Chapter 6

Non-Conventional Radiotherapy for Total Body Irradiation: Antecedents, Current Research and Perspectives

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Additional information is available at the end of the chapter

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Abstract

In addition to the conventional techniques used in radiotherapy, certain procedures, special-called for the treatment of both some cancer diseases and clinical application are usually required. Such practices typically manifest a technical problem with respect to the equipment used, which requires important adjusts that diverge significantly from the standard implemented in the common treatments. Total body irradiation is one of those special techniques, in which the radiation target is the entire patient body. In a broad sense, the concept covers all radiation processes with photon beam fields more wide than standard field size. Treatment with total body irradiation is usually applied with purpose of providing immunosuppression to prevent rejection in bone marrow transplantation procedure. Diseases such as aplastic anemia and a varied number of leukemia and lymphomas respond favorably to this treatment scheme. Beams of megavoltage photons, such as Cobalt sources and linear accelerators, are used for such purposes. In this chapter, the technique will be studied analyzing its definition and first applications. The chapter includes a description of the main treatment schemes on which it is based, covering the calibration process, ergonomic criteria as well as the main contributions in the clinical research field, opportunity fields and novel research perspectives.

Keywords: total body irradiation, radiotherapy, lineal accelerator, non-conventional, in vivo dosimetry, portal imaging, ergonomics

1. Introduction

Radiotherapy, surgery and chemotherapy are the three main modalities used in oncology for the treatment of diseases caused by malignant cells [1, 2]. Unlike other medical specialties, which essentially maintain their sureness in the clinical knowledge and experience of the

medical specialist, in radiotherapy, due to the use of ionizing radiations, it is required besides the confidence in modern technologies, as well as the nearest collaboration of many other professionals. The radiotherapy team consists of a group of oncologists, medical physicists, dosimetrists, nurses and technicians [3], all with different levels of training, but with a goal, the need to understand the physical basis of radiation therapy.

Radiotherapy is a specialized discipline in the field of medicine, which involves the use of high-energy ionizing radiation for the treatment of cancer cells [4]. The radiation sources used in this clinical field can be located throughout internally to the patients (brachytherapy) or external way (teletherapy). During the first 50 years of radiotherapy, technological progress was relatively scarce and based mainly on X-ray tubes, Van de Graaff generators and Betatrons. The invention of the Cobalt 60 machine [5] around 1950 by Harold Elford Johns in Canada, gave a new twist to the radiotherapy technique, becoming for several decades the most important tool for cancer treatments (**Figure 1**).

However, the most widely used system for radiotherapy treatments today is the use of Linear Accelerators (Linac). The concurrent development of this system overshadowed the extraordinary impact of the 60Co source, becoming the most widely used radiation source in modern radiotherapy.

Conventional radiotherapy is usually focused on traditional studies (breast cancer, cervical cancer, etc.) where the equipment is calibrated (**Figure 2**) for radiation beam emission with remote settings of 1.00 m and maximum radiation fields of 0.40 × 0.40 m [6, 7].

In addition to these conventional techniques, several procedures, special-called, for the treatment of certain diseases and clinical applications are required. Such procedures manifest a technical problem in essence because the equipment used requires certain modifications that diverge significantly from the adjustments implemented in the more common treatments. Total body irradiation (TBI) is one of those special techniques, in which the radiation target is the entire patient body. In a broad sense, the TBI concept covers all radiation processes with

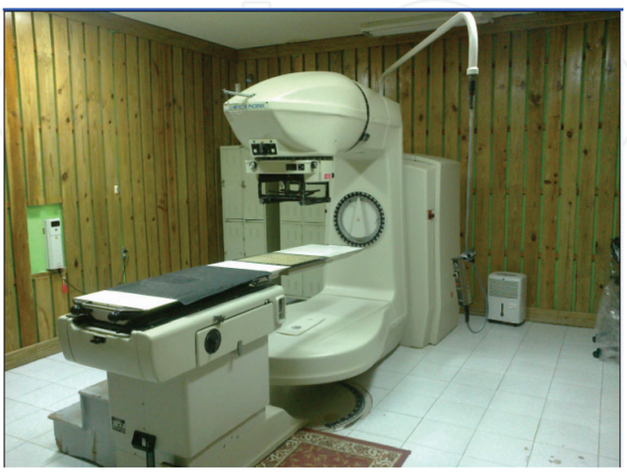

Figure 1. 60Co clinical unit (Theratronics, Ottawa, Canada). Courtesy of Ing. Antonio Almonte, from Dr. Heriberto Pieter Cancer Center, Santo Domingo, Dominican Republic.

