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Characterization and Implementation of L-Alanine dosimetry for quality assurance of Stereotactic Body Radiation Therapy (SBRT) treatments with Volumetric Modulated Arc Therapy (VMAT)

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Orientador: Leonardo Peres da Silva

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Characterization and Implementation of L-Alanine dosimetry for quality assurance of Stereotactic Body Radiation Therapy (SBRT) treatments with Volumetric Modulated Arc Therapy (VMAT)

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Abstract

Geometric and dosimetric characterization of the irradiation beam in small radiation fields is problematic in the new treatment techniques in radiotherapy. Determination of the prescribed dose in the target volume in cases of small fields is made difficult due to the absence of lateral electronic equilibrium and the accentuated dose gradient at the field edges. Thus, the choice of the radiation detector becomes relevant in the realization of dosimetry of small fields. Alanine dosimeters have been shown as a good option for measurements of high radiation doses in these field sizes. Therefore, this study aims to characterize the alanine detector by means of dosimetric tests for the VMAT technique in the cases of SBRT. The L-alanine response had a strong linear correlation with the dose (R^2 = 0.999), significant absolute reading differences between the detectors (alanine and ionization chamber) for the field 1x1cm² (13.5%), alanine positions (6%) and low significant for dose rates (2%) and beam incidence angles (3%). The doses calculated by the TPS varied by 2.6% in relation to the experimental measurements for homogeneous regions (acrylic phantom) and 0.8% for heterogeneous and low density regions (cork phantom). This work demonstrated that this dosimeter is suitable for quality control of SBRT with the VMAT technique.

Keywords: Quality Assurance, alanine, dosimetry, SBRT, VMAT.

1. Introduction

With the development of new equipment, as well as more complex techniques of radiation and verification of patient positioning, radiotherapy has become more sophisticated and accurate for cancer treatments. Among these technological advances we can mention: Intensity modulated Radiation Therapy (IMRT), Volumetric Modulated Arc Therapy (VMAT), Intracranial Stereotactic Radiosurgery (SRS); Stereotactic Body Radiation Therapy (SBRT), Image Guided Radiotherapy (IGRT) [1].

Conventional fractionation of a treatment with external radiation therapy (teletherapy) is approximately 25 fractions, which are most often administered once a day. With these technological developments, new modalities of fractionation, known as hypofractionation (1 to 5), allow to perform the treatment in a shorter period, besides obtaining a greater local control of the disease [1].

The SBRT technique can be defined by the precise delivery of high doses of radiation in a few fractions in an extracranial target [2]. Thus, an attractive and fast dose delivery option in these cases is using VMAT, which allows rotating the gantry with the radiation beam continuously on and modulated by the movement of the multileaf collimator (MLC). In addition, during rotation, some parameters may vary simultaneously, such as, gantry rotation speed and dose rate.

The geometric and dosimetric characterization of these technologies with the VMAT technique, through a detector, becomes complex, because it involves the use of small fields of irradiation, angular and dose rate dependencies with the dose rate, in addition to modulations in beam fluence. The determination of the prescribed dose in the target volume in cases of small fields is complex due the absence of lateral electronic equilibrium and the high dose gradient at

the edges of the fields [3,4], which it is aggravated in low density regions such as the lung [5,6]. Therefore, the choice of the appropriate radiation detector for such situations becomes relevant.

According to some previous studies [7], the chemical and physical properties of L-alanine have presented adequate dosimetric characteristics to be used as a radiation detector. The International Atomic Energy Agency (IAEA), recommend L-alanine as a radiation detector for dosimetry with high dose rate beams and also for intercomparison between detectors [8,9].

Furthermore, for performing complex techniques, such as SBRT, it is indispensable to verify all steps since image acquisition to dose delivery, what is known as an end-to-end test [10,11].

