. Ionization chambers for example, have low spatial resolution, while thermoluminescent dosimeters, beside a poor spatial resolution as well, have a complex and time consuming reading methodology, and imply special equipment which is not always available. Radiographic films have also a number of inconveniences; its sensibility to ambient light, the difficulty in evaluating the photon beam due to amendments in sensitivity for photon energies in the region up 10 to 200 kVp and the requirement of chemical processes for the readout [AAPM, 1998].

Therefore, there was the need of discovering a new material that could present high spatial resolution, easy handling, simple and fast readout without having to resort a chemical processing, and capable to determine the absorbed dose with precision and accuracy through a previous calibration process. All of this is achieved with radiochromic films which are composed by a layer of radiation-sensitive organic microcrystal monomers, on a thin polyester base with a transparent coating. The exposure to radiation is noticeable even just by looking to the film once it changes is color after irradiation. The increase of absorbed dose induces immediately a darker color in the film, what take place without demand thermal, chemical or even optical development [Soares, 1999]. The process behind the color change, radiochromic effect, occurs as a dye-forming or a polymerization process. A particle transfers energy to the receptive part of the leuco-dye photomonomer molecule, which initiate the color formation. [AAPM, 1998]

Due to these properties, radiochromic films have been widely used in the last years not only in medical applications such as ophthalmic applicator dosimetry [AAPM, 1998], brachytherapy dosimetry [AAPM, 1998], interface dosimetry [Ravazi *et al.*, 1995; Niroomand-Rad *et al.*, 1996], stereotactic radiosurgery dosimetry [Bjarngard *et al.*, 1990], dosimetry in the penumbra region of radiotherapy beams [Galvin *et al.*, 1993], hot particle dosimetry [Soares *et al.*, 1990], dosimetry for radiation inactivation and target size analysis [Van Hoek *et al.*, 1992], intravascular brachytherapy dosimetry [Soares *et al.*, 1996] and proton dosimetry [Vatnitsky *et al.*, 1997; Vatnitsky, 1997; Nichiporov, 1995], blood irradiation [Hillyer *et al.*, 1993], but also in nonclinical purposes as radiation and reference standard [McLaughlin & O'Hara, 1996]. There are many different types of films and they can be on various forms (thin or thicker films, liquid solutions and gels), enabling its application to a range of absorbed dose since 10^{-2} to 10^6 Gy and absorbed dose rate up to 10^{12} Gy s⁻¹ [AAPM, 1998].

In the past years various types of radiochromic films were used, such as Gafchromic HD-810, with a nominal dose range from 10 to 1000 Gy; Gafchromic MD-55-1, with a nominal dose range since 2 to 200 Gy; Gafchromic MD-55-2, with a nominal dose range since 1 to 100 Gy and approximate sensitivity of 20 mAU/G and Gafchromic HS with a nominal dose range since 0.5 to 50 Gy. The most widely used in medicine (radiotherapy and radiology) are the EBT and the XR radiochromic films [Soares, 1999].

The Gafchromic XR was the selected type of radiochromic films to indirectly access the cumulated activity $\tilde{A}$ of a geometrically constant and well defined radioactive source through the resultant *netOD*. Inside this category there are different film configurations, for instance Gafchromic XR-T, which is available in a sheet with 12.5cm x 12.5cm x 0.21mm, with 18µm of XR-T emulsion, Gafchromic RTQA which is available in a sheet with 36cm x 43cm x 0.23mm, with 17µm of RTQA emulsion under a 3 µm surface layer, Gafchromic XR-RV2 which is available in a sheet with 36cm x 43cm x 0.23mm, with 17µm of RTQA emulsion under a 3 µm surface layer, all with a nominal dose range since 0.01 to 5 Gy and Gafchromic XR-QA available in a sheet with 36cm x 43cm x 0.26mm, with 25µm of XRQA emulsion preceded by a 10 µm surface layer under a 25µm of XRQA emulsion, which gives a nominal dose range since 0.001 to 0.2 Gy [Soares, 1999].

The structure of XRQA2 has five layers: 97 μm clear yellow polyester layer, 15 μm thick pressure sensitive adhesive layer, 25 μm thick active layer, 3 μm thick surface layer and 97 μm thick opaque white polyester layer, figure 5, the last being responsible for making the film only scannable in reflective mode [ISP, 2011; Giaddui *et al.*, 2012].

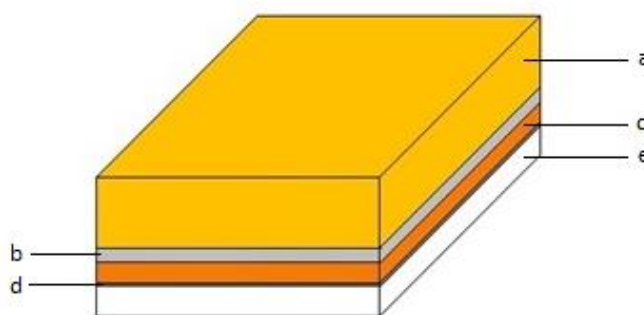


Figure 5 – Gafchromic XRQA2 Layers: a) yellow polyester layer; b) pressure sensitive adhesive layer; c) active layer; d) surface layer and e) white polyester layer.

The active layer of this film has as atomic constituents H, C, N, O, Li, Br and Cs. The elements with higher Z (atomic number) increase the sensibility of this Gafchromic film to lower energies since it increases the cross section of photoelectric effect (that happens at low energies) [Giaddui *et al.*, 2012]. This was the main reason why the XRQA2 (used in diagnostic radiology) was the type of film selected to perform the dose calibrator evaluation.

The properties of the absorption spectra response of XRQA2 radiochromic film have been amended since XR-R owing to the alteration in the active layer. The absorption peaks are located at 636 nm and 585 nm and the dose sensitivity is approximately 0.0775 OD/cCy, which makes this film suitable for perform dosimetry at low dose and low energies [Alnawaf *et al.*, 2010b].

In the groundbreaking method present in this thesis, to determine the radionuclide calibrator measurement efficiency, the Gafchromic film was used to indirectly determine the cumulated activity present in the radioactive sample. This

value is then compared with the value obtained with the radionuclide calibrator, thus serving as a default value which allows drawing inferences of the equipment accuracy. Since this material is specified by the manufacturer as a dose measuring system and has never, to our knowledge, been used for the purpose intended here, it is important to establish that the cumulated activity is a function of the activity originally present in the sample and the exposure time of the film to the radioactive source, which is demonstrated in the following formula:

$$(2) \quad \text{Cumulated Activity} = A_0 \times \frac{t_{1/2}}{\ln 2} \times \left(e^{\frac{\ln 2}{t_{1/2}} \times T_{\text{exp}}} - 1 \right)$$

where, A_0 is the initial activity (introduced in the test tube), $t_{1/2}$ is the radionuclide half-life (in this case 6 hours), and T_{exp} is film exposition time to the radioactive source.

Thereby, with the increase of the cumulated activity, the Gafchromic film darkens, which is then measured in units of net reflective optical density (Net OD), as can be seen in equation 3 [Alnawaf et al., 2010a; Garcia and Azorin, 2013].

$$(3) \quad \text{netOD}(D_i) = \log_{10} \left(\frac{pv_0}{pv} \right)$$

where pv is the mean pixel value of a given region of interest (ROI) and pv_0 is the mean pixel value of an unexposed reference film.

To get this value, first the film must be exposed to the radiation source, with the activity presented in it (obtained with the radionuclide calibrator that is being the subject of evaluation) and the exposure time adequately documented to determine the cumulated activity. To obtain the calibration curve, there has been used many different exposure times and activities to cover the entire curve.

Twenty four hours postirradiation, the films were scanned using a flat bed scanner since this is the fastest, accurate and less expensive method. The digitalization technique was performed under the same conditions for all films, as regards to position and orientation of the films in the scanner, scan delay and scanner resolution. Upon irradiated films scanning there have also been scanned in the same image, non-irradiated films to obtain the pV_0 .

After obtaining the films images with the software SF Launcher provided by the scanner manufacturer, ImageJ [Alnawaf *et al.*, 2010a; Silva *et al.*, 2010] was the software used to separate the RGB (Red, Blue and Green) components of the image to only work with the red one, to which is greater the film sensibility [Silva *et al.*, 2010], outlining a ROI (Region of Interest) centered in the middle of the films for not include mechanical damage caused when it is cut [Alnawaf *et al.*, 2010a], in order to obtain the Mean Pixel Value (MPV) of the irradiated and non-irradiated films and thus determine the *netOD* as a function of cumulated activity.

Giaddui *et al.* (2011) studied the characteristics of Gafchromic XRQA2 films for kV range image dose measurement and found that the variation on net reflectance was 3% when film sizes varied from 1 cm x 2 cm to 10 cm x 11 cm. Regarding the region of interest (ROI) size where the mean pixel value was averaged, they discovered a variation of 1% between a ROI size of 0.7 cm x 0.7 cm to 8.0 cm x 8.0 cm, which demonstrates a good uniformity of the film. Relatively to the scanning process, the authors found changes in the uniformity (difference in net reflectance in the central area and in the edges of the scanner) of 4% which is lower for high doses and they also conclude that the used of high scanning resolution introduce additional uncertainty to the scanning process. The film also shows energy dependency, presenting a response variation of 10% when irradiated at 100 and 120 kVp. Concerning to the postirradiation development with time they found that net reflectance grow rapidly with time over the first hour after exposure and changed by less than 1 % in the following 5 hours, which became even lower to values of 0,5% in the 24 hours after exposure, which make them assume that the film reaches stability 6 hours after exposure [Giaddui *et al.*, 2012].

The XRQA Gafchromic film have some net reflectance variations (2%) due to scanning orientation and polarization effects [Giaddui *et al.*, 2012] and this is the reason why it is recommended the use of the same angle of orientation during the film digitalization.

The study of the film and the readout equipment (scanner) characteristics is vital for performing a correct material manipulation and methods, allowing the construction of an accurate calibration curve which is crucial in this work as a standard measure for the dose calibrator performance on the determination of the ^{99m}Tc activity.

2.3. Scanner

To perform film's digitalization 24 hours after the exposure, it was used an Epson Expression® 10000 XL flatbed document scanner (SEIKO EPSON Corporation, Nagano, Japan).

This scanner has as features a maximum read area of 310mm x 437mm; a Xenon gas cold cathode fluorescent lamp as light source; an optical resolution of 2400 dpi; a hardware resolution of 2400 x 4800 dpi; a maximum resolution of 12800 x 12800 dpi with interpolation; an 87840 effective pixels/line; an optical density of 3.8 Dmax; a 7 levels of brightness; a one-pass scanning reading sequence; a scanning speed of 16.0 msec/line when is a color scanning and 5.3 msec/line when is a grayscale scanning, what makes it one of the fastest scanners in the market. As physical dimensions it has a 656mm width, 458mm depth, 158mm height and 13 kg of weight [Epson, 2004].

Therefore, scanning becomes faster with good resolution and smooth gradations, being this equipment able to capture more than 4 trillion colors and 4096 shades of gray. It accurately scans each image, including film and transparencies with remarkable precision [Epson, 2004]. To obtain the film image, the scanner was used in reflective mode, giving up the digitization a few minutes after turning the scanner on, using the software provided by the manufacturer, SF launcher.

2.4. Irradiator

To become possible the irradiation of Gafchromic film with standardized conditions, it was specially designed and manufactured an irradiator made of nylon since this material is easily shaped and has a great resistance to wear and traction. In figure 6 it can be seen the different irradiator constituents.

