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INVITED REWIEW

In Vivo Dosimetry In External Radiotherapy

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SUMMARY

Radiotherapy is a cancer treatment that uses ionizing radiation to kill or prevent the proliferation of cancerous cells, while also aiming to minimize the damage to healthy tissue. To achieve this in the most effective manner, many radiotherapy machines and treatment techniques have been developed. Today, advanced radiotherapy techniques, such as intensity-modulated radiotherapy, image-guided radiotherapy, and intensity-modulated arc therapy, are frequently being used in cancer treatments. These techniques are applied via computer-controlled devices; therefore, they need to be closely monitored to ensure the dose administered to the patient is as planned. It is important to check the accuracy of the plan to ensure that the correct dose is administered to the patient during treatment. The accuracy of the administered dose can be determined by in vivo dosimetry (IVD). Different measurement devices are used for IVD. In this article, the characteristics of IVD and its measurement systems will be reviewed.

Keywords: Surface dose; in vivo dosimetry.

Introduction

1. Surface Dose

In high-energy X-rays, energy dissipation occurs via primary photon bundles. The absorption of radiation by tissues usually occurs due to Compton interactions. When energy-bearing primary photons interact with the media surface, they transfer some of their energy to the electrons in the environment, causing the formation of secondary electrons with kinetic energy. These secondary electrons disperse within the tissue, where they deliver energy, affecting energy absorption. The secondary electrons formed on the surface determine the surface dose.

There are essentially three processes that occur on the skin surface: electron backscatter within the phantom, the formation of secondary electrons in the irradiated material, and the formation of contaminant electrons in the head of the therapy device.[1,2] These concomitant electrons are the main reason for the increase in skin dose. Due to the complexity of build-up region dosimetry and the lack of consideration given to the skin dose, physical data related to surface dosimetry are insufficient.[3]

Megavoltage photon beams have a skin-sparing effect because the surface dose is usually much lower than the maximum dose that occurs under the skin.[4] Although advanced radiotherapy techniques help to reduce normal tissue damage, unwanted skin reactions still occur. Many research groups have reported that a treatment planning system (TPS) cannot accurately calculate the surface dose. In the field of radiotherapy, it is important to know the precise surface dose, particularly when the patient's skin dose is a critical treatment-limiting parameter.

2. In Vivo Dosimetry And Measurement Points

In vivo is a Latin word meaning "within the living thing," whereby living organisms are used for various purposes. In terms of radiotherapy, it means the measurement of the dose that reaches the patient during

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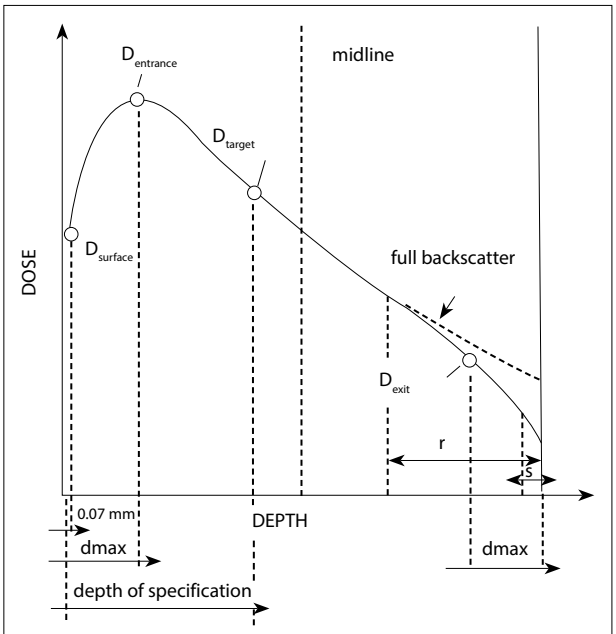

Fig. 1. Schematic representation of the percentage depth dose curve of a single photon beam. The measurement points used for in vivo dosimetry are shown on the curve.[5]

treatment, as opposed to the in vitro or ex vivo measurements of phantoms before or after treatment.

