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Original research article

Measurement of percentage dose at the surface for a 6 MV photon beam

O.O. Galván De la Cruz[a,b], *M.A. Rodríguez-Ávila*[c], *T. Rivera-Montalvo*[b], *O.A. García Garduño*[d,*]

[a] *Unidad de Radioneurocirugía, Instituto Nacional de Neurología y Neurocirugía, Insurgentes Sur 3877, México City, Mexico*

[b] *Centro de Investigación en Ciencia Aplicada y Tecnología Avanzada, Unidad Legaria, Instituto Politécnico Nacional, Legaria 694, México city, México*

[c] *Posgrado en Ciencias Físicas, Universidad Nacional Autónoma de México, Instituto de Física, Circuito de la Investigación Científica s/n. Ciudad Universitaria, 04510, Mexico City, México*

[d] *Laboratorio de Física Médica, Instituto Nacional de Neurología y Neurocirugía, Insurgentes Sur 3877, México City, México*

ARTICLE INFO

Article history:
Received 12 September 2018
Received in revised form 9 May 2019
Accepted 21 September 2019
Available online 18 October 2019

Keywords:
Radiochromic film EBT3
Energy independence
Surface dose

ABSTRACT

Aim: To evaluate if a radiochromic film (RF) Gafchromic EBT3 is suitable for surface dose measurements of radiotherapy treatments performed with a 6 MV linear accelerator. Two aspects of RF were analyzed, beam energy dependence and surface dose determination.

Background: The measurements done at the surface or near the radiation source are done without charged electronic equilibrium and also have contribution of electron contamination. The detectors used for these measurements should not alter the dose to the target. To counteract these dosimetric problems it is proposed to do the measurements with radiochromic films which are thin detectors and have tissue equivalent properties.

Materials and Methods: The measurements were done using a Novalis linear accelerator (LINAC) with nominal energy of 6 MV. To determine the surface dose, the total scatter factors (TSF) of three different field sizes were measured in a water phantom at 5 cm depth. Energy dependence of EBT3 was studied at three different depths, using a solid water phantom. The surface measurements were done with the RF for the same field sizes of the TSF measurements. The value of the percentage depth dose was calculated normalizing the doses measured in the RF with the LINAC output, at 5 cm depth, and the TSF.

Results: The radiochromic films showed almost energy independence, the differences between the curves are 1.7% and 1.8% for the 1.5 cm and 10 cm depth, respectively. The percentage depth doses values at the surface measured for the 10 cm × 10 cm, 5 cm × 5 cm and 1 cm × 1 cm were 26.1 ± 1.3%, 21.3 ± 2.4% and 20.2 ± 2.6%, respectively.

* Corresponding author.
E-mail address: oagarciag@innn.edu.mx (O.A. García Garduño).

https://doi.org/10.1016/j.rpor.2019.09.007

Conclusions: The RF-EBT3 seems to be a detector suitable for measurements of the dose at the surface. This suggests that RF-EBT3 films might be good candidates as detectors for in vivo dosimetry.

1. Background

The surface dose is defined as the dose deposited at the boundary between two media, such as air and skin, or air and water.[1] However, as all detectors, they have an active volume and the exact value of the dose at the boundary cannot be really measured, it is considered that the measurement is done at the center of the active volume of the detector.

In vivo dosimetry is a direct measurement of the radiation beam that is applied to a patient for any radiotherapy treatment.[2,3] The dose measured at the surface can be associated to the dose deposited into the target. The detectors are placed on the skin of the patient and their purpose is to verify if the dose deposited is consistent with that prescribed and planned.[4,5] Instead of surface dose, in some cases and for clinical purposes, the skin dose can be measured.[1] According to different publications, this measurement should be done at depths from 50 μm to 70 μm.[1] Unfortunately, a detector with an effective point at that depth is not commonly available in radiotherapy facilities.

It is desirable that this value is obtained as quickly as possible, so that in case a correction of the treatment plan is necessary, it can be done immediately. The detector properties should, ideally, include independence of the energy, of the type of radiation and angular incidence. High resolution and small dimensions are also desirable. In vivo dosimetry involves measurements that complement a quality assurance program and can be considered a very important part of it in a radiotherapy department.[6–8] One of the difficulties in vivo dosimetry is that the measurements are done at the surface or near the radiation source. This means that the measurements are done without charged electronic equilibrium and they have dose contribution of electron contamination of the head of the LINAC (in the case of external beam therapy).[7] Moreover, the detector used should not alter the dose to the target. To counteract some of these dosimetric problems, it is proposed to do the measurements with radiochromic films.

