INSTITUTO SUPERIOR DE ENGENHARIA DO PORTO

MESTRADO EM ENGENHARIA COMPUTAÇÃO E INSTRUMENTAÇÃO MÉDICA

Otimização do modo de registo de dados durante a técnica de Perfusão Isolada dos Membros

ANA JORGE BRANCO MONTEIRO

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Optimization of data recording during Isolated Limb Perfusion Technique

Ana Jorge Branco Monteiro

A dissertation submitted in partial fulfillment of the requirements for the degree of Master of Science, Specialisation Area of Computing and Medical Instrumentation

Supervisor: Dr. Pedro Guimarães
Co-Supervisor: Dra. Vera Antunes

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Dedicatory

Another chapter of my academic life is over and I can only thank those who, during this long and arduous journey, supported and continue to support me unconditionally, who help me and believe in me, who gave me the strength to make this possible.

So, I begin by offering my deepest thanks to the Portuguese Institute of Oncology of Porto (IPO) for accepted and made this work possible.

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To all my friends and colleagues for their help and companionship.

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Abstract

Cancer is a disease in which the cells of our organism, due to mutations in their DNA, divide without control and acquire malignant properties and, during this process of uncontrolled division, invade other tissues and don't die. Cancer cells have the ability to spread through the body using the circulatory and lymphatic systems, giving rise to metastases. With regard to cutaneous neoplasms, the therapy chosen for surgically dispersed and unresectable metastases involved amputation of the sick limb, however, many complications and short time intervals between treatment and the appearance of new lesions were associated.

In 1957, an innovative technique emerges and proves to be extremely effective and avoids limb amputation: Isolated Limb Perfusion performed with Melphalan and TNF-α. The main objective of this procedure is to isolate the limb affected by the disease from the systemic circulation so that it is possible to administer very high doses of chemotherapy without any collateral damage. In this sense, it is necessary to have a control of blood leaks from the limb to the systemic circulation, in order to ensure that no other organ or tissue is compromised.

The Portuguese Institute of Oncology (IPO) of Porto is one of the worldwide institutions that practice this type of surgical interventions, reporting an annual increase in the number of occurrences year after year. Consequently, this progressive increase and coupled with the fact that this leak control is impractical and time-consuming, led this institution to join Instituto Superior de Engenharia do Porto (ISEP) to develop an application that, in combination with an extracorporeal counter equipment called Neoprobe Gamma Detector System is able to record the values obtained automatically and allow monitoring possible leaks.

Keywords: Isolated Limb Perfusion, Cancer, Nuclear Medicine, Radioisotope, Melphalan, TNF- α

Contents

List of Figures

List of Abbreviations and Symbols

AIDS	Acquired Immunodeficiency Syndrome
DNA	Deoxyribonucleic
FOV	Field of View
FWHM	Full Width at Half Maximum
GUI	Graphical User Interface
HDI	Human Development Index
HPV	Human Papillomavirus
IPO	Instituto Português de Oncologia
LET	Linear Energy Transfer
PHA	Pulse Height Analyzer
PMT	Photomultiplier
PSF	Point Spread Function
TAC	Axial Computed Tomography
TNF	Tumor Necrosis Factor

α	Alpha
β	Beta
γ	Gamma
$t_{1/2}$	Half-life
λ	Decay Constant

Chapter 1

Introduction

1.1 Context

Nowadays, there is no doubt that technology is evolving more and more rapidly, affecting people's daily lives in all aspects. The most diverse areas make use of technology since it facilitates certain procedures that, otherwise, would not be automatic and more susceptible to human error. Thus, in the area of health, the scenario is no different and increasingly depends on what technology has to offer in order to increase efficiency and decrease risks and costs (Steger 2017).

In medical practice, all health units depend on information about the science of care, patients' personal data, clinical history, care results, among others (Lazakidou and Siassiakos 2009).

In this sense, providing the necessary health care generally involves complex tasks and depends on a lot of information. Then, the need to use information systems arises, in order to improve the provision of these health services and the excellent performance of medical care (Lenz and Kuhn 2004).

With focus on the latter, information systems can be used, for example, in nuclear medicine procedures as a way to assist in the collection and recording of data necessary for monitoring therapy so that medical care is efficient and safe.

1.2 Problem Description and Motivation

Cancer is a disease in which cells of our organism, due to mutations in their DNA, divide without control and acquire malignant properties. During this process of uncontrolled division, they invade other tissues and don't die when they should. Cancer cells have the ability to spread through the body using the circulatory and lymphatic systems, giving rise to metastases (King and Robins 2006).

A curative treatment for cancer has not been found yet, although there are techniques that are better or worse according to the stage of the disease. Consequently, scientists have been trying to develop more efficient techniques for treatment, as well as improving living conditions for end-of-life patients.

In fact, in recent years, there has been a remarkable evolution in the understanding of the characteristics proposed for the development and treatment of cancer, and the search for the most effective therapy is still a constant challenge (Schulz 2005).

Nuclear Medicine is the health area that uses radionuclide sources for diagnostic and therapeutic purposes. It has been progressing and is related to the generation of images of physiological processes and, consequently, in the evaluation of the treatment of diseases, especially cancer, by means of radiopharmaceuticals.

Radiopharmaceuticals have several characteristics and they are specific for each clinical case and allow the visualization of processes in the body, organ functions and, even, the presence or absence of a specific cellular target. The importance of this type of exams has received increasing recognition. The main limitation of the increased use of nuclear medicine is the cost of treatment. The amount of radiation that the patient receives in a nuclear medicine exam is less than the radiation received in others, such as radiography or TAC (Glaudemans et al. 2015).

Thus, one technique that has been used in the treatment of cutaneous neoplasms is the Isolated Limb Perfusion which is applied to palliative patients and aims to improve their quality of life. The purpose of this therapy is to administer very high doses of chemotherapy only to the site infected with the disease. They use equipment that, connected to an intraoperative probe, reads the radioactive decay of the radioisotope previously injected into the patient, allowing control of possible blood leaks from the limb to the rest of the body. This procedure is carried out in an impractical way, where the records of these decays together with the hours of each one are recorded manually on an Excel sheet, every 15 seconds, for approximately 1 hour.

In this segment, this work is driven by the need to optimize this technique in order to make it an easier, simpler and more robust process.

1.3 Research Goals

According to the description of the mentioned problem and the underlying motivation, this dissertation's main contribution is the development of a software capable of recognizing the connection of the equipment used and, consequently, making the automatic acquisition of the radioactive decay of the radioisotope employed.

To achieve this goal, a review of the fundamentals of cancer and the techniques used until then as therapies are presented. The proposed software was developed using some technologies, such as Anaconda Navigator, which is characterized by being a graphical user interface, associated with Anaconda, which allows to create applications, Qt Designer and Arduino for running some tests.

1.4 Dissertation Structure

In addition to the Introduction (Chapter 1), where the topic and objectives of this dissertation are presented, the following list describes the content of the other chapters:

- *Chapter 2: The Burden of Disease and the Changing Task of Medicine* - The various health problems are exposed, as well as the way they were treated, from the beginning to the present. Likewise, an approach is taken on the concept of globalization and its consequences.

- *Chapter 3: Anatomical and Physiological Review* - The fundamentals of this disease are presented as well as the causes of its appearance. The concept of nuclear medicine and its diagnostic and therapeutic modalities are discussed.
- *Chapter 4: Isolated Limb Perfusion* - A description of the treatments proposed for this disease and a more exhaustive explanation of the currently preferred technique is performed. At the end, this chapter essentially aims to provide the basis for understanding the need for the optimization of cutaneous neoplasms therapy.
- *Chapter 5: Development of acquisition and control software* - This chapter covers the work done that meets the proposed objectives in order to optimize the method of recording the mentioned technique.
- *Chapter 6: PerControl: Implementation* - This chapter explains in detail the graphical interface developed in the optimized method of data acquisition.
- *Chapter 7: Conclusion and Future Work* - The main conclusions of this dissertation are presented, as well as some notes concerning the future work.

Chapter 2

The Burden of Disease and the Changing Task of Medicine

Since the beginning, the concept of health has been dependent on several factors such as social, economic and cultural status, and is therefore different for each person. In the same way, what was effectively considered a disease varied widely and attributed essentially to divine punishment for sinful acts (Scliar 2007). On the other hand, the existing problems of this time were typically angina, diarrhea, rump, high fevers, gunshot wounds, among others. Regarding the treatment of the disease, they practiced bleeding, which establishes the withdrawal of blood and were made based on ancient medical theories that assumed that blood, and other body fluids, were seen as "moods" that had to be maintained in balance so that the body remains healthy. They also used opium or sponges soaked in alcohol to ease the pain and to stop the bleeding they used a cautery (Jones, Podolsky, and Greene 2012).

In the 16th century the Renaissance emerged and with it the renewal of the arts and sciences. The surgery begins to evolve, despite being still risky due to poor hygiene conditions, which led to a low survival rate. It was only later, with the Industrial Revolution, that these associated problems, such as pain, infections and hemorrhages, were resolved. Morphological investigations also begin and, consequently, an increase in knowledge of organic functions (David, Wolfender, and Dias 2015).

In the 19th century, pandemics such as tuberculosis began to appear, but also gonorrhea, syphilis, scarlet fever and outbreaks of yellow fever and malaria. Concomitantly, advances in the field of chemistry have allowed plants to be examined in order to study their potential therapeutic effect. Pharmaceutical companies used plant extracts to produce crude therapeutic formulas, however, it was not until 1928 that penicillin was discovered by Alexander Fleming, which allowed the treatment of some problems such as scarlet fever, pneumonia and gonorrhea (Tan and Tatsumura 2015).

In the mid-twentieth century, heart problems, cancer and other chronic diseases started to take on a more dominant role, although infectious outbreaks such as legionnaires' disease, AIDS and encephalitis were recurrent. New concerns also arise due to the terrible consequences of the thermonuclear war in 1962, as well as the indolent but devastating effects of environmental pollution and climate change (1966-1989). To face this new reality, they began further investigations on natural products or secondary metabolites, i.e., organic compounds that are not directly involved in the growth, development and reproduction processes of organisms and often have an important role in inter-species plant defenses. Thus, there have been significant advances in drugs from microbial sources allowing the creation of new drugs (Jones, Podolsky, and Greene 2012).

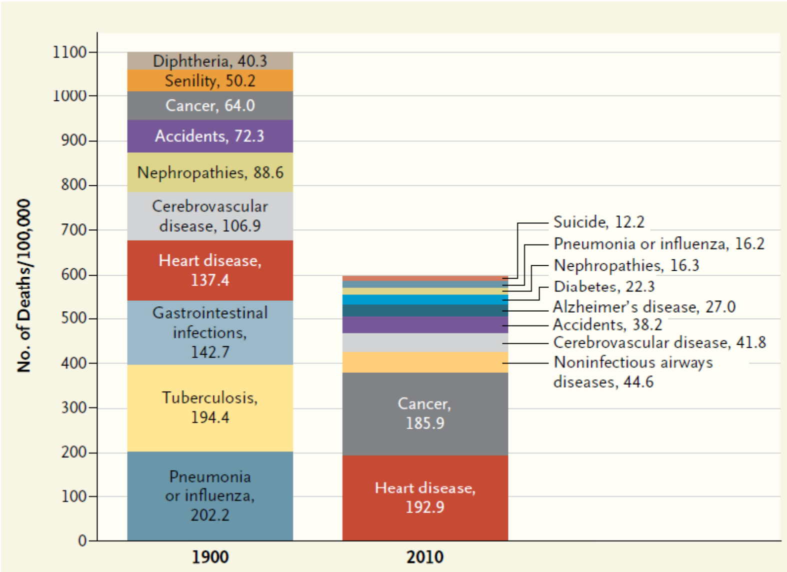

Figure 2.1: Most common causes of death between 1900 and 2010 (Jones, Podolsky, and Greene 2012)

2.1 Globalization

Nowadays, it is increasingly evident that globalization is leading to changes in health standards which are related to the progressive integration of the economy and society and guided by technological evolution, industrial evolution and new economic relations (Figure 2.2) (McMichael 2013). According to Manfred Steger, globalization is "the intensification of global social relations that link distant locations in such a way that local events are shaped by events that occur many kilometers away and vice versa." (Steger 2017).

At an economic level, it is essentially based on trade and the movement of capital across borders, which include the flow of goods, services and information. Economic globalization is an irreversible phenomenon for the world, since the expansion and integration of borders in the global market is continuous. At a social level, the most substantial impact has been on advances in technology and communication, which has resulted in deeper human interactions that have provided cultural exchanges in different nationalities and races. However, in terms of health, its effects are mediated by income, inequality, access to the health systems network, availability of sanitary and water facilities. Thus, globalization tends to affect developed countries more and better than the underdeveloped ones. (Jani, Joshi, and J. Mehta 2019).

2.2 Consequences of Globalization

Although there are several advantages inherent to it, approaching the rest of the world facilitates the spread of diseases (McMichael 2013).

In contrast, the population continues to age rapidly, as fertility rates have fallen to very low levels in most regions of the world and people tend to live longer. From another perspective, it reflects the longest-lasting human success (He, Goodkind, Kowal, et al. 2016).

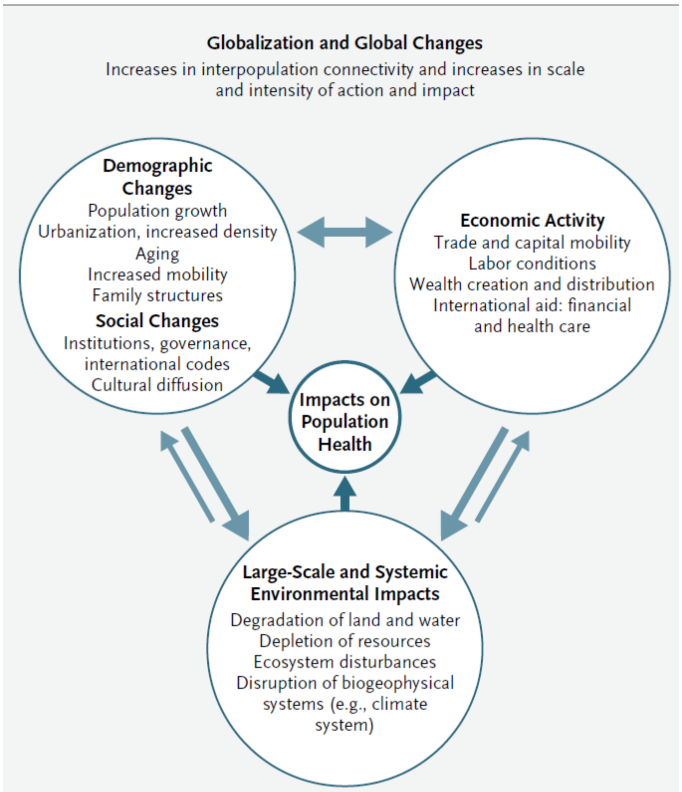

Figure 2.2: Repercussions of Globalization (McMichael 2013)

In general, the population tends to be increasingly aging in Africa and Asia, and researchers justify that it is due to slow economic development, limited improvement in women's access to education and increased mortality due to the AIDS epidemic, mainly in some regions of Africa (He, Goodkind, Kowal, et al. 2016).

The main factor that seems to be behind this increase in average life expectancy is mainly due to the decrease in deaths from noncommunicable diseases, including the decrease in tobacco use (mainly for men) and mortality from cardiovascular diseases. In other words, the historical change about the health status of the world in general is notorious (Mathers et al. 2015).

With respect to Portugal, this greater ability to survive over age is accentuated due to the decrease in the ability to procreate, as there is also a higher prevalence of matrimonial disruptions (which can make procreation impossible) and unstable and not always well-paid professional careers. On the other hand, this aging can be justified by improvements in living conditions, for example, improvements in health systems, home care and lifestyles (Fernandes 2005).