There are many reasons for using the in vivo dosimetry (IVD) method in radiotherapy. The most ambitious application of IVD is to control the dose in the target volume in order to verify that the applied beam is correct. By placing the detectors in natural body cavities, such as the esophagus, rectum or vagina, the target organ dose can be obtained. However, placement outside these regions will unlikely be able to measure the target organ dose accurately. In recent years, by means of wireless IVD systems, detectors can be placed in designated areas of the body from which the target volume can be determined. Due to the high cost of these systems, however, their use is limited.

The determination of the skin dose represents another possible application of IVD. To measure this, the dose derived from the signal of detectors on the skin surface is compared with theoretical values, and the dose is subsequently calculated by TPSs. However, the accuracy of the skin surface dose calculation is controversial, and TPSs cannot correctly calculate the surface dose.[5] Indeed, determination of the input and output doses is accepted as an indirect measure of the target dose. Therefore, the target dose can be estimated by skin dosimetry.

3. Measurement Points Used For In Vivo Dosimetry

3.1. High-Energy Photon Beams (Dentrance, Dexit, Dsurface, and Dtarget)

First, the measurement points used in IVD should be discussed. Different layers of skin, including basal and dermal layers, have varying depths. These depths differ among the layers, from patient to patient, and even where they are located in different patients. This makes skin dosimetry even more complicated. Despite the uncertainty with regard to depth values, the International Commission on Radiological Protection and International Commission on Radiation Units and Measurements (ICRU, 1985) have made some recommendations. Accordingly, the recommended depth for measuring the skin dose is 0.07 mm, which is the depth of the basal layer.[6,7]

For a single high-energy photon beam, the dose at the depth representing the maximum dose (dmax) from the entrance surface is called the "entrance dose" (Dentrance), whereas the dmax from the exit surface is called the "exit dose" (Dexit). The entrance and exit dose points are symmetrical with respect to the midline. From the entrance point of the medium irradiated by a single photon beam, the dose slowly rises from a low value on the surface to the maximum Dentrance dose, which depends on factors such as energy, collimator opening, and source skin distance.[5] Figure 1 shows the measurement points used in IVD and the depth dose curve of a single photon beam.

In general, the increase in dose, which is a function of depth from the surface to dmax, starts immediately below the surface with the slope decreasing at deeper distances and finally reaching a plateau as it approaches the dmax. This means that for Dentrance measurements, adequate material must be present around and in front of the detector placed on the skin to make the measurements repeatable. To limit the effect of head-scattered electrons on the Dentrance, a build-up cap must be used without any accessories, at a size that achieves complete build-up in the smallest collimator aperture.

The most accurate measurements are obtained when the detector is not within high-dose gradient regions. This can be achieved with the correct build-up thickness.

The build-down region, which is related to the lack of backscatter radiation from the air behind the patient, is located at the exit side of the patient. Photons and secondary electrons are responsible for this lack of backscatter, which causes the dose to decrease only a few millimeters beyond the exit surface. To achieve complete electron backscatter for Dexit measurements at dmax from the exit surface, it is important to use enough cover

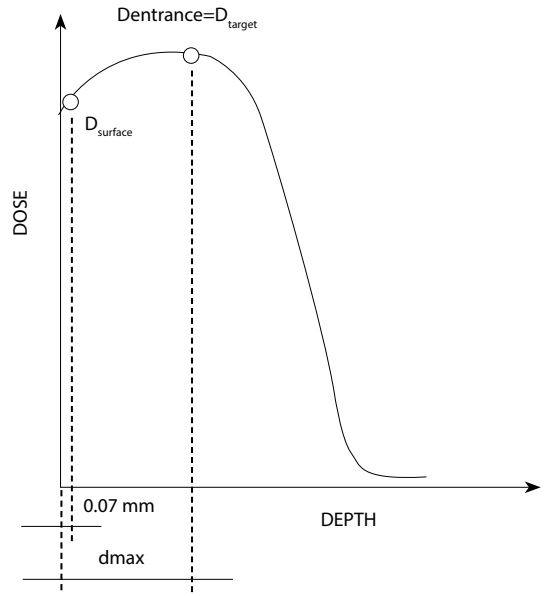

Fig. 2. Schematic representation of the percentage depth dose curve of a single electron beam. The measurement points used for in vivo dosimetry are shown on the curve.[5]

material over and around the detector. The determination of the target dose is more complicated than the dose measurements of the other points used in IVD. To identify and correct possible errors, each beam contributing to the target dose should be individually controlled, at least during the first fraction of treatment. In addition, it is important to check whether the treatment is repeatable over the following fractions.