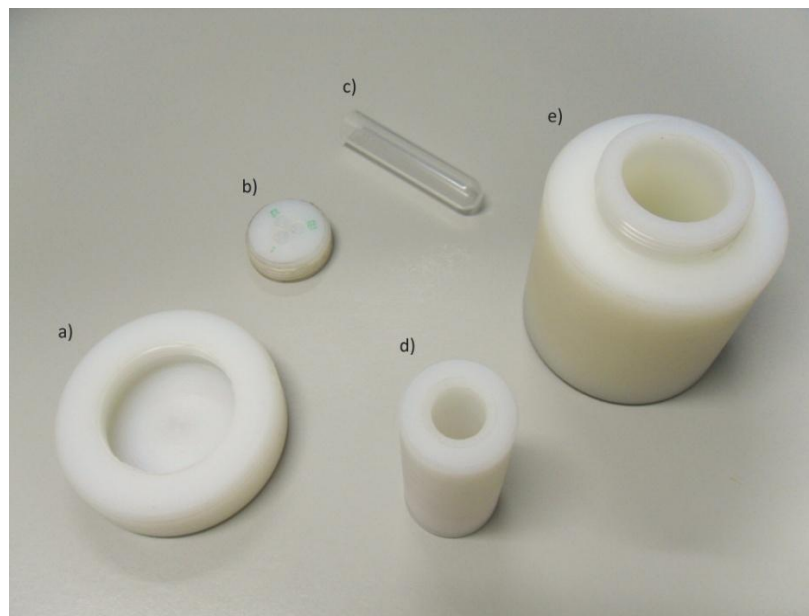


Figure 6 - Irradiator. a) upper cover; b) lower cover; c) test tube; d) inner cylinder and e) outer cylinder.

Thus, the irradiator allows the placement of Gafchromic film always in the same location and position relative to the source, reducing thereby the error associated with film movement between different measurements. It has an easy fixture system, which can be cleaned and easily assembled.

In order to make the irradiator prepared for films irradiation, primarily it must be placed the inner cylinder or test tube support inside the outer cylinder. The Gafchromic films should be placed in the space between the test tube support and the adjustable cap, with acetate film above these to reduce possible damage. Thereafter, the adjustable cap should be placed with care to ensure that the films are as close as possible to the test tube support, figure 7. The irradiation starts when the test tube is introduced into the irradiator with a given activity of ^{99m}Tc .

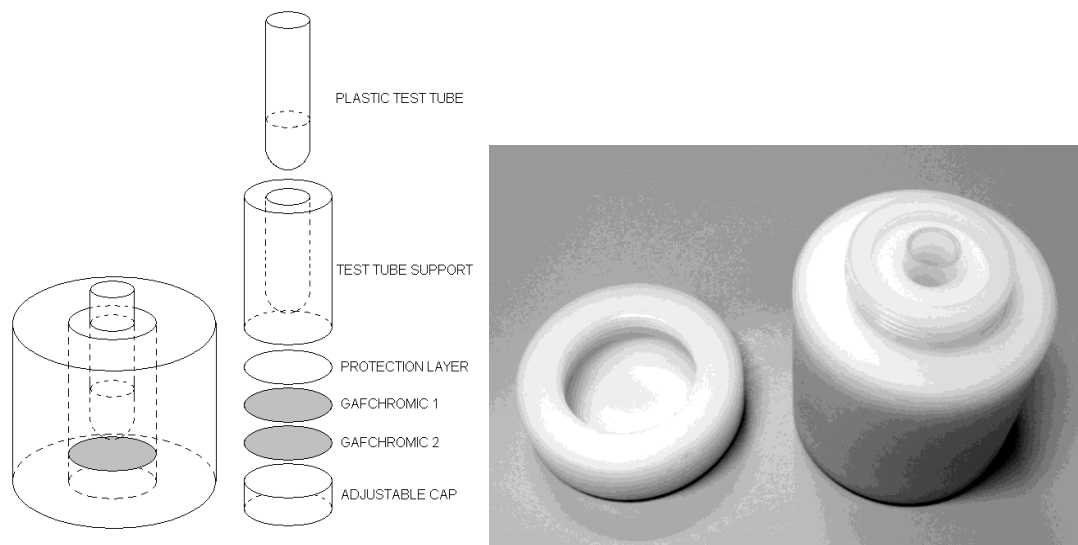


Figure 7 – Irradiator scheme and irradiator prepared for Gafchromic irradiation.

The irradiator should be closed during the irradiation with the upper cover. This procedure should always be performed in the same way and if possible, by the same person, to decrease the likelihood of occur errors.

The irradiator has cylindrical geometry particularly to be feasible the use of test tube, the same for all measurements, but also to be possible the introduction of the irradiator in lead containers, which are mostly cylindrical, to decrease the accidental irradiation of Gafchromic films by any external sources.

Chapter 3

Methods

3. Methods

3.1. Method Validation – Calibration Curve Determination

Being this an intercomparison study without resort to ion chambers or liquid scintillators or even a radionuclide calibrator recently calibrated by competent entities, for the determination of the reference activity it was necessary to validate the method chosen before proceeding with the intercomparison study. Since, as previously mentioned, it was used Gafchromic films to determine the reference activity, to make sure that it was a reproducible method it was thus necessary to determine the Gafchromic film calibration curve for this purpose.

3.1.1. Source Preparation

The activity of the source inside the irradiator needs to be previously measured, both for calibration curve determination and for calibration testing. To accomplish this task, an approximate activity, close but slightly higher than the desired activity inside the irradiator (plus approximately 10% when measuring 1 mL, to compensate for the remaining activity in the syringe and needle cap), is measured with a 5 mL syringe (Braun Omnifix[®], 5 mL) using always the same type of needle (Braun, Sterican[®], 0.8 mm, 50 mm). The measuring time, t_m , is recorded and 1 mL is introduced inside the plastic test tube. Then, the remaining activity inside the syringe is measured in the dose calibrator and the time t_r is also recorded. The activity inside the plastic test tube at time t_m is calculated as:

$$(4) \quad A(t_m) = A_m - A_r \exp\left(\ln 2 \frac{(t_r - t_m)}{\tau_{1/2}}\right)$$

where A_m is the activity measured inside the syringe at time t_m and A_r is the measured activity inside the syringe at time t_r .

The plastic test tube is then placed inside the irradiator at instant t_0 ($t = 0$ s), being also recorded this time. The final calculated activity inside the irradiator at time t_0 is finally calculated as:

$$(5) \quad A(t_0) = A(t_m) \exp\left(-\ln 2 \frac{(t_0 - t_m)}{\tau_{1/2}}\right)$$

3.1.2. Calibration Curve

The principle inherent to determine Gafchromic measurements was the follow: If a point source whose activity is a function of time, $A = A(t)$, is located at a distance d from a dose measurement location, the total dose rate dD/dt at that point can be written as:

$$(6) \quad \frac{dD}{dt} = \frac{A(t) \Gamma}{d^2}$$

where Γ is the gamma constant of the radioisotope being considered ($\text{Gy m}^2 \text{Bq}^{-1} \text{s}^{-1}$). On integrating the above equation, one obtains:

$$(7) \quad D = \frac{\Gamma}{d^2} \int_0^T A(t) dt = \frac{\Gamma}{d^2} \tilde{A}; \quad D(0) = 0; \quad \tilde{A} = \int_0^T A(t) dt$$

where $\tilde{A}$ is the cumulated activity of the source over a period of exposure time, T .

If a number n of spatially distributed measurement points is considered ($i = 1, \dots, n$), one has a distribution of doses over these points equal to:

$$(8) \quad D_i = \frac{\Gamma}{d_i^2} \int_0^T A(t) dt = \frac{\Gamma}{d_i^2} \tilde{A}$$

where d_i is the distance from the point source to the measurement point, i .

Considering a number N of point sources, ($j = 1, \dots, N$), one can write the dose at any given measuring point i as D_i :

$$(9) \quad D_i = \sum_{j=1}^N D_{i,j} = \tilde{A} \sum_{j=1}^N \frac{\Gamma}{d_{i,j}^2}$$

where $D_{i,j}$ is the dose at point i from all j sources.

This can be extrapolated to a continuous source distribution and an arbitrary distribution of dose collecting points. Equation 5 means that in the presence of a finite-size source with an arbitrary geometry, if we choose an arbitrary number of dose points (such as a plane), the dose in any of the points within this plane is only proportional to the cumulated activity $\tilde{A}$ if the collecting points geometry ($d_{i,j}$) and the radioisotope are considered to be constant over time. Thus, if the geometry of the source is fixed, with a constant volume and shape over the time of exposure, we can measure on a plane located in the vicinity of a point located at position (x,y):

$$(10) \quad D_i \propto \tilde{A}$$

meaning that at any given point i (x, y), the dose will be dependent on the initial activity $A(0)$ and the final activity $A(T) = \exp(-\ln(2) \times T/t_{1/2})$ after an irradiation period T (where $t_{1/2}$ is the half-life of the considered radioisotope).

When irradiated by a given dose D , a Gafchromic XRQA2 film will show a change in its reflectance, R (and also in the mean pixel value, pv , after

digitalization in reflection mode on a Epson Expression® 10000 XL flatbed scanner), that can be described by a response function $f_1(D)$ so that:

$$(11) \quad pv = f_1(D) \propto R$$

We can thus calculate the net optical density $netOD(D_i)$ for every point of the radiochromic film plane:

$$(12) \quad netOD(D_i) = \log_{10} \left(\frac{pv_0}{pv} \right) = \log_{10} \left(\frac{pv_0}{f_1(D_i)} \right) = \log_{10} \left(\frac{pv_0}{f_1(\tilde{A} \sum_{j=1}^N \frac{\Gamma}{d_{i,j}^2})} \right)$$

where pv_0 is the mean pixel value of an unexposed reference film. Considering a fixed geometry, i.e. $d_{i,j}$ are fixed over time during all the irradiation time, one can write:

$$(13) \quad netOD(D_i) = \log_{10} \left(\frac{pv_0}{f_1(\tilde{A} \sum_{j=1}^N \frac{\Gamma}{d_{i,j}^2})} \right) = f_2(\tilde{A})$$

that is,

$$(14) \quad netOD \text{ (at any given point i)} = f_2(\tilde{A})$$

The function f_2 is the calibration curve of the film, relating the net optical density, $netOD$, and the cumulated activity, $\tilde{A}$. The calibration curve can then be determined by irradiating the film during a period of time (e.g. 24 hours), calculating the cumulated activity $\tilde{A}$, then measuring pV_0 for a non-irradiated film and the resultant pV for the irradiated film. This enables us to calculate the $netOD$ at any point of the film and then plot $netOD(\tilde{A})$. Since the measurement of the $netOD$ at a single point is not possible, a limited area is chosen where the $netOD$ is approximately constant and with a ROI as small as possible to avoid $netOD$ non-uniformities.

The calibration curve is a graph that provides an empirical relationship between the reading obtained with the equipment and the analytical value of what is being measured. In this case, provides the mathematical relationship between the degree of film darkening and the cumulated activity to which it was exposed. To obtain that, it was thus necessary to expose several films with different cumulated activities (ranging the initial activity of the sample or the exposure time) so that covers the entire calibration curve, enabling the determination of the mathematical equation that correlates these two parameters. Several radiochromic films were irradiated with different activities and 1 mL of $^{99m}\text{TcO}_4^-$ solution, maintaining approximately the same irradiation time, $t_{exp} \approx 24$ hours. Although the irradiation time could be varied, t_{exp} was measured with an accuracy of 30 seconds (0.035%). The cumulated activity $\tilde{A}$ was calculated using equation 7. The source volume and the irradiator geometry was chosen so that: a) the activity necessary to irradiate the radiochromic film during 24 hours could be handled safely (typically 740 MBq), and b) the resultant cumulated activity could be within a convenient region of the calibration curve (approximately linear region far from saturation and with a appropriate sensibility with high signal noise ratio, as will be shown later).