It has been reported in the literature that different models of Radiochromic films (RF) have been used for surface dose measurements.[8] These studies have been carried out for field sizes bigger than 5 cm × 5 cm and with RF models that need a high dose deposition (not the 2 Gy that is the clinical range[8]). Radiochromic films are detectors used for 2D beam dosimetry. The RF change their optical density (OD) when they are exposed to ionizing radiation. An important property of the RF is that their chemical composition which is nearly tissue equivalent.[8,9] Advantages of RF are that they do not need a post irradiation process; they have a high spatial resolution and a wide dynamic range of dose detection. In particular, the radiochromic film model Gafchormic EBT3 has the active layer (26 to 28 μm width, in this work it will be considered 27 μm as the average) between two identical polyester layers (125 μm each layer).[9–11] The dynamic dose range reported by the manufacturer is from 1 cGy to 40 Gy.[12] This is appropriate for the conventional dose per fraction in radiotherapy treatments.

2. Aim

The goal of this work is to show that a radiochromic film EBT3 can be used as a detector to measure the dose at the surface for a 6 MV LINAC.

3. Materials and methods

All the irradiations were performed with a photon beam generated from a linear accelerator (LINAC, Novalis BrainLab, Germany) with a nominal energy of 6 MV with a m3 mMLC (BrainLab, Germany) which remained retracted for all the measurements. No tertiary collimators are used. The Novalis output for a field size of 10 cm × 10 cm at 5 cm depth and source to surface distance (SSD) of 100 cm is 0.9 cGy ± 1.5% per monitor unit. This measurement was done using a PTW Freiburg semiflex ionization chamber (with 0.125 cm^3 of volume) coupled to an Unidos webline electrometer (PTW Freiburg, Germany) following the International Atomic Energy Agency (IAEA) TRS-398 protocol.[13] The ionization chamber and the electrometer have been calibrated together in a secondary laboratory. During the whole irradiation process of this work, the geometry used was SSD of 100 cm, unless specified. All the fields were made with the LINAC jaws.

In addition to the semiflex chamber, a CC01 micro ionization chamber (IBA-Dosimetry, Germany) with 0.01 cm^3 volume, was used. Both cameras were coupled to the UNIDOS webline electrometer. The PTW chamber was used with the voltage of 400 V, and the IBA CC01 at 300 V, according to respective manufacturer specifications. The cameras were used to measure the total scatter factors.

For the surface measurements, radiochromic films EBT3 were used. The value of the percentage dose depth (PDD) at the surface for the field sizes of 10 cm × 10 cm, 5 cm × 5 cm and 1 cm × 1 cm were calculated using the TSF, the LINAC output and the value of the dose obtained with the radiochromic films.

3.1. *Total scatter factors*

International recommendations suggest that ionization chambers are the gold standard detector for conventional radiation fields.[14] Nevertheless, for non-conventional radiation fields its use is limited by its sensitive volume.[14,15] It is for that reason that other detectors are employed, such as micro ionization chambers.

The total scatter factors for field sizes of 10 cm × 10 cm, 5 cm × 5 cm and 1 cm × 1 cm were measured with the ionization chambers placed at 5 cm depth. The measurements were performed in a MP3-XS water phantom (PTW-Freiburg Germany). A semiflex ionization chamber was used for the field sizes of 10 cm × 10 cm and 5 cm × 5 cm field. An IBA CC01 micro ionization chamber was used for the 1 cm × 1 cm filed size as recommended by Lárraga et al.[15] The 5 cm × 5 cm field was normalized with the 10 cm × 10 cm field. For the measurement of the 1 cm × 1 cm field size TSF, the daisy chain method was used, following Alfonso et al. and Lárraga recommendations for non-conventional radiation fields[14–17] According to this method, an intermediate field size has to be used, applying Eq. (1). The intermediate field size used was the smallest field size for which the semiflex camera is appropriate, which is a 3 cm × 3 cm.

$$S^{c}_{cp} = \frac{M^{f\ clin}_{\text{det}}}{M^{f\ inter}_{\text{det}}} \times \frac{M^{f\ inter}_{IC}}{M^{f\ ref}_{IC}} \quad (1)$$

M is the electrometer lecture, *IC* refers to the ionization chamber measurement, which in this case is done with the semiflex ionization chamber, f_{ref} is the reference field, which is the 10 cm × 10 cm field. The intermediate field is abbreviated as f_{inter} and is the 3 cm × 3 cm field, f_{clin} is the field of interest, the 1 cm × 1 cm field. Finally, the abbreviation *det* is the detector used for the small field, which in this case is the CC01 ionization chamber[15] whose characteristics were previously described.