In most cases, the in vivo measurement of both the exit and entrance doses is performed simultaneously. Extreme care must be taken when placing the exit detector because of the possible shadowing effect of the entrance detector.

These techniques are valid for conventional radiotherapy. Today, by means of new-generation radiotherapy technologies, any point of the target can be obtained using 3D TPSs. Dose control can be achieved by IVD if the target is in a body cavity. Otherwise, the other points used in the IVD can be measured and compared with the TPS to check the accuracy of patient treatment.

3.2. High-Energy Electrons (Dentrance, Dexit, Dsurface, and Dtarget)

High-energy electron beams have a uniform dose distribution on the surface; however, after a specific depth, a rapid dose decrease is observed. The penetration capability of electron beams is limited. Due to these characteristics, determining an exit dose for electron irradiations is not possible, particularly for thicker anatomical structures.

Because the target volume is most often electron irradiation of the patient's skin, the Dsurface and Dtarget can be related to each other. A single electron field is generally used in clinical applications of electron irradiation. However, additional electron fields can be used, particularly for breast irradiation or total-skin irradiation. Moreover, electron beams are easily affected by a lack of homogeneity. If the target is located around or inside a non-homogenous region, over- or underdosage problems may occur. Therefore, IVD for electron beams requires great care. According to the ICRU (1985), Dsurface is defined as the dose at 0.07 mm beneath the surface. Thin detectors, such as TL chips, should be used for measurement because they do not require any build-up material. They can be covered by a piece of thin paper and stuck onto the patient's skin. According to the ICRU recommendations, the target dose (Dtarget) is defined as dmax, which is the depth at which Dentrance also occurs (Fig. 2). At some electron energies, dmax can occur at depths greater than 1 cm. In such cases, build-up material may be required. However, because electrons have high scattering characteristics, build-up material may cause a scattering artefact and negatively affect the dose distribution. To derive Dtarget from Dsurface, it may be beneficial to use correction factors to remove this problem. Correction factors can be obtained using parallel plate ion chambers, which have no polarity effect. The depth of dmax can also be accurately measured using this type of ion chamber. Measurements should be performed on a phantom with the same irradiation conditions used for the patient. The ratio of the signals obtained at the surface and at dmax give the correction factors.

4. Detectors Used in In Vivo Dosimetry

The detectors used in IVD can be classified into two categories: real-time and passive. Both types of detectors require calibration. Calibration is usually performed by comparing the dose response with a calibrated ion chamber in a specific radiation field. Most detectors used in IVD have energy and dose responses. For this reason, considering that the actual irradiation conditions differ from the calibration conditions, some correction factors should be used when determining their dose response.

Diodes, metal–oxide–semiconductor field-effect transistors (MOSFETs), plastic scintillation detectors

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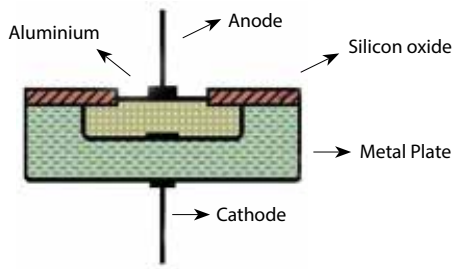

Fig. 3. Internal structure of a silicon diode.

Fig. 4. Metal–oxide–semiconductor field-effect transistor dosimetry system.

(PSDs), and electronic portal imaging devices (EPIDs) are real-time detectors used in IVD. These detectors are called real-time detectors because they provide a real-time dose response during the treatment.

Thermoluminescent dosimeters (TLDs), optically stimulated luminescent dosimeters (OSLDs), implantable MOSFET detectors, radiophotoluminescent dosimeters (RPLDs), and film (radiographic and radiochromic) are passive detectors. These detectors cannot provide immediate dose readings during treatment because the measurements need to be converted into a dose. While TLD, OSL, RPLD, and implanted semiconductor detectors allow point dose measurement, films provide 2D dose information.[8]

4.1 Real-Time Detectors Used in In Vivo Dosimetry

Silicon diodes

Silicon diodes were first used in the early 1980s. Figure 3 shows the internal structure of a silicon diode. They offer many advantages in IVD, such as real-time dose readings and high sensitivity, reliability, and durability. However, their dose response needs to be corrected in some situations, such as for different beam angles, dose rates, and energies, if the detector is used with a build-up cap.