Since irradiated Gafchromic films present a slight non-uniformity due to the irradiator design and source position relative to the film plane (employment of a test tube filled with the radioactive source, figure 7, it was necessary to test the ROI size to be drawn during the film imaging processing (carried out here with the open source software *ImageJ*) and achieving the most reproducible $netOD$ values possible. Since the test tube has a cylindrical geometry, an increase of the $netOD$ in the film central region was noticed, due to the increase of the radiation exposure due to the change in d^2 term in equation 13. This is more evident for a cumulated

activity interval between 1 and 3×10^{13} far from lower dose (poorly exposed films) and film saturation region (highly exposed films). Therefore a circular ROI was chosen, centered in the middle of the film with a small area (58.7 mm^2) to minimize noise effects ^[Woods and Baker, 2003] and to cover a fairly constant *netOD* of the film. This ROI size was the one used to obtain the calibration curve and to perform all the measurements involved in dose calibrator comparisons.

From the *netOD*($\tilde{A}$) we can now fit a calibration curve. The function used was:

$$(15) \quad \text{netOD}(\tilde{A}) = \alpha_1 \left(1 - e^{-\frac{\ln 2}{\beta_1} \tilde{A}} \right) + \alpha_2 \left(1 - e^{-\frac{\ln 2}{\beta_2} \tilde{A}} \right) + \alpha_3 \left(1 - e^{-\frac{\ln 2}{\beta_3} \tilde{A}} \right)$$

The parameters α_1 , α_2 , α_3 , β_1 , β_2 and β_3 were adjusted to fit the experimental points by a non-linear least squares model. The resultant curve can be seen in figure 8 as well as the experimental points used in the fitting.

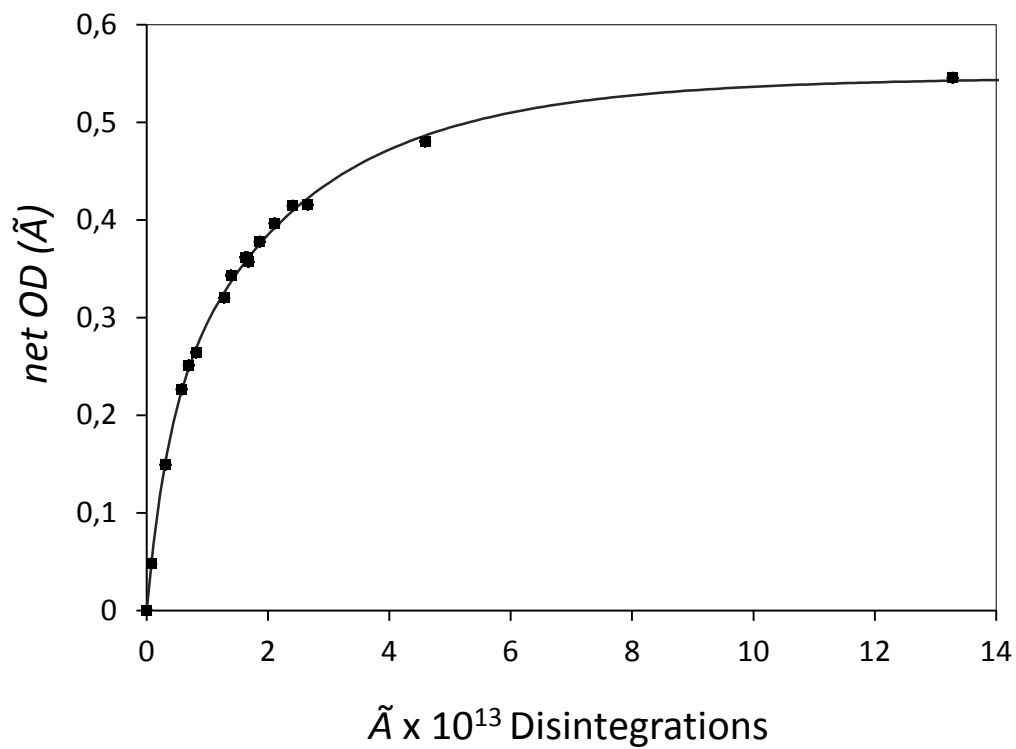


Figure 8 - Calibration curve obtained from the irradiation of several radiochromic films (with 1 mL of $^{99m}\text{TcO}_4^-$ solution with different activities and irradiation time, $T \approx 24$ hours) and experimental points.

Figure 9 depicts the percent deviation from every experimental point relative to this curve. As can be seen, this function fits all the range of the considered cumulated activity (from 0 to 14×10^{13}) reasonably well. It can also be seen that the deviation of the experimental points is higher for lower $\tilde{A}$.

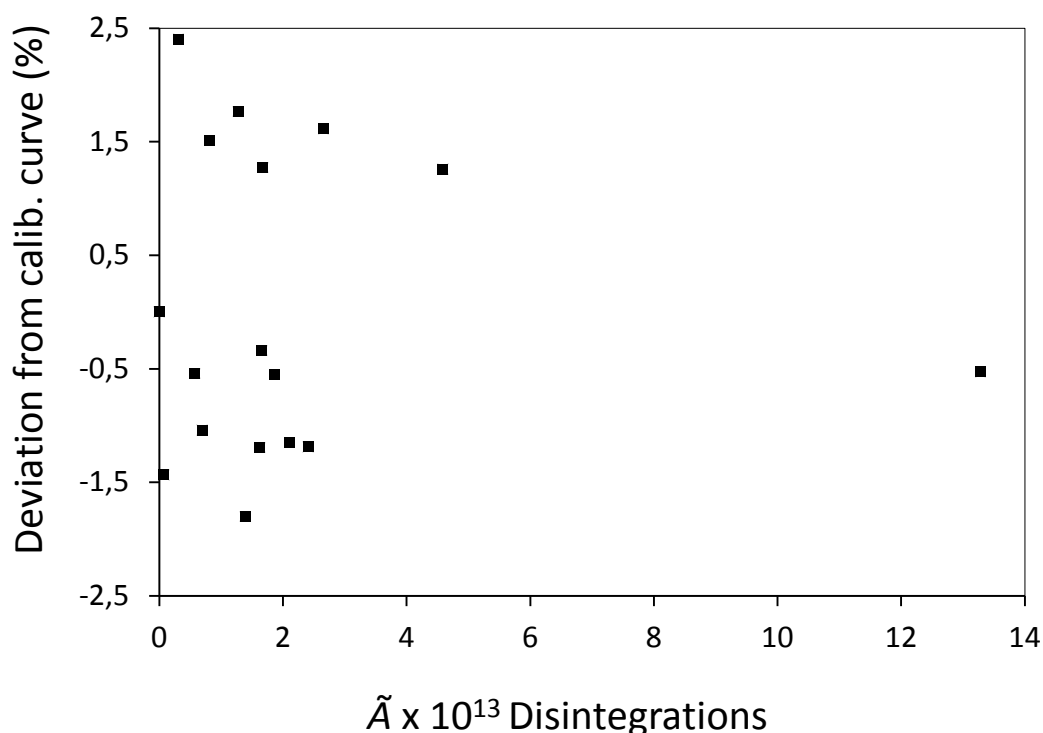


Figure 9 - Percent deviation of the experimental points from the calibration curve.

3.2. Radionuclide Calibrators Intercomparison

As has been aforementioned, once the calibration curve was determined for fixed irradiator geometry and a film exposition to $^{99m}\text{TcO}_4^-$ with a standardized technique, the final purpose in this thesis, an intercomparison of radionuclide calibrators, can be performed.

This innovative methodology is more cost effective, practical and can be used for all types of radioisotopes used in Nuclear Medicine, even the short half-life radioisotopes, since it is only necessary to mail the irradiator plus detailed procedure instructions to a distant Nuclear Medicine center to be exposed using a locally prepared source, obtained under the same conditions as the radiopharmaceuticals used in the center daily practice. Therefore, inferences can be drawn to the practices of each center as well as no longer exists concerns with transportation of unseal radioactive sources and the rapid radioactive decay of the

isotope in question which implies carry out the process in the same day (impossible when the assessment center and the center surveyed are distant from each other).

The procedure adopted for conducting the intercomparison study was divided in four stages: irradiator preparation in the assessment center, mailing the material to the surveyed center, performing the measurements in the surveyed center and sending back the material to the assessment center.

In the first stage, the irradiator is prepared. The test tube support should be placed inside the outer cylinder and the Gafchromic films and the acetate film in the space between the test tube support and the adjustable cap, as close as possible to the test tube support, figure 7.

Then, the surveyed center should be notified about the study and an employee should be nominated to carry out the measurements, preferably the responsible for the radiopharmacy. The irradiator, test tube, syringe and needle should be mailed as well as detailed procedure instructions to the distant Nuclear Medicine center.

After receiving the material, the responsible nominated should first read the procedure instructions (appendix 1) and then perform the measurements which consists in withdrawn from the eluate obtained from the generator $^{99}\text{Mo}/^{99m}\text{Tc}$ in that day, a certain activity of ^{99m}Tc (around 740 MBq). Afterwards, the volume of the syringe filled with saline solution to 1 mL should be measured with the evaluation target radionuclide calibrator to determine the activity. After documenting the exact activity and measurement time, the radioactive solution should be introduced in the test tube (provided by the assessment center), placing the syringe back into the radionuclide calibrator to determine the residual activity, thereby obtaining the precise activity in the test tube, equation 4. Thereafter, the test tube should be introduced in the irradiator (designed by us) which had already the Gafchromic films, registering the exact time of this procedure. The irradiation starts when the tube is introduced into the irradiator and ceases when it is removed, about 24 hours after initiating the exposure.

The participants should sent back the irradiator to the assessment center for digitalizing the films using a dedicated scanner (EPSON Expression 10000XL), and subsequent processed to determine the corresponding *netOD*, to be

compared with a reference value obtained from the previous measured calibration curve, figure 8. The differences between the measured OD and the calibration curve $OD(\tilde{A})$ can be attributed to the initial activity (dose calibrator read-out), or to the errors associated with the Gafchromic XRQA2 measurement, which allows then the comparison of both devices.

Until the date of thesis submission, it was not been perform any intercomparison where the material was sent and the measurements were carried out by someone from the distant center. However, a preliminary study was conducted with two dose calibrators. The first one, a Capintec CRC-12R, which was in the research center of IPO-PORTO and a second radionuclide calibrator, a Lemer Pax last calibrated in 2011 in Nuclear Medicine department of the Hospital de Santo António in Porto. In both cases, the measurements were carried out by us, not delegating the task to the service responsible for the radiopharmacy since this was a preliminary study. This help to demonstrate how this method can be easily used and what its limitations are, as will be explained forward.

Chapter 4

Results

4. Results

4.1. System Experimental Characterization – Error Sources

To validate this innovative methodology it was necessary to test it and check all possible error sources associated to all the phases involve in it application. Thus, there were analyzed the errors inherent to the radioactive source, to the Gafchromic films, to the scanner and to the image processing. In table 3 are presented the irradiations performed in the system experimental characterization with a 24 hours t_{exp} and 1 mL volume.

Table 3 – Irradiations with $t_{exp} = 24$ hours and $V = 1$ mL.