Ionization chambers were oriented with their main axis parallel to the beam. The temperature, pressure, polarity and recombination corrections for both ionization chambers were done according to the IAEA TRS-398 code of practice[13] and daisy chain recommendation.

The TSF were also compared with Monte Carlo (MC) simulations. The codes used to model the LINAC and the beam interaction were BEAMnrc V2.4 and DOSXYZ V2.4, respectively. Voxel dimensions used were 0.05 cm × 0.05 cm × 0.05 cm preserving the geometry used for the experimental measurements. The number of histories was chosen such that the statistical dose uncertainty is lower than 0.5%. The EGSnrc transport parameters were: ECUT = 0.521 MeV, PCUT = 0.01 MeV, with the XCOM cross section data base and EXACT boundary crossing. The magnitude of the ECUT and the PCUT were selected according to the values reported in literature for the calculation of the absorbed dose.[23,24] The statistical uncertainty of the TSF calculated is 0.7%.

3.2. *Radiochromic film EBT3, irradiation film procedure, scanning protocol and analysis*

The radiochromic film model used in this study was a Gafchromic® EBT3 (Ashland Inc.) film with the serial number 04151401. The RF structure consists of three layers, 28 μm of an active layer sandwiched between 125 μm matte-polyester substrates. The Gafchormic radiochromic film EBT3 has many properties that make them good candidates for measurements of the dose at the surface: they have a thickness of the order of μm. They have limited energy and dose rate dependence.[26,27] Also, weak dependence of the type of radiation is reported in the literature.[26,28] They are nearly tissue equivalent, concerning the film Z equivalent value, it is reported that the calculation of the film components gives a Z_{eff} = 9.38 for the active layer and the and polyester base has a Z_{eff} = 6.64.[29] But Crijns et al. reported a Z_{eff} = 6.73 for the whole film.[30] It is important to emphasize that the dose measured is the dose deposited in the effective point of the detector,[1] not at the interface, as it would be desirable. In the case of the RF EBT3 the dose is deposited at 133.5 μm depth.[29] It should be taken into account that the dose measured is deposited by all the irradiation particles that interact with the RF.

The RF were cut into pieces of 3 cm × 3 cm twenty-four hours before the irradiations. The films were marked to preserve the orientation.

3.2.1. *Irradiation film procedure*

The films were placed in a solid water equivalent phantom (CIRS Inc., USA) which consisted of 30 cm × 30 cm slabs of different thicknesses or at the surface. The films were perpendicularly irradiated. Two kinds of measurements were done with the RF. The first ones were to corroborate the film independence with the energy. This was done at different depths of the solid water phantom. The other ones were the superficial measurements. For this case, the field sizes measured were 10 cm × 10 cm, 5 cm × 5 cm, and 1 cm × 1 cm (the same fields of the TSF). The films were exposed to doses ranging from 0 to 10 Gy. To reduce the statistical uncertainty, each calibration point consisted of three different film pieces.

3.3. *Scanning protocol and analysis*

The digitization was performed with an Epson Expression 11000XL Photo Scanner in a transmission mode. The films were scanned after a 15 min scanner warm-up time. A cardboard template was fitted to the scanner to make the position of the films reproducible in a central location of the scan surface (to reduce the effect of the nonuniform response of the flatbed scanner).[18] Films were scanned using the Epson Scan software V3.49S with 48-bit color depth (16-bit depth by color) and 72 dots per inch resolution. All post-processing and color management options were turned off.