In the 21st century, cardiovascular disease, cancer and diabetes are linked to changes in the population's behaviors (smoking, alcoholism, overweight, physical inactivity, inappropriate eating habits, excessive exposure to radiation, etc.). The mechanisms of transmission of pathogenic causes of infectious diseases can be, for example, through the soil, contamination from transfusions, sexual contact, consumption of food or infected water, among others. Changes in lifestyles, despite influencing variations in incidence, also contribute to relative variations between different neoplasms (Kawachi and Wamala 2006).

2.3 Prevention Measures

In general, the reduction of tobacco use as a primary prevention can reduce the number of cancer deaths globally, not only in active smokers, but also in the remaining individuals potentially exposed to tobacco smoke. Measures such as banning smoking in public places seem to have a positive effect and people tend to smoke less and, at best, quit smoking (Vineis and Wild 2014).

Likewise, the elimination or reduction of exposure to asbestos, aromatic amines, benzidine, benzene and other carcinogens in countries with a high human development index (HDI) have reduced the number of cancer cases, like bladder cancer that was associated with exposure to aromatic amines and leukemias due to benzene (Vineis and Wild 2014).

Obesity is considered a risk factor for breast, colorectal, endometrial, kidney and pancreas cancer. Alcohol is also associated with the liver, upper digestive system, breast and colorectal and the consumption of red processed meats and a low fiber diet is related to colorectal cancer. Finally, lack of physical activity is still a risk factor for colon, breast and endometrial cancer (Vineis and Wild 2014).

In this sense, it is imperative to adopt healthy habits and undergo regular screening tests in order to be able to detect any diseases early.

2.4 Cancer Incidence

Currently, more than 32 million people live with this disease worldwide and, despite all efforts made to combat it, the numbers of new cases continue to increase and 8.2 million people die of cancer each year.

The most common types of cancer are lung and breast cancer, as shown in Figure 2.3 (BBC 2016).

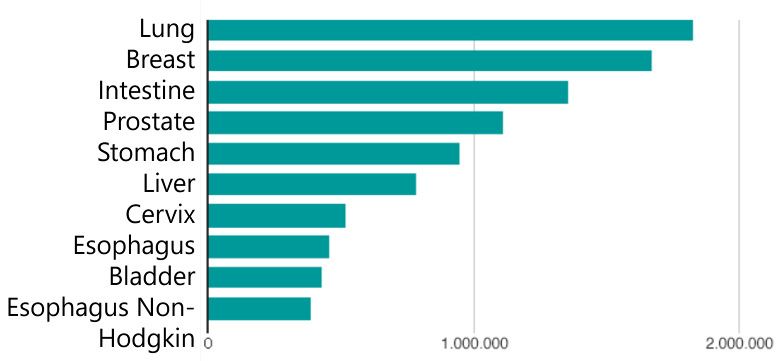

Figure 2.3: Most common types of cancer in the world in 2018 (BBC 2016)

The Human Development Index (HDI) is useful for classifying cancer globalization, because it takes into account education, life expectancy and national income, with countries classified in one of the four possible levels of development: low, medium , high and very high (Vineis and Wild 2014). Thus, in addition to a higher incidence of this disease in regions with high and very high HDI, the most common types are those mentioned in the figure above. In regions with the average HDI, esophageal, stomach and liver cancer predominates, while cervical cancer is more common in regions with low HDI (Freddie Bray et al, 2012). Cases of breast cancer have been increasing in countries with low HDI due to changes in reproductive practices, where first pregnancies are late and women choose to breastfeed for a short period. Similarly, the increase in liver cancer in countries with high HDI can be justified by the increased incidence of hepatitis C virus infection, increased obesity rates and alcohol misuse (Vineis and Wild 2014).

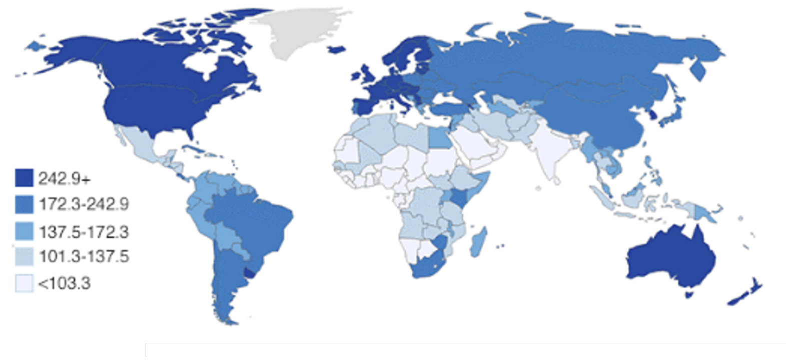

Figure 2.4: Cancer incidence in the world in 2012 (BBC 2016)

Portugal follows the trend of the so-called developed countries, which means that the Portuguese people live more and more years, revealing an improvement in living conditions, advances in medicine and technology. Although there have been improvements in the general health of the population, chronic diseases have taken an increasing weight (Rosa 2016).

According to the National Program for Oncological Diseases, in 2035 the number of cancer cases will be approximately 62,000 cases per year compared to the current 52,000 (2020). This increase is seen equally for men and women (Figure 2.5).

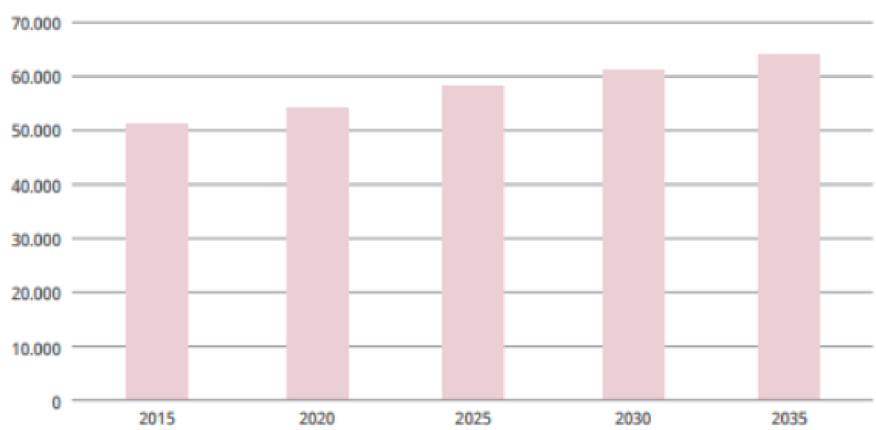

Figure 2.5: Statistical data for cancer incidence in Portugal in 2015 and forecasts until 2035 (Miranda et al. 2015)

Chapter 3

Anatomical and Physiological Review

Cells, the basic and smallest units of life, function as building blocks for the entire body, and are therefore the link between chemicals and humans. For this reason, many are recruited in order to combat possible infections of microorganisms and the functions of the body depend on the functional and structural capabilities of each one (Sherwood 2015).

They are specialized in a type of function and each one plays only a part of the existence of the living being. However, no cell can exist without the contribution of all others, with the disadvantage that the failure of some specialized cells can compromise the existence of all others, which is what happens in cancer for example (Blows 2006).

On the other hand, the human being has an immune system that is composed of a diverse network of molecules and cells in the body and has the function of protecting and defending our body against pathogenic elements (Blows 2006).

Thus, in their normal state, cells grow and divide into new cells, which are formed as they are needed, a process called cell regeneration. Then, when they get old or get damaged, they die naturally (King and Robins 2006).

As previously mentioned, in a normal cellular environment, in order to guarantee the genomic integrity and the correct functioning of the cell, there are several biological pathways with this function, such as the cell cycle, DNA repairs and the immune system. However, when these controls fail, complications arise (Nandi et al. 2019).

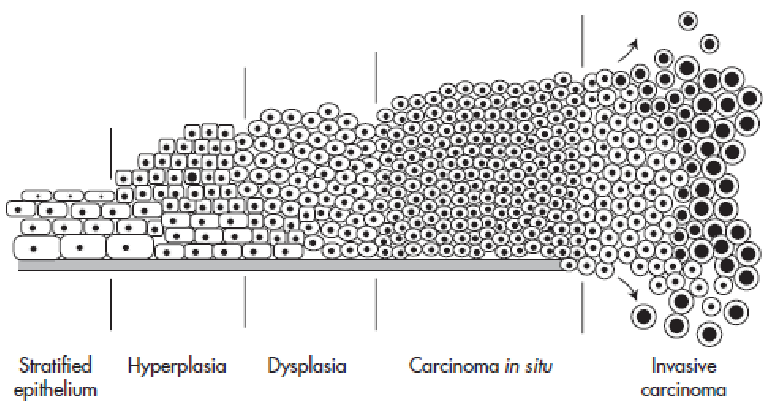

Figure 3.1: Representative illustration of obtaining malignant properties (Blows 2006)

However, the moment they lose this control mechanism they undergo changes in their genome (DNA), becoming cancer cells, which do not die when they are old or damaged and produce new cells that are not needed, in an uncontrolled way, resulting in the formation of cancer. Unlike normal cells, cancer cells do not respect the borders of the organ (Figure 3.1) and can invade the surrounding tissues, spreading to other parts of the body or through the blood (using veins and arteries) or through the lymphatic system - metastasis (King and Robins 2006).

3.1 Factors that influence the appearance of cancer

Cancer cells normally contain multiple changes in the number and structure of genes and chromosomes, where the vast majority of these changes are due to mutations in somatic cells (responsible for the formation of tissues and organs in multicellular organisms). The DNA sequence of an individual gene can be altered by point mutations (which are due to base changes in the DNA), smaller or larger deletions or insertions, or through rearrangements, which causes numerous consequences - genomic instability (Schulz 2005).

Thus, several factors pose a constant threat to the genomic integrity of a cell, influence variations in incidence and contribute to relative changes between different neoplasms, for example the environment and a person's genetic predisposition to cancer, which can eventually be triggered by maladjusted lifestyles. However, despite what people might think, according to the American Cancer Society, only 5 to 10% of cancers are hereditary (Williamson and Pizano 2020).

The external agents that promote formation of cancer are basically of three types: physical, biological and chemical. The physical ones can be any radiation rich in energy depending on the dose and absorption, such as UV irradiation. The biological ones concern certain viruses and bacteria such as Hepatitis B and HPV viruses. In turn, the chemical ones include, for example, nickel, cadmium and arsenic. These external agents affect human beings who deal differently with their presence, due to variations in the genetic constitutions of each one, where the mechanisms of carcinogenesis, i.e., cancer formation, are complex and multifactorial (Badwaik 2019).

Likewise, tobacco smoke, for example, has nicotine that affects not only the central nervous system but also influences signal exchanges and interactions between cells in the airways and lungs. Tobacco consumption is one of the most evident cancer factors, including lung, head, stomach, pancreas, liver, leukemia, among others. Similar complex interactions also occur during skin carcinogenesis caused by ultraviolet radiation. As a result, it becomes difficult to find the exact mechanism by which carcinogenesis occurs, despite being clearly associated with a specific type of cancer through epidemiological data (Schulz 2005).

Alcohol consumption is associated with cancers of the oral cavity, pharynx, larynx, esophagus, liver, breast and colorectal. The combination of alcohol and tobacco has synergistic effects on the incidence of cancer (Tannock 2005).

Medicines can also be carcinogenic. Several hormones and similar compounds favor the development of cancers in specific tissues, for example in the breast and prostate. On the other hand, the most abundant exogenous carcinogen is oxygen, which is highly reactive and can be mutagenic, i.e., it promotes the formation of potentially dangerous changes called mutations in genes (Schulz 2005).

About geographic variations, these result from environmental, genetic and even diagnostic criteria. For example, there is a wide variation in liver cancer incidence rates, where the highest rates are seen in places like China, Thailand and Taiwan, while the lowest rates are recorded in Europe and North America. These discrepancies are highly associated with the prevalence of chronic infections with Hepatitis B and C. Similarly, the variation in cervical cancer may be related to the HPV virus (Ferlay et al. 2010).

On the other hand, the incidence rate of thyroid cancer has been increasing in Europe and the United States and may be the result of changes in the morphological recognition of this tumor (Tannock 2005).

The genetic constitution of the human species has remained unchanged over the years, varying only slightly in populations from different parts of the world and, therefore, the various incidences of cancer and their geographical variation stem mostly from environmental factors. Thus, a specific and personalized treatment for each patient is necessary, achieved through a study of the individual's genetic and clinical profile for a higher rate of therapeutic success (Badwaik 2019).

Despite their diversity, human cancers do not differ much in certain fundamental properties. However, the combination of uncontrolled cell proliferation, altered differentiation and metabolism, genomic instability and invasiveness with possible metastases is unique and specific to cancer. As it progresses, the number of changes in its genome tends to increase. Therefore, an accurate classification of the tumor is important. The histological method for its classification is based on the observation of the place of origin, degree of propagation and cell morphology. Likewise, some imaging procedures detect changes in tissue shape and density, while others react to changes in metabolism and blood flow in cancers. Histological classification is performed from samples acquired by biopsy or surgical specimens, where the histological typing of tumors is performed through the evaluation of their morphology (So et al. 2020).

When a biopsy is made, i.e., a small tissue sample is taken, an abnormality analysis is carried out through a microscopic examination of light. A detailed examination of this type reveals whether the tissues and cells are normal or not, being a fundamental step in the diagnosis of the problem. Normal epithelial cells appear regular in shape and size and are well organized, with regular shaped nuclei. Basal membranes are very important in understanding of how cancers spread, and below these membranes there are blood and lymphatic vessels that supply the tissue. In contrast, cancer cells look differently. They have variable shapes for the cell and nucleus and a loss or rupture of the basement membrane. This last characteristic allows malignant cells to have access to blood and lymph for the purpose of spreading to other parts of the body (Blows 2006).

The medical term cancer, malignant tumor or even malignant neoplasm, is defined as a set of abnormal malignant cells that derive from normal cells in the body, usually epithelial cells. It cannot be defined as a disease, but as countless diseases, with most cancers being named after the cells that gave rise to it. However, the term tumor, when used alone, refers to a cellular or tissue pathological neoformation, i.e., organic tissue (Costa 2005). A distinction can also be made between benign tumors and malignant tumors, the difference in these two types of tumors translating into the fact that malignant ones can invade and destroy tissues of surrounding organs and, thus, spread to another body part. In contrast, benign tumors can only grow in volume, but do not metastasize, i.e., they can only assume characteristics of localized multiplication of normal cells (Blows 2006).

Thus, there is a need to classify tumors with a view to a better understanding of the biology of the tumor and its behavior to define the best possible treatment for each situation.

3.2 Types of Cancer

The designations used for malignant tumors are basically of two types: carcinoma and sarcoma. Carcinomas have origin in one of the four types of organism basic tissues - epithelial tissue - and their function is the external lining, secretion and excretion of substances, being the most common origin of neoplasms. Sarcoma has mesenchymal origin. These designations are preceded by the histological type and followed by the tissue of origin.

For example, breast adenocarcinoma, squamous cell carcinoma of the lung, basal cell carcinoma of the skin and leiomyosarcoma of the uterus (Ruddon, r., 2007). (Ruddon 2007).

However, if the malignant tumor is not similar to the tissue that gave rise to it, it can be called undifferentiated or anaplastic. Neoplasms of the hematopoietic system usually have no benign parts. Therefore, the terms leukemia and lymphoma always refer to a malignant disease and have cell type designations such as acute or chronic myeloid leukemia (found in the bone marrow, which is the tissue responsible for maintaining the production of red, white blood cells and platelets and causes the production of a large number of abnormal blood cells), lymphoma (they develop from lymphatic tissue, which is found in the lymph nodes and organs) of Hodgkin or not of Hodgkin and so on. Likewise, the term myeloma is a malignant disease of the bone marrow, in which the affected cell is the plasmocyte and belongs to the family of lymphocytes that are responsible for the defense of the organism through the production of special proteins - immunoglobulins, and the term melanoma reflects a malignant neoplasm derived from melanocytes (Ruddon 2007).