Irradiation Number	A_0 (MBq)	$\tilde{A} \times 10^{13}$ (Disintegrations)
1	823,99	2,41
2	637,88	1,86
3	436,97	1,28
5	278,61	0,81
6	25,53	0,07
7	106,56	0,31
8	1571,02	4,59
9	197,58	0,58
10	574,24	1,68
11	4547,30	13,28
12	238,28	0,70
13	569,43	1,66
14	721,50	2,11
15	475,82	1,39
16	558,70	1,63
18	909,09	2,66

4.1.1. Error Sources Inherent to the Radioactive Source

4.1.1.1. Exposition time

The majority of the irradiations have a 24 hours t_{exp} . (table 3). Although to test the exposition time influence in the irradiation process, there were obtained five irradiations with more than 24 hours, table 4.

Table 4 - Irradiations with $t_{exp} > 24$ hours and $V = 1$ mL.

Irradiation Number	A_0 (MBq)	t_{exp} (sec)	$\tilde{A} \times 10^{13}$ (Disintegrations)
4	268,62	89460 (≈ 25 hours)	0,79
17	1070,78	518400 (≈ 6 days)	3,34
19	894,66	169260 (≈ 2 days)	2,78
20	357,42	333480 (≈ 3 days)	1,11
21	545,38	4320000 (≈ 50 days)	1,70

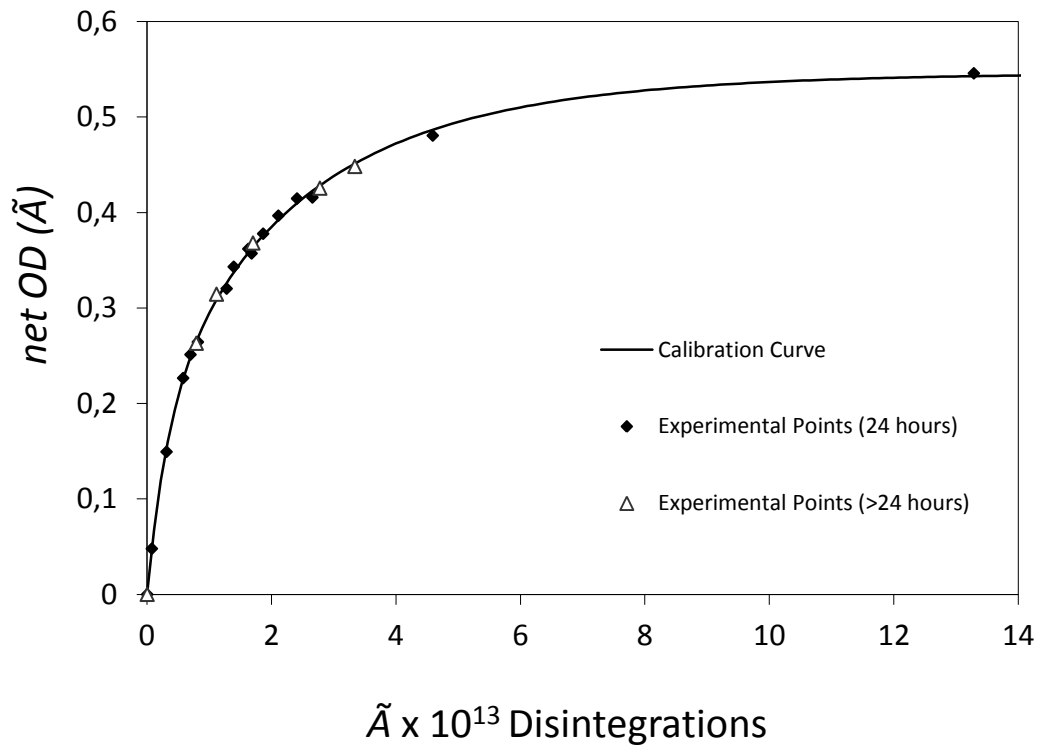


Figure 10 - Calibration curve obtained from the irradiation of several radiochromic films (with 1 mL of $^{99m}\text{TcO}_4^-$ solution with different activities and irradiation time, $T \approx 24$ hours) and experimental points acquired with a 24 hours t_{exp} and experimental points acquired with a more than 24 hours t_{exp} .

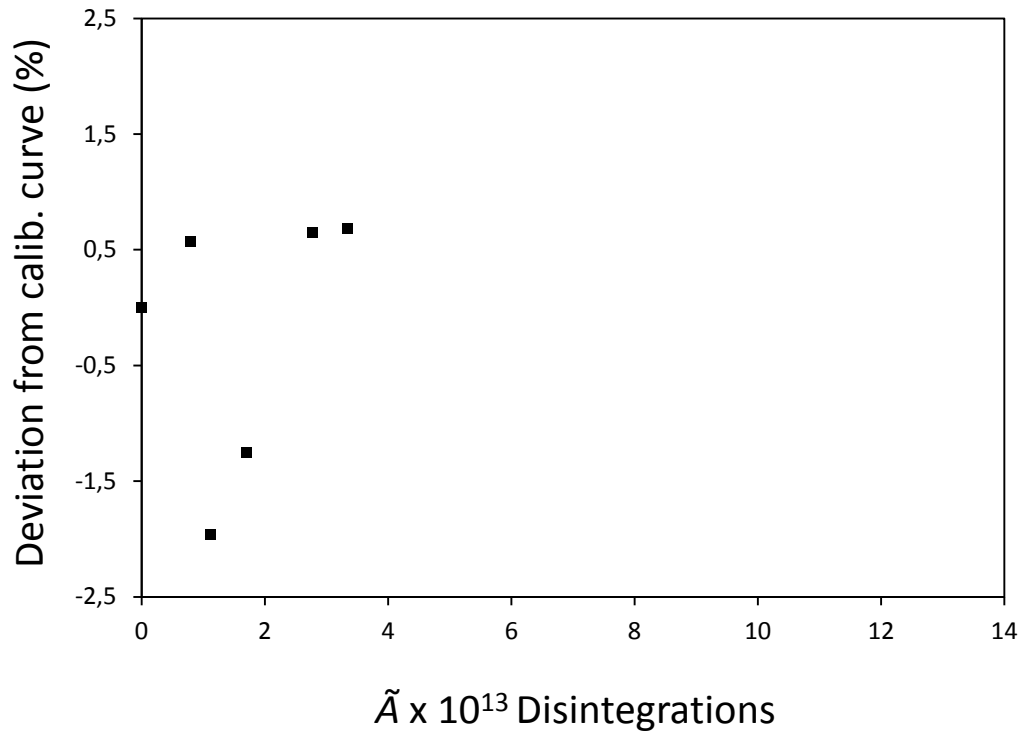


Figure 11 - Percent deviation of the experimental points acquired with a more than 24 hours t_{exp} from the calibration curve.

The major deviation to the calibration curve is -1.9% which is under the major deviation for the experimental points obtained with a 24 hours irradiation period.

4.1.1.2. Asymptote Maximum Cumulated Activity Achievable With Any Given Activity

By examining the table 4 its visible that even with high t_{exp} , the cumulated activity cannot be increase due to the radioactive decay reach a *plateau* which is demonstrated by figure 12.

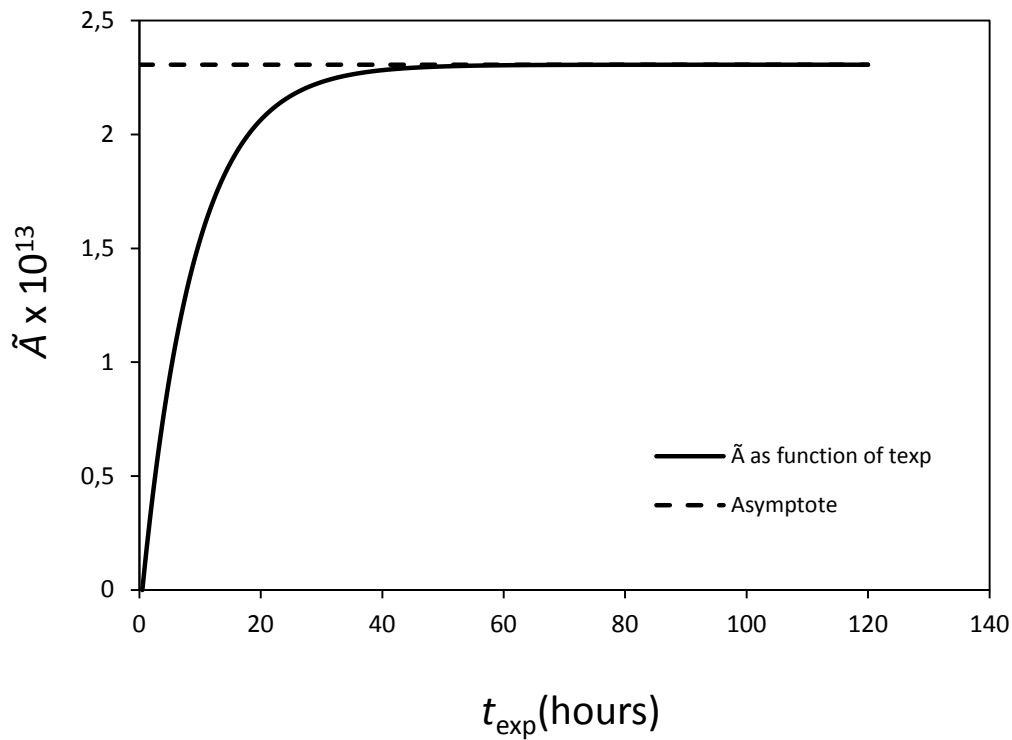


Figure 12 – $\tilde{A}$ as function of t_{exp} for $A_0 = 740$ MBq initial activity, and the time asymptote for that A_0 .

For an initial activity of 740 MBq, this plateau is reached 67 hours after initiating the irradiation with an asymptote of $2,31 \times 10^{13}$.

Therefore, to achieve a certain cumulated activity it should be especially taken into account the source initial activity rather than the exposure time, since approximately 48 hours the *plateau* is reached.

4.1.1.3. Source Volume Effect

To estimate the uncertainty due to the source volume measurement, several measurements of the $\text{netOD}(V)$ were performed with different volumes, table 5.

Table 5 - Irradiations with $t_{\text{exp}} = 24$ hours and different volumes.

Irradiation Number	Volume (mL)	A_0 (MBq)	$\tilde{A} \times 10^{13}$ (Disintegrations)
22	2	990,12	2,95
23	0,4	890,59	2,60
25	0,2	633,07	1,86
26	1,4	762,94	2,23

The percent variation from the expected point around 1 mL (relative to the calibration curve) is showed in figure 13.