Therefore, this study aims to evaluate the response of L-alanine detectors to various situations such as: arc irradiation (angular dependence), with variations of dose rates and small fields, validating it, through the end test -to-end, for quality control of the lung SBRT treatments with the VMAT technique**.**

2. Materials and Methods

2.1. Alanine

2.1.1. Features

The L-alanine dosimeters used in this study were produced in our group at the University of São Paulo (DF-FFLCRP-USP). The methodology used consists in applying a mechanical pressure in a mixture whose composition is: 90% L-alanine (Sigma Aldrich) and 10% of a binding agent (paraffin). The volume obtained in this process has a cylindrical shape with nominal dimensions of 4mm in diameter and 7mm in height, with its final mass approximately 150mg.

2.1.2. Reading

The dose on the irradiated dosimeters were measured using the first harmonic signal and the peak to peak of the central line of the ESR spectrum of L-alanine as shown in Figure 1 was used to correlate with the dose, A JEOL FA200 - Band X Electron Paramagnetic Resonance spectrometer (-) was used at Department of Physics, University of São Paulo (DF-FFLCRP-USP).

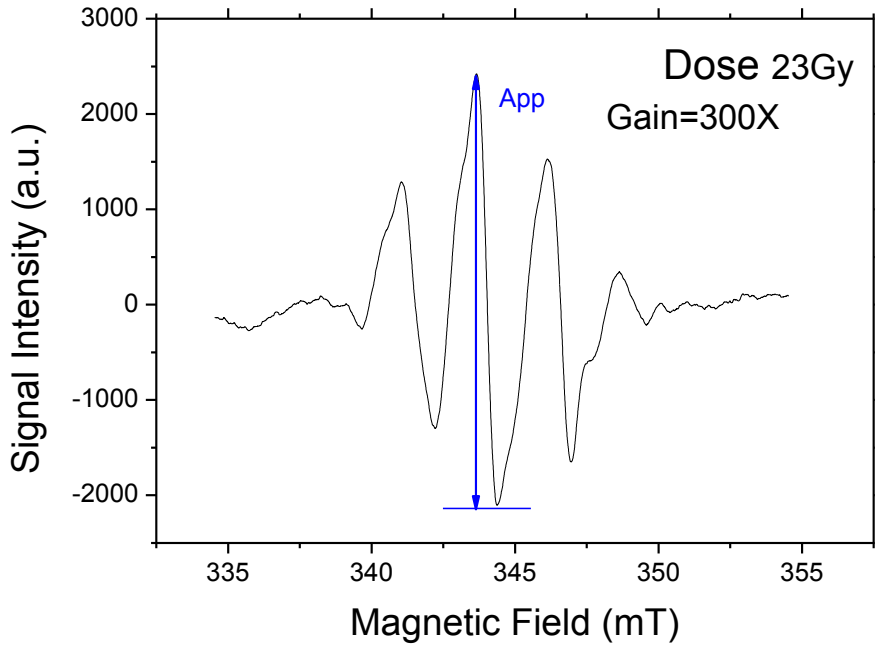
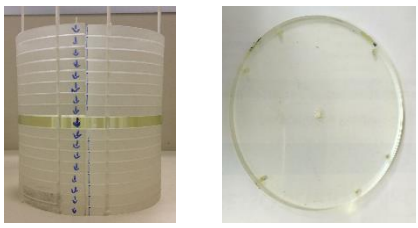


Figure 1. L- ESR spectrum of Alanine irradiated with a dose of 23 Gy on the linear accelerator Trilogy. The peak-to-peak amplitude (APP) of the center line is used for the calibration curve

2.2. Calibration, Linearity and Dependencies with Field Size and Dose Rate

The phantom used in the irradiations is composed of 11 acrylic plates with a thickness of 1cm each, 15cm in diameter, density (ρ) of 0.32 g / cm^3 and effective atomic number (Z_{eff}) 6.81 (figure 2a). The alanine was positioned on the central axis of the plaque located in the middle of the phantom as in figure 2b. The nominal energy of 6MV was used in all irradiations.



a) b)

Figure 2. Original parts of the acrylic phantom used in the irradiations. A) Side view b) Axial view of the centerpiece with alanine detector positioned at the center.