The latter can appear in various locations in the body and, at the cutaneous level, can be classified into four types: superficial melanoma, which develops in extension and is the most frequent; nodular melanoma, a papular and aggressive lesion; lentiginous acral melanoma, lesions located in the digital extremities and nails and malignant lentigo melanoma, a lesion that arises in areas of great sun exposure (Moreira 2016).

Sarcomas are divided into two main types: primary bone sarcomas and soft tissue sarcomas (which include cutaneous sarcomas). Soft tissue sarcomas, i.e., a group of tissues located between the epidermis and the viscera, except bones, constitute a heterogeneous group of malignant tumors that cover more than 50 different types (Grabellus et al. 2012). In addition, many of these subtypes can occur at any age and are not restricted to a specific location on the body. Soft tissue sarcomas usually form in muscles, joints, fat, nerves, deep skin tissues and blood vessels. As its name implies, malignant bone tumors, such as osteosarcomas and Ewing's sarcomas, are found in all bones of the body, but can also be found in cartilage (Burningham et al. 2012).

3.3 Nuclear Medicine

Nuclear Medicine is a health area that uses radionuclide sources for diagnostic and therapeutic purposes. It has been progressing and is related to the generation of images of physiological processes and, consequently, in the evaluation of the treatment of diseases, especially cancer, using radiopharmaceuticals. These consist of a radioactive element (unstable atom) linked to a chemical compound or drugs, which can be a medication, antibody, among others.

They have several characteristics and they are specific for each clinical case and allow visualization of processes in the body, organ functions and, even, the presence or absence of a specific cellular target (Glaudemans et al. 2015).

The atom is characterized by being the smallest structure of matter that reflects the properties of chemical elements. When combined, they form molecules and, the set of molecules, give rise to the chemical elements existing in Nature. Atoms have a nucleus that contains protons that in turn have a positive charge and neutrons that have positive and negative electrical charges, making them neutral; and also an orbital that has electrons with negative electric charge. Therefore, the nucleus of an atom is symbolically represented by:

$$^{A}_{Z}X \tag{3.1}$$

where X is the symbol for the chemical element, A corresponds to the mass number that refers to the number of nucleons (neutrons and protons), while Z characterizes the atomic number that reflects the number of protons, which is equal to the number of electrons (Shultis and Faw 2016).

One of the elements used in this dissertation is Technetium, which belongs to Group 7 and Period 5 in the Periodic Table, and is represented by:

$$^{98}_{43}Tc \tag{3.2}$$

having 43 protons and 55 neutrons (98-43 = 55).

Radioactivity is found in atoms collected from nature or in artificially prepared atoms. It is a property only of the nucleus of the atom and consists of the spontaneous emission of particles or energy by the nucleus of these same atoms (Heneine 2008).

Thus, whenever an atom has excess energy (Figure 3.2), it is emitted in the form of particles (alpha (α) and beta (β)) or in the form of electromagnetic waves (gamma radiation (γ)) (Gilberto Weissmüller and Bisch 2010).

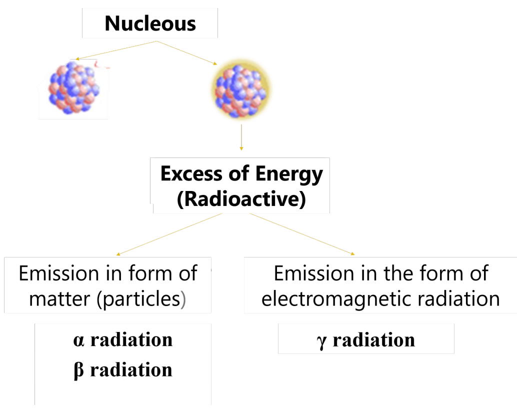

Figure 3.2: Release of excess energy from atoms

Atoms with the same atomic number and different mass number are called isotopes. For example, technetium has several isotopes, of which ^{97}Tc (has 43 protons and 54 neutrons), ^{98}Tc (has 43 protons and 55 neutrons) and ^{99}Tc (has 43 protons and 56 neutrons) (Johnstone et al. 2017).

Isotopes can be further divided into stable and unstable. The stable isotopes do not change spontaneously, i.e., they are not radioactive and, therefore, do not originate other elements, unlike the unstable ones that spontaneously emit particles or energy through the nucleus and are called radioisotopes or radionuclides (Young 2009).

On the other hand, technetium is an element that can be found in two states. When its nucleus has excess energy it is said to be in the metastable state and the letter m is represented. After emitting energy, it transit to the ground state (Figure 3.3).

Tecnecium	$^{99}_{43}Tc^{m}$	$^{99}_{43}Tc$

Figure 3.3: Different states of technetium (Heneine 2008)

The radiation emitted during radioactivity can be ionizing or non-ionizing. Ionization occurs when the radiation energy incident on a material is sufficient to pull electrons out of its atoms. The non-ionizing radiation does not have enough energy to pull the electrons out, and the excitation of the atom can occur and the electrons jump to outer layers, without being ejected. For excitation of an atom to occur, the energy supplied must be equal to the energy difference between the origin and final levels of the electron (Freire 2007).

Thus, radioisotopes that have excess of nuclear energy, to contradict this state, will undergo disintegrations called spontaneous transformations or radioactive decay to form a more stable element. As previously mentioned, it is during this process, called radioactivity, that particles or gamma rays are emitted (Shultis and Faw 2016).

Gamma radiation has no electrical charge, which corresponds to its greater penetration capability when compared to other types of radiation and is not affected by magnetic fields (Correia 2010).

3.3.1 Modes of Radioactive Decay

As seen earlier, there are several modes of radioactive decay (Figure 3.4), where an unstable nucleus tries to achieve stability due to excessive nuclear mass or energy, usually emitting particles and/or radiation (Shultis and Faw 2006).

Among the various existing radioactive decay modes, α, β and γ stand out. In α decay, the nucleus emits an α particle, while in β decay the nucleus can correct excess protons or neutrons by directly converting protons to neutrons, or vice versa. The latter can occur in three different ways, where each must involve another charged particle to guarantee energy conservation. The first process, known as β- decay, involves the creation and emission of an electron by the nucleus. The second process, known as β+ decay, involves the emission of a positively charged electron by the nucleus and the third process involves the internal absorption of an atomic electron by the nucleus, allowing the conversion of protons to neutrons and is commonly called electron capture. In γ decay, an excited state decays to a less excited state by the emission of a photon (γ radiation). The energy of γ radiation is equal to the energy difference between the nuclear states and normally occurs after the α and β decay, since these lead the initial nuclei to more excited states. These state transitions are known as isomeric transitions and the most enduring excited states as isomeric states or isomers. (or even metastable states) (Shultis and Faw 2006).

Thus, the difference between gamma decay and isomeric transitions is that gamma decay occurs just after the particle is ejected from the nucleus, whereas an isomeric transition occurs without emission of particles, with only a rearrangement of intranuclear particles. The particle whose emission gives rise to the rearrangement was previously emitted (Heneine 2008).

Radionuclides can be artificially produced by bombarding stable nuclei with high-energy particles in a cyclotron, linear accelerator or nuclear reactor, since those that exist in nature have a long life and are therefore not ideal for Nuclear Medicine procedures (Glaudemans et al. 2015).

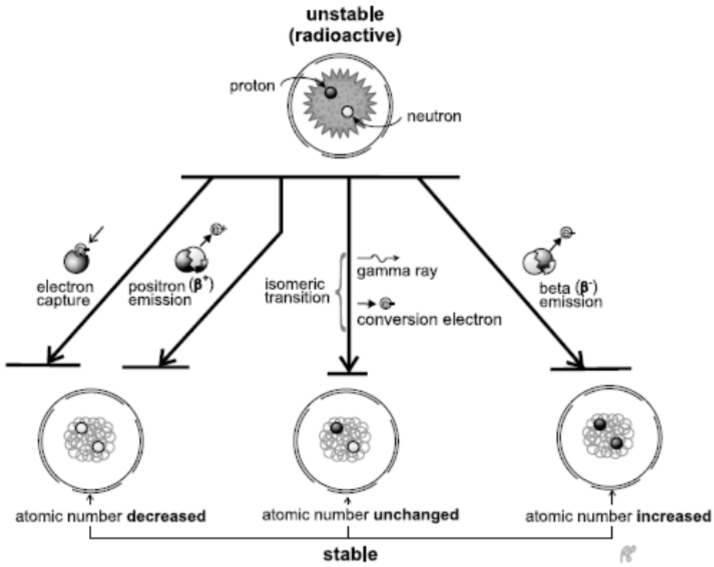

Figure 3.4: Scheming of decay modes (Shultis and Faw 2006)

On the other hand, the choice of the appropriate radionuclide is divided into two categories, physical and biochemical. The physical characteristics are related to the physical half-life, type of emissions, radiation energies, resulting products, production methods and radionuclide purity. At the biochemical level, it includes tissue targeting, retention of radioactivity in the tumor, in vivo stability and toxicity. For therapeutic purposes, radiation with high linear energy transfer (LET - energy deposition frequency in the form of charged particles in the path of a given type of radiation) is preferred. For example, α and β particles are used, because they allow a high ionization by path length. Thus, they are totally deposited within a small portion of tissue, reducing the need for additional radiological protection, since the radiation does not penetrate the patient's body. The distribution of radiation energy in terms of intensity (MeV, where 1 eV = $1.6\text{x}10^{-19}$J) and quantity is important for studying the damage caused by radiation, as well as being important in detecting emitted radiation. (Yeong, Cheng, and Ng 2014).

Two terms are also associated with radioactive decay, activity A(t) and the radioisotope half-life. Activity is the rate at which radioactive nuclei decay, i.e., the ratio of the number of nuclear disintegrations in a time interval and its international system unit (SI) is Becquerel (Bq), which is equivalent to 1 decay per second (dps). Another unit that can also be used is Currie (Ci) where 1Ci corresponds to $3.7x10^{10}$Bq. Half-life ($t_{1/2}$) is defined as the time required for half of the unstable atoms in a sample to decay (Freire 2007).

3.3.2 Interaction of gamma radiation with matter

When a γ-ray passes through the environment, interactions between the photon and matter occur and energy is transferred to the surrounding environment. However, the photon beam can undergo several changes such as attenuation, absorption and dispersion, the main forms of interaction with matter, and more relevant, are the Compton effect, photoelectric and production of pairs, represented in Figure 3.5 (S. Mehta et al. 2010).

In the Compton effect, a photon collides with an electron that is not strongly bound to the atom (free electron) and undergoes ionization. The probability of this effect happening is inversely proportional to the energy of the photon received, being the most common interaction to happen clinically. In the production of pairs, the photon interacts with the nucleus of an atom and not an electron. There is energy transfer from the photon to the nucleus, generating a positively and negatively charged pair of electrons. This effect occurs for some time in routine radiation treatment with high-energy photon beams. Finally, in the photoelectric effect, the photon received collides with an electron strongly connected to the nucleus and transfers almost all of its energy. Consequently, the electron becomes very energetic and begins to ionize the surrounding molecules (Gazda and Coia 2001).

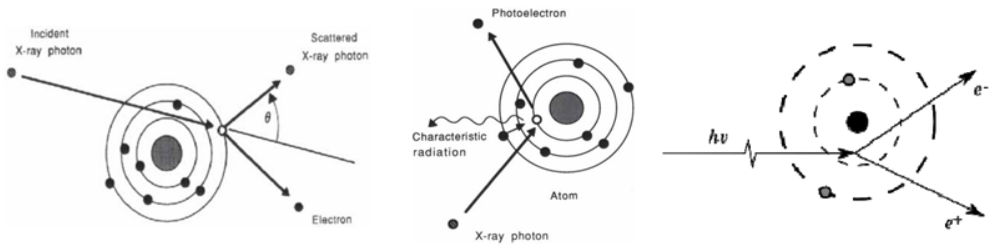

Figure 3.5: Compton effect, photoelectric effect and pair production, respectively (S. Mehta et al. 2010)

3.3.3 Radiation Detectors

However, ionizing radiation is rarely detected directly, i.e., the presence of radioactivity remains unnoticed without the use of specialized equipment, called radiation detectors. These normally measure resulting products from the interaction of radiation with the detector. The ionization of atoms/molecules creates free charges and the movement of electropositive ions and the consequent collection of these charges gives rise to a pulse or electrical current. Thus, the event rate, i.e., the pulses induced by radiation, can be used to measure the rate of radiation particles that pass through the detector. (Shultis and Faw 2016).

There are several radiation detectors and they are divided into two major groups: non-scintillation detectors and scintillation detectors. Within the non-scintillation detectors there are gaseous detectors, which measure the ionization of the radiation induced within a volume of gas, i.e., they measure the effect of radiation. There are also several gas detectors such as ionization chambers, proportional counters and Geiger-Müller counters, however, they are not ideal for the detection of gamma rays. (R. A. Powsner and E. R. Powsner 2008).

For better efficiency of higher counts, scintillation detectors are used. The light photons, emitted by the de-excitation of the atoms, are converted into electrical pulses by photomultiplier tubes (PMT's) which are later amplified. Different types of scintillation detectors are used for different types of radiation, and the most used scintillation detectors are thallium-doped sodium iodide (Na(Tl)) (Saha 2012).

The radiation principles of these detectors are based on ionization by the radiation of atoms, collection of ionized particles generating current, followed by the conversion of electrical pulses, pulse amplification and counting. The pulse size is proportional to the radiation energy absorbed in the detector, regardless the type of radiation (R. A. Powsner and E. R. Powsner 2008).

Compared to gaseous detectors, these are more efficient for the detection of gamma rays where the minimum energy for ionization is small and have a better spectral resolution of gamma photons with close energies. On the other hand, they are more expensive and take longer to produce (R. A. Powsner and E. R. Powsner 2008).

Performance parameters of detectors

The relevance of the quality and performance of these detectors is undoubtedly, namely in Nuclear Medicine practices. In practice, they can be characterized quantitatively according to their performance parameters such as sensitivity, energy resolution, contrast and spatial resolution. A detector with high sensitivity, lower energy resolution and therefore better dispersion rejection and better spatial resolution would be ideal. However, no single detector can obtain all these great performance parameters, and the type of detector should be chosen using the most important parameters for the task to be used, taking into account the radionuclide used, i.e., energies and types of radiation. (Heller and Zanzonico 2011).

Sensitivity

Sensitivity or efficiency is defined as the rate of counts per unit of activity of the source (cps/kBq), i.e., the number of photons emitted by the source and is dependent on the geometry of the source detector with two distinct components of sensitivity: geometric sensitivity and intrinsic sensitivity.

Geometric sensitivity is the fraction of radiation emitted that reaches the detector and is directly proportional to the area of the radiation sensitive detector and, for a point source, inversely proportional to the square of the source's detection resistance. For a collimator detector, geometric efficiency is still inversely related to its length (Heller and Zanzonico 2011).

On the other hand, the intrinsic sensitivity is reflected by the fraction of radiation that crosses the detector and is interrupted within it. The intrinsic sensitivity is directly related to the thickness of the detector, effective atomic number and mass density and decreases with the increase in photon energy, because those with higher energy are more penetrating and more likely to pass through a detector without interaction (Shultis and Faw 2016).