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Figure 2. Varian linear accelerator for clinical use, and the basic equipment for radiotherapy calibrations. (A) Computerized water phantom system, (B) PTW ionization chamber N31003 no. 975; (C) Scanditronix Wellhofer; (D) Fixed computer system; and (E) Keithly CNMC electrometer. Courtesy of Dr. Carlos Esquivel, from Cancer Therapy & Research Center, San Antonio, Texas, USA.

long radiation fields, that is, with fields larger than the standard maximum of 0.40 m × 0.40 m. Megavoltage photon beams, such as Cobalt-60 sources and linear accelerators, are used for such purposes.

2. Total body irradiation

TBI is a technique accepted as radiotherapy treatment and frequently used in combination with chemotherapy as a complementary regimen for bone marrow transplants [8, 9]. Diseases such as aplastic anemia [10] and a varied number of leukemia and lymphomas [11, 12] respond to the TBI treatment. Ewing's sarcoma, advanced non-Hodgkin lymphomas, lung cancer and lymphosarcoma have also been treated in combination with TBI therapy [13].

The first applications of TBI date back to the early twentieth century, when in 1907 the German Friedrich Dessauer published the first work that has been recorded [14]. Another of the pioneering works on TBI, carried out in the United States, corresponds to the studies done by Heublein [15], who implemented an arrangement in which four patients could be irradiated simultaneously using a Coolidge tube.

A large number of authors have worked on the implementation of different arrangements for TBI applications, being probably the irradiation technique that considers the beam of radiation in a fixed position and keeps the patient in vertical position, the most commonly used

by different cancer centers. However, the experimental results usually show significant variations in the dose levels between patients, which represent a poor reproducibility of the different protocols. These discrepancies may be influenced, to some degree, by illness and patient fatigue associated with chemotherapy sessions, which makes it difficult for many patients to remain in the proper treatment position during prolonged exposure times.

Many of the first clinical experiences with TBI were carried out in centers with special designs and facilities. However, and due to the increased need to treat an important variety of diseases, patients are now commonly treated in commercial units.

2.1. Treatment schemes for TBI

Basically, the TBI treatments fall inside two general categories: bilateral irradiation (lateral TBI) and antero-postero total body irradiation (AP-PA TBI). At the first one [16], patient is collocated up treatment bed, so the radiation beam is perpendicularly to the sagittal patient plane (**Figure 3**). In AP-PA TBI [17], on the other hand, the patient is placed in an anatomical position, either maintained vertically or installed in some arrangement designed so that the radiation beam is perpendicular to the patient coronal plane (**Figure 4**). In both cases, the patients are positioned in such a way that it can be completely covered by the area of the projected field. For what usually require the patient collaboration, such as asking the patient to bend their knees, in order to adequately cover the projected field.

TBI is normally implemented with the aim of achieving a homogeneous distribution of the dose at the level of the patient's median plane. However, the parameters such as the irregularities and thicknesses of the areas of the patient's contours to be irradiated have dimensions much greater than those observed in any other radiotherapy treatment therapy. Such considerations

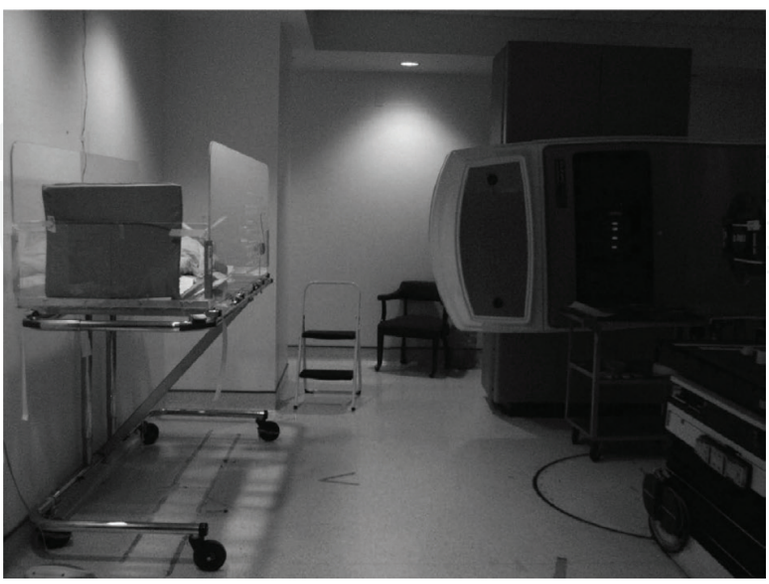

Figure 3. Image taken during one of the treatment sessions for lateral TBI at the Cancer Therapy & Research Center, San Antonio, Texas, USA. Image taken by Francisco Mesa.