The setup used for the comparison with the measurements performed with the ionization chamber was as follows: vertical phantom, SSD = 100 cm, field 10x10 cm^2 and depths of 5.5 cm for alanine and 5.75 cm for ionization chamber (Figure 3).

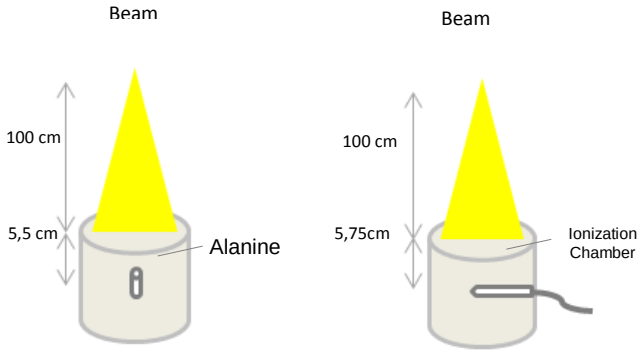


Figure 3. Experimental setup 1 for the comparison with the measurements performed with the ionization chamber

2.2.1. Calibration Factor

The alanine was calibrated with a known dose and intercompared with a cylindrical ionization chamber (Pinpoint - PTW-Freiburg 31014 with 0.015cc) connected to a PTW / UNIDOS electrometer according to the setup of figure 3. Both were irradiated with 500 monitor units (MUs), dose rate 400MU / min, field size 10x10cm². The calibration factor (Fc) was estimated using equation 1:

$$F_C = \frac{D_{CI}}{\frac{APP}{m}} \qquad (1)$$

where the symbols have the following definitions:

F_C= Calibration factor; D_{CI}= Dose measured in the Ionization Chamber (cGy); $\frac{APP}{m}$= Alanine response (peak-to-peak amplitude) normalized by mass value (mg).

2.2.2. Linearity

In order to obtain the response of the detector with the dose, a curve was created using a a dose rate of 400 MU / min and dose range from1 to 35 Gy. This dose range was defined to have a good signal-to-noise ratio and because it represents the therapeutic dose range usually employed in SBRT procedures. The calibration curve obtained is shown in figure 3.

2.2.3. Dependence with the Dose Rate

The VMAT technique varies the dose rate during irradiation and, therefore, it is necessary to evaluate the response of the L-alanine detector to irradiations with different dose rates (200, 300, 400, 500 and 600MU / Min). In this case the setup of figure 3 was used. The detectors were irradiated with 500MU for the dose rate range. The results are shown in table 3 and in graph 3.

A correction factor of the response of alanine to dose rate was determined by equation 2.

$$F_{DR} = \left(\frac{\overline{D_{DRi}}}{D_{DR\,400}}\right) \qquad (2)$$

where:

F_{DR}=dose rate correction factor; $\overline{D_{DRi}}$= mean doses detected for different dose rates (UM/min); $D_{DR\,400}$= dose value detected at dose rate of 400MU/min (calibration).

2.2.4. Field Size Dependency

The dependence of the L-alanine detector with the field size was evaluated considering 5 different field sizes and fields lower than 3x3 cm² was considered small. The detectors were irradiated with the same dose and dose rate of 400MU/min using the setup shown in Figure 3. The results obtained for both the Ionization Chamber (CI) and Alanine, are shown in table 3.

2.3. Angular Dependence

The phantom (figure 2) was scanned and planned in the Eclipse planning system with an open field 10x10cm² and radiating in an arc. The measurements were made with the phantom positioned horizontally and the following variables were used: fixed dose rate at 400MU / min, isocentric technique and 500 MU, (Figure 4).