The dose response of silicon diodes can show slight variation. The cable used to provide the connection between the diodes placed on the patient and the electrometer can be considered a disadvantage of this type of detector. However, new-generation systems use wireless technology. The diode sensitivity may change after accumulating high doses at adequate levels; therefore, they need to be calibrated regularly throughout the period of clinical use.[8]

Metal–oxide–semiconductor field-effect transistors

MOSFETs are detectors that include a p-type silicon semiconductor layer. MOSFETs are miniature silicon transistors with high spatial resolution that do not disrupt the beam too much due to its small size. MOSFETs measure the threshold voltage, which is a linear function of the absorbed dose. They require a bias voltage during irradiation, and their lifetime is limited.[9] They are also highly susceptible to variations in bias voltage, meaning that the bias voltage must be kept constant. Because the dose response slowly accumulates after irradiation, the dose can be read after irradiation has occurred for a certain period of time.

The detector has two different surfaces: round and flat. Generally, when the skin dose of the patient is being investigated, the MOSFET detector is adjusted so that the flat side faces the skin and the round side (epoxy side) faces the beam source. The water-equivalent measurement depth of the MOSFET detector is approximately 0.8 mm for the rounded portion and 1.8 mm for the flat portion. Over the past 5 years, MOSFETs have been used in in vivo and phantom irradiations, including for routine patient-dose verification, brachytherapy applications, total body irradiation (TBI), intensity-modulated radiotherapy (IMRT), intraoperative radiotherapy, and radiosurgery. Depending on the application, they can be used with or without build-up caps.[8]

The advantages of MOSFET dosimetry include their small dimensions, reproducibility, consistent results, measurements independent of dose rate, and negligible angle dependence.

One of the disadvantages of MOSFET dosimetry is their temperature and energy dependence. In addition, the dose response is reduced as a cumulative dose function, and the dose slowly decreases after irradiation.[10–12]

Plastic scintillation detectors

PSDs are promising for IVD as well as quality assurance (QA) applications due to their favorable dosimet-

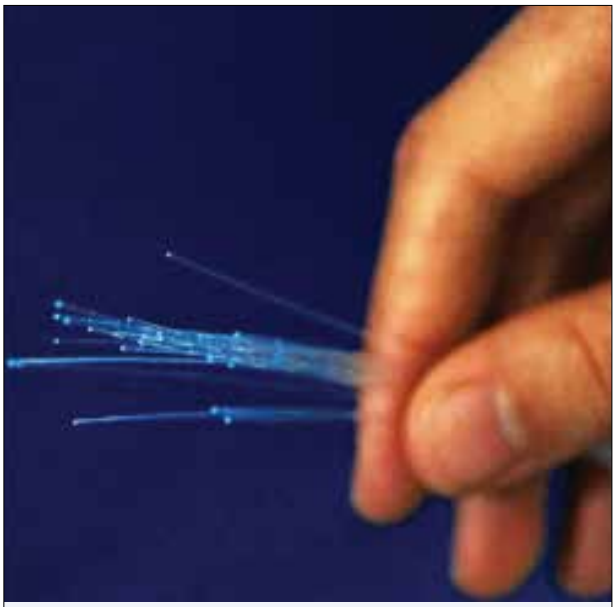

Fig. 5. Plastic scintillation detector.

ric characteristics, such as water equivalency, energy independence, dose linearity, and radiation damage resistance.[13] The word "scintillation" means "luminescence." Radiation loses its energy when it passes through a substance due to excitation. PSDs are based on the principle that the light emitted by the excited atom is detected by a photodetector.

Once calibrated, PSDs do not need correction factors, which are used by other detectors to convert the dosimeter readings into an absorbed dose. They have excellent spatial resolution due to their small size. For IVD using PSD, the difference between the measured and expected doses has been reported to be<1%.12 Unfortunately, because they are not currently available on the market, they do not yet have a wide range of clinical applications.[8]

Electronic portal imaging devices

EPIDs usually provide megavoltage portal images of the patient in a digital format that can be used to identify set-up errors during treatment. They can also be used for dosimetric purposes. They are useful for dose-control purposes, particularly for advanced treatment techniques, such as IMRT and VMAT. EPIDs are a promising system for IVD because they are not interventional and can provide 2D and 3D dosage information. Indeed, EPIDs with a flat-panel detector system based on amorphous silicon (a-Si)-photodiode technology are frequently used. The response of an a-Si EPID is independent of the dose rate and is approximately linear to the integrated dose.