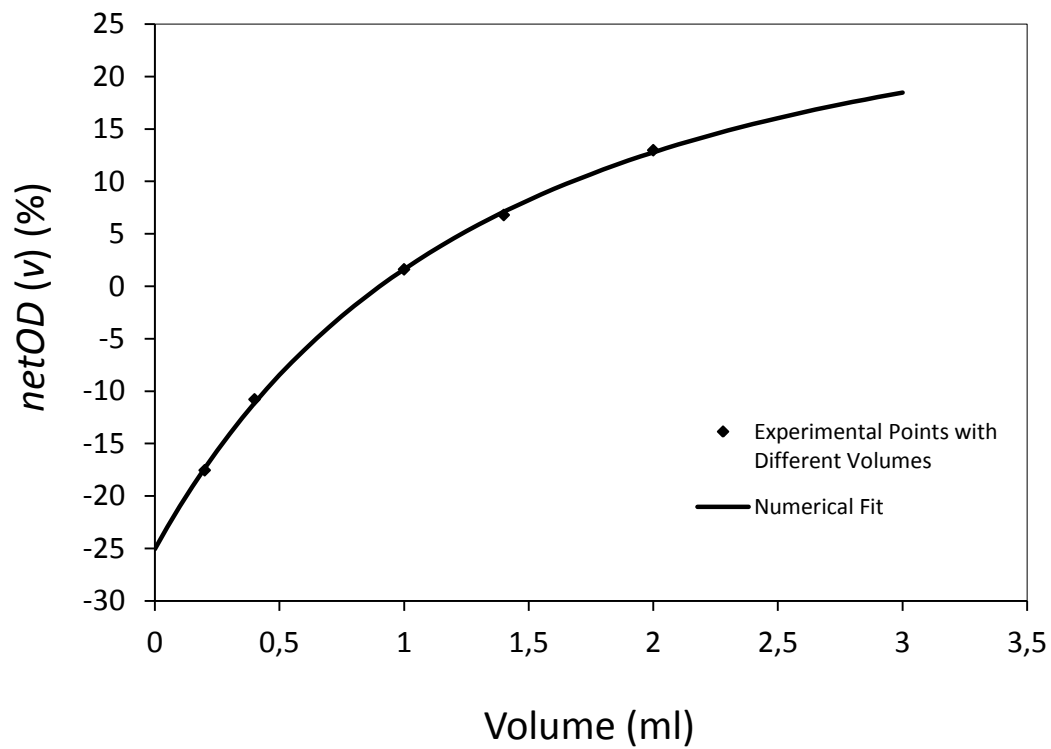


Figure 13 - Percent deviation from the calibration curve of netOD obtained using different volumes (0,2; 0,4; 1; 1,4 and 2 mL).

The following expression was fitted to the experimental points:

$$(16) \quad netOD(V) = \frac{k_1}{(V + k_2)^2} + k_3$$

where k_1 , k_2 , and k_3 are adjustable parameters and reflect the increasing average distance of the source center of mass to the film plane as the volume increases (with a $1/d^2$ dependence term) and the change in the geometrical and attenuation conditions. The volume uncertainty ($1 \text{ mL} \pm 0.05 \text{ mL}$) corresponds to a *netOD* error of 0.8% (taken from the derivative of *netOD*(*V*) at *V* = 1 mL). Notice that the percent volume error decreases with volume increase, and increases with volume decrease, as can be easily seen in figure 13.

4.1.2. Error Sources Inherent to the Film

4.1.2.1. Optical Density Homogeneity

Due to the irradiator geometry (use of test tube), the films central region has a higher radiation exposure than the peripheral region. This leads to a *netOD* increase in the central region, therefore to non-uniformities of the films.

In order to study this error source all irradiated films were subjected to image processing with a small ROI (0.091 inches) in order to include only the central region and a wider ROI (0.451) to encompass the entire film, figure 14.

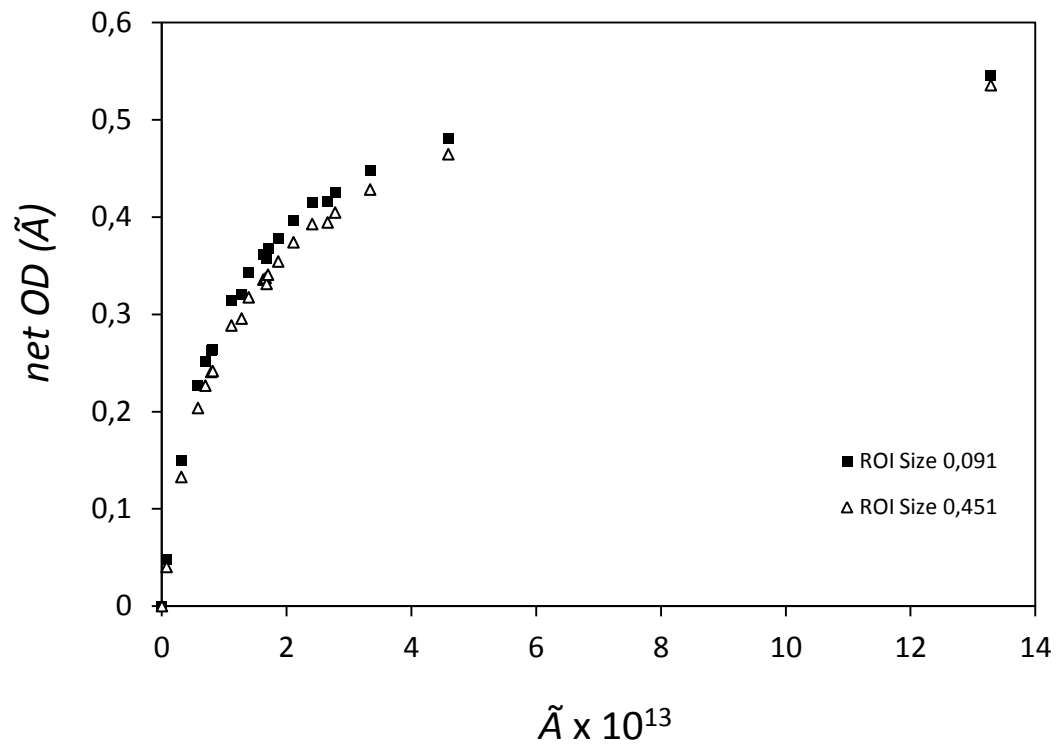


Figure 14 - $netOD(\tilde{A})$ obtained using a ROI size of 0,091 inches and 0,451 inches.

Is visible a $netOD$ undervaluation when is used a ROI diameter size of 0,451 inches since de pv (mean pixel value) obtained is a average value of all ROI, which for a wider ROI will include less exposed regions that should not be included.

4.1.3. Error Sources Inherent to the Scanner

4.1.3.1. Effects of Scanning Resolution

To calculate this error it was performed scans to three irradiated films (irradiation six, eleven and fifteen) with different scanning resolution, as is shown in figure 15.

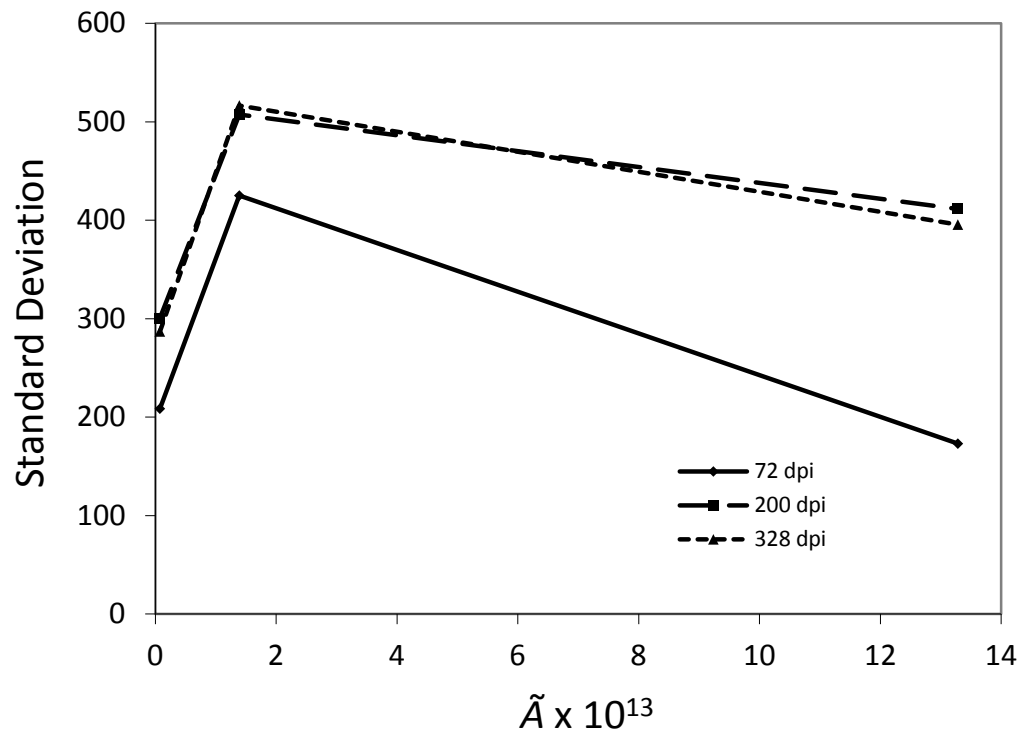


Figure 15 – p_v standard deviation as function of scanning resolution.

As can be seen, there is a decrease of p_v standard deviation for a 72 dpi (dots per inch) scanning resolution which may imply that this resolution induces a image blurring.

4.1.3.2. Effects of Film Position During Scan

a) Transversal Resolution

The scanner transverse resolution can be an important source of error to be taken into account. To evaluate this source of error there were performed successive scans along the scanner transverse line, figure 16.

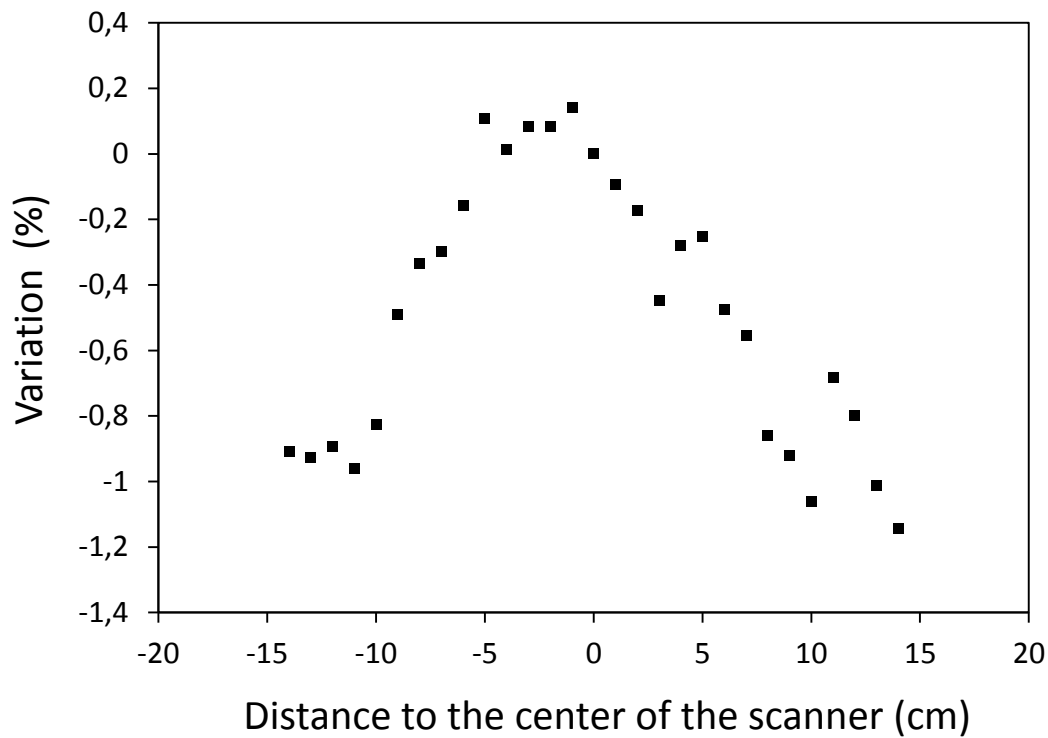


Figure 16 - Percent deviation of p_v to the p_v obtain in the scanner center along the scanner transverse line.

It can be noticed an abrupt negative variation as the scans are taking place on the scanner periphery, which may even reach a deviation of -1.3%.

b) Film Orientation

It is known that the mean pixel value varies with scan orientation relative to the film [Alnawaf *et al.*, 2010a]. In the present case, the error associated with this effect was evaluated in the region of interest (740 MBq/24h; $\tilde{A} \sim 2.16 \times 10^{13}$). To evaluate the percent variation, several scans with angles $\phi = 0^\circ, 45^\circ, 90^\circ, 135^\circ, 180^\circ, 225^\circ, 270^\circ, 315^\circ$ and 360° were performed. The results can be seen in figure 17.