Energy Resolution

Energy resolution is defined as the ability of the detention system to distinguish different ranges of energy from emitted radiation. It is generally specified as the full width at half maximum height (FWHM) of the photopeak (peak of greatest amplitude) energy (Ey) and is inversely proportional to the number of photons emitted by the radiation and is defined by the Equation 3.3:

$$EnergyResolution(\%) = \frac{FWHM}{Ey} * 100 \tag{3.3}$$

The energy spectrum for the 140 keV gamma rays emitted by ^{99m}Tc shows the geometric dependence of the primary radiation counts, i.e., the radiation that was not dispersed, and of the scattered radiation counts. There is a degradation of energy resolution with a decrease in photon energy (R. A. Powsner and E. R. Powsner 2008).

The importance of energy resolution is, therefore, in the rejection of radiation dispersion. The radiation loses energy when dispersed and the detected low energy radiation can therefore be distinguished from primary radiation. However, the energy resolution of the radiation detectors (i.e., the width of the photopeak in the energy spectrum) means that there will be overlapping of scattered and primary radiation, as shown in the figure 3.6. As the energy resolution improves (FWHM decreases and the photopeak becomes narrower), the separation of dispersed primary radiation increases and more counts corresponding to scattered radiation can be eliminated while discarding counts corresponding to primary radiation (Wierts et al. 2008).

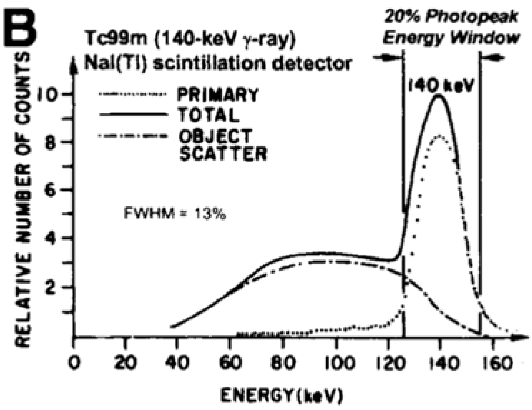

Figure 3.6: Energy spectrum for gamma radiation of 140 keV emitted by ^{99m}Tc (Heller and Zanzonico 2011)

Contrast

The contrast reflects the detector's ability to distinguish activity from the target region from background activity in the surrounding unmarked regions. It can be expressed, as we can see in Equation 3.4 as the difference in the target region count rate (T) and the background count (B), divided by the target region count (Heller and Zanzonico 2011).

$$\frac{T - B}{T} \tag{3.4}$$

The advantage of this specific detector contrast setting is that it varies between 0 and 1, with a value of 0 corresponding to no contrast and a value of 1 corresponding to the maximum contrast (i.e., without background). The contrast is related to the detector's sensitivity, energy resolution and spatial resolution (Heller and Zanzonico 2011).

Spacial Resolution

For detectors such as intraoperative probes where radiation must be located, well detected and measured, spatial resolution is a very important parameter of performance.

Spatial resolution reflects the detector's ability to accurately determine the location of a source.

The count rate detected as a function of the lateral distance from the central axis of the detector can be used to generate a point spread function (PSF). As seen in Figure 3.7, the spatial resolution of the probe can thus be expressed as the FWHM (parameter used to specify the energy resolution and the spatial resolution) of the PSF. The lower the FWHM, the better the spatial resolution. The spatial resolution of a detector decreases rapidly with increasing distance from the source to the detector. The use of a collimator limits the field of view (FOV) of the detector to the tissue and improves its spatial resolution. However, sensitivity and spatial resolution are inversely related performance parameters: sensitivity decreases as spatial resolution increases and spatial resolution decreases as sensitivity increases (Heller and Zanzonico 2011).

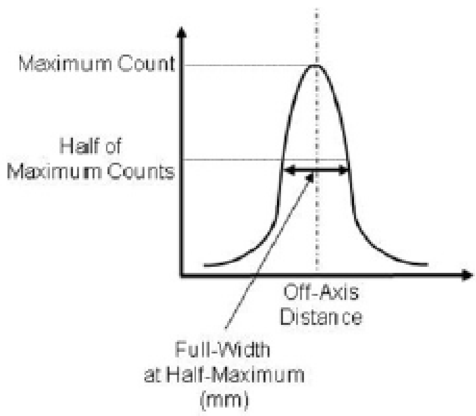

Figure 3.7: Spatial Resolution (Heller and Zanzonico 2011)

Collimation

To be able to identify radioactivity within an intraoperative probe, they are equipped with lead or tungsten collimators to protect the gamma ray detector from radiation from unwanted directions.

Thus, the main objective of the collimator is to collimate the entry of photons in order to reduce the contribution of radiation and limit the size of the incidence field by absorbing part of the radiation, directing and smoothing the beam, because it can be difficult to locate the region of interest. They are composed of numerous precisely aligned channels and allow photons to pass through the channel axis only. Photons that are emitted in any other direction are absorbed (A. Barreto 2012).

The collimator has an opening of a few millimeters, which defines the probe's FOV, corresponding to the tissue area from which gamma rays can reach the detector. A narrow FOV (collimator with small orifice) provides a more precise selection of photons and, therefore, greater precision in identifying a target, but slows down the search speed, since it takes more time to traverse the entire affected area and also requires greater attention from the health professional. On the other hand, a large FOV, collimator with a large orifice, allows the detection of photons in a large area, reducing the intervention time.

The sensitivity, like the FOV, depends on the characteristics of the collimator in which the maximum sensitivity is obtained in the center of the FOV and gradually decreases as it moves away, due to the fact that an increasing percentage of the emitted radiation is intercepted and, therefore, absorbed by the collimator (R. A. Powsner and E. R. Powsner 2008).

Chapter 4

Isolated Limb Perfusion

In fact, in recent years, there has been a remarkable evolution in the understanding of the characteristics proposed for the development and treatment of cancer, and the search for the most effective therapy is still a constant challenge (Schulz 2005).

With regard to cutaneous neoplasms (sarcomas, melanomas, carcinomas), difficult to diagnose and with high rate of morbidity, there are several treatments indicated for these tumors, each with different goals and depending on the stage of the tumor (measure of its physical extent), such as surgery, chemotherapy and radiation therapy. In situations where patients have developed a restricted number of primary lesions or small metastases, the most adopted option is the removal of part or all of the tissue (surgical excision) that aims to remove the tumor together with the normal tissue that is adjacent to it to ensure that all cancer cells are removed. It is easier for some types of cancer (skin cancer) than for others (brain, which can be difficult to reach and remove) (Grabellus et al. 2012).

Radiotherapy is sometimes administered after surgery to destroy cancer cells that may remain. When applied before surgery, it aims to reduce the size of the tumor. However, if a patient has metastasized tumor cells, radiation and surgery are not the treatments of choice (Blows 2006).

On the other hand, chemotherapy is a systemic treatment that uses drugs that destroy tumor cells as well as healthy ones, and can be administered as a main or auxiliary treatment, or as a palliative treatment to relieve pain and discomfort. Patients are treated with chemicals that prevent cells from duplicating or delaying the process (King and Robins 2006).

Initially, the therapy chosen for the treatment of metastases of dispersed and surgically unresectable cutaneous neoplasms involved amputation of the limb subject to the disease, however many complications and short time intervals between treatment and the appearance of new lesions were associated. Thus, in 1957, an innovative technique emerges that proves to be extremely effective and avoids limb amputation: Isolated Limb Perfusion performed with Melphalan and TNF-α and has been applied in Portugal since 1990 (Moreno-Ramirez et al. 2010).

4.1 Advantages of this technique

The main advantages of this technique are based on promoting total or significant remission of the tumor and, also, avoiding amputation of the limb in question, also seeking to improve the quality of patients' life (Silva 2013).

On the other hand, the perfusion offers the opportunity to treat the entire limb and remove not only the lesions that are evident, but also the minor ones that would become evident later (Nieweg and Kroon 2014).

4.2 Ambient conditions of the procedure

Therefore, the perfusion technique requires a joint effort with the surgeon, perfusionist, nuclear medicine specialist, anesthetist and the other usual team present in the operating room (Nieweg and Kroon 2014).

This procedure is performed in hyperthermia conditions because it prevents vasoconstriction of the vessels that irrigate the tissues and since a small increase in the temperature of the tumor makes the cancer cells more sensitive to radiation and chemotherapy. The degree of chemosensitization varies according to the type and concentration of the drug, the type of tumor, the increase in tumor temperature and the time difference between heat administration and chemotherapy (Chatterjee, Diagaradjane, and Krishnan 2011).

Before the patient is submitted to surgery, a prior medical consultation is carried out where several parameters will be observed and the volume of blood that will be removed from the limb affected by the disease and put into circulation in the extracorporeal circuit will be recorded. Thus, after the end of the perfusion, the same amount of blood is replaced at the time of restoration of normal circulation.

4.3 Technique Description

The procedure is based on isolating the limb affected by the disease from the systemic circulation so that it is possible to administer very high doses of chemotherapy without any collateral damage (Wierts et al. 2008). Thus, with high doses of cytotoxic drugs it is possible to achieve regional control of the tumor, without compromising vital organs and other healthy regions. The general condition of the patient must be evaluated and the responsible physician must be aware of diseases, allergies and concomitant medications (Nieweg and Kroon 2014). For a better understanding of the technique and for a better perception of the work to be developed,the procedure was witnessed and briefly described in Figure 4.1.

This technique is characterized by being a targeted therapy and the procedure is performed with patients under the effect of general anesthesia (Wierts et al. 2008). General anesthesia is an anesthetic technique that promotes the abolition of pain, muscle paralysis, the abolition of reflexes, amnesia and, mainly, unconsciousness. It makes the patient unable to feel or react to any stimulus from the outside, being the most suitable technique in complex, long and large surgeries (Brown, Pavone, and Naranjo 2018).

With the patient anesthetized, heparin is administered intravenously for later limb isolation. The main objective of heparin is to prevent events that cause blood clotting - thromboembolic events.

Isolation of the limb is achieved by separating the blood circuit of the limb/region affected by the disease through cannulation of the vessels (veins and arteries) to an oxygenated extracorporeal circuit(Wierts et al. 2008).

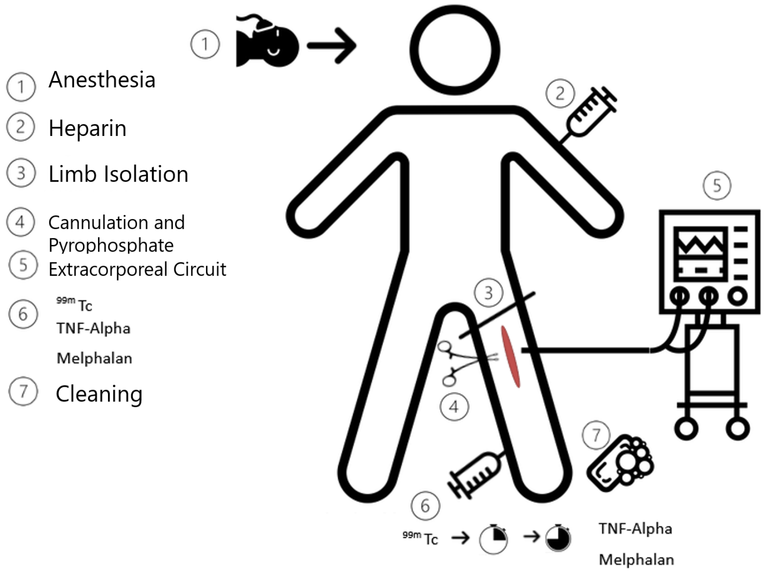

Figure 4.1: Steps performed during Isolated Limb Perfusion technique

Cannulation of the veins is done by traction of the wall with forceps, a longitudinal cut and introduction of the angled metal cannula and represents an important source of resistance to blood flow in the extracorporeal circulation system.

During cannulation, pyrophosphate is injected, which promotes better uptake of the drugs that will later be administered. A tourniquet is also used at the root of the limb to occlude superficial veins, i.e., it compresses collateral vessels and prevents leaks, interrupting collateral circulation (Wierts et al. 2008).

All the equipment that constitutes the extracorporeal circuit, represented in Figure 4.2, consists of a thermostatic bath, an oxygenator, a peristaltic pump, a temperature display and disposable material. The thermostatic bath (1) consists of a stainless steel reservoir with an internal resistance and a temperature controller to heat the water, while the peristaltic pump guarantees the circulation of the fluid. It allows a range of flow rates for different speeds of rotation and operates in the flow circuit and the return flow of chemotherapy, although in the return flow, the return of the fluid is done by generating a vacuum of the pump with the assistance of other equipment in the operating room. The temperature display (2) shows the reading of the fluid and limb temperatures, while the disposable material (3) contains the system components that are in direct contact with the chemotherapy solution and the patient's return fluids (Santos 2017).

Thus, the temperature of the limb is increased by heating the perfusate, and the oxygenator enables the exchange of oxygen, carbon dioxide, water vapor and anesthetic gases between the blood and the surrounding atmosphere (Malawer and Sugarbaker 2001). The perfusion flow must be regulated so that there is no leakage into the systemic circulation. When this circuit is started, the thermoregulation system of the water circulating in the oxygenator and its membrane ventilation system is adjusted to achieve the desired temperature values (between 38°C and 40°C) (Wierts et al. 2008).

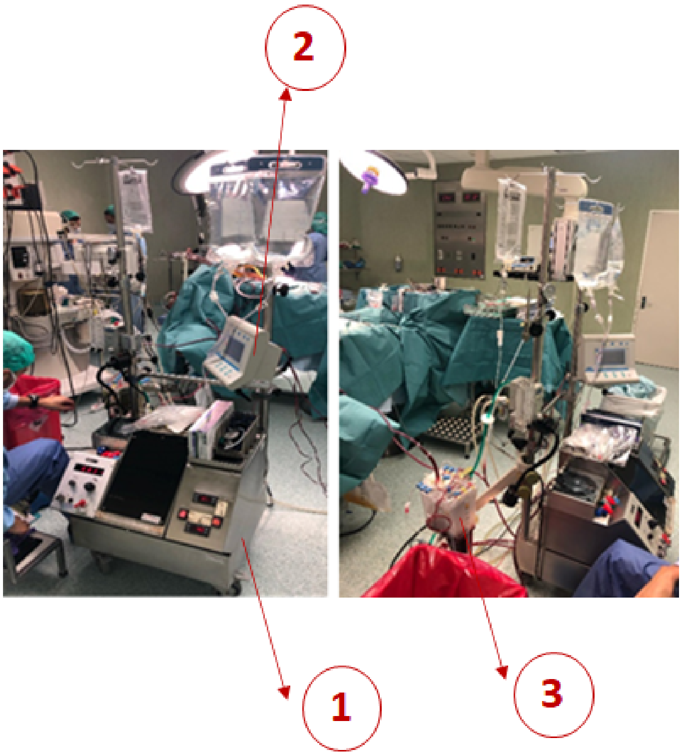

Figure 4.2: Components of extracorporeal circuit

Radioisotope Injection

^{99m}Tc is widely used in nuclear medicine as a radioactive tracer, for organ and tumor localization studies, since it meets almost all requirements and it is easily attached to a pharmaceutical, which is due to its physical and chemical characteristics. It has a half-life of 6 hours and gamma emission with 142 keV energy which allows gamma camera scans to provide images of patient's body. On the other hand, its half-life is sufficient for the preparation of the radiopharmaceutical, administration and control of leaks and is short enough to minimize the radiation dose absorbed by the patient. It has a decay constant (λ) of 0.1155, for the mathematical reason described in Equation 4.1:

$$\lambda = \frac{0.693}{t_{1/2}} \tag{4.1}$$

In isolated limb perfusion, a syringe with erythrocytes labelled with 0.3mCi of ^{99m}Tc is administered at the systemic level and remains in circulation for 2/3 minute, to assess baseline counting-rate. Subsequently, another syringe with erythrocytes labelled with 3mCi of ^{99m}Tc is administered directly into the extracorporeal circuit and remains in circulation for 5 minutes, to check if there is a leak from the extracorporeal circuit to the systemic circulation. After that, 3 blood syringes are collected from the extracorporeal circuit. Before starting chemotherapy administration, the first injection (Figure 4.3) of the collection is made into the systemic circulation (1st simulation). The next two simulations are performed throughout the perfusion. When the subcutaneous temperature reached 38C and no sign of leakage is present, chemotherapy is infused into the extracorporeal circuit.