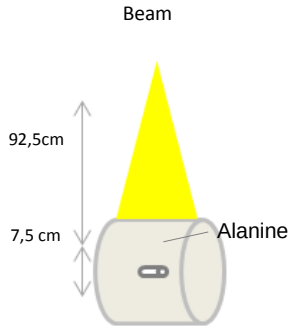


Figure 4. Experimental setup 2 to check the alanine's angular dependence with the beam incidence.

In order to compare with the arc irradiation, another measurement was made with the static gantry at 0°. For this static irradiation, the prescribed dose was the same as that of the dynamic exposure. The results obtained are shown in table 5.

A correction factor of the alanine response was determined with respect to the angle of incidence of calibration by equation 3.

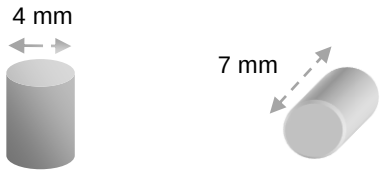
$$F_{AD} = \left(\frac{D_{arc}}{D_{ang\ 0°}} \right) \qquad (3)$$

where:
F_{AD}= correction factor angular dependence; D_{arc}= dose detected for dynamic arc irradiation; $D_{Ang\ 0°}$= Dose value detected for 0 ° angulation (calibration).

2.4 Positional dependency

In order to verify the variation of Alanine's response to the position of incidence of the radiation beam on the sensitive surface of the detector, two geometric configurations were tested in a flat surface phantom at the same depth and density near the water as shown in figure 5. Both positions were irradiated with dose rate of 400 MU/min and the same dose (500 MU) and depth.

With these results it was possible to verify the influence of the response in the two irradiated positions to characterize the detector and consequently to acquire a positional correction factor described in equation 4.



(a) (b)

Figure 5. Geometric configurations of alanine. a) Standing. b) Lying down.

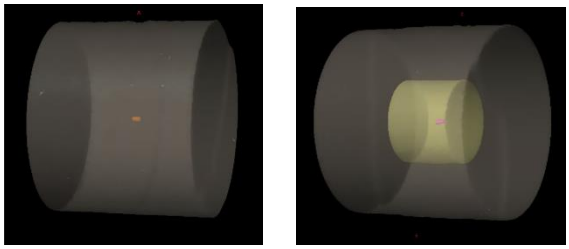
$$F_P = \left(\frac{\overline{D_{Lying\ down}}}{D_{standing}}\right) \qquad (4)$$

where:

$\overline{\mathrm{D}_{\mathrm{Lying\ down}}}$= Mean of the doses (cGy) detected for alanine positioned lying in relation to the incidence beam (Fig 5b); $\mathrm{D}_{\mathrm{standing}^{\circ}}$= Dose value (cGy) detected for alanine standing in relation to the incidence beam (Fig 5a-calibration).

2.5 End-to-End Testing

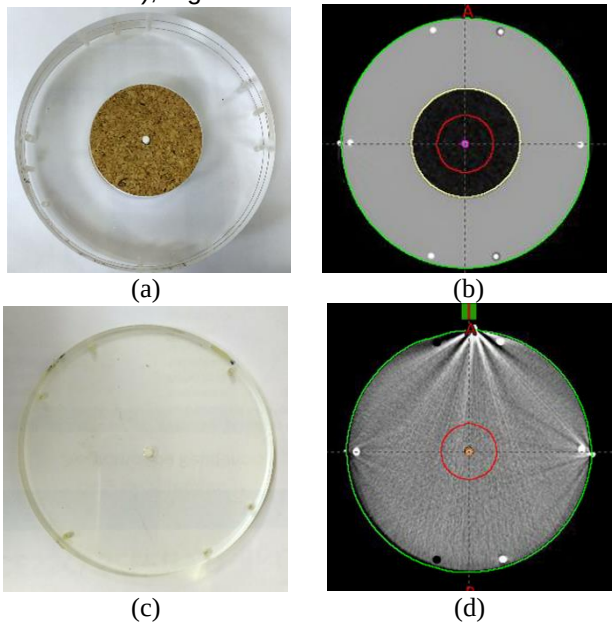
To perform the End-to-End test, two cylindrical phantoms were scanned in the CT Philips (Brilliance CT Big Bore) routinely used for acquiring the images for the treatment planning one of heterogeneous composition with acrylic to simulate the soft tissue and cork to simulate the lungs and another homogeneous (acrylic) composition. The alanine detector was positioned in the center of each phantom, as shown in figure 6.