Fig. 6. Thermoluminescent dosimeter (TLD) reader and computer system, showing TLDs of different shapes.

The disadvantages of using an EPID as a dosimeter include the fact that the flat-panel imaging material is highly sensitive to low-energy photon applications that are affected by water non-equivalent material. For example, continuing signal reception after radiation interruption is an example of a problem related to the use of an a-Si EPID (ghosting). Consequently, the EPID response is not linear to the dose.

There are two different approaches for using EPID in IVD. In the first approach, a portal dose image of the patient at the position of the EPID is predicted using the planning CT data; these data can then be compared. With this technique, it is not clear how dose differences in the EPID plane are related to dose differences in the patient. For this reason, a method known as "back-projection" has been explored by several groups. In this method, the patient dose distribution is derived from a measured portal dose image. The method applied by Piermattei et al.[14] has recently been expanded to reconstruct the 3D dose distribution within the patient from EPID measurements taken during IVD with IMRT and VMAT treatments.

4.2 Passive Detectors Used for In Vivo Dosimetry

Thermoluminescent dosimeters

The use of TLDs, a type of passive detector used in IVD measurements, is based on years ago in radiotherapy. TLD-100 (LiF:Mg,Ti) is commonly used for TLD in IVD. TLDs can be found in many different forms, including powders, chips, rods, or ribbons. TLDs can be used more than once, but they must be exposed to high heat before use. Furthermore, TLDs should be separated into groups before they are used in dosimetric applications by combining TLDs with similar dose values after irradiation. One or two TLDs from these groups can be allocated for calibration purposes. These TLDs are irradiated under the measurement conditions from which the dose efficiency of the device is obtained. The

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Fig. 7. Image of NanoDot optically stimulated luminescent dosimeters (OSLDs) in closed and open-up configurations. The OSLD reader and computer system are shown.

numerical value, corresponding to the radiation response of the TLD, is translated into the dose. For the calibration of TLDs, the use of the same feature beam that was used during patient treatment is recommended.[8] Figure 6 shows TLDs of different shapes and a TLD reader.

After irradiation, thermoluminescence signals decrease with time due to the spontaneous emission of light at room temperature (fading). The characteristics that make TLDs suitable for IVD include their ability to be used repeatedly after resetting, their ability to be placed in the patient's body cavities after being properly wrapped, and their ability to be used with a small correction factor. The use of TLD dosimetry requires great attention because the effective measurement distance changes according to the TLD material.

Optically stimulated luminescent dosimeters

OSLDs comprise carbon-doped aluminum oxide (Al2O3:C). While their application in radiotherapy is recent, they have been used for many years in radiation protection. OSLDs are similar to TLDs in terms of their dosimetric properties. The electrons released by exposure to ionizing radiation are caught in energy traps contained within the forbidden energy bands of crystal defects. This creates electron-hole pairs in the lattice. Exposing the substance to visible light stimulates the trapped electrons and causes them to recombine by emitting an optical photon. The optical photon fluence is proportional to the dose.[15] The biggest differences between TLDs and OSLDs are that OSLDs can be read again and again without resetting; the read can be performed just 10 min after irradiation; and they use light instead of heat to read and reset. Similar to TLDs, there are no energy dependencies for MeV photon energies, electrons, and protons.[16] Regarding megavoltage rays, there is an angle dependency of 3%-4%. A decrease in signal is observed within the first minute of irradiation; therefore, it is recommended to wait at least 10–15 min before reading.

Optically stimulated luminescent nanodots can be used in three different configurations: closed, open-down, and open-up. The effective measurement depths change depending on the configuration of the nanodots used. The effective measurement depths for closed, open-down, and open-up have been reported to be 0.85, 0.55, and 0.35 mm, respectively.[17]

The use of light for signal reading provides superior control over reading of the dosimeter with a quick on–off capability. The applications of OSLDs include output verification as well as phantom or in vivo surface dosimetry.