The images were stored in tagged image file format (TIFF). They were analyzed using ImageJ software V.1.2 to obtain the values of the transmitted light intensity *I* and standard deviation associated with this value of a region of interest. Due its high sensitivity in the dose range used, in this work only the red component was used.[19] The films were digitized 24 h after irradiation. The RFs were handled and used according to the general recommendations outlined by the manufacturer's specifications[20] and the AAPM TG-55 protocol.[21]

The response of the EBT3 RF is characterized by the net optical densities (netOD) and is related to the intensity *I* by Equation (2)[19,21]:

$$netOD = -\log_{10}\frac{I}{I_0} \quad (2)$$

Where I_0 and I are the readings for the unexposed and exposed film piece, respectively. The associated uncertainty of the *netOD*, SD_{netOD} Equation (3):

$$(3)SD_{netOD} = \frac{1}{\ln 10}\sqrt{\left(\frac{SD_{I0}}{I_0}\right)^2 + \left(\frac{SD_I}{I}\right)^2}$$

Where SD_{I0} and SD_I are the associated standard deviations I_0 and I, respectively.[22]

3.4. Verification of energy independence

To corroborate the film independence with the energy, as the LINAC has just one photon beam (of nominal energy of 6 MV), the variations of it were done at three different depths. The depths were 1.5, 5.0 and 10.0 cm in a water equivalent phantom (CIRS Inc., USA).The field size used was 10 cm × 10 cm. The doses deposited were 0.5, 1.0, 2.0, 4.0, 6.0, 8.0 and 10.0 Gy at the three depths. The doses were verified with the semiflex ionization chamber.

3.5. Measurement of PDD value at the surface

The field sizes used for the superficial measurements were 10 cm × 10 cm, 5 cm × 5 cm, and 1 cm × 1 cm. The films were placed at the surface of the water equivalent phantom (CIRS Inc., USA). Optical densities obtained from those measurements were associated with the dose with the calibration curve obtained at 5 cm depth. The doses measured with the films, were normalized by the product of the monitor units applied and the output of the LINAC corrected by the TSF. This will give the values of the percentage dose (PDD) at the surface. The uncertainty of this value is the standard deviation of the PDD for the different doses.

4. Results

4.1. Total scatter factors

The total scatter factor measured and the comparisons with the Monte Carlo simulation are shown in Fig. 1. The differences from the measured and the MC calculated TSF for the 5 cm × 5 cm and 1 cm × 1 cm filed sizes were 0.06% and 1.4%, respectively. As the value for the non-conventional field is inside the uncertainty of the value measured (1.87%), they are considered equal.

4.2. Energy independence

The depths used for the measurements were 1.5, 5.0 and 10.0 cm. This was done to modify the photon spectra in an interval dose range from 0 to 10 Gy. The measurements at different depths for different doses are shown in Fig. 2.

Fig. 2 shows that if it is taken as reference the 5 cm depth curve, in the dose range from 0.5 Gy to 10 Gy, the differences are, on average, 1.7% for the curve of 1.5 cm depth and 1.8% for the 10 cm curve depth. In particular, if we compare the values of 2 Gy for the 1.5 cm depth with the reference value (5 cm depth), the difference is 0.42%. If the same is done with the 10 cm depth, the difference is 1.00%.

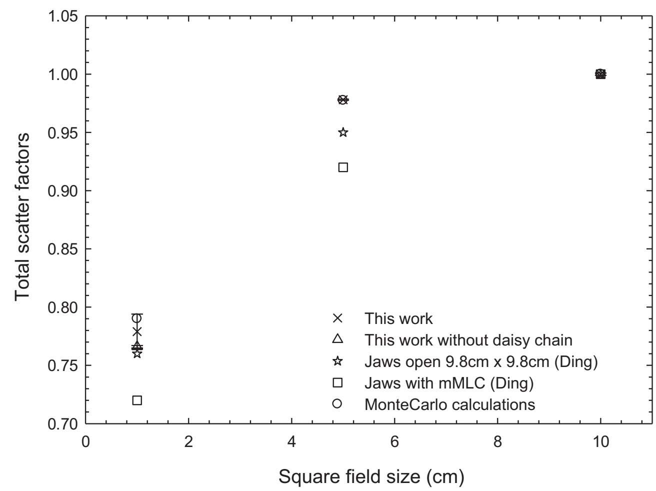

Fig. 1 – Total scatter factor (TSF) obtained with two different ionization chambers. Semiflex for 10 cm × 10 cm and 5 cm × 5 cm and CC01 for 1 cm × 1 cm. The values measured are compared with the ones reported by Ding et al.[25] and Monte Carlo (MC) simulation. There is a good agreement between MC and the TSF, for the 1 cm × 1 cm measured with the daisy chain method. The TSFs measured by Ding et al do not show a good agreement and this may be due to the way the fields are defined, which is different from this work.