A) **B)**

Figure 6. Cylindrical phantom with centralized alanine detector. A) Homogenous (Acrylic); B) Heterogeneous (Acrylic + Cork)

With the Phantom's CT images uploaded into the planning system (TPS), it was possible contouring some structures such as: Alanine (detector), PTV (target volume) with 1.5 cm margin of alanine and lung (cork material), Figure 7.



(a) (b)

(c) (d)

Figure 7. Axial section of the phantoms: (a) and (c) Original parts; (B) and (d) Tomography and structure design. Scale 1: 9.4

The dose prescription was 18 Gy and a SBRT planning using a modulated arc lung (VMAT) with heterogeneity correction was generated, using nominal energy of 6 MV. The dose distribution was calculated using Eclipse Version 8.6, using the AAA (Anisotropic Analytical Algorithm) algorithm.
After planning, the phantoms were irradiated with the treatment beamsand the measurements obtained by the alanine corrected by the factors described above were compared with the results generated by the TPS using the following equation:

$$D_{Alanine} = LxF_{c}xF_{DR}xF_{AD}xF_{P}(5)$$

where:

$D_{Alanine}$= Absorbed dose corrected for alanine (cGy); L = reading of the electrometer (nC);

2.6 Statistical Considerations

The uncertainties were determined according to the "Guide to Expression of Measurement Uncertainty (GUM)", given by the International Organization for Standardization (ISO) [12]. In Table 1, all type B uncertainties were recorded. Type A uncertainties related to statistical fluctuations were determined using the standard deviations and combined uncertainties analyzes for the calibration factor, peak-to-peak-to-peak-to-mass ratio (APP / M), and final dose calculation (Measured dose).

Table 1. Type B uncertainties

Applied Dose	
Applied dose components	Standard Relative Uncertainty in%
Fluctuations in the output of the treatment machine	0.7
Dose calculation of planning system	1.3
Positioning	2mm
Dose measured by alanine / ESR	
Components for alanine ESR measurements	Standard Relative Uncertainty in%
Primary standard	1.2
Mass of alanine	0.1
Amplitude ESR	5
Dose measured by the Ionization Chamber	
Components for measurements with the ionization chamber	Standard Relative Uncertainty in%
Electrometer	0.1
N_{DW}	1.5

3. Results and Discussion

3.1 Calibration, Linearity and Dependencies with Field Size and Dose Rate

3.1.1 Calibration Factor

Table 2 shows the values used to calculate the calibration factor.

Table 2. Values of the parameters used to calculate the calibration factor

Parameter	Value
Dose CI (cGy)	399.33 ± 2.1
App/m	10.30 ± 0.9
Fc (cGy/App/m)	38.8 ± 3.3

The calibration factor allowed establishing relationship between the dose measured with ionization chamber and alanine, which corresponds to the value of 38.8 cGy/App/m.

3.1.2 Linearity

The response of alanine to the dose is shown in figure 8.