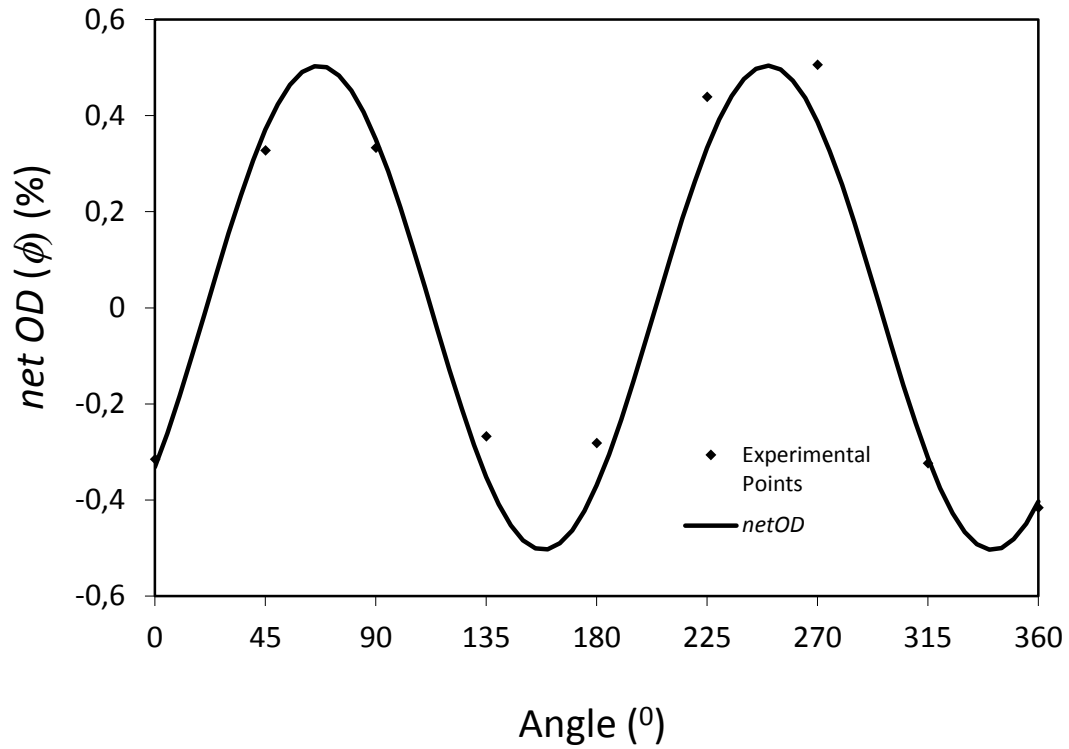


Figure 17 - Percent deviation of *netOD* with the angle varied during digitalization.

The following expression was fitted to the experimental points:

$$(17) \quad netOD(\phi) = a \sin \left(b \phi \frac{\pi}{180} + c \right)$$

where *a*, *b*, and *c* are adjustable parameters. A 0.5% error was determined due to scan orientation.

4.1.3.3. Scanner Reproducibility

Another source of error is the scanning reproducibility. This error was quantified by carrying out multiple measurements of the same film in the same scanning position and determining the corresponding pv .

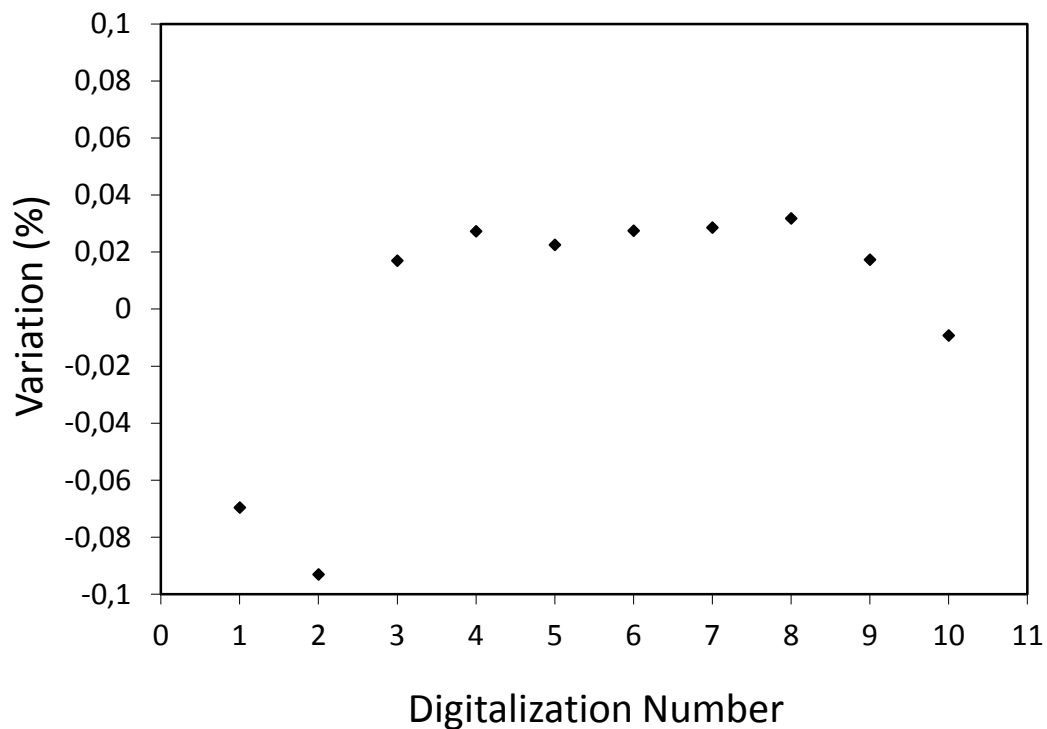


Figure 18 - Percent deviation of pv for each digitalization to the average pv .

The scanner reproducibility error was found to be less than 0.1%.

4.1.3.4. Scanner Delay Effect

Closely related to the preceding source of error is the interval between scanner switching on instant and the instance of digitalization. To obtain this error value it was carry out eight scans of the same film in the same position with a interval of 2

minutes between them, since the moment the scanner was switch on, as can be seen in figure 19.

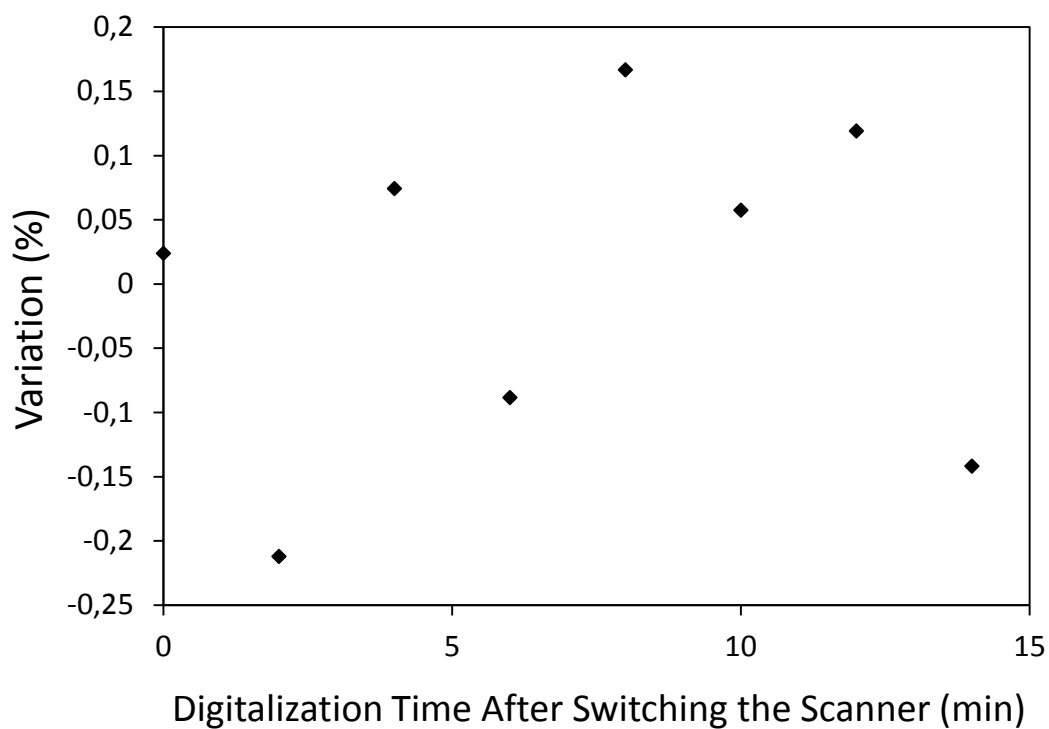


Figure 19 - Percent deviation of *netOD* for each digitalization time to the average *netOD*.

This source of error added an additional error of 0.2%.

4.1.4. Error Sources Inherent to the Image Processing

4.1.4.1. Effects of ROI Size

The last source of error is the ROI diameter size. This error was quantified by carrying out different image processing in concern to ROI size to three films irradiated (irradiation six, eleven and fifteen), shown in figure 20.

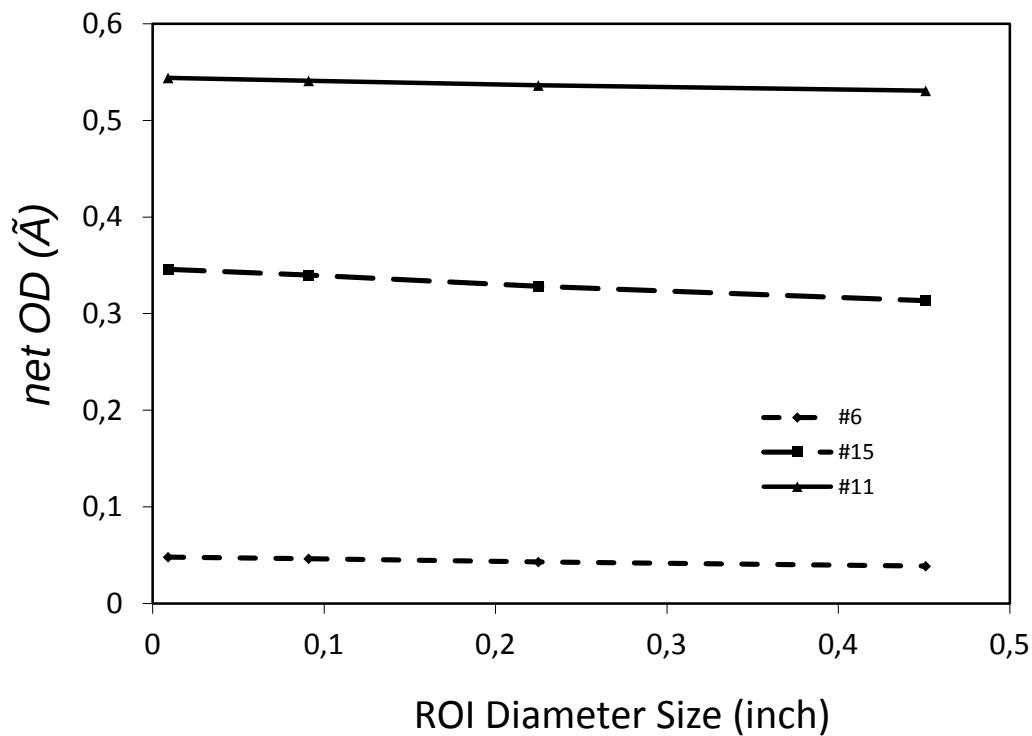


Figure 20 – *netOD* obtained for three film irradiation using different ROI diameter.