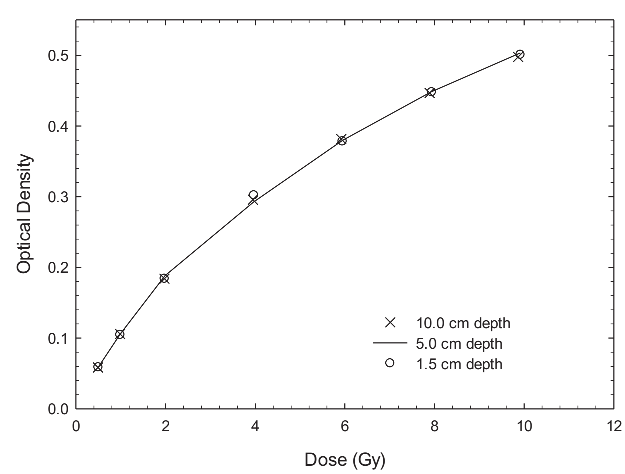

Fig. 2 – Measurements of the same doses at different depths with interval dose range from 0 to 10 Gy. It can be seen that the fitted curves have a very good agreement. For doses less than 10 Gy there is no difference of response for a beam of 6 MV as a function of depth. The curve measured at 5 cm depth was taken as reference according to the IAEA protocol.[13] The uncertainties associated with the optical densities and defined by Eq. 3 are avoided in the Figure to facilitate their interpretation. The values have an average of 1.11% (min:0.49%, max:2.33%), 1.14 (min:0.48%, max:3.40%) and 1.05% (min:0.47%, max:2.44%) for the 10 cm, 5 cm, 1.5 cm depth curves, respectively.

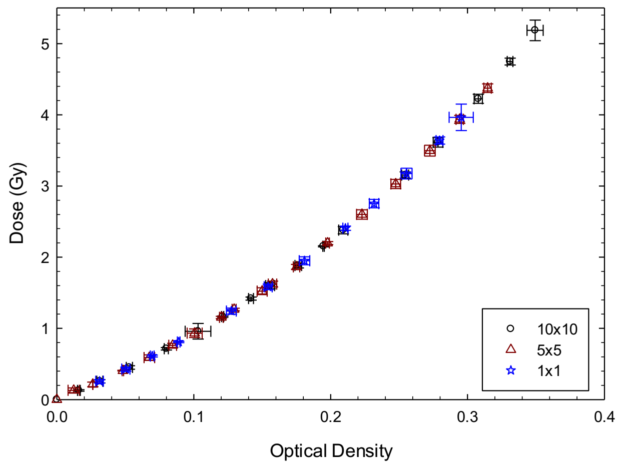

Fig. 3 – Doses measured in the surface of the solid water phantom.

Table 2 – Values of the percentage of the dose at surface. These values are normalized using the dose value at 5 cm depth and corrected by the total scatter factors.

Field size (cm × cm)	10 × 10	5 × 5	1 × 1
Percentage of dose at surface (%)	26.1 ± 1.3	21.3 ± 2.4	20.2 ± 2.6

4.3. *Superficial measurements*

The dose values measured at the surface of the solid water phantom for different field sizes are shown in Fig. 3.

It is observed that regardless of the field size the form of the curves is similar between them. A comparison for different doses is done and shown in Table 1.

The mean difference between the curve associated with these points and the calibration curve used in this work is 1.31% (maximum 6.17%, minimum 0.66%).

4.3.1. *Percentage of dose depth at surface*

The percentage of dose that is deposited at the surface was calculated with the dose measured, the LINAC output and the TSF. The values are shown in Table 2.

It is found that for low doses (less than 0.5 Gy) the value of the percentage of the dose at the surface can be different up to 88%. This is the case of the measurement obtained for the 10 cm × 10 cm field, the minimal PDD calculated is 3.15% for doses measured with RF of 1.4 cGy. For the 5 cm × 5 cm the PDD calculated is 3.7% measured with the dose of 1.7 cGy and for the 1 cm × 1 cm it is 18% for the dose of 17.9 cGy. This is the reason why the average and the standard deviations were calculated for doses bigger than 0.5 Gy for the three field sizes.