Although the basic properties of OSLD obtained using aluminum oxide have been investigated, there are still unanswered questions regarding the clinical performance of commercial OSLDs in radiotherapy.[15] OSLDs with different configurations and reading systems are shown in Figure 7.

Radiophotoluminescent dosimeters

RPLDs were historically used for personal dosimetry in the 1950s and 1960s but are now used in radiotherapy measurements.[18,19] They are produced from silver-activated phosphate glass. When exposed to ionizing radiation, luminescence centers are created. These radiation centers can be read using a pulsed ultraviolet laser, which causes excitation of the centers to create orange photoluminescence that can be read by an appropriate photodetection system. The amount of light is proportional to the amount of radiation absorbed by the detector. An unlimited number of repetitive readings can be received by RPDLs. Their dose response is independent of temperature. For 0.2-0.3 MeV high-energy photons, the dose response is independent of energy. Several preliminary studies have reported the use of RPLDs for skin dosimetry of breast cancer and for the entrance and exit doses of TBI.

Film (radiographic and radiochromic)

Film (radiographic and radiochromic) is a passive detector used in IVD. There are two different types of

films: radiographic and radiochromic. Radiographic films comprise a transparent substrate and an emulsion layer coated on either side of the substrate. There are a large number of AgBr crystals in the gelatin within the emulsion layer. The AgBr in the emulsion layer is sensitive to light and X-rays. Some changes occur in the AgBr crystals exposed to X-ray photons. A latent image, which is not visible to the naked eye, appears on the film. This image is made visible only by a series of chemical processes. Beam transmission is a function of film opacity and is measured as optical density (OD) using a densitometer. The OD is a function of the dose.

Radiochromic films are a new type of film used in radiotherapy dosimetry. Gafchromic films are the most widely used. Radiochromic films contain a special polymerized dye and emit a different color in the radiation-exposed region. The polymer absorbs the light, which is transmitted through the film and can be measured using a suitable densitometer, such as that in radiographic films. Flatbed color scanners with 48-bit image depths are usually used for reading. New-generation films exhibit polarization effects depending on the orientation of the film. For this reason, it is necessary to pay close attention to the placement of the films when taking measurements.

The responses of both radiographic and radiochromic films in the megavoltage range are stable and unchanged. The greatest advantage of radiochromic films over radiographic films is that they do not have any energy dependence, even at keV levels over a wide energy range.

Unlike TLD, OSL, and RPLD, films can give the user 2D dosing information and can permanently record radiation. The use of radiochromic films in dosimetry applications is rapidly increasing and is often preferred in IVD applications for skin dose measurements, total skin electron irradiation, and TBI measurements.[8]

Gafchromic films are more practical dosimetric systems because they are not sensitive to light, water equivalent, independent from dose rate and dose fraction, do not require a dark room and bathing, unaffected by watery or bloody environments; in addition, films can be cut into various sizes.[20] Gafchromic® EBT3 Film (ISP, International Specialty Products, USA) is part of the dosimetric equipment used in the quality control of patient plans in radiation therapy. The effective measurement depth of Gafchromic EBT3 is 0.153 mm.[20]

Implantable semiconductor detectors

Implantable semiconductor detectors were designed to measure a patient's daily dose when undergoing radiotherapy. Implantable detectors comprise a dual MOSFET detector, a data acquisition chip, a microprocessor, and a copper bobbin. All parts of the detector are encapsulated in a glass tube. The system has a portable telemetric reader attached to the dosimetry antenna, which provides power to the dosimeter, enabling data transfer. The dosimeter remains passive during irradiation and opens to measure the threshold voltage only after treatment has ended. Their dose repeatability is 5% or better. Because they are not used very often in clinical practice due to reasons including surgical implantation and permanent implantation, they are not likely to be further developed.

Conclusion

The measurement of the skin dose by IVD is an important part of current QA programs that use advanced radiotherapy techniques. While performing IVD, the characteristics of the measurement systems and their effective measurement depths should be known to evaluate the results correctly. The purpose of IVD programs is to increase the accuracy and quality of treatments, similar to other QA programs. However, it should be noted that IVD is the most reliable method to control the dose that reaches the patient during treatment.

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The author declare no conflicts of interest.

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