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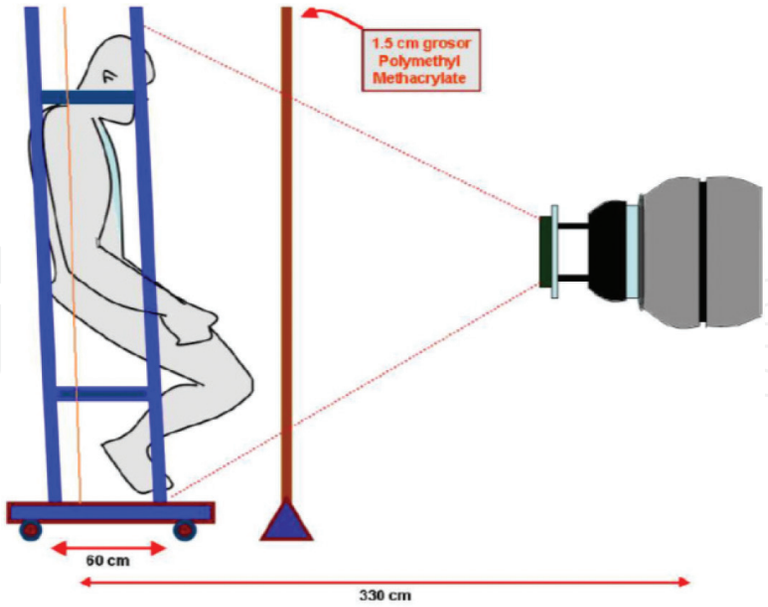

Figure 4. Illustrative diagram of the positioning of the patient during the implementation of the treatment. A vertical platform 0.015 m thick acrylic (polymethylmethacrylate) is placed in front of the patient to increase the skin dose.

seem to be more widely observable during the treatments of Lateral TBI, where in addition, the armoring technique of critical organs, such as the lung, does not turn out to be as efficient in practice as in the case of applications in AP-PA TBI.

The implementation of compensating filters is one of the most important procedures used in TBI for the correction of heterogeneity in the distribution of the dose. The arrangement formed by several sheets of lead of different thicknesses (**Figure 5**) allows the attenuation of the dose levels supplied, so that for a specific amount of *Monitor Unit* (MU) applied, different dose levels can be registered in the different contours of the body, in order to achieve the same distribution of the dose at the level of the patient's median plane. The considerable reduction of the dose levels with respect to the *build-up zone* (space or depth between the surface and the point of maximum ionization, and which is characteristic of each energy and type of radiation) is another factor to be considered regarding of the TBI applications. Such a reduction entails the application of percentages of much lower doses in skin, than the percentages in the rest of the body.

2.2. Dosimetric calibrations for TBI

The basic dosimetric parameters for TBI are the same as for standard radiotherapy, including dose rate, *percentage depth dose* (PDD), *tissue-maximum ratio* (TMR) and beam profiles (**Table 1**). However, these parameters must be measured under the specific conditions of TBI in order to obtain relevant data for clinical use (**Figure 6**). Many dosimetric problems related to the use of phantom and also radiation detectors should be considered for this type of non-conventional applications. In contrast to standard radiotherapy, for example, water phantoms are generally smaller than the field sizes and also smaller than the patient's dimensions. This causes different dispersion conditions that can generate adverse beam effects.

Figure 5. Design of the attenuation filters used to generate a homogeneous dose distribution at the level of the patient's median plane. Filter arrangements was calculated and designed to the contour of each patient. Courtesy of Cancer Therapy & Research Center, S.A., TX.