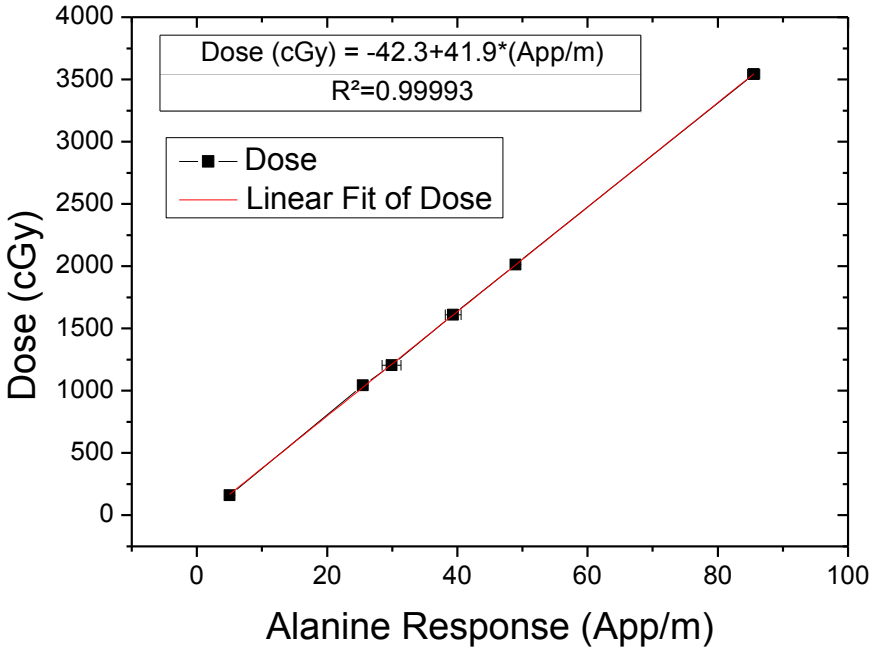


Figure 8. Dose-effect calibration curve for L-alanine. The horizontal axis shows the ratio of the intensity of the ESR signal obtained in band X (App) by mass (mg).

The amplitude of the signal resulting from alanine presented a linear response with the dose, since the correlation coefficient resulting from the linear adjustment was 0.9999. This value demonstrates the stability of the dosimeters reading and corroborates with the information found in references [13,14,15,16].

3.1.3 Dependence with the Dose Rate

Dose dependence with the dose rates for both the alanine and the ionization chamber are shown in table 3.

Table 3. Ratio of detector response to dose rates

Dose Rate (UM/min)	CI/Alanine
200	0.94
300	1.01
400	0.94
500	0.97
600	0.95

Alanine show in most the readings data greater than that obtained with ionization chamber. However, at the rate of 300MU/min, the alanine reading was 1% lower than that of the chamber. Such behavior may be associated with the sensitivity of the dosimeter.

The results obtained for the different dose rates for the L-Alanine detector, normalized to a rate of 400MU/min are show in figure 9. The relative value of the mean was 0.98 ± 0.04.

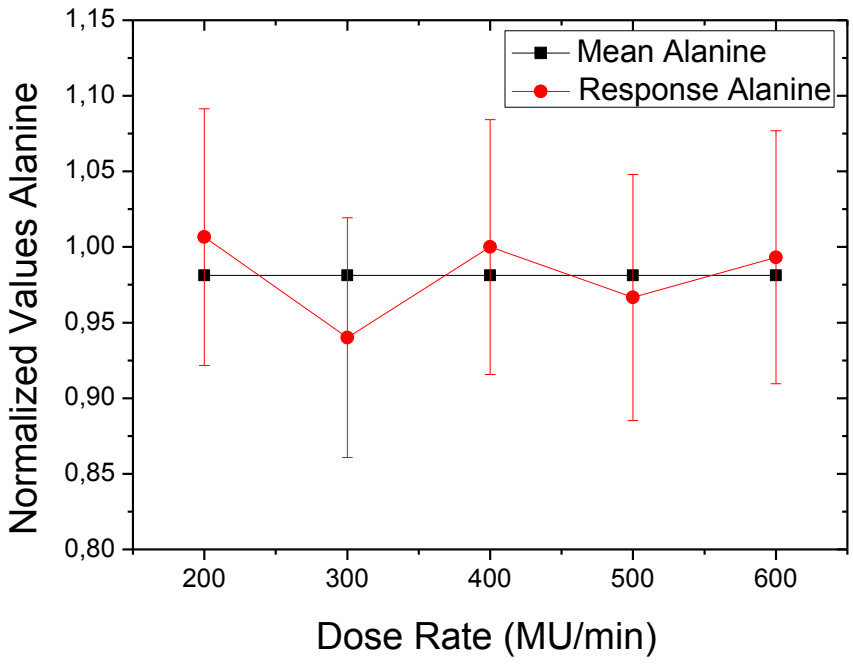


Figure 9. Dependence with the dose rate for 500MU. The relative mean of the measurements performed with the alanine dosimeter was 0.98.