Figure 4.3: Injection of the radiopharmaceutical into the systemic circulation and the extracorporeal circuit (A. Barreto 2012)

Once the safety conditions are met, TNF-α will be administered first, circulating alone for 15 minutes, and then Melphalan, which is in simultaneous for 45 minutes, being both in circulation. In addition, pressure differences between the systemic circuit and the extracorporeal circuit are taken into account so that the systemic circuit is higher than the extracorporeal circuit (Silva 2013).

Melphalan

Melphalan aims to interfere with DNA synthesis. First used in 1957, melphalan is suitable for regional chemotherapy, as it has a short half-life, low toxicity to the vascular endothelium and a relatively linear dose-response relationship with regard to cytotoxicity. On the other hand, it can cause spinal depression, changes in muscle, gastrointestinal problems, among others. Melphalan would be systematically hydrolyzed by the liver and excreted by the kidneys, however, in regional chemotherapy, it is removed by washing (Defty and Marsden 2012).

It is effective and fast-acting, but it increases the risk of local toxicity. It is particularly dangerous for peripheral nerves and its use can result in neuritis or paralysis. 1 to 2 mg is administered into the arterial line at intervals of 1 to 3 minutes until it is fully administered.

The dosage usually applied is 10 times the body volume of the patient undergoing treatment. Melphalan is typically presented in 50 mg ampoules (10 ml) and has a cost of 164 euros per ampoule (Silva 2013).

However, although it is the drug chosen in this type of treatment, when used alone, it does not guarantee a complete remission of the lesions, offering only a limited disease-free period. In this sense, the combination of melphalan with TNF-α appears, in order to improve results (Pavón Hernández et al. 2009).

TNF-α

TNF is a multifunctional cytokine (a generic term used to designate a large group of molecules involved in the emission of signals between cells during the triggering of immune responses) mainly secreted by macrophages and plays a very important role in innate and acquired immunity, binding two distinct receptors that produce antitumor effects. It has an effect on tumor vascularization reaching a pro-coagulant condition so that it results in microvascular thrombosis. It causes leukocyte junction and extravasation, which allows tumor infiltration into defense cells. It is capable of causing the death of tumor cells (apoptosis) that have a wide range of pro-inflammatory actions, i.e., that promote inflammation processes (Jakob and Hohenberger 2016).

TNF has a dual role. Firstly, in high doses it has a selective vasculotoxic effect for the tumor and, secondly, it changes the pathophysiology of the tumor and increases the uptake of chemotherapeutic agents administered to the patient. That is, an increased synergistic uptake of alkylating agents occurs during the infusion, as well as a delayed disintegration of the tumor vessels and, consequently, a thrombosis and subsequent tumor regression (Testori et al. 2011).

The administration of TNF-α during isolated limb perfusion, prevents the devastating hemodynamic effects and demonstrated strong synergistic antitumor effects with chemotherapeutic agents (Jakob and Hohenberger 2016).

On the other hand, it has known toxicity and side effects, and strict control of any leakage of this drug into the systemic circulation during the procedure is essential. Thus, this control is guaranteed by monitoring any blood leakage from the systemic circulation during the perfusion (Orero, A. et al, 2009).

Generally, for the lower limb the dose is 1 mg and for the upper limb 0.5 mg. It is presented in 1 mg ampoules (5 ml) and has a cost of 2517.5 euros per ampoule (Silva 2013).

After perfusion, the treatment end and the member is washed with sterile solutions and normal circulation is restored. The serum used for this washing process is Tetraspan (plasma starch-based expander), which is performed with muscle drainage, massage of the extremity member to the origin, forcing blood with cytostatic fluid to leave the muscle mass into the venous network and from there to a collection bag (Olofsson Bagge, Mattsson, and Hafström 2014).

At the end of this treatment, hospitalization of patients is necessary in order to analyze the physiological parameters that have undergone changes after the surgery and, also, to identify if there was toxicity due to a large amount of permanent residues and absorbed cytostatics (Moreira 2016).

4.3.1 Leaks Detection

The injection of the radiopharmaceutical is necessary, as previously stated, in order to be able to make an effective and safe control of blood leakage from the extracorporeal circuit to the large circulation, i.e., the systemic circulation. This control is performed by reading the photons emitted by ^{99m}Tc.

However, ionizing radiation is rarely detected directly, i.e., the presence of radioactivity remains unnoticed without the use of specialized equipment, called radiation detectors. The ionization of atoms/molecules creates free charges and the movement of electropositive ions and the consequent collection of these charges gives rise to a pulse or electric current. Thus, the event rate, i.e., pulses induced by radiation, can be used to measure the rate of radiation particles that pass through the detector (Shultis and Faw 2016).

The quality and performance of the probe are, in fact, influencing factors during the Isolated Limb Perfusion procedure and it is composed of a detection system and an electronic system, illustrated in Figure 4.4. The detection system consists of a scintillation detector or a semiconductor detector and, in turn, the electronic system amplifies the signal from that same crystal, so that its study is possible (Heller and Zanzonico 2011).

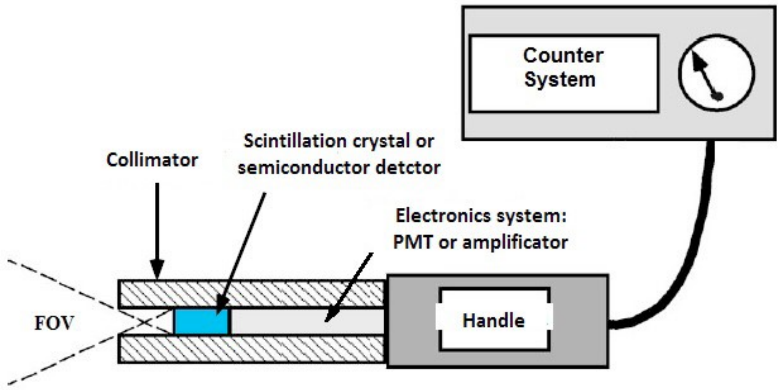

Figure 4.4: Cross-sectional representation of an Intraoperative Probe and the respective counter system (A. Barreto 2012)

The operating principles of semiconductor detectors are based on ionizing the radiation from semiconductor atoms and collecting ionized particles that generate current. Subsequently, pulse conversion occurs, followed by pulse amplification and consequent pulse counting. The pulse size is proportional to the radiation energy absorbed in the detector, regardless of the type of radiation. The minimum energy for ionization is small and has a better spectral resolution of gamma photons with close energies. However, it is more expensive and takes longer to produce (A. Barreto 2012).

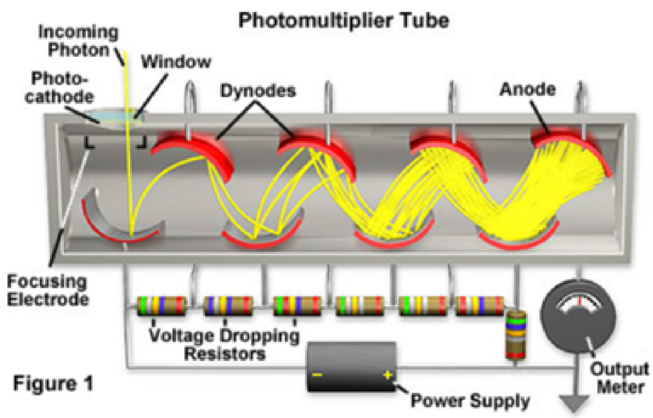

Figure 4.5: Representation of a photomultiplier tube (Saha 2012)

The probe most used in this type of procedure is composed of a scintillation detector due to its extreme sensitivity. Gamma photons detected by the crystal are converted into an auditory signal. The effectiveness of the detection depends on the ratio between the area of the detector and the area of the radiation sphere, where their relationship increases proportionally with the square of the distance between them (Schneebaum et al. 1999).

In these detectors, visible light is produced through the interaction of photons with the atoms present in the crystal (which causes its excitation). This beam of light is transmitted to its PMT (Figure 4.5), which multiplies the photoelectrons, where they are converted into electrical pulses. These PMTs consist of a light-sensitive photocathode at one end, which releases photoelectrons by absorbing light photons and is attached to the thallium doped sodium iodide detector, NaI(Tl), by light tubes; a series of metallic electrodes called dynodes in the middle; an anode at the other end and a glass tube, which wraps all the elements in a vacuum. (Saha 2012).

Subsequently, the electrical pulse is classified by a pulse height analyzer (PHA) to be recorded as a count. The function of PHA is to select only the pulses that are within a voltage range (ΔV), as illustrated in Figure 4.6 (Saha 2012).

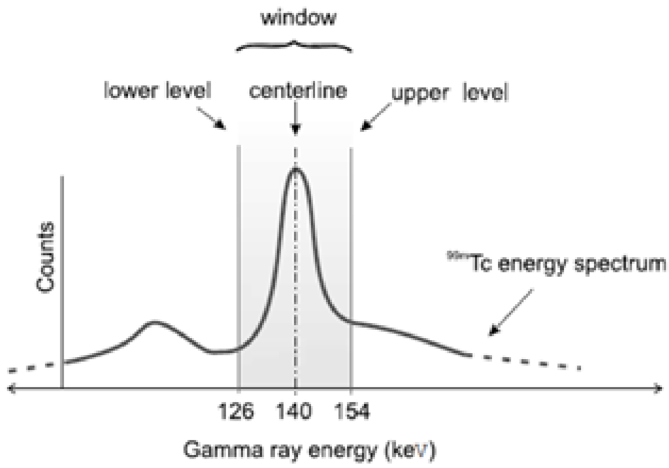

Figure 4.6: PHA analyzer (Saha 2012).

Radioactivity is then determined by measuring the current passing through the probe's constituent crystal and the ideal crystal composition is dependent on the radioisotope to be used.

The equipment used throughout the treatment of Isolated Limb Perfusion is called the Neoprobe Gamma Detection System, shown in Figure 4.7, and is used in combination with intraoperative probes. These two combined systems make it possible to detect the presence of gamma radiation emitted from radioactive isotopes in the organs or tissues of the body and provide an increasing or decreasing sound, as well as a visual indicator (Count Bar) that varies according to the increase or decreased radioactivity.

The detection of gamma radiation with a probe is based on the inverse square law of physics, which allows the detection of radiation emitted by a source. Its use involves placing a probe near the radioactive site, which increases the number of counts detected (Corporation 2011).

Through the external gamma detection of the administered isotope it is possible to provide non-invasive methods to collect important physiological information and anatomical information.

To sum up, this equipment is useful since it provides, in real time, the radioactive decay of the radioisotope injected into the patient at the beginning of the procedure, allowing to verify the occurrence of leaks to the systemic circulation.

Readings form the probe are monitored at 10-second interval throughout the procedure to detect any sudden changes in the 10s counting rate. The percentage of leakage, translated by increase in the number of photons read by the probe, must not exceed 10%. After this

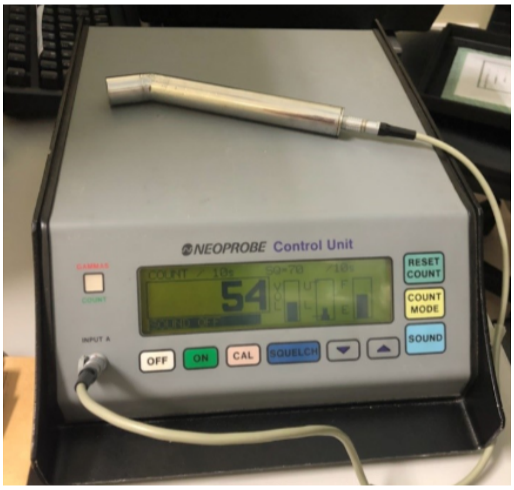

Figure 4.7: Neoprobe Gamma Detection System

limit, there are risks of systemic complications due to the high dose of injected cytostatics (Paulsen et al. 2015).

This monitoring is feasible due to the injection of the radiopharmaceutical into the circulation where the high doses of chemotherapeutic drugs will be administered, allowing leaks to be identified by increasing systemic activity. This is advantageous because the efficiency of limb isolation is measurable before chemotherapeutic agents are injected into the patient. Likewise, since blood leakage is measured in real time, intervention measures can be taken during the perfusion (Wierts et al. 2008).

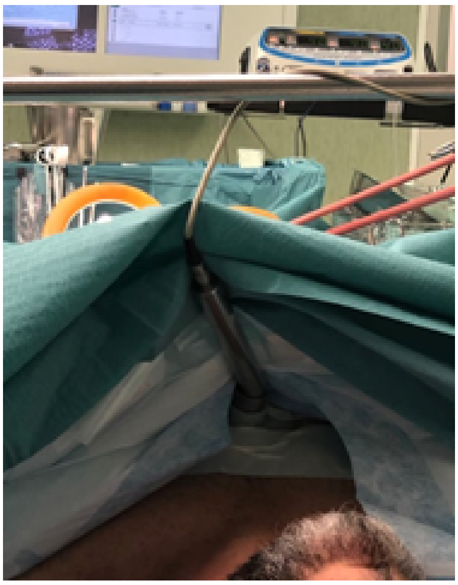

Figure 4.8: Precordium monitoring

Chapter 5

Development of acquisition and control software

Health care delivery generally encompasses complex tasks that are dependent on a lot of information. Initially, records were made on paper, however several disadvantages were associated, such as illegibility, difficulty in looking for older information, easy loss of records, etc. (Lazakidou and Siassiakos 2009).

Therefore, there is a need to use information systems, i.e., a manual or automated system used to collect, process and transmit data that contains information, in order to improve the provision of these health services and the performance of medical care (Lenz and Kuhn 2004).

All health facilities, such as hospitals and health centers, depend on information about the science of care, patients' data, care previously provided (clinical history), and care results(Lazakidou and Siassiakos 2009).

Medicine began to exploit the demanding and extraordinary capacities of computers to better meet their complex information needs, being still in constant evolution which led to the appearance of Medical Informatics. Medical Informatics is a complex domain of computer knowledge and information science that originates from the intersection of medicine and technology (Lazakidou and Siassiakos 2009) and that involves the management of information in health areas. It encompasses handling medical information management tasks such as storage, information processing, retrieval, optimal use of biomedical information, data and knowledge for future research, in order to improve the accuracy and reliability of medical services, problem solving and decision making processes of decision (Lazakidou and Siassiakos 2009).

The advantages of electronic registration over paper records include the fact that they can be accessed from multiple locations, their legibility, they can be transported everywhere and avoid the risk of loss (Musen and Bemmel 1997). In Portugal, clinical registration of patients is carried out on the health portal under the responsibility of the shared services of the Ministry of Health, which allows information to be cross-checked between the various institutions where the patient has already been and to consult relevant data on it.

5.1 Clinical records: Reality at IPO

As seen previously, clinical records are very important in the practice of medical care since they are necessary for a good clinical investigation, and they are also a powerful teaching tool. A medical record presupposes the identification of the patient, the patient's problems and the treatments already administered. Having access to the complete history can be crucial for treatment: for example, it is necessary to know the radiation doses provided or the laboratory results to continue the treatment (Dubovitskaya et al. 2017).

At any time during a patient's clinical follow-up, it may be necessary to review the results obtained from a treatment and what has been done. Thus, a report on the situation of patients is also an advantage in the provision of health services (J. Barreto and Paiva 2008). If they are well organized and structured, they provide good medical care, being easily computerized and communicable to other health professionals (Dubovitskaya et al. 2017).