5. Discussion

In order to prove if EBT3 RF can measure the percentage dose at the surface, previous measurements have to be done. One of them relates to the total scatter factors. The results obtained are shown in Fig. 1, the measurements are compared with the values reported by Ding et al.[25] These values were measured in the same geometric conditions. For each field size, Ding made two measurements, the first one with the jaws at 9.8 cm × 9.8 cm and the field constructed only with the mMLC. In the other one, the jaws were open making the same field size as the mMLC. However, for the non-conventional field, they did not apply the daisy chain correction. To make a 1 cm × 1 cm TSF comparison accurately, to this particular field size, it was calculated without the daisy chain correction, as well. The difference between the results obtained in this work and Ding are 2.4% and 2.8% for the 1 cm × 1 cm and 5 cm × 5 cm, respectively (with jaws at 9.8 cm × 9.8 cm). For the fields constructed with mMLC and jaws the difference is 7.6% and 5.9% for the 1 cm × 1 cm and 5 cm × 5 cm, respectively. In the case of the field size of 1 cm × 1 cm to compare with the results reported by Ding et al.,[25] if the daisy chain method is not used, the differences are 0.7% with mMLC alone and 6% with mMLC and jaws. It is normal that the values obtained in this work are smaller than the ones measured by Ding[25] as he did not take any special consideration for non-conventional fields.

Regarding the energy dependence of the films, it is confirmed that the radiochromic film EBT3 have a weak dependence of the energy of the beams. The difference between the curves generated at 1.5 cm and 10 cm depth is 1.7% and 1.8%, respectively, having as reference the curve obtained at 5 cm depth. This gives us the possibility to use RF EBT3 on the surface and apply the calibration curve at 5 cm depth. This agrees with the report by Sorriaux et al. that states: The calibration curves show a weak energy and particle dependence.[26] This difference is less than the one reported by Sorriaux et al.,[26] but the comparison that is reported is between the 6 MV and 18 MV beams. As we do not have access to beams generated with a different voltage, we measured at different depths. This analysis was based on the report by Saitoh et al. that showed with a Monte Carlo simulation that the energy spectrum changes as a function of field size and that the mean energy of the spectrum increases as depth increases.[31] It is expected that the difference diminishes if the beams have subtle changes, as is the case in this work. This is confirmed by Casanova et al. who report that for the beam changes that occur in an IMRT treatment the RF response is negligible up to doses of 4Gy.[27]

Concerning the measurements done at the surface, they are shown in Fig. 3 and they are done for different doses. These doses should give, as a result of the calculations, the same value of percentage dose at the surface. The discrepancies found depend mostly on the detector response for that dose interval. Taking as reference the 10 cm × 10 cm field, the doses measured at surface were as low as 1.4 cGy, which gives a PDD of 3.15%. The next dose point measured with the RF for the same field size was 17.9 cGy and the PDD calculated is 19.7%. Finally, for the dose 41.3cGy the PDD calculated is 22.8%. It is observed that the differences with the value reported 26.1% are 87.9%, 24.4% and 12.7%, respectively. The next point was the dose of 70.9cGy and this gives a particular PDD calculation of 26.09% which is a difference of the PDD value at surface reported of 0.1%. This work shows that doses lower than 0.5 Gy cannot be measured accurately on the surface, so it is recommended that radiochromic EBT3 is used for doses bigger than 0.5 Gy. This is in accordance with the study by Crijns et al. that found that relative errors for EBT3 are smaller than

Table 1 – Uncertainty associated with different doses at the surface for three different sizes (conventional and non-conventional).

10 cm × 10 cm		5 cm × 5 cm		1 cm × 1 cm	
Dose (Gy)	Uncertainty (%)	Dose (Gy)	Uncertainty (%)	Dose (Gy)	Uncertainty (%)
0.71	2.30%	0.6	6.40%	0.61	2.23%
1.62	2.60%	1.62	2.52%	1.58	2.44%
1.89	1.79%	1.86	1.80%	1.95	2.86%
2.15	0.35%	2.2	0.95%	2.41	1.26%

2% for doses between 0.6 and 4.2 Gy.[30] Clinically, this should not represent any inconvenience because the typical doses for a conventional radiotherapy fraction is 2 Gy.[10] The standard deviation associated with measurements greater than 0.5 Gy are 1.3%, 2.4% and 2.6% for the field sizes of 10 cm × 10 cm, 5 cm × 5 cm, and 1 cm × 1 cm, respectively, as shown in Table 1. As expected, the standard deviation increased for the smallest field size.