Basically, the material, equipment and general instrumentation for TBI consists of a lineal accelerator (i.e. Varian, Siemens, etc.) for clinical use; a solid water phantom (i.e. PMMA, RW3,); ionizing chambers (i.e. FC65-P Scanditronix Wellhöfer Farmer FC65/IC69; CC13 P-CC13–510-001 02); the Scanditronix Wellhofer (Farmer Scanditronix Wellhofer); a fixed basic computer system; a Keithly CNMC electrometer; a portal X-ray equipment for lateral or AP-PA linac-portal radiographs; a 1.2-cm acrylic beam spoiler and tray at the head of the gantry and thermoluminescent dosimeters for in vivo dose verification.

The determination of the type of energy used for the applications of TBI is a factor of high importance and depends on many dosimetric factors and clinical criteria.

The photon beams used for TBI have essentially the following properties: (a) point of maximum ionization is below the surface, registering, for example, for the energies of 6–18 MV, at depths of 0.018–0.032 m in water (**Figure 6**); (b) when is higher energy of the radiation beam, the lower the percentage of the dose is recorded on the surface; (c) photons have a high penetration power, registering dose levels of approximately 0.20–0.30 m deep with similar values to the surface, for energies of 6–18 MV, respectively; (d) below the *"build-up"* zone (maximum ionization), the PDD have greater intensity in photons of 18 MV than of 6 MV (**Figure 7**).

When reviewing the literature, a wider use consideration of energies of 6 MV of photons for TBI treatments is observed. However, a broader and more detailed discussion about the need and criteria of using one or another type of energy is necessary.

Dosimetric parameters	Conventional radiotherapy	Total body irradiation
Field size	≤0.40 m × 0.40 m	>1.20 m
Patient treatment distance	1.00 m	>3.00 m
Dose rate	0.05 Gy/s	0.00166–0.025 Gy/s
Dose per section	1.50 Gy/session	1.00 Gy/session
Total dose	40–50 Gy	12 Gy
Treatment technique	Source-surface distance/isocentric	Isocentric
Radiation source	Cobalt 60/lineal accelerator	Cobalt 60/lineal accelerator
Additional equipment	No	Compensation filters/special treatment bed
Calibration phantom	Computerized water phantom system	Solid phantom
Radiation detectors	PTW ionization chamber; Scanditronix Wellhofer; fixed computer system; Keithly CNMC electrometer	PTW ionization chamber; Scanditronix Wellhofer; fixed computer system; Keithly CNMC electrometer
In vivo dosimetry	No	Yes
Number of sections	1 dairy/20–40 day	2 dairy/3 day.

Table 1. Comparisons between the different dosimetric parameters that intervene in the both conventional treatment process and TBI. Description: Gy = Gray.

2.3. Treatment planning

The treatment planning stage (simulation) consists of location and identification of the area of the body to be irradiated, as well as the definition and recording of the geometric conditions and physical parameters related to the patient placement and installation. For the Lateral TBI scheme, patients are placed on the treatment bed, placed in the supine position with the knees

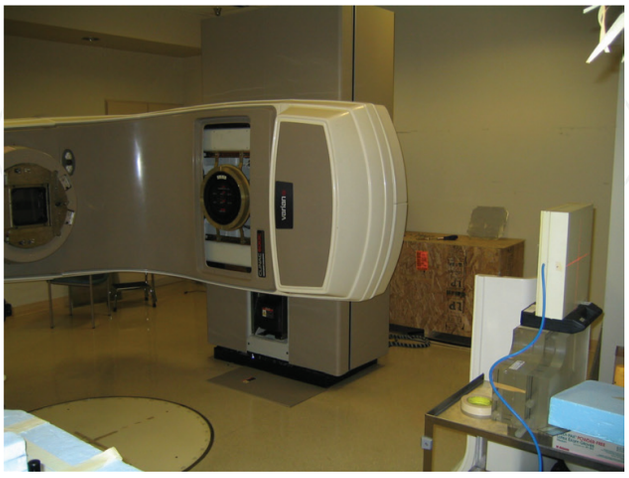

Figure 6. Experimental set-up for TBI calibration with a linear accelerator at the treatment distance (3.50 m), and an ionization chamber installed inside the PMMA solid phantom. Calibration process conduced at the Cancer Therapy & Research Center, San Antonio, Texas, USA. Courtesy of Dr. Carlos Esquivel, from Cancer Therapy & Research Center, San Antonio, Texas, USA.