5.2 Software Requirements

The Isolated Limb Perfusion technique, described in chapter 4, is a surgical procedure, performed at Instituto de Oncologia do Porto since 1990 by the Plastic and Reconstructive Surgery service to control locally advanced limb disease. The leak check was performed in the past by collecting syringe blood from the systemic circulation. It was only possible to check their presence later.

With the increase in the recurrence of this technique in treatment of neoplasms, the need arose for a more precise and safe control. On the other hand, so that a subsequent analysis of the data obtained in this procedure can be made, it is important to record these values. If the procedure went as planned, this analysis involves knowing how much chemotherapy was administered to the limb that was treated or, in case of leak, when it happened and what the values were.

For this, it was necessary to optimize the data recording in order to make it an easier, simpler and more robust process. Thus, and until today, the registration is done manually, by a physicist, on a portable computer that, with the aid of a medical device, efficiently registers and accounts for possible blood leaks.

Clinical information about patients, subject to this procedure, is collected and consulted locally by health professionals. Regular backup copies are made so that there is no loss of data resulting, for example, from a failure in the portable computer that could lead to file damaging making it impossible to access or even delete it. This data is also important for patient follow-up, as it is important to maintain the treatment process, rehabilitation after treatment and post-treatment monitoring. Likewise, the patient can visit other medical institutions for an appointment or can be transferred from one hospital to another. Thus, it is necessary to register health information in order to establish rules and limits for new treatments (Dubovitskaya et al. 2017).

5.2.1 Survey of Needs

During this treatment, various data and information are recorded, both about the patient and the technique. Although there is already a data record, its entry in the system is done manually. Before the development of the application, it was necessary to monitor, in the operating room, the different stages of the procedure as well as the understanding of all the acquired and calculated data.

The hospital physicist assigned to this procedure is the professional responsible for marking blood with the radioisotope as well as for coordinating the withdrawal and injection of syringes with blood. In addition, he is responsible for the manual recording of all patient data and values acquired in the procedure. The editing of these data is done in a spreadsheet using the Microsoft Excel program on a portable computer used exclusively for this purpose. Figure 5.1 shows the different stages of data collection, performed by the hospital physicist on duty, performed in this surgical procedure.

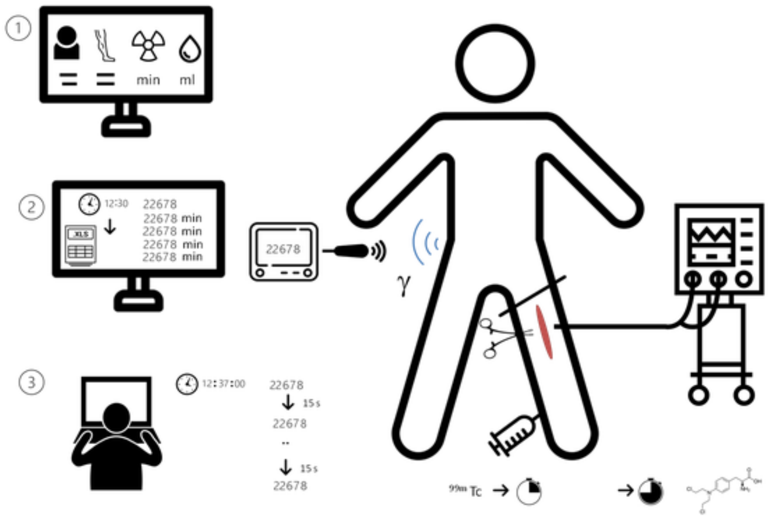

Figure 5.1: Current record mode of isolated limb perfusion technique data

The first information to be recorded in the spreadsheet, are the data related to the patient and the procedure previously defined in a preparatory meeting.

The recorded data are limb to be treated (upper or lower), name, age, weight (Kg), gender, and patient ID. Regarding the procedure, radioisotope half-life (hours), rate - that depends on the equipment and its sensitivity (30% for the Neoprobe); this value can be modified as the values are acquired, and limb blood volume subject to treatment (liters). The physicist enters the block, normally, when the medical team has already prepared the patient (Figure 5.1 - 1), i.e., when the cannulation is finished.

The next step is to determine the baseline - *Baseline (2)*. At this stage there are already two distinct circuits of blood circulation (systemic and extracorporeal). Systemic circulation is ensured by the heart while blood circulation in the limb is ensured by an extracorporeal circuit.

As mentioned in the previous chapter, ^{99m}Tc is administered in the extracorporeal circuit and in the systemic circulation, in order to check the possible existence of blood flow from the systemic circulation to the limb and vice versa and, therefore, it is performed before starting the perfusion.

Then, with the Neoprobe equipment connected to the intraoperative probe, a manual recording of five initial counts is performed every minute (Figure 5.1 - 2). At the end, we determine the average of these values (average of decays) that indicate the value of the baseline. This is the first control point for limb isolation. If there are leaks here, they do not start chemotherapy and the procedure is finished).

If the baseline values are within normal parameters (approximately 20000-30000), then the infusion is initiated where the chemotherapeutic drugs, Mephalan and TNF-alpha, are administered. From this point on, the hospital physicist inserts the radioactive decays from the Neoprobe equipment in the spreadsheet. This registration is done every 10 seconds until the end of the procedure (Figure 5.1 - 3). In Figure 5.2 is represented a spreadsheet with a record of an IPO procedure.

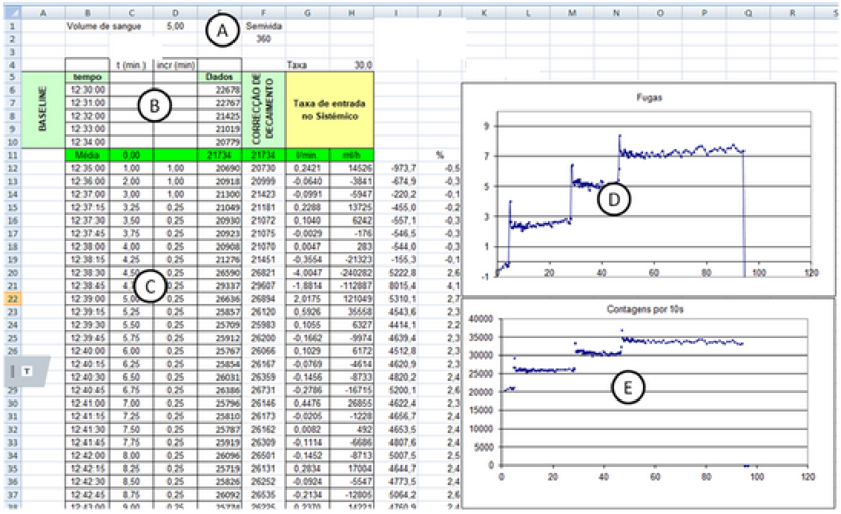

Figure 5.2: Current record sheet used in the Isolated Member Perfusion, at IPO Porto

5.2.2 Graphical Representation - Graph of counts

The graph in Figure 5.3 represents the ^{99m}Tc decay per time (minutes).

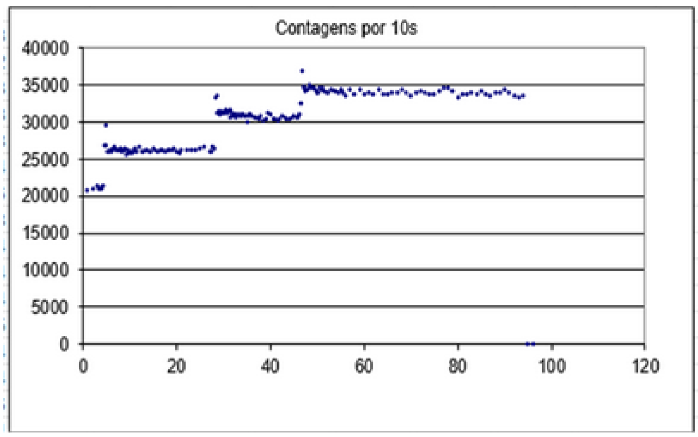

Figure 5.3: Graph of radioactive decays every 10 seconds

For the elaboration of this graph it is necessary to make a previous correction, such as the decay correction and the rate of entry into the systemic circulation (which is related to blood circulation in the extracorporeal circuit).

The decay correction is important for the control performed, since ^{99m}Tc that is marked in the erythrocytes is being quantified. The ideal would be for the radioisotope to have a long half-life so that, during the time spent in the operating room, the quantification would be constant (if the activity was always the same).

$$DecayCorrection = ReadValue \times e^{\ln 2 \times \frac{time(min)}{360}} (5.1)$$

However, and as already mentioned, this radioisotope has a half-life of 6 hours, which means that its activity is decreasing. Thus, its quantity in each instant is multiplied by what was lost with the physical decay. Basically, this correction is made to obtain a ^{99m}Tc measurement as if it had not fallen, otherwise we would have graphs with its curves falling.

5.2.3 Graphical Representation - Graph of leaks

The graph in Figure 5.4 represents the percentage of leaks from the extracorporeal circuit to the systemic circulation per time (minutes).

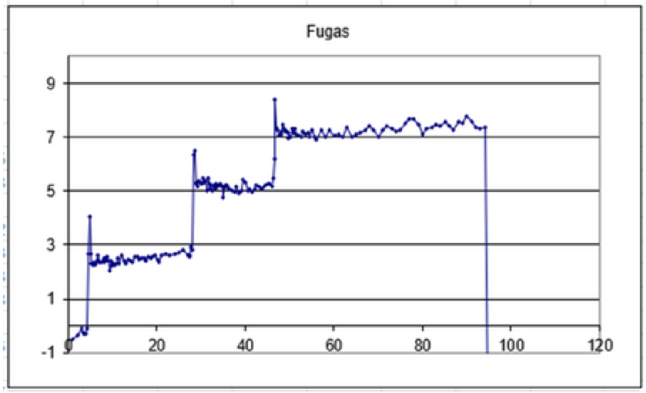

Figure 5.4: Leak percentage control graph

The peaks shown in the previous graph reflect the simulations carried out in order to ensure that the limb is well isolated from the systemic circulation, i.e., it represents the injections of blood marked with ^{99m}Tc, collected from the blood that circulates in the limb.

5.3 Advantages and Disadvantages

As mentioned earlier, data recording is done manually, by a physicist, on a portable computer. Although there is already a data record, its entry in the system is done manually.

It is possible to list some disadvantages inherent in this way of recording data. The information is not available in the system to be accessed remotely, either by the medical team that accompanied the patient or by other doctors from other institutions.

On the other hand, the use of this technique with this recording mode is not practical since these values are entered manually, in an Excel sheet, on the computer that they always use for this procedure.

Now, since this control is time consuming, it becomes extremely tiring and exhausting, since a great concentration is necessary so that no information is missing. On the other hand, it makes it impossible to pay more attention to other factors during the procedure and increases the probability of error in recording these same values.

The connection of the equipment to a computer and automatic acquisition of the decay of the administered radioisotope are one of the objectives of this work.

5.4 System Requirements

For a better understanding of the software to be developed, a description of its functionalities is made, i.e., capacities and conditions to which it must respond.

5.4.1 Functional Requirements

Functional requirements define the function of the system, representing these functions in terms of tasks and services. It documents how it should react to specific inputs, how it should behave in certain situations and what it should not do (Soltani et al. 2012).

The software to be developed must:

- Allow to record patient data;
- Allow forward and backward pages as soon as it is convenient;
- Allow to manually record the first five counts read on the equipment;
- Automatically acquire the counts as soon as the user clicks start;
- Allow to save the patient's data together with the obtained graphics;
- Allow viewing existing files;
- Send a pop-up message in case the equipment is not connected to the computer;

5.4.2 Non Functional Requirements

On the other hand, non-functional requirements define the properties and restrictions of the system. They are defined through FURPS (functionality, usability, reliability, performance and scalability) which is a model for classifying the quality attributes of the software.

The functionality specifies the utilities that are not related to the use cases (audit, reporting, interoperability and security).

Usability assesses the user interface (error prevention, aesthetics and design, help, documentation, consistency and standards).

Reliability refers to the integrity, compliance and interoperability of the software (frequency and severity of failures, possibility of recovery, extent and duration of failure (recovery/survival) and predictability (stability)).

Performance evaluates the performance requirements of the software (response time, resource consumption (energy, RAM, CPU, cache, among others), capacity and scalability) (Soltani et al. 2012).

The designed system must:

• Issue maintainability and scalability (the use of layers allows to better separate the functionalities of a system, making it modular and facilitating its maintenance);
• Have good usability, with a presentation that allows easy understanding and interaction - user friendly;
• Have a short response time.

5.5 System Design

Overview of the Implemented System

The software architecture, represented in Figure 5.5, was designed so that its use is quick and intuitive. In this sense, there are two possible scenarios: Acquisition and recording of data in real time or consultation of files.

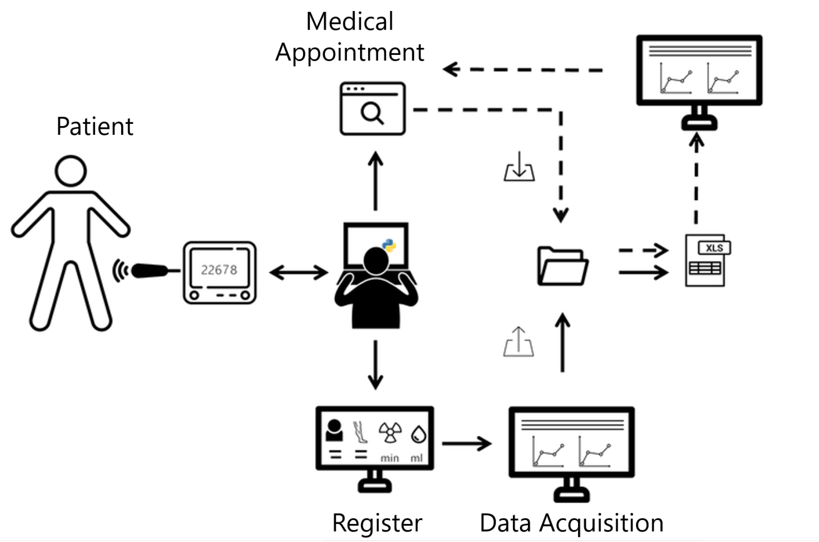

Figure 5.5: Overview of the Implemented System

The main functionality of the software, which is based on a graphical user interface, is the connection to the medical device (equipment and the intraoperative probe) whose purpose is to acquire, at regular intervals, the counts related to the decay of the administered radioisotope. In real time, two graphs will appear (leaks and counts as a function of time). At the end of the procedure it is possible to save all the acquired data in a folder, chosen by the health professional, in *xls* format.

The user may also, on the other hand, consult any procedure already performed. The 'Consultar' option will allow you to load any *xls* file related to past procedures and view the acquired data, as well as the generated graphs.

Chapter 6

PerControl: Implementation

6.1 Python - The Programming Language

For the development of the software, the programming language chosen was Python. It is a high level language, which means that it has a level of abstraction close to human language. It is multiplatform and interactive and can be run on different operating systems. Another advantage is the fact that it is object oriented, allowing the creation of structured programs and commands for functional programming as well as through its interpreter, allowing to execute parts of the code and obtain results immediately as it is programmed (Luz 2017).

It is expanding strongly in the scientific area and it is predicted that its popularity will continue to grow as it improves (Srinath 2017). Therefore, Python was the preferred language over others, since it is easy to learn and very comprehensive, allowing programmers to express concepts in fewer lines of code, having efficient data structures and a simple approach to object-oriented programming, being the most suitable for creating applications of this type. The Python interpreter (program that reads and executes the code) and the extensive standard library are available for free and can be extended with new functions and data types implemented in C/C ++ (Srinath 2017).