The dose measured at the surface it is not only deposited by photons of the beam. It is reported that the electron contamination depends on SSD and field size.[32] It increases with the field size according to Lopez Medina et al. and Ding et al.[32,33] It has been reported in the literature that electron contamination depends on several variables such as field size, source surface distance (SSD) and beam energy.[33,34] For short SSD and large field sizes the head of the LINAC is the major source, but it decreases as SSD increases and the surface dose, owing to electron contamination, increases with field sizes.[33] It is reported that at SSD of 100 cm the maximum contamination at the surface is 7% for the field size of 10 cm × 10 cm and 21% for the field size of 40 cm × 40 cm.[35] It is also reported by Farah et al. that the dependence of EBT3 response between photons and electrons is weak,[28] which makes this detector a good candidate to measure surface doses.

For measurements on the surface, the thickness of the detector has to be considered. This is important because the dose changes abruptly with the depth. That is reported in the paper of Devic et al.[1] The work says that the changes in PDD are from 14% to 40% in the first millimeter.[1] Before the maximum of the percentage depth dose (PDD) curve it is reported that the changes in the PDD are from 14% at depth of 4 μm to 43% at depth of 1 mm. In this work, it is also reported that correction factors have to be applied if skin dose is measured with EBT. As EBT3 has different structure and different composition of the active layers, a verification of the correction factors reported have to be done if dose measured is to be associated with the skin dose. As the measurements in this work are done at 133.5 μm, it cannot be considered skin dose. Further work and analysis has to be done to determine if correction factors have to be applied for EBT3. Morales et al. reported the surface dose measured from circular collimators which are tertiary collimators not used in this work, and compares the results with Monte Carlo calculations.[34] Morales et al. does not specify if the comparison is done at the active layer of the EBT3 or at the skin (70 μm). The values of PDD cannot be compared with this paper either because they normalize to the maximum dose, in this work the normalization is done at 5 cm depth because all the measurements are done at this depth. Nevertheless, Morales et al. found that the uncertainty is better than 2% if the measurements are compared with MC simulation. It is also concluded that RF Gafchromic EBT3 is suitable to use for surface measurements of non-conventional fields. In our case, we did the study for conventional and non-conventional field sizes and found that they are good detectors for surface measurements.

Based on these results, it is considered that Gafchromic RF EBT3 is a good candidate to do surface measurements, and it could be also considered a dosimeter for in vivo dosimetry protocols. It has shown a considerable energy independence for the variations of the beam with the depth. The biggest difference is with the beam at 10 cm depth with 1.8%, taking as reference the beam at 5 cm depth. This depth was chosen because it is the calibration depth for the protocol of IAEA.[13] Using the output of the LINAC and the TSF for three different field sizes, the value of the PDD at 133.5 μm depth (place of the active layer of the radiochromic film) was obtained. This is considered the surface because it is the most suitable detector available for this purpose at our facility. The values measured were 26.1% ± 1.3% for the 10 cm × 10 cm field, 21.3% ± 2.4% for the 5 cm × 5 cm field and 20.2% ± 2.6% for the 1 cm × 1 cm field which is considered non-conventional. The independence with energy and field size will allow us to evaluate the Gafchromic EBT3 film in conventional and IMRT radiation treatments.

6. Conclusion

The radiochromic films Gafchromic EBT3 are suitable detectors for surface measurements applied to clinical purposes and in vivo dosimetry. Total scatter factors were measured with the daisy chain correction method. This procedure is recommended according to the formalism proposed by Alfonso et al.[16] for non conventional fields. The RF Gafchromic EBT3 shows a weak dependence of the beam energy which makes it a suitable detector for measurements at the surface. It is also a good option since it has been reported to be almost independent of the type of radiation. The indirect method to measure the value of PDD at the surface seems to be suitable but further studies or simulations, such as Monte Carlo calculations, need to be done to verify the values.

Conflict of interest

None declared.

Financial disclosure

This work was supported by CONACYT project SALUD-2015-1-261016.

Acknowledgments

The authors wish to thank to Lárraga Gutiérrez for providing the phase space for Monte Carlo simulation, also to Leopoldo Corona Niebla and Walter Eduardo Lee Cárdenas for their help with data collection.

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