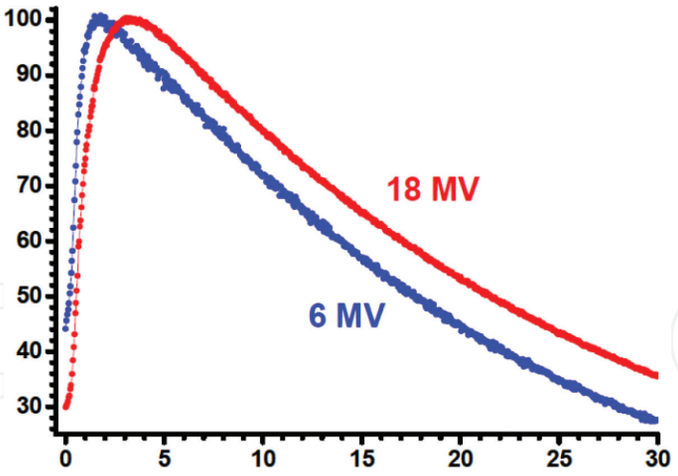

Figure 7. Behavior of the PDD for 6–18 MV photon beams, obtained with a Clinac 21EX linear accelerator, at the medical unit of high specialty, Mexican Institute of Social Security, form León, Guanajuato, Mexico.

in flexion, and placing the hands together on the abdomen. The arms in this position can serve as partial shielding of the lungs.

In the case of AP-PA TBI, for other hand, patient is placed in a kneeling chair position (**Figure 4**), and it is supported with its hands through handlebars set, holding in the chest by means of a holding strap, which keeps it in a fixed and stable position throughout the entire process. The assembly is installed inside an arrangement formed by stainless steel bars placed on a mobile base, occupying a space of 0.80 × 0.50 × 2.00 m. The system includes several cushions for the head, back and knee, in order to keep it in a comfortable position during the treatment sessions. In each case, dosimetrist must make sure that the patient is placed in a position that is comfortable and placed in such a way that it is completely localized in the projected radiation field. The contours of anatomical regions of interest (**Table 2**) are marked with permanent ink during this stage of the process. The regions of interest are usually identified in the head, neck, shoulders, breasts, abdomen, hips, thighs, knee and ankle.

The measurement of the greater thickness contour, the distance of the patient's surface area, the compensations (offset), the depth (thicknesses) of the contours (right–left, left–right, anterior–posterior, posterior–anterior), and all geometric parameter measurements were recorded at this stage of the procedure. Geometrical projections on the Gantry head, with respect to the different contours previously selected, in order to calculate the dimensions of the arrangement of sheets used for the design of the compensating filters, are determined. Subsequently, a radiographic plate of the lung is taken, which is used as a reference for the design of the protective lung blocks (**Figure 8**). For the treatment application, patients are usually cited a week after being subjected to the simulation process, and they are placed in a similar way to that process. Patients are placed inside a prismatic square box (for Lateral TBI) or stainless steel bars assembly (for AP-PA TBI). For the last one, 0.015 m thick acrylic (*polymethylmethacrylate*) vertical platform in front of the patient in order to increase the skin dose, was installed (**Figure 4**).

The system is installed at a suitable *source-axis distance* (SAD), with respect to the median plane, and in such a way that it is completely located in the field projected by the light output of the lin-

Anatomic contours	Anatomic localization descriptions	
	Lateral TBI	**AP-PA TBI**
Head	Along the longitudinal axis of the skull at the level of the pituitary fossa	Reference point defined along the longitudinal axis of the skull
Neck	Reference point defined along the patient's longitudinal axis at the level of C3/C4	It is not usually included
Shoulder	This reference point is defined as just inferior to the lateral 1/3 of the clavicle	Shoulders, lower zone 1/3 of lateral distance of clavicle
Chest	Along the patient's longitudinal axis at the level of the angle of Louis	Midline at the level of the sternum head
Abdomen	This reference point is defined as the point along longitudinal axis midplane at the level of the umbilicus	Point along navel level
Hip	Defined along the patient's longitudinal axis at the center of the pelvis at a level that is 1.0 cm superior to the symphysis pubis	Proximal femur at the level of the major trochanter
Thigh	It is not usually included	Mean distance between the ends of the femur
Knee	Along the midline in the midplane of the knee at the level of the middle of the patella	Knee, at the level of the middle of the kneecap
Ankle	Defined along the middle of the ankle at the level of the lateral malleolus	Tibia-fibula intersection

Table 2. Anatomical description of contours and location of points for dosimeter installation during dose verification for both lateral TBI and AP-PA TBI.

ear accelerator head. Once the patient is installed in the treatment position, the lead attenuation filters are placed and aligned to them so that their projections coincide with the contour marks of the anatomical regions indicated in the simulation process.