It is noticeable an undervaluation of *netOD* with the increasing in ROI diameter, which is more evident for the intermediate $\tilde{A}$ (irradiation 15).

4.2. Preliminary Results of the Intercomparison Study

After validating the method it was then conducted a preliminary intercomparison study in which it was evaluated two radionuclide calibrators. Since this was a preliminary study, all the measurements were performed by us.

The first calibrator surveyed was a Capintec CRC-12R which is on the IPO-PORTO Research Center. The other radionuclide calibrator, a Lemer Pax, is in Hospital de Santo António in Porto.

Table 6 – Surveyed Calibrators.

Surveyed Calibrator	A_0 (MBq)	t_{exp} (min)	Volume (mL)	$\tilde{A} \times 10^{13}$ (Disintegrations)	Equipment Error (%)
Capintec CRC-12R	890,59	86400	1	2,60	3,5
Lemer Pax	826,58	86400	1	2,42	0,4

In both cases, the methodology adopted for preparing the irradiator and the radioactive source, measuring the activity and irradiating the films was mentioned in the chapter Methods and described in detail in appendix 1.

However, given the proximity between the Capintec CRC-15R, used to determine the calibration curve (located in Nuclear Medicine department), and Capintec CRC-12R (located in research center in the same hospital) the first surveyed calibrator, the activity measurement of the radioactive source used to assay the Capintec CRC-12R were also performed on the Capintec CRC-15R to verify the analytical deviation between both calibrators and if it is identical to the deviation obtained with *de netOD* results.

In figure 21 one can see the location of the two tested calibrators measurements in the face of the calibration curve.

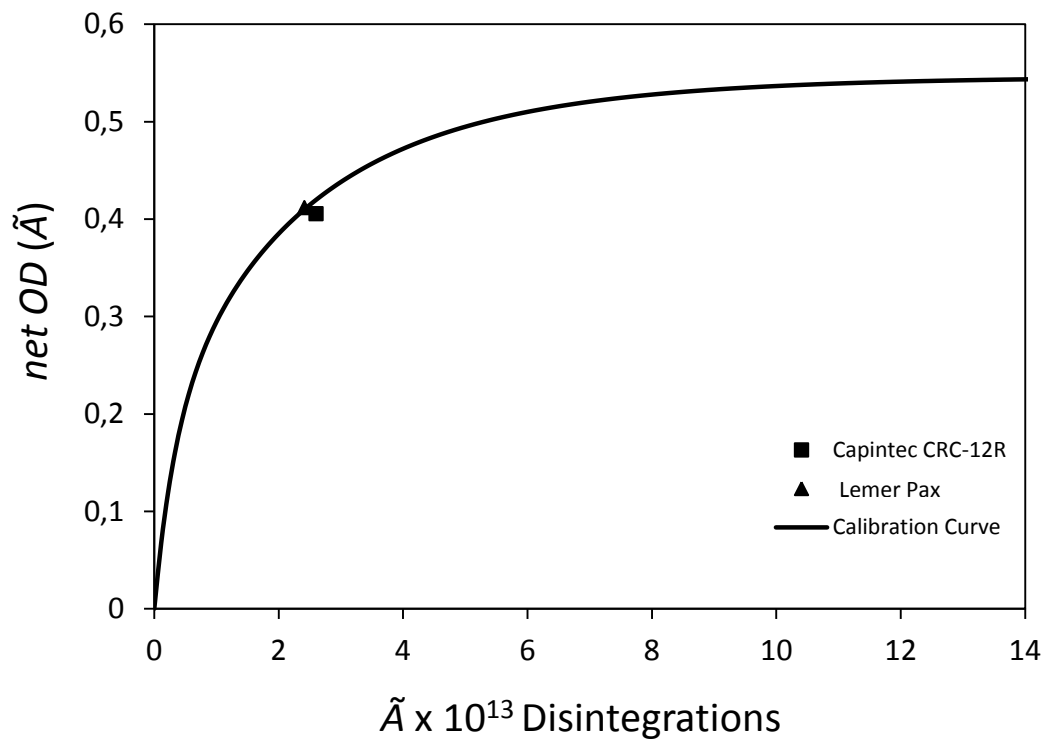


Figure 21 - Calibration curve obtained from the irradiation of several radiochromic films (with 1 mL of $^{99m}\text{TcO}_4^-$ solution with different activities and irradiation time, $t_{exp} \approx 24$ hours) and experimental points obtained for the two radionuclide calibrators surveyed.

In figure 22 is visible a deviation from the calibration curve of -3.50% for Capintec CRC-12R measurement and a 0.40% for Lemer Pax.

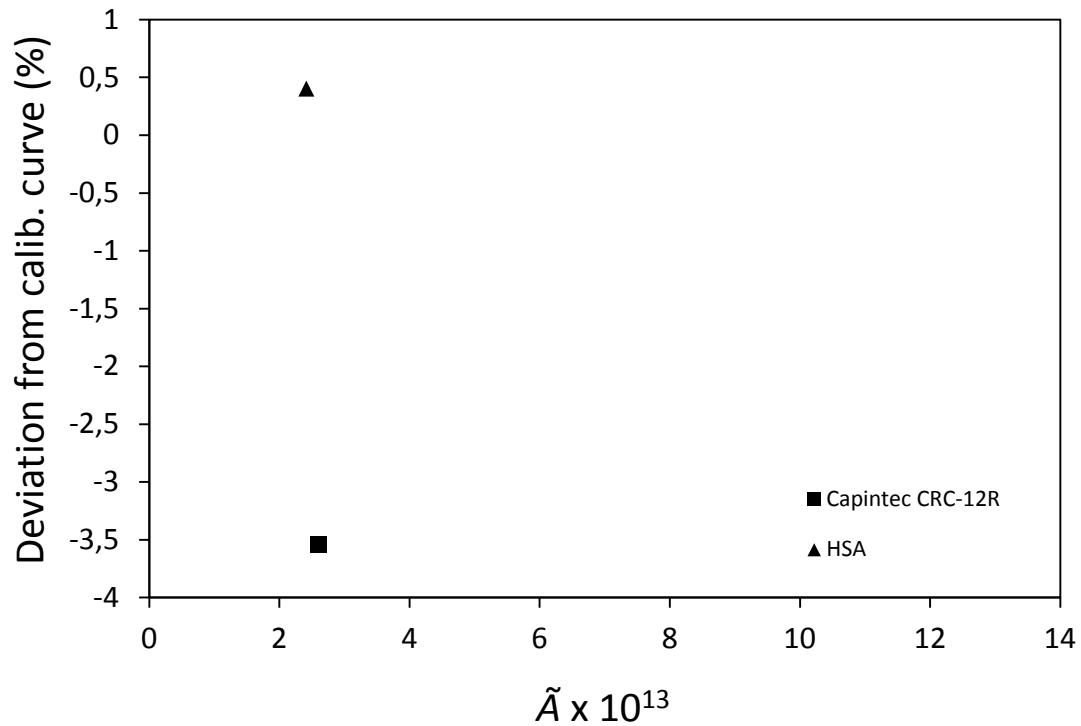


Figure 22 - Percent deviation of the experimental points obtained for the two radionuclide calibrators surveyed from the calibration curve.

To determine the analytical deviation between Capintec CRC-15R and Capintec CRC-12R (the surveyed calibrators) it was used the following expression:

$$(18) \quad Deviation (\%) = \frac{(A(t_m)_{12R} - A(t_m)_{15R})}{A(t_m)_{12R}} \times 100$$

where $A(t_m)_{12R}$ and $A(t_m)_{15R}$ were obtained using equation 4 with Capintec CRC-12R and Capintec-15R, respectively. The analytical value determined for Capintec CRC-12R deviation was 2.66%.

4.3. Discussion and Conclusions

The results obtained show that a calibration curve relating the *netOD* and the cumulated activity, $\tilde{A}$, can be established for the projected design of a Gafchromic film irradiated under the proposed geometry.

The expression chosen to define the calibration curve, equation 15 was found to fit the experimental values reasonably well, as can be seen in figure 9. Note that the fitting parameters should be changed if the geometry of the irradiator is also changed.

In what concerns to the error sources, as it was possible to verify, the t_{exp} when properly documented does not induce a significant error in the methodology adopted (for a $t_{exp} \approx 24$ hours with a maximum error of 30 seconds is 0.035%) once it was considered in the cumulated activity calculation, as well as A_0 introduced in the test tube. Nevertheless, It should be notice that to achieve a certain cumulated activity, for example $\tilde{A} \approx 2 \times 10^{13}$, it should be given more consideration to A_0 rather than the t_{exp} since after a few hours the asymptote is reached (approximately 70 hours after initiating the irradiation with $A_0 = 740$ MBq) and the cumulated activity cannot be increased due to the source radioactive decay, which in this case has a $t_{1/2} \approx 6$ hours.

The volume effect seems to be appreciable, as can be seen in figure 13, although we showed a wide variation from 0.2 mL to 2 mL. However, for the chosen volume (1 mL), the maximum associated error of ± 0.05 mL presents a low variation of the *netOD* (0.8%) for the designated syringes. A more precise way to decrease this source of error further would be to weigh the syringe before and after dispensing the solution into the plastic test tube. The mass of the liquid could be easily correlated with the volume with a much higher precision and the error could be made negligible. However, this procedure would cause an additional difficulty to the process of source preparation *in-situ* at the surveyed center, possibly inducing a higher risk of inaccuracy and consequently present a further source of error.

With regard to the film non-uniformities, it can easily be overcome by the use of a circular ROI centered in the middle of the film so that will only be included the more exposed region to radiation. The ROI diameter size used, in this case 0.091 inches and its positioning on the film, should always be the same for all the studies performed [Giaddui, 2012].

The resolution adopted in all studies was 200 dpi, since it seemed to be the best compromise between a higher resolution which can add considerable noise and very low resolution which induces an increase of image blurring [Giaddui, 2012; Niroomand-Rad *et al.*, 1998; Martisikova *et al.*, 2008].

As regards to transverse film positioning in the scanner, is denoted a strong dependence on the *netOD* value obtained along the scanner transverse line, which can induce an error of -1.3%. However, this error was overcome with the accomplishment of all scans in the scanner center.

The error associated with the film orientation was not eliminated. Although a small variation with orientation was noticed, a further error minimization can be achieved if the orientation of the film is recorded before irradiation and the digitalization is performed always in the same direction. Despite this is a feasible task, an associated error of $\pm 0.5\%$ seems acceptable when compared with other sources of error and with the magnitude of deviations we are aiming to detect.

The reproducibility of the scanner is another source of error that must be taken into account since it is something that transcends us, being this 0.1%. This also occurs with the scanner delay effect that cannot be ignored due to the utilization of the scanner by many Radiotherapy employees, which implies that it is not possible to determine when it was switched on. The error associated with this parameter is 0.2%

Therefore, in the expression used to calculate the overall error, it will be only included the sources of error that were not eliminated by manipulating the parameters associated to the methodology in question. These are: the film orientation during scan (0.5%), the scan reproducibility (0.1%), the scan delay effect (0.2%) and the volume uncertainty error for 1 mL $\pm$ 0.05 mL (0.8%).

The overall error calculation can be determined by the following expression [Taylor, 1997].

$$(19) \quad \frac{\delta A}{A} = \sqrt{\left(\frac{\delta A_1}{A_1}\right)^2 + \left(\frac{\delta A_2}{A_2}\right)^2 + \dots}$$

and was found to be approximately 1.0 %.