The alanine results obtained at different dose rates differ by about 2% from the mean except for the rate of 300MU/min which differed by 4%. Such results generally demonstrate good

dosimeter stability over the dose rate parameter.
Regarding the application of the correction factor, it is necessary to evaluate the dose rate delivered during irradiation. If the rate is between 400 and 600 MU/min, there is no need to apply it, since the variation in relation to the calibration is not statistical significant (~2%). However, if the variation is less than this range, it is necessary to apply the dose rate correction.

The correction factor of the response of alanine to the dose rate is:

$$F_{TD} = 0.98$$

3.1.4 Dependency with Field Size

The dose dependence with the radiation field size for both the alanine and the ionization chamber (IC) are shown in table 4. For irradiation fields smaller than 10x10 cm² there is a decrease in the deposited dose.

Table 4. Response of the detectors referring to the standard square fields for the field 10x10 cm²

Square field (cm²)	Relative Response of Detectors	
	IC	Alanine
1x1	0.64	0.74
2x2	0.80	0.80
3x3	0.84	0.85
5x5	0.91	0.96
10x10	1.00	1.00

In general, alanine had a greater response than that obtained by ionization chamber and this agrees with reference [17], which demonstrates that alanine has a better electronic equilibrium condition.
The response of the pinpoint ionization chamber to the 1x1 cm² field fails when compared to the Monte Carlo (gold standard) [18]. Therefore, as the alanine approaches the Monte Carlo, it becomes more adequate to measure small fields [19].
In table 3, the observed deviations of alanine with respect to IC are within 1% ~ 14%. The biggest difference was for the field 1x1 cm² (13.5%). This difference may become significant in cases of high doses in the lung where there are regions of heterogeneities in which the planning system needs to be proper data feeding [19]. Therefore, a suitable detector is required for such measurements.

3.2 Angular Dependence

The dose dependence, measured and calculated, with the two static and dynamic irradiations normalized to the calibration angle (0°) is show in table 5.

Table 5. Values of alanine detector response measured and calculated by TPS for static and dynamic irradiation

Angle	Measure Dose (cGy)	TPS Dose (cGy)	% Deviation measurement/TPS
0°	434.2	435.5	0.29

Arc	449.1	434.4	-3.41
Arc/0°	1.034	0.997	-

In relation to the 0° angle the doses measured by the detector and calculated by the TPS are in conformity having a percentage deviation of approximately 0.3%. As for the dynamic irradiation (Arc), the deviation between the measured and planned dose was slightly higher, resulting in -3.41%. This difference may be associated with non-uniformity of alanine mass distribution along of detector.
In addition, it can be observed that the detector obtained a response of +3.4% (dynamic arc) in relation to the calibration.
The correction factor of the alanine response in relation to the angle of incidence (0°) of the beam is:

$$F_{AD} = 1.03$$

3.3 Positional dependence

The results obtained due to the variation of the alanine position with respect to the incidence of the radiation beam are recorded in table 6.

Table 6. Response of alanine in the two different beam incidence configurations

Alanine	App/mass
Standing	12.88 ± 0.45
Lying Down	13.75 ± 0.41

The data obtained for the two irradiation positions of the detector (standing and lying) presented a maximum difference of 6%. This suggests the need for a reading correction factor for the alanine lying down, once it has been calibrated in the standing position.

If the alanine was irradiated on one position (lying down) and calibrated in another (standing) the correction factor should be used. In this case, the value of the correction factor for the alanine position in relation to the beam incidence is:

$$F_P = 0.94$$

3.4 End to End Test

Figure 10 shows the axial section of the SBRT planning performed on the phantoms, with the prescribing dose of 18Gy.