2.4. In vivo dose verification

In vivo dose verification are usually developed during the first treatment sessions with TLD-100 dosimeters previously characterized.

The TLD-100 is probably the best known dosimeter and the most widely used for clinical applications [18–23]. It was developed by J. R. Cameron in 1968 [24]. Chemically, it is composed of lithium fluoride doped with magnesium and titanium impurities (LiF, Mg, Ti). Widely accepted and commercially used, the TLD-100 is basically presented in the form of chips, with dimensions of 0.0032 m × 0.0032 m × 0.0009 m. They allow dose measurements between 10^{-6} and 1 Gy, in the linear response range; they present a high precision for measurements registration (from 1 to 2%); having 2640 kg/m^3 of density and an effective atomic number equal to 8.2, close to the biological tissue.

The dosimeters are placed at specific points of interest located in each contour defined in the simulation process (**Table 2**). They are installed on the skin of the patient under a few pieces

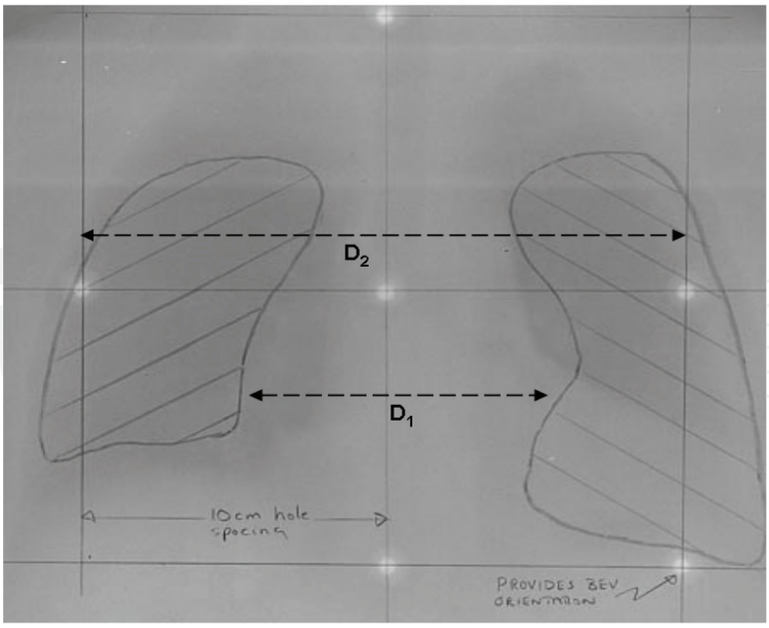

Figure 8. Lung radiography used for design of protective lung blocks. The distances from the medial plane to the medial side of the lung (*D* 1/2) and the lateral side of the lung (*D* 2/2) are shown.

(bolus) of tissue-equivalent material, to produce the maximum 0.015 m dose (*build-up*) in each reading. The dose verification at the level of the median plane is calculated for each contour by:

$$D_{\text{Midplan}} = \frac{L_{TLD}(nC) \times CF_{TLD}(^{cGy}/_{nC})}{ISL \times TMR} \quad (1)$$

where L_{TLD} is the raw thermoluminescence reading; CF_{TLD} is the calibration factor for TLD; ISL is the *inverse-square factor* and TMR is the *tissue-maximum ratio*.

2.4.1. Other in vivo dose detectors

Although thermoluminescent dosimeters are the most widely used detector for in vivo dose verification in total body irradiation, the development and implementation of new methods to determine dose levels during treatment sessions has been increasing. The use of Gafchromic EBT films [25–27], EDP-30 diodes [28] and other semiconductors [29] has been considered as an important alternative to achieve a more accurate and timely in vivo dosimetry.

However, the need to develop detectors for in vivo dosimetry that determine dose levels in a real time sense during the application of unconventional radiotherapy treatment continues to be an open opportunity for the scientific community.

3. Opportunity fields and novel research perspectives

Total Body Irradiation is a complex treatment modality that requires careful planning to specify the homogeneity in the dose distribution, as well as the location of the organs that will receive a reduced dose, or that must be completely shielded from the radiation beam.