It is thus possible to draw the calibration curve and the experimental points with the calculated overall error, figure 23.

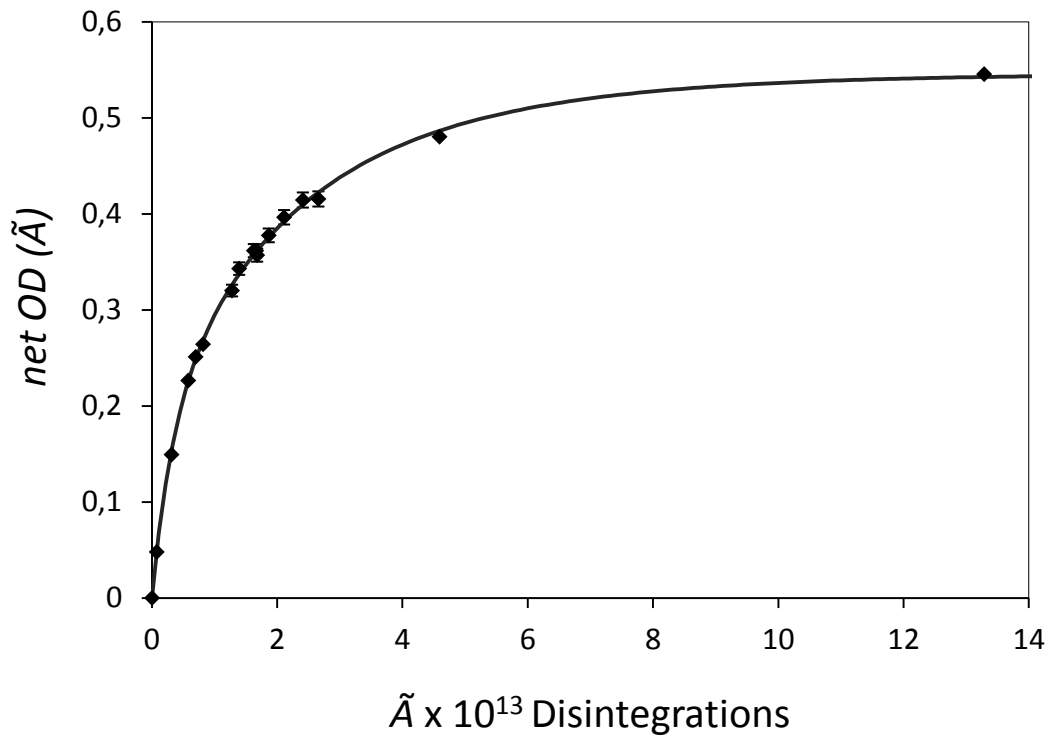


Figure 23 - Calibration curve obtained from the irradiation of several radiochromic films (with 1 mL of $^{99m}\text{TcO}_4^-$ solution with different activities and irradiation time, $t_{exp} \approx 24$ hours) and experimental points with total error bars in the region of interest around $\tilde{A} = 2 \times 10^{13}$.

From the percent deviation of each experimental point from the adjusted $netOD(\tilde{A})$, which can be seen in figure 9, one can notice that it does not exceed 2.5% at low cumulated activities. As the cumulated activity increases the percent deviation reaches 1.8% at the region where one selected to work (between 1×10^{13} and 3×10^{13}). This value, although higher than the one calculated using equation 19, correlates reasonably well with the most significant error sources noticed during this study. The observed higher error (1.8% against the calculated 1.0%) is probably related to other sources of error not yet identified. However, the difference is not

significant when compared with the maximum aimed error limits to be detected (10% for diagnostic scans [AAPM, 2012]).

To conduct the intercomparison study, the parameters chosen were: Gafchromic films irradiation with $V = 1$ mL of $^{99m}\text{TcO}_4^-$, with an $A_0 \approx 740$ MBq and $t_{exp} \approx 24$ hours; films digitalization in the scanner center in reflective mode with 200 dpi; films image processing with ImageJ using only the red component (more sensitive [Silva *et al.*, 2010; Alnawaf *et al.*, 2010a; Ohuchi, 2007]) with a ROI size diameter of 0,091 inches centered in the middle of each film.

The t_{exp} and the A_0 were chosen so that the value of cumulated activity was around 2×10^{13} because a relatively safe activity needs to be handled (approximately 740 MBq or 20 mCi) and the *netOD* region of the curve is far from saturation and above the low exposure region in which the associated errors would increase due to the digitalization process (lower signal to noise ratio).

About the results of the preliminary study, is visible that the percent deviation of the radionuclide calibrator Lemer Pax from the calibration curve is very small (0,4%), which can let us infer that if the radionuclide calibrator used to obtain the calibration curve had been recently subjected to calibration by the manufacturer, the radionuclide calibrator surveyed have a low associated error, being within the $\pm 5\%$ accuracy recommended by IAEA [IAEA, 2006] and $\pm 10\%$ recommended by ANSI [ANSI, 2004] and AAPM [AAPM, 2012]. However, Capintec CRC-12R from IPO-Porto has a higher deviation, around 3.5% (yet within the accuracy recommended) exceeding the value predicted analytically of 2.66%. This may occur due to the overall error of 1.0% owing to sources of error that cannot be eliminated.

In this paper we showed that the proposed methodology can be useful in the comparison of two dose calibrators using a ^{99m}Tc source entirely prepared in the surveyed center. This can be achieved by sending the irradiator and a set of syringe/needle ensemble with the same specifications as the ones used to obtain the calibration curve. In this case, the surveyed dose calibrator errors will exclude all the geometry errors associated with the syringe/needle geometry. Another possibility is to send the irradiator without the calibration syringe/needle information and to evaluate the whole result taking into account that this parameter can influence the observed result.

The methodology described here could be used by a National Metrology Institute laboratory to periodically survey several sites, specifically for ^{99m}Tc , the most common and widely used radioisotope in Nuclear Medicine. Moreover, the same methodology could be applied to very short-lived isotopes such as ^{18}F in FDG:PET. This could partially substitute the individual calibration, with lower costs, of dose calibrators, a practice that is always troublesome for Nuclear Medicine centers due to the need of equipment replacement during the absence period.

Chapter 5

Future Work and Method Development

5. Conclusion and Future Work

The methodology used in the development of this technique has shown to be feasible, have a low cost and can be easily reproducible with a low error associated, which makes it a potential methodology to perform radionuclide calibrators intercomparison studies. The ultimate aim is then to be used by a National Metrology Institute to periodically survey several sites so that it would be possible to make inferences about the overall performance of the radionuclide calibrators and the radiopharmacy practices in Nuclear Medicine centers national wide.

However, this requires that the radionuclide calibrator used to obtain the calibration curve, therefore the responsible for obtaining the standard $netOD(\tilde{A})$ values, has been recently subjected to calibration by the manufacturer or by the National Metrology Institute, which is not the case of the calibrator used. This means that a deviation between the values obtained in the different centers and calibration curve cannot be assumed as errors of the calibrators assayed, is thus merely comparative. Meanwhile, some more measurements will be made to other calibrators in order to demonstrate the potential of this methodology.

In the future, we intend to carry out new measurements to obtain a new calibration curve for the calibrated radionuclide calibrator and carry out the entire procedure described in the subchapter "Experimental Characterization System." This will make possible to take the $netOD(\tilde{A})$ values from the calibration curve as absolute values, allowing to infer if the measurements of the surveyed calibrator are within the accuracy recommended, thus enabling to perform the intercomparison of radionuclide calibrators study at the national level.

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Appendix

Appendix 1 – Protocol to sent to Nuclear Medicine departments surveyed

Inter-comparação de Calibradores de Dose em Serviços de Medicina Nuclear para a Energia do Isótopo ^{99m}Tc



FACULDADE DE CIÊNCIAS
UNIVERSIDADE DO PORTO

No âmbito de um projeto de investigação do Mestrado de Física Médica em parceria com o Grupo de Investigação de Física Médica e Proteção contra as Radiações Ionizantes do Centro de Investigação do Instituto Português de Oncologia do Porto Francisco Gentil, vem sendo desenvolvido um estudo de validação de uma nova metodologia para avaliação da *performance* de calibradores de dose. Esta recente metodologia vem assim permitir a avaliação deste equipamento sem que seja necessário o seu envio para fornecedor o que se torna inviável em diversos serviços que apenas possuem um calibrador de doses. A par do que já ocorreu em diversos Países, a fase final deste projeto visa um estudo de inter-comparação dos calibradores de dose a nível nacional.

Gostaríamos desde já de agradecer pela sua participação neste estudo, lembrando que todos os dados fornecidos serão mantidos em anonimato. Caso seja pretendido pelo departamento, no final do estudo os resultados obtidos com o seu calibrador de doses poderão ser fornecidos.

Material

Material cedido pelo centro de avaliação:

- Irradiador;
- Tubo de ensaio;
- Agulha de 0.8 x 50 mm;
- Seringa de 5 mL

Material fornecido pelo departamento de Medicina Nuclear:

- Luvas;
- Soro;
- Pertecnetato de Tecnécio;
- Relógio ou cronómetro a ser utilizado para TODOS os registos de horas durante o procedimento.

Procedimento

1. Acoplar a agulha e a seringa fornecidas e retirar uma atividade de 20 ± 2 mCi, do eluato obtido da eluição do gerador de $^{99}\text{Mo}/^{99m}\text{Tc}$;
2. Adicionar ao eluato retirado soro fisiológico, agitando o conteúdo para ambas as soluções se misturarem, até ser obtido um volume de 1 mL de solução;
3. Colocar a seringa com a solução radioativa no suporte do calibrador de doses e medir a atividade presente na solução;
4. Documentar a atividade e a hora exata a que tal ocorreu na folha em anexo e retirar a seringa do suporte do calibrador de doses;
5. Retirar o tubo de ensaio do irradiador;
6. Passar o conteúdo da seringa para o tubo de ensaio (1 mL) apenas com um movimento do êmbolo;
7. Colocar novamente a seringa no suporte do calibrador de doses para medir a atividade residual e registar a hora da medição na folha em anexo;

8. Introduzir o tubo de ensaio no irradiador registando novamente a hora exata na folha em anexo e fechar a tampa;
9. Mantendo o irradiador sempre na posição vertical e de preferência numa superfície plana, longe de quaisquer fontes externas (de preferência fora da radiofarmácia e em locais onde não permaneçam doentes injetados);
10. O irradiador deverá ser mantido nesse local cerca de 24 horas. Após este período dever-se-á abrir a tampa do irradiador e retirar o tubo de ensaio registando a hora exata deste momento. O tubo de ensaio deverá ser bem lavado e limpo e posteriormente colocado no irradiador e colocada a tampa.

Envio do Material

Parte do material fornecido pelo centro de avaliação, nomeadamente o irradiador e o tubo de ensaio, deve ser devolvido ao mesmo após conclusão do procedimento de irradiação. Para tal, o mesmo deve ser enviado por correio para o seguinte endereço:

Instituto Português de Oncologia do Porto Francisco Gentil, EPE

A/c responsável pelo estudo

Serviço de Física Médica

Rua António Bernardino Almeida

4200-072

Porto, Portugal

Folha a preencher durante as medições

Instituição avaliada: _____

Modelo do calibrador de doses: _____

Data da avaliação: ____/____/____

Atividade seringa (1mL): _____ mCi Hora: ____ : ____ h

Atividade residual na seringa: _____ mCi Hora: ____ : ____ h

Início da irradiação

Hora de colocação do tubo de ensaio no irradiador: ____ : ____ h

Fim da irradiação (24 horas depois)

Hora de retirada do tubo de ensaio do irradiador: ____ : ____ h