(a) (b)

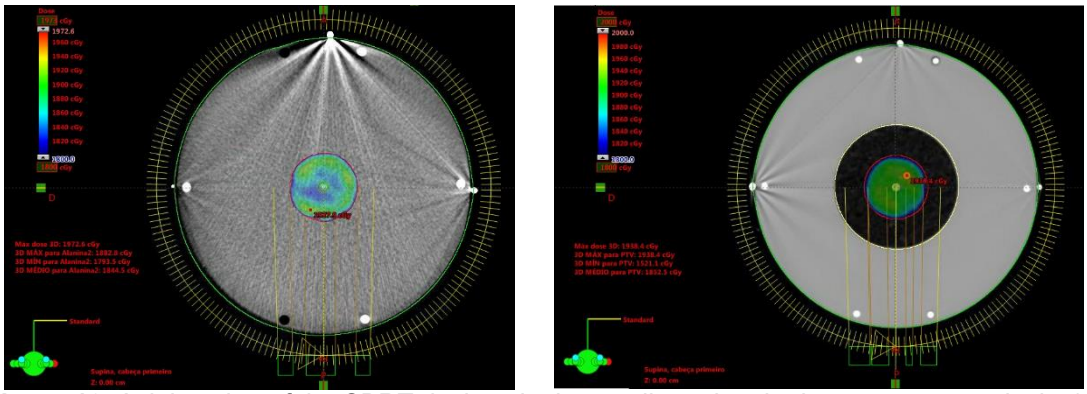


Figure 10. Axial cutting of the SBRT designs in the acrylic and cork phantoms, respectively, (a) and (b).

Table 7 shows the calibration and correction factors and their respective values used for determination of the dose in alanine.

Table 7. Values of the factors used to calculate the doses

Factors	Value
Calibration	38.79
Dose Rate	0.98
Angular Dependency	1.03
Positional	0.94

Table 8 shows the percentage difference between the doses measured in alanine and calculated by the treatment planning system.

In the End-to-End test, for the calculation of the dose, the factors presented in table 7 were adopted except for the dose rate, because the planning was done with same calibration rate.

Table 8. Values of measured and calculated doses in different phantoms

Phantom	Measured Dose (cGy)	TPS Dose (cGy)	Deviation %
Acrylic	1797.5 ± 101.6	1844.5 ± 22.8	2.6
Cork	1911.5 ± 99.7	1926.2 ± 3.7	0.8

It was observed that the doses calculated by the Planning System resembled the experimental measurements for homogeneous regions (acrylic phantom - ρ = 1.19 g / cm³), according to other studies in the literature [20,21].
In situations of irradiation of heterogeneous volumes and low density as the lung (cork phantom), the difference between the planned dose and the measured dose was 1.9%. However, in planning with modulation, an average variation of 3% is commonly adopted, which is in agreement with the result found [22].

4. Conclusions

L-alanine dosimeters showed a strong linear correlation (R^2=0.9999) with the dose range (1-38Gy). Furthermore, such detectors are more water equivalent than the ionization chamber and the observed differences between the detectors are within the experimental uncertainty. However, a significant disadvantage of L-alanine dosimeters is the difficulty of producing detectors with equal sensitivity, since a small variation in the content of alanine appears to be a critical factor in the millimetric dimensions.

These detectors presented small dependencies with the dose rate and angular distribution and significant with the position of alanine, for VMAT technique, emphasizing the need to use correction factors for these quantities. The detector demonstrated a good response for small fields which characterizes an advantage of this detector for SBRT.
With the End-to-End test, it was possible to verify all the steps of the treatment with very small discrepancy, form the acquisition of images until the delivery of the dose. Thus, we can conclude that the L-alanine detector was suitable for implementation in the SBRT quality control of small fields using VMAT;

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