Even though in general terms, aspects associated with the planning of radiation treatment have a scientific and methodological support regulated by international organizations through reports and recommendations [6, 7], it should also be considered that these regulations are essentially based on protocols associated on conventional radiotherapy. Regulations about the calibration processes based on the use of solid phantom and specific dosimetric settings for treatment distances greater than the standard (0.40 m × 0.40 m) are necessary for the strengthening of the technique. Similarly, the need to provide more evidence on the evolution of the tumor and its behavior in the face of the effect of radiation is evident [30]. Other criteria associated with the evaluation of different physical, biological, environmental and even perception variables could have a significant impact on the evolution of patients' health status.

The identification of anthropometric parameters, which are usually performed only during the first stage in treatment planning, and associated with certain very specific protocols, could provide relevant information regarding early recovery in patients with chronic diseases. In this sense, when reviewing the literature, it is clear the need to develop research works that provide more accurate information about the adequacy homogeneity in the distribution of doses during treatment sessions, as well as the location of organs that will receive a reduced dose or that must be "shielded" completely with respect to the radiation beam.

It is also observed the need to design ergonomic mechanisms that guarantee greater stability and comfort of the patients during the considerable treatment times. Together with the need for calculation and calibration systems with greater precision and accuracy, as well as the performing of in vivo dosimetry with greater reproducibility during treatment, constitute important opportunity areas for TBI.

4. Conclusions

De conventional radiotherapy concept, usually focused on traditional studies where the equipment is calibrated for radiation beam emission with remote settings of 100 cm and a maximum radiation fields of 0.40 m × 0.40 m, and is differences respect to TBI, as a non-conventional treatment scheme, was described. The TBI protocol has been carried out following the recommendations on clinical dosimetry calibrations of the TG-51 report [6], as well as the recommendations regarding the physical aspects of total body radiation provided by TG-29 [31]; last one published at 1986, what motivates the need to promote studies for its update according to the development of new technologies.

The protocol presented includes the development and description of the calculation process to determine both the dimensions and thicknesses of the dose compensation filters used to obtain a homogeneous dose distribution at the level of the patient's median plane. It also includes the development of thermoluminescent dosimetry for the verification of in vivo doses during the first sessions of treatment. The protocol was presented in two modalities: Lateral TBI and AP-PA TBI. In the first modality, the patients were placed on a treatment table, in supine position, with the knees bent upwards, inside a square prismatic box constructed of acrylic, and in such a way that they were completely inscribed in the projected field. In the second one, however, the patients were positioned within an arrangement designed for such purposes, where they were seated, adopting a kneeling chair position, and irradiated in AP and PA fields during each treatment session.

Basically both treatments have been made to be applied under the same medical prescriptions; however, the use of one or the other tends to depend essentially on the anthropomorphic characteristics, body type (size, size), and the type of cancer and stage of the cancer presented by the patients, as well as on the degree of precision desired of a certain specific part of the body.

When observing the experimental results of both techniques, obtained during the in vivo dose verification process, better levels of precision are observed with respect to the values registered for the Lateral TBI technique, which promotes, from this point of view, greater reliability regarding the other technique. It is also more convenient to apply this technique, when it is required to install the patient in a position of greater comfort, either by the state of fatigue or by the degree of disease that it presents. Treatments in AP-PA, conversely, are more convenient to perform when a more homogeneous dose distribution is desired at the level of the whole body. While the lung protection system adequately reduces the dose at the level of the lung, it is also true that this reduction affects a body area of greater area, thus generating a reduction in dose levels with respect to the different contours adjacent.

On the other hand, the AP-PA technique is also suitable for patients with greater body proportions such as: anthropometry, height, diameter, because they have a better location within the projected radiation field, as well as in obese patients, where a significant part of your chest or abdomen could result in a definition of a greater degree of irregularity in the corresponding contour, with respect to the other contours of the body.

It is important to note that both arrangements were implemented using the same facilities of a conventional radiotherapy treatment room, which is important mainly because it facilitates the implementation of both protocols in any standard radiotherapy unit.

The chapter covered the basic dosimetric parameters for TBI, calibration process and it comparison with respect to the standard radiotherapy adjusts. A description about the in vivo dose verification system with thermoluminescent dosimetry and other detector used was discussed, as well as the need to develop detectors for in vivo dosimetry that determine dose levels in a real time sense during the application of unconventional radiotherapy treatment was presented.

Finally a description about important opportunities field, future discussions and novel research perspectives were summarized.

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Conflict of interest

The authors declare the absence of any conflict of interest associated with this report. It will be a pleasure to be able to attend any observations that will be required.

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