6.2 Graphical user interface - GUI

Python also provides a wide variety of accessible structures for the effective and interactive design of a graphical user interface - *GUI*. Qt is a framework for developing graphical interfaces using the C ++ programming language as a base. Its main feature is the possibility of creating multiplatform applications from the same source code, in addition to having several other features not related to the *GUI*, such as, for example, databases, networks and 3D graphics reproduction. (Summerfield 2007).

PyQT, one of the popular Python interfaces, is a *GUI* library for design. The main different *PyQT* options for GUI development involve *Tkinter*, *PySide*, *GTK*, *Kivy*, *WxPython* and more. In this way, *PyQT* is often considered the best Python toolkit for designing graphical interfaces (Shrunkhla, Tripathi, and Reddy 2019).

The design and implementation of the complete framework is associated with tasks performed throughout the development of the program. Thus, after designing the interface, the system logic is implemented according to the functionality requirements of the project. For the development of *PerControl* it was necessary to go through two phases: Design of the graphical interface and the implementation of the backend logic and its functionalities.

6.3 Development Tools

As an integrated development environment (IDE), *Spyder* (version 3.7) was used, which is a powerful scientific environment written in Python for Python. It is a graphical interface very similar to Matlab, making it easier to edit scripts, test, debug and visualize graphics (Python 2020). It is widely used for Python developers, mainly by data scientists, since it has integration with the main libraries such as *NumPy*, *SciPy*, *Matplotlib*, *IPython* and *PyQT*.

To create the graphic component of *PerControl*, *QT Designer* was used (Figure 6.1). *QT Designer* is a graphical tool that allows you to design and create graphical user interfaces (*GUIs*) from *QT* widgets.

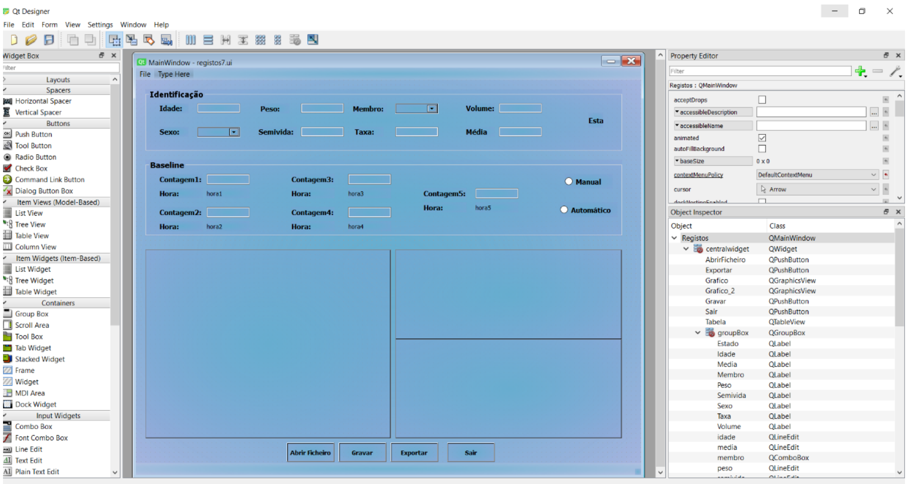

Figure 6.1: Projections in*QT Designer*

The widgets and forms created integrate with the programmed code, using *QT's* signal and slot mechanisms to easily assign the behavior to the graphic elements. In addition to being easy to design, it consumes much less time and all properties defined in *QT Designer* can be changed dynamically within the code (Designer 2020).

6.4 Implementation

In order to make it quick and intuitive for health professionals, a common shortcut and the IPO icon (Figure 6.2) were created in order to be easily identified and executed.

Figure 6.2: Main icon of *PerControl* Software on the Desktop

6.4.1 Construction of the Graphical Interface - PerControl

For the *PerControl* software, three windows were created using *Qt Designer*:

- Mainwindow.ui;
- patientData.ui;
- acquisicaoDados.ui;

For each of the projected windows, different widgets were used and, in the end, *Qt Designer* generated *.ui* files for *Qt*. After creating the *.ui* files, the *pyuic* tool was used to generate Python programs. The conversion to Python files (*.py*) was obtained, on the command line, using the command *pyuic5.bat -x filename.ui -o filename.py*.

The advantage of using Qt Designer is that whenever there is a need to make changes to the interface (add or change the position of objects) the logic behind the *GUI* is not affected.

Thus, when we run the *.py*file, the application's GUI has the same aspect of the design idealized in *Qt Designer*.

Each widget belonging to a graphical interface communicates with another widget through signals and slots. Whenever there is an action by the user, a signal (SIGNAL) is generated that calls a specific function to handle the signal (SLOT). The Worker (Figure 6.3) and *WorkerSignals* (Figure 6.4) classes are important when it comes to events and deal with all execution processes.

```
class WorkerSignals(QObject):

    finished = pyqtSignal()
    error = pyqtSignal(tuple)
    result = pyqtSignal(object)
    progress = pyqtSignal(str,str,int)
```

Figure 6.3: Class WorkerSignals

Most GUI applications are event-based, which means that execution is carried out through user interaction, signals and timers. In an event-oriented system, when a button is pressed an event is generated that the system manipulates to later produce some expected output. Events are sent and removed from the event queue and processed sequentially. Thus, the event loop is initiated when *app.exec_()* is called on the*QApplication* object and is executed on the same thread (component of a process) as Python code.

By convention, any execution triggered by the event loop is also performed synchronously in this chain. That is, whenever the *PyQt* system realizes something in the code, communication through the window and GUI interaction are frozen. In this way, and since long-running tasks are performed, such as opening or saving a file or even drawing the graphics as the data is acquired, there would be problems if it were not working outside the GUI thread and between threads. It is then possible to run independent tasks simultaneously through threads.

The threads share the same memory space and, consequently, are quick to start and consume few resources. Thus, shared memory makes data transmission between threads trivial.

```python
class Worker(QRunnable):

    def __init__(self, fn, *args, **kwargs):
        super(Worker, self).__init__()

        # Store constructor arguments (re-used for processing)
        self.fn = fn
        self.args = args
        self.kwargs = kwargs
        self.signals = WorkerSignals()

        # Add the callback to our kwargs
        self.kwargs['progress_callback'] = self.signals.progress

    @pyqtSlot() # DECORADOR QUE CONVERTE UM MÉTODO PYHTON SIMPLES NUM SLOT QT
    def run(self):
        # Retrieve args/kwargs here; and fire processing using them
        try:
            result = self.fn(*self.args, **self.kwargs)
        except:
            traceback.print_exc()
            exctype, value = sys.exc_info()[:2]
            self.signals.error.emit((exctype, value, traceback.format_exc()))
        else:
            self.signals.result.emit(result)  # RETORNA O RESULTADO DE UM PROCESSO
        finally:
            self.signals.finished.emit()  # FEITO (DONE)
```

Figure 6.4: Class Worker

There is a simple interface for executing tasks on other threads and it is created around a class: *QThreadPool* (Figure 6.5). This is the method by which the work/task to be executed for alternate threads is passed. The great advantage of *QThreadPool* is that it handles the task execution queue.

```python
self.threadpool = QThreadPool()
```

Figure 6.5: *QThreadPool*

In this way, to execute a function on another thread, an instance of the Worker class is created, which is previously created to deal with the execution processes, and then it is passed to the *QThreadPool* instance and it will be executed automatically.

6.4.2 Main Interface

When the user clicks on the symbol available on the desktop, the main window will appear. Figure 6.6 shows the main window of the *PerControl* software and consists of an image and two buttons.

The image is presented in the center of the window with the symbol identifying the institution (IPO). The 'Novo' and 'Consultar' buttons allow the healthcare professional to start a new record for a new procedure or consult an existing record on the PC.

Figure 6.6: Main window of the *PerControl* application

6.4.3 New Procedure

Figure 6.7 represents the window that will appear to the user whenever a new Isolated Member Perfusion is performed. This window is divided into two main areas: A (Patient Data) and B (Technique Settings).

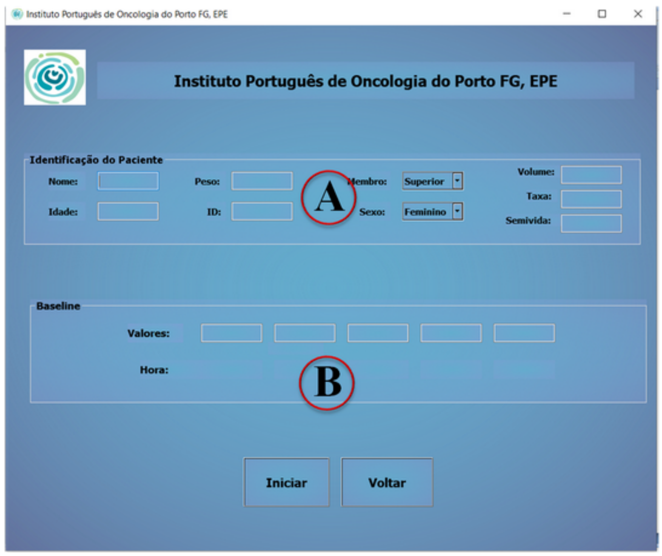

Figure 6.7: Second PreControl application window

Patient Identification

Before starting the procedure it is mandatory to insert, on the part of the user, relative data of both the patient and the technique. These configurations are shown in Figure 6.8.

Figure 6.8: Data of the patient subject to the Perfusion Technique

The *Name*, *Age*, *Weight*, *ID* and *Sex* are fields related to the patient's personal data and which will be essential for later consultation and data recording. The Member field allows you to select which member of the patient will be subjected to the intervention while in the Volume field it should be filled with blood volume of the member subject to treatment so that at the end of the treatment the patient receives exactly the same amount.

Technical Data

It is also mandatory to fill in some settings related to the technique and the radioisotope used. The rate of entry into the system (measured as a percentage) and the half-life (in minutes) of the radioisotope to be used must be entered in the 'Taxa' and 'Semivida' field, respectively.

Baseline

Later, at Baseline (Figure 6.9), the user will have to register the first five acquisitions that will serve as a test. This step is very important as it ensures that the limb subject to treatment of the patient is well isolated from the systemic circulation. In the event that these first five acquisitions have differing and unreasonable values, the procedure is terminated.

Figure 6.9: Record of values for determining the baseline of the Perfusion Technique

For each value entered, manually, the time for that entry will automatically appear. The time that will appear is the time on the computer where the program is installed, so it is essential that the PC used has the updated date and time. To obtain the information on the time of collection of this data, the *datetime* module (native Python library) was used. One of the advantages of the *datetime* class is that it can obtain the time using the *now()* method.

On the other hand, and since it would not be safe to start the automatic acquisition without these first five acquisitions being registered and evaluated, if any value of the Baseline remains to be filled, the respective field will appear in red (Figure 6.10), not allowing to proceed to initiate the procedure.

Figure 6.10: Value recording

In this sense, in case the values are considered normal, the user can then select the 'Iniciar' button in order to start the acquisition. The user will be redirected to another window where patient data will be transferred. As in the previous window, it is possible to return to the home page using the 'Voltar' button. Whenever any of these parameters are not met, by the user, the program does not allow connection to the equipment (Figure 6.10) and does not advance to the next window.

The functions that allow python to access the serial port are defined in the serial module. In the distribution used, *PySerial* is not installed by default, so it is necessary to install it. In Python, the Serial function or method (PORTA_SERIE, BAUD_RATE), located in the serial library, initiates a connection with the serial port.

For data to be received correctly, there must be synchronise, that is, the same transmission rate (BAUD_RATE), between the sending device and the receiving device. In this case, 9600 bps was used.

If the medical device is not connected to the PC, an alert message will appear (Figure 6.11) that will not allow the procedure to proceed.

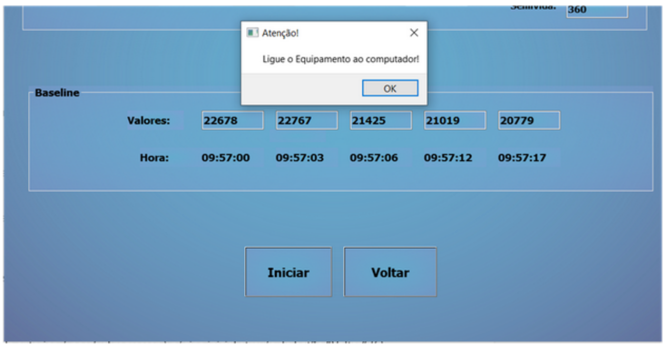

Figure 6.11: Alert message in value recording

Data acquisition

Figure 6.12 represents the window that will appear only if all initial and configuration parameters are correct and the equipment is properly connected. This window consists of four main areas.

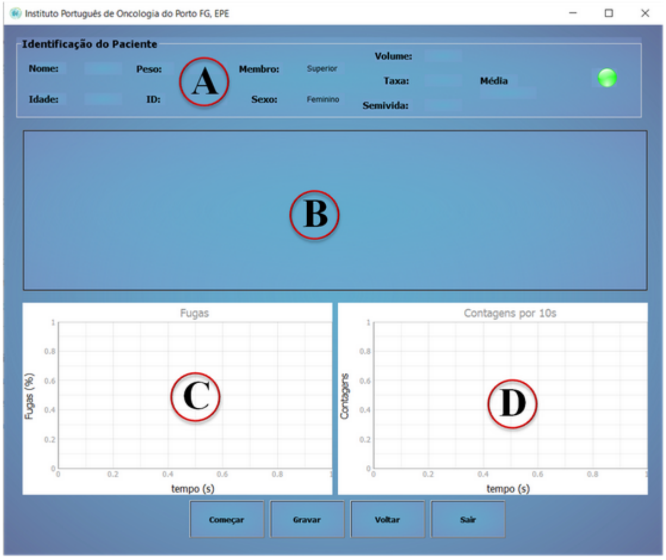

Figure 6.12: Main areas of data acquisition

In (A) the data (patient and technical data) entered in the previous window are displayed and transferred to this window. In addition to these, the baseline value (average count value) of the values entered manually and an icon that informs whether the counting equipment is connected to the computer (green) or not (red) is displayed. The status of this flag changes with the states of the Start/Stop button.

It is precisely with the activation of this button that the acquisition of the count from the equipment for processing and treatments begins. In (B), information about the acquisition date and time (10-second or pre-established intervals) and the count value sent by the medical device connected to the PC are shown in a table (rows and columns) (Figure 6.13). The remaining columns relate to intermediate calculations, i.e., indirectly determined. The Decay and % columns represent the decay of the ^{99m}T per time (minutes) and the percentage of leaks from the extracorporeal circuit.

	Data	Horas	Contagens	t	Decaímento	I	ml	aa	%	incr
1	2020/09/18	18:55:47	20690	0.07	20693.0	-3.4298	-205788.0	-1040	-0.5	0.07
2	2020/09/18	18:55:47	20918	0.07	20921.0	-2.6805	-160830.0	-812	-0.4	0.0
3	2020/09/18	18:55:47	21300	0.07	21303.0	-1.425	-85500.0	-430	-0.2	0.0
4	2020/09/18	18:55:47	21049	0.07	21052.0	-2.25	-135000.0	-681	-0.3	0.0
5	2020/09/18	18:55:47	20930	0.07	20933.0	-2.6411	-158466.0	-800	-0.4	0.0
6	2020/09/18	18:55:47	20923	0.07	20926.0	-2.6641	-159846.0	-807	-0.4	0.0

Figure 6.13: Table with the records of acquisition

In (C) and (D) graphs are displayed in real time (Figure 6.14) for the Decay and % columns calculated and displayed in (B).

In each of the graphs, the user can enlarge a certain area of the graph using the zoom tool (Figure 6.15), returning to the original display through an icon in the lower left corner.

Whenever the user wants to interrupt the acquisition, he can do it through the 'Começar'/'Parar' button and return whenever he wants.

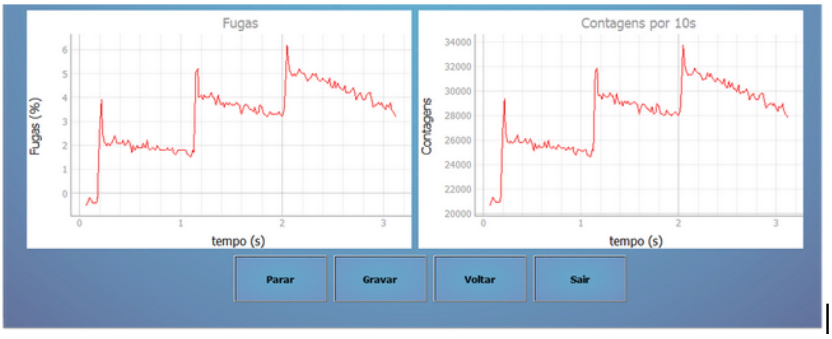

Figure 6.14: Overview of the values acquired from the equipment and the graphics obtained

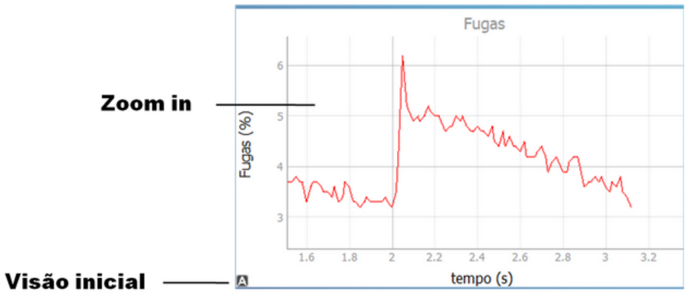

Figure 6.15: Graph of the percentage of leaks per unit of time zoomed

Data Exportation

One of the implemented features is the possibility of exporting all data related to the procedure to spreadsheet programs (Microsoft Excel, Google Docs, Open Office). When the user presses the 'Guardar' button, the file is saved in a standard folder (Figure 6.16).

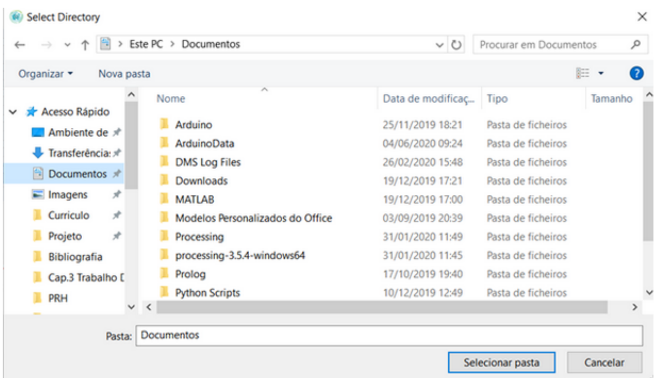

Figure 6.16: Option of choose a directory to save a document

However, it is possible to change and save the document in another location. In order to facilitate the search for a specific patient file, a specific nomenclature for these files was created. The technique used was to put the patient's personal data (first name + last name + patient id) followed by the date (year + month + day) on which the procedure was performed (Figure 6.17).

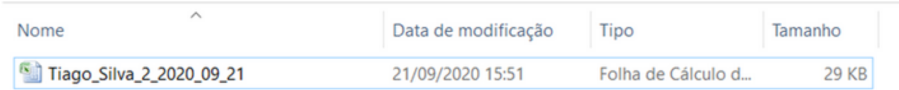

Figure 6.17: Example of an *xls* file with a patient's records

Although this nomenclature appears by default, it can be changed by the user when the file is exported. When exporting, a *.csv* file is produced with four separate spreadsheets (Figure 6.18). The first sheet *(Table)* contains the data collected in the procedure and properly organized. On the *PatientData* sheet, personal data and initial technique settings are saved. The *Leaks* and *Counts* sheets contain the graphs of the percentage of leakage per unit of time and radioactive decays per unit of time, respectively.

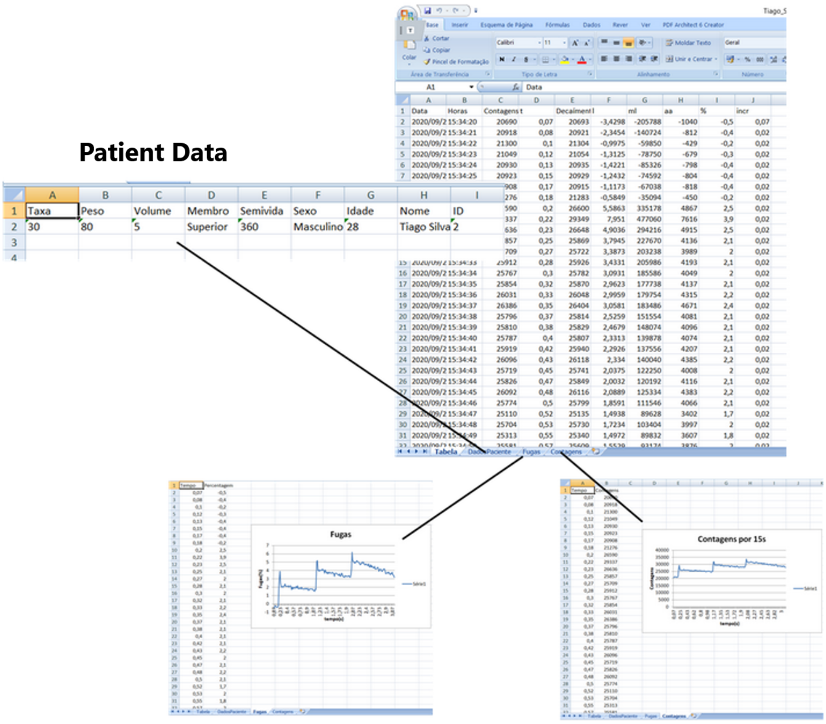

Figure 6.18: Excel sheet with information saved by sheets

At the end and as with the rest of the windows, it is always possible to go back to the initial window or exit the application.

Procedures Consultation

Whenever a health professional wants to consult the data of a certain procedure already performed, he can do it in two ways: through the *PerControl* software or using a program that allows opening a spreadsheet (*.csv*) In the *PerControl* software this functionality if available in the main window (Figure 6.19). When clicking on the 'Consultar' button, a new window will appear to the user (Figure 4.18) that will allow the consultation of existing records on the computer of previously performed procedures.

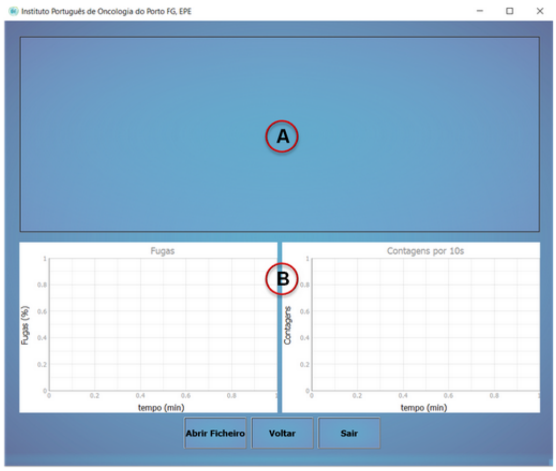

Figure 6.19: Window after pressing the consult button

In this new window, the user will be able to consult the data of a procedure already carried out and saved in *.csv* format. It has three data presentation areas. In (A) are shown all values recorded during the procedure, including the date of the technique, counts and respective hours, among others, entered by the physicist and collected by the equipment, separated by columns. This window also shows the graphs (B) relative to the percentage of leaks measured and the counts obtained by the Neoprobe equipment every 10 seconds, which allows to verify the occurrence of leaks. With the 'Abrir Ficheiro' button, the user will then be able to choose the file to which he wants to access the data. In Figure 6.20 we can see the example of consulting the registration of a procedure already carried out.

Figure 6.20: Window after pressing the consult button filled

Tests and Results

One of the objectives of the work is the automatic reading of data from the Neoprobe Gamma Detection System. This equipment has a serial port (RS232) for communication as well as several input and output ports (Figure 6.21).

(a) (b)

Figure 6.21: (a) Neoprobe® Gamma Detection System (b) Multiple entries of Neoprobe equipment

The Neoprobe Gamma Detection System equipment, in a first phase, was available for the first tests. Since it is a piece of equipment from the mid-1980s of the 20th century, it was not possible to access the paper manual. Several attempts have been made to obtain the same in electronic format from the company that produces the equipment, but without success.

To fill this gap, an Arduino development board was used to simulate the operation of the radioactive decay counter (Figure 6.22).

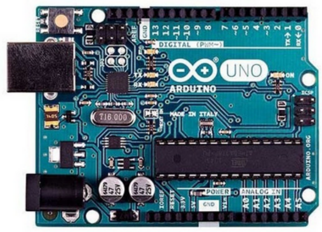

Figure 6.22: Arduino Platform

The Arduino is a development board based on the Atmel AVR microcontroller, which has low cost input/output circuits and is easily programmed through a USB port. The platform uses the programming language based on C/C ++ and programmed through the Integrated Development Environment (IDE) available on the official Arduino website (Abdullahi 2014).

Figure 6.23 depicts a diagram that allows the connection of the Arduino platform (replacing the Neoprobe® Gamma Detection System equipment) to the *PerControl* software.

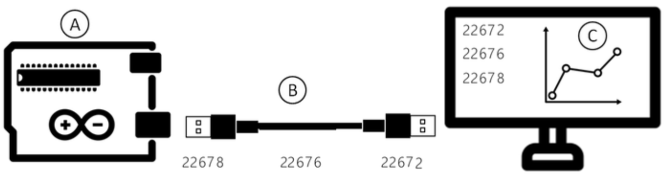

Figure 6.23: Assembly scheme

In order to simulate as accurately as possible the radioisotope decay recorded by the Neoprobe equipment during a perfusion, a program was created whose objective is to send these counts.

The counts from the technique used in an intervention already performed on a patient were collected from the Excel records sheet. These data were placed in the *countingData* vector. Figure 6.24 shows the developed program that simulates Neoprobe data.

Figure 6.24: Code developed for Arduino Uno to simulate data from Neoprobe equipment

Every 10 seconds the Arduino will read the data from the *countingData* vector and send it through the serial port (USB) that is connected to the computer that has the *PerControl* software installed. The samples are sent through the serial port with a transmission rate of 9600 bps (bits per second) with a time interval of 10 seconds. In order to check if the data were being sent correctly, the Arduino IDE's Plotter Serial tool was used (Figure 6.25).

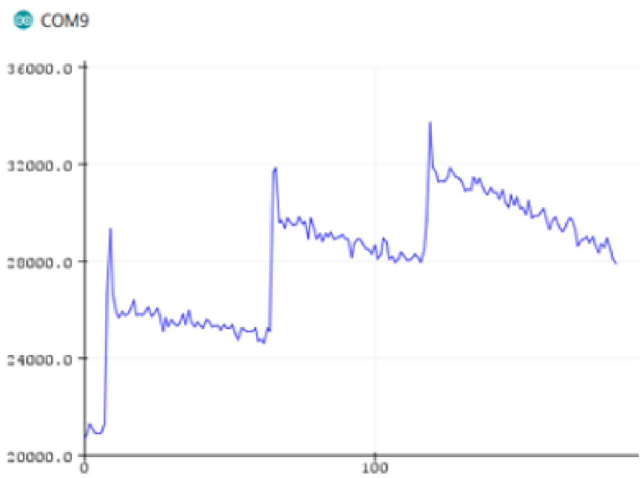

Figure 6.25: Graph obtained through the Arduino IDE's Ploter Serie tool

To test the functionality of the *PerControl* software, data from a procedure already performed and the connection to the Arduino Platform were introduced into the software. The result obtained at the end of the procedure is shown in Figure 6.26.

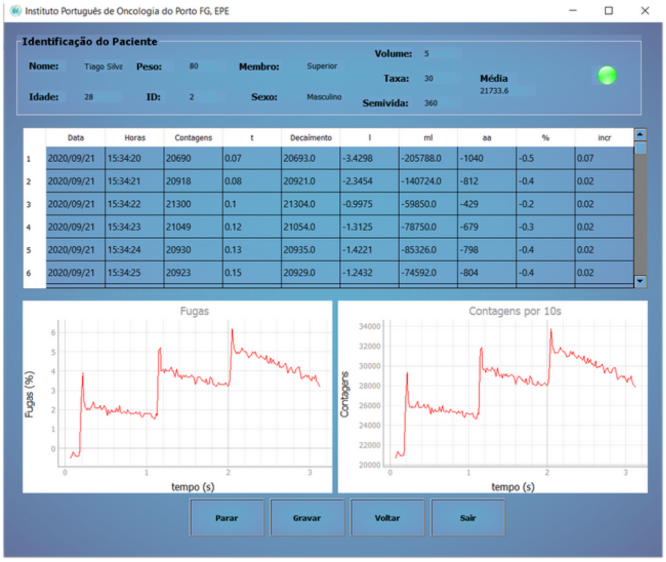

Figure 6.26: Result obtained at the end of the procedure

Finally, the values and graphs were compared between the *.csv* file available and the file generated by the *PerControl* software.

Calculation Sheet

Contagens	Decaímento	%
21734	21734	%
20690	20730	-0,5
20918	20999	-0,3
21300	21423	-0,1
21049	21181	-0,2
20930	21072	-0,3
20923	21075	-0,3

Software PerControl

Data	Horas	Contagens	t	Decaímento	%
2020/09/19	18:11:38	20690	1	20730	-0,5
2020/09/19	18:12:38	20918	2	20999	-0,3
2020/09/19	18:13:38	21300	3	21423	-0,1
2020/09/19	18:13:53	21049	3,25	21181	-0,2
2020/09/19	18:14:08	20930	3,5	21072	-0,3
2020/09/19	18:14:23	20923	3,75	21075	-0,3

Figure 6.27: Comparison of the first six samples between the spreadsheet used and the *PerControl* software

Chapter 7

Conclusions and Future Work

In this dissertation, an automated method for recording radioactive decay is presented in order to control possible blood leaks from the extracorporeal circuit to the systemic circulation during isolated limb perfusion, relieving the work of health professionals who resort to this technique.

The contributions include the development of a software capable of automatically collecting and recording data from Neoprobe Gamma Detection equipment, used for this same purpose.

Thus, the main objectives inherent to this work were the development of a simple, intuitive and versatile interface, which would reduce the probability of error in the registration of values, not allowing to pass steps, possibility of integration with other models of other devices and with other types of communication and increase the attention of health professionals.

In terms of performance, the projected methodology can be improved in some functionalities, such as the emission of an audible alert in case the number of photons read by the intraoperative probe exceeds the permitted limit, save the data in a database in order to have more security and avoid data loss, to implement the history query tool for web format in order to allow access anytime and anywhere, and implementation of a possible analysis tool based on the history of the procedure in order to assist in decision making.

In this way, the future work will focus on extending the set of features and improving the performance of the application, redirecting towards even more practical and functional solutions as an alternative to the adopted application.

Current features include data collection and recording, visualization of graphs and download of results in an excel file. The interface was designed to be simple and intuitive and with the aim of making the procedure a simpler and more practical process.

The present application was tested only with the arduino, simulating the values received from the equipment. In addition to the pandemic we were subjected, which delayed the testing process, the intraoperative probe was damaged on the process and has not yet been repaired.

Because of this, it was not possible to anticipate the testing phase. However, as soon as possible, and regardless of the delivery and/or presentation of this paper, the software will be tested with the equipment for which it was designed.

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